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TABLE OF CONTENT

EDITORIAL

LYMPHATICS OF THE MEDIASTINUM, ESOPHAGUS AND LUNGS: THORACIC SURGEON'S POINT OF VIEW.

Ciprian Bolca

Journal of Surgery [Jurnalul de chirurgie]. 2014;10(2): 113-115.

REVIEW ARTICLES

CHOLELITHIASIS - EPIDEMIOLOGY, RISK FACTORS AND ETIOPATHOGENIC ASPECTS: UP-TO-DATE.

Vladimir Hotineanu, Viorel Moraru, Petru Bujor and Sergiu Bujor

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 117-121.

ROLE OF MINIMALLY INVASIVE SURGERY IN COLON CANCER.

Ana-Maria Todosi, Mihaela Mădălina Gavrilescu and Viorel Scripcariu

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 123-128.

COMPARTMENT SYNDROME?PRESENTATIONS AND PRINCIPLES.

Krishanth Naidu and Naveen Narayanasamy

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 129-130.

RESEARCH ARTICLES

Resection of the Falciform Ligament and Ligamentum Teres Hepatis in Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

Thejus Thayyil Jayakrishnan, Avishkar Sharma, Anthony J Zacharias, Paul M Knechtges, Sam George Pappas, Fabian M Johnston, T Clark Gamblin and Kiran K Turaga

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 131-134.

Adnexectomy Versus Ovarian Conservation During Total Hysterectomy for Benign Conditions. A Difficult Dilemma.

Ion Păun, Dan Mogoş, Mariana Păun, Costin-Daniel Vidrighin, Mihai Florescu, Mădălin Teodorescu, Andrei Costin, Ecaterina Neamţu and Ana-Maria Predoi

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 135-140.

PLASMA CELL MASTITIS-ANATOMO-CLINICAL AND THERAPEUTIC CONSIDERATIONS.

Roxana Maria Livadariu, Radu Danilă, Daniel Timofte, Delia Ciobanu and Corneliu Diaconu

Journal of Surgery [Jurnalul de chirurgie].] 2014; 10(2): 141-143.

Journal of Surgery [Jurnalul de Chirurgie]
ISSN: 1584-9341

THERAPY OF SPINE METASTASIS CAUSING PARALYSIS SYMPTOMS ? OPERATION AND REHABILITATION.

Lars Homagk, Pataraia A and Röhl K

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 145-148.

ANYTHING OTHER THAN PAIN THAT MATTERS AFTER BREAST CANCER SURGERY? A RANDOMIZED CONTROLLED STUDY COMPARING THREE ANESTHETIC MODALITIES.

Nai-Liang Li, Chii-Ming Chen, Wen-Ling Peng, Skye Hung-Chun Cheng, Chen-Fang Hung and Wen-Hsin Kao

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 149-154.

Colonic Esophageal Reconstruction by Substernal Approach for Caustic Stricture: What is the Impact of the Enlargement of the Thoracic Inlet on Cervical Anastomotic Complications?

Boukerrouche A

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 155-158.

GASTROINTESTINAL STROMAL TUMORS: DIAGNOSTIC AND THERAPEUTIC CHALLENGES.

Ibrahim Abdelkader Salama, Waleed Hammam Mosa, Mohamed Elsherbini, Mohamed Abbasy, Mohamed Houseni and Mohamed Badr

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 159-165.

EFFICACY OF ELECTROGALVANIC STIMULATION IN TREATMENT OF LEVATOR ANI SYNDROME REVISITED.

Mantilla N, Paris B, Abcarian H, Cintron J, Zavala A, and Singer M

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 167-170.

CASE REPORTS

A CASE OF ACUTE NECROTIZING PANCREATITIS COMPLICATED BY PORTAL VEIN THROMBOSIS.

Saurabh Kumar, Shantanu Kumar Sahu, Jitendra P Ray, Sumit Jain, Vinamra Mittal, Kartik Nandra and Akshay Chauhan

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 171-172.

?DAMAGE CONTROL? ESOPHAGOGASTRECTOMY IN CASE OF PERFORATED AND BLEEDING GASTROESOPHAGEAL CANCER.

Bogdan Moldovan, Dumitru Pocreaţă, Dan Teodorescu, Marius Coroş, Viorica Sârbu, Lucian Băilă, Marcel Tanţău, Dragos Grusea, Florentina Pescaru, Andreea Moldovan and Laura Biriş

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 173-178.

MALIGNANT PARAGANGLIOMA; A STORY OF A LONG TIME SURVIVAL.

Ioana Vasiliu, Bogdan Hancearuc, Dan Iliescu, Cipriana ?tef?nescu, Radu Popa, Delia Ciobanu, Leti?ia Leu?tean, Voichita Mogo? and Carmen Vulpoi

Journal of Surgery [Jurnalul de Chirurgie]
ISSN: 1584-9341

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 179-182.

THEORETICAL AND PRACTICAL CONSIDERATIONS IN COLO-RECTAL DIVERTICULOSIS COMPLICATED WITH MULTIPLE SIGMOIDO-RECTO-VESICAL FISTULAS.

Călin Molnar, Ciprian Silaghi, Adrian Chiujdea, Ecaterina Daniela Dobru, Ciprian Rosca, Cosmin Nicolescu, Victor Iosif Neagoe, Vlad Olimpiu Butiurca, Claudiu Varlam Molnar and Constantin Copotoiu

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 183-186.

EMERGENCY THORACOTOMY- ISOLATED INTERNAL THORACIC ARTERY INJURY.

Islam S, Shah J and Narayn Singh V

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 187-189.

MULTIDISCIPLINARY MANAGEMENT OF AIRWAY OBSTRUCTION AND SUPERIOR VENA CAVA OBSTRUCTION SECONDARY TO HUGE RETROSTERNAL GOITER.

Chen YC, Ikhwan SM, Ziyadi MG, Zaidi Z, Amin NS and Narendran B

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 191-194.

A RARE CAUSE OF ENTERO-VESICAL FISTULA CAUSED BY A SKEWER, MULTIDISCIPLINARY MANAGEMENT AND MINIMALLY-INVASIVE SURGICAL CORRECTION.

Roberto Campagnacci, Giulio Belfiori, Pierluigi Sperti, Monica Ortenzi, Indrit Kubolli and Mario Guerrieri

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10 (2): 195-198.

SPONTANEOUS RUPTURE OF LIVER HAEMANGIOMA-A CASE REPORT & REVIEW OF LITERATURE.

Shariful Islam and Vijay Naraynsingh

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 199-201.

SURGICAL TECHNIQUES

THORACOSCOPIC LEFT SPLANCHNICECTOMY: TWO TROCAR TECHNIQUE.

George Jinescu, Ion Lica, Septimiu Andrei, Cornelia Chidiosan and Mihnea Dinu

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 203-205.

MULTIMEDIA ATICLE

LAPAROSCOPIC LEFT ADRENALECTOMY FOR A LEFT CORTICOSTEROID-PRODUCING ADRENAL TUMOR.

Radu Mircea Neagoe, Daniela Tatiana Sala and Titus Cvasciuc

Journal of Surgery [Jurnalul de chirurgie]. 2014; 10(2): 207-208.

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Editorial Open Access

Lymphatics of the Mediastinum, Esophagus and Lungs: Thoracic Surgeon's Point of View

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Abstract

The anatomy of the thoracic lymphatic system is very complex and not completely known yet. Thoracic malignancies, especially lung and esophageal cancers, are rapidly increasing as incidence. A good knowledge of the thoracic lymphatic system is very important in staging, diagnosis and treatment of these malignancies. The complete lymphadenectomy has a crucial role in both to achieve a correct postoperative stage and a complete resection of pathologic tissue. The article is a glimpse on the lymphatic anatomy of the thorax, as it should be known by surgeons involved in thoracic oncology.

Keywords: Thorax; Lymphatics; Mediastinum; Esophagus; Lungs; Thoracic surgery

Main Text

There are still many points in lymphatic embryology and anatomy to discover because of the limitation of exploratory methods that are available. The lymphatic vascular system is very complex and it hasn't been studied like the blood vascular system.

There are different lymphatic drainage pathways in the thorax that are relevant in the staging of thoracic malignancies: lung cancer, esophageal cancer, malignant mesothelioma, lymphomas and breast cancer. Each structure from which a thoracic primary tumor originates has a specific lymphatic spread that has to be known in order to be able to evaluate the spreading of the disease [1]. All these pathways are interconnected with each other and with the thoracic duct.

There are three main lymphatic ascendant pathways or lymph node chains described [2]: 1) *posterior parietal chain* that ascends along the vertebral column in the posterior mediastinum; 2) *anterior parietal chain* along the internal mammary vessels, and 3) *median visceral chain* along the esophagus, tracheobronchial tree and phrenic nerves

There is also a diaphragmatic lymphatic network which drains the diaphragm and establishes connections with above mentioned chains. The thoracic duct is the main lymphatic vessel in which all other lymphatic networks finally drains.

The *posterior parietal chain* ascends in the posterior mediastinum along the vertebral column and it gathers intercostal lymphatics which drain the chest wall, the posterior pleura and the posterior part of the diaphragm. On their course there are lymph nodes situated in the extrapleural fat adjacent to the rib heads. The drainage of this chain (both sides) is essentially ascendant, finishing in the thoracic duct or directly into the Pirogoff angle. They may also drain inferiorly and involve in this case the limphatics within the gastro-hepatic ligament and celiac nodes.

The *anterior thoracic chain* ascends along the internal mammary vessels and drains the anterior chest wall, the anterior and lateral diaphragm and the medial breast. The internal mammary nodes are found in the intercostals spaces along the sternum and are usually present from the fifth intercostals space to the clavicles [1]. This chain, like the posterior one, can also drain inferiorly through the rectus abdomen's muscle sheath to the sub diaphragmatic and sub peritoneal plexus and forward to the liver and retroperitoneal nodes. There are also connections between left and right anterior thoracic chains.

Both posterior and anterior chains, on the left and on the right side, communicate with the median visceral chain and also with each other by intercostals chains.

The *median visceral chain* is actually represented by lymphatics of intrathoracic organs and within the mediastinum. This median visceral chain gathers together a posterior para-esophageal chain, an anterior chain along the phrenic nerves and the most important, a median tracheobronchial chain that drains essentially the lung, but also the heart and the esophagus, better known by surgeons through the TNM classification used mainly for lung cancer.

Anatomic studies performed in the last decades [3] identified more clearly the lymphatic chains within the mediastinum, as it follows:

There are three lymphatic chains in the right upper mediastinum:

- Paratracheal lymph node chain corresponding to the stations superior 10R, 4R and 2R; this chain is located in an area bordered by the superior vena cava antero-laterally, the pericardium and the aorta on the left side, right brachiocephalic vein and the mediastinal pleura on the right side and by the trachea posteriorly.
- Tracheoesophageal chain corresponding to the station 3p and it is located in the tracheoesophageal groove.
- Right phrenic nerve chain corresponding to the station 3a located along the right phrenic nerve.

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There are three lymphatic chains in the left upper mediastinum:

Preaortocarotid chain corresponding to the stations 5 and 6 is located in a triangle formed by the phrenic nerve anteriorly, the vagus nerve posteriorly, pulmonary artery inferiorly, all covered laterally by the mediastinal pleura and wit a medial limit represented by ligamentum arteriosum.

Left superior bronchial recurrent chain is corresponding to the stations superior 10L, 4L and 2L. The boundaries are represented by the aortic arch superiorly, left main bronchus inferiorly, anterolaterally by the pulmonary artery and ligamentum arteriosum and medially by the trachea and the esophagus.

Left phrenic nerve chain corresponding to the station 3a located along the left phrenic nerve.

There are three lymphatic chains in the lower mediastinum:

- Inter tracheobronchial chain corresponding to the stations 7, 8, inferior 10R and 10L, located bellow the carina and bordered laterally by the main bronchi, posteriorly by the esophagus and anteriorly by the pulmonary artery and pericardium.
- A lymphatic chain on each side within the pulmonary ligament is corresponding to station 9
- There are aspects that are not yet clear regarding the limits between the mediastinal lymphatic stations. The limits between stations superior 10 and 4, between 4 and 2, between 5 and 6 or inferior 10 and 7 and 8 are still on debate. This is why, during lymphadenectomy for different thoracic malignancies, it is recommended to remove the entire lymphatic tissue and not only the nodes from different positions.

Esophageal Lymphatics

The lymphatic drainage of the esophagus is mainly longitudinal and intramural than segmental. There are lymphatic plexuses in every esophageal layer but the lymphatic network is abundant in the sub mucosal level and the lamina propria mucosae, and less developed in the muscular layer and in the adventitia. The dense sub mucosal lymphatic layer is uninterrupted and continues with the lymphatic sub mucosal layer of the pharyngx and of the stomach. In general the upper two thirds of the esophagus drain cephalic and the lower third drains caudally towards the abdomen. The sub mucous lymphatic vessels are perforating the muscular layer creating connections with lymphatic plexuses at this level, and also with the Para esophageal lymph nodes. This sub mucous network frequently has direct connections with the thoracic duct [4] and also with the anterior phrenic chain [5] and the median tracheobronchial chain.

Standardized lymph node mapping systems were described, and the most frequently used is the one described by American Joint Committee on Cancer for the staging of esophageal cancer. This lymphatic map was developed on the system first described by Casson [6] and it uses the mediastinal node stations described previously for lung cancer [7] with modifications specific to esophageal cancer. These specific modifications are addition of stations from 15 to 20 and division of the station 8 in middle and lower Para esophageal nodes (Figure 1).

It is well known that incidence of lymph nodes metastases in esophageal cancer is influenced by factors such as depth of tumor invasion, tumor location and histology. There are differences (not yet completely elucidated) regarding lymph node spread for adenocarcinoma and squamous cell carcinoma of the esophagus also related with the topography of each of these two hystologic types. As adenocarcinoma involves the lower esophageal third, usually drains downward and the squamous cell carcinoma, located in the two upper thirds, drains cephalic.

With a tumor limited to the sub mucosal layer the tumor cells will likely spread craniocaudally along the sub mucosal lymphatic plexus and involve nodes that are far from the tumor, for example cervical nodes. With a tumor that involves the muscular layer the possibility of mediastinal per esophageal nodes involvement is increased. The recent change of TNM classification for the N category is classified by the number of lymph nodes metastases and not the area where they are situated. Apparently, the second presented situation represents a more advanced stage of disease.

Pulmonary Lymphatic's

Even though there are some older descriptions of pulmonary lymphatic's, Rouvière [8] is credited with the first comprehensive description of lung lymphatic system; by selective injection of lymph vessels on 200 human specimens he managed to present the lymph nodes draining each lobe of the lung and he was the first that supposed the possibility of knowing the lymph node involvement based on the origin of the primary tumor. His drawings are still accurate today.

More studies were made in the 50's [9] and the 60's [10]. State of the art regarding description of the thoracic lymphatic system and the patterns of drainage was achieved nowadays by Riquet, who, with a constant interest and a life-long study in this subject, managed to present large and very valuable new information on this subject.

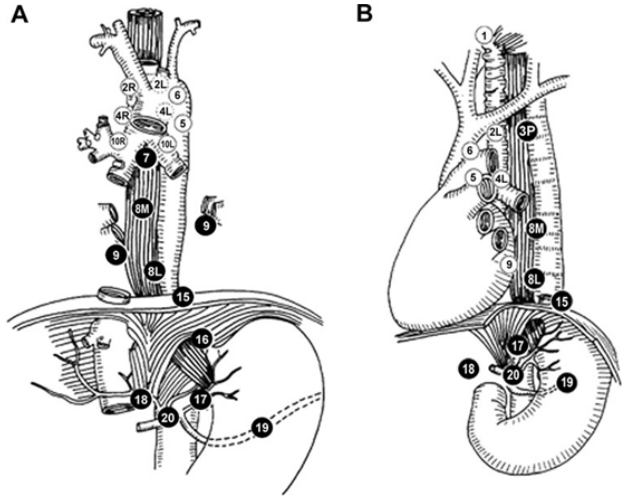

Figure 1: AJCC esophageal staging, nodal designation.
(1) *Supraclavicular nodes*: Above sterna notch and clavicles; (2R) *Right upper paratracheal nodes* - Between intersection of caudal margin of innominate artery with trachea and the apex of the lung; (2L) *Left upper paratracheal nodes* - Between top of the aortic arch and apex of the lung; (3P) *Posterior mediastinal nodes* - Upper paraesophageal nodes, above tracheal bifurcation; (4R) *Right lower paratracheal nodes*-Between intersection of caudal margin of innominate artery with trachea and cephalic border of azygous vein; (4L) *Left lower paratracheal nodes*-Between top of aortic arch and carina; (5) *Aortopulmonary nodes* -Subaortic ans para-aortic nodes lateral to the ligamentum arteriosum; (6) *Anterior mediastinal nodes* - Anterior to ascending aorta or innominate artery; (7) *Subcarinal nodes*-Caudal to the carina of the trachea; (8M) *Middle paraesophageal lymph nodes*-From the tracheal bifurcation to the caudal margin of the inferior pulmonary vein; (8L) *Lower paraesophageal lymph nodes*-From the caudal margin of the inferior pulmonary vein to the esophagogastric junction; (9) *Pulmonary ligament nodes*-Within the pulmonary ligament; (10R) *Right tracheobronchial nodes*-From cephalic border if the azygous vein to the origin of RUL bronchus; (10L) *Left tracheobronchial nodes* - Between carina and LUL bronchus; (15) *Diaphragmatic nodes* - Lying on the dome of the diaphragm, and adjacent to or behind the crura; (16) *Paracardial nodes* - Immediately adjacent to the gastroesophageal junction; (17) *Left gastric nodes* - Along the course of the left gastric artery; (18) *Common hepatic nodes* - Along the course of common hepatic artery; (19) *Splenic nodes* - Along the course of splenic artery; (20) *Celiac nodes* - At the base of the celiac artery.
The *lobar* and *(sub)segmental nodes* (11 to 14) are not figured.
(from Casson AG, Rusch VW, Ginsberg RJ, Zankowicz N, Finley RJ. Lymph node mapping of esophageal cancer. *Ann Thorac Surg.* 1994; 58: 1569-1570 – with permission from Elsevier)

Lymphatic capillaries of the lungs originate in the connective tissue between the alveolar walls and the interlobular, pleural, perbronchial and perivascular sheets [11]. More capillaries form lymphatic collecting vessels called collectors, which contain unidirectional valves and smooth muscle in their walls.

Along their course in the lung or in the mediastinum toward the venous blood circulation, most of the lymphatic collectors flow into lymph nodes which are an important part of the lymphatic system. Those structures form pathways named "lymph node chains" which terminates into the blood circulation by connecting directly with the cervical venous confluence, indirectly via the thoracic duct, or both.

The number, size and location of the lymph nodes along collectors are very variable among individuals and within the same individual. This variability must be remembered during treatment for thoracic malignancies. These lymph node chains can also present anastomoses with neighboring channels [12].

Lymphatics of the lung are represented by a visceral pleural network and a peribronchivascular or parenchymal network. The pleural collectors course over the visceral pleura towards the pulmonary hilum where they anastomose with the parenchymal collectors, or they can go further and enter directly into the mediastinum [13] - a good explanation of skip metastasis. Multiple lymphatic parenchymal channels anastomose with each other and drain sequentially into the itrasegmental, intersegmental, lobar and finally, hilar lymphatic nodes. Here, after anastomosis with the plural collectors they drain into the mediastinum.

Studies performed on lung cancer in various locations within the lung show that nodal pathways are dependent on the lobar origin of the tumor. Malignant lesions on the right upper lobe drain preferentially into the paratracheal lymph node chain and anterior mediastinal lymph nodes. Right middle and lower lobes drains usually into the subcarinal nodes and secondary into the paratracheal lymph node chain and anterior mediastinal lymph nodes. The tumors in the left upper lobe drain more frequently into the preaortocarotid chain and left lower lobe tumors drain into the subcarinal and left superior bronchial recurrent chain.

However, mediastinal metastases may occur in any of the mediastinal lymph nodes regardless the tumor origin, due to multiple connections between lymphatic channels. The hilar nodes also can be bypassed and mediastinal metastases may occur without hilar involvement, aspect that is more often encountered in the tumors involving the upper lobes. Rarely, direct passage from the parenchymal lymphatics and the thoracic duct allows the spread into the systemic circulation of metastatic cells without mediastinal node involvement. Bronchial lymphatics from both lungs usually remain ipsilateral, but they may sometimes connect with the controlateral mediastinum after crossing over at the level of lower trachea and subcarinal space [14].

In conclusion, surgical anatomy and the physiology of the lymphatic system is very important to be known by the surgeons involved in the diagnosis and treatment of thoracic malignancies, as the lymphadenectomy has a crucial role in both to achieve a correct postoperative stage and a complete resection of pathologic tissue. Removal of the lymphatic chains is a must in oncologic surgery of the thorax, even though, there still are gaps in proving the advantages in survival that a complete lymphadenectomy could bring.

Conflict of interest

The author has no conflict of interest to disclose.

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Review Article Open Access

Cholelithiasis - Epidemiology, Risk Factors and Etiopathogenic Aspects: Up-to-Date

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Abstract

Gallstone disease is the most common gastrointestinal disorder. The best epidemiological screening method to accurately determine the prevalence of gallstone disease is ultrasonography. Gallstone disease is considered a surgical disease since only cholecystectomy is capable of definitively curing the disease. Cholecystectomy is a limited indicator for the prevalence of gallbladder stones, as the perceived threshold for surgery and patient access to care differ markedly. Most patients with gallstones are asymptomatic and the risk of developing symptoms or complications related to gallstones is approximately 1-4% per year. The common complications of gallstones include biliary colic, acute cholecystitis, common bile duct stones, and gallstone pancreatitis. Although this disease has a low mortality rate, its economic and health impact is significant due to its high morbidity. Many risk factors for gallstone formation are not modifiable such as ethnic background, increasing age, female gender and family history or genetics. Conversely, the modifiable risks for gallstones are obesity, rapid weight loss and a sedentary lifestyle. The recognized risk factors of gallbladder stones for females cannot be extrapolated to men, and this demonstrates the polymorphic character of the etiopathogeny of cholelithiasis and requires further specification. Therefore, there is need for more knowledge of the epidemiological characteristics of gallstone disease in order to better identify therapeutic strategies.

Keywords

Cholelithiasis; Gallstone disease; Epidemiology; Risk factors; Etiopathogenetic aspects; Cholecystectomy

Epidemiologia Litiazei Biliare

Primele relatări în Europa referitoare la litiaza veziculară (LV) datează din sec. XIV–XV [1,2], iar cele mai numeroase cercetări au fost efectuate în sec. al XX-lea, fapt determinat de o escaladare substanțială a morbidității prin această patologie [3,4].

Litiaza veziculară are o etiologie plurifactorială (cu mecanisme intrinsece și extrinsece), caracterizată prin perturbări ale proprietăților de dispersie a particulelor biliare asociate cu procese de aglomerare, agregare și formare a calculilor biliari, punct de plecare a evoluției și persistenței inflamației cronice a peretelui vezical [2,5,6]. LV ocupă un loc aparte în patologia zonei hepato-blio-pancreatice, nu numai prin prisma diagnosticului etiologic [7,8], cât și din punct de vedere a răsunetului și impactului complex asupra funcției organelor adiacente [9,10].

La prima vedere aparent simplă, diagnosticarea ecografică a LV nu impune dificultăți deosebite [11-13], pe când precizarea factorilor etiopatogenetici [14,15] cu specificarea funcționalității organelor racordate arborelui biliar (ficat, pancreas, duoden) necesită deja o abordare mult mai complexă și nici pe de parte facilă [16]. În astfel de circumstanțe se impun metode speciale de cercetare, anumite tehnici de ultimă oră fiind actualmente prohibitive pentru majoritatea pacienților sau clinicilor [17,18]. Unele controverse privind managementul LV sunt datorate apariției la unii bolnavi a unui sindrom dispeptic de tip biliar, „sindromul postcolecistectomie", ce are o incidență în limite de 10-30% [19,20].

LV rămâne una dintre cele mai frecvente afecțiuni chirurgicale cu un impact important pentru sistemele de sănătate și practica medicală cotidiană [21,22]. În structura afecțiunilor chirurgicale ale organelor cavității abdominale, LV deține al 3-lea loc după apendicita și pancreatita acută, cu o tendință clară de creștere a incidenței și prevalenței la nivel mondial [13,23].

Conform OMS anual pe mapamond sunt efectuate circa 2,5 milioane de intervenții asupra căilor biliare (în majoritate colecistectomii laparoscopice) [24-26]. În același timp, litiaza biliară are un impact socioeconomic considerabil, comparabil cu cel al bolilor aparatului cardiovascular. Spre exemplu, în SUA costul total al tratamentului pacienților cu LV a depășit în anul 2005 suma de 5 miliarde USD [15], iar în 2011 deja a depășit 6,2 miliarde USD [7].

Unele cercetări dedicate reevaluării colecistectomiei laparoscopice [27] au constatat că 75-80% din purtătorii de calculi nu dezvoltă simptome sau complicații [22,28]. Cei mai mulți calculi biliari sunt din punct de vedere clinic "silențioși", descoperiți de multe ori incidental în timpul ecografiei abdominale efectuate din alte motive [29]. Astfel, în conformitate cu datele MICOL (Multicenter Italian Study of Cholelithiasis), din cei peste 33.000 de pacienți cu litiază biliară și vârsta cuprinsă între 30-69 ani, s-a consemnat evoluție clinică asimptomatică în 80 % din cazuri. Aceeași tendință se constată și în țările Europei de Est [30]. În grupa de vârstă 31-40 ani doar la 18% dintre pacienți ar putea fi suspectată prezența calculilor biliari în baza manifestărilor clinice, în grupa de vârstă 41-55 ani și grupa > 55 ani suspiciunea a fost confirmată respectiv în 25 % și doar 12 % observații. Totodată, persoanele cu LV asimptomatică dezvoltă proces inflamator acut cu o rată medie de 2-4% pe an, fiecare al 10-lea bolnav pe parcurs a

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5 ani de la depistare necesitând tratament chirurgical de urgență pentru colecistită acută litiazică [26,29,31]. Totuși tactica expectativă, preferată de gastroenterologi [1,27,32] nu este argumentată, rata complicațiilor și a mortalității, la fel ca și posibilitatea abordului laparoscopic fiind net diferite în urgență [23,28], comparativ cu tratamentul electiv [33,34].

Indicii epidemiologici de bază sunt reprezentați și de numărul colecistectomiilor efectuate la 100.000 locuitori, cât și mortalitatea postoperatorie. Studiile efectuate arată că odată cu amplificarea incidenței LV există și o creștere a complicațiilor, cum ar fi pancreatita acută biliară sau icterul mecanic litiazic [29,35]. Totodată, numărul de proceduri chirurgicale pentru litiază biliară a crescut semnificativ și constant în țările dezvoltate după1950 [33].

Ulterior, apariția colecistectomiei laparoscopice în 1989 a condus la o creștere importantă a ratei pacienților colecistectomizați: din 1990 până în 1993 s-a consemnat o escaladare de 28% a acestui indice [1,19]. Această schimbare a fost determinată de abordul mai puțin invaziv, mai acceptabil sub aspect cosmetic, oferind în același timp un risc chirurgical mai mic comparativ cu procedeul chirurgical "deschis" [9,21]. Colecistectomie laparoscopică este în prezent cea mai frecventă operație electivă abdominală [2,5,6,13,16].

Conform datelor OMS (WHOSIS Query Service, www.who.int.) în SUA anual sunt efectuate circa 150 colecistectomii la 100.000 locuitori cu o letalitate postoperatorie în limite de la 0,1% (în clinicile specializate) până la 0,6% (media pe țară). Autorii occidentali constată că deși rata mortalității prin LV este relativ scăzută, rămân totuși 1092 decese anuale legate de patologia calculilor biliari. Din fericire, mortalitatea s-a diminuat în mod constant cu >50% între anii 1979 și 2004, iar acest declin reprezintă cea mai mare scădere dintre toate afecțiunile tractului digestiv [14].

Conform datelor Biroului Național de Statistică a Republicii Moldova (www.statistica.md) incidența bolii este de 8-9000/100.000 persoane/an. În ultimii 4 ani se remarcă o tendință variabilă: 8396 cazuri în 2006, 8486 în 2007, 7786 în 2008, 8771 cazuri în 2009. Prevalența afecțiunilor veziculei biliare la populația adultă are o ușoară tendință de creștere de la 52830 cazuri în 2005, 53539 cazuri în 2006, 60772 cazuri în 2007, 55984 cazuri în 2008, 59679 cazuri în 2009.

În literatura de specialitate autohtonă nu am găsit date referitoare la indicii epidemiologici de bază ai litiazei biliare veziculare (numărul de colecistectomii la 100.000 locuitori și rata mortalității postoperatorii) pe parcursul ultimilor 5 ani. Datele statistice pe anii 2004 și 2005 denotă efectuarea a 1585, respectiv 2585 colecistectomii programate, cu mortalitate postoperatorie de 0,37%, respectiv 0,29%. Incidența colecistitei litiazice acute la 100.000 locuitori a constituit 85,7 în 2004 și 46,6 în 2005. În 2004 au fost operați de urgență 3085 bolnavi cu o mortalitate postoperatorie de 1,39%, iar în 2005 au fost 2016 bolnavi operați cu o mortalitate postoperatorie de 1,49%. Abdomenul acut chirurgical prin colecistită litiazică acută raportat la 100.000 locuitori a constituit 16,0 în 2004 și 11,4 în 2005 [36]. Anual în țara noastră se efectuează peste 25.000 operații adresate patologiei chirurgicale a tractului digestiv, mortalitatea generală postoperatorie constituind 3-10 % [37]. Chirurgia programată a celor mai răspândite boli digestive chirurgicale (boala ulceroasă a stomacului și duodenului, litiaza biliară, patologia pancreasului, ficatului și colo-rectală, patologia organelor endocrine) constituie până la 30-35% din numărul total de operații efectuate anual în republică (cca 72.000).

Statisticile estimează că 17-19% dintre bolnavii operați dezvoltă postoperator precoce sau tardiv diverse o serie de tulburări. Astfel, pentru Republica Moldova litiaza veziculară, constituie o problemă medico-socială importantă [36].

Bineînțeles rezultatele diferite par a fi dependente de circumstanțele locale, de experiența și expertiza echipei medicale, de factori socio-economici; unii autori occidentali consideră potențial evitabile decesele postoperatorii a bolnavilor colecistectomizați [24]. În acest context cunoașterea factorilor de risc ai litogenezei biliare, indicația chirurgicală corectă pusă în timp util, înante de apariția complicațiilor, explorarea amununțită intraoperatorie vor evita suferințele posoperatorii și litiaza reziduală. [15,18,21,26,28].

Factorii de risc și Etiopatogenie

Conform concepțiilor contemporane asupra etiopatogeniei litiazei veziculare factorii de risc importanți sunt convențional divizați în două grupe: 1) modificabili și 2) non-modificabili. Diverse cercetări au demonstrat că formarea calculilor biliari este multifactorială [3,7,35,38]. Unele caracteristici, cum ar fi etnia, genetica, înaintarea în vârsta și sexul feminin nu pot fi modificate, în timp ce altele (de exemplu, dieta, activitatea fizică, pierderea rapidă în greutate și obezitatea) sunt modificabile (Tabel I) [1,17].

Istoricul Familial și Predilecția Genetică

Susceptibilitatea genetică este un factor-cheie în evoluția litiazei biliare, studiile familiale relevând o frecvență de aproape 5 ori mai mare și un risc ridicat la rudele pacienților cu LV [31,39]. Aceste raporturi sunt îndeosebi mai mari la gemenii monozigoți, constituind circa 12% cazuri, iar în cazul celor dizigoți aproximativ 6% din gemeni dezvoltă în aceeași perioadă de timp litiază veziculară biliară [40]. Soții purtătorilor de calculi nu prezintă risc sporit, eliminându-se astfel factorul unui mediu comun (dieta de aceeași natură sau alte obiceiuri alimentare ale membrilor familiei) drept element care determină apariția LV [5].

Într-un studiu realizat de cercetătorii suedezi pe un eșantion de peste 43.000 de perechi de gemeni cu litiază biliară veziculară simptomatică efectele genetice au fost determinate în circa 25% observații, în timp ce influențele de mediu comune cu impactul respectiv au fost specificate în aproximativ 13% cazuri [40]. Apariția litiazei biliare reprezintă o interacțiune complexă a ansamblului format de însușirile genetice și factorii mediului, în mod particular a interacțiunii dietă-genă.

Cercetările în domeniul fiziopatologiei litiazei biliare efectuate în decursul ultimilor 10 ani au determinat rolul contribuției a șapte clase generale de gene candidate (în total 55 de gene), care codifică proteinele implicate în formarea calculilor: I) Enzime de reglementare a lipidelor hepatice (colesterol α-hidroxilaza), ce pot crește secreția colesterolului sau să reducă proporția de acizi biliari / fosfatidilcolină biliară; II) Receptori de lipoproteine cu proteine înrudite, responsabile pentru menținerea normală a metabolismului colesterolului; III)

Tabelul I: Factorii de risc ai litiazei biliare.

Non-modificabili	Modificabili
Istoricul familial / predispoziția genetică	Obezitate, sindrom metabolic, diabet zaharat, dislipidemie
Apartenență etnică	Medicamente: ceftriaxon, octreotide, thiazide, contraceptive
Sex feminin	Activitate fizică redusă
Vârsta (persoane de vârsta a II-a şi a III-a)	Scădere rapidă a masei corporale, anorexie
	Nutriție parenterală totală
	Dietă
	Afecțiuni diverse: ciroza hepatică, boala Crohn, diverticul duodenal şi coledocian, status post-rezecție gastrică, vagotomie trunculară, hiperparatiroidism, infecții ale arborelui biliar, hemoliză cronică
	Graviditate

Proteine hepatice şi intestinale de transport la nivelul membranei celulare (apolipoproteine E şi B); IV) Proteine hepatice şi intestinale de transport intracelular a colesterinei, sărurilor biliare sau fosfatidilcolinei (cholesterol ester transporting protein - CETP); V) Factorii care reglementează transcripţia lipidelor şi a sărurilor biliare, VI)- Colecistokinina şi receptori ei (cholecystokinin receptor A-CCKAR), care influenţează motilitatea veziculei biliare; VII) Mucina.

Prezenţa anumitor tipuri de genotip al apolipoproteinelor din clasa "E" (ce conţin alela apo-E4) este asociată cu un risc crescut de LV colesterinică [41], demonstrată la pacienţii care locuiesc în Finlanda, Germania, Spania [25,42,43]. Acest fapt se datorează sintezei semnificativ reduse de acizi biliari, odată cu creşterea absorbţiei colesterolului din intestin. Ca urmare, la bolnavii cu LV se constată un conţinut sporit de fracţii hidrofobe de acid desoxicholic. Astfel, în viitor se doreşte aplicarea ingineriei genetice în crearea bacteriilor coliforme cu capacitate redusă de sinteză a desoxicolatelor sau terapia adjuvantă în cazul 7α– hidroxilazei sau X-farnesoid receptorilor [44]. Aşadar, pornind de la cele mai vechi concepţii a predilecţiei genetice la colelitiază, bazate pe anamneza istoricului familial, ştiinţa medicală modernă a ajuns la etapa analizei propriu-zise a genomului uman, fapt ce oferă posibilitatea cunoaşterii şi înţelegerii mai profunde a mecanismelor etiopatogenetice de constituire a calculilor biliari.

Vârsta

Un alt factor major de risc al LV este reprezentat de vârsta. Frecvenţa depistării calculilor biliari creşte odată cu înaintarea în vârstă, în special după 40 de ani; riscul necesităţii tratamentului chirurgical creşte în această categorie de 4-10 ori [35,38,41]. Odată cu vârsta creşte numărul de cazuri simptomatice şi complicate, ce necesită tratament chirurgical. Datele OMS arată că la persoanele mai tinere de 50 de ani LV apare la 7-11%, în grupa de vârstă de 60-69 de ani la 11-23%, iar la persoanele peste 80 de ani afecţiunea are o incidenţă de 33-50%. Având în vedere că odată cu îmbătrânirea survine nu numai o creştere a secreţiei de colesterol în bilă, dar şi o scădere a cantităţii de acizi biliari secretaţi cu diminuarea concentraţiei lor cantitative în bilă (urmare a activităţii scăzute a colesterol- 7α- hidroxilazei) pare a fi legitimă conexiunea directă a LV cu vârsta [140,54]. Pe de altă parte, odată cu vârsta se schimbă şi tipul de calculi, iniţial fiind compuşi în principal din colesterol (corespunzător unei secreţii crescute de colesterol şi saturaţie de bilă), ulterior se modifică structura lor, fiind mai frecvent depistaţi calculi pigmentari sau micşti [24].

Sexul şi Hormonii Feminini

La ora actuală sexul feminin reprezintă un factor de risc al LV unanim recunoscut. La nivel mondial, femeile sunt afectate de LV de circa 2-4 ori mai frecvent, în unele etnii fiind atestat un raport femei/ bărbaţi de 7:1 [22]. Cercetările efectuate arată că în timpul trimestrului al treilea de sarcină la 30% din gravide apare "sludge" biliar (SB), iar la 2% apar calculi biliari colesterolici [45]. După travaliu, funcţia motorie a vezicii biliare se restabileşte şi SB dispare la 60-70% din femeile gravide [46].

În familiile cu predispoziţie pentru această patologie este detectată o rată net superioară a femeilor purtătoare de calculi [41]. Sistematizând succint unele aspecte ale etiopatogeniei LV putem evidenţia următoarele momente: ficatul absoarbe chilomicronii şi metabolizează colesterolul cu formarea colatelor şi excreţia ulterioară a colesterinei în comun cu colate şi fosfolipide sub formă de vezicule cu participarea proteinelor colat-transportatoare. Eliminarea veziculelor în bilă suplimentar este asigurată de: 1) sintetizarea esterelor de colesterină (acil- CoA: colesterinacetiltransferaza); 2) transformarea colesterinei în colate (acizi biliari) (7a-colesterolhidrolază, sterol 27- hidroxilaza); 3) sinteza şi secreţia de lipoproteine cu masă moaleculoară joasă. La rândul său micşorarea concentraţiei acizilor biliari în bila secretată poate fi determinată de următoarele mecanisme: 1) diminuarea biosintezei acizilor biliari primari, colic si chenodezoxicolic, prin inhibarea enzimei reglatoare 7α-hidroxilaza şi reducerea cu circa 25% din activitate ei [130]; 2) exacerbarea catabolismului acizilor biliari cu micşorarea cantităţii de acizi biliari (de la 5,45 ± 0,22 spre 3,38 ± 0,27 mmol) condiţionată de creşterea ciclicităţii circulaţiei entero-hepatice ale acestora.

Estrogenii sporesc conţinutul de colesterol în bilă prin acţiunea asupra receptorilor lipoproteinelor de masă moleculară joasă şi stimulează reabsorbţia colesterolului de către hepatocite [47]. Evoluează aşa-zisa colestază clasică "estrogenă fragedă", caracterizată prin creşterea raportului colesterol/fosfolipide pe membrana canaliculară cu diminuarea vitezei şi volumului secreţiei bilei hepatice [48]. Datele gamma-scintigrafiei dinamice în colestaza cronică se reflectă prin diminuarea funcţiilor hepatice de absorbţie (la cca 62% bolnavi) şi de excreţie (respectiv la 77% pacienţi) [2]. Prin prisma acestor fenomene (↑ sintetizării colesterolului; ↑ secreţiei de colesterină; ↓ raportului acizi biliari / colesterină) devine clar de ce drept factori de risc ai constituirii calculilor biliari colesterinici reprezintă sexul feminin, graviditate şi administrarea contraceptivelor [49].

Literatura consemnează ***studii sporadice referitoare la litiaza biliară la bărbaţi*** [50-53]. De regulă, sursele accesibile analizează problema în cauză fie pe cohorte generale ale populaţiei (bărbaţi şi femei), fie doar prin prisma unor particularităţi epidemiologice, clinico-evolutive, de tratament ş.a.m.d., la fel realizate pe eşantioane mixte [28,54].

În acest fel, la ora actuală datele asupra litiazei veziculare la bărbaţi rămân incerte şi necunoscute, datele prezentate de diverşi autori adesea sunt contradictorii sau sunt în conflict direct cu statisticile concepţiilor unanim recunoscute [50,55,56]. Anume această discrepanţă a şi constituit un motiv şi imbold puternic pentru efectuarea cercetărilor noastre în dorinţa de a elucida anumite aspecte ale problemei.

În linii generale în funcţie de sex LV survine la circa 7,9% bărbaţi şi 16.6% femei din ţările de vest, 3%, respectiv 15% în ţările Asiei; în ţările din Africa cu o rată generală sub 5%, în China afectează aproximativ 4,2% dintre bărbaţi şi 11% de femei [12,15,19]. Şi totuşi, datele literaturii recent publicate indică o creştere a incidenţei LV la bărbaţi [8], iar în grupa de vârstă peste 70 de ani această diferenţă aproape că dispare [26,41,57], ca urmare a creşterii numărului de cazuri de litiază biliară la persoanele de gen masculin [51-53].

În anul 2009 un grup de autori chinezi a publicat incidenţa LV pe un eşantion de 3573 bolnavi (1825 bărbaţi şi 1748 femei, repartizaţi uniform în funcţie de grupele de vârstă), cu rezultate surprinzătoare, incidenţa afecţiunii fiind practic similară - 9,9% la bărbaţi şi 11,6% la femei [8]. Conform rezultatelor cercetărilor proiectului Italian de studiu în domeniul litiazei biliare (MICOL), publicate în 1995 prevalenţa LV pe parcursul unui an creşte circa cu 0,47% la bărbaţi, comparativ cu 0,67% la femei [24]. În continuarea proiectului în 2008 au fost reevaluate datele bolnavilor incluşi iniţial în cercetare, rata cumulativă a incidenţei LV pe an constituind deja 0,67% la bărbaţi şi 0,81% la femei cu o diminuare a diferenţei în funcţie de sex [54].

Discrepanţă evidentă se constată şi la capitolul estimării altor factori de risc ai evoluţiei litiazei biliare la bărbaţi [14,23]. Astfel, dacă la femei rolul obezităţii, nivelului sporit de trigliceride, vârstei şi a administrării derivaţilor progesteronului sunt unanim acceptate, în cazul bărbaţilor datele sunt contradictorii [8].

Dacă unele cercetări [57,58] susţin că la bărbaţi dislipidemia nu reprezintă factor etiologic de risc şi nu se corelează cu constituirea calculilor biliari, alţi autori contestă aceste păreri [14,31,54]. Pare a fi plauzibilă şi argumentată concepţia C. Thijs şi colab. [59], conform căreia determinarea arbitrară (la un interval de timp scurt)

a concentraţiei lipidelor plasmatice poate fi doar o reflectare slabă a nivelului plasmatic „în perioada critică" de constituire a calculilor biliari, susţinută şi de alţi autori [46,60]. În acest caz, relaţia de cauzalitate între nivelul lipidelor şi LV poate fi subestimată. În confirmarea acestei ipoteze vom prezenta două exemple: după colecistectomie la pacienţi se consemnează diminuarea concentraţiei lipidelor plasmatice, în timp ce în cazul crizelor de colică biliară survine escaladarea fenomenului de sludge biliar cu mărirea dimensiunilor microcalculilor, concomitent fiind stabilită o creştere a concentraţiei lipidelor plasmatice [2,35,45].

Cu toate acestea, recent s-a demonstrat, că bărbaţii obezi secretă în general mai mulţi acizi biliari şi fosfolipide în bilă decât femeile supraponderale, prin urmare, bila lor este mai puţin litogenică şi ei nu au tendinţă de a forma calculi biliari [8,53]. Mai mult decât atât, se menţionează o conexiune directă între diminuarea şi fluctuaţia masei corporale (weight cycling) la persoanele obeze şi riscul sporit de constituire a calculilor biliari [54]. Regimul hipocaloric utilizat la pacienţii obezi dă naştere la aşa zisul „nămol biliar" cu litogeneză în circa 25-50% cazuri [61]. O confirmare o reprezintă următoarea observaţie: by-pass-ul chirurgical pentru obezitate sporeşte riscul LV: 40% dintre pacienţi dezvoltă calculi în termeni de 6 luni postoperatorii [21,62]. Pierderea în greutate este însoţită de niveluri ridicate de mucină şi calciu în bila veziculară, factori favorizanţi ai „nămolului biliar" şi litogenezei [1,47].

Pe lângă acestea, pierderea din masa corporală induce o diminuare considerabilă a sintezei hepatocelulare de glutationă (aproximativ la jumătate) - factor cu semnificaţie deosebită în asigurarea apărării antioxidativ, contribuind în acest sens creşterii metaboliţilor de peroxidare lipidică, şi respectiv stress-ului oxidativ al epiteliului veziculei biliare cu alterarea lui, fiind astfel create condiţii mai prielnice litogenezei [52,62].

În acelaşi timp, la bărbaţi nu se constată vreo conexiune directă între modul de viaţă (activitatea fizică) şi riscul evoluţiei LV [7,41]. Aceste concepţii sunt confirmate şi de studiul realizat de Chang Y. şi colab. (2008) [50], efectuat selectiv pe un lot de 440 bolnavi non-obezi şi non-diabetici cu litiază biliară, studiu care nu a stabilit vreo concordanţă între prezenţa calculilor şi indicele masei corporale, nivelul de colesterol şi trigliceride.

Concluzii

Factorii de risc ai LV recunoscuţi pentru persoanele feminine nu pot fi extrapolaţi "mecanic" şi la bărbaţi, fapt ce demonstrează încă o dată polimorfismul etiopatogeniei LV şi necesită cercetări suplimentare.

Conflict de Interese

Autorii nu declară niciun conflict de interese.

