Nonbacterial Thrombotic Endocarditis with Bivalvular Regurgitation

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INTRODUCTION

Nonbacterial thrombotic endocarditis (NBTE) is a rare condition in which platelet thrombi form on heart valves, typically in patients with advanced malignancy.[1] This form of noninfectious endocarditis, also known as marantic endocarditis, Libman-Sacks endocarditis, or verrucous endocarditis, can affect undamaged valves but can also occur in patients with valvular pathology. It is different from culture-negative endocarditis, which is caused by infectious agents that cannot be easily identified. The most common cause of NBTE is advanced malignancy (occurring in 80% of cases), followed by systemic lupus erythematosus. Other possible causes include antiphospholipid syndrome, rheumatoid arthritis, sepsis, and burns.[2] A conclusive diagnosis of NBTE can be achieved through pathological examination of thrombi present in autopsy or surgical specimens. However, as obtaining valvular tissue for analysis may not be a practical method, clinicians typically rely on a combination of clinical and echocardiographic evidence and an absence of microbiological evidence to arrive at a diagnosis. The identification of valvular vegetations via echocardiography in patients who are at an elevated risk for NBTE, in the absence of systemic infection, serves as a salient indication in support of a diagnosis of NBTE. Involvement of both the tricuspid valve (TV) and mitral valve (MV) in a patient with advanced malignancy is rare and has not been described in any of the available literature.

CASE PRESENTATION

The patient is a 76-year-old man who presented to the emergency department for severe hyponatremia found during routine preoperative evaluation. The patient's medical history includes pancreatic adenocarcinoma with metastasis to the liver, diastolic heart failure, atrial fibrillation, and coronary artery disease. The patient was initially scheduled to undergo port placement for chemotherapy, but during routine laboratory workup they were found to have a sodium level of 116 mmol/L and were subsequently sent to the emergency department for further evaluation. During evaluation in the emergency department, the patient was found to have x-ray findings consistent with pneumonia and was started on broad-spectrum antibiotics while receiving small boluses of fluid for hyponatremia. The patient was subsequently transferred to the intensive care unit for continued management of severe hyponatremia. On physical examination the patient was found to have jugular vein distention alongside lower extremity pitting edema. A transthoracic echocardiogram (TTE) was ordered to assess cardiac function and demonstrated a normal left ventricular cavity size with mildly reduced systolic function (visually estimated left ventricular ejection fraction of 45%-50%). There was septal flattening (right ventricular [RV] pressure/volume overload), left atrial enlargement (Figure 1A, Video 1), and suspected MV vegetation (Figure 2, Video 2) with severe mitral regurgitation (MV E wave = 1.3 m/sec; Figures 1B, and 3, Videos 3 and 4). Tricuspid regurgitation Doppler

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, apical 4-chamber view, demonstrates mildly reduced LV systolic function, left atrial dilation (left atrial volume index 59 mL/m^2), and a mobile vegetation on the TV.

Video 2: Two-dimensional TTE, apical 3-chamber view, demonstrates thickening of the MV with an associated mobile vegetation.

Video 3: Two-dimensional TTE, apical 4-chamber view, with color flow Doppler demonstrates severe eccentric mitral regurgitation (Nyquist limit = 45 cm/sec).

Video 4: Two-dimensional TTE, apical 3-chamber view, with color flow Doppler demonstrates severe eccentric mitral regurgitation (Nyquist limit = 45 cm/sec).

Video 5: Two-dimensional TEE, midesophageal 4-chamber view (0°), demonstrates vegetations on the MV and TV.

Video 6: Two-dimensional TEE, midesophageal 2-chamber view (64°) with color flow Doppler, demonstrates a vegetation on the MV associated with severe mitral regurgitation.

Video 7: Two-dimensional TEE, midesophageal 4-chamber view (0°), with color Doppler demonstrates severe mitral regurgitation (proximal isovelocity surface area radius = 1.0 cm).

Video 8: Two-dimensional TEE, midesophageal RV inflow-outflow view (75°), demonstrates vegetations on the TV and subvalvular apparatus.

