



Osteopetrosis in a Patient of Systemic Sclerosis Sine Scleroderma: A Rare Association

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Abstract

Keywords

- ▶ interstitial lung disease
- ▶ osteopetrosis
- ▶ rugger jersey spine
- ▶ systemic sclerosis sine scleroderma

Systemic sclerosis is a connective tissue disorder of unknown etiology. Although it is a multisystemic disorder, skin thickening is considered as a hallmark of the disease. It usually involves the lungs, gastrointestinal, and musculoskeletal systems. However, a rare subset of systemic sclerosis, systemic sclerosis sine scleroderma, is characterized by internal organ involvement and positive serologic markers with the total or partial absence of cutaneous manifestations. We present a rare association of osteopetrosis in a case of systemic sclerosis sine scleroderma, in a 22-year-old male patient, who presented with pulmonary symptoms as his chief complaints, unreported so far in literature.

Introduction

Systemic sclerosis is a rare generalized connective tissue disorder of unknown etiology and unclear pathogenesis. It is generally accepted that the disease is characterized by widespread fibrosis of the skin and internal organs, vascular abnormalities, and immune disturbances.¹ Skin involvement in systemic sclerosis is considered as a cardinal feature often presenting as skin thickening.² Skeletal involvement in systemic sclerosis is commonly seen that includes demineralization, arthritis and systemic inflammation, hyperostosis of the phalangeal tuft, and the resorption of bone at various sites, including the carpal bones, distal radius, and ulna.³ Here, we present a rare association of osteopetrosis in a patient with rare variant of systemic sclerosis: systemic sclerosis sine scleroderma (ssSSc). This association is unreported till date to the best of our knowledge as searched in the PubMed and other Internet search engines.

Case Report

A 22-year-old male patient was presented with complaints of shortness of breath, dry cough, and fever on and off for the

last 4 months. No similar complaints in the past were observed. Patient was a nonsmoker and nonalcoholic. On examination, pulse rate was 102/min; blood pressure was 114/76 mm Hg; oxygen saturation was 96% at room air, and respiratory rate was 20/min. On respiratory examination, bilateral basal crepitations were present. Other systemic examination was unremarkable.

Patient was referred to us for further evaluation of his pulmonary complaints. Chest radiograph revealed ill-defined reticulonodular opacities in bilateral lung parenchyma predominantly in mid and lower zone in an asymmetrical distribution. Visualized bones including spine appear increased in density (→ **Fig. 1**). For further evaluation of interstitial changes noted in the chest radiograph, high-resolution computed tomography of the chest was done. On the lung window, it revealed reticular opacities predominantly in form of interlobular and intralobular septal thickening in subpleural and peripheral regions of all lobes of both lungs with associated early honeycombing and subtle bronchiectatic changes. Peripheral areas of ground glass opacities were also seen predominantly in the basal segments of bilateral lower lobes.

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Fig. 1 Chest X-ray posteroanterior view revealed ill-defined reticulonodular opacities in bilateral lung parenchyma predominantly in mid and lower zones with asymmetrical in distribution.

Above findings are suggestive of interstitial lung disease, possibly nonspecific interstitial pneumonia (NSIP) pattern (►Fig. 2). On mediastinal window patulous esophagus is noted (►Fig. 3A and C). All major thoracic vessels including pulmonary vessels appear unremarkable. On bone window, dorsal spine reveals increase in density of both superior and inferior endplates of all the visualized vertebrae giving the appearance of rugger jersey spine (►Fig. 3B). Thoracic cage including visualized scapula and humerus shows generalized increase in density. This prompted us to do a skeletal survey. Radiograph of dorsolumbar spine reveals similar rugger jersey spine appearance in the other vertebrae also (►Fig. 4A and B). In anteroposterior view of pelvic radiograph, there is a generalized increase in bone density. In addition, both femurs in its visualized extent reveal narrowing of medullary space with increase in cortical thickness and density (►Fig. 4C). In contrast, radiograph of wrist including forearm appears unremarkable (►Fig. 4D). Above skeletal survey findings are suggestive of osteosclerosis.

