# Digital Ulcers, Systemic Sclerosis Sine Scleroderma and Paraneoplastic Phenomena Responding to Bosentan Therapy

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Paraneoplastic syndrome is defined as a constellation of signs and symptoms that are secondary to the presence of a malignancy and can present as an atypical autoimmune disease. Regression of the rheumatologic disorder occurs following treatment of the underlying malignancy [1]. Systemic sclerosis (SSc) is a severe multiorgan disease characterized by widespread fibrosis and extensive vascular damage, and activation of the immune system with production of autoantibodies. The vascular involvement of SSc manifests as Raynaud's phenomenon (RP) and digital ulcers (DU) [2]. Most patients with SSc will develop limited or diffuse scleroderma while systemic sclerosis sine scleroderma is a rare variant of SSc [3]. We present the case of a patient with systemic sclerosis sine scleroderma who later developed lung cancer.

## PATIENT DESCRIPTION

A 69 year old woman, a current smoker with a history of 80 pack-years, complained of pain and blue discoloration of the third digit of her right hand that began a few days earlier. Her past history included moderate chronic obstructive lung disease with 55% FEV1 on pulmonary function tests, malignant neoplasm of breast post-left lumpectomy and radiotherapy in 2008, gastroesophageal reflux disease, hypertension and hyperlipidemia. She denied trauma to this hand, had not taken a new medication in the past 6 months, had not experienced thrombotic events in the past, and neither she nor her family had a history of Raynaud's phenomenon. There was no history of decreased appetite, weight loss, change in cough, or dyspnea. Her relevant medical therapy included aspirin, omepradex, cilazapril, simvastatin and tamoxifen.

The rheumatology examination revealed tenderness in the third digit of her right hand with transient blue discoloration, without evidence of calcinosis, thickening of the skin on the face, trunk or limbs, sclerodactyly, telangiectasis, or arthritis. Routine laboratory tests, including complete blood count, liver, renal and thyroid function, hypercoagulability tests, cardiolipin immnunoglobulins (Ig) G and M antibodies and antinuclear antibodies (ANA), were all within normal limits. Ultrasound/Doppler of the right hand was normal. A computed tomography (CT) and CT angiography of the chest and abdomen and an echocardiogram were normal.

The patient was initially diagnosed with ischemia of the hand due to diffuse atherosclerosis. Despite treatment with enoxaparin and aspirin, the findings persisted. Over the next 2 months, her situation worsened further with cyanosis of all five digits of the right hand and in the fourth and fifth digits of the left hand accompanied by severe pain requiring therapy with opiates.

Treatment with iloprost 2 ng/kg/min IV over 6 hours was initiated for 3 weeks together with high doses of oxycontin. Nevertheless, the patient eventually developed autoamputation of the distal phalanxes of the third and fourth digits of her right hand.

Repeated serology for hypercoagulability, vasculitis and cancer markers were normal. However, a repeated serology in the same laboratory revealed elevated titers of ANA 1:320 and anticentromere antibodies that were initially negative during the first hospital admission. The patient was diagnosed with systemic sclerosis sine scleroderma where digital ulcers and the appropriate serological tests were the only manifestations of disease.

She was treated with bosentan 125 mg twice a day as a monotherapy and the response was immediate and dramatic. No new digital ulcers developed. Within 8 weeks, the necrotic areas disappeared and she could discontinue opiate therapy. The patient developed calcinosis of the finger beds.

One year after the initial presentation, she underwent a repeated CT chest scan for persistent cough which showed a 1 cm nodule in the left lower lobe and a 8 mm nodule in the left upper lobe. Fine-needle aspiration and pulmonary nodule biopsy from the two nodules revealed an adenocarcinoma on histology. Left video-assisted thoracoscopic surgery (VATS) wedge resection was performed to the nodule of the left lower lobe. Histology depicted adenocarcinoma, without vascular invasion (stage pT2A). In addition, stereotactic body radiotherapy (SBRT) to the nodule of the left upper lobe was performed. Follow-up

FDG-PET-CT (fluorodeoxyglucose-positron emission tomography-CT) revealed no pathological activity in either nodule, indicating complete remission. During the entire period the patient continued therapy with bosentan. No recurrence of digital ulcer occurred over 2 years of follow-up.

