Case Report

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Antineutrophil cytoplasmic antibody-associated vasculitis with systemic sclerosis: a fatal case report

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Introduction and importance: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a rare co-occurrence with systemic sclerosis, in around 2.5–9% of patients. The clinical manifestations and prognosis of vasculitis in systemic sclerosis depend on organ involvement. It presented with rapidly progressive acute renal failure without malignant hypertension, and with pitting hand and foot ulcers get along with purpuric vasculitis in some cases reports. Reports had found that survival in those with pulmonary-renal syndrome is poor. However, high-dose corticosteroids and cyclophosphamide increase the survival percent in those patients.
Case presentation: An 81-year-old female was admitted for newly diagnosed acute renal failure and highly elevated C-reactive protein levels. She was diagnosed with systemic sclerosis 8 years previously, with a 3-year history of interstitial lung disease, and a 2-year history of pulmonary hypertension. Treatment included home oxygen on demand, prednisone 5 mg/day, and azathioprine 75 mg daily. On physical examination, she had sclerodactyly, both extremities ulcers, severe livedo reticularis, and hyperpigmented papules on her hand and feet. Laboratory findings included a markedly positive MPO (p-ANCA), and anti-Scl-70. She was treated with pulse methylprednisolone without any improvement. After a day, she developed anuria and became comatose. Then, she developed cardiac arrest, leading to death.
Clinical discussion: The presence of ANCA in systemic sclerosis patients ranges from 2.5 to 9% of systemic sclerosis patients. It presented with rapidly progressive acute renal failure without malignant hypertension, and with pitting hand and foot ulcers. The treatment with high-dose corticosteroids and cyclophosphamide is benefit. Survival in those with pulmonary-renal syndrome is poor.
Conclusion: The presence of ANCA-associated vasculitis is rarely reported with scleroderma. It occurs most commonly in women with limited or Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia (CREST) variants of scleroderma, as well as those with overlap features. Severe manifestations including pulmonary-renal syndrome and death may occur.

Keywords: ANCA-associated vasculitis, pulmonary-renal syndrome, sclerodactylia, systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a chronic immune systemic disease manifested by skin thickening and systemic organ fibrosing. It has two types: the limited cutaneous and the diffuse cutaneous depending on the extent of skin involvement[1]. Although its pathogenesis is not unclear, the deregulated production of auto-antibodies and cytokines leads to vasculopathy, elevated collagen synthesis, and progressive vascular fibrosis may play a role, yet the vascular abnormalities in it are non-inflammatory[2–4]. Although vasculitis can laterally occur in some connective tissue diseases, it is very rare in scleroderma. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a rare co-occurrence with SSc, in around 2.5–9% of patients[3]. The reported cases described vasculitis in variant types of scleroderma, but rarely in diffuse type[5–9]. Small vessel vasculopathy and Raynaud phenomenon may be the potential mechanisms linking ANCA-associated vasculitis and systemic sclerosis[4]. The clinical manifestations and prognosis of ANCA-associated vasculitis in systemic sclerosis depend on organ involvement[5]. We reported a case of ANCA-associated vasculitis in systemic sclerosis.

All our cases has been reported in line with THE CARE 2017 guidelines[10] and THE SCARE 2020 criteria[11].

HIGHLIGHTS

- Systemic sclerosis is a chronic immune systemic disease.
- The presence of antineutrophil cytoplasmic antibody-associated vasculitis is rarely reported with scleroderma.
- The clinical manifestations and prognosis of vasculitis in systemic sclerosis depend on organ involvement.
- Severe manifestations including pulmonary-renal syndrome and death may occur.

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Case presentation

An 81-year-old female was admitted to the ICU of Al-Shami Hospital for newly diagnosed acute renal failure and highly elevated C-reactive protein levels. She was diagnosed with SSc 8 years previously, with a three-year history of interstitial lung disease, and a 2-year history of pulmonary hypertension. At that time, she reported no abnormality of the renal function and urinary protein till 3 months ago, when it was her last periodic visit. The interstitial lung disease was diagnosed by a computed tomography scan which revealed basilar fibrosis, and patchy alveolar infiltrates (Fig. 1). The patient refused to make a lung biopsy.

