Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Systemic sclerosis sine scleroderma with atypical clinical course: a rare case report

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Introduction and importance: Systemic sclerosis (SSc) is divided into three subtypes: limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), and systemic sclerosis sine scleroderma (ssSSc). ssSSc is a rare subtype of SSc that presents with internal organ manifestations but no cutaneous findings.

Case presentation: We report the case of a 58-year-old patient with a history of pulmonary hypertension who presented with symptoms of fatigue, inflammatory polyarthritis, and joint swelling. Following a comprehensive clinical examination and laboratory tests, the patient was diagnosed with ssSSc.

Clinical discussion: Due to its atypical clinical course, we present this case report, which commenced with idiopathic pulmonary hypertension. Subsequently, after 7 months, the patient presented complaints of polyarthritis with positive antinuclear antibodies. Raynaud's phenomenon was identified 2 months later during the rheumatology clinic examination. Typically, the clinical course encompasses all three features simultaneously, without any gap between them.

Conclusion: Diagnosis of ssSSc remains challenging, and it is essential to consider this disease form in all cases involving unexplained fibrotic involvement of the internal organs.

Keywords: scleroderma, systemic sclerosis, systemic sclerosis sine scleroderma, tadalafil

Introduction

Systemic sclerosis sine scleroderma (ssSSc) has been classified into three types. Type I (complete) is characterized by the lack of the typical skin changes of this disorder at least until a systemic sclerosis (SSc)-related insufficiency of any internal organ occurs. Type II (incomplete) is characterized by the absence of sclerodactyly, but there are other involvements of the skin changes (e.g. calcifications, telangiectasis, pitting scars) that can be found. Type III (delayed) is characterized by clinical involvement of internal organs typical for SSc that has occurred before skin changes (complete or incomplete)[1]. This disease was first reported in medical literature by Abrams in 1954 and later described in 1962 by Rodnan and Fennel. The etiology of the disease is still unknown, and it affects females more than males[2,3]. The disease commonly presents with organ dysfunction such as gastric or esophageal dysfunction[4], renal complications[2], arthralgias or myalgias[3], and pulmonary symptoms, as seen in our patient. The main diagnostic criteria are the absence of skin thickening, Raynaud's phenomenon or other peripheral vascular involvement, positive antinuclear antibodies (ANA), involvement of one visceral organ typical of SSc, and the absence of another defined connective tissue disease[2–5]. The differential diagnosis for this disease includes the diffused or limited form of SSc[1]. The treatment is the same as SSc, which consists of immunosuppression, in addition to the management of the involved organ, making it different from one patient to another[6]. The risk factors for mortality are male sex, cardiac involvement, systemic inflammation, and altered diffusing capacity of the lungs for carbon monoxide[7]. This case has been reported in line with the SCARE (Surgical CAse REport) criteria[8].

HIGHLIGHTS

- Systemic sclerosis sine scleroderma (ssSSc) is a rare multisystem disorder with an undetermined etiology.
- Diagnosis of ssSSc is difficult because of the lack of skin-thickening features.
- This case is unique because of its atypical symptom presentation.
- The treatment plan included tadalafil, which positively affected the course of treatment.
- This case report aims to raise awareness among clinicians regarding ssSSc.

Case presentation

A 58-year-old female presented to the rheumatology clinic complaining of fatigue, weakness, polyarthritis, and joint swelling

