Non-Bacterial Thrombotic Endocarditis as a Cause of Cryptogenic Stroke in Malignancy

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ABSTRACT

Non-bacterial thrombotic endocarditis (NBTE) is characterized by the deposition of fibrin and platelet thrombi on previously undamaged heart valves in the absence of bloodstream infection. It is associated with chronic disease states and can present with systemic embolic disease. Here we report a case of NBTE presenting as recurrent strokes in a patient with bladder cancer. Importantly, transthoracic echocardiography has limitations to detecting valvular lesions in NBTE, and providers should consider obtaining transesophageal echocardiography in the setting of high clinical suspicion.

KEYWORDS: endocarditis; cryptogenic stroke; transthoracic echocardiography; transesophageal echocardiography; non-bacterial thrombotic endocarditis

ABBREVIATIONS: NBTE; TTE; TEE; LMWH; LSE

INTRODUCTION

Non-bacterial thrombotic endocarditis (NBTE) is characterized by the deposition of fibrin and platelet thrombi on previously undamaged heart valves in the absence of a bloodstream infection.[1-3] NBTE is associated with both underlying malignancy as well as severe autoimmune disease.[4] True prevalence may be underappreciated, as NBTE usually reaches clinical detection in the setting of cryptogenic stroke. Here, we report a case of NBTE presenting as a stroke in a patient with a known malignant disease.

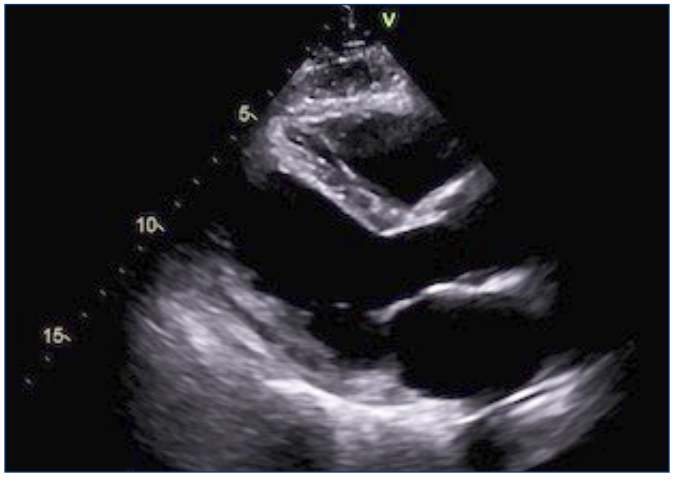
CASE REPORT

A 60-year-old male with a history of muscle invasive bladder urothelial cancer presented to the emergency department with acute onset of confusion and aphasia. Per the patient's family he had been in his usual state of health in the days prior to presentation. A code stroke was called on arrival in the emergency department. On exam the patient demonstrated expressive aphasia, right-sided neglect, and right upper extremity hypertonia. His initial NIHSS score was 12. No cardiac murmur was noted and there was no evidence of embolic phenomena on exam. The patient was not on cancer-directed therapy at the time of presentation; his oncologic treatment history to that time consisted of six cycles of cisplatin and gemcitabine completed two years prior, transurethral resection of the bladder, consolidative radiation therapy and four cycles of immunotherapy. His last treatment was a course of pembrolizumab, one year prior to presentation.

Notably, the patient had been recently admitted to the hospital three weeks prior for chest pain and was found to have bilateral subsegmental pulmonary emboli. His hospital course at the time was complicated by recurrent headaches which prompted brain magnetic resonance imaging (MRI) that revealed multiple punctate areas of diffusion restriction, believed to represent embolic infarcts. A transthoracic echocardiogram (TTE) was obtained to evaluate for valvular vegetations; however, no pathology was demonstrated (**Figure 1**). The patient received anticoagulation with therapeutic dose low molecular weight heparin (LMWH) to treat the pulmonary emboli, and was discharged home on enoxaparin 80 mg subcutaneously twice daily.