A cardiac echo revealed pulmonary hypertension at 55–60 mmHg. Treatment included home oxygen on demand, tapered prednisone from 20 mg to 5 mg/day, and azathioprine 75 (1 mg/kg) mg daily for the last 3 years. On physical examination, she had sclerodactyly, both extremities ulcers, severe livedo reticularis, and hyperpigmented papules on her hand and feet (Figs. 2, and 3).

The heart rate and rhythm were irregular, with a loud second heart sound. A lung examination revealed bilateral crackles in the lower half of the lung fields. The abdominal examination was normal. A vascular examination revealed 2/4 oedema of the lower extremities, with a mild scleredema of the distal lower extremities. Lower extremity sensation was not evaluated because the patient was unresponsive. She had elevated levels of blood urea nitrogen (263.8 mg / dl) and creatinine (3.39 mg / dl), proteinuria (+ + +), and a 24-h urine protein of 4.65 g. C-reactive protein level was 147.9 mg / l, erythrocyte sedimentation rate (ESR) was 70 mm / h, procalcitonin 0.68 ng/ml (sepsis up to 0.5). A kidney ultrasound showed no obvious abnormalities. A chest computed tomography revealed bilateral patchy shadows in both lung fields (Fig. 4).

Laboratory findings included a markedly positive MPO (p-ANCA) 20 EU/ml, normal greater than 5.0 EU/ml). Anti-Scl-70 was positive. The following tests and serologies were all negative or unremarkable: total haemolytic complement, C3, C4, SSA, SSB, RNP, Sm, Jo-1, ANA, double-stranded DNA antibodies, anti-centromere antibodies, cryoglobulins, hepatitis A, B, and C screen, and HIV screen. Coagulation studies were unremarkable, including negative lupus anticoagulant. A skin biopsy could not be done because her family refused to make this biopsy. During the 5-day hospital course, she was initially treated with urgent pulse methylprednisolone 250 mg intravenously (IV) daily for three days without any improvement. After a day, she developed anuria and became comatose, so we put her on mechanical ventilation and CRRT dialysis. After 2 days of that, she developed cardiac shock not responding to inotropes, and then cardiac arrest, leading to death.

Discussion

The presence of ANCA in SSc patients has been reported to be rare, ranging from about 2.5–9% of SSc patients[3,5]. It presented with rapidly progressive acute renal failure without malignant