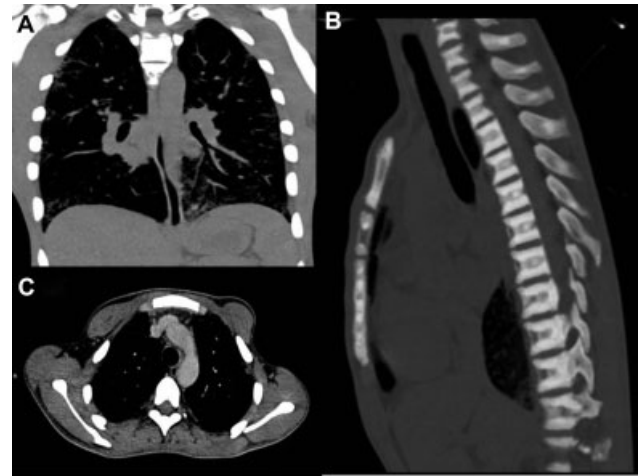


Fig. 3 (A) High-resolution computed tomography (HRCT) chest in mediastinal window with coronal reformation reveals patulous esophagus in distal part. (B) HRCT chest in bone window reveals increased density of superior and inferior endplates of vertebrae at multiple levels representing rugger jersey spine. Other bone including sternum shows generalized increase in density. (C) Axial section of CT chest in mediastinal window reveals patulous esophagus.

In view of the interstitial lung changes and the patulous esophagus, the treating physician was directed to investigate in the lines of systemic sclerosis. The laboratory investigations of the patient were positive for SCL-70 antibodies favoring a diagnosis of systemic sclerosis. Echocardiography revealed trivial tricuspid regurgitation (TR) with right ventricular systolic pressure (RVSP) of 43 mm Hg representing early pulmonary arterial hypertension. However, skin examination was unremarkable including the normalcy of the skin fold on dorsum of the wrist (►Fig. 5). In view of above findings and absence of skin involvement, the patient is diagnosed as a rare subset of systemic sclerosis; ssSSc. Moreover, renal blood parameters (serum urea: 15.21 mg/dL, serum creatinine: 0.85 mg/dL) including screening abdominal sonogram are unremarkable thereby excluding any renal pathology.

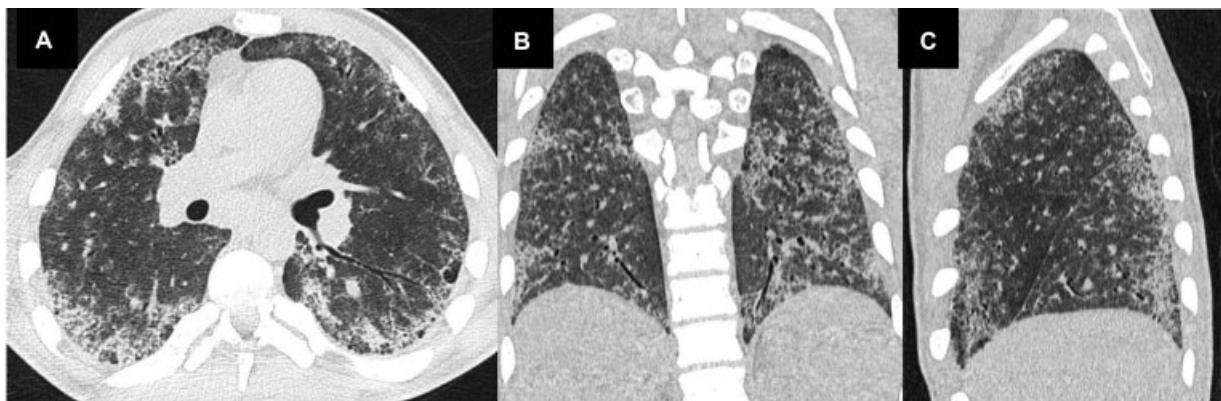


Fig. 2 High-resolution computed tomography chest in axial (A) view at right pulmonary artery level with sagittal (B) and coronal (C) reformatted images revealed reticular opacities and ground glass opacities in bilateral lung parenchyma in asymmetric pattern with predominant peripheral distribution. Early honeycombing and bronchiectasis are also seen.

