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Digital necrosis in a patient with systemic sclerosis receiving carboplatin and pemetrexed chemotherapy for lung cancer

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Abstract

We report the case of a 78-year-old Caucasian female who developed chemotherapy induced digital necrosis on a background of systemic sclerosis. The diagnosis of systemic sclerosis was established three-years-ago on the basis of pulmonary fibrosis, sclerodactyly and positive Scl-70 antibodies. Non-small cell lung cancer was diagnosed one year ago and she received six-cycles of carboplatin and pemetrexed chemotherapy. During this treatment, she developed necrosis of multiple upper and lower limb digits, as well as her right heel. This was treated with sildenafil and intravenous iloprost.

Keywords

Systemic sclerosis; digital necrosis; digital ischemia; chemotherapy; rheumatology.

Introduction

Systemic sclerosis is associated with an increased risk of malignancy. It is important therefore to distinguish between the vascular complications associated with chemotherapy and those related to systemic sclerosis. In our patient, the chemotherapy was the inciting agent. The systemic sclerosis was likely a predisposing factor due to the underlying vasculopathy.

Case Presentation

This 78-year-old Caucasian female was diagnosed three years previously with systemic sclerosis and Interstitial Lung Disease (ILD). One year ago, she underwent an interval CT scan of the chest which showed a new lingular mass. Biopsy and further staging revealed this to be a T3 N0 M0 non-small cell lung carcinoma. The patient declined to have any surgery for this.

Her other past medical history includes epilepsy, hypertension and depression. Her regular medications include mycophenolate mofetil, simvastatin, citalopram, carbamazepine, amlodipine and co-codamol. There was no use of over-the-counter medications or illicit drugs. She is an ex-smoker with a three pack-year history, having stopped 50 years ago.

She received six-cycles of pemetrexed and carboplatin chemotherapy for the lung cancer. After the first cycle, she developed painful necrosis over the tip of her left 3rd finger (Figure 1). After completing the chemotherapy course, she then developed necrosis of the left 5th finger, right 1st and 2nd fingers, left 3rd toe and right heel (Figure 2,3,4).

These events occurred over the summer and autumn months. There was ongoing weight loss and anorexia but no fever. The rest of her systems review was negative. Although she experienced Raynaud's phenomenon during the winter, this was well controlled with no prior history of digital ischaemia. There was no history of venous or arterial thromboembolism.

On examination, her blood pressure was 140/100 and oxygen saturations were 97% on room air. Peripheral pulses were palpable and there was no blood pressure discrepancy between the arms. There were no signs of infection of the necrotic areas. There was sclerodactyly extending to the metacarpophalangeal joints bilaterally but no scleroderma elsewhere. There were no digital ulcers or pitting. Nailfold capillaries appeared dilated (without the use of capillaroscopy). There was no synovitis or rheumatoid related deformities. There were fine end-inspiratory crepitations over both lower lung zones. Cardiovascular and neurological examinations were normal. There were no stigmata of infective endocarditis or vasculitis.

Full blood count showed normocytic anaemia (108 g/L) and lymphopenia (1.0 10*9/L). Renal, liver and thyroid function were within normal range. C-reactive protein (CRP) was 29 mg/L and Erythrocyte Sedimentation Rate (ESR) was 65 mm/hour. Coagulation screen was normal. Blood cultures were negative. Urine dipstick was unremarkable.

Antinuclear Antibody (ANA) was positive (homogenous pattern). Of the extractable nuclear antigens, Scl-70 was positive. Of note, centromere and DNA antibodies were negative. Rheumatoid Factor (RF) and anticitrullinated protein (CCP) antibodies were within normal range. Antiphospholipid antibodies were all negative, as were cryoglobulins and Antineutrophil Cytoplasmic Antibodies (ANCA). Immunoglobulins revealed a monoclonal band in gamma with a paraprotein of 5.4 g/L.

Transthoracic echocardiogram showed a pulmonary artery systolic pressure of 25 mm/Hg. Biventricular systolic functions were not impaired and there were no vegetations, nor was there a detectable pericardial effusion.

