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A Marantic Endocarditis Complicating a Metastatic Gastric Adenocarcinoma Initially Resistant to Low-molecular Weight Heparin: A Case Report

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Abstract

Background: Marantic endocarditis is a rare paraneoplastic syndrome which results from an hypercoagulate state. It can be associated with several tumors, particularly gastric cancer, and histology of adenocarcinoma. Mucines secreted by adenocarcinoma contribute to the activation of the coagulation pathway.

Case presentation: We present the case of a patient with a marantic endocarditis complicating a metastatic gastric adenocarcinoma. He was hospitalised for a thoracic pain. At the physical examination, we found swelling, redness, and warmth of the right lower limb, suspected for a deep vein thrombosis that was confirmed at the echo doppler ultrasound. CT scan documented a severe bilateral pulmonary embolism, a splenic infarction, and multiple liver metastases. Laboratory tests were normal. Despite a Low-Molecular Weight Heparin (LMWH) treatment, the patient presented a cerebral stroke, confirmed at the MRI. Trans-thoracic echocardiography found a small vegetation of the mobile end of the mitral valve with a normal left ventricular contractile function. LMWH was switched by continuous intravenous Unfractionated Heparin (UFH). PET scan showed multiple liver metastases and a pathological gastric hypermetabolism. Liver biopsy confirmed a metastasis of a HER-2 negative gastric adenocarcinoma. Because of the stop of heparin treatment during this procedure, the patient presented a new brain stroke. A systemic palliative chemotherapy was started by FOLFOX-4 regimen and it is now ongoing.

Conclusion: The particularity of this case relies on the impossibility to initially switch UFH by another anticoagulant treatment. Chemotherapy represents the only possibility to decrease mucine production and thrombi formation.

Keywords: Marantic endocarditis; Gastric adenocarcinoma; Stroke attack; Low-Molecular weight heparin

Introduction

Marantic Endocarditis (ME) is a rare paraneoplastic syndrome usually associated with gastric, pancreatic, and lung cancer, originally described by Ziegler in 1888 [1]. Considering its pro-emboligenic properties, it is frequently complicated by serious arterial ischemic events, the brain stroke being the most commonly first ME clinical presentation [2]. ME should be suspected in any cancer patient presenting recurrent arterial strokes in the absence of thrombophilia test alteration and positivity of bloodstream cultures. The best ME treatment relies on an efficacious anticoagulation heparin therapy which should be continued indefinitely [1,2]. ME is resistant to anti-vitamin K agents and these drugs have to not be used in this pathology [3]. The purpose of this report is to describe an unusual clinical case of ME in a 52-year old man suffering from asymptomatic, metastatic, gastric cancer, initially resistant to a Low-Molecular Weight Heparin (LMWH) treatment.

Case Report

In February 2015, a 52-year-old, Caucasian, male patient consulted to our hospital for acute chest pain. Physical examination found a right leg swelling, redness and warmth, with a positive Homans' sign, suspected for a deep venous thrombosis and a sinusal tachycardia. Venous doppler ultrasound confirmed a venous thrombosis of the superficial femoral vein up to 10 cm from the saphenous vein. Whole body CT scan showed a bilateral pulmonary embolism with a rigid proximal cardiac septum and a dilatation of the right cardiac cavities Figure 1A, a splenic infarction, multiple liver metastases, and a deep thrombosis of the right femoro-popliteal vein without iliac extension. Laboratory findings and thrombophilia tests were in the normal as well as homocysteine levels. Tumor marker test revealed increased levels of the carcino-embryonic antigen at 1290 ng/ml and of CA19-9 at 636 UI/ml. A LMWH treatment was started. Trans-thoracic echocardiography found a small vegetation of the mobile end of the mitral valve with a normal left ventricular function (VEF: 65%) Figure 1B. Reiterative bloodstream cultures were negative as well as the other infectious tests. Despite anticoagulant treatment, the patient presented an episode of acute disorientation, which spontaneously resolved. Brain CT scan showed the presence of multiple, sub-acute ischemic lesions in the right thalamus and cerebellum and in the left semioval center. EEG was normal. Brain MRI confirmed the multiple ischemic lesions Figure 1C-a. During the hospitalisation, the patient presented an acute episode of right big toe ischemia, confirmed at the doppler ultrasound. For this raison, LMWH anticoagulation was switched by continuous intravenous Unfractionated Heparin (UFH) and oral aspirin. PET scan showed multiple liver metastases associated to a pathologic gastric hypermetabolism. Cardiac MRI, performed after 7 days of full UFH

