

Presentation of Gastric Adenocarcinoma with Acute Arterial Occlusive Disease, Nonbacterial Thrombotic Endocarditis and Pyogenic Liver Abscess

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Abstract

Fatal outcome at early presentation of cancer is rare. Here, a case is discussed of a 53 year old female that presented with an acute onset of left lower extremity pain with paleness, pulselessness, abdominal cramps and vomiting that had been present for several weeks. Rapid evaluation led to the initial diagnosis of metastasized gastric cancer that had evolved to hepatic abscedation and aortic valve endocarditis. The patient rapidly developed severe sepsis with multiple organ failure and died 48 hours after presentation.

Keywords: Gastric adenocarcinoma; Trousseau's syndrome; Acute arterial thrombosis; Paraneoplastic syndrome; Nonbacterial thrombotic endocarditis; Pyogenic liver abscess

Background

Gastric cancer usually presents with nonspecific signs of weight loss, abdominal pain and nausea. Physical signs are extremely rare, a palpable mass indicates an advanced status of the disease [1]. When symptoms occur the disease has most often already reached an incurable state, however it can be cured if diagnosed at early stages for instance as part of endoscopic screening programs [2]. Metastasis typically involves the lymph nodes, "per continuitatem" the tumor can spread to pancreas, liver, large and small bowel and, less frequently, to the spleen [3,4]. Diagnosis is typically made by endoscopy and biopsy. As seen by histopathology the most common type of gastric cancer is the adenocarcinoma arising from the gastric glandular epithelium either as intestinal type or diffuse type [5]. Peak incidence is usually between 50-70 years of age with a male to female ratio of around 2:1 [6]. Curative treatment remains reserved for the early non metastasized form and involves surgical removal of the tumor and varying (neo) adjuvant chemoradiotherapy protocols. Paraneoplastic phenomena are not frequent but most commonly present with acanthosis nigricans or seborrheic keratosis [7]. Another rare paraneoplastic syndrome is Trousseau's sign of malignancy syndrome which usually presents with a hypercoagulable state and venous thromboembolism [8,9]. Trousseau (1801-1867) a professor of clinical medicine in Paris/France observed this eponymous syndrome as phlegmasia alba dolens (also called today milk leg, associated with deep vein thrombosis) on himself shortly before he was diagnosed with gastric cancer [10]. Until today, 200 years after Trousseau described the syndrome it remains poorly understood. Well-known is the association with mucin producing carcinomas of visceral origin [11]. Current research points out that Trousseau's Syndrome (TS) is not caused by a single dysfunction but a complex interplay involving secreted mucins, elevated tissue factor expression, direct factor 10 activation and tumor hypoxia [9]. Since removing of the underlying tumor causing TS is often not possible, treatment remains symptomatic in most of the cases. Heparin is reported with the best outcome preventing coagulation in this condition [12,13]. This may be the first detailed description of a case of peripheral arterial occlusion caused by gastric cancer in the English literature to the best of our knowledge.

Case Presentation

A 53-year-old woman presented with an acute onset of left lower extremity pain with associated local coldness and paleness. She also reported recurrent episodes of vomiting and stomach pains after eating that had been present since 2 months and were unresponsive to treatment with metoclopramide. The patient had undergone outpatient esophagogastroduodenoscopy 3 days before but was unaware of the result. However, treatment with a proton pump inhibitor had been initiated. The medical history was notable for asthma and cholecystectomy several years ago. Night sweats, unintentional weight loss or fever in the last 3 months were not reported. At admission, the patient was alert, fully orientated and afebrile. Physical examination revealed absent posterior tibial and dorsalis pedis pulses on the left side with normal examination on the right side. Blood was drawn for laboratory examination and bacterial culture.

