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Case Report

A rare case of metastatic pancreatic adenocarcinoma presenting as a pulmonary embolism from nonbacterial thrombotic endocarditis☆,☆☆

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ABSTRACT

Nonbacterial thrombotic endocarditis (NBTE) also called, "Marantic endocarditis" occurs due to an underlying hypercoagulable state causing tissue damage and upregulation of the coagulation cascade, with noninfective vegetation formation on heart valves. Mitral and aortic valves are most commonly involved. NBTE is rare, with an incidence of 1.6%, with 65 cases identified during a 10-year autopsy analysis. The most common malignancies associated with NBTE include gynecological cancers, lung cancer, gastric cancer, and pancreatic cancers with adenocarcinoma histology being the greatest risk. Herein, we present a rare case of a 55-year-old male who presented with acute hypoxic respiratory failure secondary to pulmonary embolism due to nonbacterial thrombotic endocarditis. He was found to have advanced pancreatic adenocarcinoma on further investigation of the 2.2 cm hypodense cystic mass in the distal pancreatic body and tail, and complex liver masses which were incidentally found on computed tomography angiography (CTA) of the chest. This is a rare phenomenon and clinicians have to consider the hypercoagulable state associated with cancers, particularly pancreatic adenocarcinoma, and the risk of NBTE.

☆ Competing Interests: There is no conflict of interest to declare.

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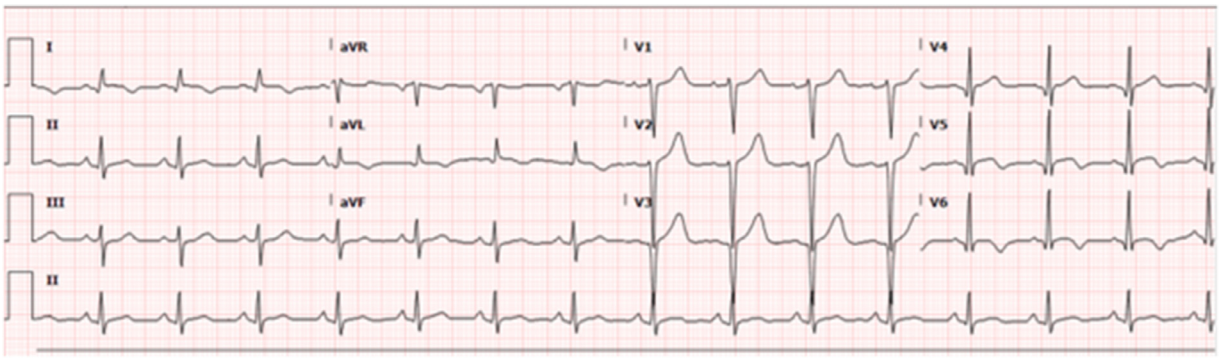

Fig.1 – Initial EKG demonstrating normal sinus rhythm, with T-wave inversions in lateral leads as well as Q-wave inversions in leads I, aVL, and V5-6.

Introduction

Nonbacterial thrombotic endocarditis (NBTE) is a deposition of a noninfectious, amorphous mixture of thrombus and fibrin on heart valves [1]. It occurs as a result of underlying hypercoagulable states such as advanced malignancies (particularly adenocarcinoma), systemic lupus erythematosus, antiphospholipid syndrome, severe burns, and uremia. The sterile vegetations appear similar to infective endocarditis (IE) but tend to be smaller with variable echogenicity and are usually located at the base of leaflets [1,2]. The hypothesis is that the mechanism behind the phenomenon of NBTE is due to a hypercoagulable state and defective endothelial repair in debilitated patients. NBTE often presents with arterial or venous thromboembolic events, such as ischemic stroke and deep vein thrombosis [2]. Herein, we present a rare case of NBTE presenting as pulmonary embolism, leading to the diagnosis of advanced pancreatic adenocarcinoma.

