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Case reports

Overlap between systemic sclerosis and polyarteritis nodosa: A case report

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ABSTRACT

Background: Systemic sclerosis (SSc) is a multiorgan connective tissue disease characterized by vasculopathy, inflammation, autoimmunity, and fibrosis in the skin, lungs and other organs. The occurrence of frank vasculitis is uncommon.

Case presentation: A 36-year old male patient with limited cutaneous SSc developed multiple necrotic ulcers on both legs and feet and gangrene of several toes, followed by an acute onset of axonal sensorimotor neuropathy affecting both radial and peroneal nerves, severe testicular pain with gangrenous patches over the scrotum. The hepatitis B virus (HBV) core antibody was positive while HB surface antigen and surface antibody, HAV and HCV antibodies were negative. The polymerase chain reaction for HBV and HCV showed no detectable viraemia. Antineutrophil cytoplasmic antibodies, cryoblobulins, anticardiolipin antibodies, lupus anticoagulant, antimitochondrial and anti- liver-kidney microsomal antibodies were negative. Pelvi-abdominal ultrasound and portal vein Doppler study showed a coarse and heterogeneous echo-texture of the liver, splenomegaly, moderate ascites and an enlarged, patent portal vein. Fibroscan revealed grade III liver fibrosis. He had an attack of haematemesis with elevation of the liver enzymes and low serum albumin and prothrombin concentrations. He was diagnosed as a case of polyarteritis nodosa. He was successfully treated by methylprednisolone intravenous pulses, followed by oral prednisone 40 mg/day. Plasmapheresis and six monthly doses of 1000 mg intravenous cyclophosphamide. Prednisone was gradually tapered to 5 mg/day with addition of azathioprine 100 mg/day.

Conclusion: The association between systemic sclerosis and polyarteritis nodosa is very rare. The co-existence of SSc and vasculitis necessitates modification of the treatment plan.

1. Introduction

Systemic sclerosis (SSc) is a multiorgan connective tissue disease characterized by autoantibody production and fibroproliferative stenosis of the microvasculature. It is classified regarding the extent of skin involvement and internal organ disorders into diffuse and limited types. If sclerosis of the skin of the upper arms, legs or trunk is found, it indicates diffuse cutaneous SSc, and if skin involvement is restricted to the fingers, hands and face, this indicates limited cutaneous SSc [1]. The pathogenesis of SSc involves a distinctive triad of small-vessel vasculopathy, inflammation and autoimmunity, and interstitial and vascular fibrosis in the skin, lungs, and multiple other organs [2]. Evidence of autoimmunity includes the presence of distinct autoantibodies and activation of both innate and adaptive immunity. Fibrosis of the skin and visceral organs results in irreversible scarring and organ failure. Involvement of the microvasculature leads to cutaneous and mucosal telangiectasias, digital ulcers, and tissue ischaemia. If medium-sized blood vessels are involved, manifestations include gangrene, digital loss, renal crisis, and pulmonary arterial hypertension. Intractable progression of vascular and fibrotic organ damage accounts for the chronic morbidity and high mortality [3].

While occlusive vasculopathy is a well-recognized feature of SSc, less is known about the co-existence and the consequences of frank vascular inflammation. Here, we report a case of medium vessel vasculitis in association with SSc.

2. Case report

We report a case of a 36 year old male, a known case of diffuse cutaneous SSc since 2011 classified and subtyped according to the 1988 *LeRoy et al* criteria [4], with tight skin, fish mouth, severe Raynaud's phenomenon, digital pitting scars, sclerodactyly, gangrene

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and subsequent auto-amputation of distal phalanges of several fingers. His autoimmune profile showed a positive anti-nuclear antibody with speckled pattern and positive anticentromere antibody. His high-resolution CT chest showed a ground glass appearance, which was diagnosed as interstitial lung disease for which he took prednisone 30 mg/day, and six intravenous doses of cyclophosphamide 1000 mg each. He was maintained on azathioprine 100 mg/day, sildenafil 100 mg/day with gradual tapering of prednisone until he reached a daily dose of 5 mg. This work is in accordance with the provisions of the Medical Health Association of Helsinki. The patient consented to publish his case and his anonymity was guaranteed.

In August 2016, the patient presented with multiple large ulcers with gangrenous floor and necrotic lesions on both feet with gangrene of several lower limb toes (Fig. 1). On examination, the pulse was 80/minute, regular, of equal volume bilaterally and normal blood pressure equal on both sides and intact pulsations of both lower limbs and upper limb vessels. Three days after admission, the patient developed bilateral wrist, finger and foot drop with impaired sensations. Examination revealed inability to extend the wrists, thumbs and fingers of both hands with lost sensations over the dorso-radial side of both hands. There was also an inability to dorsiflex both feet with absent sensations over the lateral aspects of both legs and dorsa of the feet.