Ultrasound doppler of the upper limb arteries was normal. CT angiogram of the lower limbs showed a right common femoral artery and above knee popliteal stenosis of less than 50%, a left above knee 50% popliteal stenosis and single vessel run off. CT scan of the chest, abdomen and pelvis performed after completion of the chemotherapy showed that the tumour had increased in size over the last 4 months from 4.3

X 3.4 cm to 5 X 4.2 cm. The interstitial lung disease was stable. Notably, there were no aortic aneurysms or atherosclerotic plaques.

The first diagnostic consideration was digital ischaemia due to the systemic sclerosis. Although this causes a vasculopathy, her Raynaud's was well controlled with no history of digital ulceration. Furthermore, onset during the summer months and necrosis of the heel would be atypical features. The close temporal relationship of these events to the chemotherapy makes this the most likely cause with the scleroderma acting as a predisposing factor.

Paraneoplastic digital ischaemia was also considered. However, anticancer therapy would be expected to improve this.

Vasculitis was also considered. There was no history of rheumatoid arthritis to suggest rheumatoid vasculitis. Furthermore, RF and CCP antibodies were negative. Polyarteritis nodosa can cause digital necrosis. But there were no other skin lesions such as erythema nodosum, livedo reticularis or ulcerations to support this. Also, there were no gastrointestinal or neurological symptoms and the renal function was normal. ANCA was negative and there were no other clinical features to support this diagnosis. Although there was a monoclonal gammopathy of undetermined significance, cryoglobulins were negative. The absence of a recent smoking history excludes thromboangiitis obliterans.

It was also important to consider thromboembolic causes. This patient had no history of venous or arterial thromboembolic events and negative antiphospholipid antibodies making antiphospholipid syndrome unlikely. Other thrombotic conditions such as heparin induced thrombocytopenia (HIT) and Thrombotic Thrombocytopenic Purpura (TTP) were excluded based on the blood test results.

No embolic source was identified on the echocardiogram or CT scan of the chest, abdomen and pelvis with contrast. Cholesterol embolization was unlikely as there was no history of recent vascular intervention or other features of this condition. Although the CT angiogram of the lower limbs showed stenotic regions, these would not account for the widespread presentation. The lack of risk factors for subacute bacterial endocarditis, as well as negative blood cultures and absence of cardiac vegetations on echocardiogram made this unlikely.

After developing digital necrosis in her left 3rd finger, this patient was admitted to hospital where she received an intravenous heparin infusion and aspirin 75 mg once a day. Upon discharge the rheumatology team commenced her on a 5-day intravenous iloprost infusion. After this was completed, she was commenced on sildenafil 25 mg three times a day.

After developing the necrosis in the remaining areas, she received another 5-day course of intravenous iloprost. She was unable to tolerate a higher dose of sildenafil due to the side-effects. Therefore, fluoxetine was commenced to help control Raynaud's symptoms. The aspirin was switched to clopidogrel and gabapentin was added for pain control.

The follow-up CT scan after completing the chemotherapy showed that although the tumour had increased in size, there was no metastasis. The sildenafil and intravenous iloprost helped with pain and stopped further progression of digital necrosis. However, it is unknown whether this occurred primarily due to the completion of chemotherapy. She remains under the regular follow up of the respiratory, rheumatology and oncology teams. She has not required any surgical debridement or amputation but it is likely that there will be autoamputation of the necrotic areas.

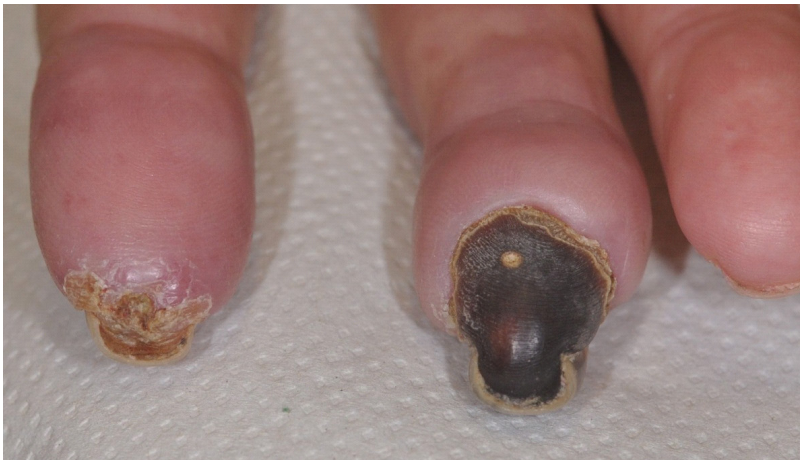

Figure 1: Left 3rd finger necrosis.

