Acute ischaemia of the lower limb due to non-bacterial thrombotic endocarditis with recent venous thrombo-embolic disease as the initial manifestation of lung adenocarcinoma: a case report

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Background
Non-bacterial thrombotic endocarditis is a rare condition. Optimal management is based on early diagnosis which remains difficult.

Case summary
A 75-year-old male patient was admitted to the hospital with acute ischaemia of the left lower limb due to popliteal artery occlusion despite anticoagulation with rivaroxaban for pulmonary embolism diagnosed 2 weeks earlier. Transoesophageal echocardiography (TOE) showed a mobile vegetation with mild mitral valve regurgitation. Positron emission tomography (PET) scan did not show hyperfixation at the mitral valve but rather lymphadenopathy hyperfixation at different sites. Biopsy of a lymph node from Baretys’s space identified a bronchopulmonary adenocarcinoma. The outcome was favourable after popliteal artery thrombectomy and low-molecular-weight heparin treatment. The patient was referred to the department of onco-pneumology for further care.

Discussion
Upon clinical presentation, the combination of an arterial and prior venous thrombotic event suggested that the origin could be either a patent foramen ovale (PFO) or a thrombosis from an underlying cancer. A transthoracic echocardiography and TOE excluded a PFO and demonstrated a mobile echogenic mass at the mitral valve site together with a mild regurgitation. The diagnosis of non-bacterial thrombotic endocarditis was suggested given the absence of clinical and biological infectious signs, negative blood cultures and serology for endocarditis, the presence of both arterial and venous thrombosis, as well as the presence of intra-thoracic lymphadenopathy hyperfixation on the PET scan for which a biopsy demonstrated lung adenocarcinoma.

Keywords
Case report • Non-bacterial thrombotic endocarditis (NBTE) • Trousseau syndrome • Lung adenocarcinoma • Venous thromboembolism • Acute ischaemia

Learning points
• A recurrent venous and arterial thrombo-embolic event in a patient with valvular vegetation and suspected malignancy could suggest a non-bacterial thrombotic endocarditis.
• A complete endocarditis check-up must be performed.
Introduction

In 1865, Trousseau identified a syndrome characterized by secondary venous thrombosis associated with occult neoplasia. The term was later extended to all thrombotic events in patients with cancer. These various thrombotic events may occur as venous thromboembolism, superficial migratory thrombophlebitis, arterial thrombosis, disseminated intravascular coagulation, thrombotic microangiopathy, and less often, as a non-bacterial thrombotic endocarditis (NBTE). Originally described, in 1888, by Ziegler, NBTE is one of the various manifestations of cancer-associated thrombo-embolic events. It is an uncommon and challenging clinical entity characterized by small sterile vegetations on normal heart valves in the absence of a bacterial infection in the blood. We report a case of NBTE associated with venous and arterial thrombotic events as the first manifestation of a lung adenocarcinoma.

Timeline

| Date              | Events                                                                                       |
|-------------------|----------------------------------------------------------------------------------------------|
| 27 July 2019      | First hospitalization for symptomatic deep vein thrombosis confirmed by ultrasound and pulmonary embolism confirmed by computerized tomography pulmonary angiography. On discharge, treatment with Rivaroxaban according to guidelines. |
| 13 August 2019    | Second hospitalization for left lower limb acute ischaemia. Treatment with subcutaneous injection of enoxaparin 1 mg/kg b.i.d. and thrombectomy of the popliteal artery. |
| 18 August 2019    | Transthoracic echocardiography/transoesophageal echocardiography: Infracentimetric mobile vegetation of the mitral valve with mild mitral regurgitation. Patent foramen ovale not identified on echocardiography. Introduction of intravenous antibiotics (amoxicillin 12 g o.d. and gentamicin 3 mg/kg o.d.) for suspicion of infective endocarditis pending the final diagnosis. |
| 23 August 2019    | Positron emission tomography scan: pulmonary and mediastinal lymphadenopathy hyperfixation without mitral valve hyperfixation. |
| 29 August 2019    | Sets of blood cultures and serology are negative. Antibiotic treatment is stopped. Treatment with low-molecular-weight heparin is continued. |
| 03 September 2019 | Diagnosis of adenocarcinoma of bronchopulmonary origin after a lymph node biopsy sampled from Barety’s space. |
|                   | Continued                                                                                     |

