Nonbacterial Thrombotic Endocarditis with Embolic Vascular Events as A Manifestation of Advanced Pancreatic Cancer: A Case Report

Filipa Duarte-Ribeiro1*, Cátia Dias1, Raquel Barreira1, Janine de Resende2 and João Valente2

1 Department of Internal Medicine, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal
2 Department of Internal Medicine, Centro Hospitalar Vila Nova de Gaia/Espinho-Intermediate Care Unit of Medicine, Portugal

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*Corresponding author: Filipa Duarte Ribeiro, Department of Internal Medicine, Centro Hospitalar Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, 4434-502 Vila Nova de Gaia, Portugal, Email: filiparibeiro@gmail.com

Abstract
Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, is a very rare complication of malignancy and other hypercoagulable states that is characterized by deposition of sterile vegetations (consisting of thrombi and fibrin) on the heart valves. The most commonly affected valves are the aortic valve, the mitral valve or both simultaneously; involvement of the right heart valves is less common. The marantic endocarditis occurs in the context of noninfectious chronic inflammatory conditions, particularly visceral malignancies, and the vegetations are much more prone to detach and embolize as compared to infectious endocarditis. Patients typically present with signs and symptoms of arterial emboli, such as ischemic cerebral events and acute coronary syndromes.

The authors present a case of a 44-year-old male, with recent history of deep venous thrombosis and pulmonary emboli and hipocoagulated with apixaban, admitted for ischemic strokes. The study shows that it was secondary to nonbacterial thrombotic endocarditis in context of unknown metastatic pancreatic cancer.

The authors reported this case because this is a rare and unusual first manifestation of malignancy, with only few reports in the literature.

Keywords: Marantic endocarditis; Embolism; Pancreatic cancer

Abbreviations: NBTE: Nonbacterial Thrombotic Endocarditis; IE: Infectious Endocarditis; TTE: Transthoracic Echocardiogram; LDH: Lactate Dehydrogenase; CT: Computed Tomography; TEE: Transesophageal Echocardiogram; MTHFR: Methylenetetrahydrofolate Reductase; PAI-1: Plasminogen Activator Inhibitor-1

Introduction
The association between cancer and thromboembolism was first described by Trouseau in 1865. In 1988, Ziegler described Nonbacterial Thrombotic Endocarditis (NBTE) as the deposition of thrombi and fibrin on cardiac valves [1]. The pathogenesis of NBTE is incompletely understood. The elevated levels of tumor necrosis factor and interleukin-1, associated with cancer, may damage the valvular endothelium leading to thrombus formation. The major clinical manifestations result from systemic emboli rather than valvular dysfunction and the presence of a new cardiac murmur is a rare finding. Common sites of embolization include the spleen, kidney, and extremities, but the most significant morbidity arises from emboli to the central nervous system [1-3]. The most frequently malignancies associated with NBTE are adenocarcinomas of the lung, ovary, biliary system, pancreas, and stomach [3]. The diagnosis of NBTE is based on visualization of endocardial vegetation associated with the absence of viable microorganisms in the bloodstream. But there are no pathognomonic signs and symptoms that allow the diagnosis of NBTE and it can be often confused with that of culture-negative Infectious Endocarditis (IE) [1,3]. The standard care of management is directed to control the underlying disease and systemic anticoagulation [1-3]. Cardiac surgery is a reasonable intervention in selected circumstances where the risk-benefit balance is favorable [2,3].

Case Report
A 44-year-old caucasian man presented to the Emergency Department with symptoms of duration of four days of dizziness, mental confusion and gait imbalance, associated with onset of
loss of strength in the upper and lower right limb and erasure of the nasolabial sulcus about 6 hours before admission; he denied sensory or visual changes, dysarthria, and dysphagia. Also denied fever, respiratory, urinary or gastrointestinal symptoms. He reported loss of appetite and a marked weight loss not quantify. Fifteen-days prior to this presentation, he was diagnosed with deep venous thrombosis of the left lower limb and pulmonary emboli. At that time, Transthoracic Echocardiogram (TTE) revealed: slight dilation of the left ventricle; valvular structures without significant morpho-functional changes; mild depression of left ventricular systolic function, with a calculated ejection fraction of 44%; right ventricular systolic function preserved; no pericardial effusion; and vena cava inferior with normal dimensions and normal respiratory variation. He started oral hypo coagulation with apixaban 5mg twice a day.

On physical examination, he was alert but inattentive, with orientation in space but not in time. Fulfill orders properly but with easy distraction. He presented left hemineglect, eyes in the midline, with apparent visual hemi extinction. There was erasure of the left nasopharyngeal sulcus, left hemiparesis with left upper limb plegia and apparent sensory hemi extinction without hypoesthesia. There were no hemodynamic changes, but he was febrile (38.3 °C). Cardiopulmonary examination revealed clear lungs and normal S1 and S2 and an apical murmur (grade III/VI) with heart rate and rhythm regular. No changes were found in other organ systems.

