

Marantic Endocarditis and Adenocarcinoma of Unknown Primary Site

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Nonbacterial thrombotic endocarditis (NBTE) is a disease characterized by deposition of thrombi and fibrin on normal or degenerated cardiac valves in the absence of microorganisms. This condition is more commonly seen in chronic inflammatory states, and is associated with higher incidence of thromboembolic events than infective endocarditis. We report the case of a 63-year old male patient with adenocarcinoma of unknown primary site and systemic embolism.

Abstract

Nonbacterial thrombotic endocarditis (NBTE) is a disease characterized by deposition of thrombi and fibrin on normal or degenerated cardiac valves in the absence of microorganisms. This condition is more commonly seen in chronic inflammatory states, and is associated with higher incidence of thromboembolic events than infective endocarditis. We report the case of a 63-year old male patient with adenocarcinoma of unknown primary site and systemic embolism.

Introduction

In 1865, Trousseau described the association between cancer and thromboembolism¹. In 1988, Ziegler described nonbacterial thrombotic endocarditis (NBTE) as the deposition of thrombi and fibrin on cardiac valves. Later studies have identified the relationship between NBTE and chronic inflammatory states, including malignancies, septicemia, and severe burns².

The elevated levels of tumor necrosis factor and interleukin-1, associated with cancer, may damage the valvular endothelium leading to thrombus formation³.

The incidence of embolic phenomena is higher than that found in infective endocarditis². In addition, clinical

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manifestations of NBTE result from systemic emboli, and the presence of a new cardiac murmur is a rare finding.

The diagnosis of nonbacterial thrombotic endocarditis is based on visualization of endocardial vegetation associated with the absence of viable microorganisms in the bloodstream².

The standard of care for management of NBTE consists of treatment of the underlying malignancy and systemic anticoagulation⁴.

The authors report the case of 63-year old male patient with adenocarcinoma of unknown primary site who developed neurological symptoms associated with peripheral emboli. NBTE was diagnosed after discovering the origin of the emboli.

Case report

A 63-year-old male patient complained of dull epigastric pain lasting six months that had worsened over the past four days, accompanied by nausea, vomiting, and weight loss of 20 pounds over the previous two months. The patient was an alcoholic, and three months before had undergone an uneventful total hip replacement.

On physical examination, he was in good general condition, alert, afebrile and with well-perfused extremities but jaundiced (+/4+). Abdominal examination: Traube's space was obliterated, the liver edge was palpable in the epigastrium, 5 cm below the right costal margin, and was hard and tender; the spleen was not palpable. Cardiac examination: The apical impulse was palpable at the fifth intercostal space, 1.5 cm of the midclavicular line; his heart rate and rhythm were regular, with normal S1 and S2, and there were no murmurs. No changes were found in other organ systems.

Laboratory testes - Laboratory findings were as follows: Hemoglobin 11.9 g/dl; hematocrit 37.1%; MCV 84.13 fL; MCHC 32.08; platelet count 500,000/mm³; WBC count 15,200/mm³, with 35% of neutrophils and 1% of band forms, C-reactive protein < 7. Urinalysis: bilirubin (+); gamma-glutamyltransferase 128 U/l; alkaline phosphatase 145 U/l; total bilirubin 0.91 mg/dl; conjugated bilirubin 0.58 mg/dl; lactic dehydrogenase 719 U/l. The other laboratory tests were unremarkable.

Abdominal ultrasonography - An abdominal ultrasound examination revealed a heterogeneous, hypoechoic, mass lesion in the left liver lobe measuring 12.3 cm in its largest diameter. The remaining organs appeared normal.

Abdominal computed tomography - A CT scan of the whole abdomen showed small-volume ascites and a macrolobulated, ill-defined, low-density, and heterogeneously-enhanced mass involving segments II, III and IV of the left liver lobe. The right liver lobe was decreased in size, with scalloped

borders and heterogeneous density, in addition to multiple small low-density areas scattered in the liver parenchyma. A thrombus was found extending from the right femoral vein to the inferior vena cava. No changes were found in any of the other structures.

Full anticoagulation therapy was initiated with unfractionated heparin and warfarin.

Liver biopsy - Histological examination of the liver revealed neoplastic tissue consisting of glandular acini lined with cubical and cylindrical cells, with signet-ring cells. Immunohistochemical stains were positive for anti-CK7 and anti-CEA, but negative for CK20, anti-CDX2, anti-TTF1, anti-CA19.9, and anti-Heppar. Therefore, a diagnosis of adenocarcinoma of unknown primary site was made.

As of the third day of admission the patient began alternating periods of disorientation and aggressiveness with periods of lucidity.

Brain computed tomography - A CT brain scan revealed diffuse, low-density, non-enhanced lesions in the white matter adjacent to the horns of the lateral ventricles, in addition to global reduction in brain volume.

On the fortieth day of admission, he developed cyanosis of the distal right lower extremity and the fingers of his right hand, with decreased local temperature (Figure 1). Because this condition occurred during full anticoagulation, drug treatment was maintained.