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anticoagulation, was normal. A percutaneous biopsy of a liver lesion was performed. Histology revealed a metastasis of an adenocarcinoma Figure 1D. At the immunohistochemical stains, tumor cells were positive for cytokeratins 7 and 20 and for the CDX2 and negative for the TTF-1, suggesting a primary gastric cancer Figure 1E. FISH test for HER-2 was negative. In order to perform this biopsy, anticoagulation was stopped and the patient presented another episode of acute cerebral stroke, with a right hemiplegia and multiple cranial nerve deficits that gradually regressed after restarting full UFH anticoagulation. Another Brain MRI was urgently performed, confirming the presence of new, multiple, bilateral, ischemic lesions Figure 1C-b, as compared to the first brain MRI. Gastroscopy was not realised considering the bad clinical patient conditions and the high risk of this procedure during anticoagulation treatment. A systemic chemotherapy with the FOLFOX-4 regimen was started with a rapid decrease of tumor markers. After 4 cycles of treatment, the patient is alive and in good clinical conditions. As trans-thoracic echocardiography was normal, UFH was stopped and switched by LMWH anticoagulation.

Discussion

Marantic Endocarditis (ME) or Nonbacterial Thrombotic Endocarditis (NBTE) is a very rare complication of malignancy and other hypercoagulable states [1-3]. About 15% of cancer patients suffer from thromboembolic event during their clinical course and evidence of venous thromboembolism is found in 50% of cancer patients at the autopsy [3]. Firstly described by Ziegler in 1888, ME is characterised by the presence of small, sterile, fibrin-thrombi rich vegetations on normal or superficially degenerated valve leaflets in the absence of a bloodstream bacterial infection and by an increased frequency of arterial embolic events in patients with chronic, tumor, inflammatory or autoimmune diseases. The most commonly sites include aortic and mitral valves [1-3].

Its diagnosis is based mainly on the negativity of bloodstream cultures, the lack of response to antibiotic treatment and the presence of vegetation on trans-thoracic or trans-esophageal echocardiography [3]. ME is the result of an hypercoagulability of the blood that is usually associated with cancer disease. This strict correlation between cancer and thromboembolic disease was originally described by Armand Trousseau in 1865 and it is named Trousseau syndrome [4]. ME pathophysiology is complex and only partially elucidated. In 2003, Wahrenbrock et al showed that mucine, frequently producted by adenocarcinomas, induces a state of hypercoagulability by activating L- and P-selectines which stimulate leucocytes to product a short half-life molecule, not yet known, causing the formation of plaletet-rich microthrombi [5]. P-selectin can also bind to and activate platelets and endothelium with an amplification of this process [5,6]. Via the P-Selectin Glycoprotein Ligand-1 pathway, microthrombi activate the CD150 receptor at different sites, including leukocytes, monocytes, and endothelium with an increased production of tissular factor which leads to a thrombus formation [5,6]. Moreover, in 2005, Bocaccio et al showed that MET oncogene can also increase the plasminogen activator inhibitor-1 (PAI-1) and cyclooxygenase-2 transcription [7]. These molecules are implicated in thrombus formation confirming the presence of a strict link between oncogene activation and hemostasis [7]. However, tumor hypoxia can also increase the PAI-1 production [8].

Another hypothesis incriminates Interleukins and Tumor Necrosis Factor (TNF), released secondary to monocytes/macrophages and