Video 9: Two-dimensional TEE, midesophageal RV inflow-outflow view (68°) with color flow Doppler, demonstrates moderate tricuspid regurgitation and mild pulmonic regurgitation.

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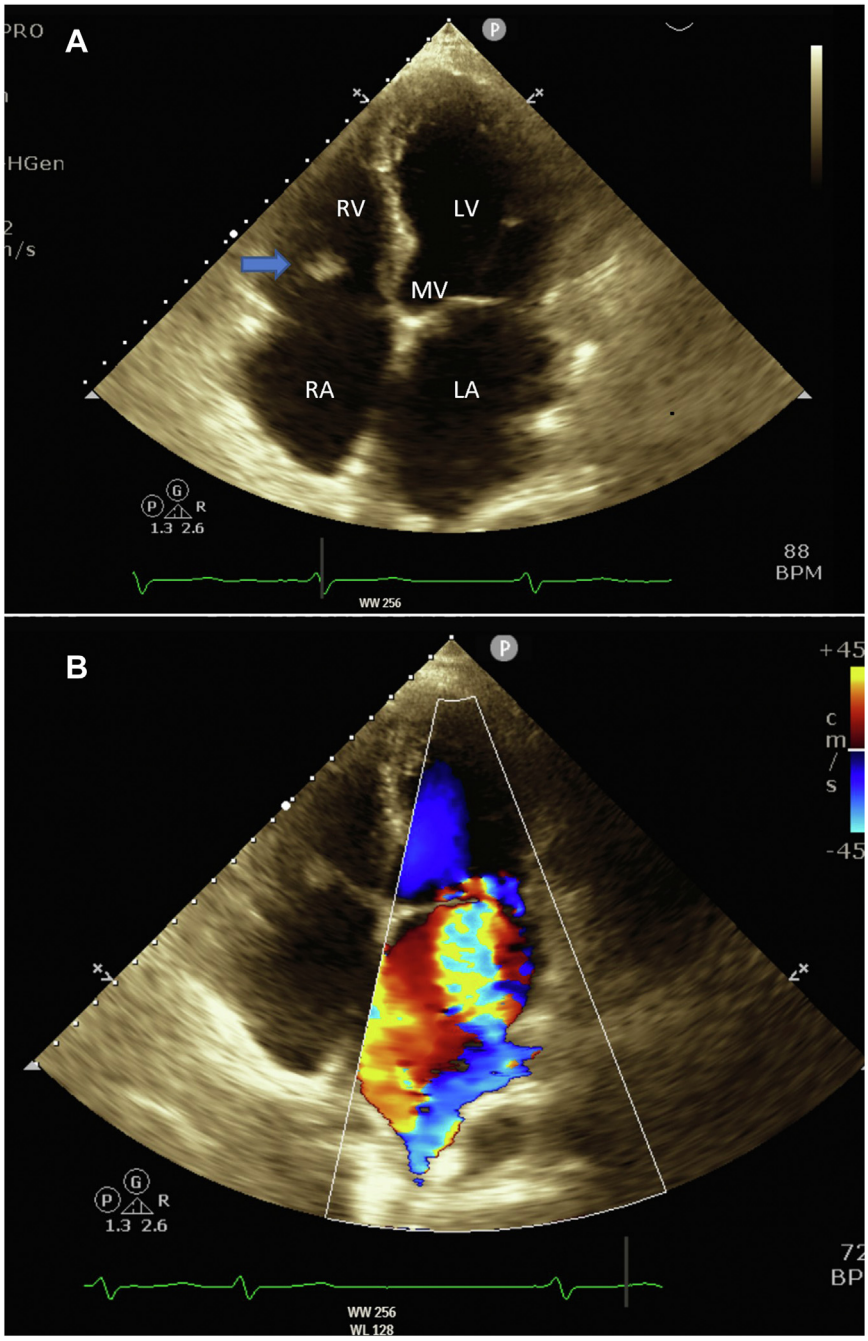