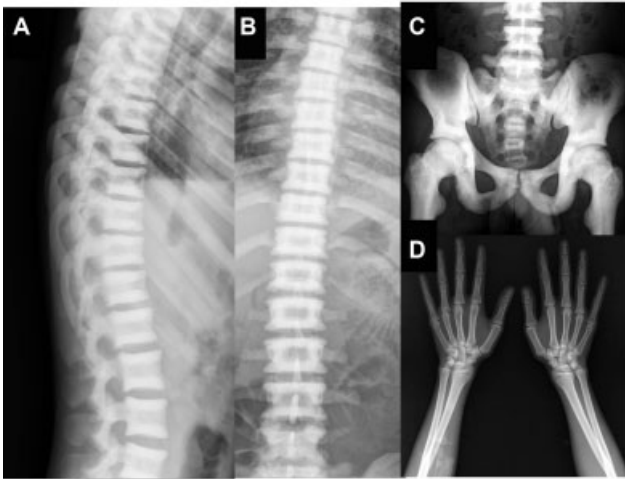


Fig. 4 Dorsolumbar spine in anteroposterior (AP) (A) and lateral (B) views reveals increased opacity of both superior and inferior endplates of all the visualized vertebrae giving the appearance of rugger jersey spine. (C) X-ray pelvis AP view reveals there is generalized increase in bone density in pelvic bones with increase in cortical thickness and density and narrowing of medullary space in its visualized extent of both femurs. (D) X-ray hand with forearm in AP view is unremarkable with no evidence of sclerotic changes.

Discussion

Systemic sclerosis is a chronic connective tissue disease that typically affects skin and internal organs to variable extent by widespread microvascular damage and excessive deposition of collagen. The main subsets of systemic sclerosis are limited cutaneous form, diffuse cutaneous form, and systemic sclerosis without skin involvement.^{1,2} Limited cutaneous form involves skin distal to elbow and knees only, whereas diffuse variety involves proximal extremities and/or trunk in addition to distal thickening.² On the other hand, ssSSc, a rare subset of systemic sclerosis, is characterized by the presence of visceral involvement in the absence of skin manifestations.^{2,4} It is believed that some ssSSc cases remain under-diagnosed and considered to be various forms of idiopathic fibrosis of internal organs.² The absence of skin involvement itself is probably the reason for under-diagnosis of ssSSc. Owing to the absence of skin changes, we would have also missed the case if the computed tomography (CT) findings of patulous esophagus would not have prompted the specific antibody tests.

Systemic sclerosis is characterized by three hallmark findings: signs of skin and/or internal organ fibrosis, signs of vasculopathy, and autoantibodies.² Skin involvement is considered a cardinal feature of systemic sclerosis that often appears as skin thickening in the fingers of both the hands extending proximal to the metacarpophalangeal joints.² The involvement of internal organs in the patients with ssSSc has been reported to be 79% for the gastrointestinal tract, 68% for pulmonary, and 9% for the heart.⁵ Others have reported that esophageal involvement was the most frequent (83%) and followed by pulmonary involvement (68%).⁶ Similar other studies also support involvement of gastrointestinal tract more frequent followed by pulmonary involvement in sys-



Fig. 5 Presence of normal skin fold along with wrinkles on proximal interphalangeal joint.

temic sclerosis patients.² Esophageal involvement is associated with dilation of esophagus with or without dysphagia. These can be readily visualized in esophagogram or CT scan.