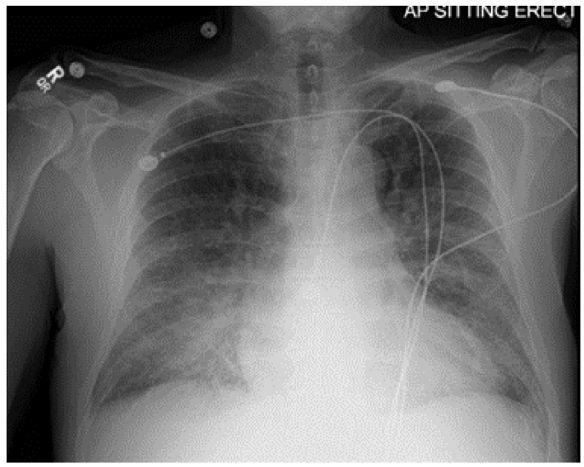

Figure 2 – Frontal CXR anterior-posterior view demonstrating hazy opacities bilaterally may reflect infiltrates of pulmonary edema or pneumonia. Layering bilateral pleural effusions are suspected. No pneumothorax was visualized.

Case Presentation

A 55-year-old gentleman with a past medical history significant for anxiety, tobacco use disorder (15 pack-years), and polysubstance abuse with cocaine, heroin, and benzodiazepines presented to the Emergency Department (ED) with 3 days of epigastric pain with associated dyspnea on exertion and orthopnea. He described the pain as dull and nonradiating and denied association with fever, chills, nausea, vomiting, or diarrhea. Additionally, the patient noted bilateral lower extremity swelling with more prominence on the right side. The patient endorsed the use of heroin and cocaine earlier that morning.

In the ED, vitals were significant for hypertension with a blood pressure of 177/90 mmHg, tachycardia with a heart rate of 110 beats per minute, tachypnea with a respiratory rate of 25 breaths per minute, and a temperature of 37.5°C. The patient's oxygen saturation was low at 82% on room air, and he was placed on supplemental oxygen. Physical exam was notable for a diastolic murmur at the left sternal border with a soft systolic murmur best appreciated at the apex.

This case occurred after the onset of the COVID-19 pandemic. The patient tested negative for COVID-19 on admission. Antibody testing of COVID-19 was not completed. The patient declined COVID-19 vaccination.

Laboratory studies were significant for an initial troponin level of 2527 pg/mL (reference range: 3-23) with a brain natriuretic peptide (BNP) value of 881 pg/mL (reference range: 1-100). Urine drug screen was positive for cocaine, benzodiazepine, and opiates. Electrocardiogram (EKG) was significant for T-wave inversions in the lateral leads along with Q-wave inversions in leads I, aVL, and V5-6 (Fig. 1). Chest X-ray (CXR) was significant for bilateral infiltrates (Fig. 2). Venous ultrasound of the bilateral lower extremities was negative for deep vein thrombosis. Computed tomography angiography (CTA) of the chest was notable for nonobstructive pulmonary em-

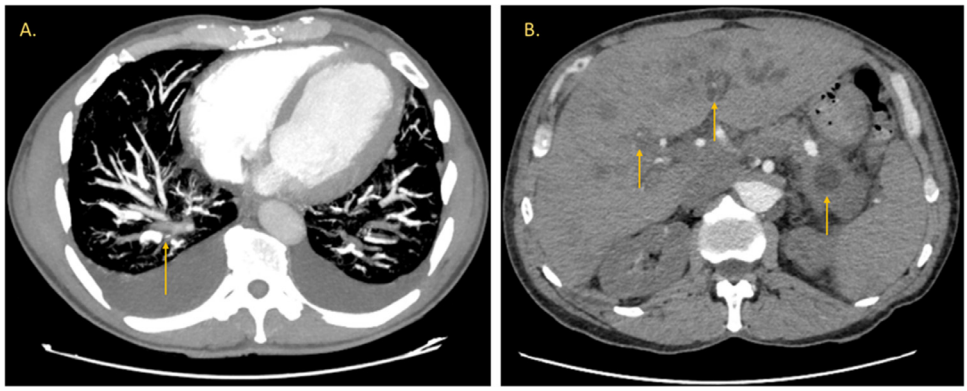

Fig. 3 – CTA Chest demonstrating acute pulmonary embolism involving subsegmental right lower lobe pulmonary arterial branches (A), with a complex solid and cystic mass in the tail of the pancreas with hepatic metastatic disease (B).

boli within branch vessels of the descending right pulmonary artery with mid-distal/distal pulmonary emboli, without evidence of right ventricular enlargement or right heart strain (Fig. 3). Additionally, on CTA of the chest, a hypodense cystic mass (2.2 cm) was noted in the distal pancreatic body and tail, and complex liver masses with concern for metastatic disease were appreciated.