Transthoracic Doppler echocardiography, using M-mode and two-dimensional imaging, revealed the following: a thickened aortic valve with a mobile, echogenic structure measuring 11 cm, consistent with vegetation; significant aortic regurgitation; mild mitral regurgitation; moderate segmental left ventricular dysfunction; left ventricular diastolic dysfunction of a restrictive pattern; and dilated cardiac chambers (Figure 2).

After the echocardiogram, the patient was treated with gentamicin and ampicillin. Six blood samples were taken from different sites and incubated in an automated Bactec blood culture system. No growth was observed after five days of incubation.



Figure 1 - Necrosis of the right lower extremity.

The patient did not respond to antibiotic therapy. He developed necrosis of the extremities, together with ventilatory failure, and finally died.

Discussion

Nonbacterial thrombotic endocarditis (NBTE), previously known as marantic endocarditis, is characterized by the deposition of thrombi on heart valves in the absence of viable circulating microorganisms².

The incidence of NBTE remains unknown. In a series of autopsy studies of 1640 adult patients, there were 10 cases of NBTE, with prevalence of 1.25% in cancer patients and 0.2% in the general population. The disease was more prevalent in patients with adenocarcinoma, especially pancreatic adenocarcinoma⁴. It has been reported that the most common malignancies associated with NBTE are cancers of the lung, pancreas and stomach and adenocarcinoma of unknown primary site². The incidence of systemic embolism ranges from 14% to 91%^{4,5}.

NBTE is more common between the fourth and eighth decades of life and has no sex predilection.

The most frequent sites of embolization are the spleen, kidney, and extremities, but cerebral and coronary embolism should alert to the diagnosis of NBTE, since they are the main cause of morbidity. In addition, the most common clinical manifestation of NBTE is a sudden, focal neurological deficit².

When present, heart murmurs are systolic and best heard at the left sternal border².

Pulmonary embolism affects 50% of the cases, but all of them were observed in patients with advanced neoplasias and systemic thrombophilia in the setting of NBTE⁶. Transesophageal echocardiography (TEE) is the most sensitive method for detecting vegetations⁶.

The most commonly affected valves, in descending order of frequency, are: the aortic valve, the mitral valve, and combined aortic and mitral involvement. Vegetations are commonly found at the coaptation surface of the valve leaflets, on the atrial surfaces of the mitral and tricuspid valves and on the

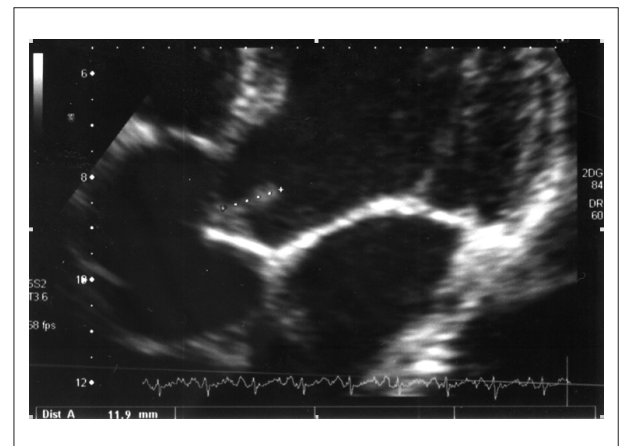


Figure 2 - Transthoracic echocardiography showing a thickened aortic valve with a mobile, echogenic structure measuring 11 cm in its largest diameter. .

Case Report

ventricular surfaces of the aortic and pulmonic valves, usually without impairing valve function^{2,4}.

Some studies suggest a synergy between the valvular injury, thrombocytosis, and coagulation factor activity². Genetic studies have shown that the MET oncogene increases the activity of type-1 plasminogen activator inhibitor (PAI-1) and cyclooxygenase-2 (COX-2) genes, contributing to thrombus formation⁷.

The differentiation between thrombotic and infective endocarditis can become a diagnostic dilemma. The presence of vegetations on the coaptation surface without destruction of valve tissue and the involvement of heart valves bilaterally or only on the right side are highly suggestive of NBTE^{5,8}. Diffusion-weighted MRI makes it possible to demonstrate that patients with NBTE tend to develop multiple, widely distributed infarcts, whereas single lesions or focal infarcts are more characteristic of infective endocarditis^{2,5,8,9}. In the present case, although there was no histopathological evidence, the absence of fever, the consistently negative blood cultures, and the lack of clinical improvement after antibiotic therapy are strongly suggestive of NBTE.

Patients with cancer who develop neurological symptoms should be evaluated, and magnetic resonance imaging is the most sensitive test for detecting metastases and strokes. Using

diffuse-weighted imaging (DWI), it is also possible to know if the origin of the embolus is related to infective or nonbacterial thrombotic endocarditis⁹.

Management of NBTE consists of treatment of the underlying malignancy and systemic anticoagulation. The most effective anticoagulant in the treatment of NBTE is unfractionated heparin; when administered continuously, it reduces the risk of recurrent thromboembolism¹⁰. Recurrent thromboembolic events were observed in patients on vitamin K antagonists, but further studies are needed to confirm this association².

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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