Investigations

Laboratory tests revealed a range of abnormalities including abnormal renal and liver function, high white cell count and elevated lactic acid. Comprehensive test results are shown in Table 1. A magnetic resonance angiography (MRA) of the lower extremities revealed an occlusion of the distal superficial femoral artery and absent perfusion from the left popliteal artery downwards (Figure 1). The clinical and radiological finding of an acute arterial occlusion indicated emergency transpopliteal thrombectomy: several thrombi were retrieved from the superficial femoral, popliteal, anterior and superior tibial and peroneal artery. The thrombi were later being found to be typical

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Variable	Reference range for adults	On presentation	24 h after presentation
Hematocrit (%)	0.36-0.46	0.475	0.4
Hemoglobin (g/dl)	12 - 16	16.4	13.3
White-cell count (per mm ³)	4300 - 10000	32.0	28.8
Differential count (%)			
Neutrophils	50-70	82	
Lymphocytes	25-40	9	
Monocytes	2-8	9	
Basophils	0-1	0.0	
Platelet count	150000-350000	147000	129000
Sodium (mmol/l)	135-145	130	131
Potassium (mmol/l)	3.5-5.1	4.6	5.4
Chloride (mmol/l)	100-108		96
Glucose (mg/dl)	60-100	164	63
Calcium (mmol/l)	2.10-2.60	2.59	
Troponin T (pg/ml)	< 100	30	
Creatine kinase (U/l)	< 140	285	31280
C-reactive protein (mg/dl)	< 0.5	32.1	
Lactic acid (mmol/l)	< 2.4	8.25	18
Pancreatic lipase (U/l)	< 60	17	
Liver function:			
Bilirubin (mg/dl), total	< 1.2	1.21	
Aspartate aminotransferase (U/l)	10-35	1702	
Alanine aminotransferase (U/l)	10-35	1170	
Gamma-glutamyl transpeptidase (U/l)	< 39	56	
Alkaline phosphatase (U/l)	< 98	292	
Lactate dehydrogenase (U/l)	< 242	1227	
International normalized ratio		1.66	2.13
Kidney function			
Creatinine (mg/dl)	0.5-1.1	1.88	2.95
Blood urea nitrogen (mg/dl)	< 23.35	31.76	
Arterial blood gases			
Fraction of inspired oxygen			0.4
pH	7.35-7.45		7.313
Partial pressure of carbon dioxide (mmHg)	32-45		23.3
Partial pressure of oxygen (mmHg)	83-108		69.3
Base excess (mmol/l)	-3.4-1.4		-12.9

Table 1: Laboratory data.

white thrombi without the presence of malignant cells in the histologic specimen. Additionally, 100000 IU of urokinase was administered intraarterially and continuous administration of heparin was initiated with an activated partial thromboplastin time target value of 80s. Postoperatively, popliteal pulses were palpable, a good venous return was achieved and the patient was admitted to the intermediate care unit. Reocclusion developed within hours and the overall condition of the patient worsened. Accelerated pathological examination of six biopsy samples taken 4 days earlier were not diagnostic for malignancy, however the gastroenterologist that had performed the procedure reported high clinical suspicion of gastric cancer (Figure 2). Sonography of the liver revealed multiple hypochoic masses which