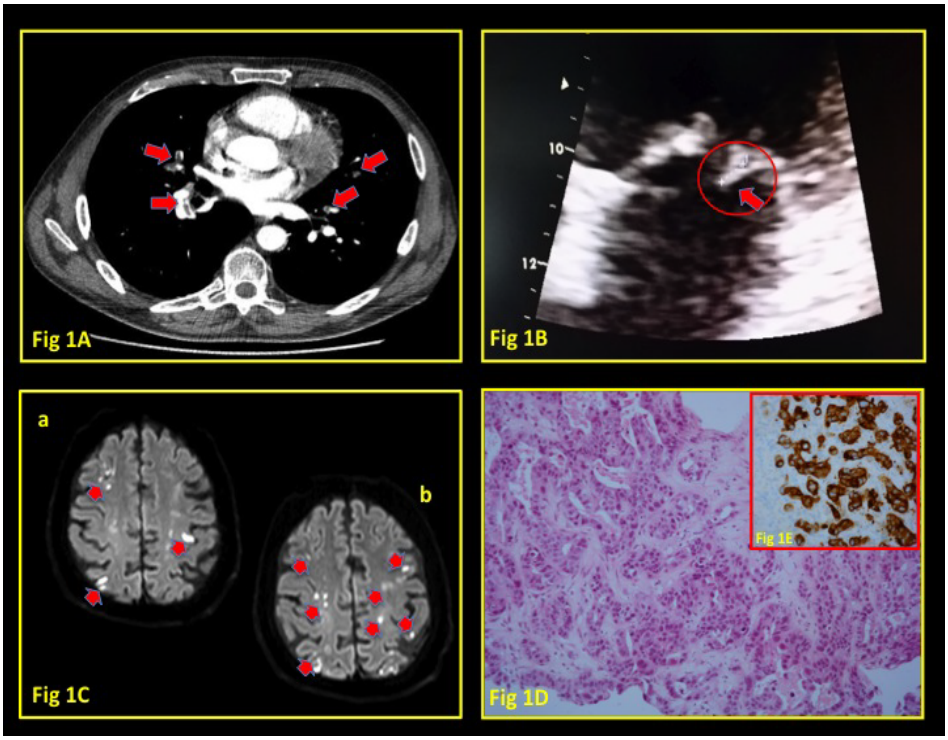

Figure 1: (A) Thoracic CT-scan: Bilateral, proximal lung embolism (red arrows). (B) Trans-esophageal echocardiography: Small vegetation of the mobile end of the mitral valve with a normal left ventricular function (red arrows). (C) a: First Brain MRI: Multiple, bilateral, ischemic lesions (red arrows). (C) b: Second Brain MRI: New, multiple, bilateral, ischemic lesions (red arrows) appeared after temporary UFH stopping before liver biopsy. (D) Histology:Histological tumor pattern is consistent with a liver metastasis of a gastric cancer. (E) Immunohistochemistry: At the immunohistochemical staining, tumor cells are positive for cytokeratin 20 according with diagnosis of a gastric cancer metastatic to the liver.

malignant cells interaction. These cytokins cause an endothelial damage and sloughing, which may lead to the thrombogenesis pathway activation [5,6].

Sterile ME vegetations are variable in size and they do not usually present any inflammatory reaction at the attachment sites. This later characteristic makes ME vegetations very friable and dangerous, with a higher tendency to detach and to embolise as compared to infective endocarditis [1-3,7]. Consequently, ME is a highly pro-emboligenic disease and it is frequently associated with arterial infarcts in various organs, including the spleen, kidney, heart and brain at the diagnosis [6,8]. Brain stroke is the most commonly first ME clinical presentation [7].

The true ME incidence is not known [1-4]. It can occur in any type of cancer except brain tumors [9-19], the most frequent being lung, pancreas, and gastric tumors, in addition to adenocarcinomas of unknown primary sites [9-18]. Clinically, there are no specific signs or symptoms, but it should be suspected in a cancer patient presenting multiple, recurrent arterial strokes without evident coagulation alteration [3,4]. Similarly to infective endocarditis, trans-esophageal echocardiography has been shown to be more sensitive in detecting vegetations than trans-thoracic echocardiography [19]. Finally, reiterative bloodstream cultures must be negative and antibiotics do not have any efficacy [3].

Diffusion-Weighted Imaging (DWI) MRI may help differentiate ME cardioembolic brain strokes from those of infective endocarditis. In an imaging study, four patterns on DWI have been described, including: i) a single lesion corresponding to a solitary embolus; ii) multiple, closely spaced lesions in a single arterial territory; iii) multiple punctuate, disseminated lesions; and iv) multiple disseminated lesions of a variable size. The latest one appears to be more specific for ME and parfectly corresponds to the pattern found in our patient [20].

The two primary goals of the ME management include the treatment of the underlying malignancy and systemic anticoagulation [3]. UFH is the most effective in reducing the incidence of embolic events. LMWHs have also been used and they seem efficacious in several cases reported in the literature. By the contrast, vitamin K antagonists, such as warfarin, should not be used as they seem to be ineffective in controlling the coagulopathy in ME [3,21,22]. The true raison remains unknown but, probably, the vitamin K-related pathway does not play a pivotal role in the ME hypercoagulability. Patients with ME should stay on anticoagulation indefinitely [21,22].

In patients with potentially curable cancer and tumor-associated ME, tumor resection as a first therapeutic priority to eliminate the cause of the coagulopathy should be considered [21]. In cases of persistent embolic events despite anticoagulation and a potentially curable cancer, valvular surgery can be considered prior to tumor resection to minimize the damage caused by the recurrent emboli [21].

Conclusion

ME is a very rare, severe, and probably underestimated and unrecognised paraneoplastic syndrome which results from an hypercoagulated state related to a tumor production of several pro-coagulation factors and the activation of many oncogenes, such as c-MET. Both UFH and LMWH seem to be efficacious, in contrast with anti-vitamin K agents.

In our case, the patient presented an unusual and unexplained initial resistance to LMWH and he was well treated by continuous intravenous UFH which is probably enable to allow a persistent effective anticoagulation by a better bioavailability. A switch to UFH was realised after 4 cycles of chemotherapy when a trans-esophageal echocardiography confirmed the absence of residual mitral vegetations.