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Role of Minimally Invasive Surgery in Colon Cancer

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Abstract

Colon cancer is a major public health problem. The treatment of colon cancer is primarily surgical using open and minimally invasive techniques. Minimally invasive surgery approaches for colon cancer include single-port laparoscopy, natural orifice transluminal endoscopic surgery, and robotic-assisted laparoscopic surgery. The techniques are based on the same principles: complete mesocolic excision, high vascular ligation, and extended lymphadenectomy. Laparoscopic surgery is characterized by short hospital stay, reduced postoperative pain, and less need for painkillers. Laparoscopic resections are less expensive than open surgery, but with similar quality of life outcomes. Robotic surgery is an alternative to open and laparoscopic techniques. This type of surgery results in a lower conversion rate and a shorter learning curve than laparoscopic surgery. When comparing the clinical outcomes of laparoscopic surgery versus open surgery no difference in disease free survival and overall survival were found. This article shows the role of minimally invasive surgery in colon cancer, the clinical outcomes of laparoscopic and open colon being similar.

Keywords

Colon cancer; Laparoscopic colectomy; Complete mesocolic excision; Minimally Invasive Surgery; Survival

Introduction

Jacobs et al. are the first to report a laparoscopic colectomy in 1991 [1]. The use of laparoscopy in colorectal cancer has been slower paced, though with a lower rate than for cholecystectomy. The initial concerns were related to the safety and efficacy of this technique. Currently, in the United States 40% to 50% of colectomies are performed laparoscopicaly, with a 10% to 20% conversion rate [2].

Laparoscopic colectomy techniques have not been as rapidely adopted as those for laparoscopic cholecystectomy because laparoscopic surgery for colon diseases is associated with a learning curve due to the need to work in all quadrants on a mobile segment, to expose and ligate substantial vascular structures, and the challenge of achieving an intracorporeal anastomosis [3].

Advantages of laparoscopic surgery in colon cancer

Over a period of about two decades, the laparoscopic approach for colorectal cancer resections has evolved from experimental procedures with oncological concern to routine practice. Numerous randomized controlled trials and meta-analyzes have shown that laparoscopic resections are associated with a more rapid recovery, similar oncologic outcomes compared to open surgery both in colon and rectal cancer. Besides improved cosmesis, there are other long-term benefits such as a lower frequency of adhesion-related intestinal obstruction and a lower rate of postoperative hernia [4].

In the USA, only 5% to 10% of 250,000 colectomies are performed laparoscopycally. Laparoscopic colorectal surgery can be successfully performed in patients with benign and malignant diseases, regardless of anatomical location. Laparoscopic resections are associated with a shorter hospital stay, decrease in intravenous narcotic and oral analgesic requirement, with improved quality of life during the first two postoperative weeks. A lower rate of postoperative infections, eventrations, and intestinal obstruction was recorded. The new approach in minimally invasive surgery is single-incision laparoscopic surgery, allowing colorectal resections through a single 2.5 cm incision with excellent cosmetic results [5].

Compared with open surgery, laparoscopic surgery has a number of benefits such as reduced postoperative pain, less postoperative pulmonary and wound complications, decreased blood transfusion requirements, rapid resumption of intestinal transit [6,7], and shorter hospital stay, with similar oncologic outcomes for the two techniques [8]. Laparoscopy provides improved short-term outcomes and at least equivalent long-term outcomes in terms of cancer control when compared with open surgery [9].

Laparoscopic surgery for colorectal cancer is characterized by a learning curve. A systematic review of the literature on the learning curve was conducted using Medline and Embase databases. Of the 23 studies found, 7 studies, representing 4852 cases and 19 surgeons, were analyzed. The factors favoring conversion to open surgery and a higher complication rate were: body mass index, pelvic dissection (for rectal cancer), and male gender. More advanced T stage and the presence of complicated inflammatory disease increase the complexity of cases. This study showed that the length of the learning curve was of 88-152 cases, and case selection criteria can prevent high conversion and complications rate [10].

Patients with various associated comorbidities are not candidates for laparoscopic surgery, as they are considered to be high risk patients. Thus, a group of patients considered high risk, associating one or more such comorbidities as age over 80 years, BMI over 30, heart, lung, kidney, or liver disease and diabetes mellitus, were subjected to laparoscopic colorectal surgery and compared to a group subjected to open surgery. The laparoscopy group had a shorter hospital stay, fewer complications and a lower nonoperative mortality rate. These

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data suggest that laparoscopic colorectal resections can be performed safely in high risk surgical patients, with better outcomes than in those undergoing open surgery [11].

Quality of life is another important aspect in a patient undergoing resection. Quality of life changes and affecting factors were assessed in patients who underwent laparoscopic colectomy for cancer. The affecting factors were tumor stage and chemotherapy, and were more common in male patients. Emotional status improved immediately after surgery, and overall quality of life improved over the first year after laparoscopy, reaching even better levels than before surgery [12].

The cost-effectiveness of each surgery type is analyzed, the more so of minimally invasive techniques. It remains unclear if laparoscopic surgery for colon or rectal cancer is profitable in terms of cost-effectiveness in comparison with open surgery because although laparoscopic surgery results in shorter hospital stay it is associated with higher equipment costs. A thorough analysis of all studies on this topic was conducted. The data were taken from previously published studies and large randomized trials. The cost-effectiveness of laparoscopic surgery versus open surgery for colon and rectal cancer, expressed as cost per quality-adjusted life-year, was measured. The results showed no differences in quality of life between the two surgery types. As to cost-effectiveness, the only thing that advocates the use of laparoscopic resections is the rate of postoperative eventrations. Due to the additional time for incisional hernia repair, laparoscopic resections are more cost-effective if eventration rate remains less than or equal to open resection surgery. The conclusions were that laparoscopic resection for colon cancer is less expensive, with a similar quality of life as with open surgery, and therefore the preferred approach in certain patients [13].

Obesity is a factor that can influence the course of patients undergoing surgery. A study comparing laparoscopic surgical resection for colorectal cancers in obese *versus* non-obese patients showed that in the obese group there was a higher proportion of males, a higher incidence of left colon cancer (49.3 *vs*. 36.8 % , P=0.033) and more associated comorbidities ($P < 0.001$) than in the non-obese group. The length of surgery was significantly longer in the obese *versus* non -obese patients (221 *vs*. 207 min, P=0.025). There were no differences in the overall incidence of postoperative complications between the two groups, however postoperative wound infections were more common in obese patients (P=0.005). Obesity was not a significant independent risk factor for all postoperative complications (P=0.289 [14]. Body mass index was associated with the presence of wound-related complications demonstrating that obesity is a growing risk factor for postoperative complications [15]. Visceral obesity is considered to favor technical difficulty and is a risk factor for postoperative complications in laparoscopic-assisted colectomy. The results showed that a body mass index over 25 and visceral fat area over 100 cm^2 independently predict the incidence of postoperative complications (p=0.040 and 0.007 respectively). Visceral obesity was associated with anastomotic fistula and postoperative infection, and proved a more useful parameter than body mass index in predicting the postoperative course in such patients [16].

Principles of Laparoscopic Surgery

Europe adopted the radical principle of complete mesocolic excision as the optimal therapeutic approach in colon cancer. This concept is similar to total mesorectal excision for rectal cancer and the precise terminology and optimal surgery are key elements. There are three components essential to complete mesocolic excision. The main component involves the dissection between the mesenteric plane and parietal fascia, with the removal of mesentery, mesenteric fascia and visceral peritoneum containing all of the lymph nodes draining the tumor area [17,18].

The second component is a central venous ligation to remove all lymph nodes in vertical direction. The third component is the resection of a suitable length of the bowl to remove the involved pericolic lymph nodes in longitudinal direction. Laparoscopic resection appears to be as adequate to these principles as open surgery [19]. Complete mesocolic excision and high vascular ligation (apical) can improve the course in patients with colon cancer, but none of the analyzed survival parameters was influenced by the type of surgical technique used, classic or laparoscopic [20].

A meta-analysis including all studies from 2009-2011 compared intracorporeal versus extracorporeal anastomosis after laparoscopic right hemicolectomy for cancer. The systematic analysis of the literature included 5 nonrandomized controlled trials including 425 patients which were evaluated for methodological quality. The results showed that intracorporeal anastomosis was associated with a more rapid resumption of intestinal transit, a shorter time to resume eating solid foods, decreased need for pain medication, and a shorter hospital stay. There were no differences in nasogastric tube reintroduction rate, operative time, incision size, total number of nodes harvested, intraoperative complications, mortality, operative complications (anastomotic fistula, anastomotic haemorrhage, wound infection, ileus), reintervention and readmission rate. All these plead for an intracorporeal anastomosis in laparoscopic resections for right-sided colon cancer [21] .

Classification of Laparoscopic Techniques

Colorectal cancer surgery may be performed by open and minimally invasive techniques. Single incision laparoscopic surgery (SILS), natural orifice transluminal endoscopic surgery (NOTES), and robotic-assisted laparoscopic surgery (RALS) are the final points to be reached in minimally invasive surgery [22]. Hand-assisted laparoscopic surgery is a technique that has developed rapidly in the mid-90s after the general introduction of laparoscopy [23]. Although at first this technique was met by reluctance from the laparoscopic community, now it is gaining increasing popularity being considered a bridge towards total laparoscopic colorectal surgery. The technique is easy: a port device is inserted in the abdominal wall which allows surgeon's hand to be introduced into the abdominal cavity while preserving pneumoperitoneum [24].

Single-port laparoscopic surgery is more difficult for sigmoid colon and rectal cancers than for right-sided colon cancers. A study including patients operated by this technique showed that the average duration of surgery was 190 min, average blood loss 20 ml, and no postoperative complications. The average total number lymph nodes harvested was 17, and the distal margin was approximately 58 mm. The procedure was significantly more difficult in the cases in which the sacral promontory protruded ventrally. Depending on tumor location and shape of sacral promontory, the introduction of an additional trocar can render single-port laparoscopic surgery feasible for sigmoid colon and rectal cancer resection [25].

Single-incision laparoscopic surgery is used for right-sided colon cancer. In a study comparing this technique with multiport laparoscopic resections for right hemicolectomy proved that the first technique is a safe approach in this type of colectomy, resulting in a smaller extraction orifice and shorter hospital stay [26]. The safety and efficacy of single-incision laparoscopic resection in stage IV colorectal cancer patients was assessed in a study and the results showed no significant differences in intra- and postoperative complications, 30-day mortality rate, total lymph nodes, and postoperative hospital stay compared to the control group [27].

In addition to single-incision colectomy, to maintain the

minimal invasiveness of this method and the quality of lymph node dissection a new technique, called hybrid single-incision colectomy, has been developed. These techniques resemble, being usual laparoscopic colectomy but excluding a lateral to medial approach. Initial identification or ileocolic vessels exposure was done through a small incision and lymphadenectomy was mainly achieved using laparoscopic techniques. During laparoscopic surgery techniques of open surgery through the small incision may be used. The procedure had no postoperative complications or recurrences and did not require skin incision extension. Operative time was 191 min. This technique is safe and feasible for selected colon cancer patients and is associated with improved cosmesis [28].

Based on recent developments in the field of laparoscopy and endoscopy, a new technique using a combination of laparoscopy and endoscopy was proposed. This technique is named laparoscopic-endoscopic cooperation colorectal surgery and involves removal of a minimal colonic segment being feasible for en block resection of some laterally spreading colonic tumors difficult to resect endoscopically [29].

Natural Orifice Laparoscopy

An abdominal incision is required to extract specimens for laparoscopy-assisted colorectal surgery, incision which brings a number of disadvantages for the surgeon and patient. Natural orifice specimen extraction (NOSE) was developed to avoid these disadvantages. A study analyzing NOSE-type surgery in 24 patients with colon and rectal cancers showed that the average duration of surgery was 110.0 minutes, with an average intraoperative blood loss of 69.1 ml. The time to resumption of intestinal transit for gas was 3.1, days, and mean post-operative hospital stay was 9.2 days. Totally laparoscopic resection with NOSE proved suitable for selected patients with sigmoid colon or rectal cancer, and this technique is worth recommending and wide spreading [30].

Transanal endosopic microsurgery is used in the management of patients with rectal polyps and early-stage rectal cancers [31]. Another minimally invasive technique is laparoscopy-assisted transvaginal resection for sigmoid cancer. With this technique the median number of resected lymph nodes was 15 and the median operative time was 150 minutes; no conversion was necessary and most patients tolerated fluid intake 24 hours after surgery. As to sexual activity in sexually active patients no changes were reported. After a mean follow up of 25 months (10- 41 months) no death or tumor relapse were recorded, suggesting that transvaginal laparoscopy for sigmoid cancer is a feasible and safe technique is in carefully selectewd patients [32].

Laparoscopy-assisted colorectal surgery requires a mini laparotomy for specimen extraction and insertion of the anvil head of circular stapler into the proximal colon. Such mini laparotomy occasionally causes local pain and postoperative infection. To avoid these complications a new technique called complete laparoscopic surgery for colorectal cancer was invented. It uses two techniques: reconstruction by double stapling technique and removal of colon or rectum through the anus. It is restricted to patients with stage T1 cancer after endoscopic resection that allows reconstruction by double stapling and impossible in patients with thin mesentery or anal stenosis. The drawbacks of this technique are bacterial contamination and infection as well as intraluminal spread of exfoliated tumor cells [33].

Robotic Surgery

In recent years, robotic surgery has become a viable alternative to laparoscopic and open surgery in the treatment of colon cancer. The first robotic surgery was performed in 2001 after Food and Drug Administration approved the Da Vinci system in abdominal surgery, and since then its usefulness has increased. Compared with the open techniques, the advantages and superiority of robotic surgery, especially in the pelvis area, have been demonstrated by many studies, being now regarded as a safe and feasible alternative. However, more randomized trials are needed to further assess the favorable oncologic and functional outcomes of robotic surgery [22].

The major advantages of robotic surgery compared with laparoscopic surgery are the lower conversion rate to open surgery and a shorter learning curve. There is evidence to support the fact that in colon cancers laparoscopic surgery and robotic surgery have similar advantages in terms of rapid recovery, although robotic-assisted colectomy is associated with increased costs without providing a clear reduction in the overall morbidity and length of hospital stay [34].

Robotic surgery offers the opportunity to leave behind the limitations of laparoscopic surgery. Three-dimensional visualization and improved dexterity due to flexible instruments should be useful in complex laparoscopic procedures in confined spaces, such as the pelvis. Colorectal resections using the Da Vinci® system are well established and are increasingly becoming standard procedures. The most promising indications are nerve sparing total mesorectal excision in patients with rectal cancer, total mesocolic excision in patients with right-sided colon cancer and rectopexies in patients with pelvic floor insufficiency [35].

Right hemicolectomy with locoregional lymphadenectomy and intracorporeal anastomosis is feasible and can be achieved with this system. Total operative time was approximately 201.4 ± 8.1 minutes, mean robotic time 14.4 ± 7.5 minutes, and the length of hospital stay 8 days. The robotic system has proven to be safe and feasible for carrying out a series of steps: accuracy of nodal dissection, intracorporeal suture of anastomosis, and specimen extraction through natural orifices [36]. In colonic surgery, robotic techniques are associated with increased operative time and higher costs compared with laparoscopic techniques. However, the robot provides a stable camera platform and articulated instruments that eliminate manual tremor. Due to these advantages, robotic systems may play a role in complex procedures such as lymph node dissection around major vessels. In addition, laparoscopy-assisted intracorporeal anastomoses can be easily performed by the surgeon without a substantial need for a competent nurse. Currently, although the short-term and oncologic outcomes of robotic laparoscopic resections are considered acceptable, the long-term outcomes remain unknown [37].

When comparing robotic surgery with laparoscopic surgery in colon cancer resections in terms of short-term outcomes, no significant differences in conversion rate, number of permanent stomies, number of intraoperative complications, level of markers of systemic cellular stress response, number of intraoperative complications, postoperative hospital stay, and postoperative 30-day mortality were found between the two groups. There was a longer preparation time for robotic surgery (77.1 *vs.* 69.7 min, P=0.000), but operative time was significantly shorter with robotic surgery (165.8 *vs.* 183.4 min, P=0.006), without differences in overall procedure time (254.0 *vs.* 243.6 min, P=0.086) [38]. In conclusion, the robotic approach has grown steadily in recent years. The advantage of three-dimensional visualization, improved articulations, and the ability to operate in the pelvis, are theoretical and real advantages in colorectal surgery [39].

Laparoscopy *Versus* Classic Surgery

Between 2000 and 2008 laparoscopic surgeries for colon cancer have increased from 1.5% to 20.7%. As a consequence, the lengths of hospital stay and 28-day readmission rate for colon cancer were reduced. Despite the increase in the number of laparoscopy-assisted resections, the vast majority of colon cancers are treated by open surgery. Laparoscopic surgery reduces the length of hospital stay and

readmission rate, and may result in improved outcomes in terms of colon cancer resection specific survival [40].

Complete mesocolic excision and central vascular ligation for colon cancers can be performed both by open and laparoscopic approach. When comparing the two approaches, the mean time to resumption of normal diet was shorter and the length of hospital stay was significantly shorter (7 days *versus* 13 days, p <0.001) in the laparoscopy groups *versus* open surgery group. The total number of lymph nodes harvested, 30-day operative morbidity, disease-free interval, and 5-year overall survival of the two groups were comparable, without significant statistical differences. The laparoscopic technique proved to be safe and feasible, and in terms short-time outcome it was more advantageous than open surgery [41].

Survival studies have shown that for colon cancer laparoscopic colectomy are safe in terms of short-term outcome, and the long-term oncologic outcomes are not inferior to those from open surgery. Thus, the 5-year recurrence rate, overall survival, and disease-free interval in laparoscopic surgery are similar those from classic surgery [42].

When comparing the long-term outcomes of laparoscopic surgery and classic surgery for TNM stage III colon cancer, laparoscopy was superior with regard to local recurrence or presence of peritoneal carcinomatosis. Open surgery showed a significantly higher probability of local recurrences or metastases (p <0.001), with a significantly increased likelihood of death from neoplastic disease (p=0.001) [43].

The role of laparoscopic surgery for advanced transverse colon cancer remains controversial, especially in terms of long-term oncologic outcomes. When comparing the oncologic outcomes of open surgery and laparoscopy-assisted colectomy the results showed reduced intraoperative blood loss, faster resumption of intestinal transit, and shorter length of postoperative hospital stay in the laparoscopy group. There were no differences in the 5-year survival rate and 5-year disease-free interval between the two groups. Laparoscopy for advanced transverse colon cancer has short-term benefits and equivalent long-term outcomes [44]. Hospital stay after laparoscopic surgery was shorter compared with open surgery (4 days *versus* 7 days). 5-year survival in the laparoscopy group was significantly higher than in the open surgery group (75.8 *versus* 72.5 %, p=0.12), meaning a possible advantage on overall survival [45].

The total number of lymph nodes harvested and of positive lymph nodes was similar in laparoscopy and open surgery patients, with a greater number of total nodes identified in patients with right-sided colon cancer. Other variables such as age, sex, race, or body mass index did not affect the total number of lymph nodes. Lymphadenectomy can be successfully performed by laparoscopic techniques, no demographic factors influencing the outcome [46-48].

All randomized trials of stage I- III colon cancer patients were included in a meta-analysis aimed at comparing the outcomes of laparoscopic and open surgery. In the five trials included in the study no differences in 5-year survival between laparoscopy and open surgery were found, with a trend in favor of open surgery in stage II patients [49]. A meta-analysis evaluated whether the 5-year recurrence and survival rate after laparoscopic colectomy were similar to those after open surgery in colon cancer patients. Five randomized controlled trials involving 2695 patients that reported 5-year survival were included in the meta-analysis. The results showed no significant differences between the two types of surgery in overall mortality (p=0.23), total recurrence rate (p=0.24), 5-year disease-free interval (P=0.96) and 5-year overall survival (P=0.55). This meta-analysis suggests that laparoscopy was as effective and safe as open surgery in colon cancer [50].

Possible Complications in Laparoscopic Surgery

The presence of exfoliated tumor cells in the abdominal cavity is considered to be one of the complications of laparoscopic surgery in colon cancer patients. A study evaluating by cytologic detection the presence of these cells before and after tumor resection showed that laparoscopic surgery does not increase the recurrence and metastasis rate, and survival was similar to open procedure [51].

Chylous ascitis was reported as a possible complication after laparoscopic colorectal cancer surgery. It can occur after right hemicolectomy and left colectomy for sigmoid cancer. Chylous ascitis can occur immediately after resumption of oral food intake, and can be treated conservatively by drainage. If a major lymph duct is involved, it must be ligated or clipped [52].

Another consequence of abdominal surgery is postoperative ileus. A study aimed to assess the duration of postoperative ileus in relation with the type of surgery (open surgery *versus* laparoscopic surgery) showed that in terms of postoperative ileus resolution the open techniques with minimal manipulation of intestinal loops and laparoscopic techniques have similar results [53]. A prospective randomized study investigated the effect of surgery on intestinal permeability, endotoxemia, and bacterial translocation in patients undergoing elective colectomy for colon cancer by comparing classical and laparoscopic surgery. It showed an increase in all monitored parameters, but without statistically significant differences between the two groups [54]. Sigmoid volvulus has also been reported after laparoscopic surgery for sigmoid colon cancer associated with ischemic necrosis of the involved colon segment. The diagnosis was made clinically and by imaging (computed tomography). Treatment consisted in the resection of the necrotic segment and creation of a descending colon stroma. A long remnant sigmoid colon and chronic constipation can contribute to the occurrence of a sigmoid volvulus after laparoscopic resection. Early diagnosis is essential for appropriate treatment and colonoscopy may be useful in detecting ischemic mucosal changes [55].

Most endoscopic surgeries involve carbon dioxide insufflation. It is not uncommon for CO2 to pass spontaneously into the subcutaneous tissue, and later into the bloodstream causing hypercapnia. During laparoscopic surgery, hypercapnia can cause acidosis, arrhythmia, hypotension, myocardial ischemia, and cardiocirculatory arrest [56] and even acute respiratory failure despite endotracheal intubation [57].

Conclusions

The treatment for colon cancer remains surgical. Minimally invasive techniques play an increasingly important role in colorectal cancer resection. The usefulness of laparoscopy has been demonstrated by numerous clinical trials, having similar outcomes compared to open surgery in terms of overall survival and 5-year disease free interval. Laparoscopy is a feasible and safe technique and can be used in the treatment of colon cancer. Robotic surgery is an alternative to laparoscopic surgery, but is associated with much higher costs.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Journal of Surgery
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Review Article Open Access

Compartment Syndrome – Presentations and Principles

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Abstract

Background: Compartment syndrome (CS) remains an elusive diagnosis with limited awareness despite progress of glorious investigative, diagnostic and imaging modalities. This review aims to reiterate the surgical fraternity to the fragility one faces with the concept of CS.

Methods: A retrospective desk review of published literature has been undertaken through the review of PubMed, Cochrane Library, Medline, EMBASE and Web of Science databases to portray the spectrum of presentation with involvement of rare sites in CS that have the capacity to stupefy the surgical fraternity.

Results: 18 articles and book chapters were reviewed from the search chain of over 200 articles. Through literature review it is appreciated that the sites of involvement with CS are varied and can encompass regions that are once thought unlikely. There is great degree of variance in the incidence of this syndrome. Though the implications are grave, the diagnosis of the syndrome is complex given the presentation spectrum.

Conclusion: Despite its immemorial descriptions and characterization as a surgical emergency, compartment syndrome remains an elusive diagnosis given its lack of awareness and wide presentation profile.

Keywords: Compartment syndrome; Osteo-fascial compartment; Fractures and trauma

Introduction

The seminal paper of Richard von Volkmann in 1872 inspired and moulded the early knowledge, understanding and awareness of the global orthopaedic fraternity to the gravity compartment syndrome (CS) posed as a result of grievous orthopaedic insult [1-3]. However, despite the invent and progress of glorious investigative, diagnostic and imaging modalities through the turn of the century, CS is still regarded a shadow in the darkness given its lack of awareness. The gravity of dealing with such an elusive diagnosis culminates in high rates of litigation.

Methods

A desk review of over 200 articles was undertaken with 18 eventually selected. Journal articles in PubMed, Cochrane Library, Medline, EMBASE and Web of Science databases were searched for CS. The focus of the review was to elucidate the history, signs and symptoms, pathophysiology, sites of involvement, prognosis, complications, treatment and essentially the irregularities with presentations in CS so as to improve the appreciation of the disease and thus improved clinical care. Apart from journal articles; book chapters were a valuable reference resource in undertaking the review.

Only articles chapters published in English were included. The resources were reviewed for the indicated impact and where warranted, articles within the pre-selected articles were reviewed.

Results

CS is defined as perfusion compromise to muscular-nervous contents within an osteo-fascial compartment as a result of increased pressure within a non-compliant intra-compartmental space that exceeds vascular perfusion pressure [3-5]. Groups of muscles and their associated neurovascular bundle comprise a muscle compartment. The latter is encapsulated by an unyielding facials surround. The clinical manifestations of CS stems from the reduction of tissue perfusion. As a fundamental of perfusion physiology, tissue perfusion is proportional to the difference between the capillary perfusion pressure and the interstitial fluid pressure [3]. A narrowed arterio-venous perfusion gradient results from an increase in intra-compartmental pressure from various mechanisms. As a consequence, capillary perfusion pressure is overcome and manifestations of CS results. The formal transmural pressure that results in complete vascular impedance is debatable. In addition to standard clinical acumen, intra-compartmental pressures greater than 30 mm Hg coupled to or in isolation of a raised intra-compartmental pressure as compared to diastolic blood pressure is an accepted requirement to necessitate a fasciotomy [3-6]. Emergent fasciotomy is known to normalize compartmental pressures with muscle cell regeneration considered the most desirable therapeutic outcome [3].

CS is known to exist in 2 forms – acute and chronic. Traumatic fractures are the most commonly implicated etiology in acute CS with the anterior compartment of leg the most commonly studied site [1,3,7]. In an analysis of 164 patients, McQueen and Court-Brown reported a higher propensity of CS occurrence in males with 69% of the sample population succumbing to a fracture - 50% were associated with tibial fractures [1]. Chronic compartment syndrome (CCS), originally described by Maver in 1956 is typically related to exertion and exercise and is primarily characterized by chronic reproducible pain and disability that is alleviated on removal of the precipitant coupled to rest and 5 minutes post-exertional intra-compartmental pressures greater

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than 15mmHg and 20mmHg respectively [8]. CCS has not been known to be an implicated in traumatic events [3].

Despite the degree of variance that exists in the incidence of the abovementioned syndrome, it is well known that the prevalence of CS is directly proportional to the nature and severity of injury sustained [9]. Children are noted to be significantly affected given a 20% incidence in CS with open forearm fractures [3,10]. With a sample of 104 patients, DeLee and Stiehl noted a 6% and 1.2% incidence of CS in open and closed tibial fractures respectively [1,3]. The incidence described previously is in isolation of associated underlying vascular insult. As noted by Blick, with the assimilation of the latter, 9.1% of the sample developed CS in the setting of an open tibial fracture [3,7]. To further complement Blick's results, Feliciano et al. noted 19% of patients who sustained a vascular insult required a fasciotomy [1,3,11].

The prognosis of CS is dependent on two interrelated entities – diagnosis and duration from injury to instituting intervention. The threshold of muscle viability was clinically validated by Rorabeck and Macnab following a finding of near normalization of limb function and return to premorbid level of function with institution of fasciotomy within 6 hours of diagnosis and injury [12]. As per Sheridan and Matsen, 68% and 8% of sampled patients had normal limb function when fasciotomy was performed within and beyond 12 hours of acute CS onset respectively [13]. Majority of fatalities are secondary to uphill battles with multisystem organ failure and prolonged intensive care admissions.

Fasciotomies of the lower limb posterior compartment have shown to have poorer outcomes than those in an anterior CS secondary to the morbidity associated with a complete posterior decompression. One risk's peroneal nerve palsy when diagnosis and or intervention in lower limb CS is delayed [1].

In the event of failure to institute any form of intervention, Volkmann's contractures have been approximated to occur in up to 10% of patients within a short duration of weeks to months [14]. Calcific myonecrosis is an uncommonly encountered manifestation of post-traumatic lower limb musculo-nervous perfusion compromise. Delayed compartmental decompression has shown to result in formidable infections that might cause one to succumb to an amputation. A retrospective analysis conducted by Matsen et al. revealed that 46% of limbs developed an infection following delayed surgical intervention. 45% of those with infections succumbed to an amputation [12].

A multitude of causative factors have been documented. Given the wide causative profile, it is essential to simplify the factors into basic mechanisms as so as to aid understanding and application of management – Increased interstitial pressure within the enclosed compartment, extrinsic compression imposed on the compartment and constriction of intra-compartmental space [15]. A non-exhaustive list of aetiological factors is provided by Hoover and associate [3].

Limb fractures – forearm, tibial and fibula – form the commonest cause of CS [3]. Reperfusion of limb after prolonged ischemia (> 6hours) is a common cause of acute CS as suggested by Rowlands in the beginning of the twentieth century (1910) [9,15]. High risk individuals include those with type 3 open fractures with significant comminution, pedestrians of motor vehicle accidents, poly-trauma, risk of delayed or missed diagnosis owing to significant or distracting injuries, prolonged anaesthesia, altered sensorium secondary to drugs and cognitive impairment, non-communicative, spinal cord injury and or transection [9].

The locations to which CS occur has expanded exponentially since its initial conception in the nineteenth century. Initial reports and understanding of CS were limited to the upper extremity. It was the report of ischemic contractures secondary to open tibial fractures in the mid-20th century that redefined CS localization [9]. Volar compartments of the forearm, anterior and deep posterior compartments of the leg are considered the most commonly involved sites given their unyielding structure [3,4,9]. Whitesides et al. in the 1960s revolutionized the concept of decompressing more than one compartment given their understanding of the existence of 4 compartments in the distal limb.[9,16] Rare and uncommon sites are continually being defined and include but not limited to the shoulder, back, foot - Manoli proposed the existence of nine pedal compartments, thigh - posterior compartment and tensor fascia lata compartment, gluteal, hand, arm, abdomen and paraspinous muscles, leg – Davey demonstrated the existence of a septated tibial posterior compartment [3,15-18].

Despite its immemorial descriptions and characterization as a surgical emergency, CS remains an elusive diagnosis given its lack of awareness and great variance in disease process and presentation. The difficulty in assessing the incidence of the syndrome is an indication that CS has the capacity to stupefy the surgical fraternity.

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Research Article Open Access

Resection of the Falciform Ligament and Ligamentum Teres Hepatis in Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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Abstract

Background: Routine resection of falciform ligament and ligamentum teres hepatis (FL-LTH) during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has been advocated but may be associated with increased complications. We aimed to study the role of FL-LTH resection at the time of CRS+HIPEC.

Methods: Retrospective review of patients who underwent CRS+HIPEC from January, 2010 to April, 2013 was conducted. Non-parametric methods were used for analyses.

Results: CRS-HIPEC was performed in 71 patients (FL-LTH resection in 57, 80.2%). The sensitivity and specificity of visual examination were calculated as 97.4% and 75.0%, respectively. Visual examination falsely classified 1/33 cases as disease free (3.0% False-negative, pathology showed carcinomatosis) and 6/24 as diseased (25% False-positive, pathology showed fibroadipose tissue). False-positive resection was not associated with increased complications (0/6). The recurrence in porta-hepatis (of n=48 with CC0 cytoreduction) was lower in the resected group (3/41, 7.3%) vs. non-resected (2/7, 28.6%), and associated with a hazard-ratio of 0.17 (95% CI 0.02 – 1.20, p-value 0.07) at a median 11 (IQR 7.0 – 16.7) months follow-up.

Conclusions: Visual examination during CRS+HIPEC may miss disease at the falciform ligament. A policy of routine resection is not associated with increased complications and should be considered.

Keywords: Peritoneal neoplasms; Liver anatomy; Porta hepatis; Liver surgery

Introduction

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS+ HIPEC) is an evolving paradigm in the treatment of cancer disseminated into the peritoneum [1,2]. While the therapeutic role of CRS-HIPEC has been well established through multiple studies, efforts are ongoing to improve the surgical techniques such as the use of minimally invasive approach for patient selection [3-6]. A common site of disease recurrence resulting in treatment failure in these patients is the perihepatic region and porta hepatis [7,8]. This could potentially be attributed to the complex anatomy of the liver surface with its fissures and ligaments that may result in inadequate visualization of disease and incomplete cytoreduction [8]. Falciform ligament and ligamentum teres hepatis (FL-LTH) are remnants of the ventral mesentery and fetal umbilical vein respectively, and connect the anterior surface of the liver to the anterior abdominal wall. The ligament may serve as a potential nidus for occult disease resulting in recurrence. Even though routine resection of FL-LTH has been proposed to avoid the possibility of any missed disease, [8] in clinical practice, it is often performed based on the visual examination for disease that may not be reliable.

The current study aimed to examine the correlation of visual findings of a surgeon with the pathological findings of resected specimens of FL-LTH, and to evaluate the impact of FL-LTH resection during CRS-HIPEC on the oncological outcomes in terms of recurrence of disease at porta hepatis.

Methods

Retrospective review of patients that underwent CRS+HIPEC for peritoneal carcinomatosis between January, 2010 and April, 2013 was performed after approval by the Institutional Review Board (IRB). Patients who underwent more than one cytoreductive surgery and those who underwent CRS at an outside center were excluded. Data on tumor characteristics, operative details, hospital course and morbidity, recurrence and survival outcomes were extracted and entered into a pre-specified data extraction sheet. Length of hospital stay was calculated from the date of surgical procedure to the date of discharge and survival was calculated from the date CRS+HIPEC. All patients being evaluated for CRS+HIPEC undergo cross sectional imaging with contrast enhanced CT scans, diffusion weighted MRI with a 1.5 or 3 Tesla coil and a PET/CT fusion scan based on the histology being evaluated. Patients with extensive disease (PCI score>11 for gastric cancer, and >19 for colorectal and non-gastric primaries) are usually excluded from CRS+HIPEC.

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Technique of falciform ligament resection at the time of cytoreductive surgery

CRS is undertaken after adequate pre-operative preparation and appropriate placement of central venous catheters. A diagnostic laparoscopy is usually performed for high grade histology to allow staging through the left upper quadrant optical trocar. Upon performing a laparotomy, the anterior peritoneum is stripped away from the midline and a window is created in the peritoneum to examine the surfaces. The anterior peritoneum is stripped with the falciform ligament from the umbilicus all the way up to the investing peritoneum over the inferior vena cava, and then stripped off the surface of the liver until it becomes contiguous with the LTH. The pont hepatique is divided to allow for complete resection of the LTH as it inserts into the left portal vein.

Complete cytoreduction is performed using the techniques described by Sugarbaker and others. HIPEC is performed using the closed technique [9].

Follow up

The first post-operative imaging study is usually performed at 6 weeks. Subsequent visits were planned as 3 monthly visits for 2 years and 6 monthly visits for next 3 years and less frequently for low grade histology. All image reports were reviewed along with re-review by an independent radiologist to evaluate for radiologic evidence of recurrent disease.

Statistical analyses

Statistical calculations were performed using STATA software Version 12.1 (StataCorp, Texas, USA). Continuous data are summarized as mean and standard deviation. Comparison was performed using student's t-test for continuous data. Categorical variables were expressed as valid percentages and compared using Kruskal-Wallis tests assuming non-parametric distribution. Survival outcomes were explored using Cox proportional hazards model. Alpha was fixed at 0.05 for statistical significance.

Results

The demographic details of the subjects are described in Table I. CRS was performed in 71 patients (Median age 55.1, IQR 47.1 – 61.8 years), of whom FL-LTH resection was performed in 57 patients (80.3%). The most prevalent primary was appendiceal (46.5%), followed by colorectal (32.4%) and gastric (5.6%). The median PCI score at laparotomy was 13 (IQR 6-23). CC0 cytoreduction was achieved in 81.4%. The median length of stay was 10 (IQR 8 - 14) days. Grade 3-5 complications were reported in 13 (18.0%). At a mean follow up of 11.3 ($\pm$7.3) months 61 (85.9%) were alive and under follow up. Of these, 24 were disease free (39.3%), 16 (26.2%) reported stable disease and 21 (34.4%) progressive disease.

In 38 cases, FL-LTH was performed for visible disease of which 6 were false positive. This occurred due to fibroadipose tissue that appeared to be tumor ridden. Of the 19 patients that underwent routine resections without any obvious disease, 1 (5.3%) was positive for carcinomatosis. Serial sectioning of the tissue in this patient revealed a well circumscribed nodule on gross examination that was identified as a focus of metastatic adenocarcinoma on microscopic examination.

The sensitivity and specificity of visual examination were 97.4% and 75.0%, respectively, assuming pathological examination (microscopic) as gold standard. Visual examination falsely classified 1/33 cases as free of disease (3.0% False-negative, patient had carcinoma) and 6/24 as diseased (25% False-positive patients had fibrous tissue) as described in Table II. The visual findings of the operating surgeons and pathology findings of the resected FL-LTH specimens are described in Table III along with their primary tumor histology. False-positive resections were not associated with increased complications (0/6). Overall, FL-LTH specific complication was reported in 1 case (0.2%) in which bleeding was encountered from the left portal vein which was easily controlled with a prolene suture.

The recurrence in porta-hepatis (of n=48 with CC0 cytoreduction) was lower in the resected group (3/41, 7.3%) vs. un-resected (2/7, 28.6%), and associated with a hazard-ratio of 0.17 (95% CI 0.02 – 1.20, p-value 0.07) at a median follow-up of 11 (IQR 7.0 – 16.7) months.

Discussion

The sub-peritoneal space is invested with lymphatics and vasculature and play an important role in the intra-abdominal spread of pathology including malignancies [10]. The falciform ligament and ligamentum teres hepatis (FL-LTH) are part of the large pre-peritoneal

Table I: Baseline Characteristics and Outcomes of Patients Who Received CRS+HIPEC for Peritoneal Carcinomatosi.

Characteristic (n=72)		Median (IQR)	Frequency n (%)
Age of cytoreductive surgery (in years)		55.1 (47.1 – 61.8)	
Gender			
	Male		36 (50.7)
	Female		35 (49.3)
Primary Tumor Diagnosis			
	Appendiceal		33 (46.5)
	Colorectal		23 (32.4)
	Gastric		4 (5.6)
	Ovarian		3 (4.2)
	Sarcoma		2 (2.8)
	Others		6 (8.5)
Preoperative imaging			
	CT		65 (91.5)
	PET		48 (67.6)
	MRI		36 (50.7)
PCI score at laparotomy (n=55)		13 (6-23)	
Completeness of cytoreduction (n=59)			
	CC0		48 (81.4)
	CC1		9 (15.2)
	CC2		2 (3.4)
Length of stay (days)		10 (8-14)	
Grade 3-5 Clavien- grade complications			13 (18.0)
Patients alive and under follow up			61 (85.9)
Status at last office visit (n = 60)			
	No disease		24 (39.3)
	Stable disease		16 (26.2)
	Progressive disease		21 (34.4)

CRS Cytoreductive surgery, HIPEC Hyperthermic intraperitoneal chemotherapy, CT Computerized Tomography, PET Positron Emission Tomography, MRI Magnetic Resonance Imaging, CC Completeness of Cytoreduction.

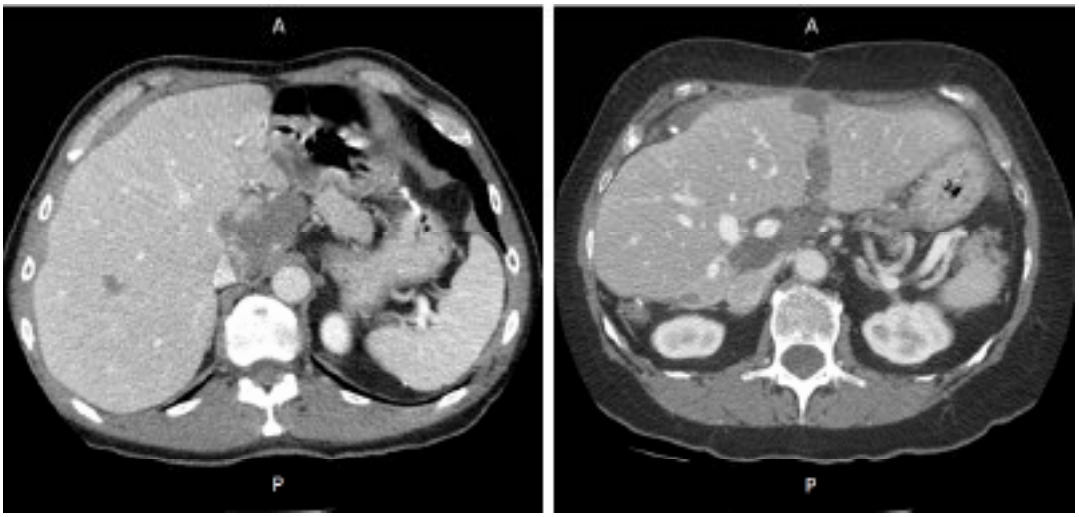
Table II: Comparison of Visual Findings of Surgeons with the Final Pathology Findings for Falciform Ligament and Ligamentum Teres Hepatis (N = 57).

Visual Finding	Pathological Finding for Cancer		Total
	Positive	Negative	
Appears diseased	32	6	38
Not diseased	1	18	19
Total	33	24	57

P-value<0.001

Table III: Comparison of the Visual Finding from Surgeon's Operative Dictation and Pathology Finding (Microscopic) for the Discordant Cases along with Primary Tumor Histology (n = 7).

Category	Visual Finding from Surgeon's Operative Dictation	Pathology Finding (Microscopic)	Primary Tumor Histology
Visual positive for disease and pathology negative			
Case#1	"There was disease on the patient's gallbladder, surface of the liver, on the patient's spleen, and then on both hemidiaphragms that had caked the diaphragms"	Fibro fatty tissue, negative for malignancy	Mucinous cystadenocarcinoma, low grade appendiceal primary
Case#2	"This (Falciform Ligament) was covered in tumor as well"	Fibroadipose tissue, negative for malignancy	Moderately-differentiated, mucinous adenocarcinoma appendiceal primary
Case#3	"The patient had disease over the falciform ligament and the ligamentum teres hepatis"	Fibrocollagenous tissue with no diagnostic abnormality	Ovarian high grade papillary serous carcinoma
Case#4	"There were nodules noted by the ligamentum teres hepatis"	Negative for malignancy	Metastatic poorly-differentiated mucinous adenocarcinoma appendiceal primary with signet ring cell features
Case#5	"We also noticed mucinous implants over the falciform ligament and ligamentum teres hepatis"	Fragments of mesothelial-lined fibroadipose tissue. No tumor seen	Well-differentiated mucinous appendiceal adenocarcinoma appendiceal primary
Case#6	"The patient had disease over the right hemidiaphragm, falciform ligament"	Negative for malignancy	Metastatic mucinous adenocarcinoma with signet ring cell features appendiceal primary
Visual negative for disease and pathology Positive			
Case#7	"LS1 in zone 1, LS0 in zone 2"	Metastatic poorly different adenocarcinoma	Diffuse poorly differentiated adenocarcinoma with signet ring cell features Appendiceal primary



Figures 1: (a) and (b) CT Cross Sectional Images From Two Patients Demonstrating Recurrence of Cancer in Porta Hepatis following CRS + HIPEC.

space anchoring liver antero-posteriorly to the abdominal wall [10,11]. The superficial lymphatics of the liver traverse through the FL-LTH, and may potentially play a role in the peri-hepatic recurrence of cancer demonstrated in Figures 1 (a) and (b) [11]. Therefore, routine resection of this ligament is an important consideration to delay disease progression. The present study revealed trend towards decreased porta-hepatis recurrence in patients that underwent FL-LTH resection. Further, the study also demonstrated that visual examination as a basis for resection of FL-LTH result in missed disease and supports the role of a routine resection.

The necessity of routine resection can be weighed against any increased risk of complications. In our study, there was no increased risk of complications in those who underwent resections in the absence of disease (final pathology negative). One of the feared complications of dissection in this area is the damage to left portal vein and left hepatic artery (LHA) due to the proximity of liver attachment of FL-LTH [7]. Alterations in the anatomy due to adhesions from cancer and past surgery may enhance the risk of this complication. In the current sample none of the patients that underwent FL-LTH resection reported LHA damage. However, the current study maybe underpowered to detect a difference and investigation in a multi-centric setting is warranted. It is also important to note that our center is a high volume center for CRS+HIPEC. The complication rate may be higher in a center with less experience in CRS+HIPEC.

The technique for FL-LTH resection has been described by Sugarbaker and others [7]. We have employed the use of the LigaSure to obtain a hemostatic margin of the ligament which can be done expeditiously. It is fairly safe in the setting of minimal or no disease, but can be technically challenging in patients with extensive mucinous disease in the porta hepatis. In such cases, dissection of the left portal vein to protect it is important before resection of the LTH. We also concur that opening the pont hepatique is essential to the complete clearance of disease and failure to do so, often leads to early recurrences in this area [7].

Imaging for peritoneal disease is difficult and recurrences are often occult on imaging. We have employed diffusion weighted Magnetic Resonance Imaging (MRI) technology for follow up of high risk patients but the increased duration and discomfort for patients makes it difficult to utilize for all patients. The porta hepatis is unique in its radiographic interface due to its clearly defined boundaries and lack of adjacent bowel motion which can obscure small implants. Subsequently, early recurrences can be easily detected. We believe therefore that the chance of detecting early recurrences is much higher than other sites

of peritoneal disease. Nevertheless, we recognize the limitations of imaging only assessment of peritoneal recurrence.