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2023) 85:5656–5661

Received 31 July 2023; Accepted 23 August 2023

Published online 5 September 2023

http://dx.doi.org/10.1097/MS9.0000000000001266

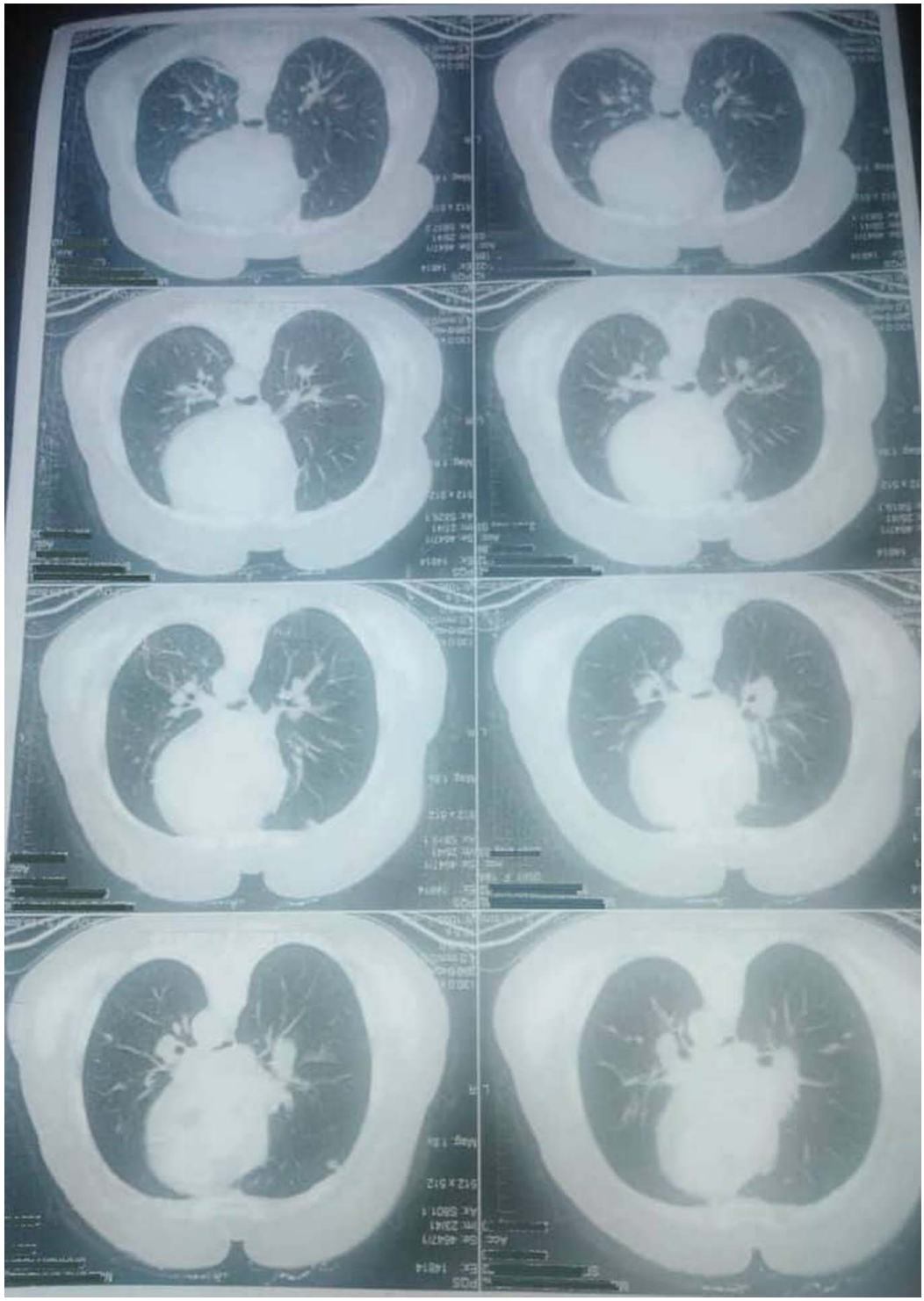

Figure 1. Alveolar infiltrates in the posterior segment of the left basal lobe and multiple regular lung nodes with a diameter of 6–8 mm that is peripherally distributed in the lung.