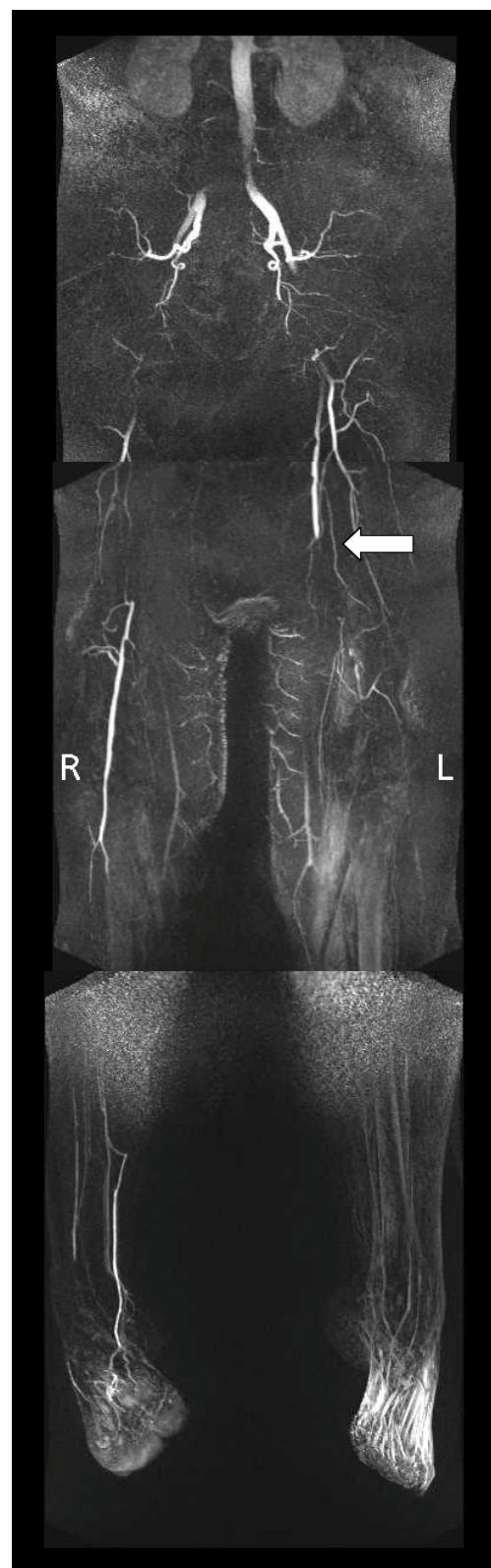


Figure 1: Coronal 3D MRA step-table examination showing occlusion of the distal right superficial femoral artery.

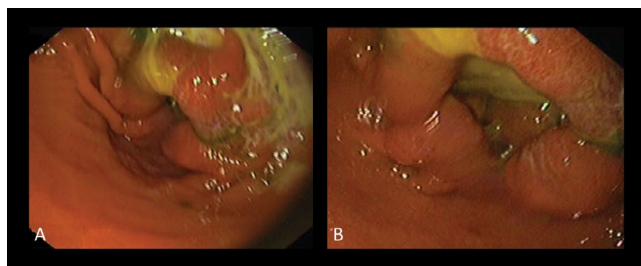


Figure 2: Endoscopic image showing a partially circumferential mass obstructing the antrum [A], close up underlining the circumferentially constricting character of the mass [B].

partially contained gas and partially were solid, raising concern for hepatic metastasation and abscedation. Evaluation of the spleen showed segmental hypoperfusion raising concern for septic embolism from a suspected gastric origin. Transesophageal echocardiography (TEE) showed a 2 mm in diameter large hypoechoic vegetation floating into the left ventricular outflow tract (Figure 3). Three sets of blood cultures were drawn at different time points and antibiotic treatment for suspected infective endocarditis with sultamicillin, gentamicin and ceftriaxone was initiated. The patient was transferred to the intensive care unit. At the time of transfer, the patient was alert and responsive, afebrile, tachycardic, hypertonic with a systolic blood pressure of 200 millimetre of mercury and anuric. She complained about severe abdominal cramps. Blood lactic acid level was 18 mmol/l, raising concern of low flow abdominal ischemia. A central venous catheter was placed and fluid replacement was intensified, together with analgesic therapy. Computed tomography (CT) of the abdomen was performed with the application of oral contrast media. It showed a large mass obstructing the gastric pylorus as well as pathological lymph nodes along the lesser curvature. In the right liver lobe, several hypodense lesions with ill-defined margins suggestive of metastases were noted. Additionally, presence of a 4 × 3 cm wide collection in diameter of intrahepatic gas in segment seven confirmed the presence of a hepatic abscess. CT guided percutaneous transhepatic puncture with aspiration was performed. Fluid that was sent for bacterial culture grew *Escherichia coli* (*E. coli*). Out of seven pairs of blood cultures drawn during stay the first pair obtained at admission was positive for *E. coli*, *Staphylococcus epidermidis* grew in one aerobic bottle, all others remained sterile. Esophagogastroduodenoscopy was repeated. It revealed a tumour of the prepyloric antrum that was barely passable with a flexible endoscope. Eight biopsies were taken from the lesion. Microscopic examination eventually showed a poorly differentiated, signet cell containing mucinous adenocarcinoma of the diffuse type (Figure 4). TNM stage was pTx, G3. Rx. On the following day, septic shock with renal failure required initiation of hemofiltration and pressure support. Abdominal CT with the injection of contrast material showed progression of the hepatic gas collections and occlusion of the celiac trunk (Figure 5). A decision not to escalate treatment (inotropes, mechanical support) due to poor prognosis was taken after extensive discussion with the patient's family. She died nine hours later of sepsis and multiple organ failure. A post-mortem examination was not performed as consent was not given by the next of kin.