Laboratory investigations showed an elevated erythrocyte sedimentation rate (ESR) 127 mm/1 hour (normal 0–20 mm/1 hr). His blood picture showed a microcytic hypochromic anaemia with a hemoglobin level of 9.2 g/dl (normal 13–16 g/dl), a total leucocytic count of $8.1x10^3$ /mm^3 and a platelet count of $244 \times 10^3/mm^3$. Alanine aminotransferase (ALT) was 31 IU/L, aspartate aminotransferase (AST) 24 IU/L and alkaline phosphatase 90 IU/L. The serum albumin was 4.2 g/dl and the prothrombin concentration was 100%. The patient had a normal serum urea of 20 mg/dl, normal serum creatinine of 0.5 mg/dl and a normal urine analysis. Antibodies of the hepatitis virus; hepatitis A virus (HAV) and hepatitis C virus (HCV) were negative. The hepatitis B virus (HBV) core antibody was positive while the HB surface antigen and surface antibodies were negative. The polymerase chain reaction test (PCR) of both HBV and HCV showed no detectable viraemia. Similarly, cryoglobulins, antiphospholipid antibodies (anticardiolipin IgG and IgM and lupus anticoagulant), anti-neutrophil cytoplasmic antibodies (ANCA) with specificities against myeloperoxidase (MPO) and proteinase-3 (PR3) were negative. In addition, testing for autoimmune hepatitis showed negative results for anti-mitochondrial, anti-liver kidney microsomal antibodies (Anti LKMA) and anti-smooth muscle antibody. Pelvi-abdominal ultrasound and portal vein Doppler study showed a coarse and heterogeneous echo-texture of liver with splenomegaly and moderate ascites, enlarged portal vein 18 mm and a slow portal venous flow 10 cm/s. Fibroscan revealed severe liver fibrosis (grade III). Arterial and venous Doppler on both lower limbs and CT angiography showed normal arterial and venous circulation with no evidence of occlusion or thrombi. A skin biopsy was done from the edge of an ulcer but unfortunately, results were non-conclusive due to severe necrosis. Nerve conduction velocity studies showed markedly decreased amplitude of the response of both radial and peroneal nerves both sensory and motor fibers and mildly decreased conduction velocity suggesting an evidence of axonal sensorimotor polyneuropathy.

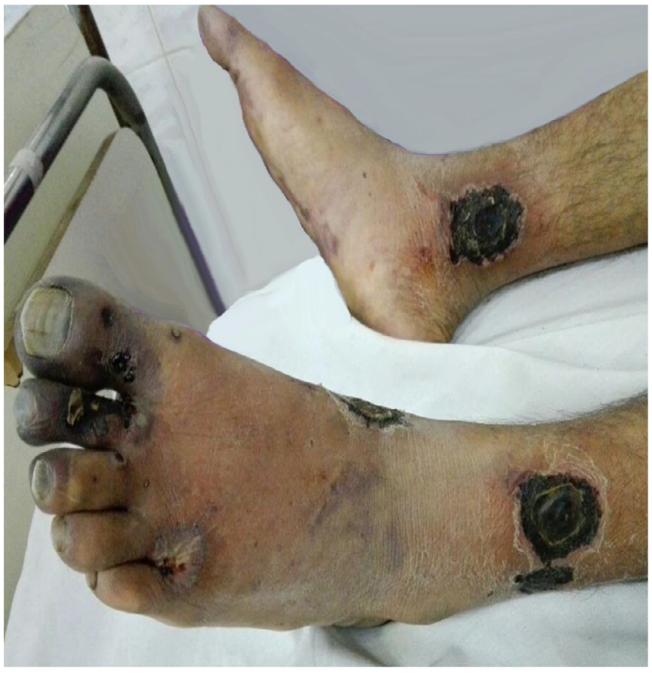

Fig. 1. Skin ulcers with necrotic lesions and gangrene affecting both lower limbs in a 36 years old male patient with diffuse cutaneous systemic sclerosis.

The patient then experienced severe testicular pain and multiple gangrenous patches over the scrotum. A testicular ultrasound revealed multiple intra-testicular cysts denoting testicular necrosis. At that stage, the diagnosis of HBV associated polyarteritis nodosa (PAN) was made in accordance with the American College of Rheumatology classification criteria of PAN [5].