2 months ago. Medical history is significant for idiopathic pulmonary hypertension 9 months ago, with dyspnea that started 3 years ago and progressed to class 4 dyspnea, and orthopnea without cough and sputum, associated with fever of unknown origin and sweat, with no drug history or family history. The diagnosis was confirmed by echocardiography with 80 mmHg pulmonary arterial systolic pressure (PASP), ejection fraction of 60%, mild mitral valve regurgitation, and moderate to severe tricuspid valve regurgitation, and by multislice computed tomography, which revealed the presence of alveolar infiltrates and lung nodes (Fig. 1). Vital signs were within normal limits and the pulmonary function test was normal. Laboratory tests included

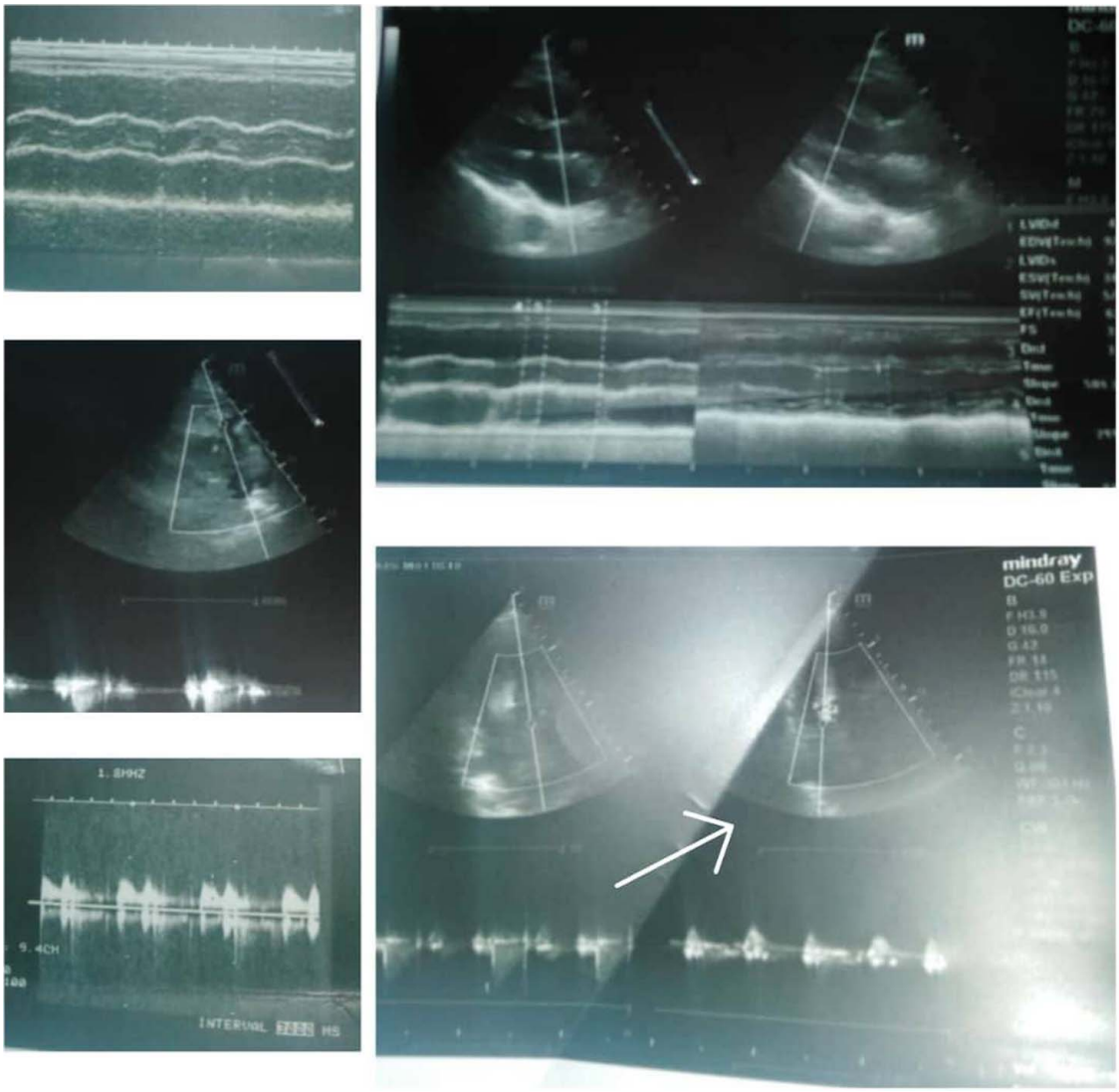

Figure 2. Echocardiography that illustrates pulmonary hypertension.

