

Non-bacterial thrombotic endocarditis: a case report with favorable evolution and literature review

Endocardite trombótica não bacteriana: relato de caso com evolução favorável e revisão da literatura

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ABSTRACT

Nonbacterial thrombotic endocarditis is an uncommon disease characterized by formation and deposition of sterile fibrin vegetations on heart valves. This condition is more related to states of chronic inflammation, mainly related to malignancy. This report describes the case of a Brazilian woman, 50 years old, smoker, diagnosed with pulmonary adenocarcinoma with pleural and bone metastases after presenting with deep venous thrombosis and pulmonary embolism. During the investigation, a transthoracic echocardiogram was performed, which revealed a mobile echogenic mass in the mitral leaflet. As there were no suggestive signs or laboratory tests that corroborated a systemic bacterial infection, the diagnosis of non-bacterial thrombotic endocarditis was confirmed. Given the poor prognosis related to the disease, suspicion and early treatment were determining factors for the favorable evolution presented.

Keywords: Endocarditis; Endocarditis, Non-infective; Carcinoma, Non-small-cell lung; Splenic infarction.

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RESUMO

A endocardite trombótica não bacteriana é uma doença incomum caracterizada pela formação e deposição de vegetações estéreis de fibrina nas válvulas cardíacas. Essa condição está mais relacionada a estados de inflamação crônica, principalmente relacionados à malignidade. Este relato descreve o caso de uma mulher brasileira, 50 anos, tabagista, diagnosticada com adenocarcinoma pulmonar com metástases pleurais e ósseas após apresentar trombose venosa profunda e embolia pulmonar. Durante a investigação, foi realizado ecocardiograma transtorácico, que revelou massa ecogênica móvel em folheto mitral. Como não havia sinais sugestivos ou exames laboratoriais que corroborassem infecção bacteriana sistêmica, foi confirmado o diagnóstico de endocardite trombótica não bacteriana. Diante do mau prognóstico relacionado à doença, a suspeição e o tratamento precoce foram fatores determinantes para a evolução favorável apresentada.

Descritores: Endocardite; Endocardite Não Infecciosa; Carcinoma pulmonar de células não pequenas; Infarto esplênico.

INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE), also called marantic endocarditis, is an uncommon condition, usually diagnosed at autopsy, that encompasses non-infectious lesions of the heart valves. NBTE is associated with conditions such as systemic lupus erythematosus, antiphospholipid syndrome, and other inflammatory conditions, but mainly in patients with advanced malignancies. Studies have shown rates ranging from 0.9 to 1.6% of patients at autopsies,^[1,2] being more frequently associated with tumors of the lung, pancreas, stomach, and occult primary site adenocarcinomas^[3].

Despite being an unusual manifestation, these progressive and friable lesions can lead to devastating consequences, such as systemic embolization and valve dysfunction. Therefore, this disorder must be considered and highly suspected in patients with embolic phenomena, especially if they are oncological, excluding an infectious cause.

CASE REPORT

Female, 50 years, smoker, diagnosed in February 2018 with pulmonary adenocarcinoma with pleural and bone metastasis after deep vein thrombosis (DVT) and pulmonary embolism. The oncological chemotherapy treatment was started with carboplatin and pemetrexed, in addition to zoledronic acid for bone metastasis. A few days later, due to the onset of right lumbar pain, she was investigated and had a diagnosis of segmental infarction in the right kidney and spleen, in addition to being submitted to magnetic resonance imaging (MRI) of the skull, which identified small areas compatible with infracentimetric cerebral infarcts. A transthoracic echocardiogram revealed a mobile echogenic mass in the posterior mitral leaflet, suggestive of endocarditis (Figure 1), determining moderate valve regurgitation. On cardiac auscultation, the patient had a slight systolic murmur in the mitral focus. However, the patient did not present fever



Figure 1. Mobile echogenic mass next to the posterior mitral leaflet.



and the blood cultures requested were negative. So, enoxaparin was started at an anticoagulation dose and chemotherapy was followed. A new echocardiogram, performed approximately 15 days after the first one, already showed a reduction in the valve lesion, without functional repercussions (Figure 2).

The patient followed treatment with enoxaparin, and warfarin was introduced, but due to difficulty in adjusting the dose, warfarin was replaced by dabigatran and enoxaparin was discontinued. Molecular tests were performed with negative EGFR and ALK results. PD-L1 was tested by immunohistochemistry with 22C3 PharmDx antibody, which resulted in 95% expression. The treatment with carboplatin and pemetrexed was kept for 5 cycles, until release of the medication pembrolizumab, which was started after as monotherapy.

Upon reaching two years of using pembrolizumab, it was discussed with the patient and decided to continue with the medication, which she has been using to this day. She has not had any more thromboembolic events, and the latest CT scans have shown a complete response to the lesion (Figure 3). The present echocardiogram also does not identify valve lesions. Currently, she recovered her work activities and is in performance status 0, more than 60 months after starting treatment.



Figure 3. Current computed tomography of the chest with complete reduction of the lesion.