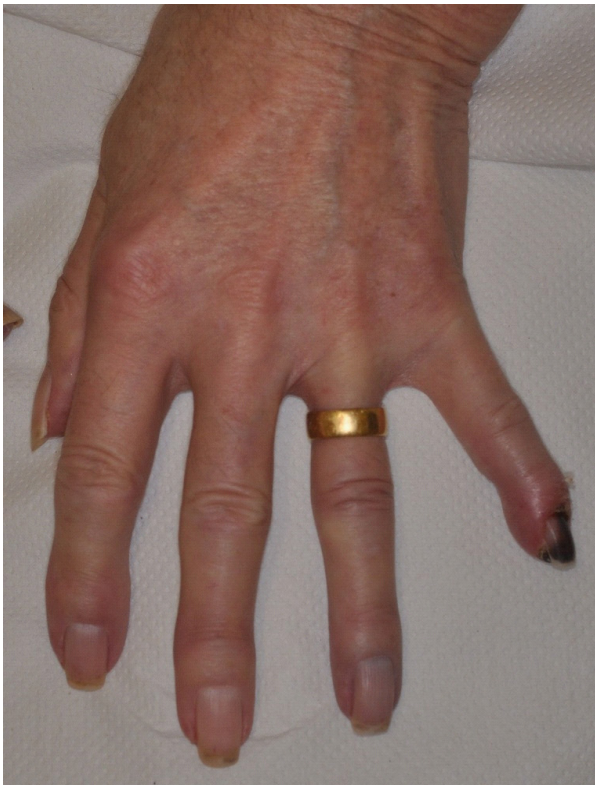

Figure 2: Left 5th finger.

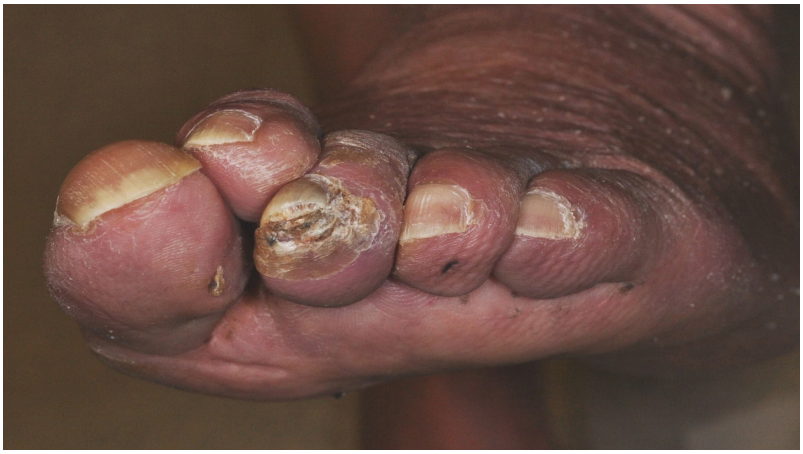

Figure 3: Left 3rd toe.

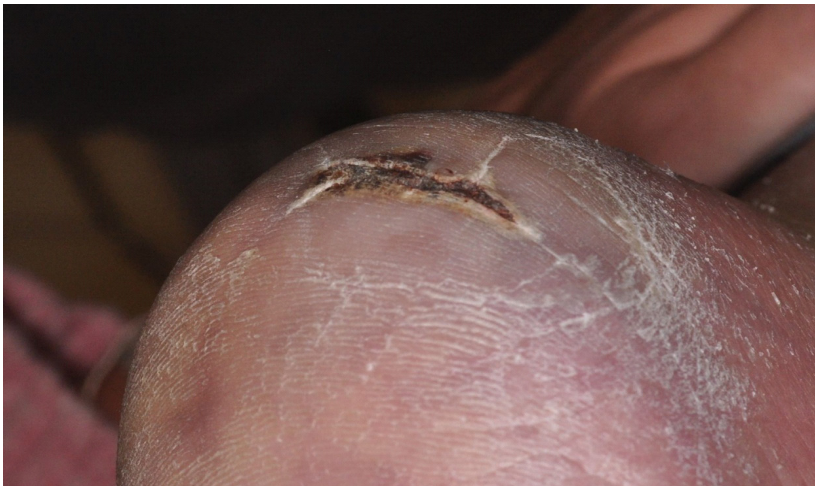

Figure 4: Right heel.