the following results: erythrocyte sedimentation rate (ESR): 45 mm/h; antinuclear antibody (ANA): 1:320; anti-centromere antibody (ACA): 94.8 AU/ml; while anti-scl-70, HBsAg (hepatitis B surface antigen), anti-HCV (hepatitis C virus), and rheumatoid arthritis (RA) tests were negative. On clinical examination, right 2,3,4 metacarpophalangeal (MCP) joints effusion and right 2,3 proximal interphalangeal (PIP) joints effusion, left 2,3,4 MCP and left 4,5 PIP effusion were noticed, along the diagnosis of Raynaud's phenomenon after 2 months, by placing the patient's hands in cold water. On chest auscultation, coarse crackles were present. Echocardiography illustrated a PASP of 55 mmHg after being treated for pulmonary hypertension (Fig. 2). Electrocardiogram revealed sinus bradycardia with P pulmonale, which is the consequence of right atrial enlargement and pulmonary hypertension (Fig. 3). The presence of pulmonary hypertension, Raynaud's phenomenon, positive anti-centromere antibodies, and the exclusion of another connective tissue disease confirmed the diagnosis of systemic sclerosis sine scleroderma (ssSSc). The treatment included tadalafil (5 mg), prednisone (5 mg), esomeprazole, furosemide (40 mg), and rivaroxaban (20 mg). On follow-up, drug doses were adjusted; bisoprolol fumarate and molsidomine were added along with tadalafil. There are no long-term complications after one year of follow-up, along with periodic follow-ups every 3 months. The patient is in good condition and his dyspnea has improved with a PASP of 52 mmHg.

Discussion

The diagnosis of ssSSc requires a high level of clinical suspicion due to its rarity and the lack of typical skin changes[9]. Several studies have been conducted to investigate the prevalence of ssSSc among patients with SSc and to identify the clinical features and organ involvement associated with this subtype. Studies have reported a female predominance and a high prevalence of pulmonary involvement and pulmonary arterial hypertension in ssSSc[3,10,11].

De Angelis *et al*. reported a frequency of 3% for ssSSc among 1800 patients with SSc, with a female predominance of 95.1%.