Discussion

The association of cancer with thrombotic disorders of the venous and arterial system is well recognized and was first described in 1861. TS has since then undergone numerous extensions and been

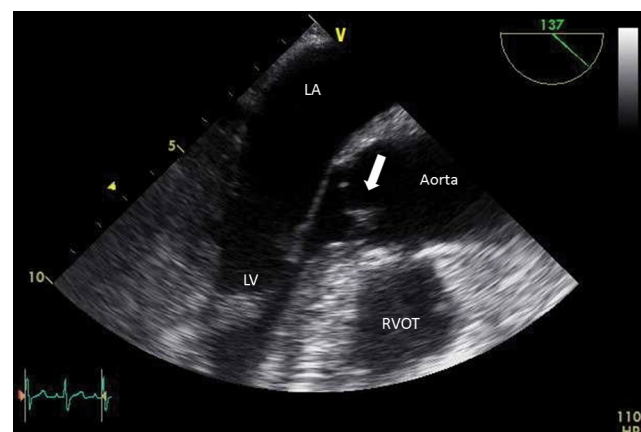


Figure 3: 2D TEE midesophageal long-axis view showing aortic valve vegetation (arrow). LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract.

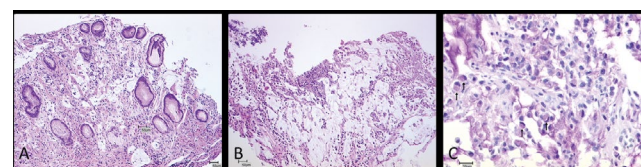


Figure 4: Biopsy specimens from the gastric tumor. The findings are consistent with the presence of poorly differentiated, diffuse type signet-cell containing adenocarcinoma. [A] Section demonstrating diffusely infiltrating tumor-cell complexes within differentiated glands, [B] Section showing typical appearance of diffuse type gastric carcinoma consisting of loose, mucin producing cells within large pools of mucus (both hematoxylin and eosin stain) [C] Close up showing signet cells characterized by abundant cytoplasmic mucin that displaces the nucleus to the periphery (arrows, 100X periodic acid-Schiff stain, 400X).

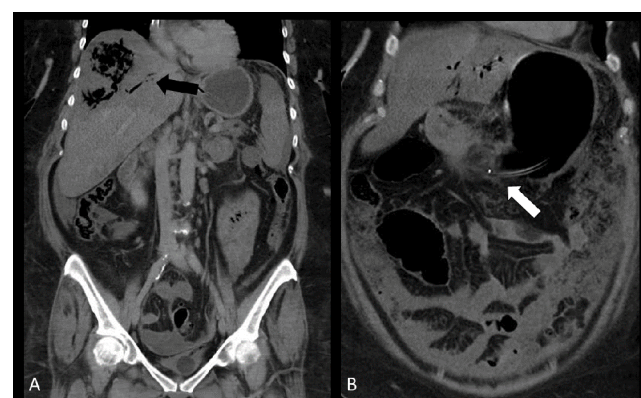


Figure 5: Coronal abdominal computed tomography scan with the injection of contrast material [A] showing extensive gas-collections in the right liver lobe (black arrow) as well as disseminated hypodense areas in both liver lobes. Coronal image of the abdomen [B] showing a large nodular mass with ill-defined borders in the pyloric region (white arrow).

