

## Case Report

# Nonbacterial Thrombotic Endocarditis and Widespread Skin Necrosis in Newly Diagnosed Lung Adenocarcinoma

Katerina Zakka<sup>a</sup> Patrick Zakka<sup>b</sup> Amir Davarpanah<sup>c</sup>  
Nikoloz Koshkelashvili<sup>d</sup> Mehmet A. Bilen<sup>a</sup> Taofeek Owonikoko<sup>a</sup>  
Bassel El-Rayes<sup>a</sup> Mehmet Akce<sup>a</sup>

<sup>a</sup>Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; <sup>b</sup>Department of Internal Medicine, Emory University School of Medicine, Atlanta, GA, USA; <sup>c</sup>Department of Radiology, Emory University School of Medicine, Atlanta, GA, USA; <sup>d</sup>Department of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

## Keywords

Nonbacterial thrombotic endocarditis · Lung adenocarcinoma · Skin necrosis

## Abstract

Nonbacterial thrombotic endocarditis (NBTE) is a rare entity most commonly diagnosed post-mortem with rates in autopsy series ranging from 0.9 to 1.6%. A 63-year-old female with past medical history of hypertension and mitral valve prolapse presented to the hospital with shortness of breath, headache, and necrotic skin lesions on her hands and feet. Computed tomography (CT) scan of her chest demonstrated a pulmonary embolus in the right lower lung segmental artery and right upper lobe lobar to segmental pulmonary artery, a mass-like consolidation in the left upper lung field impeding the hilum. CT scan of the abdomen demonstrated metastatic disease in liver and bone and bilateral femoral deep vein thrombosis. Transesophageal echocardiography revealed severe mitral regurgitation with two small mobile plaques on the mitral valve and two immobile plaques on the descending aorta. Magnetic resonance imaging of the brain was consistent with subacute infarcts and metastatic disease. Bronchoscopy was performed and pathology revealed primary adenocarcinoma of the lung. She was treated with anticoagulation and systemic chemotherapy. The patient and family elected to proceed with hospice due to her clinical decline, poor performance status, and poor prognosis after a prolonged hospital stay. Underlying malignancy is detected in approximately 40–85% of patients with NBTE. Lung cancer is the most frequently associated malignancy followed by pancreatic, stomach, breast, and ovarian cancer. Widespread necrotic skin lesions as presenting symptoms of primary lung adenocarcinoma are rare. In the present case, the

Mehmet Akce, MD  
Department of Hematology and Medical Oncology, Winship Cancer Institute  
Emory University, 1365 Clifton Rd NE  
Atlanta, GA 30322 (USA)  
mehmet.akce@emory.edu

diagnosis of necrotic skin lesions and NBTE preceded that of the neoplastic disease. Necrotic skin lesions and NBTE can be the first manifestations of an occult malignancy causing extensive multi-organ infarcts. NBTE can present with such extensive skin lesions as a first presenting sign of malignancy. To the best of our knowledge, this is the first case to present with such extensive skin lesions as the first presenting symptom of lung adenocarcinoma.

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## Introduction

Nonbacterial thrombotic endocarditis (NBTE) is a rare entity most commonly diagnosed postmortem with rates in autopsy series ranging from 0.9 to 1.6% [1]. Malignancy as an underlying disease is detected in approximately 40–85% of NBTE cases [1]. Lung cancer is the most frequent underlying disease, although cases of pancreatic, stomach, breast, and ovarian cancer have also been reported. The major clinical manifestations of NBTE result from systemic emboli to common sites including the spleen, kidney, skin, and extremities that could present as flank pain, hematuria, rash, and digital ischemia [2].

NBTE was first described in 1888 by Zeigler and named in 1936 by Gross and Friedberg [3], who suggested that the disease was an event in which fibrin attaches to the cardiac valve. Recently, NBTE was defined as a state of hypercoagulability due to a malignancy, which causes a rise in tumor necrosis factor and interleukin-1, leading to thrombi formation [4]. Although the pathological mechanisms underlying the development of NBTE have not been fully investigated, various inflammatory reactions, necrotic conditions, and abnormalities in protein metabolism in patients with malignancy have been postulated to be important contributors [5].

Reported cases of NBTE in patients with lung cancer confirm that necrotic skin lesions as the first presenting symptom are rare [6]. Heart murmurs are frequently absent in NBTE and the diagnosis is usually missed; therefore, transesophageal echocardiography (TEE) is a necessary diagnostic test [7]. The presence of vegetation on the coaptation surface of valves, normal valvular tissue, and negative blood cultures are strongly indicative of NBTE [8]. Here we report an intriguing case where the diagnosis of necrotic skin lesions and NBTE preceded that of the neoplastic disease diagnosis. The patient has provided written informed consent to publish this case.