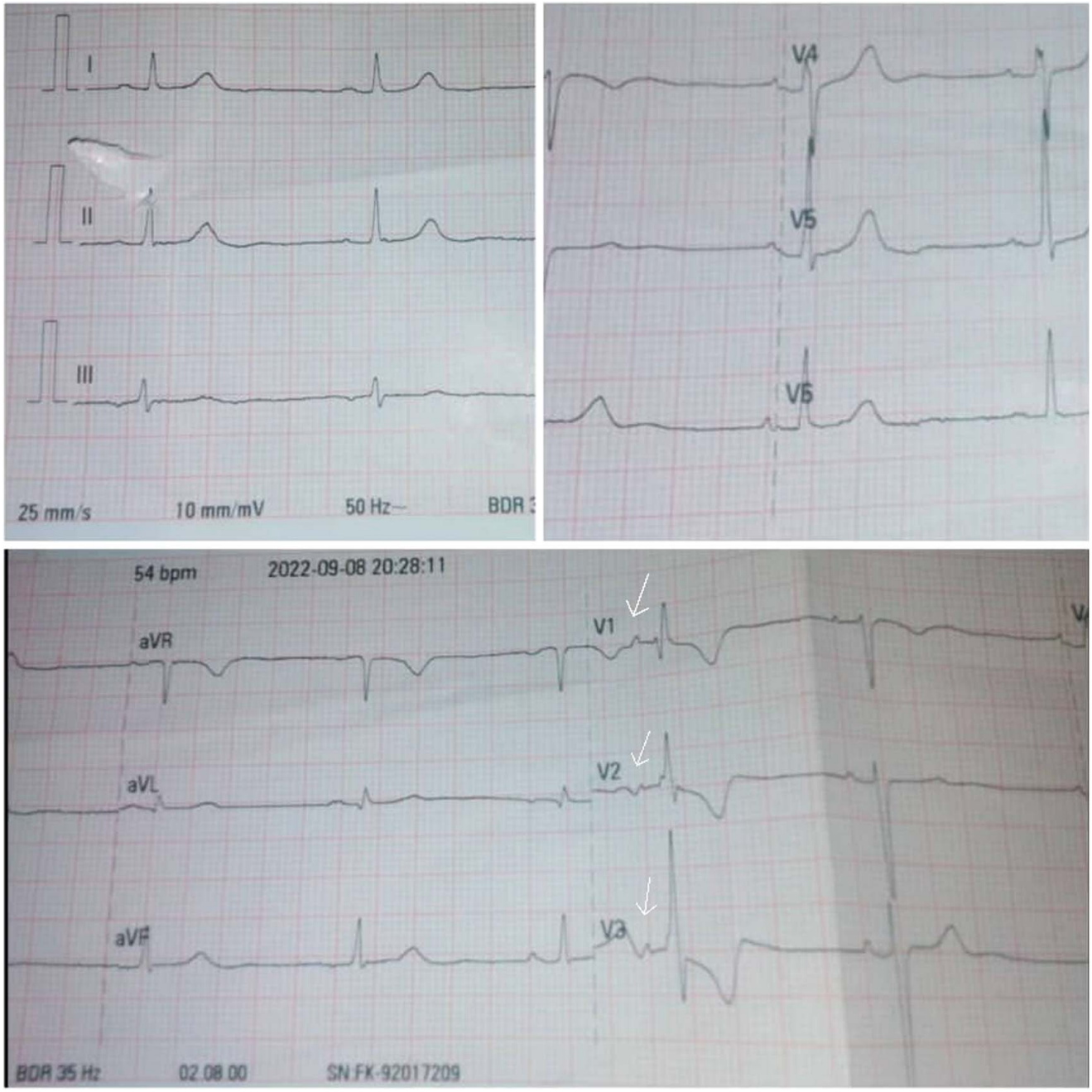

Figure 3. Electrocardiogram: sinus bradycardia with biphasic P wave and P pulmonale, increased P wave amplitude in both leads, which is a consequence of pulmonary hypertension and right atrial enlargement.

Pulmonary involvement was present in 68% of ssSSc patients, and pulmonary hypertension was present in 23% of cases. The prevalence of arthritis was 11.5%. Moreover, the frequency of positive anti-centromere autobody's was 40%[10]. Diab *et al.* conducted a multicenter study involving 1400 patients with SSc, of whom 57 were initially diagnosed with ssSSc. However, 30 of these patients were later reclassified into other subtypes of SSc, leaving only 27 ssSSc cases, out of which 24 (88.9%) were females. Pulmonary hypertension was present in 11% of all three subtypes (ssSSc, lcSSc, and dcSSc). The prevalence of inflammatory polyarthritis in ssSSc cases was present in 11.5%[11]. Poormaghim *et al.* reported a prevalence of 9% for ssSSc among patients with SSc who were not diagnosed with dcSSc. Pulmonary involvement was present in 68% of ssSSc patients and 60% of lcSSc patients, while pulmonary hypertension was present in 23% and 13% of ssSSc and lcSSc patients, respectively. The diagnosis of pulmonary hypertension was made by echocardiogram, right heart catheterization, or clinical evidence of right heart failure[9]. Marangoni *et al.* reported a prevalence of ssSSc of 8.3% among 947 patients with SSc, with a female predominance of 96.2%. Pulmonary hypertension was present in 22.8% of ssSSc cases[3].

