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CASE REPORT

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A case report of clubbing as the initial sign of systemic sclerosis sine scleroderma: A rare possible presentation

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Key Clinical Message

Even in the absence of characteristic cutaneous symptoms of scleroderma, systemic sclerosis should be considered in the differential diagnosis of patients initially diagnosed with idiopathic interstitial lung disease.

Abstract

Systemic sclerosis (SSc) is an idiopathic connective tissue disorder characterized by multisystem involvement. Although skin thickening is a hallmark manifestation of SSc, a subset known as systemic sclerosis sine scleroderma (ssSSc) presents with internal organ involvement and positive serologic markers in the absence of significant cutaneous manifestations. We report the case of a 36-year-old Iranian woman who presented with clubbing as an initial symptom of ssSSc. Notably, clubbing as the sole initial sign of the disease has not been previously reported. Timely diagnosis of ssSSc is crucial to facilitate appropriate treatment and prevent disease progression. Physicians should adopt a comprehensive approach when evaluating patients presenting with limited clinical features, as they might be indicative of underlying ssSSc.

KEYWORDS

atrial septal defect, case report, clubbing, interstitial lung disease, systemic sclerosis sine scleroderma

1 | INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue condition characterized by skin thickening, internal organ fibrosis, vascular disorders, and immunological abnormalities.[1] However, a subtype known as systemic sclerosis sine scleroderma (ssSSc) is defined by organ involvement without significant cutaneous manifestations.[2] The epidemiology of ssSSc remains poorly understood, with estimates suggesting that it accounts for approximately 5% of all SSc cases.[3] Despite being a less common variant, ssSSc often presents challenges in diagnosis due to its varied clinical manifestations and potential underdiagnosis.[4,5]

Delays in the diagnosis of ssSSc can have detrimental consequences, as the disease frequently involves vital internal organs such as the cardiovascular and respiratory

systems. Studies have indicated variable 10-year survival rates ranging from 50% to 84% in SSc, highlighting the importance of early identification and intervention.[3]

The diverse clinical presentations of ssSSc contribute significantly to the diagnostic challenges associated with this condition. Therefore, recognizing the various early symptoms of ssSSc is crucial for timely management and improved outcomes.[6] To the best of our knowledge, there are no reported cases discussing the association between clubbing and ssSSc. In this case report, we present the unique case of a 36-year-old Iranian woman who presented with clubbing as the initial symptom of ssSSc.

2 | CASE PRESENTATION

We present the case of a 36-year-old Iranian female nurse with no significant medical or family history. The patient noticed clubbing in both hands 9 months prior but did not seek medical attention for diagnostic assessments. The clubbing was confined to the hands and was not observed in the toes. By chance, a doctor at the patient's workplace recognized the clubbing (see Figure 1) and recommended consultation with a pulmonologist, but the patient did not follow-up. After 1 month, the patient experienced cyanosis on the metacarpophalangeal (MCP) joints of both hands during strenuous exercise. The patient also complained of exertional dyspnea and chest discomfort, prompting a visit to a cardiologist. Trans-esophageal echocardiography (TEE) revealed mild to moderate right ventricular (RV) enlargement, mild systolic dysfunction, and an aneurysmal interatrial septum at the inferential posterior aspect, consistent with a moderate-sized secundum type atrial septal defect (ASD). The patient underwent angiography and underwent an ASD occlusion procedure, resulting in improvement of symptoms such as chest discomfort and dyspnea. However, clubbing and MCP cyanosis persisted. The cardiologist suggested that the association between the clubbing and cyanosis and the ASD could not be explained, prompting consideration of an alternative etiology.

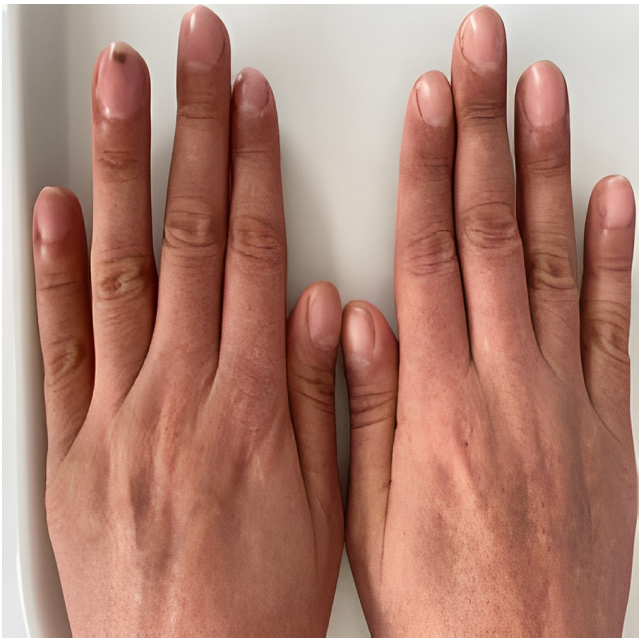

FIGURE 1 Clubbing as first manifestation of our patient.

