

## Case Report

# Diagnosis of Trousseau Syndrome Due to Lung Adenocarcinoma in a 77-Year-Old Man who Presented with Blue Toe Syndrome and a High CA125 Level: A Case Report

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**Abstract**

The patient was a 77-year-old man who initially presented with blue toe syndrome (BTS) and multiple cerebral emboli. He was diagnosed as having Trousseau syndrome due to lung adenocarcinoma. BTS is a rare presenting symptom in Trousseau syndrome, which is caused by blood hypercoagulability and is mainly associated with mucin-producing adenocarcinoma. Serum CA125 levels, a mucin production marker, increased together with plasma D-dimer level because of lung adenocarcinoma, which is rare. Anticoagulant therapy with heparin temporarily improved the D-dimer level and skin discoloration of BTS. Therefore, we believe that the BTS in this case was consistent with Trousseau syndrome.

**ABBREVIATIONS**

BTS: Blue Toe Syndrome; CT: Computed Tomography

**INTRODUCTION**

Abnormal blood coagulation has been recognized in a subset of patients with malignancy. The association of thromboembolic disorder with occult malignancy was first described by Armand Trousseau in 1865 [1]. The mechanisms underlying Trousseau syndrome include thrombosis caused by disseminated intravascular coagulation syndrome associated with malignant tumors and cardiogenic embolism caused by nonbacterial thrombotic endocarditis [1,2]. Trousseau syndrome often presents as multiple cerebral emboli. However, blue toe syndrome is rare in patients with Trousseau syndrome. Solid cancers particularly lung and gynecological cancers, are the most common cause of Trousseau syndrome [3,4]. Histologically, these cancers are most likely to be adenocarcinomas, particularly mucin-producing adenocarcinoma [5]. CA125 is a well-known diagnostic marker of gynecological cancers. A member of the mucin family, CA125 acts as an embolizing substance in the blood by directly activating prothrombin, which can lead to thromboembolism and nonbacterial thrombotic endocarditis [6].

We encountered a patient with Trousseau syndrome who

presented with blue toe syndrome and was found to have multiple cerebral emboli and an abnormally high CA125 level. To our knowledge, there have been no previous reports of Trousseau syndrome in which the presenting symptom was blue toe syndrome. In this article, we discuss the association between CA125 and Trousseau syndrome caused by lung adenocarcinoma and review the relevant literature.

**CASE PRESENTATION**

The patient was a 77-year-old man who was referred to our hospital by a local doctor in late February 2019. On presentation, he was found to be disoriented in time and place. He had an approximately 6-week history of coldness in the distal limbs and discoloration of the tips of the fingers and toes bilaterally. These lesions had become increasingly painful and some were ulcerated. His responses had been slower than usual during the previous 2 weeks. He also reported unintentional weight loss of 5 kg in the previous 2 months. He had been diagnosed with prostate cancer at the age of 60 years.

On admission, his level of consciousness was □-2 on the Japan Coma Scale. He had body temperature of 37.1°, blood pressure of 198/100 mmHg, and heart rate of 78 beats/min. Blood pressure measurements were the same in the upper and lower limbs.

On initial examination, all fingers were cool to the touch; the fingertips in both hands were discolored except for the right first finger (Figure 1A). The tip of the right fifth finger was necrotic. The tips of all fingers on the left were discolored from the first joint. The tips of all toes were discolored, and the right fourth toe and left first toe were ulcerated (Figure 1B). Heartbeat was regular with no murmurs and the distal pulses were palpable and symmetrical in all four extremities. There were no clinical features of connective tissue disease, such as skin rash or joint pain. Neurological examination revealed disorientation. There was no cranial nerve abnormality or paralysis, sensory disturbance, or ataxia involving the extremities. All limb tendon reflexes were markedly exaggerated. A pathological plantar reflex was elicited on both sides.

At admission, blood coagulation test results were as follows: platelets  $10.5 \times 10^4/\mu\text{L}$ , fibrin/fibrinogen degradation products  $78.60 \mu\text{g/mL}$ , D-dimer  $23.35 \mu\text{g/mL}$ , prothrombin time 13.9 s, and activated partial thromboplastin time 25.2 s. Hemoglobin level was 12.7 g/dL. An extensive investigation followed, including serum complement testing, assays for antinuclear, antineutrophil cytoplasmic, and anti-Sjogren syndrome A and B antibodies, cryoglobulin testing, and hepatitis B and C virus serology, as well as screening for syphilis and lupus anticoagulant, protein S and C deficiency, antithrombin III deficiency, and anticardiolipin and beta-2 glycoprotein antibodies. The results of all these tests were negative. Chest X-ray revealed a mass in the right lower lung field. Brain diffusion-weighted magnetic resonance imaging revealed infarctions in multiple vascular territories (Figure 3A). Findings on magnetic resonance angiography of the intracranial and extracranial vessels from the common carotid artery to the circle of Willis were unremarkable (Figure 3B).