On this admission, after stabilization in the emergency department, the patient was admitted to the neurology service and continued on therapeutic LMWH. Computed tomography (CT) angiography of the brain and neck was negative for hemorrhagic stroke or occlusion of a major cerebral vessel. Brain MRI showed multiple new bilateral supra- and infratentorial acute non-hemorrhagic infarcts, worsened since his prior study, and most consistent with

Figure 1. Transthoracic Echocardiography (TTE) image on prior hospitalization showing a structurally normal mitral valve.



thromboembolic disease (**Figure 2A, 2B**). With the interval worsening of apparent embolic disease, a repeat TTE was obtained. Echocardiography now showed thickened mitral leaflets with new moderate mitral regurgitation **(Figure 3)**. There was no evidence of a right to left shunt following injection of agitated saline contrast, nor signs of a cardioembolic source of emboli, and no apparent tricuspid or pulmonic valve pathology. Transesophageal echocardiography (TEE) revealed a homogenous irregular fixed thickening of the anterior and posterior mitral valve leaflets suspicious

Figure 2A. Brain Magnetic Resonance imaging (MRI) on prior hospitalization showing patchy multifocal cerebral foci of diffusion restriction suggestive of multiple small acute and subacute cardioembolic ischemic infarcts.

Figure 2B. Brain MRI on index hospitalization showing multiple new bilateral supra- and infratentorial acute non-hemorrhagic infarcts, consistent with progression of embolic disease.

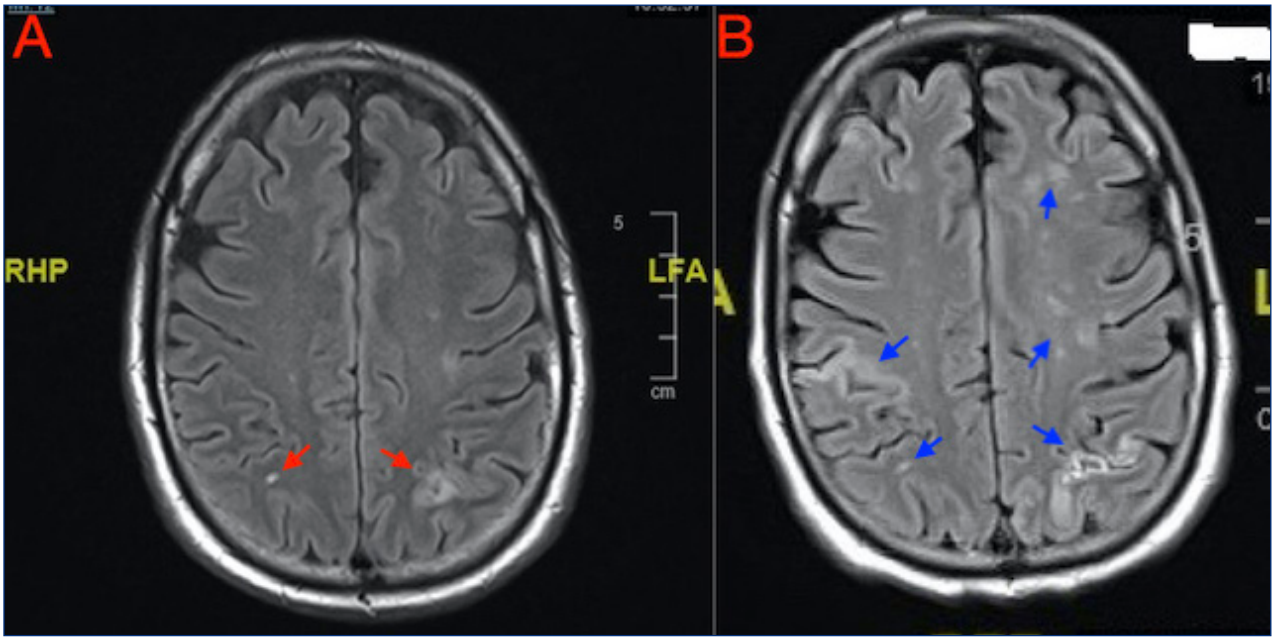


Figure 3. TTE image on index hospitalization displaying thickened mitral valve leaflets, with a restricted posterior leaflet and color doppler evidence of new mitral regurgitation when compared to prior.