The additional time and cost of a FL-LTH resection is minimal and can be performed expeditiously by an experienced surgeon. This can also be done easily laparoscopically and lends itself to incorporation into the surgical algorithm for patients undergoing cytoreduction. Surprising in our study was the inconsistencies between the visual examination and the final pathology. While, this was mainly due to fibrous obliteration or mucin, it speaks to the need for better intra-operative assessment of peritoneal disease. Routine resection of FL-LTH is easy, but lends itself to another controversial subject of routine versus selective peritonectomies for patients with peritoneal disease. At present, there is no consensus for this practice although most centers employ selective peritonectomy techniques.

Conclusions

Visual examination during CRS-HIPEC may be unreliable for detecting disease at the falciform ligament, and can adversely impact on the treatment outcome if used as the basis for resection. Resection is not associated with increased complications and should be routinely performed during CRS+HIPEC.

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Research Article Open Access

Adnexectomy Versus Ovarian Conservation During Total Hysterectomy for Benign Conditions. A Difficult Dilemma

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Abstract

Introduction: Bilateral adnexectomy is a surgical procedure that is frequently associated with total hysterectomy performed for benign uterine conditions. Given the relatively wide range of indications for the aforementioned type of salpingo-ooforectomy which in it self is not devoid of potential risks the patients' and physicians' decision-making should take into account several parameters (most helpful to individualize treatment) such as published ratio of removal versus conservation of uterine adnexae, patients' age, pre/postmenopausal status at the time of surgery, relevant family and personal history including current use of hormonal replacement therapy.

Material and Method: This retrospective cohort study was conducted among 457 women aged 18 years or older who underwent abdominal total hysterectomies for benign uterine conditions between 2000 and 2011. The study patients were stratified by age for better characterization and according to recent publications.

Results: Uni- or bilateral oophorectomy was performed in 50% of the subgroup of hysterectomized women younger than 35 years old whereas in the other half of the same age category of patients the uterine adnexas were conserved. Among the study patients aged between 35 and 45 years in 50.5% of the cases the unilateral type of oophorectomy was undertaken while for the other 49.5% of women the bilateral adnexectomy was the rule. Finally, in all patients older than age 45 years the bilateral salpingo-oophorectomy was the procedure of choice. Moreover, out of the 55 study patients in which at least one ovary was preserved, 30.9% of cases underwent the removal of the remaining adnexa when affected de novo by malignant (n=3) or benign (n=14) pathology. Last but not least, in order to reduce both cancer risks and early menopause hazards, our analysis based on recent literature attempted to identify patient characteristics (relevant factors) associated with or without bilateral oophorectomy at the time of benign hysterectomy and to estimate modern trends in the performance of oophorectomy.

Conclusion: When considering options for treatment of benign conditions of the uterus both physicians and patients should ponder carefully the risk/benefit ratio of salpingo-oophorectomy according to each patient clinical profile.

Keywords: Uterus; Adnexa; Hysterectomy; Adnexectomy; Oophorecteomy; Salpingo-oophorectomy

Introducere

Extirparea uneia sau a ambelor anexe sau dimpotrivă menţinerea lor, cu ocazia histerectomiei totale efectuate pentru afecţiuni benigne, constituie o dilemă în faţa căreia este adesea pus chirurgul care practică astfel de intervenţii.

Indicaţiile în ceea ce priveşte efectuarea anexectomiei sunt foarte variate însă, în luarea acestei decizii trebuie ţinut cont de o serie de factori precum riscurile sau beneficiile menţinerii sau îndepărtării anexelor, vârsta pacientelor, momentul efectuării intervenţiei (pre- sau postmenopauză), antecedentele personale şi cele familiale, precum şi de oportunitatea sau nu a unei hormonoterapii substitutive (riscuri, beneficii, cost).

Pornind de la statistica realizată în clinica noastră şi ţinând cont de datele oferite de literatură, adesea cu rezultate divergente, încercăm în această lucrare să evaluăm oportunitatea conservării sau extirpării anexelor, din punct de vedere al rezultatelor postoperatorii.

Material şi metodă

A fost analizată retrospectiv statistica clinicii de chirurgie a Spitalului Căi Ferate Craiova în perioada 2000-2011. Au fost incluse în studiu toate cazurile la care s-a realizat histerectomia totală pentru afecţiuni benigne ale uterului. În lotul pacientelor cu anexectomie bilaterală au fost incluse şi acelea care aveau efectuate în antecedente anexectomie unilaterală şi la care s-a extirpat anexa restantă cu ocazia noii intervenţii. Histerectomiile realizate pe cale vaginală au fost excluse. Datele au fost introduse într-o bază de date şi analizate statistic.

La niciuna dintre paciente nu s-a intervenit prin abord laparoscopic.

Rezultate

În perioada menţionată s-au efectuat 457 de histerectomii totale pentru afecţiuni benigne ale uterului.

Tipurile de afecţiuni care au impus histerectomia totală au fost următoarele: leiomiom sau leiomiofibromatoza uterină 56,9% (n= 260);

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endometrita sau endomiometrita cronică rebelă la tratament 10,9% (n= 50); metroragii sau menometroragii în perioada premenopauzală rezistente la orice tratament 15% (n= 69); adenomioza difuză sau localizată cu simptomatologie rebelă la tratament 9,4% (n= 42); displazia colului uterin 7,8% (n= 36).

Au fost excluse din acest studiu cele 53 histerectomii realizate pe cale vaginală, efectuate numai în cazuri de prolaps genital gradul IV, toate pacientele având vârsta de peste 70 de ani.

Vârsta medie a fost de 51,34 ± 8,63 ani (limite 23- 63 ani). Repartiția cazurilor în funcție de grupa de vârstă a fost: 1) sub 35 ani – 3,5% (n= 16); 2) 35 - 45 ani – 19% (n= 87); 3) peste 45 ani – 77,5% (n= 354).

Anexectomia a fost asociată histerectomiei totale în 98,2% (n= 449); aceasta s-a realizat unilateral în 10,4% (n= 47) și bilateral în 89,6% (n= 402). De notat că în lotul pacientelor cu anexectomie bilaterală au fost incluse și cele 27 de cazuri care aveau în antecedente o anexectomie unilaterală și la care s-a extirpat anexa restantă cu ocazia histerectomiei totale. Vârsta medie a pacientelor la care s-a practicat anexectomie unilaterală a fost semnificativ mai mică decât a pacientelor cu anexectomie bilaterală: 41,12 ± 4,54 ani (limite 23- 45 ani) vs 49,52 ± 6,06 ani (limite 23-63 ani), *P*< 0,001 (Figure 1).

Analiza distribuției pe grupe de vârstă a cazurilor cu anexectomie unilaterală și respectiv, bilaterală, s-a constatat o asociere înalt semnificativă statistic (χ^2; *P*<0,001) (Tabelul I, Fig. 1).

Indicația anexectomiei uni- sau bilaterale, la pacientele sub 35 ani a fost: inflamația anexială cronică în 6 cazuri (37,5%) și respectiv tumoră ovariană benignă în 2 cazuri (12,5%) (chist seros simplu 1 caz (6,25%); chist dermoid 1 caz (6,25%)).

La pacientele între 35-45 ani indicația a fost reprezentată de: inflamație anexială cronică în 46 cazuri (52,8%), tumori ovariene benigne în 21 cazuri (24,1%) (chist seros simplu 9 cazuri (10,3%), chist adenom mucinos 4 cazuri (4,5%), chist dermoid 3 cazuri (3,4%) (în 2 cazuri fiind bilateral), chistadenom seros 2 cazuri (2,3%), fibrom ovarian 2 cazuri (2,3%), fibroadenom 1 caz (1,15%), ovar polichistic 11 cazuri (12,6%). În 9 cazuri (10,3%), la femei cu vârste cuprinse intre

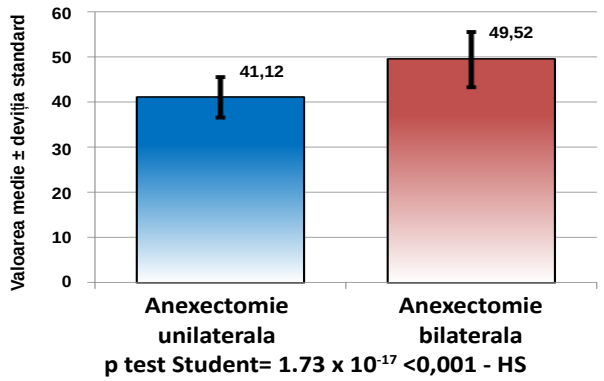

Figure 1: Vârsta medie în cele două grupuri: paciente cu anexectomie unilaterală vs bilaterală.

Tabelul I: Distribuția cazurilor în funcție de tipul de anexectomie și grupa de vârstă.

Grupa de vârstă	*n*	Anexe conservate *n* (%)	Anexectomie *n* (%)	
			Unilaterală	Bilaterală
< 35 ani	16	8 (50%)	3 (18,8%)	5 (31,2%)
35 – 45 ani	87	0	44 (50,5%)	43 (49,5%)
> 45 ani	354	0	0	354 (100%)
Total	457	8 (1,7%)	47 (10,4%)	402 (89,6%)

43-45 ani la solicitarea pacientelor s-a practicat anexectomie bilaterală în condițiile în care anexele erau indemne. În 6 dintre aceste cazuri au existat antecedente heredocolaterale de cancer ovarian.

La pacientele peste 45 ani anexectomia bilaterală a fost practicată de "principiu". În 76 cazuri (21,4%) s-au constatat urmatoarele tipuri de leziuni: ovar polichistic 27 cazuri (7,6%); chist seros simplu 15 cazuri (4,2%); chistadenom mucinos 12 cazuri (3,3%); chistadenom seros 10 cazuri (2,8%); chist dermoid 3 cazuri (0,84%); chist endometrial 3 cazuri (0,84%); papilom 3 cazuri (0,84%); fibroadenom 2 cazuri (0,56%); fibrom 1 caz (0,28%).

Antecedentele personale ca și cele heredo-colaterale pot fi implicate în etiologia afecțiunilor, eventual apărute pe anexe restante posthisterectomie totală; astfel, din punctul de vedere al antecedentelor personale am consemnat următoarele: neoplasm colic (0,4%; n=2); neoplasm mamar (0,2%; n=1); neoplasm tiroidian (0,2%; n=1); cancer pulmonar (0,2%; n=1); afecțiuni benigne ale sânului (1,5%; n=7).

Din cele 55 cazuri în care una sau ambele anexe au fost conservate, în 17 cazuri (30,9%) am constatat apariția unei patologii maligne sau benigne pe anexa sau anexele restante, care a impus anexectomia:

- v cancer ovarian în 3 cazuri (17,6%) din care:
- pacientă în vârstă de 46 ani care dezvoltă cancerul ovarian la 5 ani postoperator și care avea în antecedentele heredo-colaterale (tatăl) cancer colic;
- pacientă în vârstă de 51 ani care dezvoltă cancerul ovarian la 7 ani postoperator și care cu 4 ani în urmă fusese operată pentru cancer mamar;
- pacientă în vârstă de 54 ani care dezvoltă cancerul ovarian la 12 ani postoperator;

◊ chist ovarian în 7 cazuri (41,2%), apărut între 1 și 5 ani;

◊ tumori benigne solide de ovar în 3 cazuri (17,6%), apărute între 3 și 6 ani;

◊ endometrioza ovariană în 2 cazuri (11,7%), apărută la 2 și respectiv, 3 ani postoperator;

◊ torsiune acută de ovar un caz (5,9%), la un an postoperator impunând anexectomia în urgență;

◊ hidrosalpinx, un caz (5,9%) la 3 ani postoperator.

Vârsta medie a pacientelor care au dezvoltat cancer de ovar a fost 50±4,04 ani (limite 46-54 ani) în timp ce vârsta medie a pacientelor care au avut patologie benignă pe anexa sau anexele restante a fost de 36,86 ± 6,91 ani (limite 26- 44 ani) (*P*= 0,011) (Figure 2).

În toate cele 3 cazuri de cancer ovarian s-a recurs la intervenție chirurgicală cu viză radicală în primul timp urmată apoi de polichimioterapie

Între cele două loturi de paciente cu ovar restant posthisterectomie, adică între cele la care a apărut o patologie anexială și cele la care această patologie nu a fost semnalată nu s-au constatat diferențe semnificative din punct de vedere statistic legate de factori precum: vârsta primei menstruații, numărul de sarcini, tipul de naștere (natural sau prin cezariană), tratamente privind infertilitatea ori recurgerea la contraceptive și durata folosirii lor (Tabelul II).

De notat că dificultățile de monitorizare pe termen lung a pacientelor la care s-a indus menopauza precoce ca urmare a anexectomiei bilaterale nu au permis evaluarea consecințelor acesteia în ceea ce privește funcția aparatului cardiovascular, densitatea osoasă sau calitatea vieții sexuale.

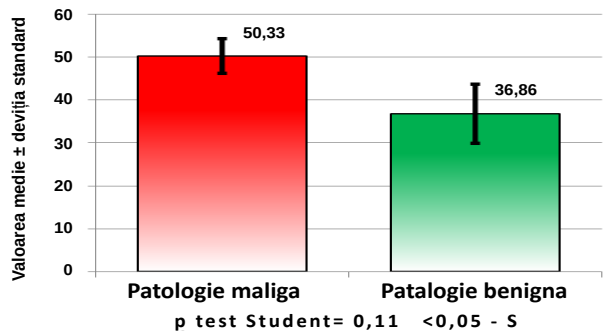

Figure 2: Vârsta medie a p acientelor care au dezvoltat patologie malignă vs benignă pe ovarul restant.

Discuţii

Histerectomia totală continuă să rămână cel mai frecvent procedeu chirurgical aplicat în cazul afecţiunilor benigne ale uterului [1-4]. Incidenţa acestei intervenţii chirurgicale variază de la o ţară la alta în funcţie de o serie de factori care ţin fie de pacienţi (rasă, status socio economic, status educaţional etc.), fie de sistemul de sănătate şi variază între 5,1-5,8 histerectomii la 1000 paciente în SUA. În această ţară, anual se practică, in medie 600000 histerectomii, iar dintre acestea 90% se efectuează pentru afecţiuni benigne [4,5].

Cu ocazia histerectomiei, chirurgul îşi pune problema exerezei sau a conservării anexelor, în particular a ovarelor. Anexectomia uni- sau bilaterală nu prelungeşte în mod semnificativ durata intervenţiei şi nici nu sporeşte riscul complicaţiilor imediate, dar poate să aibă repercusiuni pe termen scurt sau lung asupra stării de sănătate şi a calităţii vieţii pacientelor [4,5].

Statisticile americane evidenţiază faptul că incidenţa anexectomiilor bilaterale efectuate cu ocazia histerectomiei a crescut cu mai mult de două ori, de la 25% în anul 1965 la 55% în anul 1999. Din aceste statistici reiese că, în grupa de vârstă între 18 şi 44 ani, incidenţa anexectomiei a fost de 18%, pe când între 45 şi 65 ani, această incidenţă a crescut la 76%. [1,2].

Cazurile au fost grupate în cele trei categorii de vârstă, în funcţie de datele din literatură [4,6] şi considerând că fiecare dintre aceste categorii ridică probleme caracteristice în ceea ce priveşte conservarea sau extirparea anexelor.

Astfel, la pacientele având vârsta sub 35 ani indicaţia anexectomiei trebuie foarte bine cumpănită având în vedere riscurile importante pe care le implică o menopauză precoce. În 50% dintre pacientele aparţinând acestei categorii, tipul de afecţiune care a condus la indicaţia de histerectomie (leiomiofibromatoza, adenomioza, sau leziunile displazice ale colului uterin) a permis conservarea anexelor. Pe de altă parte, leziunile inflamatorii cronice ale endometrului şi/sau miometrului, rebele la terapia conservatoare, cel mai adesea se insoţesc sau au drept punct de plecare o infecţie anexială, situaţie care impune efectuarea anexectomiei uni sau bilaterale, aşa cum s-a întâmplat la cealaltă jumătate din lotul de vârstă analizat. În SUA, aproximativ 12% din histerectomii sunt efectuate pentru durerea pelvină, ca primă indicaţie, iar în 5,1% pentru boală inflamatorie cronică pelvină (ex: metroanexită cronică), care de asemenea presupune prezenţa durerii. Se consideră că orice inflamaţie pelvină, cel puţin la nivelul endometrului si viceversa, acest lucru fiind în concordanţă cu originea embriologică şi vascularizaţia care sunt comune acestor structuri [7].

La cea de-a doua categorie de paciente, cele cu vârste cuprinse intre 35 şi 45 ani, indicaţia conservării sau a extirpării anexelor a fost rezultatul analizei, la fiecare caz în parte, a consecinţelor extirpării anexelor, cu menopauza precoce consecutivă sau a conservării unei anexe, cu riscurile apariţiei unei patologii anexiale, în special a unei leziuni maligne. În statistica noastră, pacientelor din această categorie li s-a practicat, aproape de paritate, anexectomie uni- sau bilaterală. În cazul pacientelor cu antecedente heredocolaterale de cancer ovarian sau cancer maamr ori la cele la care s-a demonstrat existenţa unor mutaţii ale genelor BRCA 1 şi BRCA 2 se recomandă efectuarea de principiu a anexectomiei bilaterale cu ocazia histerectomiei totale pentru afecţiuni uterine benigne. La aceste paciente riscul cancerului ovarian variază între 10%-46%, iar ooforectomia bilaterală reduce riscul cancerului mamar cu procente cuprinse între 465 si 56% [8-12]. Pentru celelalte paciente, fară astfel de antecedente s-a constatat că, simpla histerectomie reduce riscul de cancer ovarian la 2,1 % comparativ cu 2,7 % la restul populaţiei [13]. Acest efect protectiv se menţine între 10 si 20 ani după care dispare. La pacientele cu anexectomie bilaterală, menopauza indusa precoce creşte riscul afecţiunilor cardiovasculare cu dublarea riscului de infarct miocardic, crescând totodată şi riscul fracturilor datorate osteoporozei, aceasta contribuind la scăderea speranţei de viaţă [4]. De asemenea, la această categorie de paciente s-a constatat o îmbunatăţire a calităţii vieţii cu afectarea funcţiilor cognitive, scăderea calităţii somnului, depresie şi declin al dorinţei sexuale [4]. În cazul conservării unuia dintre ovare, deşi calitatea vieţii şi spsperanţa de viaţă sunt mai ridicate se constata, totuşi o instalare mai precoce a menopauzei şi apariţia mai frecventă a unor formaţiuni chistice benigne pe ovarul restant [14,15]. De asemenea, riscul cardiovascular şi de instalare a osteoporozei se menţine destul de ridicat şi în cazul conservării doar a unuia dintre ovare [13].

La cea de-a treia categorie de paciente, peste 45 de ani, s-a practicat anexectomia bilaterală având în vedere pe de o parte că multe dintre acestea erau deja la menopauză, iar pe de altă parte s-a luat în consideraţie riscul apariţiei unei leziuni maligne pe ovarul restant. În cazul pacientelor cu antecedente familiale de neoplasm ovarian sau a celor purtătoare a unor mutaţii la nivelul genelor BRCA 1 şi BRCA 2 riscul apariţiei unei leziuni maligne pe ovarul restant este acelaşi în postmenopauză ca şi în cazul femeilor sub 45 ani [8,10,11]. În schimb, la femeile cu risc familial scăzut, incidenţa cancerului pe ovarul restant creşte odata cu înaintarea în vârstă , fiind de 20 la 100.000 femei între 50- 60 ani, de 33 la 100.000 femei între 60-70 ani şi de 40 la 100.000 femei peste 70 ani [19]. Dezavantajele anexectomiei bilaterale la pacientele aflate în postmenopauză, constau în sporirea riscului de deces prin boli cardiovasculare precum şi a riscului afectării funcţiei cognitive mergând până la demenţă, depresie şi anxietate [17,18]. În schimb, nu reiese clar, rolul acestui tip de intervenţie în scăderea densităţii osoase şi creşterea riscului de fractură [4,19].

Aşa cum indică şi titlul prezentei lucrări, histerectomia efectuată la lotul de paciente studiat s-a realizat pentru afecţiuni benigne. În acest context considerăm că este corect să deschidem o paranteză referitoare la una dintre leziunile pentru care a fost indicată histerectomia totală şi anume displazia colului uterin. În timp ce în displaziile uşoare şi moderate, celulele atipice nu ocupă întreaga grosime a epiteliului şi sunt considerate leziuni cu potenţial reversibil, în formele severe,

Tabelul II: Analiza cazurilor în funcţie de prezenţa modificărilor patologice pe ovarul restant.

	Patologie pe ovar restant		
	Da	Nu	P
n (%)	17 (30,91%)	38 (69,09%)	
Vârsta primei menstruaţii	11,72 ± 3.56 ani (9-14)	12,31 ± 2.84 ani (10-14)	0,51
Nr de sarcini (0s/1s/2s/3s/4s)	0-3 s (1/4/10/6/0)	0-4 s (1/7/19/8/3)	0,70
Tip de naştere: natural / cezariană	25 / 17	42 / 39	0,41
Tratament pentru infertilitate	3 (5,45%)	5 (9,09%)	0,66
Terapie cu contraceptive	5 (9,09%)	10 (18,18%)	0,81

leziunile pot interesa întreaga grosime a epiteliului și netratate pot evolua spre forme invazive, studii recente demonstrând o similitudine histopatologică și evolutivă între displazia severă și carcinomul în situ (CIS). Cu toate acestea, în statistica noastră am inclus toate cele trei grade de leziuni displazice în categoria afecțiunilor benigne și care beneficiază toate de același procedeu curativ și anume histerectomia totală simplă. Intervenții precum conizația sau amputația de col aplicabile în cazul leziunilor displazice cervicale nu pot fi discutate în lucrarea de față al cărei subiect se referă exclusiv la histerectomiile totale efectuate în cazul afecțiunilor uterine benigne [20-22].

Numeroase studii retrospective și prospective subliniază riscurile induse pe termen lung de menopauza postchirurgicală precum riscurile unor afecțiuni cardiovasculare, osoase, psiho-sexuale sau de apariție a unor disfuncții cognitive [4,17-19]. Multe dintre pacientele aflate în această situație sunt supuse unei terapii hormonale substitutive în încercarea de a atenua aceste riscuri [17-19,23].

Date recente însă, demonstrează faptul că estrogenul exogen poate acționa în mod diferit față de estrogenii produși de organismul uman și că, pe termen lung, hormonoterapia se asociază cu riscuri semnificative, care pot uneori depăși beneficiile unei astfel de terapii; astfel s-a demonstrat că terapia îndelungată hormonală mixtă cu estrogeni și progesteron determină o creștere a riscului de cancer mamar, lucru care nu a fost constatat în cazul administrării numai a medicației estrogenice [24,25]. Rămân, de asemenea neclare efectele hormonoterapiei efectuate la pacientele cu menopauză indusă chirurgical în ceea ce privește funcțiile cardiovasculare ori cognitive [6]. De aceea, Colegiul American al Obstreticienilor și Ginecologilor (ACOG) recomandă recent multă precauție și reținere în stabilirea indicației de ovariectomie bilaterală în cazul pacientelor sub vârsta de 45 ani și la care nu există un risc genetic crescut de cancer ovarian [6]. Cu toate acestea, un studiu recent efectuat relevă faptul că, la femeile tinere supuse unei histerectomii totale cu conservarea unuia sau a ambelor ovare se constată un risc crescut de insuficiența ovariană, deci de menopauză precoce, risc care este de două ori mai mare decât în cazul femeilor cu vârste similare și la care uterul este intact. Cauza insuficienței ovarelor restante rămâne necunoscută, însă au fost formulate o serie de ipoteze; astfel, se consideră că, în urma histerectomiei se produce o scădere a fluxului sangvin către ovarele restante, cu reducerea consecutiva a producției hormonale iar prezența uterului ar exercita o influență inhibitorie asupra secreției hipofizare de FSH și deci histerectomia permite o creștere a producției de FSH ceea ce accelerează depleția foliculilor ovarieni conducând astfel la menopauza precoce. [5,25]

Cele mai frecvente indicații ale ovariectomiei efectuate cu ocazia histerectomiei totale pentru afecțiuni benigne sunt:

Reducerea riscului de cancer ovarian la femeile care nu prezintă un risc familial crescut

La femeile aflate în premenopauză și cu risc familial scăzut, incidența cancerului ovarian la momentul histerectomiei este foarte mică. Cu toate acestea, conform lui Parker și colab. [8] ovariectomia este frecvent efectuată la pacientele aflate în premenopauză, în vederea reducerii unui viitor risc de cancer ovarian. Incidența acestui tip de cancer la femeile cu risc familial scăzut crește o dată cu vârsta fiind de 20 la 100.000 femei între 50-60 ani, de 33 la 100.000 femei între 60-70 ani și de 40 la 100.000 femei peste 70 ani [16].

După unele studii, la aceasta categorie de femei simpla histerectomie reduce riscul cancerului ovarian cu 36% comparativ cu femeile având uterul și ovarele intacte, acest efect protectiv menținându-se până la 15 ani [26].

Un alt studiu relevă faptul că ligatura tubară ar reduce riscul de cancer ovarian cu 35-40%, mecanismul prin care s-ar realiza acest lucru nefiind foarte clar. Se presupune că obstrucția tubară prin ligatură reduce pasajul factorilor carcinogeni spre tractul genital superior [27].

Parker și colab. în 2007 [8] și Harman și colab. în 2005 [28] au arătat că, din punct de vedere al consecințelor menopauzei induse chirurgical, dezavantajele ovariectomiei profilactice depășesc avantajele acestui tip de intervenție, în cazul femeilor de până la 65 ani. În principal, aceste dezavantaje țin de creșterea riscului afecțiunilor cardiovasculare, cu dublarea riscului de infarct miocardic, de sporirea riscului de fractură datorată osteoporozei, acestea conducând la scăderea speranței de viață, la care se adaugă o înrăutățire a calității vieții prin afectarea funcțiilor cognitive, depresie, scăderea calității somnului si declinul dorinței sexuale(17-19).

Reducerea riscului de cancer ovarian în cazul femeilor prezentând un risc crescut

Existența unui istoric de cancer ovarian și/sau cancer mamar sau cancer de colon în antecedentele familiale ale unor paciente cu afecțiuni benigne ale uterului și care urmează să fie supuse unei histerectomii ridică problema existenței unor mutații genetice responsabile pentru aceste tipuri de neoplasm. În acest context, astfel de paciente ar trebui supuse unor investigații de specialitate, în curbe de profil pentru depistarea unor astfel de anomalii genetice. Cancerul ovarian pare a fi legat de mutații ale genelor BRCA 1 și BRCA 2 precum și de modificările genetice asociate cu cancerul colic non polipozic ereditar. Femeile purtătoare a unor mutații la nivelul genei BRCA1 prezintă în cursul vieții un risc de cancer ovarian cuprins între 36 și 46%, pe când la cele purtătoare de mutații la nivelul genei BRCA2, acest risc este cuprins între 10 și 27%. Mutațiile genice asociate cu HNPCC conferă un risc de cancer ovarian 9-12%, dar și un risc crescut de cancer endometrial de până la 40%. [29,30] Pe de altă parte, numeroase studii efectuate relevă faptul că anexectomia profilactică asociată histerectomiei totale pentru afecțiuni uterine benigne reduce într-o manieră semnificativă și riscul de cancer mamar. Acești autori constată o reducere cu 56% a riscului de cancer mamar la purtătoarele de mutații ale genelor BRCA1 și cu 46% la purtătoarele de mutații ale genelor BRCA2 [29,31,32]. Reducerea acestui risc este mai mare în situațiile în care anexectomia este realizată înaintea vârstei de 40 de ani. De asemenea, acest efect protector al anexectomiei totale a fost evident în primii 15 ani postoperator [32].

Un alt aspect important îl constituie extirparea concomitentă atât a ovarului cât și a trompei deoarece ambele formațiuni anexiale prezintă un risc crescut de malignizare. Mai mult chiar, s-a observat că la femeile purtătoare de mutații la nivelul genelor BRCA punctul de plecare pentru cancerul ovarian îl constituie terminația fimbrială a trompei uterine. Acest lucru poate explica faptul că echografia transvaginală nu constituie o modalitate de screening eficientă pentru depistarea cancerului ovarian în stadii incipiente la fel ca și dozarea CA125 [33,34]

În acest context, singura modalitate efectivă de a reduce incidența cancerului ovarian la femeile purtătoare de modificări ale genelor BRCA1 și BRCA2 o constituie anexectomia bilaterală [34,35]. La aceste paciente simptomele specifice menopauzei pot fi eficient atenuate printr-o terapie hormonală substitutivă.(36)

Pe de altă parte se știe că femeile purtătoare de modificări ale genelor BRCA1 și BRCA2, pe lângă riscul de cancer ovarian prezintă, de asemenea, un risc semnificativ de cancer mamar, care în opinia unor autori ar putea fi precipitat de terapia hormonală substitutivă [9,28].

Există însă o serie de studii prospective și retrospective, relativ recente, care infirmă această supoziție în condițiile administrării numai a unei monoterapii hormonale cu estrogeni [11,28]. Mai mult chiar, Anderson și colab. în 2004 [25] și Eisen și colab, în 2008 [28], constată pe loturi semnificative de femei cu modificări ale genelor BRCA1 și

BRCA2 o reducere semnificativă a riscului de cancer mamar în urma terapiei substitutive cu estrogeni. În schimb, la femeile cu antecedente personale de cancer mamar, riscul recurenţelor acestei afecţiuni este semnificativ mai mare în cazul pacientelor supuse unei terapii hormonale substitutive în postmenopauză comparativ cu cele care nu primesc niciun fel de tratament [29].

De asemenea, mai trebuie reţinut faptul că riscul de a face un cancer ovarian pentru femeile fără modificări genetice confirmate, dar având în antecedentele familiale o rudă de gradul I cu o astfel de afecţiune este de 7 ori mai mare decât cele fără astfel de antecedente [30].

Evitarea apariţiei unor afecţiuni chirurgicale benigne pe anexele restante

În statistica noastră, din cele 55 paciente la care s-au conservat una sau ambele anexe, 14 cazuri (25,4%) s-au reinternat la intervale diverse postoperator, cu o patologie anexială benignă (chist ovarian, tumoră solidă de ovar, endometrioza ovariană, torsiune acută de ovar sau hidrosalpinx), în toate situaţiile impunându-se reintervenţia.

Din datele oferite de literatură reiese faptul că până la 50% dintre pacientele supuse histerectomiei totale pentru afecţiuni benigne prezintă în urma examinărilor ultrasonografice patologia chistică ovariană, iar dintre acestea, până la 5% sunt supuse unei reintervenţii [31-33]. Un recent ghid al American Colege of Obstetricians and Gynecologists (ACOG) subliniază faptul că femeile având endometrioză afecţiuni inflamatorii pelvine şi dureri cronice pelvine au un risc crescut de a face o afecţiune pe anexa (anexele) restantă(e) şi care să impună reintervenţia. În astfel de situaţii se recomandă anexectomia bilaterală în acelaşi timp cu histerectomia pentru afecţiuni benigne [37,38].

Reducerea simptomelor asociate cu forme avansate de endometrioză şi care nu rspund la alte terapii medicale ori chirurgicale

Reducerea sau supresia producţiei de estrogeni endogeni se poate constitui într-o terapie eficientă a simptomelor generate de prezenţa endometriozei la femeile aflate în premenopauză. Un studiu retrospectiv canadian efectuat pe un lot de 8000 paciente a arătat că intervenţiile conservative efectuate pentru endometrioză s-au asociat cu o rată crescută a reintervenţiilor într-un interval de 2-5 ani postoperator [37].

Un alt studiu american efectuat în 2008 pe un eşantion de 250 paciente cu forme avansate de endometrioză raportează cea mai mică rată de reintervenţie (sub 10%) pentru simptome specific endometriozei, în cazurile în care s-au practicat concomitent histerectomia totală cu anexectomie bilaterală [38]. La femeile tinere sub 40 ani cu forme avansate de endometrioză, unii autori iau în considerare efectuarea numai a histerectomiei, cu rezultate satisfăcătoare ţinând cont de importantele consecinţe pe care o menopauză precoce le atrage [31,37,38].

Concluzii

La femeile cu risc relativ scăzut de cancer ovarian, se impune o analiză riguroasă a riscurilor sau a beneficiilor pe care conservarea sau extirparea ovarelor le atrage, tendinţa fiind de conservare a ovarelor până spre vârsta de 65 ani cu probabile beneficii ale supravieţuirii pe termen lung.

Această analiză a riscurilor şi beneficiilor conservării sau extirpării ovarelor trebuie să ţină cont de riscurile pe termen lung de producere a cancerelor de sân sau de ovar, de apariţie a unei suferinţe coronariene, a osteoporozei sau a unor tulburări psihice precum şi de eficacitatea şi siguranţa unei eventuale hormonoterapii substitutive. Se cunosc relativ puţine lucruri despre fiziologia ovarului în postmenopauză şi este posibil ca extirparea acestor ovare să aibă consecinţe mai grave decât se crede în momentul de faţă.

Conflict de interese

Autorii nu declară nici un conflict de interese.

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Journal of Surgery
[Jurnalul de Chirurgie]

Research Article Open Access

Plasma Cell Mastitis-Anatomo-Clinical and Therapeutic Considerations

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Abstract

Plasma cell mastitis is a rare chronic inflammatory disease of the breast. Its cause and treatment have not yet been clearly identified. The aim of the study is to present the author's experience with various treatment methods applied on this disease. MATERIAL AND METHODS: We retrospectively analyzed the clinical findings, biological tests, imagistic results, therapeutic approach and the pathological response from 25 patients diagnosed with plasma cells mastitis between 2005 and 2013. RESULTS: Only 7 cases underwent from the beginning to wide surgical excision of the inflammatory mass with favorable evolution. The rest of the patients, treated with antibiotherapy, corticotherapy or surgical drainage of the collections (when needed) presented early relapse that required surgical treatment: large excision to subcutaneous mastectomy. CONCLUSIONS: Surgical treatment represented by wide excision going up to subcutaneous mastectomy is the most effective therapeutic method for this benign, but with high relapsing potential, disease. It also has the advantage of giving a more accurate positive and differential diagnosis, most important with breast carcinoma.

Keywords: Plasma cells mastitis; Granulomatous mastitis

Introduction

Also known in literature as granulomatous lobular mastitis, plasma cell mastitis is a rare chronic inflammatory disease of the breast. It is a non-infectious, non-neoplastic mastitis, not occurring during the post-partum and breastfeeding period [1]. Its etiology is unknown and controversial. There are two theories regarding the etiology of granulomatous mastitis: autoimmune and hypersensitivity processes versus an infectious pathogenesis. Although the majority of cases of plasma cells mastitis appear aseptic, case reports of documented coinfection with *Corynebacterium sp*. have been reported in the United Kingdom, France and Italy [2,3]. It commonly presents with the clinical symptoms of inflammation, breast mass, breast indurations, erythema, "peau d'orange", ulcerative lesions, and even cutaneous fistulae with pus discharge. Most of the patients develop recurrences and many other develop complications such as abscess formation and fistulae. Histopathological examination is the most definitive method of diagnosis and makes it possible to differentiate granulomatous mastitis from breast cancer, other granulomatous diseases and infectious etiologies. There is no agreement about the most appropriate treatment approach for these patients, although surgical excision and corticosteroid therapy have been recently shown to be effective for the disease.

The aim of the study was to review the clinical and diagnostic features of the disease and to discuss the results of medical and surgical treatment in a series of 25 patients with granulomatous mastitis.

Material and Methods

We retrospectively evaluated the clinical findings, biological tests, imagistic results, therapeutic applied methods and postoperative evolution of 25 patients diagnosed, treated and followed by the same surgical team between 2005 and 2013.

Results

The age of the patients ranged from 29 to 39 years old, with a median of 34 years old, time of last childbirth ranged from 2 to 7 years; all of the patients have history of breastfeeding. We did not detect any history of using contraceptive medication, smoking, trauma of the breast, sarcoidosis, tuberculosis or other infectious diseases. On admission, 16% of the patients (n= 4) presented breast painful tumor mass, other 16% (n= 4), breast mass and abscess of the mammary gland, 64% (n=16) had multiple abscesses and fistulae of the breast and 4% (n= 1) presented multiple abscesses accompanied by neurological symptoms and peripheral vasculitis. In all cases the lesions were unilateral, occurring in any quadrant of the breast.

The ultrasound exam revealed the presence of intraglandular collection, some with important modification (retraction) of the surrounding glandular tissue. The blood tests showed leukocytosis (with a median of 12,000/mm^3) and increased values of C reactive protein (CRP), median value of 5.2 mg/L. The chest X-rays were normal in all cases.

The initial surgery consisted in wide surgical excision of the inflammatory mass in 7 cases (28%), with favorable local outcome and no recurrence (Table I). The rest of the patients refused the initial radical approach and drainage of the intraglandular collections associated with antibiotherapy was performed. All of these 18 last patients (72%) presented early relapse (from 1 to 9 months) with intraglandular abscesses that required surgical treatment: subcutaneous mastectomy in 28% (5 cases) and large excisions of the inflammatory tissue in 66,6% (12 cases) (Table II). The postoperative recovery was uneventful with satisfactory healing of surgical wound.

A particular difficult evolution was noticed in one patient that, following the initial drainage of collections, presented recurrent abscesses despite antibiotherapy and corticotherapy; these local

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Table I: Patients who underwent initial surgical excision.

	Age	Symptoms	Biologic tests	Ultrasound	Treatment	Follow-up
1.	28	Pain, local mass, fistulae	WBC=16,000/mm^3 CRP=5.2 mg/L	Multiple abscesses, glandular mass in the same quadrant	Quadranectomy ATB	Favorable, no relapse
2.	31	Induration, multiple fistulae	WBC=14,000/mm^3 CRP=6 mg/L	Intraglandular abscesses, same quadrant	Large excision - Biquadranectomy ATB	Favorable, no relapse
3.	32	Induration, multiple masses	WBC=14,200/mm^3 CRP=6.3mg/L	Multiple abscesses, same quadrant	Large excision - Biquadranectomy ATB	Favorable, no relapse
4.	34	Pain, erythema, mass, fistulae	WBC=11,500/mm^3 CRP=4.1mg/L	Intraglandular mass and abscess, same quadrant	Sectorectomy ATB	Favorable, no relapse
5.	34	Pain, erythema, fever, extended induration	WBC=13,200/mm^3 CRP=4.8mg/L	Multiple abscesses, same quadrant	Quadranectomy ATB	Favorable, no relapse
6.	35	Erythema, multiple fistulae	WBC=11,000/mm^3 CRP=4.1mg/L	Multiple abscesses	Quadranectomy ATB	Favorable, no relapse
7.	38	Induration, painful tumor mass	WBC=11,600/mm^3 CRP=3.8mg/L	Intraglandular mass, important tissue retraction	Sectorectomy ATB	Favorable, no relapse

WBC White Blood Cells; CRP C reactive proteins; ATB Antibiotherapy

Table II: Patients who underwent initial conservative treatment.

	Age	Symptoms	Biologic tests	Ultrasound	Initial treatment	Follow-up	Final treatment
1.	29	Induration, mass	WBC=11,600/mm^3 CRP=5.6mg/L	Glandular mass, tissue retraction-	ATB; AINS	Relapse after 2 & 4 months	1. Antibiotics 2. Quadranectomy
2.	29	Induration, mass	WBC=12,200/ mm^{3}CRP=4.5mg/L	Abscesses, mass – same quadrant	Drainage; ATB; AINS	Relapse after 9 months	Quadranectomy
3.	30	Mass, fistulae	WBC=14,200/mm^3 CRP=5.9mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 6 months	Quadranectomy
4.	31	Pain, mass	WBC=12,100/mm^3 CRP=0.8mg/L	Tissue retraction, glandular mass – same quadrant	ATB; AINS	Relapse after 1 month	Quadranectomy
5.	31	Erythema, mass	WBC=10,400/mm^3 CRP=4.4mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 4, 6 & 9 months	1. Antibiotics 2. Drainage 3. Subcutaneous mastectomy
6.	32	Mass, fistulae	WBC=13,000/mm^3 CRP=5.6mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 3 months	Quadranectomy
7.	33	Multiple masses	WBC=11,600/mm^3 CRP=3.8mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 7 months	Subcutaneous mastectomy
8.	34	Pain, mass, erythema	WBC=10,800/mm^3 CRP=4.4mg/L	Abscess, glandular mass-	ATB; AINS	Relapse after 3 months	Quadranectomy
9.	34	Mass, erythema	WBC=11,400/mm^3 CRP=5.1mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 3 months	Subcutaneous mastectomy
10.	35	Mass, fistulae	WBC=10,400/mm^3 CRP=4.8mg/L	Important tissue retraction, mass	Drainage; ATB; AINS	Relapse after 2 months	Quadranectomy
11.	36	Mass, local adenopathy	WBC=12,200/mm^3 CRP=6mg/L	Multiple abscesses, glandular mass – same quadrant	ATB; AINS	Relapse after 1 month	Quadranectomy
12.	37	Mass, fistulae	WBC=12,800/mm^3 CRP=5.3mg/L	Profound abscess	Drainage; ATB; AINS	Relapse after 4 months	Quadranectomy
13.	37	Induration, multiple fistulae	WBC=14,400/mm^3 CRP=5.2mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS; AIS	Relapse after 5 months	Subcutaneous mastectomy
14.	37	Mass, pain	WBC=11,100/mm^3 CRP=5.3mg/L	Small abscess, glandular mass – same quadrant	ATB; AINS	Relapse after 8 months	Quadranectomy
15.	38	Mass, pain	WBC=10,800/mm^3 CRP=4.8mg/L	Glandular mass, tissue retraction-	ATB; AINS	Relapse after 2 & 6 months	1. Drainage 2. Biquadranectomy
16.	38	Induration, fistulae	WBC=12,000/mm^3 CRP=5.1mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 4 months	Subcutaneous mastectomy
17.	39	Mass, fistulae	WBC=13,300/mm^3 CRP=6.3mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS	Relapse after 3 months	Biquadranectomy
18.	39	Abscesses, fever, neurologic symptoms	WBC=39,800/mm^3 CRP=9.6mg/L	Multiple abscesses, glandular mass – same quadrant	Drainage; ATB; AINS; AIS	Multiple relapse within 21 days, despite therapy	Subcutaneous mastectomy

modifications were accompanied by high fever (up to 40 Celsius degrees), frequent and persistent chills, neurologic symptoms such as violent headaches during fever access and peripheral symptoms - vasculitis (Figure 1). The blood cultures were negative and she presented high values of leukocytes (up to 40,000/mm^3) with no identification of other infection source. Suspecting cerebrovascular thrombosis by septic micro embolus, we performed a cerebral CT that did not reveal any cerebral modifications. After a prolonged hospital stay during which she underwent for several surgical procedures consisting of multiple drainage of the intraglandular collections and multiple associations of antibiotics with corticotherapy, when the general status allowed, we performed a subcutaneous mastectomy. Within 6 days, the recovery of the patient was perfect with no sign of infection, neurological or peripheral symptoms. The pathological exam of the resected specimen showed multiple abscesses of different sizes, surrounded by inflammatory sclerosis tissue (Figure 2). Histopathology revealed suggestive aspects for chronic inflammation, presence of multiple granulomatous lesions with a centrilobular distribution and the destruction of the glandular architecture. The granulomatous masses contained epithelioid hystiocytes, giant cells, central infiltration

of neutrophils and eosinophils, and surrounding lymphocytes and plasma cells (Figure 3). The bacterial, fungal and *Mycobacterium* cultures of the intraoperative specimen were negative.

Discussion

Idiopatic granulous masitis is a rare inflammatory disease of the breast whose etiology and treatment have not yet been clearly identified despite the efforts of many researchers. The treatment methods known to date include observation, antibiotics, steroids, drainage, excision, and mastectomy, but an optimal treatment method still needs to be determined [5-7]. In this study, various treatment methods were applied based on the medical conditions of the patients and on the stage of the lesions.

It has been reported that plasma cells mastitis is a self-limiting condition and can be expected to disappear on its own within 6-12 months with close surveillance [8]. We have not experienced this on our patients. Although steroid treatment was not effective in this study, many studies have reported the importance and effectiveness of steroids on granulomatous mastitis treatment [9].

The drainage method is also still controversial in treating this disease because the incision wound does not heal easily and can leave a fistula tract, and treatment can last for an extended time. In our study, all the patients that underwent at the beginning with surgical drainage associated with antibiotics and/or corticotherapy presented long lasting treatment of the wound and early relapse. All the patients who underwent surgical excision as an initial treatment recovered faster, with an average recovery period of 6 days compared to the recovery periods for the other treatment methods that came up to 21 days.

Figure 1: Peripheral vasculitis.

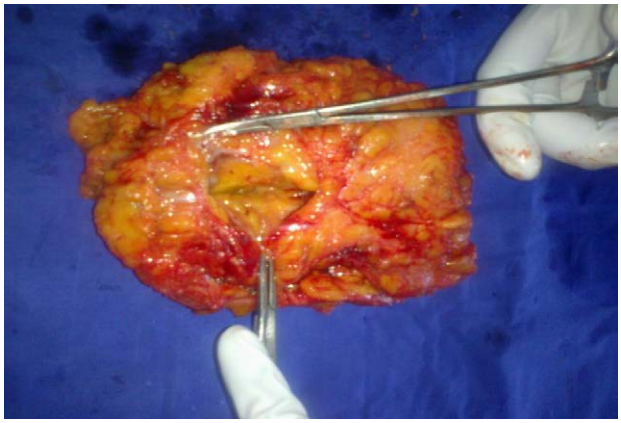

Figure 2: Macroscopic image in granulomatous mastitis; presence of abscess.