Figure 1 **(A)** Two-dimensional TTE, apical 4-chamber view without **(A)** and with **(B)** color flow Doppler, midsystolic phase, demonstrates left atrial enlargement (left atrial volume index, 59 mL/m^2), a mass on the TV (*arrow*), and severe eccentric mitral regurgitation (MV E max 1.3 m/sec). *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

confirmed an elevated RV systolic pressure (RVSP = 53 mm Hg) using an inferior vena cava-estimated right atrial pressure of 15 mm Hg. The elevated right heart pressure was attributed to type 2 and type 3 pulmonary arterial hypertension, assuming a combination of underlying left heart dysfunction and undiagnosed obstructive sleep apnea. Further evaluation of the TTE showed ill-defined thickening in the TV leaflets (Figure 1A, Video 1). The patient was afebrile but had leukocytosis with a history of recent urethral instrumentation for a urological procedure. Blood cultures were obtained on day 1. An infectious disease specialist was consulted for evaluation of possible infective endocarditis, and the patient was continued on broad-spectrum antibiotics.

The patient was subsequently scheduled for a transesophageal echocardiogram (TEE) the following day. Results of the TEE showed normal left ventricular size and function, ejection fraction of 60%-65%, normal RV size and function (Figure 4A, Videos 5, and 6), hypermobile interatrial septum without patent foramen ovale and with no left atrial or left atrial appendage thrombus (Figure 5, Video

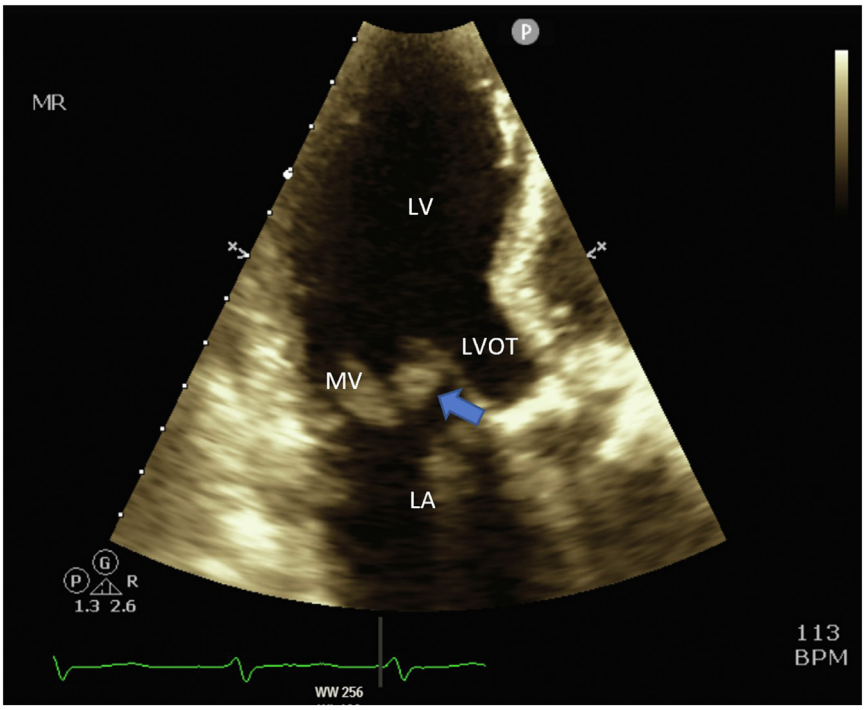

Figure 2 Two-dimensional TTE, apical 3-chamber view, early systolic phase, demonstrates thickening of the MV with an associated mass (*arrow*). *LA*, Left atrium; *LV*, left ventricle; *LVOT*, left ventricular outflow tract.

6). Significant findings included 2 large vegetations on the atrial aspect of MV leaflets, anterior leaflet measuring 1.3 × 1.1 cm, and posterior leaflet measuring 1.2 × 0.9 cm alongside severe mitral regurgitation with systolic flow reversal in the pulmonary vein (Figures 4A–C, and 5, Videos 5, 6, and 7). Imaging of the TV showed a large 1.6 × 1.1 cm vegetation on the TV leaflet with tricuspid regurgitation and RVSP 47 mm Hg (Figures 6, and 7, Videos 8, and 9).