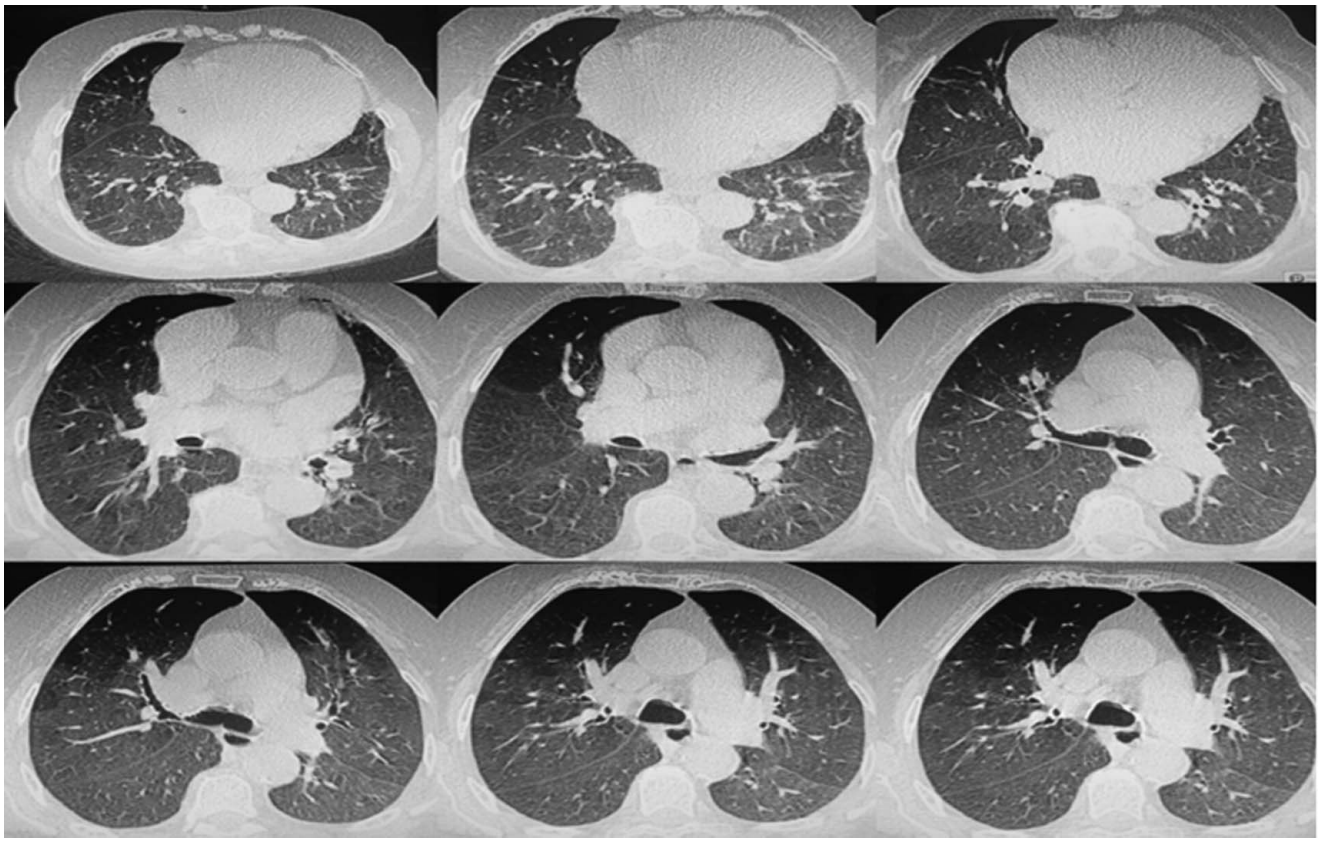

Figure 1. Computed tomography scan findings.