The cardiac critical care unit was contacted, and the patient was admitted for non-ST elevation myocardial infarction (NSTEMI) and acute hypoxic respiratory failure in the setting of pulmonary embolism (PE). The patient was initiated on a Heparin drip, which was later transitioned to therapeutic Enoxaparin. The patient's NSTEMI was treated medically with aspirin, (statin was held secondary to hepatic lesions). Two-dimensional (2D) echocardiogram was significant for aortic thickening, possible aortic vegetation, aortic insufficiency, with a left ventricular ejection fraction of 35%. Two sets of blood cultures obtained demonstrated no growth to date since the time of admission. Both the Gastroenterology and Hematology-Oncology teams were consulted for the patient's pancreatic lesion with possible liver metastases on imaging. Carbohydrate antigen-19-9 (CA-19-9) was found to be elevated at 55,362 U/mL (reference range: 0-35). Liver biopsy was notable for metastatic adenocarcinoma of pancreatic primary (Fig. 4). The Hematology-Oncology team proposed a tentative plan of completing genetic testing and pursuing palliative chemotherapy with Leucovorin calcium, Fluorouracil, Irinotecan hydrochloride, and Oxaliplatin (FOLFIRINOX) outpatient.

Due to the abnormal 2D echocardiogram findings and a high clinical suspicion for endocarditis, a transesophageal echocardiogram (TEE) was completed, significant for a left ventricular ejection fraction of 40%-45% and thickening of aortic valve leaflets from both sides with small vegetation, severe aortic regurgitation consistent with endocarditis, which is not typical for bacterial endocarditis, and suggestive of NBTE (Fig. 5). Further imaging of computed tomography of the head without contrast was obtained to evaluate for metastatic disease versus cardioembolic stroke; however, findings were negative for acute intracranial abnormality or metastatic disease. The patient was continued on therapeutic Lovenox and was discharged home with close outpatient follow-up.

Discussion

NBTE occurs as a result of a hypercoagulable state where thrombi are made up of platelets and strands of fibrin, leading to tissue damage and upregulation of the coagulation cascade, with subsequent vegetation formation on heart valves, with mitral and aortic valves most commonly involved [3,4]. Microscopic analysis of these lesions is notable for platelet thrombi and blood agglutination without an inflammatory reaction [5]. In this unique process, the valvular tissue involved is typically normal or with a minimal exhibition of abnormal elastic fibers or collagen [2]. NBTE has been associated with proinflammatory scenarios such as malignancy, where inflammation releases both interleukin-1 (IL-1) and tumor necrosis factor (TNF) which act toward damaging tissue, leading to thrombus deposition [6]. In contrast to bacterial IE, these patients are found to have an absence of bacteremia [2]. In our patient's case, he had multiple risk factors for IE, given his history of illicit drug use; however, in the absence of IE, his newly diagnosed malignancy was sought to be the etiology for his development of NBTE.

The incidence of NBTE has been reported as 1.6%, with 65 cases identified during a 10-year autopsy analysis [4]. NBTE mainly impacts patients ages 40-80 years old with no difference in gender reported [7]. In patients with malignancy-associated NBTE, adenocarcinoma was reported as the most common cancer type, with the most common malignant origins representing gynecological, lung, gastric, and pancreatic cancers reported [2–4]. In another study, patients with malignancy were found to have a higher risk of developing NBTE (1.25% vs 0.2% with a P-value of $<.05$) with adenocarcinoma most commonly identified (3.7% vs 0.47% with a P-value of $<.05$). Patients with pancreatic adenocarcinoma specifically were at the highest risk when compared with patients with adenocarcinomas outside of the pancreas [8]. Our patient represented the majority of patients with NBTE as a 55-year-old with adenocarcinoma. Given his new diagnosis of pancreatic adenocarcinoma, as above, this is consistent with a higher predisposition for NBTE.