DISCUSSION

Nonbacterial thrombotic endocarditis (NBTE) is characterized by the formation and deposition of sterile fibrin vegetations in the heart valves,^[4] which can occur in any valve, but predominantly in the aortic and mitral.^[5]

Since its initial knowledge, this entity has been associated with malignancies and with chronic inflammatory states, such as infectious and autoimmune diseases.^[6] NBTE can cause valve



Figure 2. Echogenic mass posterior to the left atrium without restricting cavity filling.

dysfunction, cardiac manifestation and systemic embolization, and its pathogenesis is not clearly understood, but it involves a hypercoagulable state of the patient.^[4] In addition, the local inflammatory response is weak, which may explain the high frequency of detachments and embolizations (mean of 42%).^[3,5]

There is a hypothesis that the interaction between monocytes or macrophages and tumor cells leads to the release of tumor necrosis factor and interleukins, triggering tissue damage and making the surface thrombogenic, leading to the deposition of platelets and consequent formation of vegetations.^[3,7-9] The vegetations are composed of degenerated platelets and fibrin filaments, and may be microscopic or large masses with a tendency to detach and cause embolisms/infarctions more easily than in cases of infective endocarditis.^[3,7]

NBTE can be found in any age group, but it predominates between the fourth and eighth decades of life, it has no sexual predilection^[3] and its real incidence is unknown and discordant among the literature, since it is commonly diagnosed only in autopsies. In a study with 1,640 autopsies performed over 24 years, 10 cases of NBTE were found, 8 cases in cancer patients. Patients with adenocarcinomas – especially pancreas – were at greater risk than other malignancies, and systemic embolization was the main cause of morbidity for these patients.^[10]

Other literatures state that NTBE occurs in 4% of patients with terminal cancer,^[4,11,12] reaching a 32% postmortem prevalence in patients with cancer and cerebral ischemia.^[4,13] In general, NTBE is found in between 0.9 and 1.6% of autopsies.^[1,2]

The highest rates of pathology usually occur among adenocarcinomas, especially of the lung, ovary, stomach, occult primary site and pancreas^[3,9], and are often mucin- secreting adenocarcinomas.^[9]

NBTE is usually silent until serious complications occur, such as embolization and valve dysfunctions. ⁽⁴⁾ The detachment of vegetation mainly affects the brain, spleen, kidneys, and, less commonly, the coronary arteries, and may cause acute myocardial infarction. Stroke is the most common clinical presentation, usually affecting the middle cerebral artery, and may involve both hemispheres.^[14] Progressive valve lesions can result in heart murmurs of recent onset, arrhythmias, and manifestations of heart failure, such as dyspnea, orthopnea, and peripheral edema.^[4]

Diagnosis is challenging and the first step is high clinical suspicion, especially in the presence of neoplasia. There are no laboratory tests that confirm the diagnosis of NBTE, they can only help to exclude infective endocarditis.

Demonstration of valve vegetation on echocardiography without systemic signs of infection confers a high NBTE risk.^[4] However, many cases are asymptomatic, and the echocardiogram may not show small or friable vegetation, and the diagnosis is often made only in the post-mortem.^[14,15]

The treatment is mainly based on therapy underlying against the pathology and anticoagulation.^[3] The most important guidelines recommend therapy based on low molecular weight heparin (LMWH) or unfractionated heparin (UFH),^[16,17] which should be maintained indefinitely due to high rate of recurrence of thromboembolic events in these patients if anticoagulation is discontinued.^[18] Valve repair or replacement is indicated in patients with severe valve dysfunction, large vegetation, or recurrent embolism despite long-term anticoagulation therapy.^[4] Surgical treatment can also be considered in patients with vegetation larger than 10 mm in diameter.^[19]

Meta-analysis of individual patients' data demonstrated that lung cancer was the most common tumor site and are frequently associated with more advanced cancer stages. The 6-month overall survival rate was 20.8% for lung cancer versus 37.0% for other types of cancer, respectively (p=0.06), identifying a poor prognosis especially in cases of lung cancer.^[20]

Although the prognosis of cases diagnosed in recent years is more favorable in terms of survival,^[20] numerous reports document instances of patient death before the initiation of cancer treatment.^[21-24] A systematic review of 163 cases with newly diagnosed NBTE identified an in-hospital mortality rate of 30%. It further demonstrated that factors such as splenic infarction, renal infarction, pulmonary embolism, and mitral valve regurgitation (all present in the patient in our case) were among the factors associated with an increased risk of in-hospital mortality.^[25]

There are case reports of favorable evolution in patients with advanced lung cancer with driver mutation^[26] and without this description,^[27] however, NBTE generally had a poor prognosis in most identified cases, particularly in those with lung cancer or metastatic tumours.^[28]

The present case is peculiar due to its favorable evolution. Low back pain led to the diagnosis of renal and splenic infarction, in addition to cerebral infarction discovered in the sequence, leading to the performance of echocardiography that demonstrated vegetation on the mitral valve. The suspected and early treated NBTE prevented the potentially irreversible outcomes that the pathology can generate, conferring a favorable evolution and a longer survival to the patient, who, in this case, continues with anticoagulation and clinically well more than five years after the diagnosis and without evidence of vegetation or dysfunction on echocardiography.

To the best of the authors' knowledge, this is the case with the longest documented survival (more than 5 years) of NBTE in a patient with advanced stage lung adenocarcinoma.

AUTHORS' CONTRIBUTIONS

- NTH Collection and assembly of data, Conception and design, Final approval of manuscript, Manuscript writing, Provision of study materials or patient
- MBCM Conception and design, Manuscript writing
- RBGSG Collection and assembly of data, Final approval of manuscript, Manuscript writing

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