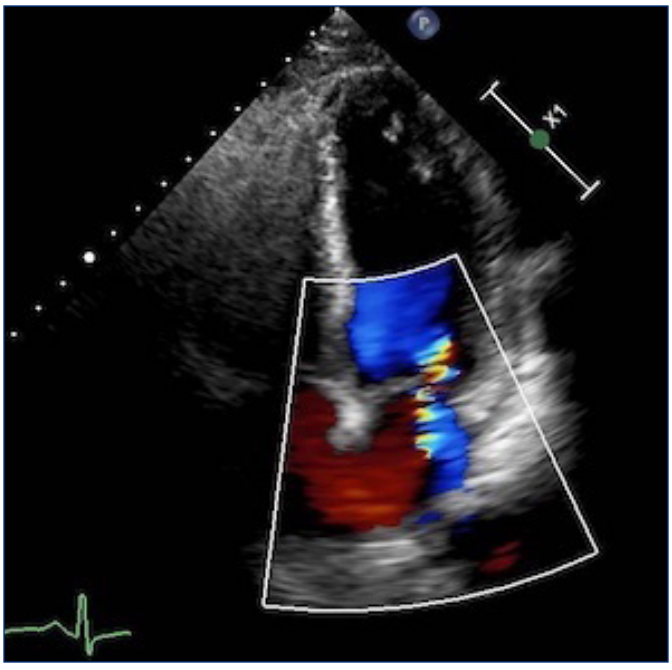
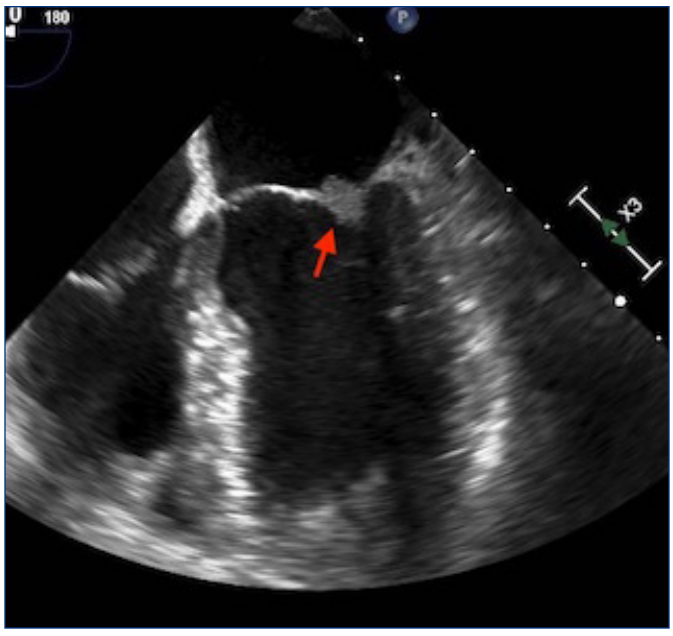


Figure 4. Transesophageal Echocardiography (TEE) image on index hospitalization showing a homogenous irregular fixed thickening of the anterior and posterior mitral valve leaflet tips concerning for a thrombus or vegetation, with evidence of moderate mitral regurgitation.



for a thrombus versus vegetation and highly concerning for NBTE (**Figure 4**). Peripheral blood cultures, which had been obtained on admission, remained negative and the patient remained afebrile without a leukocytosis. In addition, the patient received abdominal CT imaging which demonstrated splenic infarcts, renal infarcts, and diffuse peritoneal thickening and omental nodularity, all concerning for progression of malignancy and systemic emboli. Anticoagulation was transitioned briefly to warfarin; however, the patient was ultimately treated with an increased LMWH dosage titrated to elevated anti-Factor Xa levels. A baseline anti-Factor Xa level was obtained at 4 hours after the prior dose, and LMWH dosage was increased to achieve a 25% greater peak anti-Factor Xa level.