ascribed to various clinical situations, from the classic descriptions to any kind of coagulopathy occurring in the context of cancer [8]. While venous thromboembolism is the second leading cause of death in cancer patients, data on arterial ischemic events is rare. Khorana et al, in a retrospective cohort study report on the incidence

of thromboembolism in 66,106 adult neutropenic cancer patients with 88,074 hospitalizations over eight years at 115 medical centers in the United States. In that cohort, thromboembolism was reported in 5,272 (7.98%) of the patients, whereas acute arterial embolism was only reported in 171 (0.26%) patients. Of these events, only one was attributable to stomach cancer (0.17% of patients with stomach cancer) [14]. In contrast to venous thromboembolism, there was no difference in incidence of arterial thromboembolism between subgroups divided by type of malignancy and presence or absence of metastatic disease [15]. The optimal treatment for cancer associated arterial embolism is unclear. Operative revascularization is unlikely to be successful and repeated attempts may be required. Systemic anticoagulation may be beneficial and can be evaluated according to the severity of ischemia and the life expectancy. Arterial embolization in this case likely resulted from nonbacterial thrombotic endocarditis (NBTE), the cardiac manifestation of systemic hemostatic activation resulting in platelet and fibrin vegetation on cardiac valves. A prospective, echocardiographic screening study of a cohort of 200 cancer patients found a prevalence of cardiac valvular vegetations of up to 19% in the cancer cohort compared to only 2% ($P < 0.001$) in the control group [16]. This was considerably lower than the prevalence of 0.9 - 1.3% reported in postmortem autopsy studies of patients dying of cancer [17]. It has been suggested that nonbacterial vegetations are relatively frail, therefore have a high tendency of embolization and may thus be underreported in postmortem studies [15]. NBTE has been associated with the presence of disseminated intravascular coagulation (DIC) [18], underlining the multifactorial etiology and overlap of both processes. Contributing factors include procoagulant alterations such as tissue factor and cancer procoagulant expression by tumor cells, host immune responses, and factors related to treatment [19]. Moreover, hepatic insufficiency may have contributed to the coagulation disorder in this case due to altered coagulation factor production. Infective endocarditis as a differential diagnosis, although improbable, cannot be totally ruled out, formally, it was possible according to the modified Duke criteria [20]. The hereby reported case is unique in its association of Trousseau's syndrome including nonbacterial thrombotic endocarditis with gastric cancer and its rapidly fatal clinical course. The absence of specific early symptoms of gastric cancer may have contributed to clinical outcome. At the time of admission, first steps had been made to explore the reported symptoms, but the results were unknown to the patient. Interestingly, histologic examination of the specimen obtained at the first endoscopy revealed no signs of malignancy. A prospective evaluation found a sensitivity of 100% for pathological diagnosis of gastric cancer from seven biopsy specimens [21], six had been taken in this case. The authors of that study recommend a minimal number of 4 biopsies (95% sensitivity for gastric cancer), current American and European guidelines make no recommendations about the number of biopsies to be taken at endoscopy [22,23]. In this case of gastric cancer, it was further complicated by pyogenic liver abscess (PLA) that had a rapid and unfavorable evolution. PLA for itself is a critical infectious disease with high morbidity and mortality; it is relatively rare in western countries with a reported incidence from 1-2.3/100,000 and has a known association with gastrointestinal cancers [24]. Clinical features and outcome varies according to the causative agent. In a retrospective analysis of 72 patients with *E. coli* PLA, 30.6 % were found to have underlying malignancy, together with diabetes mellitus the most common concomitant disease [25]. Treatment involves empiric antibiotic therapy, percutaneous drainage and surgery in selected cases. In the aforementioned study, overall mortality due to *E. coli* PLA was high at 26.4%. In this patient, gastric cancer presented in a rare and nonetheless fatal form, leading to rapid clinical deterioration and death.

Conclusion

Arterial occlusion may be the first sign of an undiagnosed cancer. Especially when other signs of malignancy are present a thorough investigation is mandatory to reduce morbidity, mortality and, eventually unnecessary procedures.

Authors' Contributions

JD, HZ, and GW were involved in treatment of the patient. JD and PB wrote the manuscript and GW and HZ revised and edited the manuscript. All authors read and approved the final manuscript.

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