Interstitial lung changes are most commonly presented as ground glass opacities and findings of fibrosis in form of reticular opacities, traction bronchiectasis, and honeycombing. Peripheral and subpleural distribution is more common involving predominantly lower lung zones as well as posterior lung fields. NSIP is more frequent as compared with usual interstitial pneumonia.⁷ Moreover, interstitial lung disease is included as a disease identification criterion in the American College of Rheumatology/European League against Rheumatism Collaborative Initiative joint classification.¹

Signs of vasculopathy include Raynaud's phenomenon, digital vasculopathy, and pulmonary arterial hypertension.² Multiple autoantibodies are described in the literature to be associated with systemic sclerosis. Most of these patients have positive antinuclear antibody by indirect immunofluorescence (85–90%). Among scleroderma-specific antibodies, antitopoisomerase (Scl-70) and anti-RNA polymerase III are more specific for diffuse variety, whereas anticentromere is more specific for limited variety.²

The index case having strong positivity for SCL-70 immunoglobulin G and antinuclear antibodies, a NSIP pattern of interstitial lung disease, esophageal dilatation, without any skin involvement led to the diagnosis of ssSSc. The trivial TR on two-dimensional Echo with RVSP of 43 mm Hg could represent early pulmonary arterial hypertension. However, there is no evidence of Raynaud's phenomenon or digital vasculopathy seen in our patient.

Skeletal involvement is common in systemic sclerosis. To quote Morrisroe et al—“Musculoskeletal involvement in systemic sclerosis occurs more frequently than expected, with a prevalence of 24% to 97%.” Both articular and nonarticular

involvements are described in the literatures. Common articular manifestations are arthralgia, synovitis, and flexion contractures, while generalized and localized osteopenia, acro-osteolysis and osteolysis in other body regions are common nonarticular manifestation.³ Arthritis in this disorder often simulates rheumatoid arthritis except for distal interphalangeal joint involvement. Exact etiopathogenesis of bone involvement is unclear; however, it is postulated that digital ischemia combined with retractile pressure of thickened skin may predispose to distal tuft resorption.³

However, skeletal survey in our case shows generalized increased bone density in most of the bones and rugger jersey appearance of the thoracolumbar spine representing osteosclerosis. To the best of our knowledge supported by the search on PubMed and other Internet search engines, osteosclerosis is not yet reported to be associated with systemic sclerosis.

Osteosclerosis can be seen in various conditions like osteopetrosis, secondary hyperparathyroidism, heavy metal poisoning, and blood dyscrasias. The fluorosis will show heterogenous sclerosis to start with but not like that of a rugger jersey spine and is associated with ossifying ends of the ligaments and tendons.⁸ The sclerosis associated with beryllium, lead, or bismuth poisoning shows sclerotic metaphyseal band along with relevant history.⁹ Blood dyscrasia like myelofibrosis is usually associated with splenomegaly and extramedullary hematopoiesis along with osteosclerosis.¹⁰ However, in our case, there was no such band or soft tissue changes or relevant history leaving us with osteopetrosis as a more plausible diagnosis.

Osteopetrosis is a rare sclerosing bone dysplasia characterized by reduced osteoclastic activity due to defect in formation and function of osteoclast with resultant increase in bone mass.¹¹ Broadly, it comprises three types: infantile malignant autosomal recessive form, intermediate autosomal recessive form, and the benign autosomal dominant form. Clinical presentation of autosomal dominant form varies from recurrent bone fractures to asymptomatic incidental finding as in this index case.¹² The rugger jersey spine is considered as pathognomonic sign for osteosclerosis associated with secondary hyperparathyroidism of chronic renal failure.¹³ However, in our case, the serum calcium and phosphorus were in normal range with no elevation of serum parathormone levels thus excluding secondary hyperparathyroidism. Moreover, it may also be seen in other diseases like osteopetrosis.⁹ It is a very rare and yet undocumented association of osteopetrosis in a patient of ssSSc.

Conclusion

Even if the clinical cutaneous markers are absent, the presence of a patulous esophagus and interstitial lung changes should lead us to investigate in lines of systemic sclerosis that can result in diagnosis of rare variant of systemic sclerosis; ssSSc. Moreover, presence of atypical skeletal changes in

form of rugger jersey spine leads us to do skeletal survey resulting in diagnosis of osteopetrosis. This will initiate an early treatment thus reducing the morbidity and mortality.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of Interest

There are no conflicts of interest.

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