Methylprednisolone pulse intravenous infusion was commenced with a dose of 1 g for three successive days followed by oral prednisone 40 mg/day and we started 6 sessions of plasmapheresis every other day. Few days after, the patient had an attack of haematemesis. He was haemodynamically unstable with an increased pluse rate of 120/minute and decreased blood pressure of 90/60 mmHg. The liver enzymes were elevated with ALT 120 IU/L, AST 89 IU/L and alkaline phosphatase 282 IU/L. Serum albumin dropped to 2.2 g/dl and the prothrombin concentration was 27%. Two units of packed red blood cells were given and his condition was stabilized. Urgent upper gastrointestinal endoscopy showed grade II to III oesophageal varices. Injection of oesophageal varices with octreotide was done and haematemesis stopped. The patient had no further attacks of haematemesis.

Liver enzymes normalized with supportive liver treatment in the form of silymarin 200 mg, acetylcysteine 200 mg and ascorbic acid 30 mg each tid for one month. Hepatologists advised not to give antiviral treatment for hepatitis B infection as there was no viraemia due to the negative hepatitis B PCR testing. We started a new cycle of monthly intravenous cyclophosphamide for 6 months 1000 mg each, with gradual tapering of oral prednisone till 10 mg/day and then continued on azathioprine 100 mg/day.

The condition stabilized with no new skin lesions appearing and healing of old ones. Auto-amputation of gangrenous toes soon followed (Figs. 2 and 3). Neurologically, he had a slight improvement of the dorsiflexors both hands and feet with cockup splints worn in both hands and a below knee accustomed prosthesis in both lower limbs. Follow up laboratory investigations showed normal complete blood count, ESR 20 mm/l, repeatedly normal liver function tests with ALT 20 IU/L, AST 23 IU/L and alkaline phosphatase 89 IU/L. The serum albumin was 3.6 g/dl and the prothrombin concentration was 100%. Repeated HBV PCR test was negative. The patient has been on oral prednisone 5 mg and azathioprine 100 mg/day until last follow up visit in the outpatient clinic in January 2020 and a follow up with a phone call in August 2020 due to the corona virus disease (COVID-19) outbreak.

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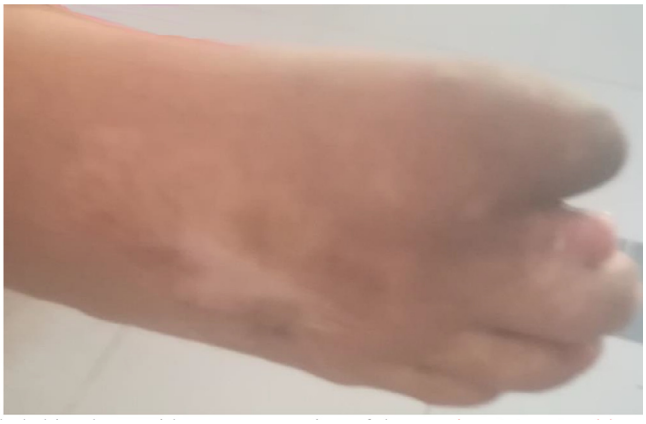

Fig. 2. Healed skin ulcers with auto-amputation of the toes in a 36 years old male patient with diffuse cutaneous systemic sclerosis.

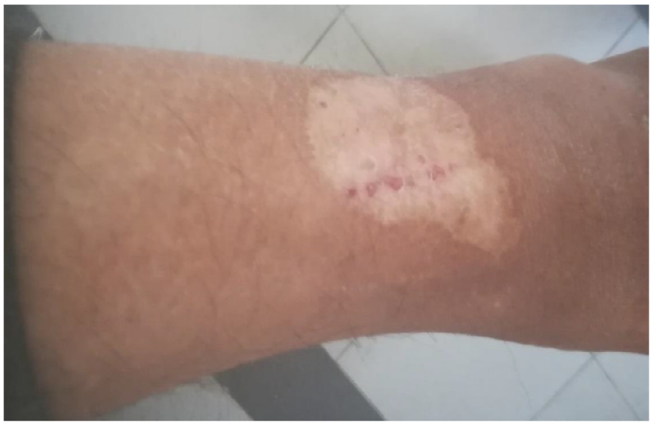

Fig. 3. Healed skin ulcer on leg in a 36 years old male patient with diffuse cutaneous systemic sclerosis.