Two months later, the patient developed a cough that exacerbated with talking. A pulmonologist evaluated the patient and conducted spirometry and a spiral lung CT scan. Additional movie files provided a parenchymal and mediastinal view of the spiral lung CT scan (see Video S1 and S2). Spirometry revealed a forced expiratory volume in 1 second (FEV1) of 2.6 L and a FEV1/forced vital capacity (FVC) ratio of 82%. The CT scan demonstrated mild esophageal dilation and peripheral bilateral fine interlobular septal thickening in the lungs, suggestive of interstitial lung disease (ILD), possibly secondary to scleroderma. To confirm the diagnosis of a rheumatologic disorder, various rheumatologic tests were performed, and treatment with 2 g of cellcept and 7.5 mg of prednisolone daily was initiated, considering scleroderma. Prior to receiving the rheumatologic evaluation results, the patient was admitted to the hospital for 11 days due to dysphagia and abdominal pain. Treatment with proton pump inhibitors (PPIs) for gastroesophageal reflux disease resulted in symptom improvement. A repeat lung CT scan showed progressive bilateral lung fibrosis. During hospitalization, the patient received cyclophosphamide and was considered for esophageal manometry, which revealed ineffective motility and hypotonia of the lower esophageal sphincter (LES), consistent with esophageal manifestations of scleroderma. Anti SS-B/La, Cyclic Citrullinated peptide Ab, Anti ds.D.N.A.Antibodies (ELISA), ASMA, Anti Smith Ab, S/M RNP, Anti Centromere-CREST, Anti JoI, IgG immunoturbidimetric, C3-immunoturbidimetric, C4-immunoturbidimetric, CH50-SRID, HBS Ag, HCV Ab, Anti Beta-2 Glycoprotein-IgG, Anti Beta-2 Glycoprotein-IgM, Anti Cardiolipin Antibody-IgG, Anti Cardiolipin Antibody-IgM, Phospholipid Antibody-IgG, and Phospholipid Antibody-IgM were within reference values. The antinuclear antibody (ANA), SS-A/Ro, and anti-SCL-70Ab tests yielded positive results with a value of 9.4, 82.1 U/mL, and 640 RU/mL, respectively. The clinical examination and laboratory testing did not reveal any significant findings suggestive of other rheumatologic diseases. Additional causes of clubbing were excluded based on earlier cardiac and pulmonary assessments. Considering the symptoms of clubbing, internal organ involvement (ILD), and a positive ANA test, the criteria for ssSSc were met. Treatment with daily prednisolone (7.5 mg) was resumed.

After 2 months of treatment, the patient's symptoms improved without complications. The patient was followed up for 6 months, during which time dyspnea significantly improved, spirometry results improved, and there was no recurrence of clubbing.

3 | DISCUSSION

To diagnose ssSSc, a rare subtype of SSc, the presence of the following three symptoms is necessary, along with the absence of typical skin thickening: (A) damaged nail fold capillaries or Raynaud's phenomenon; (B) a positive result for ANA, typically accompanied by a nucleolar or speckled immunofluorescence assay; and (C) involvement of at least one internal organ (e.g., ILD, kidney failure, esophageal dysmotility, or pulmonary hypertension) in the absence of an alternative rheumatologic diagnosis.[7,8] Therefore, in addition to chest imaging, clinical presentation, and the administration of nail fold capillaroscopy, positive serum ANA antibodies, echocardiography, and esophageal assessment are crucial for enabling the diagnosis of ssSSc.[9] Kucharz reviewed articles related to ssSSc and observed that the female-to-male ratio in ssSSc patients is approximately 9:1, based on studies involving over 1500 patients, which is similar to the overall SSc patient population. In our case, the patient is female. Regional hypoxia, platelet stimulation, production of signaling proteins including vascular endothelial growth factor (VEGF), activation of revascularization, and other cellular processes are likely contributors to the pathophysiology of digital clubbing.[10] In this case, the presentation of clubbing was the initial symptom of the disease, which might have resulted from damage to the nail fold capillaries.