Case presentation

A 75-year-old male was referred by general practitioner to our hospital for recurrent deep vein thrombosis (DVT) of the lower limbs. His past medical history consisted of chronic obstructive pulmonary disease treated with a beta-adrenergic agonist and a smoking cessation several years ago. On admission, he described progressive shortness of breath and general fatigue. Clinical examination did not find any noticeable abnormality. Computerized tomography (CT) pulmonary angiography revealed bilateral and multisegmental pulmonary embolism (PE) (Figure 1) associated with bilateral paratracheal and left hilar lymph nodes of which the largest measured 20 mm. There was no abnormality detected in the pulmonary parenchyma. On admission, anticoagulation treatment with enoxaparin 1 mg/kg b.i.d. was started, then switched on discharge to rivaroxaban according to European Society of Cardiology (ESC) guidelines. Direct oral anticoagulant was preferred for patient’s comfort pending the investigation of thoracic lymph nodes by positron emission tomography (PET) scan. The results of the coagulopathy and thrombophilia testing were negative.

Two weeks later, the patient was readmitted to the hospital with an acute ischaemia of the left lower limb. His blood pressure was 163/78 mmHg, pulse rate was 81 beats/min, peripheral oxygen saturation on room air was 94%, and body temperature was 37.6°C. On physical exam, the left lower leg was painful, pale with decreased local temperature and popliteal, and distal artery pulses were diminished. Cardiovascular auscultation revealed a regular heart rate without an evident murmur. A standard laboratory examination showed an anaemia with a haemoglobin of 10.4 g/dL (13.5–17.5 g/dL), an inflammatory reaction with a C-reactive protein level of 40 mg/L (<10 mg/L), and a hypereosinophilia at 3 × 10^9/L (0–0.5 × 10^9/L). An electrocardiogram revealed normal sinus rhythm. A thrombosis occluding the popliteal and the medial sural arteries was detected on colour-Doppler ultrasound and confirmed by CT angiography (Figure 2). Treatment with subcutaneous injection of enoxaparin 1 mg/kg b.i.d. was started, and thrombectomy of the popliteal artery was performed. In our patient who had a recurrent DVT, low-molecular-weight heparin (LMWH) was preferred to unfractionated heparin as it has shown to be the treatment of choice for DVT/PE recurrences.

Post-operatively, the patient presented a single episode of fever 38.5°C that resolved spontaneously. Pathology examination of the thrombectomy-related material showed a fibrinous clot. Holter...
monitoring found sinus rhythm with rare supraventricular and ventricular extrasystoles without atrial fibrillation. Transthoracic echocardiography showed only mild mitral regurgitation and transoesophageal echocardiography (TOE) detected an infracenticmetric mobile vegetation of 0.5 cm × 0.3 cm on atrial side of the posterior mitral valve leaflets with mild regurgitation (Figure 3). There was no evidence of a patent foramen ovale. Bacterial endocarditis was suspected at this point, and the patient was treated with intravenous antibiotics, amoxicillin 12 g o.d., and gentamicin 3 mg/kg o.d. pending the results of blood cultures and the final diagnosis. Multiple aerobic and anaerobic blood cultures and an extensive thrombophilic and autoimmune testing were conducted and came back negative, including assays for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, lupus anticoagulant, anticardiolipin antibodies, beta-2
glycoprotein 1 antibodies, anti-cyclic citrullinated peptide antibodies, anti-extractable nuclear antigen antibodies, and anti-rheumatoid factor.

Whole-body PET scan showed pulmonary and mediastinal lymphadenopathies suggesting the presence of an underlying neoplasia (Figure 4). There was no evidence of mitral valve hyperfixation on PET scan. Brain magnetic resonance imaging (MRI) revealed a small hypersignal lesion on T2 FLAIR images, suggestive of embolic infarction in the left parietal lobe (Figure 5). The patient did not complain of any symptoms. Lymph node biopsy from Barety’s space was taken, and the pathology report indicated micropapillary predominant adenocarcinoma of bronchopulmonary origin. Sets of blood cultures and serology were negative, and there were no clinical manifestations of infective endocarditis (IE).

Based on the medical background and clinical context, the final diagnosis was in favour of an NBTE associated with advanced pulmonary adenocarcinoma KRAS+ PDL1 - (T3N3M1a).

According to ESC guidelines,8 the evidence of a small vegetation measured at 0.5 cm × 0.3 cm without heart failure and without uncontrolled infection despite thrombo-embolic episodes did not require surgical intervention. Conservative medical treatment was adopted after discussion with a multi-disciplinary team.