### Clinical course after admission

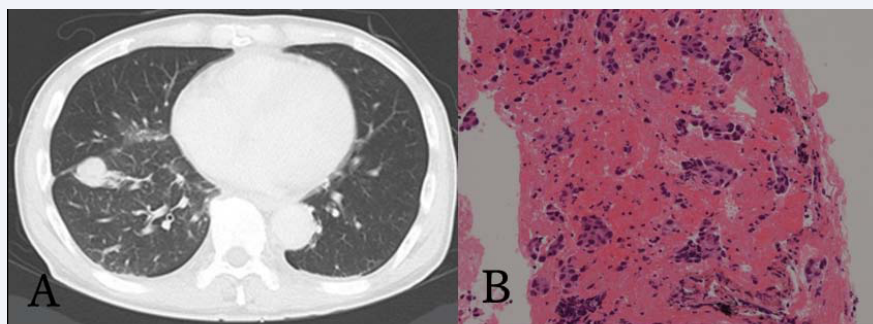
He had no history of catheterization or trauma and the patient's radial and dorsalis pedis arteries were palpable. Blue toe syndrome was diagnosed based on skin findings. Chest and abdominal computed tomography (CT) showed a normal aorta with vessels of normal caliber and no distal filling defects. Biopsy of a cutaneous lesion on the finger showed no cholesterol clefts in the blood vessels, which excluded cholesterol embolism. There was no evidence of vasculitis.

Electrocardiography showed normal sinus rhythm with no sign of myocardial ischemia. Echocardiography did not reveal intracardiac thrombi or evidence of nonbacterial thrombotic endocarditis, such as vegetations or valve deformity. There was no right-to-left shunt.

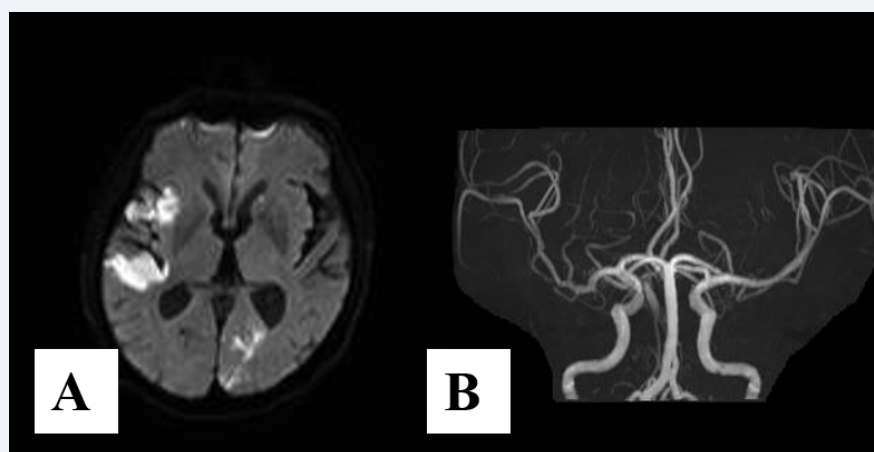
We speculated that the blue toe syndrome with increased coagulation markers and multiple cerebral infarcts might be manifestations of Trousseau syndrome. Examination of tumor markers demonstrated elevated CA125, sialyl Lewis X-i antigen, and progastrin-releasing peptide levels (416 U/mL, 74.0 U/mL, and 81.5 pg/mL, respectively). A subsequent chest CT scan revealed a mass lesion in the right lung (Figure 2A). Endobronchial ultrasound-guided transbronchial needle aspiration was performed, and lung adenocarcinoma was diagnosed histologically (Figure 2B). Bone scintigraphy showed multiple bone metastases. The diagnosis was lung adenocarcinoma stage T1cN3M1c (stage IVB). We concluded that the blue toe syndrome and Trousseau syndrome were caused by coagulation abnormalities associated with lung adenocarcinoma. The color in the extremities worsened day by day and D-dimer level gradually increased. Therefore, heparin was started on the third hospital



