Antemortem diagnosis of nonbacterial thrombotic endocarditis in a patient with previously resected pancreatic adenocarcinoma: a case report

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Background
Nonbacterial thrombotic endocarditis (NBTE) is a rare manifestation of a number of systemic diseases, which include advanced malignancy and hypercoagulable states.

Case summary
We present a 67-year-old woman who had presented with chest pain and heart failure. Eight years ago, she had a successful Whipple resection for pancreatic adenocarcinoma. Echocardiography revealed mitral valve vegetations with negative blood cultures. She had multiple infarcts in the kidney, spleen, and brain. She was found to have a mass in the left 8th rib, consistent with metastatic pancreatic adenocarcinoma on biopsy. Ultimately, a diagnosis of NBTE was made after excluding other causes for her presentation. Because of her general poor condition, she expressed the wish for palliative care and later died 28 days after presentation.

Discussion
This case illustrates the possibility of NBTE in patients successfully treated for pancreatic adenocarcinoma and highlights the consideration of this relatively rare differential in patients with a previously treated malignancy presenting with heart failure.

Keywords
Nonbacterial thrombotic endocarditis • Pancreatic adenocarcinoma • Hypercoagulability • Systemic embolization • Case report

Introduction
Nonbacterial thrombotic endocarditis (NBTE) is a rare non-infectious inflammation of the heart valves, often associated with hypercoagulable states. It is characterized as having vegetations composed of a spectrum of lesions ranging from sterile platelets, fibrin-based thrombi to large vegetations on previously undamaged heart valves.
valves, most commonly the mitral and aortic valves. Clinical manifestations are usually related to systemic embolization rather than from valvular dysfunction. Nonbacterial thrombotic endocarditis has been associated with various conditions and most commonly with advanced adenocarcinoma-related malignancies and autoimmune conditions. We present this case report of NBTE in a patient, previously diagnosed and treated for pancreatic adenocarcinoma.

**Timeline**

| Timing                        | Events                                                                 |
|-------------------------------|------------------------------------------------------------------------|
| 8 years before current presentation | Patient had a successful resection of Stage 1b pancreatic adenocarcinoma by Whipple's procedure |
| Initial presentation          | Patient arrived at the Emergency Room with left-sided chest pain, shortness of breath, orthopnoea, and paroxysmal nocturnal dyspnoea |
| Day 1                         | Transthoracic echocardiogram revealed free-floating vegetation 1.1 cm × 1.7 cm mobile mass attached to anterior mitral valve leaflet. Blood cultures drawn |
| Day 5                         | Transesophageal echocardiogram revealed an additional mobile mass on the posterior mitral valve leaflet and a patent foramen ovale |
| Day 6                         | Blood cultures returned negative. Computed tomography-pulmonary angiogram revealed mediastinal and hilar lymphadenopathy, soft tissue lesion in 8th lateral rib. CT abdomen revealed splenic and left renal infarcts. Vegetation likely due to nonbacterial thrombotic endocarditis |
| Day 7                         | Left chest biopsy done. Rheumatoid factor and cardiolipin G and M negative |
| Day 12                        | Biopsy result shows adenocarcinoma with the primary cancer from the pancreas. Cardiovascular surgery ruled out mitral valve surgery considering malignant disease |
| Day 16                        | Diuretics increased |
| Day 18                        | Oxygen increased. Antibiotics discontinued. Oncology ruled out treatment for metastatic disease. Plan to transfer to palliative care |
| Day 21                        | Patient transferred to palliative care |
| Day 28                        | Patient died |

**Case presentation**

A 67-year-old female, who had a successful Whipple's procedure 8 years ago for Stage 1b pancreatic adenocarcinoma, presented to our hospital with a 1-day history of left-sided chest pain, accentuated with coughing, and shortness of breath, orthopnoea, and paroxysmal nocturnal dyspnoea. Her past medical history included hypertension (treated with amlodipine 5 mg (once daily) and telmisartan/hydrochlorothiazide 80–12.5 mg (once daily)), chronic obstructive pulmonary disease (treated with Umeclidinium bromide inhaler 62.5 µg 2 puffs (twice daily)), and mood disorders for which she was on the appropriate treatment. She was hypoxic at 92% on 4 L of oxygen, afibrile, with an elevated jugular venous pressure and 3/6 holosystolic apical murmur. Chest auscultation revealed bilateral lung base crackles.