## Case Description

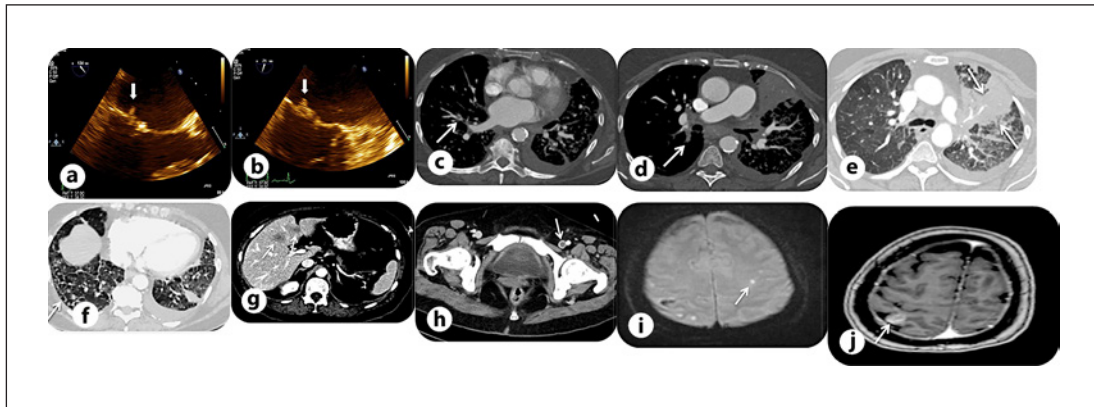
A 63-year-old female with a past medical history of hypertension and mitral valve prolapse initially presented to a primary care physician with bruises on the dorsal surface of her left hand which slowly extended to her left fifth digit and eventually became necrotic and painful. She subsequently developed a similar lesion on the dorsal surface of her right hand as well as toes on both of her feet, for which she was empirically treated with a course of doxycycline and prednisone without improvement. Upper extremity venous/arterial Doppler ultrasounds were negative. A skin biopsy revealed superficial thrombotic vasculopathy with overlying epidermal necrosis and ulceration. In the interim, she presented to an outside hospital with progressive shortness of breath, fatigue, dysgeusia, weight loss, headaches, and worsening skin lesions and was transferred to our institution for further evaluation.

Physical examination revealed a dark violaceous patch throughout the second toe with bluish discoloration noted on the third and great toe (right foot; Fig. 1a, b), a dark violaceous patch on the tip of the third toe with mild violaceous discoloration on the second toe (left foot;



**Fig. 1.** Dermatological findings. **a** Right foot (dorsal view). **b** Right foot (ventral view). **c** Left foot (dorsal view). **d** Left foot (ventral view). **e** Right hand (dorsal view). **f** Left hand (dorsal view).

Fig. 1c, d), a large necrotic eschar on the dorsal hand with undermining borders and mild erythema (right hand; Fig. 1e), and a large necrotic eschar extending from the dorsal hand over to the fifth digit with circumferential necrosis of the digit from the tip to just distal of the proximal interphalangeal joint (left hand; Fig. 1f). No purulent drainage or crusts were noted. The rest of the exam was unremarkable. Laboratory examination revealed elevated D-dimer (26,772 ng/mL), heterozygosity of factor V Leiden mutation, positive lupus anticoagulant, increased levels of anti-cardiolipin IgM (25.6 CU) and anti-beta-2-glycoprotein IgM (30.9 CU) antibodies, elevated protein S activity level (205%), and increased factor VIII activity (249.4%), whereas the rest of the hypercoagulability panel was within normal limits. Human immunodeficiency virus and hepatitis serologies, as well as blood cultures, were negative. Electrocardiogram revealed normal sinus rhythm. TEE demonstrated a normal left ventricular ejection fraction (65%), two small mobile masses (the largest of which is on the anterior leaflet and measures 0.3 cm in diameter) noted on the anterior and posterior leaflets (Fig. 2a, b), severe mitral valve regurgitation, and a small amount of immobile plaque involving the descending aorta. Computed tomography (CT) of the chest with contrast demonstrated several pulmonary emboli within the right lower lobe segmental pulmonary artery (Fig. 2c) and right upper lobe lobar to segmental pulmonary artery (Fig. 2d). There was a mass in the left upper lobe with extension to the hilum (Fig. 2e) causing narrowing of left upper pulmonary artery. There were multiple enlarged mediastinal and subcarinal lymph nodes, diffuse nodular septal thickening compatible with lymphangitic carcinomatosis (Fig. 2f), and numerous sclerotic osseous metastases. Subsequent CT of the abdomen with contrast demonstrated multiple hepatic hypo-enhancing metastases (Fig. 2g), left femoral deep vein thrombosis (Fig. 2h), and numerous sclerotic osseous metastases in the thoracolumbar spine and pelvis. Magnetic resonance imaging of the brain with and without contrast revealed numerous foci of restricted diffusion scattered throughout multiple vascular distributions concerning for embolic infarcts (Fig. 2i). In addition, there were multiple enhancing cortical and subcortical lesions compatible with metastatic disease (Fig. 2j). Bronchoscopy was performed and immunohistochemical