During hospitalization, repeat TOE was performed as a routine follow-up in accordance with the ESC guidelines8,9 and showed a significant regression of the mobile echodensity of the mitral valve 10 days after the first TOE. Antibiotic therapy was stopped at Day 11. The patient was referred to the oncology department with lifelong LMWH for NBTE and cancer-associated thrombosis according to the ESC guidelines.6,8 Carboplatin and Taxol chemotherapy was started. Ultimately the patient did not respond to chemotherapy and subsequently died from cancer 4 months after the NBTE diagnosis.
**Discussion**

Non-bacterial thrombotic endocarditis is a rare entity. Incidence reports have ranged from 0.3% to 9.3%.4,5

Antemortem diagnosis is difficult and prognosis is poor as in our patient. NBTE is mostly documented in patients with advanced cancer most commonly pulmonary, gastrointestinal, mammary, or gynecological adenocarcinomas. However, it may also complicate other chronic diseases, such as systemic lupus erythematosus, Loeffer endocarditis, Behçet’s disease, anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, rheumatoid arthritis, Still’s disease, systemic sclerosis, Cogan’s syndrome, Sneddon’s syndrome, and Histiocytosis.10 Cases of NBTE are described in a context of malignant hematoma such as lymphoma, multiple myeloma, and chronic myeloproliferative disorders.11

The aetiology and pathogenesis of NBTE is not fully elucidated, and it has been postulated that NBTE occurring in association with malignant neoplasms might be related to a hypercoagulable state. Potential mechanisms for this hypercoagulable state include hypo and hyperfibrinogenemia, thrombocytopenia, decreased levels of factors V, VIII, and XIII, and impairment of platelet function by circulating fibrin degradation products.1,4,5,12

The main challenge is to discriminate between IE and NBTE. Non-bacterial thrombotic endocarditis can be associated with fever and valve dysfunction but if present, it is rarely asymptomatic or severe.2,13,14 As in our case report, the main clinical manifestations of NBTE are the ischaemic events as a consequence of systemic embolism. This occurs in approximately 42% of patients (with a range of 14.1–90.9%).2,5,15 The common sites of embolization include the central nervous system, splenic, renal, mesenteric, coronary, and the extremities. Although the TOE does not make it possible to direct towards the infectious origin of the vegetation, the arguments for NBTE are that it is characterized by small (<1 cm in diameter), broad-based and irregularly shaped areas of vegetation along coaptation lines without destruction of valvar tissue.10 These vegetations are usually found on the atrial surfaces of the mitral and tricuspid valves and the ventricular surfaces of the aortic and pulmonic valves.4,5,10

When the clinical context does not suggest an IE as in our patient and before concluding that the origin is a NBTE, it is appropriate to rule out the other causes of systemic embolism and valvar vegetations, such as paradoxical emboli, the antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, mural thrombi associated with cardiomyopathy, atrial myxoma, acute rheumatic fever, Lambli’s excrescences, fibroelastoma, cardiac rhabdomyoma, cardiac hamartomas, and malignant cardiac tumours.10 Mckay and Wahler proposed a triad for diagnosis of NBTE, that combines the presence of a disease process known to be associated with NBTE, the presence of heart murmur, and the evidence of multiple systemic emboli.16 Lack of clinical improvement after treatment of IE, negative blood cultures, and history of cerebral embolism of unknown aetiology are other clues of NBTE.5

The primary approach to treating NBTE is to correct the underlying cause and manage the risk of embolization. Unfractionated heparin and LMWH have been found to be the most effective anticoagulant treatments in reducing the incidence of embolic events.2,8 Valvular repair or replacement can be performed in patients with valvar dysfunction, large vegetations, or recurrent embolism despite anticoagulation therapy but should be avoided whenever possible.4,8,10

This case report shows how the diagnosis of NBTE is complex. The association of venous thromboembolism, lower limb, and cerebral artery thromboembolism of unknown cause and the recurrence of thrombotic events despite adequate anticoagulation helped to direct the diagnosis towards a cancer origin. We highlight the importance of the combination of TOE that showed a mobile echogenic mass on the atrial side of the mitral valve leaflets with mild regurgitation and PET scan imaging in order to discriminate between an infective endocarditis and an NBTE diagnosis. The diagnosis of NBTE is suggested by the absence of mitral valve hyperfixation on PET scan ruling out the diagnosis of infective endocarditis together with the negative blood cultures, and by the presence of lymphadenopathy, which following biopsy, confirmed the presence of an adenocarcinoma of bronchopulmonary origin.

**Conclusion**

This case report highlights the arguments for a non-infectious and potentially a cancer-related thrombotic origin of a valve vegetation that are the following: the absence of clinical and biological infectious context, the absence of positive blood cultures and positive serology for endocarditis, the context of arterial and venous thromboembolism with recurrent events despite anticoagulant therapy as well as the presence on the PET scan of intra-thoracic lymphadenopathy hyperfixation of which biopsy demonstrated the lung adenocarcinoma.

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**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 these cases and suitable for local presentation is available online as Supplementary data.
Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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