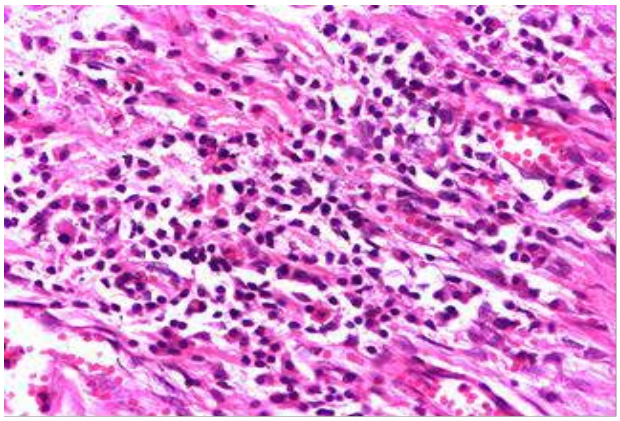

Figure 3: Microscopic image in plasma cell mastitis: inflammatory infiltrate with numerous plasma cells.

Conclusions

We consider that surgical excision as an initial treatment is the most effective therapeutic method for this benign but with high relapsing potential disease. Surgical excision of affected and surrounding normal tissue as well showed particularly fast recovery and a high success rate. It also has the advantage of giving a more accurate positive and differential diagnosis, most important with breast carcinoma, of plasma cells mastitis.

Conflict of Interests

Authors have no conflict of interests to disclose.

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Research Article Open Access

Therapy of Spine Metastasis Causing Paralysis Symptoms – Operation and Rehabilitation

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Abstract

Most common manifestation of tumor metastasis after lungs and liver is the skeletal system with 60-80% of spine metastasis. In 30% of all cancer patients with metastatic spinal complaints are initial presentation of malignant primary disease while the primary paraplegia occurs in 5-10% of all spinal metastases. Thus a further operational metastases treatment is dependent on the entire metastasis status, the type and Tomita score as well as the risk of surgery considering general patient status. From 01.01.11 to 31.12.12 we included 16 patients with tumors. In 27% of the cases the first symptoms were paraplegia, but the primary tumor was determined in only one of these cases. 73% of patients underwent surgical treatment within the first 24 hours after admission. The hospital stay was 22 days. 56.3% of patients had incomplete paralysis at admission and 71% of these patients had postoperative improvement in neurological outcomes. All patients benefited as part of operational and rehabilitative treatment of a significant reduction in pain and 50% of patients were able to be discharged home. At the onset of paralytic symptoms we recommend immediate operation. In a multidisciplinary case conference the oncological treatment regimens should be defined also for the necessary paralysis treatment. Decision guidance is the height of paralysis, tumorgenesis, ASA classification and the pain symptoms of the patient. The treatment must adjusted and individualized according to the patient's general health, life expectancy, the primary tumor, the grading of metastasis and extent of neurological deficit.

Introduction

Tumors of the spine are primarily categorized by their location to the spinal cord. Thereby are intramedullary tumors with 5-10% of spinal tumors rare. The intradural extramedullary tumors make 40% of spinal tumors and are often meningiomas or peripheral nerve sheath tumors. Extradural tumors and metastases are with 50-55% the most common spinal tumors [1]. The skeletal system is the lung and liver after the third most common manifestation of tumor metastases [2]. Thereby the spine with 60 - 80% represents the most common manifestation of localization. In almost one third of all cancer patients metastatic spinal complaints are the first manifestation of malignant primary disease [3]. These metastases usually are hematogenous and can be morphologically indicative of the primary tumor. The incidence of spinal metastases is dependent on the primary tumor, and with 60-80% of the most frequent prostate tumor in men and up to 80% belongs to a mammary tumor in women. Other primary tumors are of the lung, kidney and thyroid. At 10%, it cannot be found a primary tumor (CUP= carcinoma unknown primary) [2,4]. The hematogenous dissemination along with the lymphatic spread and spread by continuity is the most common way of metastatic spread [5].

Thus spinal metastases are a common complication of underlying malignant disease at an advanced stage. Due to demographic changes of our population not only the incidence of tumors, but also the paraplegia incidence rises due to spinal metastasis. A spinal cord injury is a complex, resulting from a complete or incomplete spinal cord injury, paralysis with loss of motor, sensitive and autonomic functions below the lesion. The classification and progression are based on ASIA scheme of the American Spinal Injury Association [6], which is based on the modified Frankel scale [7]. The primary symptoms of paraplegia may be the first manifestation of an underlying malignant disease and occurs with 5-10% of all spinal metastases. Here range the neurological deficits from sensory disturbances to a complete paraplegia [8]. Acute neurological deficits require rapid surgical decompression.

This paraplegia underlay a primary disease with a limited life expectancy. Their treatment is not only responsible for the spine surgeon. The initial diagnosis of paraplegia is at first limited to the related causes. Nevertheless, the secondary tumor therapy has an important role in the treatment of these patients and their outcome [9,10]. In addition to the clinical neurological examination and a tumor-specific laboratory tests, the imaging methods have a high priority. The magnetic resonance imaging (MRI) represents the current method of choice in showing the number, size and spread of the metastases in the diagnosis and assessment of spinal tumors. Computed tomography (CT), if necessary myelography, serve to depict bone erosions, instability or fractures. The X-ray in 2 planes is particularly used in the postoperative control of instrumentation. As part of the diagnosis in the absence of surgical indication or capability can also a CT or ultrasound-assisted biopsy be performed [11,12].

The first goal of the surgical therapy in case of additional paralysis symptoms is not only the complete removal of the tumor and the decompression of the neural structures, but also relief of pain and neurological deficits, as well as the obtaining positioning or exercise stability. Nevertheless, there should be an interdisciplinary preoperative assessment of benefit and risk of the procedure, particularly in patients with severe neurological deficits, multiple metastases or progressed cancer and a reduced overall prognosis. Classifications of severity and prognosis have been established by the Tomita or Tokuhashi score [13]. Therefore a further operational metastases treatment is dependent on the entire metastasis status, the Tomita-type and -score as well as

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the risk of surgery considering the general patient status. Moreover, the temporary progression of neoplastic disease should be considered [11]. The surgical options range from decompression in prostate metastases or patients with very poor overall prognosis to combined ventrodorsal tumor resection with vertebral body replacement and stabilization. In case of bad Tomita score, a survival time of 12 months or reduced general health condition, the resection of the tumor is recommended only with stabilization. Other less invasive procedures are the augmenting of vertebral bodies with bone cement, a mono- or bisegmental laminectomy/laminoplasty or hemilaminectomy in small or lateralized tumors [14,15].

Material and Methods

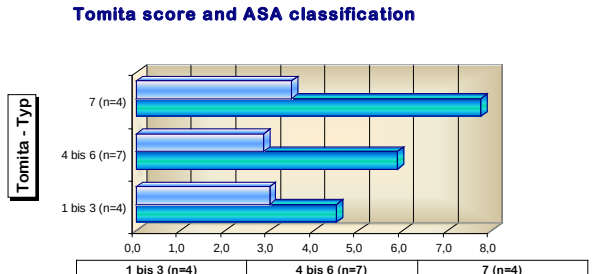
From 01.01.11 to 31.12.12 we have treated 104 acute spinal cord injuries. Therefrom 16 patients, at an average age of 67.1 years, were already tetra- ore paraplegic due to spinal metastasis or a primary tumor. Within the preoperative diagnosis according to the general condition of the patient were classified by the anesthesiologist using the ASA-classification. The ASA classification is widely used in medicine for classifying patients into different groups with respect to the physical condition [16,17] .

In addition to it the corresponding tumor score is classified after Tokuhashi and Tomita. Tokuhashi et al. designed 1994 a tumor score for spinal metastases, which takes into consideration the general condition of the patient, the number of extraspinal bone metastases, the number of metastases in the spine, the presence of metastases in internal organs, the primary tumor site and the severity of spinal cord injury. A maximum of 12 points can be obtained [13]. In 2001 Tomita et al. set up a strategy for the surgical treatment of spinal metastases. Their scoring system evaluates different prognostic factors and divides the expected therapeutic result into long-, medium-or short-term improvement of symptoms or terminal stage [18].

In the electronic medical records in our hospital, the pain intensity of inpatients are obtained and evaluated using the numeric rating scale (NRS). The further registration of pain intensity was performed daily, at rest, at expression of pain, at changes in the treatment of pain and at movement [19] (Figures 1 and 2).

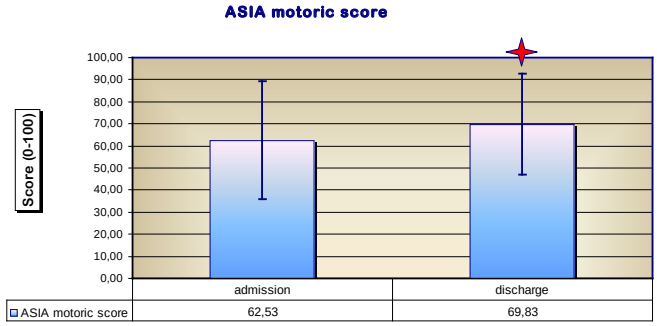
Results

Due to an impending or present paraplegia, after neurological diagnosis, immediate computed tomography and magnetic resonance imaging were done. Surgical treatment with spinal decompression and spinal fusion was carried out until the next day after admission of patients. In 26.7% of cases was the paraplegia first symptom of a previously unknown tumor. The primary tumor could not be determined in 2 cases in the postoperative staging and vertebral body histology (12.5%, CUP). In the other cases it was a metastasis in at least for 1 year known primum. From the entity the genitourinary tract tumors were most common with 43.8%. Specifically, there were 3



	1 bis 3 (n=4)	4 bis 6 (n=7)	7 (n=4)
ASA	3,0	2,9	3,5
ASIA motoric score	4,5	5,9	7,8

Figure 1: Distribution Tomita score and ASA classification by Tomita-type.



	admission	discharge
ASIA motoric score	62,53	69,83

Figure 2: ASIA motor score during the inpatient treatment, * p <0.1.

prostate tumors and 3 renal cell carcinoma, as well as a Urethelkarzinom tumors. Other entities were breast, pancreatic cancers and lung cancer. A plasmacytoma and a Pancosttumor in NSCLC (non-small cell lung cancer) also led to paraplegia. The average hospital stay was 22.1 days with a minimum of 3 days and a maximum of 65 days.

At the time of admission, patients were due to the underlying disease in a reduced general condition. At the time of operative preparation by the anesthesiologists, the average ASA score was 3.2. 44% patients were classified as ASA 4. Nevertheless 73% of patients received surgical treatment within the first 24 hours. The localization of tumor was in 74% of the thoracic spine, in 16% cervical spine, and 11% in the lumbar spine. Respectively 4 cases were from Tomita-type 1-3 and 7. 8 cases were the Tomita type 4-6. The Tomita score of patients increased in the Tomita-type groups of 4.5 (Tomita-type 1-3) with 5.9 to 7.8 in Tomita-type 7. Simultaneously the same Tokuhashi score decreased from 7.0 to 3.8 or 4.5. The correlation of this classification scores with the general condition of the patient shows the proportional increasing of the ASA classification in rising Tomita score and -type.

13 of 15 patients underwent a surgery with decompression of spinal canal and internal fixation after preoperative diagnostic. One patient died before surgery because of poor health. In total 3 Patients died during the inpatient stay (18.8%).

At the admission 4 patients had no motor deficits (ASIA E) and could be discharged without neurological disorders. 3 patients were complete plegic (ASIA A) and showed no motor recovery. At the admission 56.3% of patients had incomplete paralysis (ASIA BD). 71% of these patients showed a postoperative improvement in neurological outcomes. 3 patients converted and improved from ASIA B to C and C to D. The ASIA motor scores of the 5 extremity muscles in this group of patients improved from 54 points to 67 points and in all patients from 62 to 70 points.

94% of patients were transferred to our center for secondary diagnostics and treatment from the other hospitals. Nevertheless, all patients benefited in a significant reduction of pain after operational and rehabilitative treatment.

After an acute-treatment, rehabilitation and an oncological aftercare, due to consensus of an interdisciplinary tumor boards, were initiated. 50% of patients could be discharged to follow-up outpatient treatment. 2 patients were transferred for further oncological treatment in hospitals nearer to their homes. 2 patients were discharged directly into the inpatient rehabilitative follow-up and 1 patient in a hospice near home (Figures 3 and 4).

Due to the reduced general condition of the patient and the underlying primary disease the higher rate of complications is to be expected. From the same patient population 2 patients died postoperatively, and 2 patients had to be re-operated because of an early surgical termination and a wound infection. 2 patients occurred

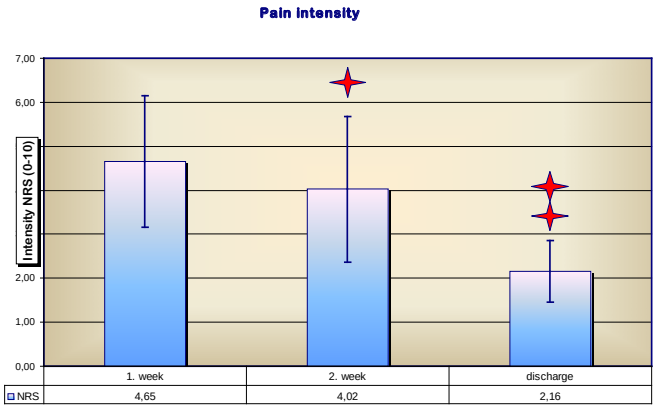


Figure 3: Pain intensity during the course of hospitalization, * = p <0.05.

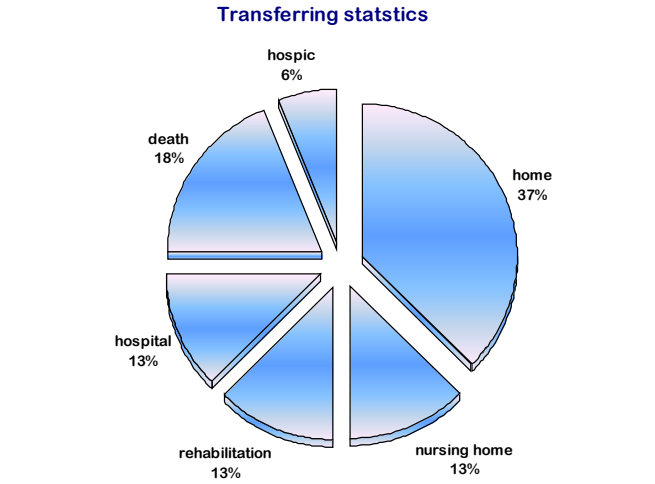


Figure 4: Transferring statistics after inpatient treatment.

a pneumonia with pneumothorax postoperatively. The overall complication rate was 37.5% and thus surgical complication rate 13.3%.

Discussion

The 1-year survival rates of patients with spinal metastases depend on the primum and lies between 10 and 50% [20,21]. In patients with paraplegia the 1-year survival rate is under 10% [8]. Therefore crucial for this group of patients is a supportive, quality of life-sustaining therapy. In the comparative analysis of our results with the current recommendation to treat metastatic related spinal cord injury, we are convinced that these patients do not have fixed guidelines or treatment recommendation compliance. The expected treatment benefit should be rather weighed against the risks of surgery and intensive care treatment [11]. However significant positive effects in terms of pain reduction, quality of life and attain long-term preservation of self-sufficiency could be observed based on our studies. Also patients with severe neurological deficits, who did not recover after surgery, benefited in regard to pain reduction. Thereby surgical treatment timing is significant for neurological outcome.

Thus, in a beginning paraplegia symptom an urgent surgical care should be sought within 24 hours. Also depending on the overall condition, patients should be timely operated within 48 hours after admission [22]. Despite controversy regarding the injection of methylprednisolon after NASCIS scheme, we think the indication for preoperative and postoperative dose given over 24 hours is given [8,23]. The surgical procedure in the case of metastasis-related acute paraplegic symptoms should be restricted to the timely and most gentle version of decompression and stabilization. Our research shows that patients are often in poor general condition. In addition to an acute, through metastasis caused, paraplegia there is a lack of time to carry out a comprehensive preoperative staging. Nevertheless, when spinal decompression is timely done, a regression of the neurological deficits can be achieved.

As surgical techniques are mono- or bisegmental laminectomy or laminoplasty. The reduction of a deformity and stabilization of the thoracic and lumbar spine is usually done by a dorsal fixation with a locking screw/rod system. If necessary, a mono- or multisegmental vertebral body resection is done with vertebral body replacement using bone graft or cage and augmentation with bone cement [24,25]. Postoperative application of the intensity-modulated radiotherapy, radionuclide therapy, androgen suppression or application of bisphosphonates should be decided in the interdisciplinary tumor conference [26,27]. Radiotherapy alone shows neither advantage in terms of neurological outcome nor in pain reduction. Thus it should be considered in inoperable patients and should vary in terms of tumorgenesis [12].

Decisive factors for the outcome and increase of quality of life are not only relieve of pain but timely mobilization and maintain or restore individual autonomy [20,28]. We could prove that it is possible to reduce pain through appropriate therapy for metastatic related acute paraplegia. In addition, a timely spinal decompression can improve neurological outcome [22]. Crucial to improving the neurologic symptoms is in addition to the surgical treatment, the consistent and timely physiotherapy and supporting these patients with appropriate technical aids [29].

To consolidate these results, it is essential to present patients postoperatively on an interdisciplinary tumor conference. Here can be set out the oncologic procedure of cancer, as well as additional surgery for tumor resection planned. The goal of the operation is prevention or elimination of instability and neurological deficits as well as adequate pain relief. Our studies show that all patients, regardless of initial neurological status, benefit from a post-operative pain relief.

Especially in spinal cord injury patients achieving a high degree of independence is essential. The control of bladder and bowel function should be achieved soon. Moreover, the transfer between wheelchair and bed should be trained. The home environment should be explored and if necessary adjusted. With intermittent self-catheterisation (ISK) or nurse-assisted Clinically Clean Intermittent Catheterisation (CCIC) urinary tract infections and pyelonephritis can be prevented. To prevent pressure ulcers, especially for the immunocompromised cancer patients, special positioning techniques should be used. Also thrombosis prevention and treatment of spasticity requires a proper therapy. Due to the complexity of the paraplegic aftercare, these rehabilitative measures should be initiated as soon as possible, at the same time offering advice and involving parents and relatives of the patients.

Not only the primary tumor but also the paraplegia is for the patient hard fate that changed the previous situation completely. We therefore consider it highly recommended that a psychological complementary treatment is included from the very beginning of the therapy. After initiation of these treatment measures we could discharge half of our patient's home, so that the other outpatient oncological therapy could be done with the support of family members. 2 of our patients were transferred to the oncological treatment in a specialized facility.

Due to the multi-morbidity of these patients in the studied group, a relatively high postoperative complication rate of 37.5% was found. Patients with metastatic tumors often exhibit a wide range of comorbidities. A significant influence on wound healing was observed

for example by a poor nutritional status [30]. In our population of patients surgical complication rate was 13.3%. Material failure or the necessity for surgical revision of internal fixation is a relatively rare complication [21].

Conclusion

In Summary, spinal metastases are an indication for surgical treatment, especially when they cause neurological deficits. The urgency of the operation depends on the status of metastasis, Tomita-type, Tomita-score, the risk of surgery, coagulation disorder, pain and the progression of neoplastic disease. Nevertheless, a complete paraplegic symptom should be relieved quickly surgically [31,32]. The natural course of the tumor disease cannot be affected by a palliative operation on the spine. For this reason, conservative and adjuvant measures should also be considered. With an appropriate therapy of metastatic related acute paraplegia, pain reduction and the neurological outcome improvement can be achieved. Here is essential besides the operation, consistent and timely physiotherapy and an appropriate medical aid supply [12,26]. A neurological deficit may be the first manifestation of a tumor disease. Symptoms like over months existing back pain, bladder and bowel dysfunction and a gait disorders in an often slow progressive tumors indicate an impending paraplegia. These symptoms should also be detected in patients with known prostate or breast cancer as hint of spinal metastases for a proper treatment to minimize the consequences of paraplegia. During this acute treatment a tumor staging is done by intraoperative biopsy and histology, tumor marker detecting and staging-CT [15,24]. As part of an interdisciplinary case conference the treatment regimen of the tumor should be specified ahead of the paraplegia treatment. The treatment must be individually adjusted according to the patient's general health, life expectancy, the primary tumor, metastasis and extent of neurological deficit. In any case, before any invasive therapy, specialized paraplegic centers should be contacted, to provide an optimal paraplegic and oncological treatment as well as supply of medical aids [20,28].

Conflict of Interests

Authors have no conflict of interests to disclose.

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Anything Other than Pain that Matters after Breast Cancer Surgery? A Randomized Controlled Study Comparing Three Anesthetic Modalities

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Abstract

Background: Paravertebral block (PVB) was shown to reduce postoperative pain and postoperative nausea and vomiting for breast surgery. However, there is no evidence showing that these benefits were solely provided by PVB and positively influence patient-perceived outcomes after breast cancer surgery.

Methods: One hundred breast cancer patients were randomized into three groups: general anesthesia (GA, n=34), GA with PVB (GA+ PVB, n=33), PVB with sedation (PVB, n=33). The quality of recovery (QoR) score was assessed preoperatively as baseline, 6 hours postoperatively, and on postoperative day (POD) 1. Analgesia effects, adverse events, and perioperative satisfactions were also assessed.

Results: The rate of QoR 6 hours reaching 18 in GA group (25.53%) seemed to be lower compared with GA+PVB (30.3%) or PVB (42.42%) but without statistical significance. Nevertheless, multivariate logistic regression analysis demonstrated that modality of PVB affected QoR 6 hours (p=0.04). Analgesic consumptions and pain scores were significantly higher and time to first request of analgesics shorter in GA group. The incidences of the GA-related undesired effects were significantly lower and satisfaction with emergence significantly better (P < 0.0001) in PVB group when compared with GA group. There was no difference between GA and GA+PVB in these outcomes.

Conclusions: Anesthesia modalities containing PVB provided better pain control. Anesthesia modalities avoiding GA, i.e. PVB alone, led to significantly lower incidences of GA-related adverse events, significantly better satisfaction with the process of emergence, and contribution to QoR 6hours reaching 18.

Keywords: Breast Cancer Surgery; Paravertebral block; General Anesthesia; Patient-Perceived Outcome

Abbreviation: PVB: Paravertebral Block; GA: General Anesthesia, QoR: Quality of Recovery

Introduction

Acute postoperative pain is a risk factor for the development of persistent chronic postoperative pain after breast surgery, [1,2] which further affects the quality of life in the long run [3,4]. General anesthesia (GA) is a popular anesthesia modality for breast cancer surgery. However, GA does not provide postoperative analgesia. In addition to postoperative pain, myriads of side effects including sore throat, postoperative nausea and vomiting (PONV) are common in the immediate postoperative period, [5,6] and may adversely affect patient-oriented outcomes. Paravertebral block (PVB) for breast surgery was shown to reduce pain and PONV compared with GA [7-11]. A recent study also showed that combining PVB with total intravenous anesthesia improved quality of recovery (QoR) compared with GA in ambulatory breast tumor resection [12].

Despite the emphasis on measuring patient-oriented outcomes in many fields of health care and acceptance of these outcomes as a valid endpoint in clinical trials, [13-15] few studies have examined the effect of anesthesia-related complications on patient-oriented outcomes in the immediate postoperative period.

We hypothesized that anesthetic modality containing PVB would positively while that containing GA would negatively affect patient-perceived outcomes for breast cancer surgery. We conducted a randomized controlled study to further discern the impacts of GA, PVB, and GA combined with PVB on QoR and satisfactions after breast cancer surgery.

Materials and Methods

This study was registered on ClinicalTrials.gov (NCT01499836) and approved by Institutional Review Board of Koo Foundation Sun Yat-Sen Cancer Center. This was a parallel, prospective, randomized controlled trial. All participants provided their written informed consent prior to surgery.

Patients were eligible for inclusion if they had histological proven unilateral breast cancer and were scheduled to have unilateral wide excision or mastectomy with sentinel lymph node biopsy or axillary dissection. American Society of Anesthesiologists(ASA) physical status class 3 or less, female,18 to 70 years of age, being able to read a newspaper in Chinese, without contraindication of GA or PVB, and being able to provide informed consent were inclusion criteria. Exclusion criteria included a history of chronic pain or long term analgesics usage, allergy to local anesthetics or nonsteroidal anti-inflammatory drugs, being pregnant, or breast-feeding.

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The purposes of the study and the risks and benefits of each anesthetic technique were explained by physicians to eligible patients in the preoperative evaluation clinic. If eligible patients consented to join the study, they would be randomized into one of three groups, GA, GA+ PVB and PVB groups. We used a computer generated randomization list produced by a statistician in the Office of Clinical Research. Sealed, opaque envelops with allocation codes concealed inside and sequential number outside were put in a locked drawer. After reconfirmation of the eligible and consenting patients' willingness to join the study on the day of surgery, envelops were retrieved sequentially just before surgery for each participant by an administrating nurse anesthetist neither involved in the anesthetic intervention in the operating room nor in the data collection postoperatively.

Preoperative anxiety makes an independent contribution to predicting acute pain after breast surgery [16]. To have this variable controlled, all patients were evaluated preoperatively with a validated questionnaire, the Hospital Anxiety and Depression Scale [17].

Procedure of anesthesia

In GA and GA+ PVB groups, propofol (2–3 mg/kg), cisatracurium (0.15 mg/kg) and fentanyl (100 μg) for endotracheal intubation and 5-8% desflurane titrated according to age, blood pressure, and vital signs for maintenance were given.

In PVB group, the patients received PVB after sedation with intravenous midazolam 3–5 mg and intravenous fentanyl 50–100 μg. Intraoperative sedation were provided with target controlled infusion (TCI) propofol driven by the Schnider model in effect site control titrated to reach moderate sedation defined as Observer Assessment of Alertness/Sedation score of 2 to 3. During operation, individualized emetic prophylaxis including one or a combination of the following medications: dexamethasone 4mg, granisetron 1 mg and droperidol 0.625 mg, was given according to each patient's Apfel Risk Score and consensus guidelines [18,19]. Granisetron 1 mg was used for PONV after surgery as the rescue antiemetic medication.

Procedure of ultrasound-guided paravertebral block

The block was performed using the in-plane technique described by Renes [20] and multi-level injection technique from T2 to 6 according to a previous study demonstrating that multilevel injections lead to optimal anesthesia [21]. After induction of general anesthesia or sedation, patients in the GA+PVB and PVB groups were placed in a lateral decubitus position with the side to be operated upward. After aseptic preparation, a high-frequency (HFL38X linear probe, 6-13 MHz, SonoSite, inc., WA, US) probe was placed lateral to the spinous process at the level of interest to locate the wedge-shaped paravertebral space. Then a 22- gauge, 3.5-inch spinal needle (Terumo®) was inserted in a lateral-to-medial direction from the outer edge of the probe and advanced until the needle tip penetrated through the internal intercostal membrane. Depending on the patient's body mass, 3-5 ml of 0.5% bupivacaine with 1:400,000 epinephrine was injected after a negative aspiration of blood or air at each level. Direct visualization of the needle-tip position and the pleura being seen pressed ventrally during local anesthetic injection was considered the end point of a successful block.

Quality of Recovery (QoR) Score

We adopted the nine-item QoR [22] as it is a validated and easy-to-use instrument to assess general quality of recovery in the immediate postoperative period. A QoR summary score, ranging from 0 to 18, was obtained by asking the patient questions regarding degree of general well-being, support from others; general mental function, ability to perform personal hygiene, bowel/bladder function, ease of respiration, presence of headache-backache-myalgias, emesis, and pain. The validated Chinese version nine-item QoR [23] questionnaire was used. A baseline QoR score was obtained preoperatively. QoR scores 6 hours and POD1 were collected.

Satisfaction

At the preoperative visit, the research assistant verified the telephone number, obtained best contact times, and informed patients that they would be called. She made four attempts to contact each patient within 24 hours after discharge to minimize recall bias with increasing time between treatment and survey completion.

Patients were queried about whether they were satisfied: 1. that they didn't recall during operation, 2. with the process of emergence, 3. with postoperative pain control. Responses to questions requiring patients to rate their experiences based on a five-point Likert scale of strongly agree, agree, undecided, disagree, and strongly disagree.

Postoperative pain and adverse events

NRS pain scores at rest and with movement were collected 1 hour, 6 hours postoperatively, and on POD 1. Patients were asked to move their arms ipsilateral to the surgical areas to an angle of 90° away from their bodies when assessing pain with movement. Postoperative analgesics including intravenous 0.1 mg/kg morphine and intravenous 30mg ketorolac were provided to achieve the numeric rating scale (NRS) pain score less than 4. The amounts of morphine and doses of ketorolac required and time to first request of rescue analgesics were recorded.

We recorded PVB-related (accidental vascular puncture, pneumothorax, nerve damage, local anesthetics toxicity, and so on) and other anesthesia-related adverse events.

Statistical methods

The primary endpoint was the rate of QoR 6 hours postoperatively reaching 18. Sample size was calculated based on a pilot study in which the rate of QoR 6 hours of 18 among control subjects in GA group was 0.36 and for experimental subjects in GA+ PVB group was 0.73 [14]. We need to study 32 experimental subjects in GA+ PVB group and 32 control subjects in GA group to be able to reject the null hypothesis that the rate of QoR=18 for experimental and control subjects are equal with probability of 0.8. Two pair-wise comparisons of the control arm (GA) to each experimental arm (GA+PVB, PVB) were made. We assumed the difference of the rates of QoR=18 between GA and PVB groups would be greater than or at least equal to that of GA and GA+ PVB groups. The Type I error probability associated with this test of this null hypothesis is 0.025. We used Fisher's exact test to evaluate this null hypothesis. We inflated the sample size to 33/34 in each group to take into account loss to follow-up and withdrawal.

Normally distributed data were presented as mean (SD) (standard deviation). Non-Gaussian data were presented as median (25th percentile and 75th percentile). Nonparametric Wilcoxon two-sample test and Fisher's exact test were used to test differences between control arm and each experimental arm. A P-value of 0.025 was considered significant. The Kaplan Meir survival graph was used to analyze the post-operative time to first request of analgesics interval. Multivariate logistic regression analysis was used to adjust the confounding variables. All of the analyses were carried out using SAS 9.3 software (SAS Institute INC, Cary, NC).

Results

During Oct 2012 to Apr 2013, a total of 100 patients were included. Data from all 100 patients were subjected to the final analysis (Figure 1). Patient characteristics showed no difference between groups (Table 1).

Although a trend of higher rates of QoR 6 hours reaching 18 was

shown in the experimental arms (30.3% in GA+ PVB, and 42.42% in PVB group, vs. 25.53% in GA group), pair-wise comparisons showed no significant difference (Table 2). Nevertheless, in the multivariate analysis adjusted for breast procedure, axillary procedure, operation duration, baseline QoR, and anesthesia technique, only anesthesia technique of PVB influenced the rate of QoR 6 hours=18 with significance (p=0.04) (Table 3).

GA group had the highest pain scores and the largest cumulative morphine and ketorolac consumptions compared to the other two groups. In the two groups with PVB, patients took longer to request analgesics compared with group GA on the log-rank test (p=0.0002) (Figure 2).

There was no difference between GA and GA+PVB in the incidences of PONV, sore throat, headache, and dizziness. The incidences of these adverse effects were significantly lower and injection site soreness significantly higher in PVB group when compared to GA group (Table 2).

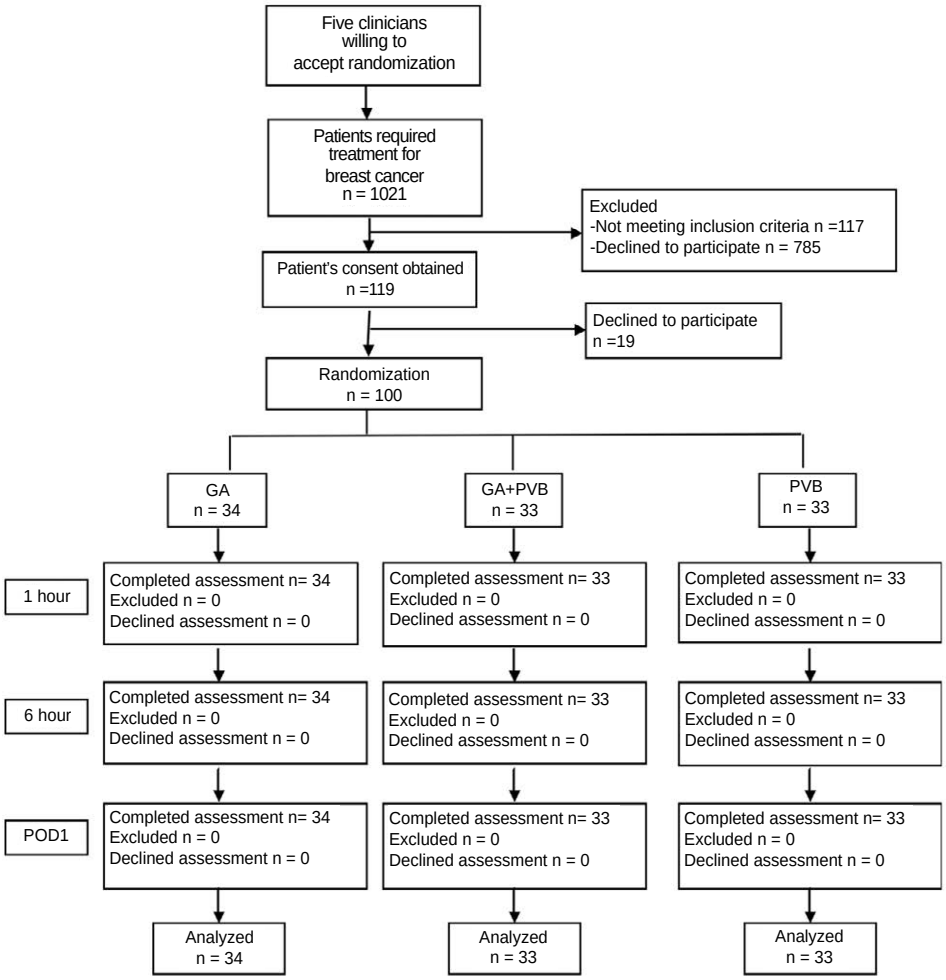

Figure 1: Chart showing flow of participants through the trial.

Table I: The main demographic and clinical characteristics of three gorups are shown according to treatment arm.

	GA (n= 34)	GA+PVB (n= 33)	P[1]	PVB (n= 33)	P[2]
Age(year) mean(SD)	47.41 (8.70)	48.45 (10.93)	0.67	47.39 (9.00)	0.99
BMI (kg m^{-2}) mean(SD)	22.68 (2.54)	23.33 (2.85)	0.32	22.36 (2.61)	0.62
ASA I/II/III(n)	9/24/1	14/19/0	0.25	9/22/2	0.92
Risk for PONV low/medium/high (n)	0/29/5	4/26/3	0.11	3/25/5	0.27
Preoperative anxiety scale mean(SD)	8.29 (3.66)	8.58 (3.56)	0.75	7.33 (4.21)	0.32
Preoperative depression scale mean(SD)	4.21 (2.96)	5.21 (4.43)	0.28	4.58 (4.00)	0.67
Preoperative QoR = 18 n (%)	19 (55.88)	19 (57.58)	1	21 (63.64)	0.62
Mastectomy n (%)	21(61.76)	16(48.48)	0.33	13(39.39)	0.09
ALND n (%)	14(41.18)	6(18.18)	0.06	14(42.42)	1
Operation duration (min) mean(SD)	103.71 (27.32)	105.39 (29.51)	0.81	121.21 (37.45)	0.03

Risk of PONV = low risk denoted Apfel Risk Score of 1; medium risk denoted Apfel Risk Score of 2-3; high risk denoted Apfel Risk Score of 4
GA: General Anesthesia, PVB: Paravertebral Block, SD: Standard Deviation, BMI: Body Mass Index, ASA status: American Society of Anesthesiologists Physical Status Classification, PONV: Postoperative Nausea and Vomiting, QoR: Quality of Recovery, ALND: Axillary Lymph Node Dissection Values are expressed as the mean (SD), or the number of patients
P^1, P^2:= the p values of Group GA compared with Group GA+PVB and Group PVB, respectively

All patients were successfully contacted within 24 hours after discharge. In contrast to GA and GA+ PVB groups in which quite a few patients were not satisfied, PVB group had every patient satisfied in every dimension. However, the P-values were greater than 0.025 except that of the dimension comparing comfort at emergence. In this dimension, PVB group had significantly more satisfied patients than GA group did ($p < 0.0001$). No difference was shown between GA+ PVB and GA groups (Table 2). None of the patients had pneumothorax, or other PVB-related complications.

Discussion

By comparing three anesthetic modalities, interesting findings of better pain control in modalities containing PVB, i.e. GA+PVB or PVB alone; while a trend of higher rate of QoR 6 hours reaching 18 without statistical significance, significantly lower incidence of GA-related adverse events, and significantly better satisfaction with emergence in modality avoiding GA, were revealed.

In previous studies, length of hospital stay was shortened by PVB in major breast surgeries [7,8]. Since it is the institutional policy to discharge uneventful breast surgery patients 1 day after surgery, using economic end point such as length of stay was not feasible for our study. We used QoR score because it is a validated summary measure of outcome in perioperative clinical trials [22]. Our study failed to show the difference of the rate of QoR 6hours reaching 18 when comparing each experimental arm (GA+PVB, PVB) to GA group. However, we demonstrated that the modality of PVB without GA is the only factor affecting QoR 6 hours after adjusting possible confounding factors. Technique of PVB combined with GA would not improve the rate of

Table II: Two pair-wise comparisons of outcomes between the control arm (GA) and each experimental arm (GA+PVB, PVB).

	GA (n= 34)	GA+PVB (n= 33)	P[1]	PVB (n= 33)	P[2]
QoR 6 hours n (%)	8 (25.53)	10 (30.3)	0.59	14 (42.42)	0.12
QoR POD1 n (%)	19 (55.88)	19 (57.58)	1	21 (63.64)	0.62
Dissatisfied/Undecided/Satisfied n/n/n					
1. I am very satisfied that neither did I recall nor was I aware during operation.	1/2/31	0/1/32	1	0/0/33	0.36
2. I am very satisfied with the process of emergence.	7/6/21	3/6/24	0.47	0/0/33	< 0.0001
3. I am very satisfied with the postoperative pain control.	2/3/29	0/5/28	0.48	0/0/33	0.05
Postop 1 hour					
Pain at rest	5.5 (3, 7)	2 (1, 4)	0.0003	0 (2, 3)	< 0.0001
Pain with movement	6 (3, 7)	3 (1, 5)	0.0009	0 (2, 3)	< 0.0001
Postop 6 hours					
Pain at rest	2 (1, 3)	1 (0, 2)	0.01	1 (0, 2)	0.03
Pain with movement	2.5 (1, 3)	1 (0,2)	0.05	1 (0, 2)	0.08
POD1					
Pain at rest	1 (0, 2)	1 (0, 3)	0.43	0 (0, 2)	0.43
Pain with movement	1 (0, 2)	1 (0, 3)	0.99	1 (0, 2)	0.50
Morphine (mg) mean(SD)	6.24 (4.09)	3.73 (2.58)	0.003	4.03 (2.73)	0.008
Ketorolac (dose) mean(SD)	0.29 (0.52)	0.06 (0.24)	0.02	0	0.003
PONV n (%)	14(41.18)	12(36.36)	0.80	4(12.12)	0.01
Sore throat n (%)	18 (52.94)	18 (54.55)	1	0 (0)	< 0.0001
Headache n (%)	7 (20.59)	3 (9.09)	0.30	0 (0)	0.01
Dizziness n (%)	15 (44.12)	14 (42.42)	1	4 (12.12)	0.006
Soreness on back n (%)	0 (0)	2 (6.06)	0.24	5 (15.15)	0.02

GA: General Anesthesia, PVB: Paravertebral Block, QoR: Quality of Recovery, POD 1: Postoperative Day 1, PONV: Postoperative Nausea and Vomiting
QOR 6 hours: Patients with QoR of 18 at postoperative 6 hours, QoR POD1: Patients with QoR of 18 on postoperative day 1
Values are expressed as the mean (SD), or the number of patients. The paired numbers in each parenthesis indicate 25th percentile and 75th percentile
P^1, P^2, the p values of Group GA compared with Group GA+PVB and Group PVB, respectively

Table III: Multivariate logistic regression analysis of effects of surgery, operation duration, baseline QoR, and anesthesia technique on QoR 6 hours in women after breast surgeries.

	No (%) of patients		Unadjusted		Adjusted*	
	QoR = 18	QoR < 18	OR (95% CI)	P	OR (95% CI)	p
Breast procedure						
mastectomy	9	25	1.00 (0.43 - 2.32)	0.40	1.11 (0.45 - 2.72)	0.82
BCS	23	43	1		1 (reference)	
Axillary procedure						
ALND	16	34	0.67 (0.27 - 1.68)	1	0.69 (0.25 - 1.88)	0.47
SLND	16	34	1		1 (reference)	
Operation duration			1.00 (0.98 - 1.01)	0.48	0.99 (0.98 - 1.01)	0.37
Baseline QoR						
= 18	11	14	2.02 (0.79 - 5.16)	0.14	2.45 (0.91 - 6.64)	0.08
< 18	21	54	1		1 (reference)	
Anesthesia technique						
GA+PVB	10	23	1.41 (0.48 - 4.19)	0.53	1.37 (0.44 - 4.27)	0.59
PVB	14	19	2.40 (0.84 - 6.85)	0.10	3.34 (1.05 - 10.64)	0.04
GA	8	26	1		1 (reference)	

QoR: Quality of Recovery, BCS: Breast Conserving Surgery, ALND: Axillary Lymph Node Dissection, SLND: Sentinel Lymph Node Dissection, GA: General Anesthesia, PVB: Paravertebral Block.
*Adjusted for mastectomy/BCS, ALND/SLND, operation duration, baseline QoR, and anesthesia techniques among 100 patients

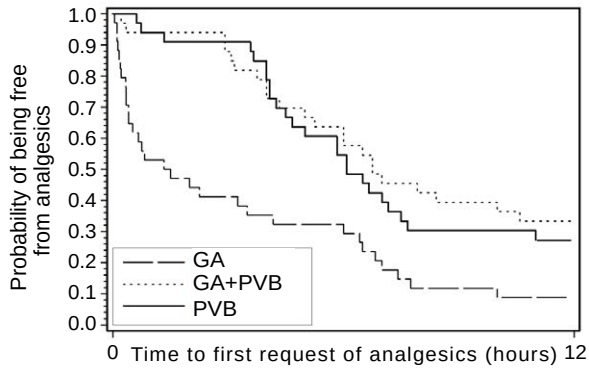

Figure 2: Time to first request of analgesics. Kaplan Meir analysis showing the proportion of patients in each group with bearable level of pain until patient's first request of analgesics. P = 0.0002.

QoR 6hours=18, although GA+ PVB and PVB groups both showed significant better pain control.

Unsurprisingly, better analgesia was found in the two groups with PVB. These findings were compatible with those of previous studies [7-11]. However; the difference was not clearly evident in the rate of QoR6 hours reaching 18. Neither was the difference evident in the satisfaction with pain control. The minor nature of breast surgery with median worst-pain scores of NRS 4 or less on the first day of surgery [24] could be responsible for the insignificant impact of anesthesia modalities on patients' satisfaction with postoperative analgesia. Nine-item QoR was found to be highly related to satisfaction with anesthesia [25]. Patients who experienced any of several perioperative complications, not just postoperative pain, had lower nine-item QoR Scores [25]. Thus the significant difference in postoperative pain might not be considered the only factor relevant for clinical practice in breast surgery.

Patients in PVB group were significantly more satisfied with the process of emergence. There was no difference in satisfaction in this dimension between the two groups with inhalational gas and intubation, with or without PVB. This could be explained by the followings. The common undesirable effects of inhalational gas-based and intubated general anesthesia, such as sore throat, headache, and dizziness, were noted to be significantly lower in PVB group. These results were compatible with previous studies [5,6]. Among these discomforts, incidence of sore throat in the groups with GA was relatively high. Avoiding intubation by using supraglottic airways or by adopting regional anesthesia may decrease this airway discomfort. Besides, early recovery was more comfortable in PVB group probably due to a significantly infrequent PONV by virtue of using propofol infusion and avoidance of desflurane [26].

The analgesic effect of PVB in our study did not last that long as described in previous studies [7,9]. There could be multiple causes. Although there were no statistical differences among the three groups in surgical types or operation duration, PVB group had the largest proportion of patients with ALND, in which intercostal nerve injury is more likely than in SLND [16]. Secondly, longer operation duration in PVB group, although without statistical significance, implied inherently more extensive procedure albeit under randomization. These could have been sources of potential bias to the outcome of the study.

There are several limitations of the current study. Previous study showed a significant decrease of nine-item QoR scores at POD1, POD3 and POD5 compared with baseline in hepatectomy [27]. However, the difference of nine-item QoR scores=18 in the immediate postoperative period was not as evident in the current study. Minor nature of breast surgery, low postoperative pain level, and sensitivity of the nine-item QoR may have contributed to it. The modified QoR-40 [28] for day surgery adopted in Abdallah et al.'s recent study [12] might be more sensitive for breast surgery as they have demonstrated the difference. However, since ours were inpatients due to the institutional policy, the recovery questionnaires for the ambulatory setting [28–30] were not considered for our study. QoR-40 [14] and nine-item QoR [22] was designed for both inpatient- and outpatient- surgeries. QoR-40 may be more sensitive 31 for breast surgery. We chose nine-item QoR for its superior feasibility, 32 being reliable for group measurement and comparison [22] and its validated version in Chinese [23]. More studies are needed to confirm the sensitivity of nine-item QoR as a tool in assessing recovery after breast surgery. To increase the sensitivity of the study and decrease type two error, increasing the sample size should also be considered in the future study. Besides, we didn't perform sham block in the GA group. Patients in the groups with PVB might be aware of the group assignment due to soreness on the back. This might have contributed to bias of the outcome.