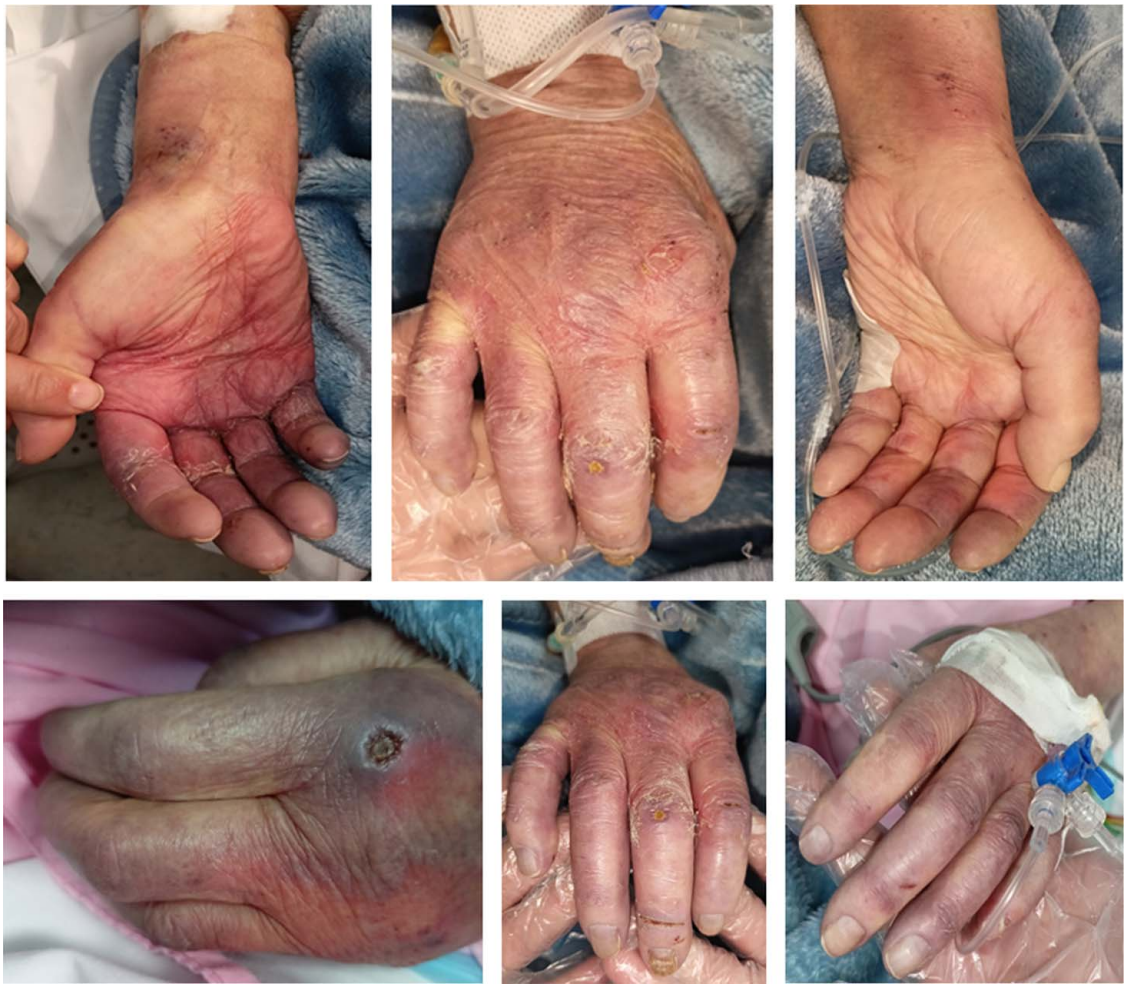

Figure 2. Clinical manifestations of the hands.

hypertension, and with pitting hand and foot ulcers get along with purpuric vasculitis in some cases reports[5,12,13], which is compatible with our patient's case. Multiple case reports and case series described that SSc patients with normotensive renal failure were found to have ANCA positivity and pauci-immune necrotizing crescentic glomerulonephritis on renal histopathology[5,13,14]. We could not make a renal biopsy due to the bad condition of our patient. The majority of such patients derived benefit from treatment with high-dose corticosteroids and/or IV or oral cyclophosphamide[7], as we had done. In the literature, some had found that ANCA vasculitis in scleroderma may be related to exposure to D-penicillamine[5,14]. However, in such cases, the patients clinically improved after D-penicillamine withdrawal and initiating treatment with immunosuppressants. Our patient had previously been treated with Azathioprine. Some authors found pre-existing idiopathic pulmonary fibrosis in these patients, which may be a complication of ANCA antibody-mediated lung damage[15], but it demands further investigation. Our patient had interstitial lung fibrosis 3 years ago at the time of vasculitis diagnosis. Reports had found that survival in those with pulmonary-renal syndrome is poor[5,12,16], as in our patient who died. However, high-dose corticosteroids and cyclophosphamide increase the survival percent in patients with scleroderma, complicated by pulmonary-renal syndrome[3]. Only the case series by Oddis *et al.*[4], who describe seven patients with established systemic sclerosis who developed clinical evidence of vasculitis 1 to 33 (mean 12.7) years after the first symptoms of scleroderma. Six had the Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia (CREST) variant of systemic sclerosis. Vasculitis presented primarily as cutaneous lesions with ulceration and/or mononeuritis multiplex, and six patients had severe systemic manifestations. Herrick *et al.*[17], found that vasculitis does occur in SSc, at least in that subgroup with severe peripheral ischaemia, and these findings could have implications for treatment of this subgroup of patients with SSc. Liag *et al.*[5] who revealed that it occurs most commonly in women with limited or CREST variant of scleroderma, as well as those with sicca symptoms and/or "overlap" connective tissue disease features, and most frequently include pulmonary and/or renal involvement and death may occur. The treatment with high-dose corticosteroids and cyclophosphamide appears to afford benefit. The presence of cANCA is exceedingly rare in scleroderma patients with clinically evident vasculitis. Their case suggested that vasculitis presented primarily as cutaneous lesions with severe digital ischaemia, and ulceration, as in our case report. Some cases reported overlap syndrome in these patients such as Poly Myositis features, systemic