## COMMENT

This is an unusual presentation of SSc sine scleroderma where the hallmark single feature was severe digital necrotic ulcers. The patient did not develop thickened skin, Raynaud's phenomenon or visceral disease, and the diagnosis was based on the single manifestation and appropriate autoantibody status which included elevated titers of ANA and anticentromere antibodies. Hence, we could not classify the patient as limited or diffuse scleroderma [4]. The unusual manifestation of SSc sine scleroderma was actually the expression of an occult cancer that became clinically evident within a year. In one study, SSc sine scleroderma was found in 8.3% of 947 patients in a SSc cohort. The diagnosis was determined in patients who suffered from Raynaud's phenomenon, positive ANA, and one visceral involvement. These patients were more often females, had anticentromere antibodies, and 12.5% were referred from vascular surgery due to digital ulcers. Digital ulcers were present in 24.1% of these patients. These findings correlate with our case [3]. The unusual findings prompted us to search for paraneoplastic disease. The literature lacks information regarding the systemic sclerosis sine scleroderma subset and the association with paraneoplastic syndrome.

We reviewed the literature and identified another 14 reported cases of digital ulcer as a paraneoplastic syndrome of lung cancer [Table 1]. The male to female ratio was 1.8:1, and the age range was 40–78 years in males and 52–69 years in females. Eighty percent of the patients developed digital ischemia/ulcer or Raynaud's syndrome within a year prior to diagnosis of lung carcinoma; 33%, including our patient, had elevated titers of ANA, and only 13% had elevated anticentromere antibody titers. Of the 15 reported cases, 5 had adenocarcinoma.

**Table 1.** Paraneoplastic digital ulcers and/or paraneoplastic Raynaud's syndrome in lung carcinoma

| No. | Author, year | Age/ Gender | Serologic investigation | Histological type of lung cancer |
|---|---|---|---|---|
| 1 | Sharabi et al. (present) | 69/ F | ANA positive 1:320, anticentromere positive, anticardiolipin negative | Adenocarcinoma |
| 2 | Adedayo, 2012 | 40/ M | ANA, antipospholipid antibody, anticardiolipin, lupus anticoagulant – all negative | Non-small cell |
| 3 | Moulakakis, 2010 | 70/ M | N/A | Lung Ca diagnosed by CT only |
| 4 | Schildmann, 2010 | 78/ M | ANA negative | Non-small cell |
| 5 | Schmid, 2008 | 62/ F | ANA, RF, cryoglobulin, ANCA, HIV – all negative | Non-small cell |
| 6 | Kopterides, 2004 | 65/ F | ANA, antiphospholipid anticardiolipin, RF and cryoglobulin – all negative | Adenocarcinoma |
| 7 | Wong, 2003 | 62/ M | ANA, RF, extractable nuclear negative | Non-small cell |
| 8 | Imandi, 2002 | 73/ M | ANA positive 1:1280 | Small cell |
| 9 | Vaidya, 2001 | 52/ F | ANA positive 1:320 elevated IgG anticardiolipin | Non-small cell |
| 10 | Wang, 1996 | | Elevated cryoglobulinemia | Non-small cell |
| 11 | Arrowsmith, 1991 | 63/ M | Positive Hep2 cell substrate for centromere-specific ANA 1:2560 | Small cell |
| 12 | Wilmalaranta, 1987 | 69/ M | ANA, RF, cryoglobulin – all normal | Adenocarcinoma |
| 13 | Field, 1986 | 70/ M | ANA, RF cryoglobulin – all negative | Small cell anaplastic carcinoma |
| 14 | Petri, 1985 | 62/ M | ANA positive 1:320 | Adenocarcinoma |
| 15 | Domz, 1961 | 50/ F | Elevated cryoglobulinemia | Adenocarcinoma |

ANA = antinuclear antibody, N/A = not available, RF = rheumatoid factor, ANCA = antineutrophil cytoplasmic antibodies, HIV = human immunodeficiency virus

Bosentan, an endothel-1 antagonist, is beneficial for digital ulcers in SSc [5]. Compared to the 14 other cases of paraneoplastic digital ischemia/ulcer that we reviewed, our case was the only one, to our knowledge, where bosentan was initiated and proved effective as treatment for paraneoplastic digital ulcer, showed an excellent response on healing, and prevented new ulcers despite ongoing cancer.

In conclusion, this case emphasizes that patients who develop unusual manifestations of systemic sclerosis, like SSc sine scleroderma with digital ischemia and digital ulcer in whom the accepted causes have been excluded, deserve the fullest investigation in an attempt to discover an occult malignancy. We emphasize that the digital ulcers responded immediately to therapy with bosentan, before the malignancy was removed.

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