In conclusion, PVB provided better analgesia, with or without GA. But only when adopting PVB and avoiding inhalational gas and intubation, could we observe that the QoR 6 hours postoperatively be affected, side effects of general anesthesia be reduced, and satisfaction with emergence process significantly improve.

Conflict of interest

The authors have no conflict of interest to report.

Acknowledgement

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Research Article Open Access

Colonic Esophageal Reconstruction by Substernal Approach for Caustic Stricture: What is the Impact of the Enlargement of the Thoracic Inlet on Cervical Anastomotic Complications?

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Abstract

Background: The two most commonly employed options for esophageal reconstruction are the posterior mediastinal route and the substernal route. Therefore, the biggest disadvantage of the retrosternal approach is the potential risk for compression of the graft at the site of the thoracic inlet. The purpose of this study is to report our results by analysing the impact of the enlargement of the thoracic inlet by removing the left half of manubrium and internal third of clavicle on the cervical anastomotic leakage.

Methods: From 2005 to 2013, 82 left colonic interpositions for oesophageal caustic stricture were performed at our institution. There were 70 women and 12 men. Ten patients had a hypopharyngeal stricture that required also reconstructive surgery. Dilation was done in 56 patients.

Results: An esophagocolic anastomosis was performed in 72 patients. A gastroenteroanastomosis was performed before reconstruction in 10 patients. A pharyngoplasty was associated in 10 patients. The thoracic inlet was enlarged in 35 patients .The colonic graft was anastomosed to the posterior surface of the stomach in 69 patients. The mortality rate was 2.43 %. Graft necrosis occurred in two patients. Cervical leakage was occurred in 25 patients. Eight patients developed a cervical structure. Statistical analysis revealed that the non-enlargement of the thoracic inlet was a predictive factor of cervical leak (OR; 3.63, CI; 1.06 -12.40, P= 0.039) .therefore the enlargement is associate with lower rate of cervical leak. The functional results were good.

Conclusion: The non-enlargement of the thoracic inlet is a predisposing factor of cervical leak in substernal colonic interposition. Therefore the enlargement seems reduce the cervical leakage.

Keywords: Esophageal reconstruction left colic graft; Substernal Route; Cervical Leak; Enlargement of thoracic inlet

Introduction

The construction of a long graft requires the sacrifice of the blood supply, leading to reduced circulation to the graft. The key point of Esophageal reconstruction is to ensure that the cervical anastomosis is without tension by using a graft with sufficient length and sufficient blood supply. Colon interposition is the method of choice to restore the digestive tract after esogastrectomie or for caustic stricture. Isoperistaltic left colic transplant supplied by the left colic pedicle and interposed by RS is an excellent long-term replacement organ for an esophageal caustic stricture. When performed by an experienced surgeon, it is an effective procedure with acceptable operative mortality, early morbidity, and good long-term functional results [1].

There are multiple options for the placement of the digestive conduit therefore the two most commonly employed options are the posterior mediastinal route and the retrosternal route. The use of the mediastinal route needs the ablation of the native esophagus .This and other disadvantages of the posterior mediastinal (PM) route have prompted some surgeons to advocate an alternate route of reconstruction, namely the retrosternal (RS) approach. In 1955, Dale and Sherman firstly introduced colonic reconstruction by retrosternal approach [2]. Therefore, the biggest disadvantage of the retrosternal approach is the potential risk for compression of the graft at the site of the thoracic inlet, which can lead to mechanical ischemia. To prevent this event, some surgeons suggested to the enlarge of the thoracic inlet [3-5]. The aim of this study is to report the impact of the enlargement of the thoracic inlet on the cervical anastomotic leakage after sub sternal colonic interposition for esophageal caustic stricture. The purpose of this study is to report our results by analyzing the impact of the enlargement of the thoracic inlet by removing the left half of manubrium and internal third of clavicle on the cervical anastomotic complications.

Patients and Methods

Patients

In a continuous prospective study conducted from 2005 to 2013, 82 left colonic interpositions for oesophageal caustic stricture were performed at our institution. There were 70 women (85, 3%) and 12 men (14.6%). The mean age of patients was 25 years (ranging 15 to 70). Ten patients (12.1%) had a hypopharyngeal stricture that required also reconstructive surgery. Fifty five patients with esophageal caustic stricture had undergone previous dilation. Median delay from caustic injury to chirurgical reconstruction was 12 months (ranging 3 months to 10 years).

Methods

The preoperative evaluation of the colon was performed in

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patients aged 45 or older by only colonoscopy. No patients underwent preoperative angiography. Nutritional disorders of surgical patients were corrected by enteral nutritional support before date of surgery. The surgical technique of choice used was the left isoperistaltic colon graft based on the left colonic vessels and pulled up to the neck by substernal approach. The adequacy of colonic graft blood supply was judged by preoperative inspection, palpation, transillumination and it was ascertained by the presence of a pulsatile flow in the marginal artery. The colic transplant was positioned behind the sternum snugly, avoiding tension, twisting and redundancy by resection of the proximal portion in excess of the graft. The thoracic scared oesophagus was not resected. We enlarge the thoracic inlet by resection of the left half of the manubrium and the sternal head of the left clavicle to ease the acute angulation created when the esophagus substitute deviates from its normal course into the posterior mediastinum and turns superficially to pass under the sternum (Figure 1 and 2). The scarred cervical esophageal tissue was resected completely and the cervical anastomosis was performed on healthy tissue using a hand-suturing technique in one layer and end-to-end. A pharyngoplasty was performed when necessary with the proximal portion of the transplant. The distal anastomosis was performed at the posterior side of the gastric antrum when the stomach is available. The pyloroplasty was not performed routinely, and a gastric tube was inserted into the fundus through the colon transplant to avoid the dilation of the graft. The third jejuna loop is isolated and used to insert a tube of jejunostomy and an exclusive early postoperative enteral nutrition by jejunostomy was started 24 hours after surgical reconstruction. Between 8th and 10th postoperative day and in the absence of clinical cervical leak, a barium study was done to assess the oesophagocolique anastomotic integrity.

Statistical Analysis

Statistical analyses were performed using Student's *t*-test or the chi-square test. The multivariate analysis was performed by SPSS 11.0 for Windows (SPSS, Chicago,IL, USA). A *P* value of less than 0.05 was considered significant.

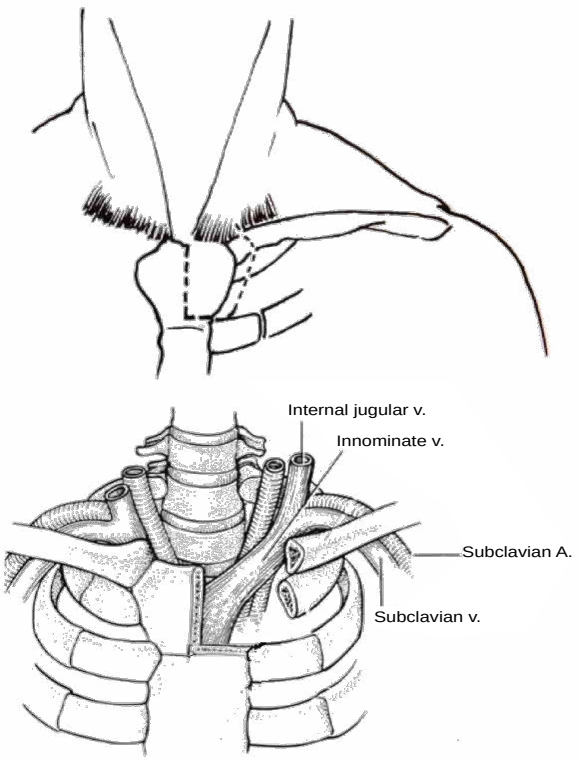

Figure 1: Time to first request of analgesics. Kaplan Meir analysis showing the proportion of patients in each group with bearable level of pain until patient's first request of analgesics. P = 0.0002.

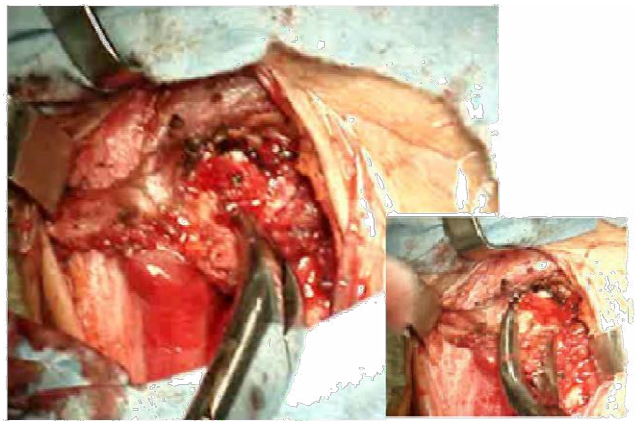

Figure 2: Operative view of resection of the manubrium and the left clavicle.

Results

The Median operative time was 3 hours (ranging 2h30 to 6 hours). Emergency total esophagogastrectomy was required in three patients. A gastroenteroanastomosis was performed before reconstruction in 10 patients because of early gastric stenosis .An esophagocolic anastomosis was performed in 87.8% of patients (n=72). A pharyngoplasty was associated in 10 patients (12.1%) using the proximal portion of the transplant. The thoracic inlet was enlarged In 45.1% of patients (n=37), by the resection of the left half of manubrium and the head of the left clavicle (Table I). The distal end of the colonic graft was anastomosed to the posterior surface of the stomach in 84.1% of patients (n=69) and to the anterior surface in 12.1% (n=10). A colojejunal anastomosis was performed in three patients because of emergency esophago-gastrectomy. Jejunostomy was performed either before or concomitant with reconstructive process. The median hospital stay was 14 days (ranging 12 to 27 days).

There were two operative deaths at 2nd and 3rd day for a mortality rate of 2.4%. The causes of death were pulmonary emboli and visceral failure.

The main postoperative complications was listed in Table II .Graft necrosis occurred in two patients (2,4%). The necrosis was partial and involved the proximal portion of the transplant. It was diagnosed on first and second postoperative day .Cervical anastomotic leakage was occurred in 25 patients (30.4%), at median postoperative day 9 (ranging 7 to12 days). The leakage was treated conservatively and the spontaneous closure was obtained in all patients, after a median delay of 7 days (ranging 5 to 10 days). Eight patients (9.7%) developed a cervical anastomotic stricture after a median postoperative delay of 12 months (ranging 2 to 18 months). Two of these patients had a previous postoperative cervical leakage. The cervical anastomotic stricture was treated successfully by endoscopic balloon dilation in six patients and in the two other patients reoperation was needed. The result of the univariate and multivariate analysis revealed that the non-enlargement of the thoracic inlet was a predictive factor of cervical leak (OR; 3.63, CI; 1.06 -12.40, P= 0.039). Therefor the rate of cervical leak was significantly lower (P=0.023) in the group of patients in whom the thoracic inlet was enlarged (Tables 2 and 3).

The graft redundancy was observed in two patients and it was treated by resection of the redundant portion and end -to -end colon anastomosis.

Table I: Thoracic Inlet.

Thoracic inlet	No. of patients	No. Cervical leak
	(%) n = 82	(%) n=25
Opening (+)	37 (45.2)	5 (13.)
Opening (-)	45 (54.8)	20 (44.4)

Table II: Postoperative complications.

Complications		No. patients (%)
Graft necrosis		2 (2,4)
Cervical	leakage	25 (30.4)
Cervical	stricture	8 (9.7)
Graft redundancy		2(2.4)

Table III: Results of univariate analysis.

Variables	No. Patients	p.value	signification
Enlargement of thoracic inlet			
Yes	37	0.072	ns*
No	45	<0.0105	s*

ns*: non-significant s*:significant

Table IV: Results of multivariate analysis.

variables	Odd ratio	95 % CI	P value	Signification
Non- Enlargement of thoracic inlet	3.63	1.06 12.40	0.039	S*

s*:significant

All the patients could be evaluated for functional results with the follow-up ranging between 6 months and 9 years. The entire patients had an oral feeding with good deglutition. Body weight, as compared with the preoperative body weight increased in all patients.

Discussion

Following esophagectomy or esophageal caustic stricture, there are a number of options to restore continuity of the upper gastrointestinal tract .Some considerations for reconstruction include: choice of conduit; technique of conduit construction; location of anastomosis; and the route of reconstruction are Important [4]. Each of these factors may have a significant impact on postoperative morbidity particularly the route of reconstruction. The substernal and the posterior mediastinal routes are most commonly applied. As reported in literature, the posterior mediastinum (PM) is preferred for immediate reconstruction after esophagectomy and the retrosternal route (RS) for delayed reconstruction of the upper gastrointestinal tract when access to the posterior mediastinum is difficult or technically not possible [6]. In case of esophageal caustic stricture, the scared esophagus adheres to adjacent organs which make its dissection risky and hemorrhagic, in addition patients with esophageal stenosis often are fed by jejunostomy and so they have a degree of malnutrition which represents an additional factor of operative complications [1]. Indeed we use exclusively the RS approach during esophageal reconstruction for caustic stenosis. The retrosternal route has been an alternative for oesophageal reconstruction after esophagectomy. But the longer route and the higher incidence for cervical anastomotic leakage compared with the posterior mediastinal approach have always hampered its wider use [7,8]. The biggest disadvantage of the substernal route is the potential risk for compression of the graft at the site of the thoracic inlet, which can lead to mechanical ischemia of the cervical portion of the graft causing a leakage or localized necrosis.

Cervical anastomotic leak has always been one of the major complications associated with the anterior reconstruction approach. The incidence of anastomotic leakage was higher than that of oesophageal reconstruction through the posterior mediastinum [9,10]. This incidence varied from 19 to 70% [11-14]. It has been reported that nearly 50% of cervical anastomotic leaks result from anastomotic strictures and the subsequent need for chronic dilatations, which negate the merits of an operation intended to restore comfortable swallowing [15]. Some authors have suggested that the increased risk of anastomotic leakage in patients who undergo retrosternal reconstruction is due to the additional length of reconstruction that is required if anastomosis is made over the neck and the tight angulation of the thoracic inlet [5,16] .When the graft is interposed via a RS, the position of the vessels must be checked constantly to ensure there is no compression on the transposed colon at the thoracic inlet because venous blood flow is very sensitive to a mechanical obstacle, which is thought to be the usual precipitating event for necrosis [1,2].

In order to facilitate exposure and to avoid compression of the interposed graft when it is brought up to the neck through the Retrosternal Route (RS), some author favor removal of a portion of the manubrium, associated costal cartilage, and the medial portion of the left clavicle [2,5]. How to reduce the incidence of cervical anastomotic leaks has always been a priority for studies in the field of oesophageal surgery .Abo and colleagues [10,17], Orringer and Sloan [16] thought that the high rate of cervical leak in substernal esophageal reconstruction was caused by the increased pressure around the anastomosis stoma due to compression of the surrounding dense tissues, which deteriorates the blood supply in that region, leading to mechanical local ischemia and hypoxia. These authors used to expand the thoracic inlet by resecting the left sternoclavicular joint during the oesophageal reconstruction through the substernal approach [10,16,17].

Our results of the multivariate analysis revealed that the non-enlargement of the thoracic inlet was a predictive factor for cervical leak (OR; 3.63, CI; 1.06-12.40, P=0.039). Therefore the enlargement by excision of the left half of manubrium and the head of the left clavicle was associated with statically significant lower rate (P=0.023) of cervical anastomotic leakage of patients in whom the thoracic inlet was enlarged. We remind that the enlargement is a non-invasive procedure without risk of secondary complications. It takes twenty minutes to achieve it without significant impact on the operative duration. In addition this procedure allows for sufficient access to the left internal thoracic vessels, which can be advantageous for successfully performing microvessel anastomosis of the graft when necessary.

At our institution and during colonic interposition through retrosternal approach, we expand systematically the thoracic inlet by excision of the left half of the manubrium and the sternal head of the left clavicle in order to ensure there is no compression on the transposed conduit at the cervical level. Many surgeons recommend to associate this procedure to the substernal esophageal reconstruction [3-5,18-22]. Statistically our study has some bias. It is not randomized and has an unrepresentative sample number. So the results are not highly reliable however the study is ongoing and further results will be published later when the number of patients will be sufficient.

Conclusion

The non-enlargement of the thoracic inlet is a predisposing factor of cervical leak in substernal colonic interposition. Therefore the enlargement seems reduce the cervical leakage. So we feel it is beneficial to expand the thoracic inlet during esophageal reconstructive surgery by substernal digestive graft interposition.

Conflict of interest

The authors have no conflict of interest to report.

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Research Article Open Access

Gastrointestinal Stromal Tumors: Diagnostic and Therapeutic Challenges

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Abstract

Background: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the digestive system. They originate from the interstitial cells of Cajal and are characterized by the over expression of KIT protein (Tyrosine Kinase), and they pose a diagnostic and therapeutic dilemma.

Objective: A challenge in diagnosis and treatment of GIST

Patients & Methods: This is a retrospective study of GIST cases that diagnosed and treated in our center during the past 5 years. These studies include clinical characteristics, imaging techniques, neoadjuvant therapy, surgical techniques, immunohistochemistry, and prognosis of such cases.

Results: Sixteen patients were diagnosed as having GIST (12 males/4 females) with a mean age 62 years (31-83 years). Diagnosis was made preoperatively in 11 patients (69%) and intraoperatively with histopatholgical confirmation in five patients (31%). The site of the tumor was detected in the stomach in 6 cases (37.5%), one in duodenum (6.25%), five in small intestine (31.25%), one in mesentery (6.25%), two in colon (12.5%) and one rectal GIST (6.25%). The main presentation of the disease was anemia, GIT bleeding and abdominal mass. Fourteen patients considered resectable and they were operated upon (87.5%) and in two patients (12.5%) neadjuvant therapy was started with favorable response in one case and poor response in other one with advanced GIST. All patients received Imatinib as adjuvant therapy. Mean follow up period was 33 months (4-54 months).

Conclusion: GIST is a complex and challenging disease that requires a multidisciplinary approach in specililized center for better prognosis of such disease.

Keyword: Gastrointestinal stromal tumors; Neoadjuvant therapy; c-KIT treatment; Prognosis

Introduction

Gastrointestinal Stromal Tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal (GI) tract, [1,2] account for <1% of all digestive tract tumors [3,4].

GIST can develop anywhere along the whole GI tract from the esophagus to the rectum, however, stomach (60%) and small intestine (30%) are the most common locations for GIST. Only 10% of GISTs are found in the esophagus, mesentry, omentum, colon or rectum. Upto 30% of GIST exhibits high –risk (Malignant) behavior such as metastasis and infiltration [5-8].

The metastatic pattern is predominantly intra-abdominal spread throughout the peritoneal cavity and to the liver, but lymphatic spread is uncommon [9].

GIST presents overexperssion of the transmemebrane protein KIT (Tyrosine Kinase) Receptor, coded by c-Kit proto-oncogene located in chromosome 4 (49^{11} - 9^{12}) believed to control cell proliferation and apoptosis [10,11]. This protein expression allows the differentiation and diagnosis of these tumors using CD117 monoclonal antibody, which is positive in >95% of stromal tumors, however, in 5%, of neoplasms the result are negative for CD 117 (KIT- negative GIST) [11,12].

GIST demonstrates almost equal distribution between males and females, however some literatures suggest that there is a slight male predominance [13].

Although GIST has been reported in patients of all ages, including children, most of them are between the age of 40-80 years at the time of presentation, with a median age of 60 years. The majority of GISTs are sporadic nonetheless; there are several cases reports of familial germline mutations in KIT proto-oncogenes [13].

The clinical manifestations of GISTs are variable and rendering accurate diagnosis challenging. The current diagnoses of GISTs are based on histological and immunohistochemical criteria, the most important of which is the expression of the receptor tyrosine kinase KIT (CD117, c kit) [14,15].

Imaging in the form of contrast-enhanced computed tomography (CECT) is the modality of choice. It is used to characterize the lesion, evaluate its extent, and assess the presence or absence of metastasis at the initial staging workup. CECT also used for monitoring response to therapy and performing follow –up surveillance of recurrence. [12,16].

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Endoscopic ultrasound (EUS) has been used in the diagnosis of GIST; it assesses the depth of invasion and is useful in obtaining a tissue sample. Preoperative percutaneous biopsy should not be used because of a significant tumor rupture or dissemination [12].

GISTs are positron emission tomography (PET) avid tumors because the receptor tyrosine kinase increases the glucose transport protein signaling [12]. PET is useful in revealing small metastasis which would otherwise not picked up on CECT as it helps differentiate an active tumor from necrotic or inactive scar tissues [6].

PET also differentiates malignant from benign tissues and recurrent tumor from nondescript benign changes. Changes in the metabolic activity of tumors precede anatomic changes on CECT: it is hence used to assess complex metastatic disease in patients who are being considered for surgery [17,18].

Surgery is the primary treatment of choice for all tumors which can be resected without significant morbidity. Conventional chemotherapy and radiotherapy are not usually effective. Imatinib mesylate is a potent and specific inhibitors of the KIT-Protein tyrosine –kinase and has been approved for the treatment of KIT (CD117) positive irresectable or metastatic cases of GISTs as it plays an integral role in the treatment of GISTas a neoadjuvant and adjuvant therapy [19].

Imatinib is effective in reducing the like hood of negative margins without significant morbidity [20,21].

The purpose of this study is to present the challenges in the diagnosis and treatment of GIST cases in our institute during the past 5 years and compare the results obtained with the results of other centers.

Patients and Methods

This review retrospective study in sixteen patients with GIST, that operated upon at the department of surgery, National liver Institute, Menophyia University in association with Clinical oncology department in Cairo University and Menophyia University from January 2009 to January 2014.

This clinical study was based upon reviewing the patients data retrieved from the medical records with ethical and scientific approval.

Disease presentation and diagnostic methods were analyzed including upper GIT endoscopy, lower GIT endoscopy, ultrasound, endoscopic ultrasound (EUS), contrast-enhanced computed tomography (CECT), fine needle aspiration (FNAB), large core needle biopsy (LCNB) and positron emission tomography (18F-FDG-PET).

Tumors were assessed for resectability as well as complete removal of the neoplasm. Imatinib was used as a neoadjuvant therapy for the cases that diagnosed as having locally advanced or metastatic tumors, with continuation as adjuvant therapy for all cases after surgery.

Surgical techniques depend on the site of the tumor and the possibility of complete resection intra-operatively.

Histological parameters were reviewed by experienced pathologists for histological confirmation of the diagnosis of GIST and evaluation of the morphological and immunohistochemical characteristics. Tumor size and necrosis on fresh specimen was examined. The mitotic rate was assessed by counting the number of mitoses per 50 high-power field (HPF) and imunnohistochemical markers (CD 117), (CD 34), Vimentin, smooth muscle actin and S-100 protein in all patients. Microscopic positive margins (<1 mm) and, in some cases, cell proliferation index measures through Ki-67. The tumors were classified according to risk prognosis using Fletcher's classification in accordance with the U.S. National Institute of Health (NIH) guidelines as very low risk, low risk, intermediate risk and high risk [12].

According to the risk prognosis guidelines and intraoperative tumor breakage, Imatinib was given postoperatively.

Follow up was carried out at 1,3,6 months after surgery then yearly using CT scan and in some cases PET scan was used in order to assess the possibility of local recurrence or distal metastasis, and disease free period.

Results

Sixteen patients were diagnosed with GIST tumors, twelve patients' males (75%) and four females (25%) with average age 62 years (31-83 years of age). Among those patients 11 cases (69%) were diagnosed as GIST preoperatively by radiological, histopathological & immunohistochemesity examination.

Five cases were diagnosed as suspicious GIST intraoperatively and confirmed postoperatively by histopathological examination of surgical specimens; these cases were classified as, one gastric GIST, one Duodenal GIST, one mesenteric GIST and two intestinal GISTs.

Tumors location of this series were as follows: six in stomach, one in duodenum, five in small intestines, one in the mesentery, two in colon and one in the rectum.

All patients presented with different signs and symptoms such as anemia in 14 cases (87.5%), gastrointestinal bleeding in 5 cases (31.25%), abdominal pain in 4 cases (25%), palpable mass in 5 cases (31.25%), nausea, vomiting and early satiety in 3 cases (18.75%), constipation in 2 cases (12.5%) and weight loss in 6 cases (37.5%), most of the patients has one or more symptoms at the time of presentation.

CT scan with oral & intravenous contrast was used as a gold standard diagnostic test for all patients (Figure 1). UGI endoscopy plus biopsy was used in 4 patients (25%) with positive for GIST in only 2 cases (Figure 2). Endoscopic ultrasound (EUS) was used in 3 patients (18.75%) (Figure 3). Large core needle biopsy (LCNB) was done in 2 cases (12.5%) in large tumor to confirm the diagnosis and to start neoadjuvant therapy.

Fludoexyglucose positron emission tomography (18F-FDG-PET)

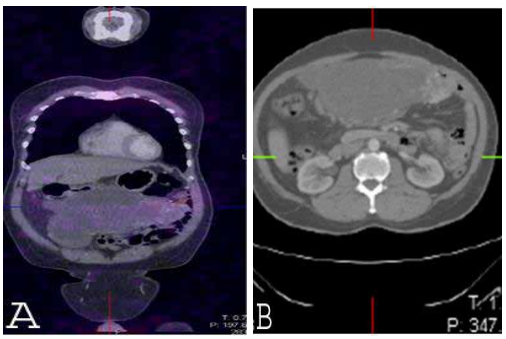

Figure 1: Abdominopelvic CT scan for Gastric GIST Tumor 33 cm in Diameter A. Coronal Section B. Axial Section (Huge intrabdominal swelling occupied the abdomen and pelvis).

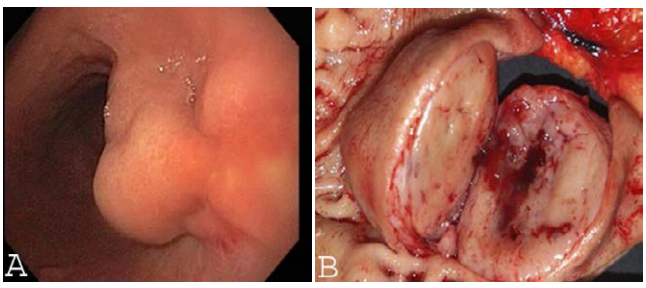

Figure 2: Gastric GIST Tumor A. Upper Endoscopy B. Tumor bisected after Excision.

was carried out before starting and after-neoadjuvant Imatinib therapy for follow up response in 5 cases (31.25%).

Fourteen patients were diagnosed as resectable tumors and were operated upon (87.5%). Nine patients were diagnosed preoperatively and 5 patients were assessed for resectability intraoperatively. In two patients that were considered unresectable at the initial assessment (12.5%) one had advanced tumor and the other had metastatic spread at the time of presentation therefore they received 400 mg/day Imatinib as neoadjuvant therapy for 6 months, with good response in one patient with huge gastric GIST (about 33 cm in diameter) revealed by PET scan and the patient become a surgical candidate (Figure 4). On the other hand the second patient had metastasis with poor response to neoadjuvant therapy and still on the treatment since 2 years.

Surgery was the treatment of choice for 15 patients (93.75%) aiming to remove the disease in all cases. The type of surgery depends upon the location of the tumor: 4 patients did partial gastrectomies, 2 patients did distal gasterctomies (Figure 4) one duodenopancreatectomy (Whipple's operation) (Figure 5), one mesenteric excision with adjacent intestinal resection, (Figure 6) 5 intestinal resection, (Figure 7) one transverse colectomy, and one anterior resection for rectal GIST ,with all negative safety margins (Table I).

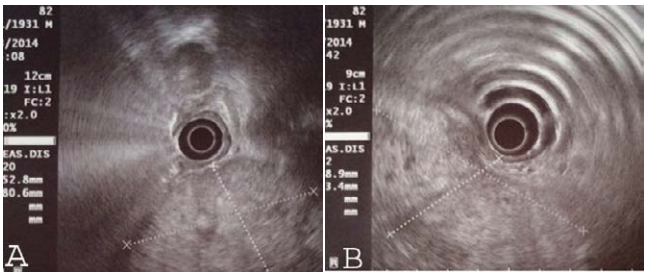

Figure 3: Endoscopic Ultrasound of Gastric GIST A.GIST 5×8 cm in diameter B-8× 4 cm in diameter.

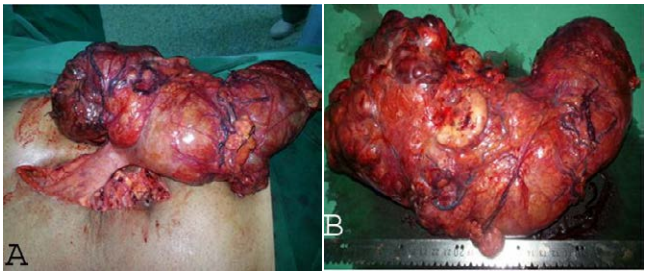

Figure 4: Huge gastric GIST 33 cm in diameter with wedge resection of the stomach.

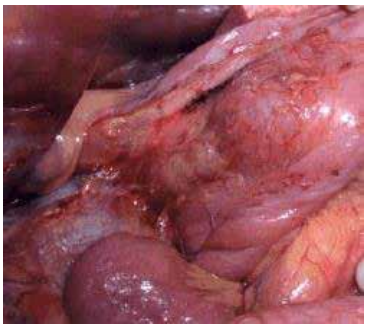

Figure 5: Duodenal GIST treated with pancreaticoduodenectomy (Whipple's operation).

Figure 6: Mesenteric GIST with segmental resection of adjacent bowel.

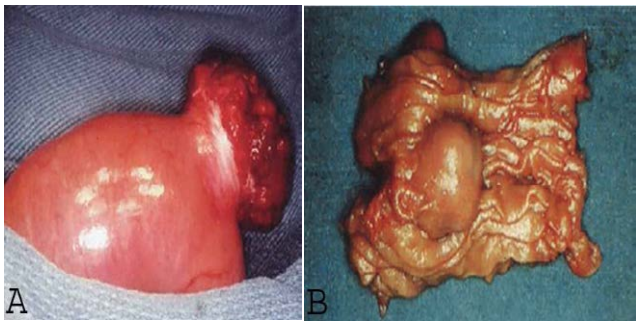

Figure 7: Intestinal GIST A. Intestinal GIST B. Resected intestinal GIST.

Table I: Operative procedures performed in 15 GIST Tumors out of 16 Tumors.

Origin of GIST	Type of Resection	No. %
		15 cases
Stomach (6)	-Partial or wedge gastric resection	(4)26.66%
	-Distal gastric resection	(2)13.33%
Duodenum (1)	-Pancreaticodudenectomy (Whipple's operation)	(1)6.66%
Intestine (5)	-Small bowel segmental resections	(5)33.33%
Mesentery (1)	-Mesenteric excision with adjacent intestinal segmental resection	(1)6.66%
Colon (1)	-Transverse colectomy + Segmentectomy seg.7 (Metastatectomy)	(1)6.66%
Rectum (1)	-Anterior resection	(1)6.66%

Histological analysis revealed: 8 tumors (50%) had a mitotic index <5 mitosis/50 HPF, 5 tumors (31.25%) had a mitotic index >10 mitosis/HPF and 3 tumors (18.75%) had necrosis. Classification of tumors according to Fletcher prognostic scale was as follow 5 tumors (31.25%) with low risk, three tumors (18.75%) with moderate risk and eight tumors (50%) with high risk (Table II).

According to the cell type 10 tumors (62.5%) were fusiform (spindle) cell, 4 tumors (25%) were epitheliod cell and 2 tumors (12.5%) were mixed types (Figure 8).

Average tumor size was ranged from 3.5 cm to 33 cm in diameter. The average tumor weight from 200 mg to 11 kg.

Immunohistchemistry study revealed 14 neoplasms (87.5%) positive for CD 117 and CD 34, five patients positive for vimentin and actin (31.25%) and four patients positive for S-100 protein (12.5%) (Figure 9).

Average hospital stays 6.5 days (4-20 days)

There was no mortality in this series but there was 3 morbidity (one patient with wound infection, one patient with lung collapse both treated conservatively and one patient with incisional hernia treated surgically with mesh)

Five patients (31.25%) received 400 mg /day Imatinib as

Table II: Fletcher Prognostic Classification of 16 GIST Tumors.

Risk	Size (cm)	Proliferation index (Mitotic count)	(No= 16) %
Very low	< 2 cm	< 5/50 HPF	(n= 0) 0%
LOW	2- 5 cm	< 5/50 HPF	(n= 5) 31.25%
Medium	< 5 m 5-10 cm	6- 10/50 HPF < 5/50 HPF	(n= 3) 18.75%
High	> 10 cm Any	Any > 0/50 HPF	(n= 8) 50%

HPF, high power field

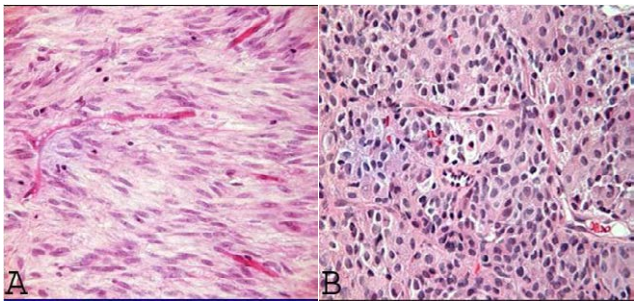

Figure 8: Histopathology of GIST Tumor A. Spindle cell B. Epitheliod cell.

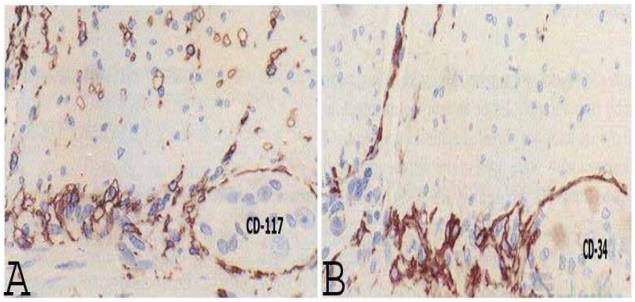

Figure 9: immunohistochemeistry of GIST Tumors A. CD117 Positive B. CD 34 Positive.

neoadjuvant therapy for 3-6 months to decrease the size of the tumor preoperatively and then surgical intervention depends on the response to therapy. All patients received Imatinib postoperative as adjuvant therapy for 6 months. One patient considered not a candidate for surgery due to advanced and metastatic disease, received Imatinib for 24 months and still on treatment.

Average follow up was 33 months (4-54 months) during follow up period two patients developed metastasis in the liver. One patient did transverse colectomy for colon GIST presented with metastasis in the segment VII of the right lobe of the liver for which segmentectomy of segment VII (Metastatectomy) was done (Figure 10), the other patient had huge liver metastasis central in the liver about 20× 25 cm in diameter 6 months after intestinal GIST resection and the patient put on Imatinib therapy for 1 year with poor response, but the course still stationary (Figure 11).

Discussion

Gastrointestinal stromal tumors (GISTs) are common mesenchymal tumors that arise predominantly in the gastrointestinal tract (GIT). In the past, there has been considerable debate regarding its nomenclature, cellular origin, diagnosis and prognosis [22-24]

Due to their similar appearance by light microscopy, GISTs were previously thought to be smooth muscle neoplasms and most were classified as liomyomas, liomyoblastomas, liomyosarcomas or schwannomas [24]. It was in 1998, after the discovery of gain-of function mutations in the c-KIT proto-oncogene that these tumors were reliably distinguished from other histopathological subtype of mesenchymal tumors [22,25].

GISTs represent the most common mesenchymal neoplasms of the GIT with an incidence o.1-3.0 % for malignancy transformation [26,27]. It is thought that these tumors differentiate from intestinal pace maker cells, also known as interstitial cell of Cajal [28].

They affect mostly males between the ages of 50 and 70 years, but it can be discovered incidentally at young age groups. Large or advanced lesions may present with a variety of clinical findings, include bleeding, abdominal pain, early satiety, bowel obstruction or perforation [29,30].

The most frequent location of GIST is the stomach (60-70%) followed by the small intestine (20-30%), colorectal (<5%), esophagus (<2%), with lower frequency in the peritoneum, mesentery and omentum [31]. Our series showed a higher prevalence in the stomach (37.5%) followed by small intestine (31.25%) and colon (12.5%) ,which constitute with what has been reported in the literatures.

Only 70% of patients with GIST are symptomatic while 20% are asymptomatic in which the tumors are detected incidentally, 10% of the lesions are detected only at autopsy, symptoms and signs are not disease specific, and are related more to the site of the tumor [27,32]. Anemia considered a predominant sign for all cases of GIST [33,34] and this constitutes with our series as anemia represent 87.5% of the cases. Bleeding comprises the most common symptoms after anemia (30-40%), and it is attributed to the erosion into GIT lumen causing hematemesis, melena, or anemia which is usually more chronic on presentation [27-32].

The symptoms reported in our series were similar to those reported in the literatures.

Diagnosis was occasionally incidental while studying another disease through imaging studies , suspected cases intraperativelly or through histological study from surgical specimen obtained as

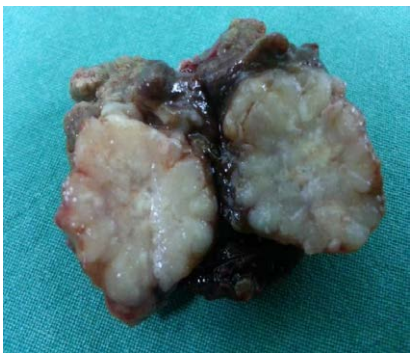

Figure 10: Metastatectomy of segment VII of the liver after transverse colectomy for Colonic GIST.

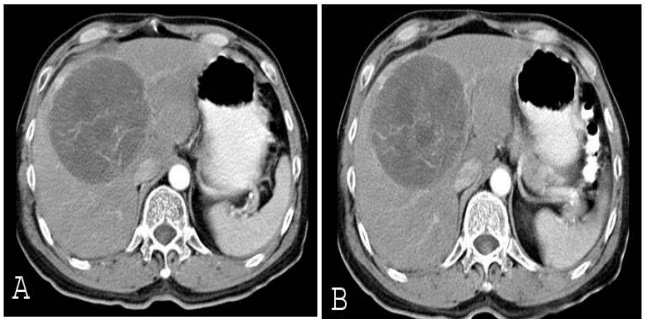

Figure 11: Hepatic Metastasis from Intestinal GIST A. Pre-Imatinib therapy B .Post-Imatinib therapy (Shows limited response to the therapy).

occurred in (31.25%)in our cases, but the diagnosis was confirmed preoperatively in (68.75%) of cases.

CT scan using oral and intravenous contrast is the method of choice for patients with suspected abdominal tumor. CT scan reveals exophytic heterogenous, vascular tumors associated with hemorrhage and necrosis [35].

In our series CT was the method of choice for diagnosis and follow up.

Upper GIT endoscopy for gastro-duodenal or esophageal cases usually shows a protruding submucosal lesion with or without mucosal ulcer [36].

Endoscopic biopsy usually does not provide sufficient evidence to establish GIST diagnosis because of its submucosal nature [37].

This also occurred in our study as endoscopy was carried out in 4 cases of gastro duodenal GIST with submucosal lesion and endoscopic biopsy confirm the diagnosis of GIST only in two out of 4 cases.

Endoscopic Ultrasound (EUS) can detect small GIST tumors (round or oval, hypoechogenic and those found in muscularis propria), allowing the study of the relationship between different sheets of the gastrointestinal wall. Echo endoscopic puncture has a better outcome than endoscopic biopsy with a success rate of 80%-90% [38]. Only 3 patients of our series with suspected GIST in the gastric wall were subjected to EUS and the diagnosis of GIST tumor was confirmed by FNAB guided through EUS.

The Task Force Report (NCCN GIST) does not recommend carrying out preoperative biopsy from easily resectable tumors because this may lead to hemorrhage and dissemination [34,35]. However, locally advanced tumors that might be treated using Imatinib required immunohistochemical study on CD 117. Two cases of our series (12.5%) that had locally advanced tumors required large core needle biopsy (LCNB) to achieve the diagnosis of GIST. Imatinib started as a neoadjuvant therapy to down stage the tumors. One patient had a good response after treatment with Imatinib for 6 months, and the GIST become surgically resectable, the other one had poor response to the treatment.

PET-18F-FDG offers information about metabolic activity and allows the estimation of neoplastic malignancy because a higher glucose uptake represents higher metabolic activity and, therefore, this suggests a more aggressive tumor [36]. Also, this technique has high sensitivity in assessing early-and long-term response to Imatinib in patients with advanced GIST positive to CD 117 [39,40]. However, CT scan is more cost-effective in suspected abdominal tumor.

Tumor response is assessed for other entities as size decrease according to RECIST criteria (Response Evaluation Criteria in Solid Tumor. However, these criteria may underestimate response for GIST neoplasms because there are several changes revealed by CT scan in addition to tumor size changes, especially the addition of intratumoral nodules or decreased vascularization [41].

Choi et al concluded that CT scan is sensitive and specific to assess metastatic GIST response to Imatinib, considering response as size decrease >10% or tumor density decrease >15% at 2 months after the initiation of therapy with a 97% sensitivity, and 100% specificity, when compared to PET response [17].

The consensus conference of Lugano [35] established that PET should be used when an early assessment of tumor response to Imatinib is required to consider surgery or when there is some confusion that raises suspicion of metastasis. In our series, only five patients were diagnosed and follow up using PET pre-neoadjuvant Imatinib therapy and follow up response of this therapy. The rest of patients were studied using CT scan with 100% sensitivity. MRI provides more valuable information than CT scan for rectal GIST [36]. In our series, one case of rectum the MRI used in evaluation and follow up.

GIST vary greatly in size from a few millimeters to more than 30 cm, the median size being between 5cm-8cm. Macroscopically, GIST usually has an exophytic growth and a common intra-operative appearance is that a mass attached to the stomach, projecting into the abdominal cavity and displacing other organs [26,32]. On gross appearance they are smooth gray, and white tumors which are well circumscribed, usually with a pseudo capsule. A small area of hemorrhage or cystic degeneration and necrosis may be visible [32]. In our series one tumor size reaches 33 cm in diameter and weight up to 11 kg which constitute with other reports in literatures.

Because there is a wide range of differential diagnosis of GIST histology, these tumors are confirmed through immunohistochemical and molecular biological techniques with c-KIT overexpression (CD117) as the key marker. Approximately >75% of tumors are c-KIT positive for CD117, whereas 60-70% are positive to CD 34, 30-40% positive to Vimentin & smooth muscle Actin, 5% to S-100 protein and 1-2% to desmin or Keratin [5,7,9,32]. In our series 87.5% of cases positive for CD117 & CD34, 31.25% for Vementin & Actin while 25% positive for S-protein, which is similar to the results reported in other literatures.

GIST has three essential histological patterns, 70% fusiform (spindle) apparently with the best survival rate, 20% epitheliod and 10% mixed. C-KIT negative GIST are usually epitheliod and extra-intestinal [42]. In our cases, fusiform (spindle) histological pattern are the predominant type (62.5%), followed by the epitheliod type (25%) and mixed type (12.5%).

Based on studies by Fletcher et al. [12] the two most important prognostic variables for GIST are tumor size (<2 cm, 2-5 cm, >5 cm) and mitosis index per 50 high-power fields (HPF) (<5 mitosis/50 HPF or >5mitosis/50 HPF), therefore ,tumors are classified according to the prognostic risk as 'very low Risk'(<2 cm and <5 mitosis/ 50HPF),'low Risk' (2- 5 cm and <5 mitosis/50HPF), 'Medium Risk' (<5 cm and 6- 10 mitosis/50 HPFor 5-10 cm and <5 mitosis/ 50 HPF) and 'high Risk'(>5 cm and >5 mitosis/50HPF, 10 cm/any mitosis index or any size and >10 mitosis/50HPF). Considering the prognostic risk in our series there were 5 tumors with low Risk (31.25%). 3 tumors with moderate Risk (18.75%) and 8 tumors with high Risk (50%). Other poor prognostic factors are necrosis, infilteration, metastasis and hypercellularity [43,44]. In our series there were 3 cases (18.75%) that had necrosis with poor prognosis.

Surgery is the primary treatment of choice in localized or potentially resectable GIST. It is important to avoid tumor rupture. The tumors are fragile and should be handled with care, aiming to achieve complete gross resection, with an intact pseudocapsule. Multiviseral and radical surgery should be avoided whenever possible: segmental or wedge resection with an aim to obtain histologically negative margin is sufficient. Resection should be accomplished with minimal morbidity. Lymphadenectomy is not required as GISTs have low incidence of nodal metastasis [9,12,16]. In our series, 15 patients (93.75%) underwent surgery with complete surgical excision, 4 had partial gastrectomies, 2 had distal gastrectomies, one had local mesenteric excision with adjacent intestine, 5 had intestinal resection, one transverse colectomy,one anterior resection and one duoedonpancreatectomy for duodenal GIST.

All surgical interventions were open techniques. Laparoscopic approach was not used in our cases, as some authors don't recommend laparoscopic surgery for tumor >2 cm or extra-wall neoplasm because of the increased risk of tumor breakage and peritoneal dissemination,

[36] however, other authors consider this as a valid alternative in addition to open surgery [34].

Overall report 5-years survival rate after complete surgical resection of primary GIST is from 40%-55% [13,36].

Disease free survival is associated with tumor size and mitosis index. Therefore, low risk GIST has a 5-year disease free survival of 96%, median-risk of 54% and high-Risk of 20% [45].

Disease free survival in our series was 87.5% at 4.5 years in all cases. Only 2 cases had liver metastasis, one case had small metastasis in segment VII of the right lobe of the liver in which segmentectomy (metastatectomy) was carried out. The second one was huge liver metastasis therefore put on Imatinib therapy since 2 years with little response.