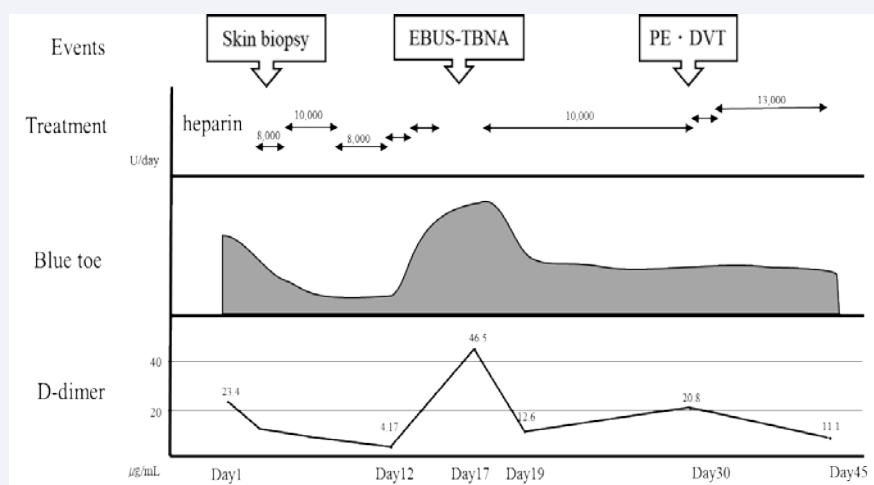
**Figure 1** Clinical photographs of the hands and feet. (A, B) All fingers were cool to the touch and showed purple discoloration, except for the right first finger. The tip of the right fifth finger was necrotic. The tips of all fingers on the left hand were purple, as were the tips of all toes on both sides. The right fourth and left first toes were ulcerated.



**Figure 2** (A) Chest computed tomography shows a mass 2 cm in diameter (white arrow) in the right lower lung field (S8). (B) Histological examination of a subcarinal lymph node aspiration biopsy specimen shows adenocarcinoma (hematoxylin-eosin staining,  $\times 20$ ).



**Figure 3** (A) Brain diffusion-weighted images on admission revealed multiple cerebral infarctions in the cerebral cortex and subcortex bilaterally. (B) Magnetic resonance angiography did not show any atherosclerotic changes.



**Figure 4** Clinical course of the case. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; PE, pulmonary embolism; DVT, deep venous thrombosis.

day. The skin discoloration in the extremities disappeared rapidly and the D-dimer level improved to 4.17  $\mu\text{g/mL}$  by the 12th hospital day. Heparin was discontinued temporarily so that ultrasound-guided transbronchial needle aspiration could be performed, and there was a marked increase in D-dimer level and worsening of the skin discoloration. When heparin was resumed after the examination, the D-dimer level improved, as did the skin discoloration of the extremities. The patient's respiratory status worsened suddenly on the 30th hospital day. Enhanced CT showed occlusion of the right pulmonary artery and deep vein thrombosis in the left femoral vein. Because of the progression of lung adenocarcinoma and severe brain damage in this patient, he was transferred to a palliative care facility on the 45th hospital day. The clinical course is summarized in Figure 4.

## DISCUSSION

Blue toe syndrome manifests as blue or violaceous discoloration of one or more toes in the absence of obvious trauma, serious cold-induced injury, or a disorder producing

generalized cyanosis. There are many causes of blue toe syndrome, as documented in the Table. These are common and many of these pathologies can be distinguished with a detailed history, associated clinical features, and physical examination supported by investigations (Bedside and Laboratory Tests and Imaging). However, if they are ruled out, a peripheral acral vascular syndrome should be considered. These syndromes present as Raynaud's phenomenon, gangrene, or acrocyanosis of the fingers or toes with underlying malignancy. Unusual features, such as sudden onset in a patient over 50 years of age, an acral distribution, and associated symptoms such as unrelated pain and weight loss should raise concern for underlying malignancy [7].