**Fig. 2.** Radiographic findings. **a** TEE mobile plaque on the mitral valve. **b** TEE mobile plaque on the mitral valve. **c** CT chest with contrast. Acute pulmonary embolism within a right lower lobe segmental pulmonary artery. **d** CT chest with contrast. Acute pulmonary embolism within a right upper lobe lobar to segmental pulmonary artery. **e** CT chest with contrast. Left upper lobe mass (approximately 6.6 × 5.9 × 6.4 cm) with left pulmonary artery narrowing. **f** CT chest with contrast. Lymphangitic carcinomatosis. **g** CT abdomen and pelvis with IV contrast. Multiple ill-defined hypo-attenuating metastatic hepatic lesions (2.3 × 2.1 cm segment IVb lesion and an adjacent 2.1 × 2.3 cm lesion). **h** CT abdomen and pelvis with IV contrast. Left common femoral vein deep vein thrombosis. **i** MRI brain with and without contrast. A few scattered punctate foci of restricted diffusion in the bilateral cerebral white matter (left greater than right) compatible with embolic phenomenon. **j** MRI brain with and without contrast. Enhancing lesion in the right postcentral gyrus with associated intrinsic T1 hyperintense signal and susceptibility artifact, compatible with hemorrhagic metastatic lesion.

staining of a transbronchial biopsy was positive for CK7 and TTF-1 and CK20 negative, consistent with an adenocarcinoma of lung origin. PD-L1 expression was low (partial or complete cell membrane staining [ $\geq 1+$ ] in 15–20% of viable tumor cells).

The patient was treated with high-intensity heparin drip for her hypercoagulable state and she also developed heparin-induced thrombocytopenia. While further details of the pathological evaluation of her biopsy specimen were pending, the patient was started on chemotherapy with carboplatin and pemetrexed in the hospital. The patient and family elected to proceed with hospice due to her clinical decline, poor performance status, and poor prognosis after a prolonged hospital stay.

## Discussion

Cancer-associated thrombophilia generally presents with venous thromboembolism. Other presentations include migratory superficial thrombophlebitis, arterial thrombosis, disseminated intravascular coagulation, and NBTE [2]. NBTE usually affects the aortic valve and to a lesser extent the mitral valve and more rarely the right-sided valves [9]. The diagnosis of NBTE requires a high degree of clinical suspicion. In the absence of infective etiology in endocarditis, NBTE should be strongly considered. When NBTE is diagnosed, investigating for an underlying malignancy is of paramount importance as timely intervention on cancer promises successful treatment for both cancer and associated embolic events. Treatment consists of systemic anticoagulation to prevent further embolization and underlying cancer treatment. Among all forms of anticoagulation, intravenous or subcutaneous unfractionated heparin has been shown to be the most effective in reducing the incidence of embolic events.

Low-molecular-weight heparin has also been used and appears to be effective [2]. Vitamin K antagonists such as warfarin should not be used since the activation of cytokines (interleukins 1, 6), cyclooxygenase-2 genes, type 1 plasminogen activator inhibitor, cysteine proteases, and tissue factors in malignancy renders these agents less effective in controlling the coagulopathy associated with NBTE and patients should stay on anticoagulation indefinitely [2]. In patients with potentially curable cancer and tumor-associated coagulopathy, tumor resection to eliminate the cause of the coagulopathy should be considered as a first therapeutic priority [10].

Cutaneous manifestations of NBTE have rarely been reported in the literature, described merely as purpura [11] and petechiae [12]. A case of necrotic toes as the initial sign for NBTE was reported in a patient with underlying pancreatic adenocarcinoma [13]. However, NBTE presenting with such widespread necrotic skin lesions as the sole manifestation of lung adenocarcinoma has not been previously reported, making this case very unique [14]. The major clinical manifestations of NBTE in this case result from systemic emboli rather than valvular dysfunction [2]. These vegetations are easily displaced due to the limited inflammation at the site of attachment [2]. Common sites of embolization include the spleen, kidney, and extremities, but the most significant morbidity arises from emboli to the central nervous system and coronary arteries. The likelihood of systemic embolism secondary to NBTE varies widely (14–91%, average of 42%), with a higher incidence of stroke due to NBTE compared to infective endocarditis (19%) [4]. Pulmonary emboli appear to be common findings in patients with NBTE, found in as many as 50% of cases, although it is difficult to establish if these emboli arise from the right-sided heart valves or the more distal venous circulation (e.g., from a deep vein thrombosis) [15].

## Conclusion

The diagnosis of NBTE presenting with severe necrotic skin lesions and widespread thromboembolism can be the first manifestation of an occult malignancy causing extensive multi-organ infarcts. To the best of our knowledge, this is the first case to present with such extensive skin lesions as the first presenting symptom of lung adenocarcinoma.

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## Statement of Ethics

We have obtained ethical approval from the patient to publish this report.

## Disclosure Statement

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## Author Contributions

All authors contributed to the manuscript and approved the final manuscript.

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