Advanced and metastatic GIST (peritoneal dissemination or long distant metastasis (liver/lung) represent a treatment challenge. Until recently, overall survival of these patients was <1 year and 5-years survival was only 20% [46].

Imatinib Mesylate, a tyrosine kinase inhibitor, plays a key role in the management of GISTs. It can be used as neoadjuvant therapy, adjuvant therapy and to treat tumor recurrence [47]. Its mechanism inhibits c-KIT tyrosine-kinase, which has a positive effect over c-KIT positive GIST. Several studies confirmed the beneficial effect of this medication in advanced GIST.

Consensus [35] and expert guidelines indicate Imatinib therapy may increase survival in patients with c-KIT-positive advanced GIST, allowing some patients to undergo primary surgery then to start as initial dose of Imatinib 400 mg/day (except for exon q mutation on c-kit, changing dose to 800 mg/day).

Early response will be assessed after 2-4 weeks of therapy using CT and PET scan (ideally) in order to determine functional response. In case of response, treatment will be continued until maximum response is achieved (3-6 months) and patient will undergo surgery if total resection is possible [48].

In this series, we have 5 patients who received Imatinib 400 mg/day for 6 months as neoadjuvant therapy one of them had advanced gastric GIST, after 6 months of Imatinib therapy there was a dramatic response and the patient became candidate for surgical resection.

Postoperative Imatinib therapy has been reserved for patient with high risk of recurrence although there is insufficient evidence about optimal length of such therapy [49]. In our series all patients received Imatinib as adjuvant therapy for at least 6 months.

Metastatic GIST in the liver in the commonest site followed by peritoneal cavity, but can also occur in bone, skin, soft tissue and lymph node [50].

Patient with hepatic metastasis who is medically fit and with surgically accessible but focally progressive disease should be considered for resection. The rationale behind this approach is to eliminate of drug-resistance clones that will allow ongoing therapy with Imatinib [51].

Surgery in metastatic liver patients is a case based decision. Residual tumor resection is safe but multifocal resection is not recommended without considering the patient's performance status and personal situation [51,52].

When surgery may not be possible, limited evidence exists that similar benefits could be obtained from other nonsurgical ablative techniques such as radiofrequency ablation or embolization [53,54].

In our series we have 2 patients with liver metastasis one of them cured with surgical resection and adjuvant Imatinab therapy, the other case had huge focal hepatic metastasis from colonic GIST and was not considered a candidate for surgery, had received the Imatinib therapy with poor response.

Conclusion

Gastrointestinal stromal tumor (GIST) is a complex and challenging disease requiring an effective multidisciplinary management team involving integrated specilities such as a pathologist, radiologist, gastroenterologist, oncologist, and a surgeon for better outcome of such cases.

Conflict of interest

The authors have no conflict of interest to report.

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Research Article Open Access

Efficacy of Electrogalvanic Stimulation in Treatment of Levator Ani Syndrome Revisited

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Abstract

Introduction: Electrogalvanic stimulation (EGS) has been established as a safe and effective treatment for the management of levator ani syndrome (LAS). There is a paucity of recent literature regarding this treatment modality. The purpose of this study is to review recent experience with EGS in the treatment of levator ani syndrome at a single center.

Methods: A retrospective review of 22 patients treated with EGS for LAS from 07/04 to 08/08 was done. The EGS protocol begins with 30 minute sessions. Voltage is adjusted based on patient tolerance (range 100–330 volts) and is delivered at a frequency of 100 pulses per sec (pps). Length of treatment is gradually increased with increasing patient tolerance, from 30 to 60 min. Each session starts with minimal voltage and is slowly increased to maximum tolerance, held for 15–20 minutes, then intensity is gradually reduced from the peak of 100–330 volts to a minimum of 10–100 volts. Most patients were treated three times weekly for two weeks (average, six treatments per patients). The mean number of sessions was 7.5 (range 2–15). The average of duration of each session was 29 minutes for the initial visit and 46 minutes for the concluding visit. The intensity was 70% at initial visit, and 88% by the last treatment (330 volts=100%).

Results: Twenty two patients were treated (72% males). The mean age was 56 years. The mean duration of symptoms was 60 months (range 3–240). 41 percent of patients had additional anorectal pathology. Over 60% of patients were taking muscle relaxants and/or analgesics. In this cohort, 59% of patients had previous treatment, including biofeedback (32%), botox injection (14%) and epidural injection (14%). Patient assessment of results at the last treatment session: complete relief or significant improvement in 8 patients (36%); moderate improvement in 2 (9%); slight improvement in 7 (32%); and no improvement or worsening of pain in 5 patients (23%). The mean follow up was 11 months (range 0.4–38). There were no complications associated with the EGS. Both multiple linear regression and logistic regression showed the same results. The outcome of patients with levator ani syndrome treated with EGS is related to the number of treatment sessions and history of previous treatments (of any sort).

Conclusions: EGS is an effective treatment option in a selected group of patients with LAS. It offers significant to moderate improvement in 45% of patients with essentially no risk. Due to its safety profile and moderate efficacy, it should continue to be considered as a treatment operation for levator ani syndrome.

Keywords: Anismus; Electrogalvanic stimulation; Muscle spasm

Background

The Levator ani syndrome, also known as anismus, levator spasm, puborectalis syndrome, chronic proctalgia, pyriformis syndrome and pelvic tension myalgia [1,2], produces chronic anal pain which is often debilitating and characteristically referred to as constant and/or frequent dull anorectal pain. Tenderness to palpation of the levator ani can be elicited in all patients. The pathophysiology of levator ani syndrome is poorly understood but the pain is a direct result of levator ani muscle spasm without an underlying organic disease.

There are no controlled studies of treatments for chronic intractable anorectal pain. However, some uncontrolled studies have reported very acceptable overall success rates with electrogalvanic stimulation [3-7], biofeedback training [3,8,9] digital massage of the levator ani muscles [10,11], and sitz baths [12].

Objectives

We review our experience using EGS in the treatment of levator ani syndrome.

Methods

A retrospective chart review was conducted in 25 patients treated with EGS for levator ani syndrome from July 2004 to August 2008. All patients who underwent EGS in a single center were included for review. The study was done under an Institutional Review Board approval.

Patients' clinical histories were taken to ensure they did not have a pacemaker, as this is a contraindication for EGS. Patients were then educated about the procedure and placed in the left lateral decubitus position. Digital rectal examination was performed prior to each session to assess the point of worst tenderness. The dispersive pad was placed under the patient's left thigh and an intra–anal probe was inserted. Both

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were connected to the EGXtra® Model EGS4000 (Cen–Med Enterprise Inc., East Brunswick, NJ) (Figure 1). The pulse per second dial was turned up to 100. Voltage was adjusted based on patient tolerance but ranged from 100–330 volts and was delivered at a frequency of 100 pulses per sec (pps). The treatments began with 30 minute sessions. The length of sessions was gradually increased from 30 to 45 min. Each session started with minimum voltage (generally around 150 volts), and slowly increased to the patient's maximum tolerance. During the increments of voltage, patients were asked about their tolerance, so they that the voltage could be appropriately adjusted. The intensity was kept at this level for half of the session and, then gradually decreased from 100–330 volts to 10–100 volts. Lastly, the dispersive pad site is checked for any signs of burns. Multiple linear regression and logistical regression analysis was performed using NORM software.

Results

A total of 22 patients were treated. The majority were males (72%). The mean age was 56 years old (range 30–86). The mean duration of symptoms was 60 months (range 3–240). 41 percent of patients had additional anorectal pathology (anal fissure, anal fistula and hemorrhoids). Over 60% of patients were taking muscle relaxants and/or analgesics. Fifty–nine percent of patients had previous treatments, including biofeedback (32%), botox injection (14%) and epidural injection (14%). The mean number of EGS sessions was 7.5 (range 2–15). The average duration of each session was 29 minutes for the initial visit and 46 minutes for the concluding visit. The intensity was 70% at initial visit, and 88% by the last treatment (330 volts=100%). Patients' assessment of results at the last session is shown in Figure 2. Complete relief or significant improvement in 8 (36%); moderate improvement in 2 (9%); slight improvement in 7 (32%); and no improvement or worsening of pain in 5 (23%). The mean follow up was 11 months (range 0.4–38). There were no complications associated with the EGS. Table 1 summarizes our patient population based on gender, time with the diagnosis (months), previous treatments before undergoing EGS, number of EGS sessions and the outcomes after the last session. In the "Results" column we assessed the outcomes according to the Visual Analog Scale for pain reported by the patients in the chart during the initial and final sessions. Empty cells meant that the information was not available in the patient's chart, and results for patients 08, 09 and 12 were not reported using the Visual Analog Scale, therefore data was reported the same way it was collected in the medical needs.

Figure 1: EGXtra Model EGS4000.

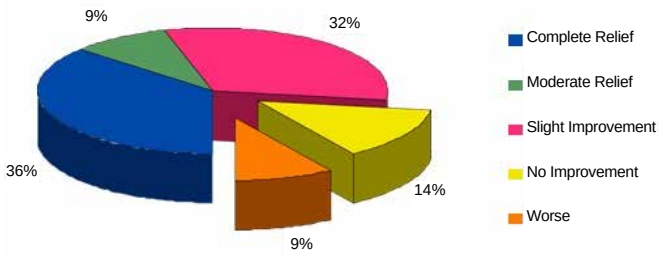

Figure 2: Distribution of patients' assessments of outcomes at the last EGS session.

Table 1: Distribution of patients' population by gender, time with the diagnosis, number of EGS sessions, previous treatments and final results.

Patient	Gender	Time with the Diagnosis (months)	Number of sessions	Previous Treatments	Results
1	F	15	10	1 Botox injection	8 -->9
2	M	8	15		7 --> 2
3	M	20	6	Biofeedback	8 --> 4
4	M	5	10	Biofeedback 2 Botox injections	8-9 --> 7-8
5	M	1	5	Biofeedback	10 --> 8
6	F	0.5	2		5 --> 10
7	F	0.42	6		8 --> 0
8	M	1.5-2	6		Increased
9	M	0.33-0.42	3		Increased
10	M	0.33	12		5-->3
11	M	3	15	Biofeedback	7 --> 3
12	M	2.5	7	Biofeedback	Decreased
13	M	0.67	6		5.5 --> 0
14	F		6	Epidural injection	9 --> 10
15	M	10	6		6 --> 3
16	M	13	4	2 Epidural injections	7 -->5-6
17	F	2	12	2 Epidural injections Biofeedback	10 -->7
18	F	1.16	6		9-10 --> 1-2
19	M	1.5	9	Biofeedback 1 Botox injection	9 -->6-7
20	M	0.42	6		6-7 -->0
21	M	7	6		10 --> 4
22	M	4	6		6-7 --> 0

Source: Medical Records. University of Illinois at Chicago Medical Center.

Both Multiple Linear Regression and Logistic Regression show the same results that The EGS treatment results were influenced by the number of sessions and the previous treatment prior the EGS. In addition, a greater number of sessions can help the EGS treatment to decrease the pain score remarkably; however, the more previous treatment affect the results adversely. Both of the two approaches indicate that a patient is more likely to be treated successfully by the EGS treatment with a greater number of sessions. But a patient is not more likely to be treated successfully by the EGS after other prior treatments.

Scatter plots were used to indicate whether there are linear relationship between the continuous predictor variables and the outcome variable. Figure 3 shows that there is a linear relationship between number of sessions and treatment success. However, there is no clear cut linear relationship between the time withthe diagnosis and treatment success.

Discussion

Early in the 1980's, high voltage electrogalvanic stimulation for the treatment of the levator ani syndrome started to be utilized. In 1982, Sohn et al published a series of 80 patients treated successfully with EGS, with total relief of pain in 69% of the patients [6].

Nicosia and Abcarian in 1985 showed that electrogalvanic stimulation provided total relief of pain symptoms in eighty percent of a cohort of 45 patients with only two patients reporting no benefit [13].

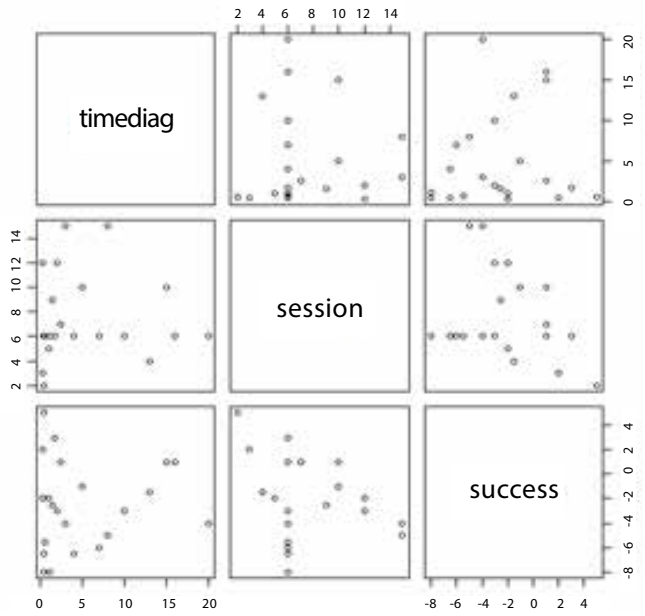

Figure 3: Scatter plots showing the relationship between number of sessions and success with treatment with EGS.

Also in 1985, Oliver et al. stated that of those correctly diagnosed with levator ani syndrome, seventy–seven percent experienced symptomatic relief with EGS [14]. Most articles stress that the diagnosis of levator ani syndrome requires that organic causes of anorectal pain be excluded [15]. In 1987, a study of twenty–eight patients showed success of 50% after eight treatments. The authors noted that patients with irritable bowel syndrome (IBS) or previous anorectal surgery were least likely to benefit from EGS [16].

Drossman et al. reported that the prevalence of symptoms compatible with levator ani syndrome in the general population was 6.6% and that more than 50% of this of patients were 30–60 years old. Women were noticeably more affected than men (7.4% vs. 5.7%) [2]. However, these results were contrary to our patient population where men predominated (72.3%).

Diagnosis of levator ani syndrome is one of exclusion and many patients are refractory to treatment. Patients describe the pain as a vague, dull ache, fullness pressure sensation high in the rectum that often gets worse with sitting. On physical examination, overly spastic levator ani muscles can be felt; tenderness to palpation of pelvic floor muscles represents a cardinal symptom and prominent finding. For unknown reasons, the tenderness is frequently asymmetric, affecting mostly the left side [3]. The pathophysiology remains unknown. Patients with levator ani syndrome are often troubled with psychological co–morbidities associated with chronic anal pain which may result in social isolation. In a study by Ger et al., one fourth of patients had coexisting psychiatric conditions most commonly anxiety and depression [3]. It is uncertain if the association between chronic pelvic pain and psychosocial distress in multiple domains represents an underlying cause or a consequence of pain [1-5]. Electro–physiologic testing suggests increased anal pressures which may reflect increased external and/or internal anal sphincter tone [1]. Noninvasive treatment options for levator ani syndrome include sitz baths, biofeedback, analgesics and muscle relaxants while more invasive options include digital message, botox injection, steroid and epidural injections, and electrogalvanic stimulation (EGS) [17].

Hull and colleagues in 1993 reported forty–three percent of patients had at least partial relief of symptoms with a mean follow–up of more than two years [18].

Most treatments provide temporary relief and often require multiple visits [19]. Billingham et al. confirmed this in a study of twenty patients with levator ani syndrome treated with EGS. Sixty percent of their patients had immediate pain relief, one–third of which eventually had recurrent pain [20]. Few recent trials have looked at the efficacy of EGS in the treatment of levator ani syndrome. We hypothesize that EGS is still a viable adjunct in the management of this troubling disorder and an effective treatment for levator ani syndrome. In 2003 women with pelvic pain from levator spasm were treated with vaginal EGS by gynecologists and more than half of them had long–lasting relief of 6 months or more [21]. Our data support results similar to the above mentioned studies, with 45% of patients showing benefit from EGS.

Conclusion

Electrogalvanic stimulation for the treatment of LAS seems to have similar success rate for more than three decades. The vast majority of publications have reported the utility and superiority of EGS to other therapeutic modalities. Therefore, it is safe to conclude that EGS is an effective treatment option in a selected group of patients with levator ani syndrome offering moderate or complete symptomatic relief in 45% of patients with essentially no risk. Analysis of our data confirms that the more EGS sessions performed yields more successful symptom relief based on visual analog pain scales. The results also showed that patients who had other treatments prior to EGS benefited less from it. Due to the safety profile and moderate efficacy, EGS should be considered as a treatment option for levator ani syndrome.

Conflict of interest

The authors have no conflict of interest to report.

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Case Report Open Access

A Case of Acute Necrotizing Pancreatitis Complicated by Portal Vein Thrombosis

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Abstract

Portal vein thrombosis is an unusual complication of acute pancreatitis. It occurs in some cases of severe acute pancreatitis particularly those associated with pancreatic necrosis. A review of relevant literature suggests a role of anticoagulants in such cases but further studies are needed to establish the advantage of such therapy conclusively. We present a case of acute necrotizing pancreatitis complicated by portal and splenic vein thrombosis managed with anticoagulants. This resulted in recovery without development of portal hypertension and its complications.

Keywords: Acute necrotizing pancreatitis; Portal vein thrombosis

Introduction

Portal vein thrombosis is an unusual complication of acute pancreatitis. It occurs in some cases of severe acute pancreatitis particularly those associated with pancreatic necrosis. Role of anticoagulants in such cases is not well established [1]. We present a case of acute necrotizing pancreatitis complicated by portal and splenic vein thrombosis managed with anticoagulants which resulted in recovery without development of portal hypertension and its complications.

Case Report

A 20 years old boy presented to surgery emergency ward of our hospital with complaints of severe abdominal pain predominantly in epigastric region and repeated vomiting for last six days. He was being treated at a peripheral health centre so far but, as the symptoms became more severe he was referred to our hospital. There was no history of similar pain in past but he used to have some abdominal discomfort occasionally. He was a known alcoholic and used to consume alcohol in moderate amount regularly. On examination he was conscious and oriented. He had a pulse rate of 110/min and his blood pressure was 110/60 mm of Hg. A nasogastric tube and a Foley's catheter were already in place. After initial care he was subjected to laboratory and radiological investigation. He was having a total leukocyte count of 14,000/microlitre. His serum amylase was 946 U/L and serum lipase was 262 U/L. An X-ray of abdomen showed dilated bowel loops with few air-fluid levels and the X-ray chest showed mild left sided pleural effusion. An ultrasound of abdomen was done which did not reveal any significant abnormality. But in view of a strong clinical possibility of acute pancreatitis a contrast enhanced CT scan of abdomen was done. It revealed a bulky pancreas with multiple hypodense areas suggestive of pancreatic necrosis. Another striking feature was the presence of a thrombus in the portal vein and the splenic vein (Figure 1). The patient was shifted to intensive care unit and was managed conservatively. He was put on injection Meropenem one gram intravenously eight hourly. In view of portal vein thrombosis he was put on low molecular weight heparin for initial few days. The patient continued to have paralytic ileus for a few days with a persistent complaint of abdominal distension but had a smooth recovery thereafter. Once orally allowed he was switched to oral anticoagulants and was later on discharged from the hospital. Later on he developed a pseudocyst for cystogastrostomy was done. A follow up CT scan of abdomen showed the thrombus to have resolved and the patient did not develop features of portal hypertension.

Discussion

Acute pancreatitis has a variable clinical course regardless of its etiology. Most cases are self-limited. But approximately one quarter of patients develop vascular complications. The most common complications are hemorrhage into a pseudocyst, erosion of upper gastrointestinal arteries, thrombosis of the portal venous system, formation of varices or pseudoaneurysms and rupture of a pseudoaneurysm [1]. Splanchnic vein thrombosis is an unusual complication of acute pancreatitis and is particularly seen in association with necrotizing pancreatitis. It is rare in absence of pancreatic necrosis [2]. It may include thrombosis of one or more of splenic vein, portal vein and superior mesenteric vein. Isolated splenic vein thrombosis is relatively common but portal and superior mesenteric vein thrombosis are much less common [3]. In our case both splenic and portal veins were thrombosed.

Although splanchnic vein thrombosis is often an incidental finding on imaging in cases of acute necrotizing pancreatitis, its significance lies in the potentially fatal consequences. These include portal hypertension, and its complications especially upper GI bleed, small bowel ischaemia and liver failure. Although splanchnic vein thrombosis is assumed to arise usually in association with hypercoagulable state but in cases of acute pancreatitis the thrombosis of splanchnic veins probably occurs as a direct result of inflammation in the vicinity [3,4].

The role of early institution of anticoagulation in such cases is controversial [4,5]. The European Network for Vascular Disorders of the Liver (EN-Vie) recommends the utilization of anticoagulation early in patients with acute PV thrombosis in non-cirrhotic, non-malignant patients [5]. The rate of recanalization is higher if anticoagulants are started earlier [3]. But the use of anticoagulants in this scenario

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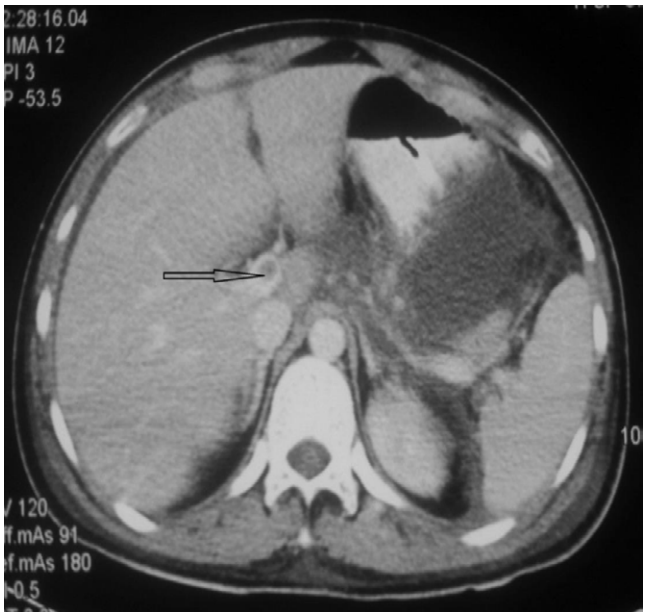

Figure 1: CECT image of abdomen showing portal vein thrombosis with acute pancreatitis.

poses challenge as these patients are at increased risk of hemorrhage because of pseudoaneurysms and the need for surgical interventions for management of pancreatic necrosis and abscess [4]. Nevertheless available evidence favors the use of anticoagulants and we used first the low molecular weight heparin followed by oral anticoagulant for three months. Review CT scan done three months later showed recanalization of portal vein and although the patient developed a pseudocyst he, at no point of time, showed any evidence of portal hypertension or development of varices. But certainly randomized controlled trials are needed to establish the role of anticoagulants in such cases.

Conclusions

Splanchnic vein thrombosis is an unusual complication of acute pancreatitis and is seen particularly in cases complicated by pancreatic necrosis. Although in our case institution of anticoagulants resulted in recovery without development of portal hypertension, randomized trials are required to establish the exact role of such therapy in case of splanchnic vein thrombosis.

Conflict of Interests

Authors have no conflict of interests to disclose.

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Case Report Open Access

"Damage Control" Esophagogastrectomy in Case of Perforated and Bleeding Gastroesophageal Cancer

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Abstract

Introduction: The term "damage control surgery" or "laparotomie écourtée" is not a new concept, but a recent paradigm in the surgery of abdominal trauma, when the ability to maintain homeostasis is impaired due to severe hemorrhage. It can be defined as a surgical method that prevents the trauma triad of death by hemorrhage control and the prevention of peritoneal contamination, while time is an essential factor. Damage control surgery is followed by vigorous resuscitation and definitive reconstruction. The concept of "damage - control" is less reflected in the literature related to surgical oncology. **Case Presentation:** A 45-year-old patient, BMI 35, presented to the Emergency Services of the Regional Hospital with abundant hematemesis and shock. The patient had been previously diagnosed with adenocarcinoma of the gastroesophageal junction subsequent to CT scan and endoscopic evaluation and was under the way to complete surgical - oncological balance with scheduled neoadjuvant chemotherapy due to the size and extension of the tumor. Emergency gastroscopy revealed an accumulation of blood in the stomach with ongoing massive hemorrhage while emergency CT scan revealed left hemopneumothorax and hemoperitoneum. Due to the hemorrhagic shock caused by hemodynamic collapse, the patient was performed emergency damage control esophagogastrectomy in the same block with the esophageal hiatus and liver segment 2. Thus the greater curvature of the stomach was preserved, stapled, as well as the intrathoracic esophageal stump and jejunostomy for alimentation were performed. During evolution, several interventions were performed sequentially: hemostasis by packing for hemorrhage control in the hiatal area (day 0), depacking (day 3), left pleural drainage (day 5), left cervicostomy for salivary drainage (day 8), right transthoracic esophagogastric anastomoses by using the Ivor-Lewis technique (day 63) and esophagogastric stenting for the treatment of anastomotic fistula (day 71). **Results:** Final evolution after three months of hospitalization, seven surgical interventions, more than 20 units of transfusion, is favorable. The jejunostomy tube was removed on day 95, after resuming in advance oral nutrition in parallel with enteral feeding, cervicotomy closed spontaneously. The esophageal stent was removed 6 months after placement. The pathological examination revealed a G3 poorly differentiated intestinal-type gastric adenocarcinoma (Lauren classification), which infiltrated the last 4 cm of the esophagus and 6 cm of the superior gastric pole towards the lesser curvature of the stomach (pT4N2M0). The patient underwent 6 cycles of adjuvant chemotherapy with DCF, 1 year and 6 months postoperatively becoming disease free and fully reintegrated from the social-professional point of view. **Conclusion:** The presented case is a "damage control" type model approach in an imminent life-threatening situation, which successfully implements the principles of traumatology in case of a complex oncology situation and also a multidisciplinary model of approach and collaboration between multiple hospital units for saving a young cancer patient's life.

Keywords: Damage control; Perforated gastric cancer; Emergency esophagogastrectomy

Motto: *"In life-threatening situations, prognosis improved when surgeons learned not to exaggerate with doing too much to patients."*

H. Bismuth *Damage control laparotomy*

Introduction

Back in the 90's "damage control surgery" or "laparotomie ecourtée" or "abbreviated laparotomy" was described as a life-saving technique in cases of severe abdominal traumas inspired by liver traumatology where perihepatic packing dramatically improved patient's survival rate [1]. Later, the same methods were "borrowed" for other major non-traumatic life-threatening situations such as severe postoperative bleeding or sepsis [2,3]. References to damage control surgery in case of cancer management are extremely rare in the literature, hence the particularity of this case.

Case Presentation

In June 2012, a 45-year-old obese patient, BMI (Body Mass Index)

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of 35 kg/m^2, presented at the Cardiology Department complaining of retrosternal pain, weight loss, fatigue and anorexia. The results of the cardiology investigations were within normal limits, exams continued with native abdominal CT, which revealed an important thickening of the gastric wall at the level of the upper pole, lesser curvature and terminal esophagus (Figure 1).

The primary gastroscopy showed a semi-circumferential lesion in the lower esophagus, the examination of the stomach could not be completed due to lack of cooperation. The patient was diagnosed with inferior esophageal cancer without retroversion examination. Due to mismatches in the CT-endoscopy results, the CT-scan was repeated with oral and i.v. contrast, which confirmed the presence of a massive gastroesophageal tumor that dilated and invaded the diaphragmatic hiatus and had no cleavage plane with the juxta-hiatal left hepatic lobe. The second gastroscopy highlighted the gastric tumor too and a biopsy sample was also prelevated.

Given the size and local-regional extension of the tumor, the patient's age and very good biological characteristics, the surgical oncology colloquium decided that the patient should be treated by neoadjuvant chemotherapy followed by radical surgery.

The proposed strategy could not be followed due to a complication that suddenly occurred at home. The patient was brought to the emergency room of the Regional Emergency Hospital with massive hematemesis and shock. An intensive care therapy was started concomitant with several exams. The upper gastrointestinal endoscopy revealed a large amount of fresh blood in the esophagus, the stomach was filled with fresh blood and clots which prevented the examination of the lining. This case proved to be beyond endoscopic therapeutic resources. The thoraco-abdominal CT scan (Figure 1) showed: left hemopneumothorax of 13 cm in diameter, mediastinum shifted to the right, esophageal dilation in the region of the aortic arch with anfractuous contour and air around the cardia region, (possible perforation site) and pneumoperitoneum. Laboratory results on admission: Hb 8.6 g/dL, Htc 27.9%, platelets 416 000/mm^3 rapidly degrading to 5.5 g/dL Hb and 15% Htc, Ph 7.097, base excess -11.8 mmol/L indicating progressive hemodynamic deterioration. Emergency surgery was decided immediately for hemostatic reasons; the proposed strategy was damage control esophagogastrectomy.

Day 0, 18:25 hour

We performed bisubcostal laparotomy incision, while the patient was agonizing before intubation, his blood pressure was 70/55 mmHg and pulse rate 153/min. We positioned the Thompson retractor and identified a massive tension hemoperitoneum ("moribond à gros ventre") of over 2000 mL, which was immediately removed. Subsequently we detected an perforated gastric tumor, with a niche of more than 3 cm, while the stomach and terminal esophagus were a mass of blood clots. We performed a rapid evacuation of the stomach content and temporary hemostasis with intraluminal manual compression. After hemodynamic stabilization, we used intraluminal tamponade. After ensuring the eso-gastric junction from exposure, the intervention continued with the skeletonization of the upper gastric pole by using a 10 mm termofusion vessel sealing device, the resection of the diaphragmatic hiatus adherent to the tumor and of a portion of the hepatic segment II adherent to the tumor. The transhiatal preparation of the intrathoracic esophagus continued which was then stapled transversally by using a 60 mm stapler at about 3 cm cranially from the macroscopic edge of the tumor. Subsequently a gastric upper polar resection was performed, preserving most of the greater curvature and cutting more of the lesser curvature at the same time doing locoregional lymph node dissection. The stomach was completely closed by using 3 60 mm staplers. In the final stage of the intervention we performed Albert feeding jejunostomy with double subhepatic and juxta-hiatal drainage. A naso-esophageal tube was also positioned at the level of the esophageal stapled stump. The intervention lasted for 90 minutes and the parameters after transfusion on exit from the operating theatre were: blood pressure at 111/70 mmHg, pulse rate at 135/min, Hb at 6 g/dL, Htc at 15.8%, pH at 7.24, base excess -6 5 mmol/L.

Day 0, 00:45 hour

Reoperation was necessary because of hemorrhage (1500 mL) through the two drains. Diffuse bleeding ("biological" not "surgical" bleeding) was identified in the area of the diaphragmatic hiatus, followed by the evacuation of the hemoperitoneum, lavage with warm fluids and local packing, laparorrhaphy just on the anterior rectus sheath to prevent compartment syndrome. Postoperative course was favorable; the total amount of transfusions in the first 24 hours was of 15 units of packed red blood cells and 14 units of fresh plasma.

The pathological examination of the sample collected during esophagogastrectomy revealed a poorly differentiated adenocarcinoma

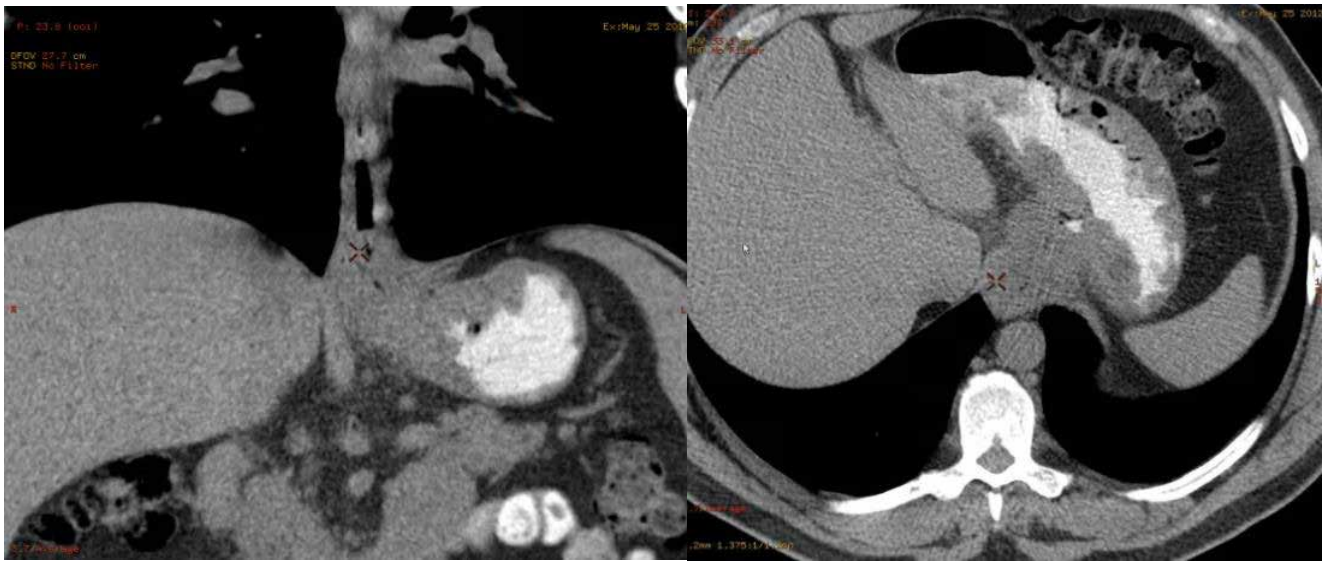

Figure 1: Initial CT showing a stenosing esophagogastric bulky mass.

(G_3) of intestinal type (Lauren classification) that invaded all layers of the cardia, presenting a central perforation, the invasion of the hiatal muscle and adjacent hepatic parenchyma. The tumor was 4 cm long at the level of the terminal esophagus and its overall dimensions were 12 x 7 cm. There were 22 lymph nodes examined in total, out of which three presented metastatic adenocarcinoma with infiltration beyond the capsule. There were no lymphatic emboli, only the signs of perivascular and perineural invasion; the stage was pT4N2Mx.

Day 3

Reintervention was performed for depacking, lavage and drainage, while no active sources were observed. Unfortunately the naso-oesophageal tube had been removed accidentally during postoperative transfer, which had negative consequences afterward.

Day 5

The patient presented fever, dyspnea, inflammatory syndrome, the chest X-ray showed left-sided pleural effusion. Left pleural drainage evacuated about 700 mL hemato-purulent fluid. In the absence of the naso-esophageal tube, we suspected the presence of a left esophageal-pleural stump fistula, which was confirmed on day 6 with a hydro soluble contrast passage.

Day 7

The intervention for cervicostomy of salivary drainage was relatively difficult due to obesity and the depth of the intervention. We used a silicone drainage rod. The esophagus subjacent to the silicone rod was ligated with two relatively loose PDS® sutures, so that they could not have produced ischemia and sectioning of the esophagus. The opened esophagus, superior to the stent, was attached to the skin with crown PDS® 3-0 sutures. The patient experienced postoperative recurrent palsy syndrome associated with dysphonia and tirage and dyspnea with spontaneously favorable evolution in about 4 weeks. The pleural drain was suppressed 14 days after cervicotomy, when the drainage was stopped.

Preparing thoracic intervention

This stage consisted of combined parenteral and enteral nutrition over a period of two months. During this time the patient was hospitalized in the ICU for over 50 days, and then transferred to the general ward 7 days preoperatively.

The list of medical problems prior to reconstructive surgery comprised the followings:

1. Despite enteral and parenteral nutrition the patient had a poor nutritional status. Because of multiple septic foci the patient had lost about 15 kg and proteinemia oscillated between 5.2 and maximum 5.7 g/dL. A persistent diarrhea syndrome secondary to enteral feeding created difficulties in managing the enteral route.

2. Foci of infection: initially left pleural effusion by esophago-pleural fistula with *Enterococcus faecalis* revealed in culture, then infection of the operative abdominal wound due to repeated interventions and episodes of septicemia caused by immunosuppression (initial oncological disease associated with prolonged hospitalization and series of abdominal surgery and transfusions), isolation of *Klebisella pneumoniae* ESBL + followed by a central venous catheter sepsis with positive cultures of multi-resistant *Pseudomonas aeruginosa, Acinetobacter spp*. and methicillin-resistant *Staphylococcus aureus* (MRSA) sampled from the site of the catheter. The following germs were sampled at the level of the cutaneous insertion of the jejunostomy: non-ESBL producing *Escherichia coli*, multi-resistant *Serratia rubidaea, Pseudomonas spp* and *Candida krusei* (natural resistance to fluconazole, sensitive to amphotericin B, itraconazole). These infectious episodes required prolonged antibiotic therapy, adapted according to the antibiogram and the high level resistance of isolated germs to basic antibiotics (ceftriaxone + metronidazole, augmentin, vancomycin, imipenem + linezolid, fluconazole, subsequently itraconazole then finally trimethoprim-sulfamethoxazole). Regarding all these infectious problems the evolution of the patient was favorable. There were no signs of clinical or biological parameters suggesting infection before reconstructive surgery.

Timeline of reconstructive surgery

24 hours before surgery we carried out a cervical exploration. We removed the wires used for esophageal ligation and established the integrity of the cervical esophagus.

Abdominal assessment consisted of exhaustive adhesiolysis, complete discharge of the gastric tube, total duodeno-pancreatic mobilisation, extramucosal pyloromyotomy by re-laparotomy. Permeability was manually regenerated in the completely closed esophageal hiatus by performing combined thoracic and abdominal intervention.

The next step of the intervention on the time line was a thoracic intervention (Ivor-Lewis) consisted of right inferior posterolateral thoracotomy in the seventh intercostal space, the identification and isolation of the inferior esophagus below the azygos vein, the resection of an oesophageal sample of about 3 cm (the resection margins were free of tumor according to the initial histopathological results), the insertion of a gastric tube through a transhiatal intrathoracic approach and biplane esogastric termino-terminal anastomosis with running suture (3-0 Prolene® externally, PDS® 3-0 internally). Passive right chest drainage and abdominal drainage were applied. The ascending stomach was anchored to the prevertebral fascia in an unstressed position. The consistency of the gastric tube was carton-like, without flexibility and length in comparison to the initial operation, this issue being one of the disadvantages of a two-step approach.

Immediate postoperative evolution was favorable, the patient was extubated in the evening of the surgery. Due to low-dose parenteral and enteral protein intake proteinemia decreased to 4.8 mg/dL. On day 7 postoperatively there was a quantitative increase of the right pleural drainage and the oral administration of methylene blue revealed the extravasation of dye through chest drainage without altering the patient's general condition. So we had two options: 1) to re-operate the patient for the removal of the anastomosis and return to the initial status or, 2) to manage the patient conservatively by placing an esophageal endoprosthesis. As the general condition was stable, we opted for the second alternative; so the patient was referred to a gastroenterological unit and stenting of the anastomosis using a 10 cm waterproof stent was performed (Figure 2).

Post-procedural follow-up was immediately favorable thus oral feeding with liquids was reintroduced in about 48 hours, the pleural drain was removed on day 14 and feeding jejunostomy at four weeks after surgery.

Patient received adjuvant chemotherapy, 6 cycles of DCF (docetaxel 75 mg/m^2 day 1, Cisplatin 75 mg/m^2 day 1, 5-Fluorouracil 750 mg/m^2/day day 1- 4 continuously) and underwent repeated imagistic follow-up (CT, MRI) (Figure 3). The patient did not show any clinic, imagistic and biologic signs of relapse 18 months after to surgery. The stent was suppressed 6 months after installation with no particular difficulties and cervicotomy closed spontaneously (Figure 4). The patient is presently fully reintegrated from the social-professional point of view.

Discussions

"Damage Control Surgery" addresses dramatic cases with severe active bleeding and hemodynamic instability in cases when death is imminent and is defined as a short-term intervention limited to lesion control. It comprises a series of physio-pathogenic aspects: heavy bleeding, massive transfusion, hypothermia and consumption coagu-

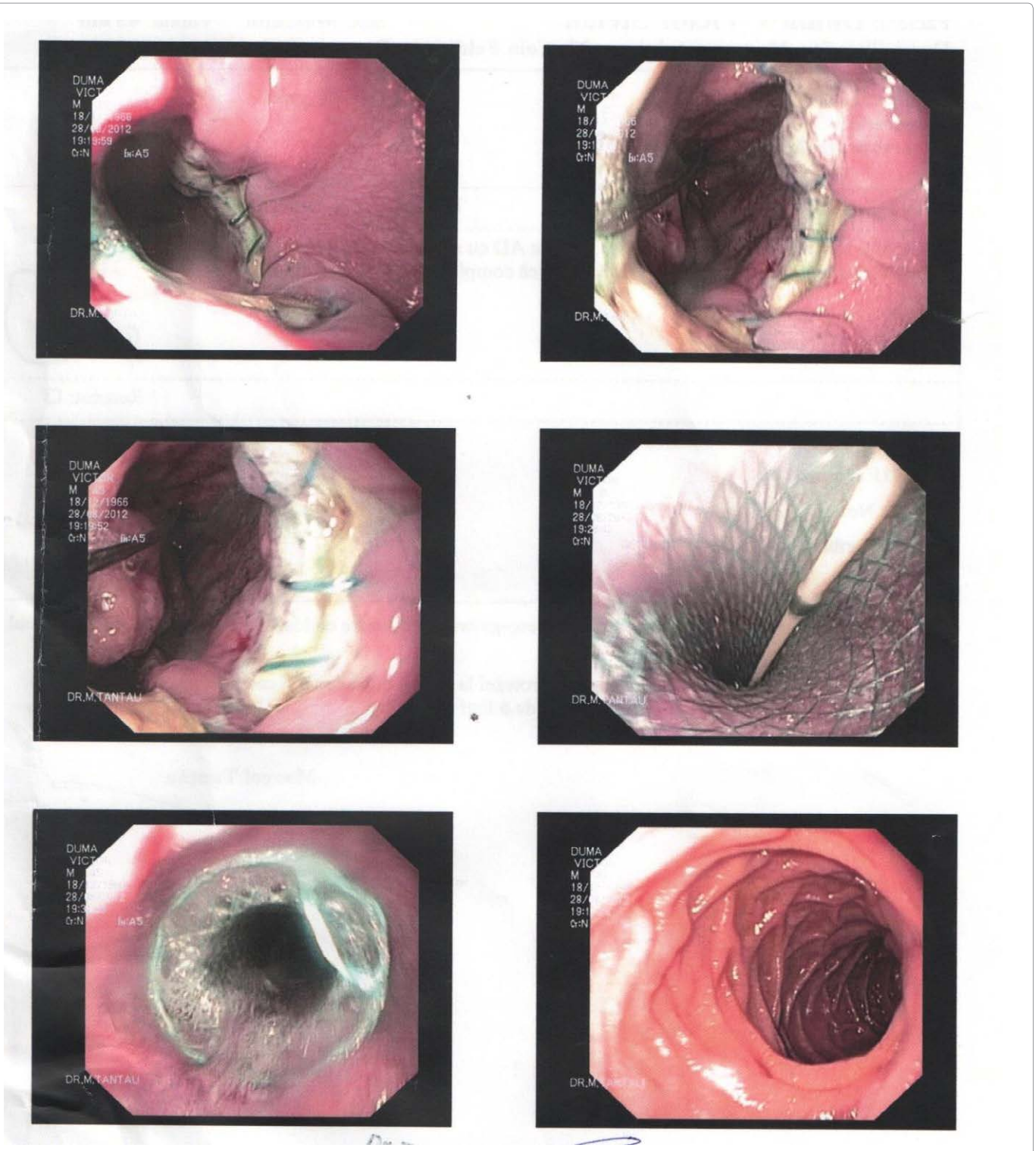

Figure 2: Endoscopic aspect of the minimal anterior anastomotic dehiscence. Mounting the stent.

lopathy responsible for the so-called "biological hemorrhage" which is not "surgical hemorrhage" [4]. There are many severity and risk factors with prognostic values in relation to coagulopathy, all being positive in this case: hypotension below 70 mmHg, active bleeding requiring minimum 2 units/ h, massive transfusion of more than 5 units, hypothermia below 34°C and acidosis with a pH value below 7.25. [4-6]

The main goal of the intervention was: to achieve rapid homeostasis by removing the damaged body part and the secondary purpose was to avoid the contamination of the peritoneal cavity by stapling the digestive lumens or external drainage through the stomas without the restoration of digestive continuity. This was followed by vigorous resuscitation, hypothermia, acidosis and coagulation disorders had to be controlled and only then reconstructive surgery performed.

In the literature the term damage control is scarcely met for non-traumatic situations, in the surgery of colic diverticular perforation or the surgery of the pancreas and in cases of re-interventions for hemorrhage or sepsis following the Whipple procedure [2,3].