Discussion

Chemotherapy related digital ischaemia has been reported in the literature, and multiple agents have been implicated [1]. To our knowledge, only three previous cases have been described for patients with underlying systemic sclerosis [2-4]. All three had received combination chemotherapy that included gemcitabine, an agent with an established profile of vascular toxicity. The other additional agents were carboplatin [2], cisplatin [3] and S1 [4].

In these three cases, the digital necrosis occurred 3, 16 and 27 weeks after the onset of chemotherapy [2-4]. All three patients developed gangrenous changes despite vasodilatory therapy. Two of the patients required surgery in the form of debridement or amputation [2,3].

Our patient received carboplatin and pemetrexed. This is the first reported case of a patient with systemic sclerosis developing widespread digital necrosis with this chemotherapy regime. Interestingly, carboplatin and pemetrexed combination chemotherapy has been reported as a cause of acute limb ischaemia in a patient without systemic sclerosis [5].

The only case reports describing digital ischaemia following carboplatin also included gemcitabine [6,7]. Long term maintenance pemetrexed has been reported to cause digital ischaemia, but this occurred after 32 cycles [8], a significantly greater cumulative dose than that received by our patient. Owing to the paucity of data, it is unknown which of the two chemotherapy agents in our patient's case was implicated in this complication.

It is likely that the underlying cancer and systemic sclerosis were predisposing and aggravating factors. Cancer causes an acquired thrombophilia, and patients are also more susceptible to embolic events, including non-bacterial thrombotic endocarditis, tumour cell emboli and paradoxical embolus from deep vein thrombosis (DVT) [9]. Systemic sclerosis causes a vasculopathy, with endothelial dysfunction, intimal proliferation, microvascular thrombosis and reversible vasospasm leading to tissue ischaemia-reperfusion injury [10]. Our patient also had hypertension, an additional cardiovascular risk factor.

The mechanism of chemotherapy induced digital ischaemia remains poorly understood. It has been postulated that damage to the endothelium, increased platelet adherence, hypercoagulability and immune complex deposition as an immune-allergic effect all play a role [11].

The onset of digital ischaemia in a patient receiving chemotherapy requires a comprehensive diagnostic evaluation. As well as excluding thromboembolic causes, it is important to consider whether digital ischaemia has occurred as a paraneoplastic phenomenon, as this will likely improve with anticancer treatment [12].

Chemotherapy related digital ischaemia has been reported to improve following withdrawal of chemotherapy [12]. However, progression to digital gangrene can still occur despite discontinuation of the chemotherapy and institution of medical therapy [13]. It is important to consider that continuing chemotherapy in a patient with evolving digital necrosis can increase the risk of infected necrotic tissue.

Many treatments have been used with the aim of improving perfusion of the ischaemic area. These treatments include calcium channel blockers [13], nitrates [13], prostacyclin analogues [12], endothelin receptor antagonists [4], antiplatelets [6,7], heparin [6,7] brachial plexus blockade [7] and sympathetic nerve root blockade [4]. Mixed results were achieved but the case numbers are low, multiple confounding variables are present and most pertain to gemcitabine induced digital ischaemia [13]. Further studies are required in this field.

Conclusion

Patients with systemic sclerosis are at higher risk of malignancy. Digital ischaemia may develop as a consequence of the underlying cancer, scleroderma vasculopathy, or chemotherapy. Clinicians need to consider this risk when treating these patients with chemotherapy. It is important to perform a thorough diagnostic evaluation to determine the aetiology of the digital ischaemia. This requires a multidisciplinary approach.

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