Her initial blood work revealed a marginally elevated white blood cell count 11.65 × 10⁹/L (normal range: 4.00–11.00 × 10⁹/L) with neutrophils 8.49 × 10⁹/L (normal range: 1.50–7.50 × 10⁹/L), haemoglobin 130 g/L (normal range: 110–160 g/L), platelet count 138 × 10⁹/L (normal range: 150–400 × 10⁹/L), International Normalized Ratio 1.2 (normal range: 0.8–1.2), partial thromboplastin time 27 s (normal range: 27–39 s), troponin T 292.2 ng/L (normal value < 14 ng/L), and brain natriuretic peptide 1581 ng/L (normal value < 300 ng/L).

A transthoracic echocardiogram (TTE) demonstrated a free-floating 1.1 cm × 1.7 cm mobile mass (Figure 1) attached to the anterior mitral valve leaflet associated with moderate mitral regurgitation (Figure 2). Her symptoms were felt to be associated with the mitral regurgitation found on the echo. She had preserved left ventricular systolic function. Transesophageal echocardiogram (TEE) revealed an additional mobile mass on the posterior mitral valve leaflet and a patent foramen ovale. Infective endocarditis was suspected, and the patient was started on empiric broad-spectrum antibiotics. However, three consecutive sets of blood culture did not reveal any growth including for Brucella, Bartonella, and Coxiella. Based on the high pre-test probability for infective endocarditis, antibiotics were continued for possible culture-negative endocarditis.

Computed tomography-pulmonary angiography (CT-PA) and CT abdomen and pelvis showed no pulmonary embolism; however, mediastinal and hilar lymphadenopathy, a soft tissue lesion in the left lateral 8th rib (Figure 3), and splenic and left renal infarcts (Figure 4) were identified. Computed tomography brain revealed a right occipital lobe infarct. Cardiolipin G and M antibodies and rheumatoid factor were assessed for the multiple infarcts, but were negative. Biopsy of the chest wall lesion (Figure 5), which was found on CT-PA, revealed...
a poorly differentiated invasive adenocarcinoma consistent with pancreaticobiliary origin.

In view of the above results, a diagnosis of NBTE secondary to metastatic pancreatic disease was established. Mitral valve surgery or therapies for her metastatic disease were ruled out because of her worsening general health condition.

Despite aggressive heart failure therapy, she remained oxygen dependent and with worsening of her overall health status, the patient expressed the desire to have comfort care only and died within 28 days of her presentation.

**Discussion**

Nonbacterial thrombotic endocarditis is a relatively rare complication of advanced malignancy and other hypercoagulable states, almost always diagnosed post-mortem with incident rates reported between 0.3% and 9.3%. Unfortunately, a substantial proportion of patients with NBTE have an underlying malignancy and as highlighted in 2340 autopsies of whom 217 had NBTE, a malignant neoplasm was evident in 51.6%.

Nonbacterial thrombotic endocarditis vegetations are sterile without inflammation or bacteria, and as such easy to dislodge and therefore frequently presenting with systemic embolization—as evident in our patient in whom emboli were present to the spleen, left kidney, and right occipit. Our patient did not have fever, which is quite uncommon in NBTE, but when present can confound the diagnosis of
NBTE because of similarities with infective endocarditis. The presence of a heart murmur is not specific to NBTE, but the presence of a new murmur in a patient with known or suspected malignancy should raise suspicion and be investigated. Our patient had TTE and TEE to evaluate the presenting heart failure symptoms and understand the mechanism of mitral regurgitation. As demonstrated in Figures 1 and 2, she had severe mitral regurgitation resulting from bileaflet endocarditis. However, serial blood cultures drawn prior to broad-spectrum antibiotic administration remained negative, including serologies for organisms typically causative for culture-negative endocarditis (Coxiella, Brucella, Bartonella) raising the clinical threshold for NBTE.