The present case involves a female patient who presented with primary pulmonary arterial hypertension, followed by inflammatory polyarthritis 9 months later. The diagnosis was based on the presence of positive anti-centromere autoantibodies, pulmonary hypertension, and Raynaud's phenomenon, along with the exclusion of other diseases that could have caused the patient's symptoms. The diagnosis of pulmonary hypertension was confirmed by echocardiography. The patient did not have esophageal dysmotility symptoms which are present in 56% of cases[11]. The importance of this case lies in its atypical presentation, with the patient initially presenting solely with pulmonary hypertension, followed by the later development of inflammatory polyarthritis, and later on with Raynaud's syndrome. Such a clinical course is rare and highlights the need for vigilant monitoring and multidisciplinary care in patients with ssSSc.

The initial treatment regimen included prednisone (prednisolone) (5 mg), esomeprazole, furosemide (40 mg), rivaroxaban (20 mg), and tadalafil (5 mg). During the follow-up period, the corticosteroid dose was gradually reduced and eventually discontinued, while bisoprolol fumarate (2.5 mg) and molsidomine (2 mg) were initiated. The patient did not report any adverse effects caused by the treatment. Interestingly, Raynaud's syndrome did not recur after discontinuing prednisone, which may be attributed to the effectiveness of tadalafil, a phosphodiesterase inhibitor. Numerous studies have reported the efficacy of phosphodiesterase inhibitors in the treatment of Raynaud's syndrome[12,13]. However, the efficacy of tadalafil in SSc is not well-established. In a randomized trial conducted by Schiopu *et al.*[14], tadalafil was deemed safe to use but showed no significant improvement over placebo in treating Raynaud's syndrome secondary to SSc. While more research is needed to confirm the effectiveness of tadalafil in SSc, the presented case provides promising evidence for tadalafil as an optional therapy for pulmonary hypertension and Raynaud's syndrome in SSc patients.

Conclusion

In conclusion, the particular importance of this case is its unusual presentation, wherein the patient initially exhibited pulmonary hypertension, followed by subsequent development of inflammatory polyarthritis and Raynaud's syndrome. Such an atypical clinical course is infrequent and accentuates the necessity for diligent monitoring and multidisciplinary management in individuals with ssSSc. This case highlights the importance of considering ssSSc in patients presenting with internal organ manifestations of SSc, even in the absence of cutaneous findings. In addition, it emphasizes the significance of conducting further research that addresses the efficacy of tadalafil in this condition. Early diagnosis and treatment are crucial in preventing disease progression and associated complications. Therefore, increasing awareness of this rare condition among clinicians is essential for improving patient outcomes.

Ethical approval

Ethical approval is not required for this case report because the research does not require any practical actions or interventions on patients; it is an observational study, and patient consent is available upon request.

Consent

Written informed consent was obtained from the patient 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.

Sources of funding

No funding was required.

Author contribution

R.S: conceptualization, data curation, formal analysis, investigation, project administration, resources, software, validation, writing – original draft, critical revision, and approval of the final manuscript; S.A.G: conceptualization, data curation, formal analysis, investigation, resources, critical revision, writing – original draft, and approval of the final manuscript; M.R: conceptualization, data curation, formal analysis, critical revision, investigation, resources, writing – original draft, and approval of the final manuscript; S.A.A.: supervision, patient care, conceptualization, data curation, formal analysis, critical revision, investigation, writing – original draft, and approval of the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: research registry.
2. Unique identifying number or registration ID: researchregistry 9432.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/.

Guarantor

Safaa Abd Alhadi.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

Not applicable. All data (of the patient) generated during this study are included in this published article and its supplementary information files.

Acknowledgements

Not applicable.

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