The patient's blood cultures were negative for growth on 4 repeat cultures. Polymerase chain reaction testing for *Coxiella urnetiid, Legionella* spp, and *Brucella* spp was also negative. Workup for

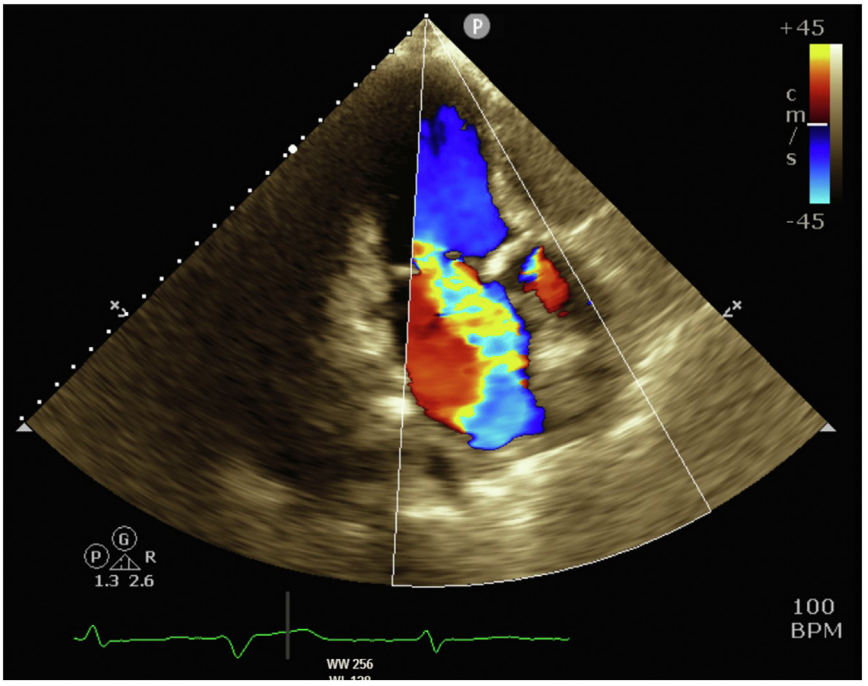

Figure 3 Two-dimensional TTE, apical 3-chamber view with color flow Doppler, midsystolic phase, demonstrates severe eccentric mitral regurgitation.