Paraneoplastic acral vascular syndrome is associated with certain cancers, particularly adenocarcinoma and metastatic disease [8]. In our case, blue toe syndrome and multiple cerebral infarctions were observed but there was no embolic source in the arterial region and no complications of connective tissue disease or coagulopathy. The diagnosis turned out to

be Trousseau syndrome secondary to lung adenocarcinoma. The response to heparin was favorable based on changes in D-dimer and skin findings, and we considered that blue toe syndrome was consistent with Trousseau syndrome in this patient. Blue toe syndrome is a rare phenomenon in Trousseau syndrome and is rarely associated with malignancy. We were able to identify only 7 such cases in the literature, including the present case. Of these 7 cases 3 were described as blue toe syndrome, 3 as paraneoplastic acral vascular syndrome, and 1 as paraneoplastic Raynaud's phenomenon. The underlying malignancies in these patients included carcinomas of the lung, pharynx, esophagus, ovary, and pancreas, chronic lymphocytic leukemia, and epithelioid hemangioendothelioma [7-11]. Only one case was associated with multiple cerebral infarctions. Poszepczynska et al. speculated that the pathophysiological mechanism of paraneoplastic acral vascular syndrome was thrombotic occlusion, and histologic examination in their case revealed fibrinoid necrosis of the vessels, intimal proliferation, heterogenous inflammatory cell infiltrates, and tissue necrosis with venous and/or arterial thrombosis [8]. These skin findings were not noted in the skin pathology reports for our patient. Additionally, the skin findings in our case improved rapidly with heparin treatment. If the pathological mechanism of blue toe syndrome and multiple cerebral emboli in our case were to be explained centrally, it would be assumed to be systemic embolism resulting from nonbacterial thrombotic endocarditis.

CA125 level, which is increased in gynecological diseases such as ovarian cancer, was high despite the patient being male and having lung adenocarcinoma. CA125 is a repeating peptide

epitope of the mucin MUC16 and is a marker of mucin-producing malignant tumors. It is widely used as a diagnostic marker for gynecological cancers and evaluation of therapeutic effects [12]. This marker has been the subject of increasing attention because high levels may be observed in mucin-producing tumors, including lung, pancreatic, and ovarian cancers [13]. Furthermore, marked elevation of this mucinous tumor marker has been reported to be associated with cerebral infarction, even in benign conditions [14]. High-molecular weight mucins such as CA125 are closely involved in the background of thrombosis due to Trousseau syndrome. CA125 exists as a mucin molecule in the blood and behaves directly as an embolizing substance, causing thromboembolism and nonbacterial thrombotic endocarditis that leads to cerebral infarction [6]. Mucin promotes platelet aggregation by causing an interaction between L-selectin on the surface of white blood cells and P-selectin on the surface of platelets [15] and also directly activates prothrombin [16]. Moreover, a correlation between serum CA125 and D-dimer levels has been reported in patients with ovarian cancer [17]. Even in patients with Trousseau syndrome associated with mucin-producing tumors, serum CA125 and D-dimer measurements over time can be a predictor of onset and recurrence of cerebral infarction and thromboembolism.

Anticoagulant therapy is indicated in Trousseau syndrome, and the first-line agent is heparin. Heparin suppresses the proliferation of endothelial and smooth muscle cells, decreases the heparinase activity in tumor cells which regulates the tissue factor/tissue factor pathway inhibitor system, and interferes with the activity of growth factors and angiogenesis inhibitors. Heparin is reported to inhibit tumor growth via promotion of apoptosis and is considered to have a wide range of effects over and above inhibition of a and a [18,19]. As with all paraneoplastic syndromes, treatment of the underlying malignancy can be expected to alleviate coexisting blue toe syndrome, as demonstrated in several case reports of paraneoplastic blue toe syndrome [20-22].

## CONCLUSION

We encountered a 77-year-old man with Trousseau syndrome who presented with blue toe syndrome and was found to have multiple cerebral emboli and abnormally high CA125 level. Cases of blue toe syndrome caused by a malignant tumor are rare. Measurement of CA125 level is clinically significant in patients with Trousseau syndrome.

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<b>Table 1:</b> Causes of blue toe syndrome.
Intraluminal
1) Embolic
Cholesterol crystal embolism
Atrial fibrillation
Infective endocarditis
Nonbacterial thrombotic endocarditis
Cardiac myxoma
2) Thrombotic
Antiphospholipid syndrome
Disseminated intravascular coagulation
Malignancy
Essential thrombocythemia
Thrombotic thrombocytopenic purpura
3) Hyperviscosity syndromes
Cryoglobulinemia
Cryofibrinogenemia
Cold agglutinins
Polycythemia vera
Paraproteinemia
Intramural
1) Infectious and noninfectious inflammation
Microscopic polyarteritis
Classic polyarteritis nodosa
Systemic lupus erythematosus
Syphilis
Behçet's disease
2) Vasoconstrictive disorders
Acrocyanosis
Perniosis
Medication-induced vasoconstriction

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