3. Discussion

Although rare, typical vasculitis with inflammatory infiltrates damaging blood vessels has been reported in patients with SSc. Distinguishing between non-inflammatory vasculopathy and vasculitis can pose a significant diagnostic challenge in the absence of histologic examination [6]. We present an extremely rare case in which necrotizing vasculitis occurs in a known SSc patient. The clinical findings of necrotizing skin gangrene, multiple mononeuropathies, testicular pain and gangrene raise the suspicion of medium sized vasculitis. With an evidence of hepatitis B infection, the diagnosis of PAN is most likely according to the 1990 ACR criteria [5]. The rapid and aggressive course of the disease warranted the intervention with the use of pulsed methylprednisolone, cyclophosphamide and arranging sessions of plasmapheresis.

Studies point out that the occurrence of severe digital ischaemia (especially that requiring amputation) in SSc patients may be an evidence of underlying vasculitis. Their evidence was the presence of histological vasculitis in amputation specimens from patients with limited cutaneous SSc and severe digital ischaemia, suggesting that inflammatory changes of the blood vessels may occur in patients with SSc more often than is suspected clinically [7]. The co-occurrence of severe digital ischaemia and neuropathy may point to inflammatory blood vessel wall changes being a common etiological factor in both conditions. The occurrence of mononeuritis in patients with SSc has been reported uncommonly. Lateral popliteal nerve palsies were reported in two patients with limited cutaneous SSc detected both clinically and electrophysiologically; one patient had a raised ESR and an ankle ulcer suggesting a vasculitic component without clearing up the type of vasculitis presumed [8]. *Kano et al* reported a case of 68-year-old woman with SSc presented with numbness of the lower limbs and left drop foot. She was diagnosed with multiple mononeuropathy based on the laterality of her symptoms, muscle weakness, thermal hypoalgesia, and nerve conduction study findings. Left sural nerve biopsy showed vasculitis [9]. Another possible evidence for the occurrence of vasculitis in SSc is the development of isolated central nervous system vasculitis a young woman with diffuse SSc [10].

The most famous type of vasculitis reported with SSc is ANCA associated vasculitis (AAV). *Arad et al.* reviewed 40 cases of SSc and AAV. Patients with AAV may present with normotensive renal crises, differentiating them from the hypertensive scleroderma-renal crisis. These patients are diagnosed by positive serology mostly to MPO antibodies and by renal biopsy showing necrotizing vasculitis [11]. Another case of SSc and ANCA associated vasculitis reported by *Radwan et al.* of a 65-year-old man with diffuse cutaneous SSc presenting with new-onset peripheral neuropathy. The patient had a positive PR3 and cytoplasmic ANCA, and histopathology confirmed an inflammatory vasculitic neuropathy [12]. On the other hand, overlap between PAN and SSc was very rarely reported in SSc. To our knowledge, only one case of cutaneous PAN was reported in a 28-yearold woman with diffuse SSc. The patient developed brownish tender nodules on her legs over three months. Biopsy of these lesions revealed necrotizing arteritis in the deep dermis [13].

Overlap between SSc and other vasculitic syndromes has been reported. *Quéméneur et al.* [14] and *Ostojic et al.* [15] reported SSc overlap with mixed cryoglobulinemia without associated chronic HCV infection, while *Giuggioli et al.* [16] and *Gheita et al.* [17] reported SSc overlap with mixed cryoglobulinaemia associated with chronic HCV infection. Rare cases of overlap of SSc with Takayasu arteritis (4 cases), giant cell arteritis (3 cases) and Behçet's disease (2 cases) were also reported [6].

Vasculitis may occur in SSc overlapping with other connective tissue diseases. Central nervous system vasculitis occurring in a polymyositis- SSc overlap patient with autoimmune hepatitis has been reported [18]. *Kubota et al.* reported a case of AAV in a patient with SSc overlapping with Sjögren's syndrome [19]. Severe acral ischaemia with extensive gangrene has been described in a case with limited SSc overlapping with rheumatoid arthritis [20]. Also, the presence of anticardiolipin antibodies in patients with SSc was reported, however, its association with vasculitis causing severe digital ischaemia has not been confirmed [7].

To conclude, we report an extremely rare case of SSc overlapping with PAN. The main limitation of this case is the absence of histopathological confirmation. The co-occurrence of vasculitis and SSc prompts a change of the management plan. The use of corticosteroids and immunosuppressives in such patients becomes mandatory. Further studies regarding the pathogenesis of SSc and analyzing pathological specimens of SSc amputations can give us a clue to a better understanding of this disease.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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