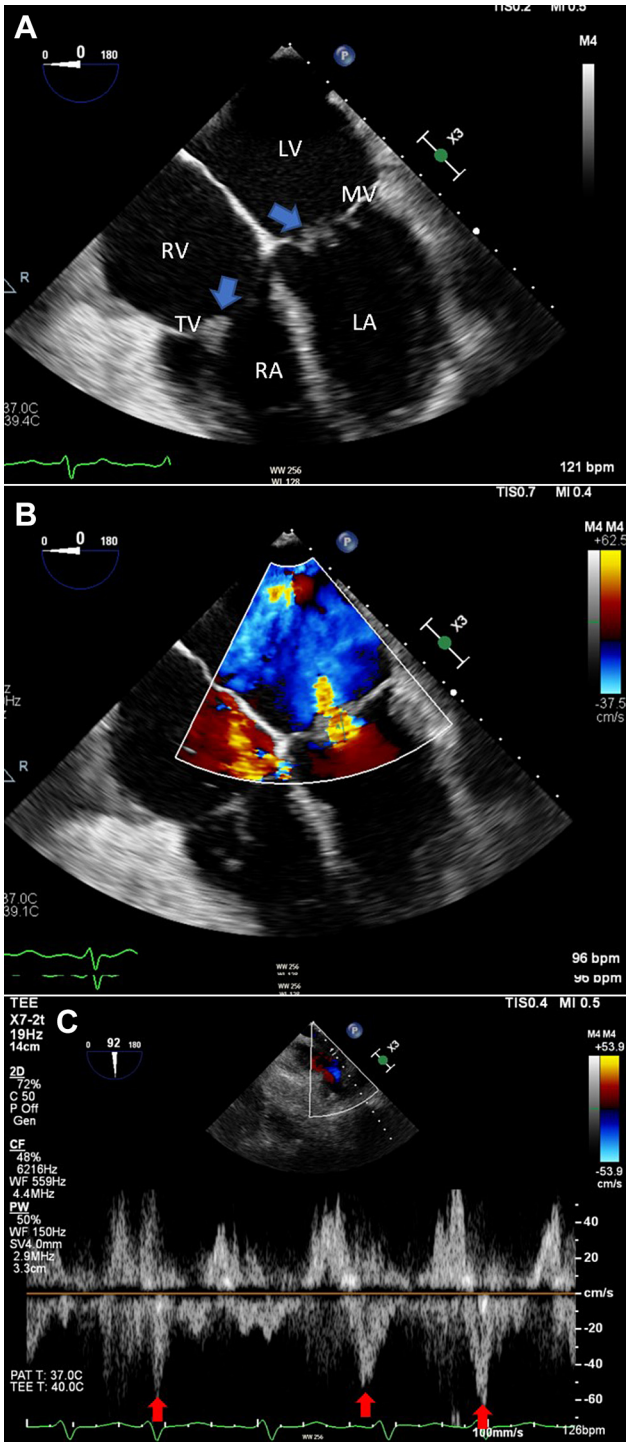

Figure 4 Two-dimensional TEE, 4-chamber view (0°) during early systole, without **(A)** and with **(B)** color flow Doppler, demonstrates vegetations on the MV and TV (*blue arrows*) with associated severe mitral regurgitation (proximal isovelocity surface area radius, 1.0 cm; effective regurgitant orifice area, 0.68 cm^2). **(C)** Pulsed-wave Doppler, 2-chamber (92°) view, sample volume within the right upper pulmonary vein demonstrates systolic flow reversal (*red arrows*). *L,* Left; *LA*, left atrium; *LV*, left ventricle; *R,* right; *RA*, right atrium; *RV*, right ventricle.

antiphospholipid syndrome was unremarkable. Given the presence of vegetations on both the MV and TV in the setting of persistently negative blood cultures in a patient with metastatic pancreatic cancer, the suspected diagnosis was marantic (nonbacterial) endocarditis. The patient was previously treated with the direct-acting oral anticoagulant apixaban, which was discontinued by their hematologist oncologist

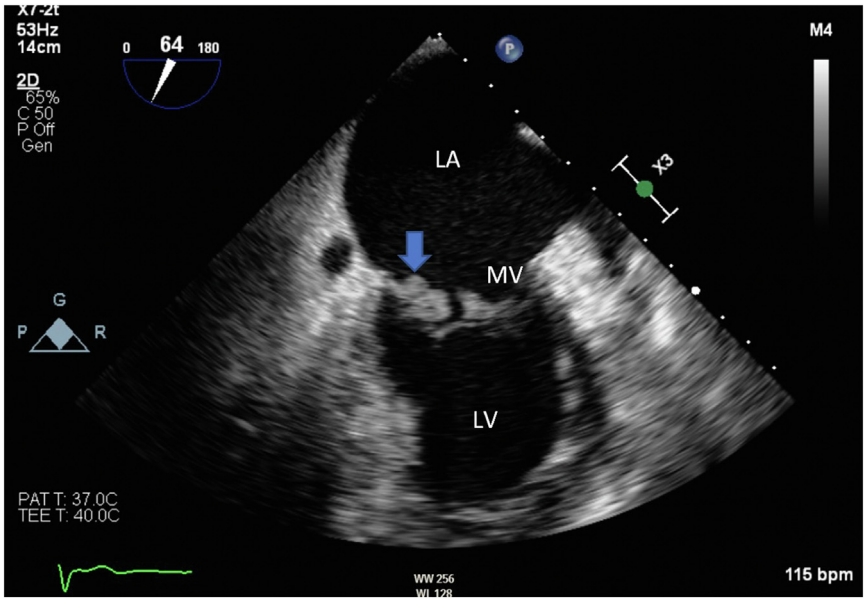

Figure 5 Two-dimensional TEE, midesophageal 2-chamber view (64°) during end diastole, demonstrates a vegetation on the MV (*arrow*) and severe LA dilation. *LA*, Left atrium; *LV*, left ventricle.