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References

1. Piovanelli B, Rovetta R, Bonadei I, Vizzardi E, D'Aloia A, et al. (2013) Nonbacterial thrombotic endocarditis in pancreatic cancer. Monaldi Arch Chest Dis 80: 189-192.
2. Mazokopakis EE, Syros PK, Starakis IK (2010) Nonbacterial thrombotic endocarditis (marantic endocarditis) in cancer patients. Cardiovasc Hematol Disord Drug Targets 10: 84-86.
3. el-Shami K, Griffiths E, Streiff M (2007) Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. Oncologist 12: 518-523.
4. Trousseau A (1865) Medical Clinic of the Hôtel-Dieu de Paris. Paris : Ballière ;. Phlegmasia dolens alba 654-712.
5. Wahrenbrock M, Borsig L, Le D, Varki N, Varki A (2003) Selectin-mucin interactions as a probable molecular explanation for the association of Trousseau syndrome with mucinous adenocarcinomas. J Clin Invest 112: 853-862.
6. Varki A (2007) Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood 110: 1723-1729.
7. Boccaccio C, Sabatino G, Medico E, Girolami F, Follenzi A, et al. (2005) The MET oncogene drives a genetic programme linking cancer to haemostasis. Nature 434: 396-400.
8. Denko NC, Giaccia AJ (2001) Tumor hypoxia, the physiological link between Trousseau's syndrome (carcinoma-induced coagulopathy) and metastasis. Cancer Res 61: 795-798.
9. Yoshii Y, Numata T, Ishitobi W, Takahashi N, Wakui H, et al. (2014) Lung adenocarcinoma complicated by Trousseau's syndrome successfully treated by a combination of anticoagulant therapy and chemotherapy. Intern Med 53: 1835-1839.
10. Shatila W, Rizkallah A, Aldin ES, Tfayli A (2014) Nonbacterial thrombotic endocarditis as the sole manifestation of stage IV gastric cancer: a case report. J Med Case Rep 8: 267.
11. Ito S, Yoshitomi H, Pak M, Kawahara H, Oshima T, et al. (2013) Trousseau syndrome with nonbacterial thrombotic endocarditis in a patient with uterine cancer. Intern Med 52: 1353-1358.
12. Wong SF, Seow J, Profitis K, Johns J, Barnett S, et al. (2013) Marantic endocarditis presenting with multifocal neurological symptoms. Intern Med J 43: 211-214.
13. Arvold ND, Hsu L, Chen WY, Benzaquen LR, Weiss SE (2011) Marantic endocarditis with cardioembolic strokes mimicking leptomeningeal metastases in breast cancer. J Clin Oncol 29: e743-746.
14. Vlachostergios PJ, Daliani DD, Dimopoulos V, Patrikidou A, Voutsadakis IA, et al. (2010) Nonbacterial thrombotic (marantic) endocarditis in a patient with colorectal cancer. Onkologie 33: 456-459.
15. Pons F, Poyet R, Daranda E, Prunet B, Jego C, et al. (2011) [Ischemic strokes as a presenting feature of marantic endocarditis despite heparin treatment]. Ann Cardiol Angeiol (Paris) 60: 233-235.
16. Marglani O, Al-Herabi A, Odell P (2009) Marantic endocarditis as an unusual paraneoplastic syndrome of head and neck squamous cell carcinoma. J Otolaryngol Head Neck Surg 38: E76-77.
17. Jameson GS, Ramanathan RK, Borad MJ, Downhour M, Korn R, et al. (2009) Marantic Endocarditis Associated with Pancreatic Cancer: A Case Series. Case Rep Gastroenterol 3: 67-71.
18. Smeglin A, Ansari M, Skali H, Oo TH, Maysky M (2008) Marantic endocarditis and disseminated intravascular coagulation with systemic emboli in presentation of pancreatic cancer. J Clin Oncol 26: 1383-1385.
19. Lee RJ, Bartzokis T, Yeoh TK, Grogin HR, Choi D, et al. (1991) Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke 22: 734-739.

20. Singhal AB, Topcuoglu MA, Buonanno FS (2002) Acute ischemic stroke patterns in infective and nonbacterial thrombotic endocarditis: A diffusion-weighted magnetic resonance imaging study.Stroke 33: 1267-1273.

21. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, et al. (2004) Antithrombotic therapy in valvular heart disease--native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126: 457S-482S.

22. Bell WR, Starksen NF, Tong S, Porterfield JK (1985) Trousseau's syndrome. Devastating coagulopathy in the absence of heparin. Am J Med 79: 423-430.