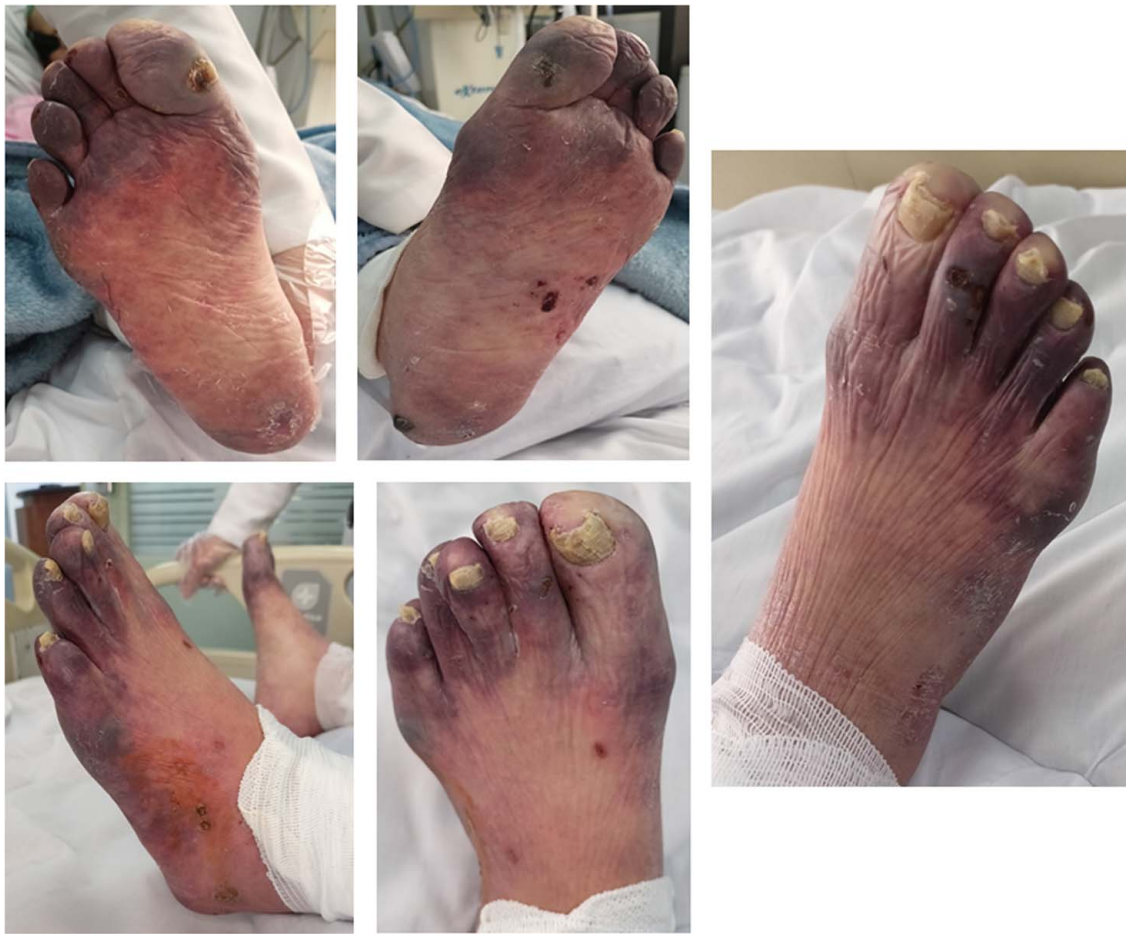

Figure 3. Clinical manifestations of the feet.

lupus erythematosus features, and Sicca syndrome[18]. We did not find any feature of overlap in our patient. Caramaschi *et al*. and the Australian Scleroderma Cohort Study[9,19] found that SSc patients with a high titre of ANCA, and anti-SCL-70 had rapidly progressing skin and lung lesions, and death events, which is in concordance with our case. The prognosis is worse in those patients with pulmonary-renal syndrome[16–20]. The morbidity and mortality of these patients in comparison to other patients with SSc are uncertain[5]. As some patients need renal replacement therapy[9], and our patient had haemodialysis two times without any improvement. Our case is different from other cases, as our patient is older 81 years old, diagnosed 8 years ago with SSc till she had vasculitis, which is a long duration, with normal blood pressure and renal function. The P-ANCA titre was not highly elevated. Although she was treated with an immunosuppressant for the last 3 years, she developed vasculitis. She had a coma and died within a week, which is a short duration, even though she was treated with dialysis.