Spontaneous rupture of gastric tumors with hemoperitoneum and

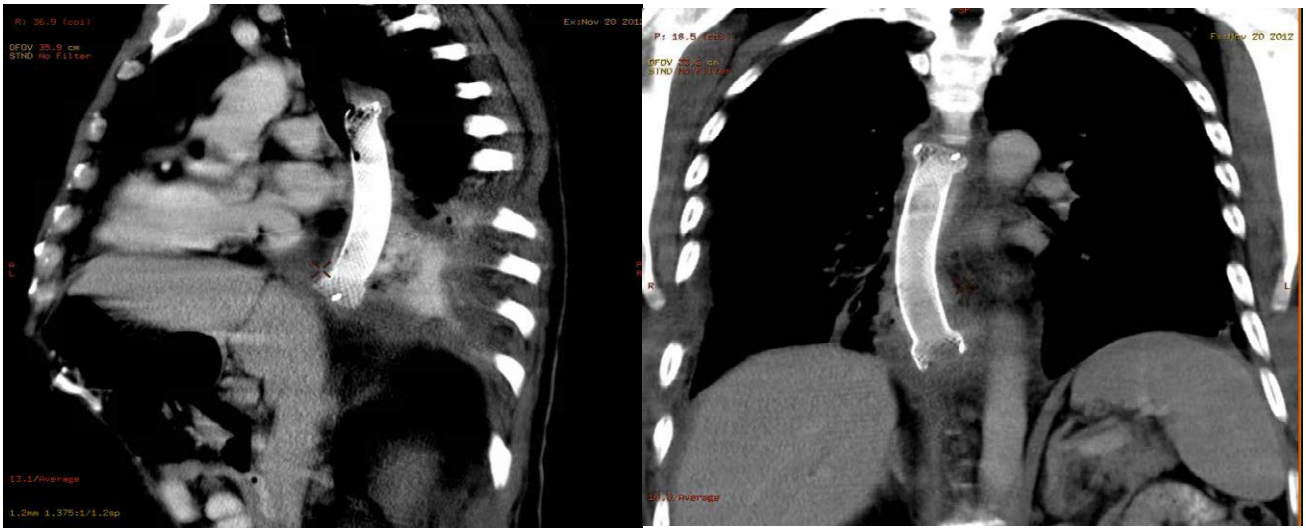

Figure 3: CT images 3 months after surgery; stent in position.

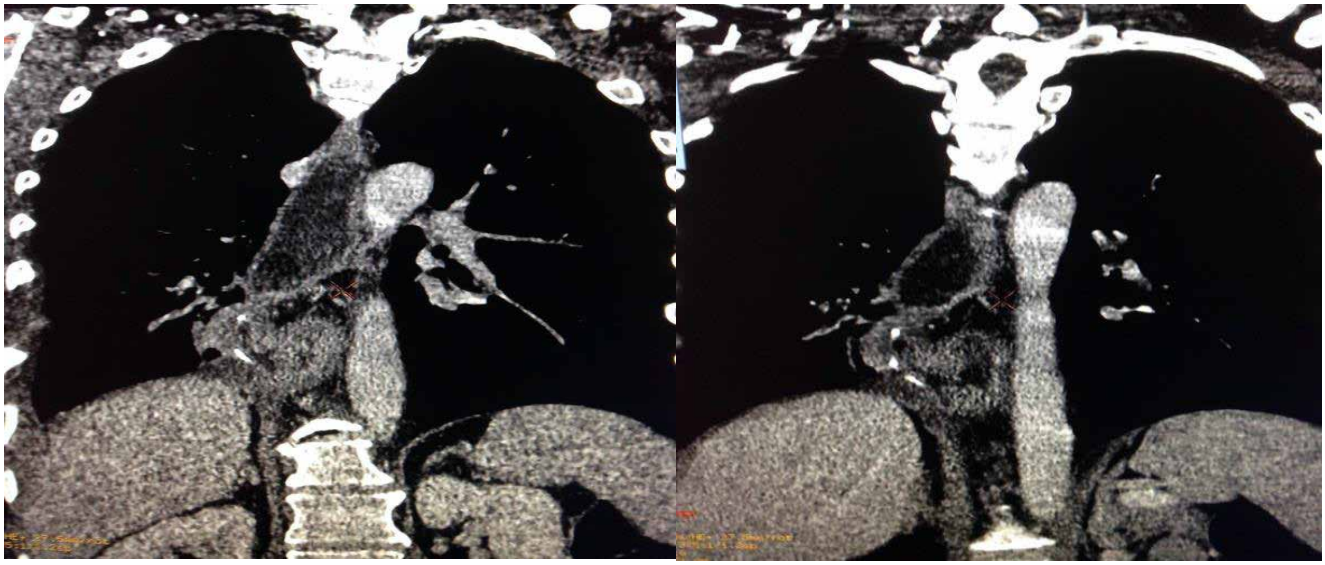

Figure 4: Chest CT scan: esogastric anastomosis after the stent removal; there are no signs of recurrence 18 months postoperatively.

gastrointestinal bleeding is a very rare and very severe clinical entity, case in which surgery is the only therapeutic solution. In our case, the final outcome, the survival of the patient and R_0 character of the surgical resection performed under the condition of an imminent catastrophe are arguments for the rightness of the attitude we opted for. Because the patient was young with preserved biological resources despite the advanced character of the disease, our therapeutic goals were the following: 1) to save the patient's life by achieving homeostasis, than 2) to restore digestive continuity and presently 3) to obtain a disease-free life as long as possible.

We would like to emphasis the importance of a multidisciplinary team: surgeon, anesthesiologist-reanimator, radiologist, gastroenterologist, infectious disease specialist, especially for solving non-surgical postoperative complications, which in our case was the stenting of the esogastric anastomosis, this way avoiding the surgical removal of the anastomosis and return to the initial situation, which significantly shortened recovery time in the patient.

Conclusions

This case is an example of "damage control" adopted in surgical oncology in case of an imminent life-threatening situation. The joined effort of four hospitals in three counties, which meant 7 interventions under general anesthesia, three months in the hospital, 60 days of intensive care, saved the patient's life.

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Conflict of Interests

Authors heave no conflict of interests to disclose.

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Case Report Open Access

Malignant Paraganglioma; a Story of a Long Time Survival

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Abstract

Pheochromocytoma and paraganglioma are catecholamine secreting tumors. Malignancy is uncommon - approximately 10% for pheochromocytoma and 20% for paraganglyoma. Surgery, when possible, is the first line treatment. Prognosis is poor because of a frequent local recurrence and/or metastases and the lack of specific chemotherapeutic agents. We report the case of a 60 years old man who was hospitalized at the age of 48 for episodes of paroxystic hypertension with spells. The high levels of vanillylmandelic acid (VMA), more than 50 mg/24h at 3 determinations, confirmed the excess of catecholamine, but the CT scan failed to reveal the tumor. The iodine-131-meta-iodobenzylguanidine (I-MIBG) scintigraphy showed the presence of a 1.5 cm nodule in the left abdominal para-aortic region. The patient refused surgery and had a satisfactory evolution with antihypertensive therapy. 11 years later he was admitted in the Vascular Surgery Department for acute ischemia of inferior limbs; a voluminous para-aortic tumor was diagnosed and resected. The pathology confirmed paraganglioma and described some atypical cells without being able to discriminate between benign or malignant pattern. Anamnesis could not identify any other case in the family. After another year he was admitted in the Endocrine Department for the reappearance of the adrenergic syndrome, with VMA at 30.8 mg/24h. The thoracic and abdominal CT-scan showed abdominal and thoracic metastatic tumors. The patient was referred to a specialized center were octeotride scintigraphy confirmed local recurrence and metastatic tumors in the lungs. He was treated with Sunitinib with a good initial response and he died after 16 years from the initial diagnostic of paraganglioma.

Keywords: Paraganlioma; pheochromocytoma; Surgery; Adrenergic syndrome; Long term outcome

Introduction

Pheochromocytoma and paraganglioma are catecholamine secreting tumors. The term of pheocromocytome is reserved to intra-adrenal tumors, the tumors derived from extraadrenal cromaphine cells being defined as paragnagliomas. [1,2]. The distinction between pheochromocytoma and paraganglioma is important because of its implications: evolution, risk for malignancy, and genetic testing [1]. Catecholamine-secreting tumors are rare, with an annual incidence of 2 to 8 cases per 1 million people [3]. Based on screening studies for secondary causes of hypertension in outpatients, the prevalence of pheochromocytoma has been estimated at 0.1% to 0.6% [4-7].

Paragangliomas, representing 10% of the catecholamine secreting tumors, are also characterized by their site: along the paraaortic sympathetic chain, within the organ of Zuckerkandl (at the origin of the inferior mesenteric artery), in the wall of the urinary bladder, and along the sympathetic chain in the neck or mediastinum. During early postnatal life, the extra-adrenal sympathetic paraganglionary tissues are prominent; later they degenerate, leaving residual foci associated with the vagus nerves, carotid vessels, aortic arch, pulmonary vessels, and mesenteric arteries. Odd locations for paragangliomas include the neck, intra-atrial cardiac septum, spermatic cord, vagina, scrotum, and sacrococcygeal region [1,8]. Paragangliomas in the head and neck region (e.g. carotid body tumors, glomus tumors, chemodectoma) usually arise from parasympathetic tissue and typically do not hypersecrete catecholamines (CA) and metanephrines (MN) [8,9]. On the other hand paragangliomas of the mediastinum, abdomen, and pelvis usually arise from sympathetic chromaffin tissue and do hypersecrete CA and MN [8,9].

Recent genetic advances helped to recognize the genetic origin of 1/3 of malignant pheochromocytoma and paragnagliioma. Hereditary catecholamine-secreting tumors typically manifest at a younger age than sporadic neoplasms do. Sporadic pheochromocytoma typically is diagnosed on the basis of symptoms or as an incidental discovery on CT or MRI, whereas syndromic pheochromocytoma (associated with familial syndromes like multiple endocrine neoplasia, von Hippel Lindau syndrome or neurofibromatosis type 1) is frequently diagnosed earlier in the course of disease as a result of biochemical surveillance or genetic testing [1,10].

Approximately 15% to 25% of patients with catecholamine secreting tumors have germline mutations (inherited mutations present in all cells of the body). Paragangliomas are characterized by loss of function mutation in the subunits A, B, C, and D subunits of succinate dehydrogenase suunit B gene, and a mitochondrial enzymatic complex. The affected subunit seams to determine the clinical features of the disease and the risk of malignancy [10,11].

Case Report

We report the case of a 60 years old man who was hospitalized

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at the age of 48 for episodes of paroxystic hypertension with spells. Anamnesis could not identify any other case in the family. The high levels of VMA (>50 mg/24 h at 3 determinations) confirmed the catecholamine excess, but the abdominal scanner was not diagnostic. The Iode Metaiodobenzylguanidine (I-mIBG) scintigraphy showed the presence of a 1.5 cm nodule in the left abdominal para aortic region (Figure 1). The patient refused surgery and had a satisfactory evolution with triple association of antihypertensive therapy.

After 11 years he was admitted in the Vascular Surgery Department for acute ischemia of the inferior limbs due to a voluminous para aortic tumor, which was resected. The pathology exam confirmed paraganglioma and described some atypical cells without being able to discriminate between benign or malignant pattern (Table I). At that time no endocrinological or cardiological control was performed.

After another one year he was admitted in the Endocrine Department for the re occurrence of the adrenergic syndrome (dyspnea, tremor, fatigue, weight loss, ventricular arrhythmia, hypertension with paroxystic episodes). The VMA was at 30.8 mg/24 h.

The thoracic and abdominal CT-scan showed abdominal and thoracic metastatic tumors (Figures 2-4). The patient was referred to a specialized center were octreotide scintigraphy confirmed local recurrence and metastatic tumors in the lungs. He was proposed for therapy with Sunitinib with an initial good evolution. He died after 16 years from the initial diagnostic of paraganglioma.

Discussion

Paragangliomas are extra-adrenal tumors of neural crest-derived paraganglia that exist throughout the body in the distribution of the sympathetic and parasympathetic nervous [1]. The immunohistochemical markers, chromogranin and synaptophysin immunoreactivity proved to be diagnostically useful, allowing, together with the absence of immunoreactivity for inhibin and melan A, an unequivocal diagnosis of cathecolamine secreting tumors without discrimination between benign or malignant. To note, the mean count of sustentacular S-100 positive cells is lower in malignant than in benign pheocromocytomas [12].

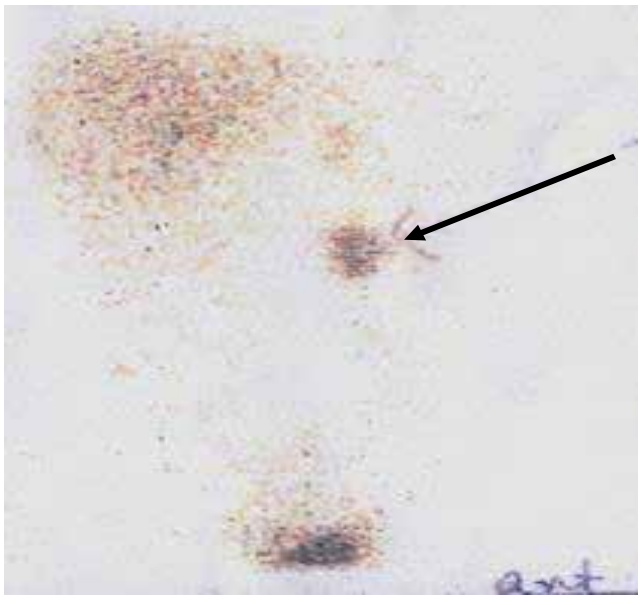

Figure 1: I^{123}-mIBG scintigraphy showing para aortic tumor.

Table I: Tumor immunohistochemical pattern.

Parameter	Result
MNF116	Negative
Chromogranin	Low positivity
Synaptophysin	Low positivity
Neuron specific enolase	Low positivity
S100 protein	Positivity in sustentacular cells
Ki67	Rarely positive

Figure 2: Chest X-ray: disseminated pulmonary nodules.

Figure 3: Thoracic CT-scan: disseminated pulmonary nodules.

Figure 4: Abdominal CT-scan: abdominal recurrence.

Since there are no discriminatory markers for benign or malignant paraganglioma, the diagnosis of malignancy is established by demonstrating local tumor invasion or the presence of metastatic tumor at sites not known to contain chromaffin tissue. It is equally difficult to differentiate between malignant and benign tumors based on histological data since metastasis may be produced by histologically mature neoplasms [13]. In the presented case histological aspects and immunohistochemistry failed to establish the benign or malign pattern of the tumor.

Malignant paragangliomas have been well described in carriers of mutations of the succinate dehydrogenase B (SDHB) gene, but have rarely been associated with mutations in the succinate dehydrogenase D (SDHD) gene [14]. The mutations in SDHB may be associated with metastatic, clinically indolent, abdominal paraganglioma in some families [15]. The long evolution of the disease suggests that SDHB was the probable mutation in our case, but we did not have the possibility of genetic tests. He had 11 years of survival without any specific treatment (surgical or chemotherapy). After this period the adrenergic syndrome reappeared and the thoracic and abdominal CT-scan showed abdominal and metastatic tumors. He started therapy with Sunitinib with a good initial response and he died 4 years later.

Metastatic pheochromocytomas and paragangliomas are associated with increased angiogenesis. Sunitinib is an oral multitargeted receptor tyrosine-kinase inhibitor with antiangiogenic and antitumor activity, which targets platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factors (VEGFR) 1 and 2, KIT, FLT3, and RET. This agent might be one therapeutic strategy for malignant pheochromocytomas and paragangliomas [11,16].

Formerly, survival rate in malignant paraganglioma with distant metastases was considered quite low (12-34% at 5 years). According to the recent literature, 5 years survival rate for patients with malignant catecholamine-secreting paragangliomas is significantly higher, 74%. However, all these data are for patients who have been operated [17]. A recent study on 17 patients with progressive metastatic pheochromocytoma and paraganglioma showed an overall survival 0f 26.7 months with a progrerssion-free survival of 4.1 months [11].

Improvements in disease recognition and diagnosis over the past decades allow earlier diagnostic and treatment, and better survival. Nevertheless, many tumors remain unrecognized until they cause severe complications [18]. Nowadays in pheochromocytoma and paraganglioma 18F-FDG PET/CT is a superior tool in the localization of recurrent tumors [19].

Standard therapies (advanced surgery, radiometabolic therapy, chemotherapy and radiotherapy) have revealed suboptimal results in tumor size reduction and survival rate. Currently, there is no standard therapeutic protocol and thus some patients end up with overtreatment while others are undertreated. An effective molecular target therapy aiming at permanent control of these highly complex neoplasms should be the aim of future efforts [20].

Patients with progressive metastatic tumors and overwhelming symptoms are currently treated with systemic chemotherapy and radiopharmaceutical agents such as metaiodobenzylguanidine [21]. These therapies lead to partial radiographic response, disease stabilization, and symptomatic improvement in approximately 40% patients, and are associated with a modest improvement in overall survival duration [22]. Over the past decade, substantial progress has been made in clinical, biochemical, and radiographic diagnosis of pheochromocytomas and sympathetic paragangliomas. Approximately 50 % of patients with malignant pheochromocytomas and sympathetic paragangliomas have been found to carry hereditary germline mutations in the succinate dehydrogenase subunit B gene (SDHB), and anti-angiogenic agents such as sunitinib have been found to potentially play a role in the treatment of malignant disease, especially in patients with SDHB mutations. In some patients, treatment with sunitinib has been associated with partial radiographic response, disease stabilization, decreased fluorodeoxyglucose uptake on positron emission tomography, and improved blood pressure control. These findings have led to the development of prospective clinical trials of new targeted therapies for metastatic disease [23].

A significant reduction in tumor volume of the malignant paraganglioma was observed when using sorafenib, a novel multi-tyrosine kinase inhibitor that targets angiogenesis, the Raf-kinase pathway, the platelet-derived growth factor Ret, and c-Kit [24]. Recent molecular characterization of pheochromocytoma suggests new treatment options with targeted therapies, such as 90 kDa heat shock protein (Hsp90) can be a potential therapeutic treatement for advanced pheochromocytoma [25].

Conclusion

The diagnosis of malignant pheochromocytoma and paraganglioma is challenging, since there is no a specific marker (molecular or histological) and the diagnosis remains a retrospective one, based on the presence of metastasis. Due to the rarity of the disease, the survival rate in these patients remains difficult to appreciate. Advances in molecular genetics helped in a more accurate evaluation of the malignant potential and in finding targeted therapy addressed to molecular mechanisms responsible of the initiation and progression of the malignant process. Thyrosine kinase inhibitors like sunitinib may induce a significant amelioration of survival rate, inducing disease stabilization in some patients. Prospective multi-center studies are needed in order to evaluate the efficacy of targeted molecular therapy in these rare diseases.

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Conflict of Interests

Authors have no conflict of interests to disclose.

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Case Report Open Access

Theoretical and Practical Considerations in Colo-Rectal Diverticulosis Complicated with Multiple Sigmoido-Recto-Vesical Fistulas

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Abstract

Although there is a complete anatomical separation between urinary and digestive tract, in certain pathological conditions, the direct proximity between the bladder and the sigmoid colon allows the development of entero-vesical fistulas. Colic diverticulosis is the second leading cause of entero-vesical fistulas, after malignancy. Usually, the entero-vesical fistula is unique, on a single bowel segment; rarely is multiple, involving different intestinal segments. We present the case of a 41 years old man, with a double fistula: sigmoido-vesical and recto-vesical, respectively. The diagnosis was challenging despite the clinical aspect included pneumaturia and fecaluria. A particular symptom was sexual dysfunction. CT scan and a pelvic MRI revealed the two fistula colo-vesical and recto-vesical. A recto-sigmoid resection with subperitoneal colo-rectal anastomosis and partial cystectomy were performed with uneventful postoperative recovery. CONCLUSION: The multiple entero-vesical fistulas developed on a single intestinal segment are extremely rare, and, to our knowledge this is the only case reported in the literature. The management is challenging, and in our opinion the resection with anastomosis and partial cystectomy is the best choice.

Keywords: Colic diverticulosis; Diverticulitis; Entero-vesical fistula; Multiple Colo-vesical fistula

Introducere

Fistulele entero-vezicale au fost descrise pentru prima dată în urmă cu peste două milenii de catre Rufus și Ephesus [1], dar diverticuloza colică a fost semnalată ca o entitate patologică doar în secolul al XVIII-lea [2]. Etiologia acestora este variată: malignitățile (20%), diverticulita și afectiunile inflamatorii ale intestinului, traumatisme (accidentale, ingestia de oase, corpi străini), iatrogenii (radioterapie, intervenții în micul bazin și regiunile herniare, explorări endoscopice) [1,3]. Anatomic, fistulele entero-vezicale se împart în colo-vezicale, recto-vezicale, ileo-vezicale și apendiculo-vezicale [1]. Respectând legile fizicii elementare, apariția unor fistule multiple pe același segment intestinal sau pe segmente aflate unul în imediata continuitate a celuilalt sunt aproape imposibile. Sunt citate în literatura fistule duble (ileo-colo-vezicală, apendico-ileo-vezicală) [4]. Nu am găsit publicații care să certifice prezența unei fistule colo-recto-vezicale, în care partenerii digestivi implicați să presupună structuri parietale și gradiente presionale similare.

Patognomonice pentru fistula entero-vezicală sunt din punct de vedere clinic fecaluria și/sau pneumaturia (63%) [1], diagnosticul anatomo-topografic fiind dificil (CT cu contrast, urografia micțională, cistoscopia cu contrast și IRM). Tratamentul chirurgical cu morbiditatea [5] și mortalitatea cea mai scăzută este cel într-un singur timp, presupunând rezecția colică cu anastomoză și cistectomie parțială cu cistorafie [1].

Prezentare de caz

Prezentăm cazul unui pacient de sex masculin, în vârstă de 41 ani, din mediul urban, internat în clinica Chirurgie I din cadrul Spitalului Clinic Județean de Urgență Târgu Mureș în condiții de programare. La internare pacientul acuză subfebrilitate (37,5-38˚C), frisonete, fecalurie și pneumaturie, tenesme vezicale, tulburări de dinamica sexuală. Istoricul afecțiunii se întinde pe o perioada de 4 ani, pacientul prezentând fecalurie și pneumaturie intermitentă, infecții urinare repetate cu uroculturi pozitive pentru *Escherichia coli*, urmând la indicația urologului cure repetate de antibioterapie "țintite" argumentate prin antibiograme. Evoluția bolii este trenanta, cu perioade scurte asimptomatice (maxim 7-10 zile), după care constată reinstalarea simptomatologiei urinare, însoțită de frisonete, subfebrilitate și tulburări psiho-sexuale.

Se prezintă în mai multe servicii private de gastroenterologie și urologie, unde în urma examinărilor clinice și paraclinice (colonoscopie endoscopică, colonoscopie virtuală, cistoscopie) este etichetat și "tratat" cu prostatită recidivantă și ulterior chiar "operat" pentru boala hemoroidală. Având în vedere persistența simptomatologiei, apariția unor tulburări de dinamică sexuală cu implicații în viața de cuplu, pacientul este îndrumat la Clinica de Urologie a Spitalului Clinic Județean Târgu Mureș unde se practică CT cu contrast (Figura 1) și urografie micțională și cistografie (Figura 2) care ridică suspiciunea unei fistule "în supapă" între domul vezical și colonul sigmoid.

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Figura 1: Computer tomografie: obiectivarea fistulei superioare sigmoido-vezicale.

Figura 2: Cistografie: evidențierea orificiului fistulos.

Consultul chirurgical ridică suspiciunea unui dublu traiect fistulos, de aceea se recurge la IRM care semnalează prezența celui de-al doilea orificiu la nivelul rectului superior, în vecinătatea joncțiunii uretero-vezicale drepte, obiectivat ulterior printr-o recto-sigmoidoscopie (Figura 3 and 4). În momentul internării pacientul prezintă o stare generală bună, subfebril, fără fecalurie manifestă, dar cu urocultura pozitivă pentru *Escherichia coli*, leucocitoză (13.000/mm^3), restul parametrilor biologici fiind în limite normale.

După o pregătire preoperatorie adecvată (locală antimicrobiană și mecanică anterogradă) se intervine chirurgical sub anestezie generală printr-o laparotomie mediană. Se descoperă prezența unui sindrom aderențial inflamator secundar unei diverticulite, care acolează și ultima ansă ileală, aceasta putând fi însă eliberată (Figura 5).

La nivelul buclei inferioare a sigmoidului aderentă la domul vezical precum și la nivelul rectului superior (sub repliul peritoneal) în vecinătatea implantării ureterului drept în vezica se constată cele două fistule "etajate", sigmoido- și respectiv, recto-vezicală (Figura 6). Se eliberează colonul și rectul și vezica cu verificarea instrumentară a orificiilor fistuloase.

Se exclud endoluminal alte leziuni sincrone și se procedează apoi, după expunerea ureterelor pelvine bilateral, la rezecția recto-sigmoidiană de la nivelul joncțiunii descendentului cu sigma până la 2-3 cm subperitoneal. Se verifică endoluminal existența altor orificii

Figura 3: Colonoscopia: fistula superioară (sigmoido-vezicală).

Figura 4: Colonoscopia: fistula inferioară (recto-vezicală).

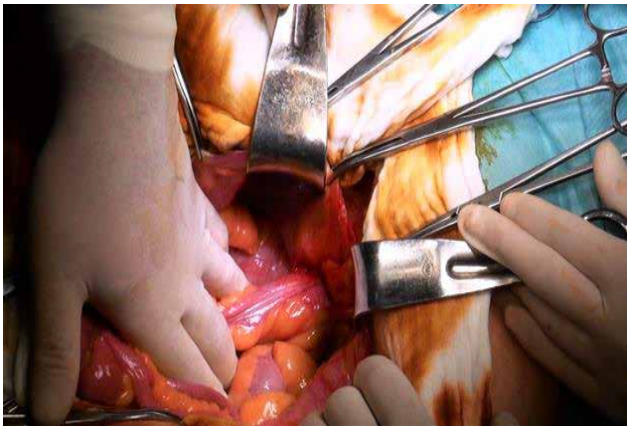

Figura 5: Aspectul procesului inflamator local.

Figura 6: Evidențierea introperatorie a fistulei superioare și suprimarea prin digitoclazie a traiectului fistulos sigmoido-vezical.

fistuloase și apoi se realizează o cistectomie parțială cu cistorafie per primam monoplan cu fire lent resorbabile și lăsarea "à demeurre" a unei sonde Foley de 14 Ch.

Continuitatea tubului digestiv se restabilește printr-o anastomoză colo-rectală termino-terminală monoplan. Se verifică etanșeitatea cistorafiei cu albastru de metilen instilat pe sonda vezicală și după toaleta cavității peritoneale se plasează un tub de dren decliv, peri-anastomotic exteriorizat în fosa iliaca dreapta prin contra-incizie. Evoluția postoperatorie a fost favorabilă, cu externare în ziua a 14-a, plaga vindecată per primam și uroculturile postoperatorii repetate fiind negative. La 21 zile post-operator se suprimă sonda urinară, iar 2 luni post-operator pacientul este asimptomatic, fără acuze digestive și urinare, re-inserat social și familial. Examenul histopatologic al pieselor operatorii confirmă diverticuloza acolo-rectală și a infirmat malignitatea.

Discuții

Din punct de vedere clinic diverticuloza colică poate fi simptomatică sau asimptomatică. Prevalența diverticulozei și a diverticulitei este strâns corelată cu vârsta (aproximativ 30% la indivizii de peste 50 de ani și 66% la populația peste 85 ani) [6]. Există o distribuție anatomică diferită a bolii diverticulare în funcție de arealul geografic al pacienților; alimentația săracă în reziduuri crește riscul apariției afecțiunii, dieta săracă în fibre crescând incidenta bolii [7]. Este demonstrată statistic implicarea mai frecventă a colonului stâng în țările vestice (99%) și a colonului drept în țările asiatice [7,8]. Migrația populațională și împrumutarea dietelor vestice în țările asiatice au crescut incidenta diverticulozei colonului stâng și în această zonă geografică[8]. Diverticulita este cea mai frecventă complicație a diverticulozei și apare în peste 90% din cazuri pe colonul sigmoid [9,10]. Din totalul pacienților spitalizați cu diagnosticul de diverticulită acută un număr important (15-30%) necesită tratament chirurgical [9]; unii autori recomandă colectomiile după al doilea episod de recurență [9] alții doar după al patrulea [11]. În cazul pacienților imunodeprimati chirurgia este indicată după primul episod [9]. Young-Fadok semnalează apariția fistulelor entero-vezicale în 2% din cazuri [12], iar dintre cei ce reclamă tratament chirurgical pentru boala diverticulară, aproximativ 20% prezintă fistule, 65% dintre acestea fiind colo-vezicale [12]. Dintre afecțiunile inflamatorii ce duc la apariția fistulelor entero-vezicale, diverticulita este responsabilă în 50-70% din cazuri. Alături de aceasta sunt citate: boala Crohn (10%), diverticulita Meckel, coccidiomicoza genito-urinară, actinomicoza pelvină și boala Fabry. Etiologia inflamatorie este secundară însă, pe primul loc situându-se neoplasmele (colo-rectal, vezico-urinar, col uterin, prostată, ovarian, limfomul intestinului subțire). Cauzele iatrogene sunt secundare intervențiilor în micul bazin (prostatectomii, histerectomii, cura laparoscopică a herniilor). Radioterapia poate duce la enterită radică cu posibilitatea apariției fistulelor chiar la intervale lungi (ani) după iradiere. Ingestia unor corpi străini (oase de pui sau de pește) poate duce în mod excepțional la dezvoltarea unor comunicări patologice între intestin și vezica urinară [1]. Privind mecanismul apariției fistulelor entero-vezicale în cadrul bolii diverticulare, factorul inflamator și relația de vecinătate a organelor sunt decisive. S-a constatat o prevalență a sexului masculin comparativ cu cel feminin (4,1/1), uterul interpus între colorect și vezica urinară constituind un factor protector [1].

Legea gradientelor presionale enunțata de Laplace [9] și apariția țesuturilor inflamatorii peri-diverticulare pot sugera două mecanisme de apariție a fistulelor entero-vezicale: extensia directă a diverticulului inflamat dinspre partenerul digestiv cu perforația acestuia în vezică și cel de al doilea, mai plauzibil în diverticulita acută, eroziunea parietală a partenerului urinar de către un abces diverticular [13,14] prin "foaierul intermediar" descris de către Chavannaz [15]. De altfel gradientul presional dintre cele două sisteme cavitare și apariția acestei comunicări anormale, explică specificitatea și sensibilitatea simptomelor majore (pneumaturia 71,4% din cazuri, fecaluria 51% din cazuri) [8]. Pe de altă parte, frecvența simptomelor urinare (polakiurie, disurie, tenesme vezicale, hematurie) și absența aproape completă a micturiei sesizabilă de pacienți la defecație, amână nejustificat diagnosticul etiologic al acestor bolnavi [13], etichetați și tratați timp îndelungat în mod eronat cu infecții urinare recidivate, boala hemoroidală, prostatite cronice, fapt constatat și în cazul clinic prezentat.

Țesutul inflamator periorificial poate constitui o clapetă ce explică parțial caracterul intermitent al infecțiilor urinare recurente, tipice unui mecanism "cu supapă". În observația noastră existența unui dublu orificiu fistulos pe segmente digestive aflate în imediata vecinătate și continuitate (sigmoid și rect superior) a fost dificil de diagnosticat. Suspiciunea unor fistule "etajate" a justificat reexplorarea suplimentară a pacientului (colonoscopie totală, cistografie micțională, cistoscopie cu contrast, CT cu contrast) care au permis în final obiectivarea a doua traiecte fistuloase separate: sigmoido-vezical și recto-vezical. Examinarea paraclinică cu cea mai mare sensibilitate și specificitate este computer tomografia cu administrare de contrast (40-100%) [12,16]. Aceasta obiectivează traiectul fistulos în condițiile în care acesta este activ, certificată prin prezenta aerului în vezică [1]. Pneumaturia însă poate fi și expresia unei infecții cu clostridii sau a unei candidoze genito-urinare [1], de aceea excluderea acestora prin examenul sumar al urinei și urocultura este obligatorie. În cazul nostru singurul germene obiectivat a fost *Escherichia coli*. Autorii japonezi arată importanță limitată a altor examinări (testul clinic cu ingestia de semințe de mac, irigografia 45%, cistoscopia 23,2%, cistografia retrograda 11,6%, rezonanță magnetică 3,2%) [1]. Rolul imagisticii prin rezonanță magnetică nucleară este important în cazurile cu fistule multiple. Localizarea anatomică, aspectul țesuturilor din jur, morfologia traiectelor fistuloase au implicație în alegerea procedeului chirurgical [13,17]. În ultimii ani colonoscopia virtuală pare să capete un rol important la pacienții ce nu tolerează explorări invazive [18]. Tratamentul diverticulitei colo-rectale complicat cu fistulă este prin excelență chirurgical, închiderea spontană a fistulei fiind excepțională. W.J. Mayo descrie în 1907 trei procedee chirurgicale adresate atât colonului cât și vezicii urinare [19]. Indicațiile tipului de intervenție trebuie individualizate în funcție de statusul biologic al pacientului (vârsta, prezența sepsisului local și general, starea de nutriție) dar și de performanță anastezico-chirurgicală a echipei. În condițiile unui pacient tânăr, fără patologie asociată, operația într-un singur timp (rezecție colică cu anastomoza per primum fără colostomie de protecție) este cea mai utilizată (70%) [20]. Pacienților cu condiții mai precare (vârstnici, tarați) vor beneficia de rezecție cu anastomoză și

colostomie în amonte, sau procedeul Hartmann. Intervenția în trei timpi este astăzi adresată doar pacienților cu risc anestezico-chirurgical crescut, cu abcese peri-diverticulare și semne de impregnare septică, colostomia fiind primul gest chirurgical asociat însă unei terapii intensive energice [21].

În observația noastră s-a practicat operația într-un singur timp, pregătirea generală și locală a colonului fiind posibile. Fiind vorba de o fistulă dublă "etajată", s-a efectuat rezecție recto-sigmoidiană cu anastomoză colo-rectală termino-terminală monoplan, fără colostomie. Pentru a preveni recidiva și a permite ridicarea orificiului inferior, intervenția a respectat ghidul Societății Americane de Chirurgie a Cancerului Colonic și Rectal (2006), conform căruia marginea de rezecție distală trebuie să coboare sub locul în care tenia colică atinge rectul superior [22].

Atitudinea asupra vezicii urinare este diferențiată. În situația în care orificiul fistulos nu este găsit intraoperator se poate recurge la plombaj cu epiploon a zonei vezicale implicate în procesul inflamator și plasarea unei sonde Foley pentru 1-2 săptămâni. Dacă fistula este evidențiată sutura acesteia poate fi opțiunea de ales [23]. Uneori, datorită procesului aderențial se recurge la cistotomie diagnostică [8]. Cistectomia parțială până în țesut sănătos, menajând implantările vezico-ureterale, cu cistografie per primam și sondaj vezical "à demeurre" 2-3 săptămâni este astăzi cea mai acceptată [1,8]. În situația fistulelor duble, sutura este iluzorie; de aceea noi am optat pentru rezecție parțială a vezicii cu sutură per primam monoplan și plasarea unei sonde Foley ce permite și controlul intraoperator al etanșeității acesteia, folosind instilarea de albastru de metilen.

Concluzii

Posibilitatea unei fistule colo-recto-vezicale etajate în diverticulita acolo-rectală este o entitate rară, nemaifiind citată în literatură. Pneumaturia și fecaluria sunt patognomonice; în condițiile unui pacient tânăr, netarat, cu perturbări ale vieții sexuale și modificări psihosomatice datorate unei afecțiuni non-neoplazice, examinările și reexaminările imagistice și endoscopice sunt cele justificate, nicidecum tratamentele "simptomatice". Intervenția chirurgicală într-un singur timp (rezecția recto-sigmoidiană cu anastomoză colo-rectală concomitent cu cistectomia parțială urmată de cistorafie) pare a fi soluția de ales.

Conflict de interese

Autorii nu declară niciun conflict de interese.

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Journal of Surgery
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Case Report Open Access

Emergency Thoracotomy- Isolated Internal Thoracic Artery Injury

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Abstract

Aim: A tension haemothorax is an uncommon injury after penetrating chest trauma. Presentation of a Case: We present a case in which a 55 year old man sustained multiple thoracic stab wounds. He had emergency right antero-lateral thoracotomy and laparotomy. A massive haemothorax secondary to complete disruption of right internal mammary artery and a laceration to middle lobe of right lung was noticed. Conclusion: Penetrating thoracic injury with isolated internal mammary injury is a very rare cause of massive haemothorax and associated with high mortality. Emergent thoracotomy can be life-saving for these patients. Introduction: Anterior thoracic penetrating injuries may result in life-threatening complications. One of these is massive tension haemothorax with pericardial tamponade as a result of stab wounds to the internal mammary artery.

Case Report

A 55 year old chronic alcoholic, male presented to the San Fernando General Hospital of Trinidad and Tobago after sustaining multiple [1] stab wounds (SW) to the chest &upper abdomen [2]. He was in hypo-voluemic shock with a blood pressure of 70/30 mm Hg and pulse rate of 140 beats per minute. Multiple [3] stab wounds were noted, in his right anterior chest wall medial to mid-clavicular line and one in left parasternal area at 4th ICS just cutting through the cartilage but not penetrating into the chest and two stab wound just below the tip of xyphoid process of sternum of which one is penetrating into abdomen (Figure 1).

A right chest was placed and immediately drained 1200mls of blood FAST & CXR were done moment after arrival in ED. The FAST revealed no blood in pericardial sac, however minimal free fluid was noted in the abdomen. The CXR later on showed complete opacification of entire right lung (Figure 2).

Right chest tube continue to drain blood with further drop in blood pressure of 40/25 mm Hg, immediately take to OR within 15-20 minutes of arrival in ED. However, en-route to OR, patient had a sudden cardiac arrest which was successfully resuscitated with a minutes of CRP and proceeds immediately to the OR. The pleural cavity was entered through a right antero-lateral thoracotomy incision in the 4th intercostal space under aseptic condition (Figure 3).

Right hemothorax was confirmed with laceration of right internal thoracic artery with active bleeding and small 1x1cm laceration to middle lobe of right lung. The pericardium was felt empty with no evidence of blood in the pericardial cavity. The bleeding vessel was controlled initially by digital pressure and then ligated proximally and distally. Simple repair of lung laceration was done (Figure 4).

Figure 1: Sites of Stab wound on chest and wound.

A midline laparotomy revealed a 3 cm laceration to left lobe of live with no active bleeding and there were minimal blood in the peritoneal cavity with no other visceral injury. The chest and abdomen was closed respectively leaving a 32 size chest tube in right pleural cavity. The estimated blood loss was approximately 6 litres. Patient received multiple transfusions of blood and blood products. Patient was managed in ICU for 2 day and subsequently transferred to the surgical ward where he developed delirium tremens secondary to with drawl of alcohol. Patient recovered completely well from the incident and discharged home on 8th post-operative day.

Discussion

Injury to Internal mammary artery is infrequently reported in literature. It can be a result of penetrating or blunt trauma, both of rare in occurrence but still with serious consequences [4,5]. Others have described internal mammary injury that had occurred from central line insertion [5]. There are only five cases of isolated IMA injury patient with successful recovery after emergency thoracotomy has been reported in the literature.

Among the 4 penetrating injuries two [6,7] were hemo-dynamically unstable & the next 2 [8] were hemodynamically stable. Only one patient had early [7] and next two patients had late pericardial tamponade [9,10] and last one [6] presented with early external pericardial tamponade. Of the 4 penetrating injuries patients only 2 had early [6,7] and 1 had delayed massive hemothorax [8] however,

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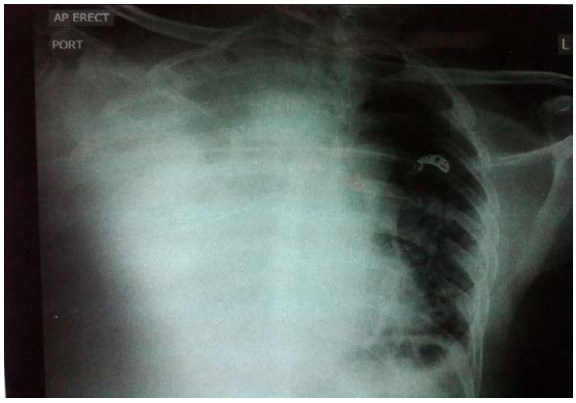

Figure 2: C x R AP showing complete white out of right hemi-thorax.

Figure 3: Right antero-lateral thoracotomy incision..

the next one had no massive hemothorax [9] Two of the penetrating injuries patients underwent median sternotomy [7,9] and the next two underwent anterolateral thoracotomy [6,8]. The lone blunt injury patient presented with delayed peri-cardial tamponade and was hemo-dynamically stable with no massive hemothorax and underwent median sternotomy [10] . Only one case has documented pre hospital arrest [6]. Our patient presented in a hemo-dynamically unstable condition with multiple stab wounds in the chest with massive tension hemothorax with early external cardiac tamponade. Our patient had a witnessed cardic arrest just moment before OR, was successfully resuscitated and underwent emergency thoracotomy with ligation IMA with an excellent full recovery (Table I).

As noted from the above, the presentation of internal-mammary injury varies from relatively stable patient that can be studied in a timely manner to identify the source of hemothorax, to a delayed presentation of massive hemothorax that mandate thoracotomy [11,12] . The treatment depends on patient hemodynamic status. With simultaneous resuscitation with placement of a chest tube to immediately release the tension hemothorax is the first line of intervention in patient who has signs of life in ED. However, once cardiac arrest is witnessed 5 minutes prior to Ed or in ED ER thoracotomy should the performed, if there is a surgeon in the institution rendering the care. The injured internal mammary may be treated based on the clinical presentation. If patient is hemo-dynamically stable and facilities are available the angio-embolization of the injured vessels are recommended.

Conclusion

Penetrating thoracic injury with isolated IMA injury is a very rare cause of massive haemothorax and associated with high mortality. Appropriate and Quick selections of the ideal patients for ED or OR thoracotomy are paramount important for successful outcomes.

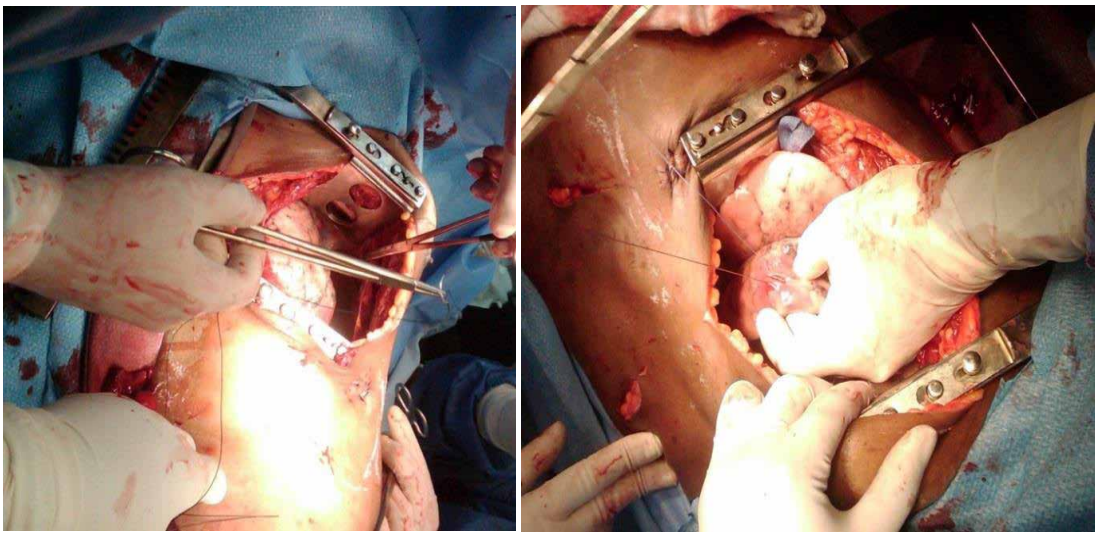

Figure 4: Chest opened & Right IMA is clamped & suture ligated, repair of lung laceration.

Table I: Summary of the Review of literature of internal mammary artery injuries.

Study	Mechanism of injury	Hemodynamic	Pericardial Tamponade	Massive Hemothorax	Surgery	Outcome
Curley et al. (1987)[12]	Penetrating	Unstable	Early	Early	Sternotomy	Alive
Vinces (2005) [6]	Penetrating	Stable	Delayed	Delayed	Thoracotomy	Alive
Holt et al. (2005) [11]	Penetrating	Stable	Delayed	No	Sternotomy	Alive
Irgau et al. (1995) [8]	Blunt	Stable	Delayed external	No	Sternotomy	Alive
Hassani (2012) [1]	Penetrating	Unstable	Early external	Early	Thoracotomy	Alive
Current case	Penetrating	Unstable	Early external	Early	Thoracotomy	Alive

Conflict of interest

The authors have no conflict of interest to report.

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Journal of Surgery
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Case Report Open Access

Multidisciplinary Management of Airway Obstruction and Superior Vena Cava Obstruction Secondary to Huge Retrosternal Goiter

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Abstract

Airway obstruction and superior vena cava syndrome (SVC) secondary to huge retrosternal goiter are medical emergencies which need meticulous attention to prevent potentially life threatening events. We reported a case of huge retrosternal goiter which was neglected for years and later complicated by obstruction to airway and superior vena cava. Team effort which mainly involved endocrine surgeon, cardiothoracic surgeon and anaesthetist had successfully removed the gland without significant morbidity. He was on tracheostomy due to tracheomalacia and was managed by ENT surgeon. He was discharged well after 2 weeks.

Keywords: Retrosternal goiter; Airway obstruction; Superior vena cava syndrome

Introduction

Retrosternal goiter is defined as more than 50% of thyroid gland descends in the thorax [1]. Goitres are often idiopathic; however can be caused by the following 1) Iodine deficiency, 2) Goitrogens, 3) Hereditary, 4) Autoimmune diseases and 5) Malignancy [2].

Its progressive extension may lead to compression of the surrounding structures such as trachea, esophagus, nerves and great vessels which leads to disastrous symptoms; dyspnea, dysphagia, hoarseness of voice and facial plethora [3]. An identified retrosternal goiter is an absolute indication for surgery.

Airway obstruction and superior vena cava syndrome (SVC) secondary to huge retrosternal goiter are medical emergencies which need meticulous attention to prevent potentially life threatening events. Airway obstruction results in hypoventilation, difficulty in breathing and impaired gas exchange with development of hypercarbia and ultimately hypoxemia if left untreated. Obstruction resulted from the compression may be partial or complete. Partial obstruction will have more insidious onset whereas complete obstruction will rapidly cause hypoxia and cardiac arrest [4].