The definitive treatment of NBTE is to ideally remove the source of the emboli, i.e. the affected valve and initiation of systemic anticoagulation. However, definitive treatment of NBTE even after a diagnosis is established is often challenging. There have been few reports where replacement of the affected valves has led to the resolution of the disease. In some reports, resecting the cancer or treating them with chemotherapy have improved the haematological profile and prevented recurrent embolic events. Nonetheless, in the majority, the advanced nature of the underlying malignancy and concomitant comorbidity often precludes definitive surgery as was evident in this patient with an extremely high perioperative risk. She was therefore managed conservatively with therapies aimed at volume overload, afterload reduction, and systemic anticoagulation. Anticoagulation remains an important aspect of therapy of NBTE and both low-molecular-weight heparin and unfractionated heparin have been shown to be effective in reducing recurrent thromboembolism. Of note, warfarin is not effective in NBTE especially in the context of an underlying malignancy as patients continue to remain at an increased thromboembolic risk.

Although there are some reports of NBTE associated with pancreatic cancer, very limited if any literature exists for NBTE in patients with resected pancreatic cancer. Impetuous is a meticulous history with resected pancreatic cancer. Imperative is a meticulous history.

**Conclusion**

Nonbacterial thrombotic endocarditis is a rare presentation of advanced malignancy and other hypercoagulable states. A high index of clinical suspicion is required to make an antemortem diagnosis when associated with malignancies, but its occurrence often portends a poor long-term prognosis.

**Lead author biography**

Hamza Zahid Ullah Muhammadzai is a graduate of Khyber Medical College, Pakistan of the year 2015. Currently, he is working as a research fellow in Cardiology at the Royal University Hospital, University of Saskatchewan, Canada.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

** Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

**References**

1. Gross L, Friedberg CK. Nonbacterial thrombotic endocarditis: classification and general description. Arch Intern Med (Chic) 1936;58:620–640.

2. Lopes JA, Ross RS, Pohlebein MC, Siegel RJ. Nonbacterial thrombotic endocarditis: a review. Am Heart J 1987;113:771–784.

3. Kuramoto K, Matsushita S, Yamanouchi H. Nonbacterial thrombotic endocarditis as a cause of cerebral and myocardial infarction. Jpn Circ J 1984;48:1000–1006.

4. Asopa S, Patel A, Khan OA, Sharma R, Ghori SK. Non-bacterial thrombotic endocarditis. Eur J Cardiothorac Surg 2007;32:696–701.

5. Nagano N, Morin JF, Joyal D, Rudski L. Acute myocardial infarction and limb ischemia as manifestation of nonbacterial thrombotic endocarditis. J Thorac Cardiovasc Surg 2009;137:1278–1280.

6. Oueida Z, Scola M. Ovarian clear cell carcinoma presenting as non-bacterial thrombotic endocarditis and systemic embolization. World J Oncol 2011;2:270.

7. Jameson GS, Ramanathan RK, Borad MJ, Downhour M, Korn R, Von Hoff D. Marantic endocarditis associated with pancreatic cancer: a case series. Case Rep Gastroenterol 2009;3:67–71.

8. El-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. Oncologist 2007;12:518–523.

9. Devulapalli S, Pinto N, Gandhi C, Jayam-Trouth A, Kurukumbi M. A rare case of occipital stroke as a consequence of nonbacterial thrombotic endocarditis in ovarian clear cell carcinoma: a case report. Case Rep Neurol 2012;4:84–91.

10. Shibata N, Matsumoto K, Kitamura S, Sakashita A, Kizawa Y, Hirata KI. A case of nonbacterial thrombotic endocarditis concomitant with repeated systemic embolization that received palliative care based on the antemortem diagnosis. Intern Med 2018;57:3559–3558.