Conclusion

The presence of ANCA-associated vasculitis is rarely reported with scleroderma. It occurs most commonly in women with limited or CREST variants of scleroderma, as well as those with overlap features. Severe manifestations including pulmonary-renal syndrome and death may occur. Treatment with high-dose corticosteroids and cyclophosphamide appears to be a benefit. It remains a challenge to make a timely and accurate diagnosis. Therefore, we need to further clarify this incidence. Further studies are needed.

Ethical approval

Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

Consent

Written informed consent was obtained from the patient's daughter for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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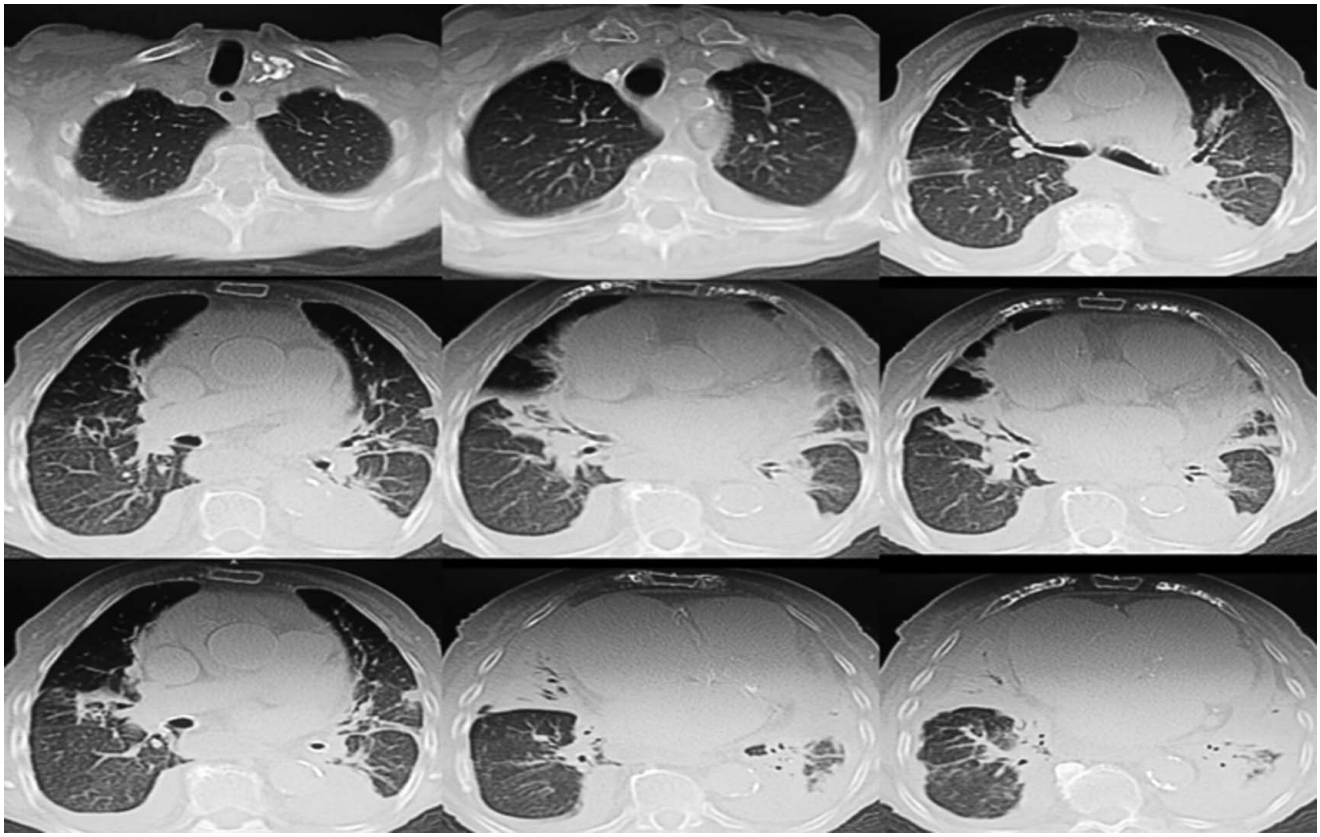

Figure 4. Chest computed tomography findings revealed bilateral patchy shadows.