An initial blood count revealed hemoglobin of 13.6g/dl, leukocytosis (16.390/mm³) with 84.6% of neutrophils and thrombocytopenia (70.000/mm³); the biochemical panel showed a Lactate Dehydrogenase (LDH) of 700U/L, high-sensitive cardiac troponin T of 522 ng/L and increased C-reactive protein (14.56mg/dl); the other laboratory tests were unremarkable. Brain Computed Tomography (CT) showed recent ischemic lesions in the superficial territory of the right middle cerebral artery. The TTE revealed a significant new aortic regurgitation; no evident images suggestive of vegetations or endocavitary thrombi; left ventricular systolic function slightly depressed. In the Transesophageal Echocardiogram (TEE) was evident a mitral valve with a slight thickening of the leaflets and an echogenic mass adhering to the atrial face of the free edge of both leaflets suggestive of thrombus/vegetation (Figure 1a); mitral regurgitation (Figure 1b & 1c); a trivalve aortic valve with diffuse thickening of the cusps at the level of its free edge, suggestive of inflammatory/infectious involvement (Figure 1d); moderate to severe aortic regurgitation; large, mobile echogenic mass image adhering to the tricuspid sub valvular apparatus compatible with thrombus and/or vegetation.
Despite failure to meet the modified Duke criteria, the patient was febrile, with increased inflammatory parameters and findings of IE on the echocardiogram, so it was decided to initiate empirical therapy with ceftriaxone, gentamicin and ampicillin. Serial blood and urine cultures were collected and were all negative. A CT scan of thorax, abdomen and pelvis showed: diffuse liver metastases; hepatic, renal and splenic infarcts; pancreas with a nodular area in the upper planes of the tail (± 30mm) suspected to be a neoplastic lesion (Figure 2). The hypercoagulable states panel [including prothrombin time, fibrinogen, protein C deficiency, protein S deficiency, antithrombin III deficiency, Factor V Leiden, anticardiolipin antibodies (IgG and IgM), anti-β2 glycoprotein 1 antibodies (IgG and IgM), lupus anticoagulants and screening for Methylene tetrahydrofolate Reductase (MTHFR), Plasminogen Activator Inhibitor-1 (PAI-1), and prothrombin gene mutations] showed an elevated D-dimer and lactate dehydrogenase, and also heterozygosity for MTHFR and PAI-1 mutations. As for the malignancy workup, tumor markers (carcinoembryonic antigen, CA 19-9, CA-125, Cyfra 21-1, Alpha-fetoprotein and prostate-specific antigen) were taken and the results were significant elevated for CA-125, Cyfra 21-1 and carcinoembryonic antigen.

![Figure 2: Axial CT thorax, abdomen and pelvis showing diffuse liver metastases (filled arrow); hepatic, renal and splenic infarcts (dashed arrow); pancreas with a nodular area in the upper planes of the tail (± 30mm) suspected to be a neoplastic lesion (circle).](image)

With the suspicion of IE subsiding in light of a malignancy and a hypercoagulable state, the patient was started on enoxaparin to treat a possible NBTE. He progressively worsened until the 15th day of hospitalization when he died.

Discussion

This case report describes a previously healthy young man with a new diagnosis of metastatic cancer presenting with evolving ischemic hepatic, renal, splenic, and cerebral lesions secondary to NBTE. NBTE is an uncommon hypercoagulable condition, which results in the development of sterile vegetations on the heart valves and is most commonly associated with advanced visceral malignancies and systemic inflammatory processes such as lupus erythematosus and disseminated intravascular coagulation [4]. The most common affected valves, in descending order of frequency, are the aortic valve, the mitral valve and the involvement of both simultaneously; the right-sided heart involvement is rare and much more difficult to detect clinically. The majority of such valve involvement is typically diagnosed in the postmortem period [1,4]. In the case reported the affected valves were the aortic and mitral simultaneously; the TEE was more sensitive in detecting vegetations than TTE, similar to that described in IE.

Pancreatic adenocarcinoma has demonstrated a strong association with NBTE, although most data are obtained postmortem. Many cases of NBTE in the setting of advanced malignancy are asymptomatic and are diagnosed only after the onset of manifestations of arterial embolization. The clinical diagnosis can be challenging, as the disease can be insidious or easily conflated with IE. In the case reported, the presentation clinic was the stroke associated with cardiac murmur cardiac; the study show, multiple arterial embolization, vegetation in aortic and mitral cardiac valve, serial blood cultures negative, diffuse liver metastases with a pancreatic with a nodular area suspected of a neoplastic lesion and tumor markers elevated.

The mainstay of treatment is to control the underlying inflammatory cause. Systemic anticoagulation is indicated, and the unfractionated heparin is considered to be the most effective in reducing the incidence of embolic events, but success has been seen with low-molecular weight heparin as well. Vitamin K antagonists such as warfarin should not be used. In the case of malignancy, surgery, radiation therapy, and chemotherapy may be considered, depending on the extent of disease and the patient's performance status. This may be difficult to achieve in patients with advanced disease, and pancreatic cancer in particular is
Conclusion

Cancer is associated with significant hypercoagulable state that increases the risk of thromboembolism. NBTE is a serious and potentially underdiagnosed manifestation of a prothrombotic state that can cause substantial morbidity in affected patients, most notably recurrent or multiple ischemic cerebrovascular strokes. Diagnosis requires a high degree of clinical suspicion. The long-term outcome for most patients with NBTE associated with malignancy is poor, because it is typically associated with disseminated and incurable malignancies. Nevertheless, antitumor and anticoagulant therapies often have significant palliative benefit and so should be used for the most patients with NBTE.

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