SVC syndrome is caused by gradual compression of the SVC, leading to edema and retrograde flow; clinically manifested as cough, dyspnea, dysphagia, and swelling or discoloration of the neck, face and upper extremities. The involvement of collateral venous circulation often causes distension of the superficial veins in the chest wall [5]. Complications such as downhill esophageal varices and exudative pleural effusion tend to occur [6].

Case Summary

A 61-year-old gentleman, known case of advanced follicular thyroid cancer for 10 years, presented with progressively worsening shortness of breath and altered consciousness associated with fever for 3 days prior to admission. He was ventilated in casualty.

Upon further history from his wife, the anterior neck swelling was progressively increased in size for the past 3 months which was associated with stridor, unable to lie flat during sleep, hot flush and irritability. However there was no pain and difficulty during swallowing as well as no hoarseness of voice. He did not seek for any treatment.

On current examination there was multinodular swelling at anterior neck, firm in consistency with retrosternal extension and presence of dilated vein. He was admitted to ICU and treated as airway and SVC obstruction secondary to huge retrosternal goiter with concurrent severe community acquired pneumonia.

CT scan was done and showed follicular thyroid carcinoma with retrosternal extension with local mass effect and lung metastasis.

Semi emergency Total thyroidectomies with sternotomy were performed after 4 days ICU admission. Intraoperative, there was a huge retrosternal thyroid gland compressing on the right brachiocephalic vein, brachiocephalic trunk from behind the vessel and right carotid artery along with right internal jugular vein. There was presence of hard nodule at isthmus measuring 3cm x 2 cm. Tracheostomy was created due to presence of tracheomalacia (weakening of trachea due to long standing compression).

Postoperatively patient was recovering well and transferred out from ICU at Day 3 post operatively. He was referred to ENT surgeon for vocal cord assessment and tracheostomy was successfully re moved at Day 14. He was discharged 2 days later with oral Thyroxine supplement. Histopathological report revealed multinodular goiter with component of left papillary thyroid carcinoma. He was further referred to Oncologist for Radioactive Iodine Therapy.

Discussion

A multidisciplinary team comprises of surgeons, anesthesiologists, ENT specialists/surgeons, oncologists and pathologists warrants a coordinated team effort in approaching and managing patient with

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huge retrosternal goiter with compressive symptoms such as airway obstruction and superior vena cava syndrome.

Surgeons

With multidisciplinary team involvement, the proper diagnosis is ascertained. Surgery is the treatment of choice for retrosternal goiter [7]. Thyroidectomy for retrosternal goiters should be performed by surgeons with a specific interest and experience in thyroid surgery to ensure that complications are minimized [1,8,9].

Multiple studies have revealed that conventional cervical approach; cervical collar incision is best performed, accomplished and successful in the maximum number of cases under experienced hand. The majority of cervicomediastinal type goiters can be removed through the conventional approach. The operative mortality is negligible and the incidence of complication is reduced by abiding the strict surgical principles [1,7,8,10,11].

Sternotomy should be performed without hesitation when required [7]. Hardy et al. and Singh et al. reviewed only approximately 2% of patients undergoing thyroidectomy for retrosternal goitre will require surgical access other than a standard collar incision; either by manubriotomy, sternotomy or thoracotomy [1,11].

In cases with huge retrosternal goitre extended to below the aortic arch, the cervical approach alone can increase the risks of surgery due to poor access. Therefore, intrathoracic approach should be employed for full access and exposure including manubriotomy, full sternotomy and lateral thoracotomy. Full sternotomy has been proven to be more advantageous over lateral thoracotomy as the incision can be performed quickly and reliably with very low morbidity, providing excellent exposure to the retrosternal portion of the gland without having to reposition the patient. Thus, it is the main choice of approach [9,10,12].

The prognosis was good after resection except for lymphomas [8]. It is undeniable that thyroidectomy carries certain risks of complication such as hemorrhage, laryngeal edema, recurrent laryngeal nerve damage, superior laryngeal nerve damage, tracheomalacia, hypoparathyroidism, pneumothorax and thyroid storm. The associated complications must be kept in mind so the surgeon can carefully evaluate the surgical and medical therapeutic options, have more precise surgical indications and adequate information can be given to patients [13,14].

Anesthesiologists

The anesthesiologists face numerous daunting tasks in dealing with retrosternal goiter preoperatively, intraoperative and postoperatively. The role of the anesthesiologist, as a part of the interdisciplinary treatment team, is to ensure a safe perioperative period [15].

Airway examination is the foremost preoperative evaluation which needs to be done. It should include assessment of neck movements in all planes (especially atlanto-axial flexion and extension), estimation of thyro-mental distance, any protruding incisors, protruding or retrognathic mandible and Mallampatti grading [16-18]. Classical predictive criteria (mouth opening <35 mm, Mallampati III or IV, short neck, neck mobility <80 degrees, thyromental distance <65 mm, and a retrognathic mandible) were significantly reliable in the univariate analysis as risk factors for difficult intubation [19].

Large retrosternal goiter extension presents several potential difficulties for anesthetists. The airway management is planned in advanced after a thorough airway examination in order to prevent airways problems during induction of general anesthesia. CT scan of the airway is mandatory as the diameter of the trachea and the site of obstruction must be measured accurately as well as prediction for the need of sternotomy. Furthermore, dynamic airway function studies enable to assess the functional degree of impairment. Therefore, maximal inspiratory and expiratory flow volume loops will be obtained with the patient in upright and supine positions. Safe and logical technique like awake fiberoptic intubation as an early option for patient with retrosternal goiter will be planned. William's airway has been reported to be superior to the other airways in directing the fiberscope towards the glottis. This will ensure successful endotracheal intubation later [18,20].

Anesthetic management of patients with mediastinal masses such as huge retrosternal goiter remains very challenging as acute intraoperative or postoperative cardiorespiratory decompensation and critical hemodynamic situation might occur that may results in death after induction of general anesthesia [21-23].

The standard of intraoperative management stated by Erdös includes induction of anaesthesia in the operating theatre on an adjustable surgical table, the use of short-acting anaesthetics, avoidance of muscle relaxants and maintenance of spontaneous respiration which is the anesthetic goal whenever possible [15,23].

ENT specialists/surgeon

Detailed ENT examination should be carried out perioperatively. Indirect laryngoscopy should preferably be carried out by an ENT specialist as 3-5% of population invariably has unilateral paralysis of vocal cords [24].

The presence of an ENT surgeon in the Operation Theater is also essential as there can be need for establishing a definite surgical airway during the induction period. The presence of a retrosternal goiter, especially being present more than 5 years and causing significant tracheal compression, is likely a risk factor for tracheomalacia and tracheostomy [12,25].

Tracheomalacia can usually be recognized only following extubation [10]. Elective ventilation for few days is carried out if tracheomalacia occurs in these patients. It allows a fibrous connection to develop between the tracheal wall and the surrounding structures hindering its collapse [12,13].

Meticulous approach from ENT specialists/surgeon will avoid preoperative complications and ensure a speedy postoperative recovery of the patients.

Radiologists

Imaging specialties are essential in the diagnosis and staging of

Figure 1: Preoperative picture showed huge thyroid swelling with dilated veins (arrow).

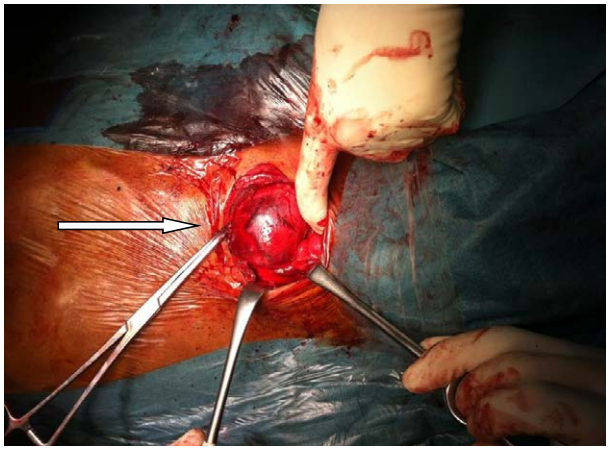

Figure 2: Thyroid gland which was first mobilized via collar incision.

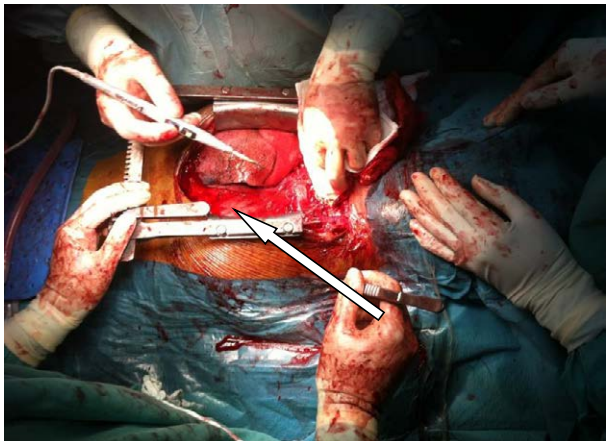

Figure 3: Sternotomy and mobilization of retrosternal goiter (arrow).

Figure 4: Total thyroidectomy specimen.

cancer. They work in hand with oncologists for subsequent detailed management. They would be able to delineate the exact location and extension during preoperative assessment. A written report is thus, mandatory. Although it is commonplace to order standard menus, it is up to the radiologists' discretion for the best techniques in particular problems.

Conventional chest X-ray, tracheal laminography and CT scan provide the most important information for diagnosis purposes. Thyroid scans and fine-needle aspiration often failed to show the intrathoracic goiter [8,10].

However, CT scan has been said to be the most useful tool showing the nature and extent of the lesion. Cross-sectional images provided by CT or MRI allow good understanding of the complex anatomy of the mediastinum. Thus, CT scan is an important component of the preoperative evaluation and operative planning [12,26-28].

Oncologists

The medical oncologist should participate in the decisions concerning the choice of therapy. Radioactive iodine (RAI) is used in treatment of patients with differentiated papillary and follicular thyroid cancer. It is typically used after thyroidectomy, both as a means of imaging to detect residual thyroid tissue or metastatic disease, as well as a means of treatment by ablation if such tissue is found. According to NCCN 2012 guidelines, it is indicated in all patients with gross extrathyroidal extension, primary tumor size >4 cm, and distant metastases [29].

Pathologists

The pathologist is arguably an indispensable member of every interdisciplinary team. The pathologist is responsible for giving as definitive a description of the tumor as determined effort can guarantee: its extent, its relationship to surgical margins, and normal structures, and the involvement of lymph nodes, lymphatics, and blood vessels.

Conclusion

Multidisciplinary management is essentially crucial to deliver comprehensive healthcare and provide the best possible outcome for the physical and psychosocial needs of a patient and their caregivers. The medical professionals from a range of disciplines with complementary skills, knowledge and experiences work in unity alongside with patients as the center of care in order to meet their needs and improve their quality of life.

Conflict of interest

The authors have no conflict of interest to report.

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Journal of Surgery
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Case Report Open Access

A Rare Cause of Entero-Vesical Fistula Caused by a Skewer, Multidisciplinary Management and Minimally-Invasive Surgical Correction

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Abstract

Entero-vesical fistulae (EVf) occurs rarely but it is a serious clinical condition often correlated with other pathologies. It accounts for 1 to 3000 hospital accesses/year. We present a patient with a sigmoid-vesical fistulae caused by the accidental ingestion of a wood skewer two years before. In literature about 6,09 % of accesses in the first aid area(FAa) are due to the ingestion of foreign bodies(FBs) but in 80-90% of them they are expelled with stools. In frequently FBs in the lower gastrointestinal tract can be the result of an orally ingested sharp object that becomes impacted. The management of this case was multidisciplinary, and the correction was a laparoscopic one time approach.

Introduction

Entero-vesical fistulas (EVf) are a communication between the bowel and the bladder. They can be of four types: colo-vesical, rectum-vesical, ileum-vesical and appendix-vesical according to the bowel tract involved. Most frequently they are colo-vesical and usually between sigma and the dome of the bladder. The colovesical are 70% , the ileovesical are 15% and the rectum-vesical are 10% [1] . They occur more frequently in male, about three times than female [2], due to the presence of the uterus. EVf can be caused by embriological abnormalities, infections, inflammatory bowel diseases, tumours, trauma and iatrogenic lesions [3]. The most frequent cause is the diverticular disease (Dd), 2/3 of total cases [4-7] and about 2-4% of patient with Dd have an EVf [5-10] ,after surgical treatment this percentage increases to 20% [9]. In neoplasia EVf can be caused by the primitive tumour usually from the bowel tract and rarely from the urinary tract or can be caused after radiotherapy [11-13] . The EVf in Crohn disease are usually ileo-vesical [10] while fistulas with the appendix are rare, less than 5 % [5,14], generally after appendicitis. Exceptional is the EVf after the perforation of Meckel's diverticulum [15]. Even more rare situations are iatrogenic lesions after surgery [3,16-19], and bullet wounds involving at the same time bowel and bladder [20,21]. At least there are FBs in the lower gastrointestinal tract like chicken bones and fish bones or Foley's catheter in the bladder. The clinical presentation of EVf is characterized by pneumaturia, fecaluria and, recurrent urinary tract infections [2,4,22,23]. Other symptoms are abdominal pain that occurs in the 40 % of patients and fever related with infections or inflammation [2,24,25]. The presentation is more often related to the urinary tract as the high pressure in the bowel tract define an unidirectional flow to the bladder [26,27]. For this reason these patients at the beginning apply to the Urologist and then their management becomes multidisciplinary involving the radiologist, the gastroenterologist and the surgeon.

Case Report

A 22 years old man presented with hematuria started 2 days before even though he was already treated with antibiotic therapy at home. He refers multiple episodes of urinary tract infections in the last 6 months that were resolved with common antibiotic therapy. Moreover he refer that at the last access in FAa, the urinary culture was positive for Escherichia Coli and so it was changed his antibiotic therapy and so he restored. Also at the interview he refers from some days bubbles in the urine and malodorous urine with the presence of vegetable pieces. His history is negative for other pathologies or trauma. So it was performed a cystoscopy that revealed two small lesions of the anterior wall of the bladder. But cystography resulted negative for the presence of fistula or wall discontinuity (Figure 1 and 2). So without a clear diagnosis even though the persistence of the symptoms it was performed a TC scan. At this exam we found a radiopaque filiform form (foreign body?), angled to the caudal third, with a maximum longitudinal size of about 6.5 cm and with a caliber of about 1-1.5 mm whose proximal and distal portions, crossed the wall and reaches both the lumen of the pelvic sigmoid loop and the lumen of the bladder (Figures 3-6).

That seems FBs thin and sharp towards the sigma and the bladder.

Figure 1: Right obligue projection: No abnormalities of the bladder wall or fistulas in place.

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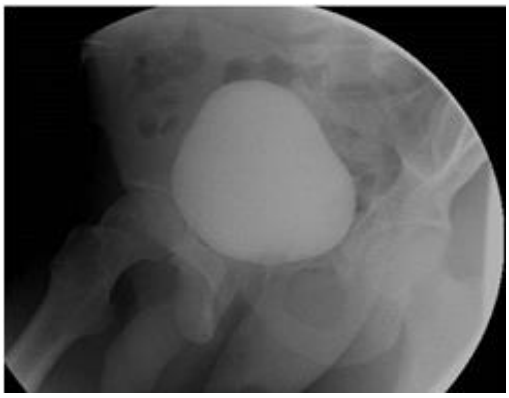

Figure 2: Left obligue projection: Confirms the absence of parital lesions.

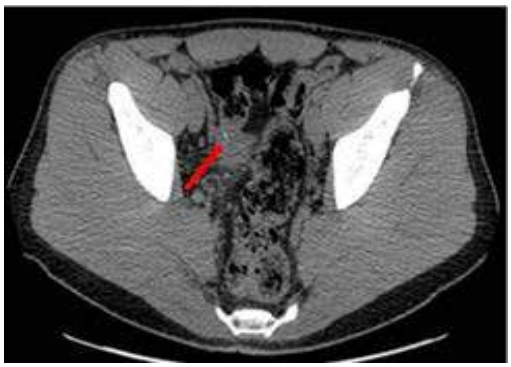

Figure 3: Axial.

Figure 4: Coronal (1).

Only at this time the patient remembered the accidental ingestion of a wood skewer two years before. So it was performed a laparoscopic approach combined with an intra-operative cystoscopy. During this operation it was divided the sigma from the bladder with identification of the two orifices of the fistula and the remove of the FBs that really was a skewer (Figure 7 A and B). A small part of the sigma involved in the fistula was resected and an end to end anastomosis was executed. The other orifice of the fistula was closed with 2 continuous sutures and an omental flap interposition after the identification of distal ureter tract and bladder's ostium by combined cystoscopy/laparoscopy. After the operation the vesical cathether was maintained for 12 days until the patient performed a new cystography that was negative. No recurrence of fistula occurred.

Discussion

The diagnosis of an enterovesical fistula poses a significant challenge as there is no consensus on any clear gold standard for EVf workup. Nevertheless, diagnosis of EVf is necessary not only to establish the presence of a fistula but also to exclude stricture of the bowel and presence of abscess and to evaluate the tract of involved intestine to guide the subsequent treatment. Cystoscopy has the capability to identify potential but nonspecific lesions, such as erythema, oedema, and congestion. Even though cystoscopy can fail to detect EVf in 54-65 % of cases, its use is essential for the entire investigation process [4,6,28,29] . Considering that 10%–15% of colovesical fistulae are secondary to neoplasms, colonoscopy should be part of the diagnostic work-up of EVf in order to determine the bowel pathology responsible for the fistula formation [4,5,29] Cystography can demostrate the presence of contrast outside the bladder but may not a fistula [29] its detection rate for EVf ranges between 20% and 30% [30] . Another test that could be used is the poppy seed test that yielded the best detection rate (100%) in some series30. However Computed tomography (CT) is the procedure of choice for the diagnosis of entero-vesical fistulae due to its high accuracy (90-100%) for the detection of EVf, but

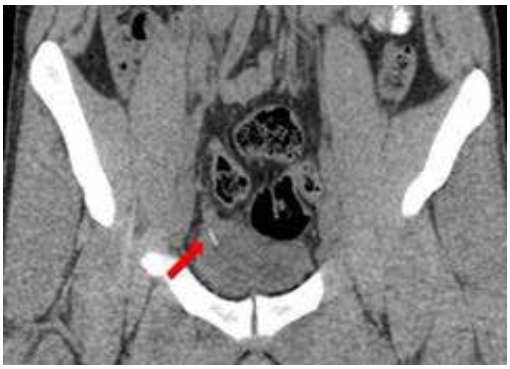

Figure 5: Coronal (2).

Figure 6: Volume rendering.

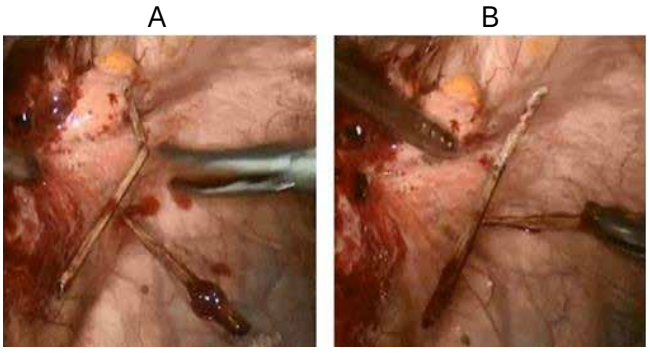

Figure 7A & B: Fragments of Foreign body removed laparoscopicaly.

more importantly it provides essential additional information about the adjacent anatomical structures [5,29] . In this case it was initially used cystoscopy and cystography as the patient was managed by the urologist because of his clinical signs. Since the strong clinical suspicion of an EVf, it was next performed directly a CT, in order to define and characterize it in the absence of other pathologies or comorbidities in a substantially well-being young patient.

About the Management of EVf, it can be considered a non operative one, based on the use of bowel rest, total parenteral nutrition, antibiotics, steroids, immunomodulatory drugs, and urethral catheter drainage. This one is preferred for patients minimally symptomatic with nonmalignant EVF origin, particularly in those with Crohn's disease [3]. Endoscopic, open, and laparoscopic approaches have all been used in surgical treatment of enterovesical fistulae [10,31,32] . Operative management of enterovesical fistulae is mainly dependent on the underlying pathology, site of the bowel lesion, and patient's preoperative status. The use of a laparoscopic treatment depends on the ability of the Surgeon in this technique. The aim of operative management is to resect and reanastomose the offending bowel segment and to close the bladder. The treatment may involve single-stage or multistage procedures [31,32] . Staged procedures have been advocated in patients with gross faecal contamination and large intervening pelvic abscesses or in those with advanced malignancy or radiation changes [32,33] . Bowel resection with primary anastomosis is advocated in the majority of EVF cases [32]. Successful one-stage resections have been reported in 18% to 92% of EVF cases [34] Surgical technique involves blunt dissection of the bowel from the bladder, resection of the intestine, and primary anastomosis. As an opening of a fistulous tract in the bladder may not be directly visible, distention of the bladder with methylene blue solution instilled through a catheter may be helpful. The type of bladder repair, whether excision or oversewing, is not of critical importance since small defects do not require closure and may be left to heal spontaneously. Although no strong evidence is available, if technically possible, interposition of the omental flap between the bladder and intestine may be employed. Such maneuver might improve healing process and reduce the fistula recurrence rate due to high vascularity and immunological properties of the omentum [35]. In this case we performed a laparoscopic one stage procedure in order to offer to the patient all the benefits of this technique as we are more familiar with it. Intraoperative cystoscopy was preferred than methylene solution as the skewer was near the ureter's outlet. In this way it was easily identified the bladder's opening, that was too big to heal spontaneously and so then it was sutured in safety.

Conclusions

Entero-vesical fistula is an uncommon complication of both malignant and benign processes and even a rare etiology must be considered, like in our case. Computed tomography is the most sensitive test for entero-vesical fistula as it allows the delineation of its course, and characterization of its complexity and its etiology, affecting the EVf management. The outcome of entero-vesical fistulae management is, in the majority of cases, positive. For this reason, we believe that in benign etiology lesions, a surgical one-stage preferably by a minimally invasive approach represents the management of choice in most cases.

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Journal of Surgery
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Case Report Open Access

Spontaneous Rupture of Liver Haemangioma: A Case Report & Review of Literature

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Abstract

Hepatic haemangioma is a most common benign tumour of the liver. Detected incidentally, often asymptomatic and undergoes enlargement in <10% of cases. Spontaneous rupture of a giant hepatic haemangioma (diameter >4 cm) with hemo-peritoneum occurs very rarely. Limited numbers of cases are reported in the world literature with an operative mortality of >35%. We report here a case of spontaneously ruptured hepatic hemangioma managed conservatively.

Keywords: Hepatic hemangioma; Spontaneous rupture

Case Report

A 31yrs old female patient presented with three day history of sudden right upper quadrant pain which progressively worsened over the last 24 hours. She is a known asthmatic controlled by Nasacort inhaler and also a known case of polycystic ovary diseases using oral contraceptive pills over the last 9 years.

On physical examination revealed a young female in mild painful distress. Her mucous membrane was pink and moist. She was warm to touch with a temperature of 38.4°C and her vitals were within normal limit. Abdominal examination revealed moderate tenderness in right upper quadrant with mild guarding but no rebound tenderness.An USS of abdomen revealed a normal gall bladder with no peri-cholecystic fluids or gall stones with a normal CBD. However, a 7.77 x 9.42 cm cystic mass was noted in right lobe of liver and there was no free fluid (Figure 1). A CXR revealed right basal consolidation. Her WBC was elevated 26.2 and she was also anaemic with an Hb of 11 mg/dl. Her renal function as well as electrolytes were within normal limit, however her liver enzymes were elevated AST-600, ALT-1900, ALP-238, GGT-166 with normal serum bilirubin and amylase level.

After 24 hours her pain became severe and she became tachycardic with a pulse of 130 bpm with persistently elevated temperature (38.0°C). Her blood pressure and Spo2 was normal. There was decreased air entry at right lung base. Abdominal examination revealed marked tenderness with guarding but no rebound tenderness and there was sluggish bowel sound. Patient Hb had dropped from 10 gm/dl to 8 gm/dl. An Urgent CT scan of abdomen and pelvis with intravenous contrast revealed that the cyst (haemangioma) has ruptured with free fluid (blood) in Morrison pouch and in right Para-colic gutter (Figure 2). Subsequently patient developed moderate respiratory distress and was reviewed by medicine specialist. A Spiral CT of the chest-revealed mild right pleural effusion with fluid in oblique fissure but no evidence of pulmonary embolism. An MRI of abdomen was also performed which reconfirm the ruptured hepatic haemangioma. Patient was admitted in HDU and was managed successfully and discharged home on day-12.Patient had a high ESR of 39 and her liver function test became normal. Her serum alpha fetoprotein, CEA, Ca 19-9, anti-nuclear DNA levels were within normal limit.

Discussion

Hemangioma is the most common benign tumour affecting the liver [1,2]. Hepatic haemangioma are mesenchymal in origin and usually are solitary. Haemangioma are composed of masses of blood vessels that are atypical or irregular in arrangement and size. Exact aetiology remains unknown [3-5].

Several pharmacologic agents have been postulated to promote tumour growth. Steroid therapy [6], oestrogen therapy, and pregnancy [7,8] can increase the size of an already existing hemangioma. Our patient was on inhalational steroid therapy for her asthmatic condition and was also on oral contraceptive pills for her polycystic ovarian disease.

Incidence rate 2% in USA & the prevalence rate at necropsy is 7.4%, usually see in multipara women, more female predominance and occur most frequently at age 30-50 years [1,2]. Our patient is 31years old and she has no children.

Hepatic haemangioma can occur as part of well-defined clinical syndromes. In Klippel-Trenaunay-Weber syndrome. In Kasabach-

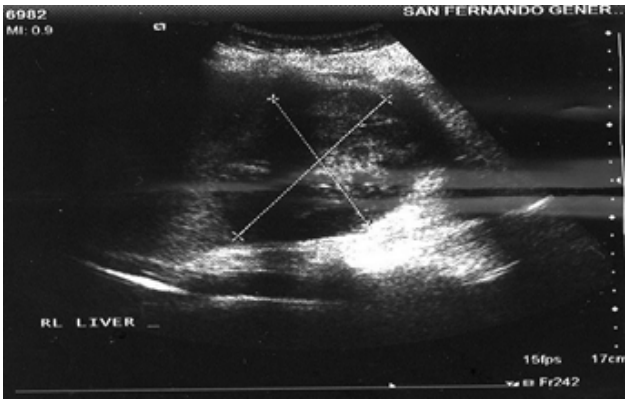

Figure 1: USS of abdomen: 7.7 x 9.4 cm cystic mass in Right lobe of liver.

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Merritt syndrome, Osler-Rendu-Weber disease, Von Hippel -Lindau disease, multiple hepatic haemangioma [9] have been reported in patients with systemic lupus erythematous. Suzuki T, Tsuchiya N, Ito K. Multiple cavernous haemangioma of the liver in patients with systemic lupus erythematous.

Haemangioma are more common in the right lobe of the liver, usually small and asymptomatic can be larger and multiple usually presents as Right upper quadrant pain or fullness, may presents as an enlarged liver or the presence of an arterial bruit over the right upper quadrant. Rarely, haemangioma may present as a large abdominal mass or other atypical presentations like 1) cardiac failure from massive arterio-venous shunting [10], 2) jaundice from compression of the bile ducts, 3) gastrointestinal bleeding from hemobilia [11] and 4) fever of unknown origin (12).

An illness that resembles a systematic inflammatory process has been described with findings of fever, weight loss, anaemia, thrombocytosis, increased fibrinogen level, and elevated erythrocyte sedimentation rate. Our patient presents with RUQ pain & fever, with elevated WBC, ESR, low Hb and she was not icteric and auscultation revealed no arterial bruie.

Large tumours very rarely rupture spontaneously. Patients may present with signs of circulatory shock and hemo-peritoneum [12,13]. Our patient initially present as an un ruptured hepatic haemangioma as confirmed by initial USS (Figure 1) and spontaneously ruptured on day -1 of admission without any historyof traumaand confirmed radiologically by CT scan & MRI (Figures 2 and 3).

Figure 2: CT Scan of abdomen- showing ruptured haemangioma with free fluid in right sub-hepatic space &right paracolic gutter.

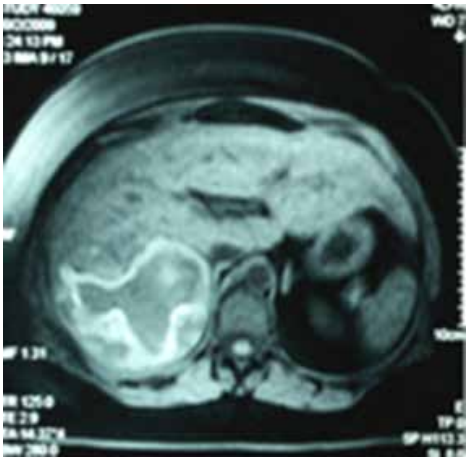

Figure 3: MRI of abdomen confirming the hepatic haemangioma.

Routine laboratory tests - are usually normal. There could be thrombocytopenia or hypo-fibrinogenemia. Normal alpha-fetoprotein, CA 19-9, and carcinogenic embryonic antigen (CEA) levels bolster clinical suspicion of a benign hepatic mass lesion. Serum alpha fetoprotein, CA-19-9, CEA levels were normal in our patient.

Modalitiesused to diagnose it are Ultrasonography (US) 46% sensitivity [3], Dynamic contrast-enhanced computed tomography (CT) 66% sensitivity [14,15], Nuclear medicine studies using technetium (Tc) 99m-labeled RBCs [16,17], Magnetic resonance imaging (MRI) 96% sensitivity [17,18], Hepatic arteriography, and Digital subtraction angiography (DSA). Liver biopsy can help provide an unequivocal histologic diagnosis. Ultra-sonogram as well as CT and MRI were used in our case for diagnosis.

Most hepatic haemangioma are small and asymptomatic at the time of diagnosis, and they are likely to remain that way. Hence long term follow up radiograph probably not necessary providing that no change in haemangioma size has occurred. Finally, patients with large haemangioma (i. e, >10 cm) may deserve long-term follow-up radiologic studies, perhaps annually, because of their probable increased risk of complications [1, 6,8,19].

The management of a large (i. e, >10 cm) hepatic haemangioma is controversial .However, a literature search identified only 32 published cases of spontaneous rupture in adults without a history of trauma [1,6,8,12,15,19-30]. However, actual radiological documented before and after ruptured are not well documented. In our case we have radiological evidence before and after rupture of the haemangioma.

Treatment option includes surgical resection [8,17,27,31-33] surgical enucleation, arterial embolization [7,8,15,18,27,34,35], radiofrequency ablation, hepatic irradiation, and orthotopic liver transplantation. However surgical resection and enucleation are the treatments of choice. It has been reported that patient with hemoperitoneum who underwent surgical intervention the mortality rate was 36.4% [1]. In rare instances, once patient remained hemodynamically stable can be managed conservatively like ours. Patient are usually followed up with serial ultrasound. Our patient was followed up with serial USS and after two years of follow up there was no increase in size and she remained asymptomatic throughout her follow up.

Conclusion

Although hepatic haemangioma is common, however spontaneous ruptures are very rare and associated with a very high mortality rate. High index of suspicion should be kept for prompt diagnosis of this rupture. Early intervention should be taken to prevent a fatal outcome.

Conflict of interest

The authors have no conflict of interest to report.

Acknowledgement

Patient's consent is obtained for publication of this case report.

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Surgical Techinique Open Access

Thoracoscopic Left Splanchnicectomy: Two Trocar Technique

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Abstract

Background: Abdominal hyperalgic syndrome in unresectable pancreatic cancer worsens the quality of patients' life. The goal of this article is to evaluate the feasibility of performing the left splanchnicectomy using a two trocar thoracoscopic approach.

Material and Methods: One patient suffering from intractable pain due to unresectable pancreatic cancer (stage IV) with liver metastasis underwent thoracoscopic unilateral left splanchnicectomy. The procedure was performed using only two trocars, one of 10 mm for the optic and one 5 mm working trocar for Hook electrocautery, scissors and grasper. To assess pain severity and the impact of this palliative procedure for pain relief, the patient completed Wong-Baker Faces Pain Rating Scale with a preoperative pain degree of 9.

Results: Surgical procedure time was 30 minutes. Pleural drainage tube was removed 24 hours postoperatively. There were no complications. Immediate pain relief (pain degree 0 to 2) was achieved after thoracoscopic unilateral splanchnicectomy, same level beeing registered at first checkup after one month.

Conclusions: Thoracoscopic unilateral left splanchnicectomy using two trocars is feasible in selected cases, decreasing substantial the pain and significantly improving the quality of life in patients with unresectable pancreatic cancer.

Keywords: Pancreatic Cancer; Unresectable Cancer; Pain; Thoracoscopy; Splanchnicectomy

Introduction

Thoracoscopic splanchnicectomy is a palliative procedure for the management of upper abdominal pain from unresectable pancreatic cancer. Thoracic splanchnic nerves conduct pain sensation from the abdominal organs around the celiac ganglion. Celiac plexus is the largest sympathetic plexus located at L_1 level posterior to the vena cava on the right side and just lateral to the aorta on the left side. The plexus is composed of a dense network of interconnecting presynaptic sympathetic nerve fibers derived mainly from the greater splanchnic nerve – GSN (T_5 - T_9), lesser splanchnic nerve – LSN (T_{10} - T_{11}) and least (T_{12}) splanchnic nerve. It also receives parasympathetic fibers from the vagus nerve [1]. Worsey and colleagues [2] reported in 1993 the first thoracoscopic left splanchnicectomy to relieve pain. This procedure is performed under direct vision and it is an alternative to celiac plexus block with a higher degree of precision and with less associated morbidity. Thoracoscopic splanchnicectomy consists in identification and division of all the roots of the splanhnic nerves from T_5 to T_{10}. This procedure can be repeated controlateral in case of recurrence of pain or it can be performed bilateral from the beginning [3,4].

Case Report

A 60-year-old woman recently diagnosed with pancreatic cancer was admitted in the Department of Surgery of Bucharest Clinical Emergency Hospital, for intractable epigastric pain. Pain was severe in intensity, radiating to back, resistant to usual and opioid analgesics. There was loss of weight and appetite. Physical exam revealed diffuse upper abdominal pain without any other symptoms and without a palpable tumoral mass. All routine laboratory tests were within normal range. The serum concentration of tumoral marker Carbohydrate-Antigen 19.9 (CA 19.9) was elevated at 1881 U/mL. Chest X-ray showed no metastases and upper digestive endoscopy was normal. Abdominal ultrasound revealed a pancreatic body solid nodule with non-homogenous structure, 5 × 3.5 cm in diameter with irregular shape. CT scan of the abdomen and MRI revealed a pancreatic body mass lesion with extension into peri-pancreatic fat encasing adjacent vessels, with invasion of superior mesenteric artery and the celiac trunk and liver metastases which placed our patient in a preoperative stage IV (T_4, M_1) of pancreatic cancer.

Preoperatively pain assessment was done using the Wong-Baker Faces Pain Rating Scale (Figure 1) [5]. This scale is often helpful for patients with any degree of education, being very easy to understand and to answer. It uses faces from happy to tearful to demonstrate how a person might be feeling. Our patient preoperative pain level was 9.

The patient was prepared for a palliative surgical procedure–thoracoscopic left splanchnicectomy–in order to alleviate the symptoms of the abdominal hyperalgic syndrome.

Surgical Technique

The surgical procedure of thoracoscopic left splanchnicectomy was made under general anesthesia without selective intubation. The patient was placed in right-lateral decubitus position with slightly tilt anteriorly to expose the left thorax. We used a two trocar technique with

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a 10 mm trocar (optical trocar) placed in through 6th intercostal space on anterior axillary line and a 5 mm working trocar placed under direct vision in 9th intercostal space on the posterior axillary line (Figure 2).

The key point of our operation was intrathoracic carbon dioxide insufflation to a pressure level of 10 mmHg, which allowed a better exposure and a more distal division of the greater splanchnic nerve (GSN) and lesser splanchnic nerve (LSN). We used the standard thoracoscopic kit, with a 0° optical angle videoscope, hook cautery, scissors and an atraumatic grasper. The surgeon stands in front of the patient with the assistant on his left side. Working trocar insertion was done under direct vision. Identification of splanchnic nerves (GSN – T_5-T_9 and LSN – T_{10}-T_{11}) through the transparency of the parietal pleura down to the diaphragm was easy (Figure 3). This might be difficult in case of pleural adhesions.

The GSN was identified through the parietal pleura from its first root along the descending aorta, to the diaphragmatic recess. To expose the trunk of the GSN, a pleural incision using hook electrocautery was made in the region between the descending aorta and the sympathetic trunk. Pleurotomy from the fifth intercostal space to the diaphragmatic recess was then performed. The main trunk of the GSN was isolated using the hook electrocautery as distally as possible and sectioned using electrosurgical scissors. The LSN was identified laterally to the GSN, dissected and divided. The excised nerves were sent for pathological examination (Figure 4).

We finished the operation by pleural drainage connected to water seal with a chest tube of 20 F inserted under direct vision through the space created by the 5 mm trocar in the 9th intercostal space on posterior axillary line (Figure 5).

After controlling the hemostasis, the lung is reinflated by the anesthesist, and the optic trocar is removed and the chest wounds are closed. Surgical intervention duration was 30 minutes. A postoperative chest X-ray is performed routinely at 24 hours postoperatively and then the chest tube is removed.

Figure 1: Wong-Baker Faces Pain Rating Scale.

Figure 2: Trocars' placement.

Figure 3: Identification of Greater Splanchnic Nerve (GSN) through the transparency of parietal pleura.

Results

There was no postoperative complications. In this case, thoracoscopic left splanchnicectomy performed with a two trocar technique using intrathoracic carbon dioxide insufflation proved itself as a good method of pain control in unresectable pancreatic cancer.

Pain was totally relieved and drug addiction stopped. In our experience we encountered pain at the site of the trocars so we decided to inject locally lidocaine 1% at the end of the surgical procedure [6]. Pain level was assessed at 24 hours postoperatively and the results were good with a pain level of 2 on Wong-Baker Faces Pain Scale. Our patient was discharged after 72 hours postoperative and she was referred to a territorial oncological department for chemotherapy. Results remained good at one month control.

Discussion

The first left splanchnicectomy was performed in 1942 by Mallet-Guy [7] through laparotomy in order to alleviate intractable pain due to chronic pancreatitis. In 1990, Stone and Chauvin [8] first reported the clinical results of splanchnicectomy by thoracotomy. In 1993 Worsey et al. [2] described the use of videothoracoscopy to perform a left splanchnicectomy in patients with intractable pain due to advanced pancreatic cancer. An easier and faster procedure was proposed by Pietrabissa et al. [9] consisting in dividing only the main trunk of the greater and lesser splanchnic nerves with the same good results. Recently, many authors have reported good results with thoracoscopic unilateral left splanchnicectomy for pancreatic pain relief [3,4,10,11].

Thoracoscopic splanchnicectomy is a percutaneous procedure performed under direct vision. The advantages include higher precision video assisted identification and division of all the roots of the splanchnic nerves, from T_5 through T_{11}. Use of CO_2 insufflation to create the working space allows us to perform a two trocar technique. The limitations include difficulty created by strong pleural adhesions and the likelihood that pain relief reduces with increased period of survival in cancer patients. This procedure has been reported with either few or no complications [12]. The patients referred for palliative

Figure 4: Dissection and division with hook electrocautery of Lesser Splanchnic Nerve – LSN (left) and Greater Splanchnic Nerve–GSN (right).

Figure 5: Pleural drain.

surgery have on an average 6 months survival time, and subjecting these for procedures that can become an important source of morbidity is not justified.

Conclusion

Thoracoscopic left splanchnicectomy performed through only two trocar ports is an effective and safe minimally invasive procedure with good results for pain control in abdominal hyperalgic syndrome from unresectable pancreatic cancer. Necessitating a short hospital stay and having a short learning curve this procedure could become highly accepted among patients and surgeons as treatment of choice of intractable pancreatic pain in selected cases.

Conflict of Interest

Authors have no conflict of interest to disclose.

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Laparoscopic Left Adrenalectomy for a Left Corticosteroid-Producing Adrenal Tumor

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Abstract

Cushing Syndrome (CS) is a chronic condition due to sustained exposure to glucocorticoid excess. Most frequent clinical manifestations are obesity, "moon face", muscle weakness, osteoporosis, menstrual irregularities, high blood pressure, diabetes. Sometimes the signs and symptoms are overt (subclinical Cushing Syndrome). The most frequent tests used are 24 hours urinary free cortisol, dexamethasone suppression tests, plasma ACTH levels as well as CT/MRI to localize the adrenal tumor. The surgical treatment is adrenalectomy. This video present a left laparoscopic adrenalectomy for a CS secondary to a left adrenal adenoma. The patient is placed in a right lateral position. Operative steps are: mobilization of the left colon, mobilization of the spleen and tail of the pancreas by dividing the splenoparietal ligament, division of the splenorenal ligament, identification of the adrenal vessels, dissection of the adrenal gland (starting medial, continuing posterior and ending lateral on the surface of the kidney) and extraction of the specimen in an endobag. Postoperative follow-up was uneventful. CONCLUSION: In our opinion laparoscopic adrenalectomy is the gold standard procedure for adrenal CS.

Keywords: Cushing Syndrome; Adrenal Tumors; Laparoscopic Adrenalectomy

Introducere

Sindromul Cushing (CS) se caracterizează prin secreția în exces de glucocorticoizi. Ne referim în continuare la CS endogen, ACTH independent, care reprezintă 20-30 % din cazuri și este determinat de tumori adrenale corticosecretante (adenoame și mai rar carcinoame) [1,2].

Simptomele și semnele clinice frecvente ale acestei afecțiuni sunt obezitate, pletoră, față de „lună plină", atrofie tegumentară, echimoze, hipertensiune, diabet sau alterarea toleranței la glucoză, disfuncție sexuală, slăbiciune musculară, striuri roșii cutanate, tulburări psihice, osteoporoză, edeme gambiere. Simptomele pot fi discrete – așa numitul sindrom Cushing sub clinic [3-6].

Pentru diagnosticul biochimic se determină cortisolul liber din urina de 24 de ore, cortisolul salivar nocturn sau se efectuează testul de supresie la dexametazonă (1 mg). În situația în care unul din aceste teste este modificat, se efectuează testul de supresie la dexametazonă de 48 de ore (8 mg/zi timp de 2 zile) care, dacă este pozitiv, confirmă diagnosticul. Determinarea ACTH-ului seric permite stabilirea diagnosticului de formă clinică (valori scăzute = sindrom Cushing ACTH independent). Imagistica (CT/RMN) va confirma prezența adenomului suprarenalian [3-7].

Suprarenalectomia Stângă - timpi Operatori

Operația de elecție pentru adenomul stâng suprarenalian corticosecretant este adrenalectomia stângă laparoscopică. Instrumentarul cuprinde, pe lângă trusa "clasică" de laparoscopie, depărtătorul de tip "șarpe", instrumentar de termofusiune, 3 trocare (2 de 10 mm și unul de 5 mm) și camera de 30 grade [8-10].

Poziția pacientului este decubitul lateral drept. Trocarul optic (10 mm) este introdus prin metoda „open" , pe linia axilară anterioară (aproximativ la 2-3 cm de rebordul costal); al doilea trocar (10 mm) se introduce pe linia axilară medie sau posterioară, astfel încât să obținem o triangulatie optimă, iar al treilea trocar (5 mm), pe linia medioclaviculară. Opțional, când avem nevoie de un depărtător, folosim un trocar de 5 mm subxifoidian [8-10].

Operația începe prin mobilizarea adevată a flexurii stângi a colonului; următorul pas constă în mobilizarea splinei împreună cu coada pancreasului, prin secționarea ligamentului splenoparietal (mobilizare efectuată până la diafragm, cu vizualizarea fundusului gastric). Se secționează ligamentul splenorenal, astfel încât la sfârșitul disecției, splina și pancreasul să „cadă" medial, în mare parte datorită gravitației. Disecția splinei și pancreasului distal expune rinichiul și glanda suprarenală stângă; intervenția continuă cu identificarea venei diafragmatice stângi și a venei suprarenale principale, aceasta din urmă fiind disecată, clipată și secționată (a nu se face confuzie cu vena renală stângă, mai ales în tumorile de dimensiuni mari). Disecția este continuată în plan posterior și lateral, cu detașarea glandei tumorale de pe planul muscular posterior și suprafața rinichiului stâng; pediculii vasculari mai mici pot fi clipați sau sectionați cu pensa cu ultrasunete. Extragerea tumorii se face într-un „endobag"; nu utilizăm tuburi de dren de rutină, iar închiderea plăgilor se face în manieră obișnuită [8-10].

Suprarenalectomia necesită, alături de măsurile generale de îngrijire postoperatorie (antibioprofilaxie, profilaxia bolii trombo-embolice etc.) și câteva măsuri specifice. Controlul hipertensiunii arteriale și a diabetului zaharat sunt deosebit de importante la acești pacienți. În ceea ce privește substituția cu glucocorticoizi, pentru prevenirea insuficienței corticosuprarenaliene, utilizăm pentru început hidrocortizon i.v. iar ulterior, după reluarea alimentației, tablete de prednison sau prednisolon. Durata terapiei este de 6-12 luni pentru adrenalectomia unilaterală și pentru restul vieții pentru cea bilaterală [8-10].

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Conflict de Interese

Autorii nu declară niciun conflict de interese.

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