Author contribution

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Conflicts of interest disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Research registration unique identifying number (UIN)

Our work is not the first in man and doesn't required a unique identifying number.

Guarantor

Dr. Maysoun Kudsi.

Data availability

Data sharing is not applicable to this article, because our manuscript is a case report.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Sobolewski P, Maślińska M, Wieczorek M, *et al*. Systemic sclerosis - multidisciplinary disease: clinical features and treatment. Reumatologia 2019;57:221–33.
[2] Furue M, Mitoma C, Mitoma H, *et al*. Pathogenesis of systemic sclerosis-current concept and emerging treatments. Immunol Res 2017;65:790–7.
[3] Wutzl AL, Foley RN, O'Driscoll BR, *et al*. Microscopic polyangiitis presenting as pulmonary-renal syndrome in a patient with long-standing diffuse cutaneous systemic sclerosis and antibodies to myeloperoxidase. Arthritis Rheum 2001;45:533–6.
[4] Oddis CV, Eisenbeis CH Jr, Reidbord HE, *et al*. Vasculitis in systemic sclerosis: association with Sjogren's syndrome and the CREST syndrome variant. J Rheumatol 1987;14:942–8.
[5] Liang KP, Michet CJ. ANCA-associated vasculitis in scleroderma: a case series of fourteen patients. Rheumatol Rep 2011;3:e2.
[6] Kamen DL, Wigley FM, Brown AN. Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis in scleroderma--a different kind of renal crisis. J Rheumatol 2006;33:1886–8.
[7] Cheung G, Chew G, Wyndham R, *et al*. Myeloperoxidase-antineutrophil cytoplasmic antibody seroconversion and fulminant vasculitis in Scl-70-positive scleroderma. Intern Med J 2007;37:205–7.
[8] Omair MA, Mohamed N, Johnson SR, *et al*. ANCA-associated vasculitis in systemic sclerosis report of 3 cases. Rheumatol Int 2013;33:139–43.
[9] Wu R, Su J, Zou YR, *et al*. ANCA-associated vasculitis overlaps with systemic sclerosis: a case report and literature review. Eur J Med Res 2021;26. Article number: 30.

[10] Riley DS, Barber MS, Kienle GS, *et al*. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol 2017;89: 218–35.
[11] Agha RA, Franchi T, Sohrabi C, *et al*. for the SCARE Group. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines. Int J Surg 2020;84:226–30.
[12] Endo H, Hosono T, Kondo H. Antineutrophil cytoplasmic autoantibodies in 6 patients with renal failure and systemic sclerosis. J Rheumatol 1994; 21:864–70.
[13] Kiraz S, Simsek H, Ertenli I, *et al*. Antineutrophil cytoplasmic antibodies in systemic sclerosis. Clin Rheumatol 1996;15:519–20.
[14] Locke IC, Worrall JG, Leaker B, *et al*. Autoantibodies to myeloperoxidase in systemic sclerosis. J Rheumatol 1997;24:86–9.
[15] Tzelepis GE, Kokosi M, Tzioufas A, *et al*. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. Eur Respir J 2010;36:116–21.
[16] Helfrich DJ, Banner B, Steen VD, *et al*. Normotensive renal failure in systemic sclerosis. Arthritis Rheum 1989;32:1128–34.
[17] Herrick AL, Oogarah PK, Freemont AJ, *et al*. Vasculitis in patients with systemic sclerosis and severe digital ischemia requiring amputation. Ann Rheum Dis 1994;53:323–6.
[18] Casari S, Haeney M, Farrand S, *et al*. Antineutrophil cytoplasmic antibodies are a "Red Flag" in patients with systemic sclerosis. J Rheumatol 2002;29:2666–7.
[19] Caramaschi P, Biasi D, Tonolli E, *et al*. Antineutrophil cytoplasmic antibodies in scleroderma patients: first report of a case with anti-proteinase 3 antibodies and review of the literature. Joint Bone Spine 2002; 69:177–80.
[20] Quéméneur T, Mouthon L, Cacoub P, *et al*. Systemic vasculitis during the course of systemic sclerosis: report of 12 cases and review of the literature. Medicine (Baltimore) 2013;92:1–9.