The clinical manifestation of ssSSc is uniform, with gastrointestinal and pulmonary symptoms being the most prevalent. Respiratory and gastrointestinal involvement often leads to numerous symptoms and is frequently identifiable, which could explain their high frequency in both series of patients and individual case reports. A study by Marangoni et al. on a large population of ssSSc patients revealed esophageal involvement (83%) and lung involvement (68%) as the two most common systemic manifestations. This literature supports our patient's reported respiratory and esophageal symptoms.[11]

Gastrointestinal symptoms in ssSSc patients include difficulty swallowing, severe abdominal discomfort, nausea, or vomiting. Gastroesophageal reflux disease (GERD) is a common condition among individuals with SSc, particularly those with ssSSc. Our patient presented with dysphagia and abdominal pain, and her symptoms improved after treatment for GERD with PPI. Shortness of breath during the initial stages of exercise is indicative of pulmonary disease. Pulmonary hypertension and ILD are the most prevalent pulmonary manifestations. Similarly, our patient experienced dyspnea and was diagnosed with ILD. In a study by Toya et al., which documented and examined 108 cases of ssSSc, 25% of patients had confirmed cardiac involvement. The most typical symptoms in these cases were persistent heart failure, pericardial effusion, conduction problems, or arrhythmias. Myocardial fibrosis is likely the primary cause of cardiac symptoms. However, none of these complications were observed in our patient, except for an ASD, which was probably unrelated to ssSSc.[12]

The main symptom in our patient's case was clubbing, and the pathophysiology of clubbing is not yet fully understood. It involves a combination of vascular, connective tissue, and platelet abnormalities. The primary mechanism is believed to be associated with increased blood flow and vasodilation in the nail bed, leading to tissue expansion.

Clubbing is commonly associated with various respiratory and cardiovascular conditions. Underlying lung diseases such as chronic obstructive pulmonary disease (COPD), lung cancer, bronchiectasis, and interstitial lung disease are known causes. Chronic hypoxia and tissue injury associated with these respiratory conditions can contribute to clubbing. Cardiovascular disorders, including congenital heart disease, endocarditis, and cyanotic heart disease, can also lead to clubbing due to chronic hypoxemia.

In addition to respiratory and cardiovascular conditions, clubbing may also be observed in gastrointestinal disorders, including inflammatory bowel disease, cirrhosis, and celiac disease, can be associated with clubbing, possibly due to the release of pro-inflammatory mediators. In our case, the patient was suffering of GERD and ASD disease that we cannot explain the reason of clubbing. Autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus have also been linked to clubbing. We should consider other rheumatologic disease as reason for clubbing. Clubbing is a clinical finding with a wide range of potential underlying causes. It is often associated with respiratory and cardiovascular disorders, but can also be indicative of other diseases. Proper evaluation and investigation are necessary to identify and manage the underlying condition contributing to clubbing in each individual patient.

4 | CONCLUSION

ssSSc is a subtype of SSc characterized by Raynaud's phenomenon (RP), visceral involvement without skin thickening, and the presence of antinuclear antibodies (ANA).

In this study, we presented the case of a 36-year-old Iranian woman who exhibited clubbing as the initial symptom of ssSSc disease. The unique aspect of this case lies in the manifestation of clubbing, which had not been previously observed despite symptoms of an internal organ disorder, rendering it a noteworthy and distinct case within the context of ssSSc. This highlights the significance of considering SSc even in patients initially diagnosed with idiopathic interstitial lung disease (ILD) in the absence of characteristic scleroderma cutaneous symptoms. Timely recognition and consideration of SSc in these cases can lead to accurate diagnosis and appropriate management strategies.

AUTHOR CONTRIBUTIONS

Anahita Amirpour: Conceptualization; supervision; validation. **Parastoo Ghorbani:** Writing – original draft. **Erfan Ghadirzadeh:** Supervision; writing – review and editing. **Elham Charkazi:** Data curation; investigation. **Elham Paraandavaji:** Project administration; validation; visualization.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data are available with the corresponding author and can be reached on request.

ETHICS STATEMENT

An Ethics Committee for the publication of this Case Report was not applicable; however, all management methods were in line with relevant guidelines.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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