Unfortunately, given his functional limitations, the patient was not a candidate for further cancer-directed therapy. Palliative care services were enlisted, and hospice services were offered but ultimately declined. The patient was discharged from the hospital to a rehab facility. He passed away two weeks after the admission.

DISCUSSION

In 1924 Dr. Eugene Libman categorized endocarditis into four major classes: rheumatic, syphilitic, bacterial and indeterminate. This indeterminate class was further characterized in a case series completed with Dr. Benjamin Sacks.[5] Within this indeterminate category the authors included 'terminal or cachectic endocarditis' and noted the association between this entity and advanced chronic diseases such as malignancy, tuberculosis and chronic nephritis. Today we classify this indeterminate group as NBTE, also referred to as marantic endocarditis or verrucous endocarditis, and within it include the classic Libman-Sacks endocarditis (LSE) associated with systemic lupus erythematosus. The pathogenesis is thought to be related to a complex interplay between immune complexes, hypoxia, increased tissue factor (TF) and the hypercoagulable state of malignancy or other inflammatory conditions.[1-3] Malignancy and rheumatological disorders lead to increased levels of circulating proinflammatory cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor alpha.[2] The effects of these cytokines can lead to endothelial injury, one of the three hallmarks of Virchow's Triad contributing to thrombosis. Endothelial damage leads to exposure of subendothelial connective tissue to platelets, promoting aggregation and propagating thrombus formation. The host's inflammatory response also plays a role, with increased leukocyte TF expression, and increased levels of factor VIII, fibrinogen and von Willebrand factor.[1-2]

Prevalence data regarding NBTE and NBTE related to malignancy remains sparse. An autopsy series from the 1990s found 10 cases of NBTE among 1640 adult patients, 8 of which were associated with malignancy.[6] An earlier autopsy series from the 1970s performed in patients with known malignant disease noted 75 cases of NBTE in 7,840 patients.[7] The most comprehensive epidemiological review of NBTE to date comes from Lopez et al who examined 82,676 patients across fourteen autopsy studies and found prevalence rates of NBTE ranging from 0.4–9.3 %, with a combined total prevalence of 1.3%.[4]

Echocardiography is critical to diagnosing NBTE. Lack of sensitivity in detecting valvular vegetations with TTE may necessitate the need for TEE in cases where high clinical suspicion exists, as was evident in this case. A randomized controlled trial compared the diagnostic accuracy of TTE compared to TEE in detecting LSE.[8] TEE was significantly more likely to detect LSE then TTE, and TTE demonstrated a subpar sensitivity (63% overall, 11% for valve vegetations) and low negative predictive value (40%). The authors concluded that TEE should be considered as the initial test, or complement to a negative TTE, in cases of suspected cardiac-embolism in patients with LSE. Additionally, a prospective study evaluated patients with acute embolic stroke of undetermined source (ESUS) and the effects of TEE findings on therapeutic management for secondary stroke prevention.[9] These patients had received TTE prior to TEE as part of the diagnosis of ESUS. Of sixty-one patients who underwent TEE, abnormal findings were discovered in 52% of patients and these findings affected therapeutic management in ten (16%) of the cases.

Patients with NBTE are managed with anticoagulation, in contrast to patients with infective endocarditis and acute ischemic stroke. Vegetations in NBTE are easily dislodged, owing to the scant inflammatory reaction at the attachment site.[1,2] As evidenced in this case, recurrent thromboembolism can occur despite treatment with subcutaneous LMWH. In instances of treatment failure, an increase in the dose of LMWH or a transition to direct oral anticoagulants are reasonable alternatives.[10]

In conclusion, we report a case of recurrent stroke due to NBTE in a patient with a known malignant disease. A high clinical suspicion is paramount for diagnosis in these cases, and in patients with recurrent stroke and malignancy, TEE should be pursued to rule out valvular vegetations given the lack of sensitivity with TTE. Anticoagulation remains the cornerstone of management, as well as treatment of the underlying disease. Unfortunately our patient continued to have embolic disease despite anticoagulation. Further research is needed to clarify disease prevalence and to compare anticoagulation strategies.

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