Although no pathognomonic signs or symptoms have been identified for NBTE, a diagnosis should be considered in pa-

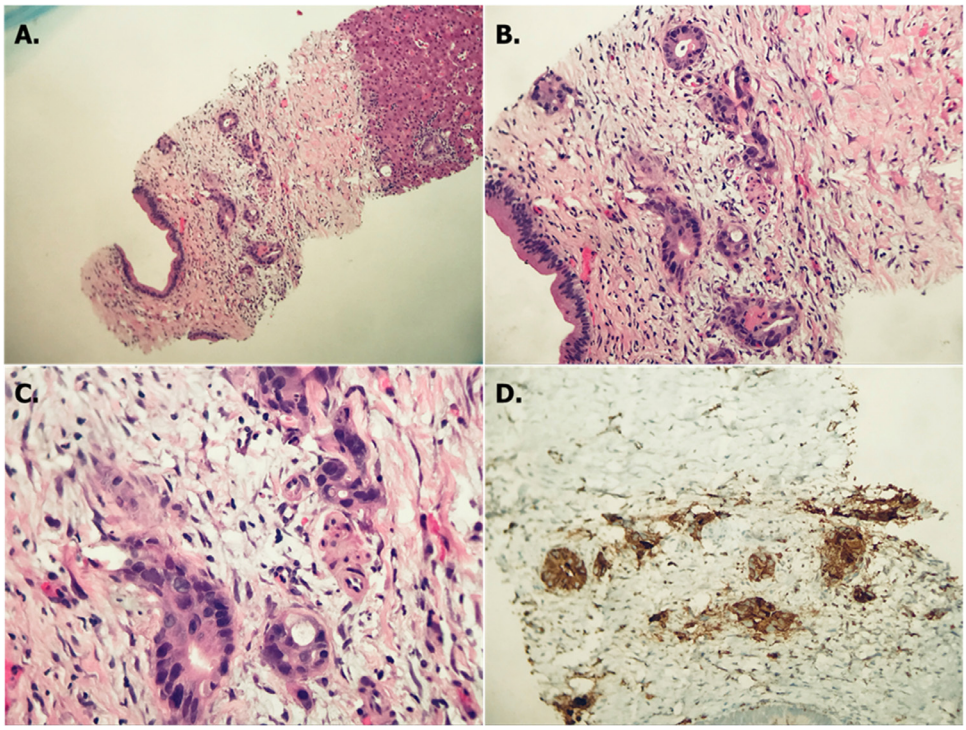

Fig. 4 – Liver mass biopsy, indicative of liver parenchyma with metastatic adenocarcinoma, consistent with a pancreatic primary. A-C. Liver parenchyma with focal infiltration of marked atypical glands; D. Immunohistochemistry staining with CA19-9 positivity.

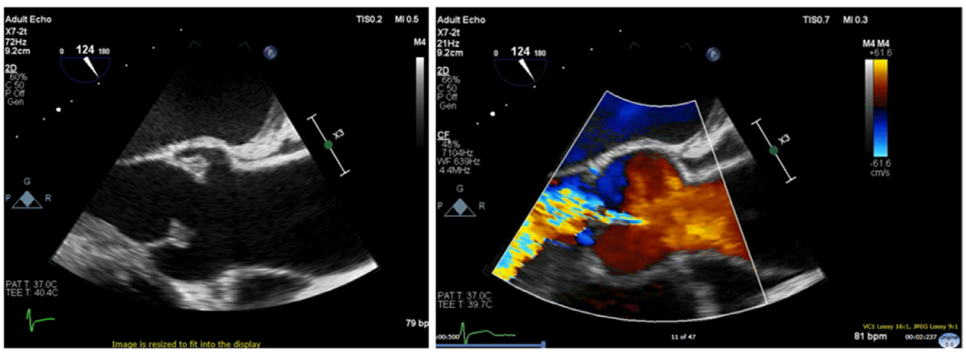

Fig. 5 – Transesophageal echocardiogram findings, consistent with severe aortic insufficiency (AI). Right image with color flow doppler demonstrating severe AI.

tients with ischemic stroke and underlying malignancy. Most of the patients present with new-onset focal versus diffuse neurologic deficits with an active malignancy, and in the absence of a known etiology [2,3,9]. NBTE associated with pancreatic cancer is often difficult to diagnose in living patients as the vegetations are often brittle and their remnants are too small to be identified by echocardiography. However, this disease process continues to remain a potential cause of recurrent embolisms [7].