due to their severe thrombocytopenia. It was recommended that the patient be started on low molecular weight heparin or unfractionated heparin rather than a direct-acting oral anticoagulant when it was deemed safe to do so by the hematology oncology team. Computed tomography imaging of the head was completed to rule out intracerebral hemorrhage related to embolic disease due to the patient's persistent level of confusion. Infectious disease recommended the patient be discontinued from broad-spectrum antibiotics with observation of clinic course to clarify the diagnosis of marantic endocarditis. The patient started on enoxaparin once platelets had recovered to above 50,000 10^9/L.

DISCUSSION

Originally described by Ziegler in 1888, the lesions of NBTE were considered to be fibrin thrombi deposited on normal or superficially degenerated cardiac valves.[3] In 1936, Gross and Friedberg introduced the term "nonbacterial thrombotic endocarditis."[4]

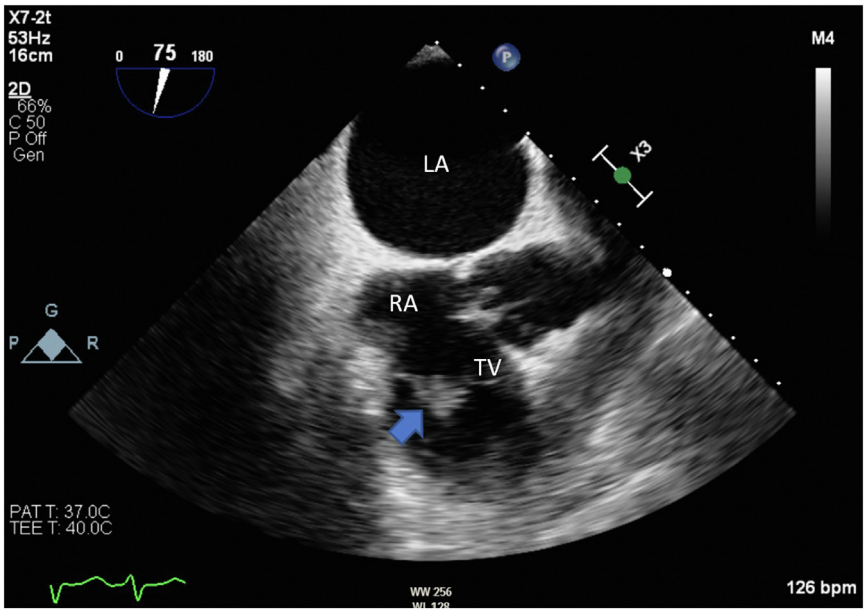

Figure 6 Two-dimensional TEE, midesophageal RV inflow-outflow view (75°) demonstrates a vegetation on the TV and subvalvular apparatus (*arrow*). *LA*, Left atrium; *RA*, right atrium.