In terms of cancer patients with NTBE, deceiving factors such as presentation of fevers may mask NBTE as patients with malignancy may present with febrile illness in the setting of a noninfectious process or an additional infection unrelated to endocarditis [2]. Patients with NBTE more commonly present with clinical presentation of systemic embolization instead of cardiac valve dysfunction. These recurrent embolisms account for 42% of patients, with common sites in the spleen, kidney, peripheral extremities, coronary arteries, and CNS [2]. This may explain why cardiac murmurs are oftentimes absent in NBTE, unlike in the setting of IE; however, when murmurs are present with NBTE, they are typically low-grade systolic murmurs best appreciated at the left lower sternal border [2]. Patients with suspected malignancy, with a new-onset murmur, negative blood cultures, and a lack of response to antibiotic therapy should be considered for NBTE [2].

With NBTE, TEE is the most sensitive to detect vegetations; however, currently, prospective studies of how to optimally evaluate patients with malignancy-related NBTE have not yet been published[2]. In our patient's case, a transthoracic echocardiogram was obtained initially given the less-invasive nature and clear physical exam findings, later followed by a TEE which confirmed the diagnosis of NBTE of the aortic valve.

The treatment options for NBTE mainly address the underlying malignancy and comprise full-dose systemic anticoagulants [10]. When compared to IE, vegetations found in NBTE tend to more frequently and freely detach and lead to a thromboembolic phenomenon [2].

Therefore, long-term or even indefinite systemic anticoagulation is warranted, whether or not embolism is observed at initial presentation [10]. The American College of Chest Physicians Antithrombotic and Thrombolytic Therapy for Valvular Disease recommended the use of intravenous (IV) unfractionated heparin (UH) or subcutaneous (SC) low molecular weight heparin (LMWH) at anticoagulant dose [10]. Evidence for anticoagulant treatment choice comes from reported case series and retrospective studies which demonstrate that UH/LMWH are superior treatment options when compared to vitamin K antagonists (such as Warfarin) to prevent recurrent thromboembolism in patients with cancer-related NBTE [11]. In the era of direct oral anticoagulants, there is currently not enough data to support their use in cancer-related NBTE. Recently, a few cases were reported in which patients with cancer-associated NBTE on optimized doses of rivaroxaban had developed multiple discrete embolisms [12–14].

When evaluating the surgical options for NBTE, the indications and timing remain under investigation. However, cardiac surgery has proven to be an appropriate option in certain situations where the risk/benefit ratio is favorable [15]. Surgery may be warranted in circumstances including patients with symptomatic valvular dysfunction, recurrent thromboembolism despite appropriate anticoagulant therapy, vegetation size greater than 1 centimeter, patients with unclear diagnosis or etiology of NBTE, and/or patients with potentially treatable cancer [15].

It is important to review the impact NBTE has on the prognosis of cancer. NBTE has been a major hidden cause of recurrent strokes, and these strokes play an important role in the prognosis by increasing the mortality rate of such cancers [2,9]. Therefore, NBTE with the recurrent thromboembolic phenomenon is one of the main factors that worsen the prognosis and increase the mortality rates of these cancers. Additionally, a retrospective study of 65 patients with cancer-associated with NBTE performed over a 10-year period showed coagulation abnormalities including disseminated intravascular coagulation (DIC) identified in 18.5% of the cases and thus increased the mortality rate of these patients [4].

Conclusion

The frail nature of vegetations in NBTE is associated with an increased risk of recurrent embolic attacks such as cerebrovascular accident, pulmonary embolism, and deep venous thrombosis. We report a case of NBTE presenting as a pulmonary embolism in order to bring awareness to clinicians regarding this phenomenon. There is a need for high clinical suspicion to detect signs of embolism in patients with advanced cancer, particularly with pancreatic adenocarcinoma. The early diagnosis of NBTE and initiation of therapeutic anticoagulation has mortality and morbidity benefits. However, the mainstay of treatment is always treating the underlying cause.

Authors' contributions

Brooke Kania and Erinie Mekheal are the article guarantors. Brooke Kania, Erinie Mekheal, and Sindhusha Veeraballi performed the literature review and wrote the manuscript. All authors assisted in the collection of the patient's clinical data. All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at St. Joseph's University Medical Center as well as St. Michael's Medical Center.

Patient consent

As this is a case report, consent was obtained for the purpose of this paper.

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