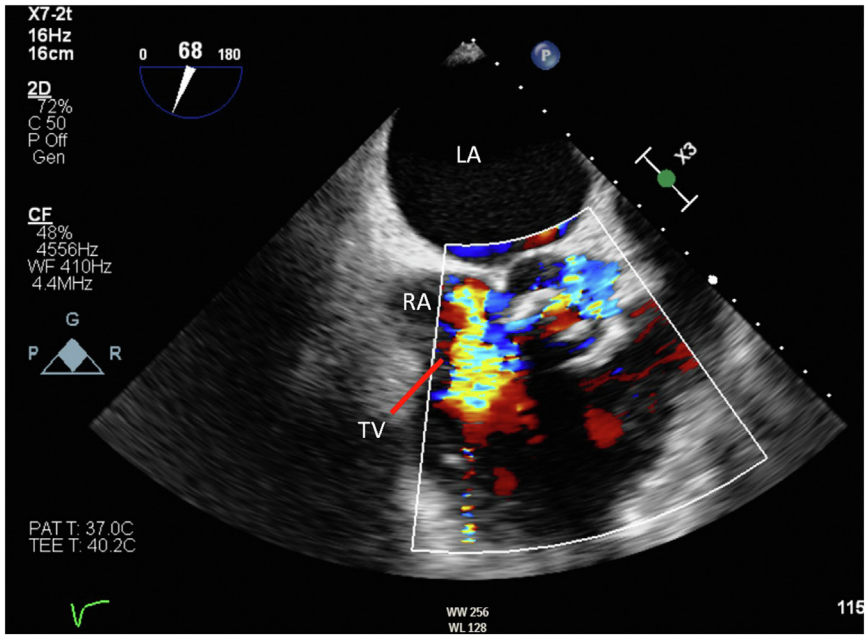

Figure 7 Two-dimensional TEE, midesophageal RV inflow-outflow view (68°) with color flow Doppler demonstrates moderate tricuspid regurgitation. The line demonstrates the TV. *LA*, Left atrium; *RA*, right atrium.

Nonbacterial thrombotic endocarditis is a subset of noninfectious endocarditis usually characterized by the formation of sterile platelet thrombi on heart valves, most commonly the aortic valve or MV. The usual initiating factor in the pathogenesis of NBTE is not known but may be attributed to endothelial injury in the setting of an existing hypercoagulable state, which is thought to be imperative for its development. Endothelial damage caused by circulating cytokines including interleukin-1 may be a trigger for platelet aggregation and fibrin deposition.[4] This is usually compounded in states that promote a hypercoagulable tendency such as malignancy.

Up to 9% of autopsies of cancer patients show noninfectious valvular masses. Although bivalvular involvement is rarely described in the existing literature. Moreover, bivalvular involvement with progression to valvular regurgitation is not typically present. Vegetation formation in NTBE is composed of platelets and fibrin, but the underlying valvular tissue is usually entirely normal or may show histological signs of abnormal collagen and elastic fiber deposition; thus, the valvular integrity is usually preserved. Patients with NBTE frequently exhibit no symptoms. The primary clinical presentations of NBTE are a result of systemic emboli as opposed to valvular dysfunction (i.e., heart failure). In as many as 50% of cases, patients with NBTE display embolic phenomena.[5] A case series revealed that stroke was the initial complaint in 60% of instances.[6] The symptoms of valvular dysfunction are seldom observed, with scarce case reports of cardiac failure resulting from aortic or tricuspid regurgitation in patients with NBTE.[7] In this case of NBTE the patient's native valve integrity was compromised, leading to not only bivalvular involvement but also bivalvular regurgitation. In a previously described case of NBTE with valvular regurgitation, treatment with anticoagulation led to resolution of the valvular dysfunction.[8] Our patient expired shortly after discovery of their valvular regurgitation, and so we were unable to assess resolution.

Differential diagnosis for an echogenic mass attached to the heart valves on echocardiogram is infectious endocarditis, which is typically associated with valvular destruction. Especially in cases involving patients with an immunocompromised state or active malignancy it is imperative to effectively rule IE.

Treatment of NBTE usually involves the administration of unfractionated heparin, which is considered to be the most effective choice of anticoagulation.[1] The use of vitamin K antagonists such as warfarin may induce a thrombotic coagulopathy in patients with NBTE.[9] Surgical intervention may be considered in patients with NBTE with a favorable risk profile, although our patient did not meet this criterion. Surgical intervention is reserved for those patients with indications such as heart failure and acute valve rupture, but reports suggest that prevention of recurrent embolization is the most common reason for surgical intervention.

CONCLUSION

Bivalvular involvement of NBTE is rarely described especially in the setting of coinciding valvular dysfunction due to the lack of valvular destruction involved in the pathogenesis of NBTE. In a previously described patient, management with anticoagulation led to the resolution of valvular dysfunction. Unfortunately, treatment progress was unable to be assessed in our case due to the rapid progression of underlying malignancy. Outpatient follow-up was not possible as the patient died within weeks of discharge, with the major contributor being the advanced pancreatic malignancy.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a non-interventional, retrospective, observational study utilizing deidentified data, informed consent was not required from the patient under an IRB exemption status.

FUNDING STATEMENT

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2023.02.004.

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