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CASE REPORT

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Concomitant uterus agenesia and Marfan syndrome with systemic sclerosis: A rare case report

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Key Clinical Message

It seems that the association of two connective tissue disorders, including Marfan syndrome and systemic sclerosis, the first is associated with the loosening of the subcutaneous tissue and the second with its tightening, is a very interesting and controversial paradox at the same time and need finding possible genetic etiologies.

KEYWORDS

connective tissue disorders, Marfan syndrome, systemic sclerosis, uterus agenesia

1 | INTRODUCTION

Connective tissue disorders (CTDs), such as Marfan syndrome (MFS) and systemic sclerosis (SSc), are characterized by abnormal fibrillinogenesis. Systemic sclerosis, also known as scleroderma, is an idiopathic autoimmune disease that is characterized by the excessive accumulation of collagen in different tissues, such as the skin, lungs, kidneys, and gastrointestinal system; therefore, it is accompanied by multi-organ involvement. Its pathophysiology is complicated, involving early endothelial damage, an inflammatory infiltrate, and a fibrotic reaction as a consequence.[1] There is a growing body of evidence that supports the idea of the intricate interplay between dysfunctional fibroblasts, other cellular entities, and inflammatory mediators in SSc.[2] Marfan syndrome is a disorder of the extracellular matrix with characteristic manifestations in the eye, skeleton, and cardiovascular system that is mainly caused by mutations in the gene encoding fibrillin (FBN1).[3] There have been reports indicating an association between systemic sclerosis and Marfan syndrome. Systemic sclerosis has been linked to FBN1 haplotypes and single nucleotide polymorphisms.[4] Moreover, in the Tight skin mouse (Tsk) model, the duplication of the FBN1 gene results in SSc-like disease.[5] Additionally, a novel effect of the matricellular signaling protein CCN3 has been defined in extracellular homeostasis that is relevant to connective tissue disorders, including SSc and MFS, and causes same effects.[6]

To the best of our knowledge, there has been one report of MFS and SSc co-existing in a patient,[7] which has emphasized cardiac manifestations of the patient. Here we describe a rare known case of diffused scleroderma that is presenting MFS features beside uterus agenesis, highlighting an important potential association in the pathogenesis of these disease processes. The present case report has been documented in accordance with the CARE guidelines.[8]

2 | CASE PRESENTATION

A 48-year-old female patient presented to the emergency department with a chief complaint of severe fatigue associated with nausea and dyspnea. The patient had a confirmed diagnosis of scleroderma made 2 years ago, with symptom onset occurring 6 years prior. Her condition was associated with complications including interstitial lung disease (SSc-ILD), gastroesophageal reflux disease (GERD), iron deficiency anemia (IDA), a history of primary amenorrhea, and uterus agenesis.

The initial symptoms 6 years ago were Raynaud's phenomenon and skin thickening of the fingers extending proximal to the metacarpophalangeal joints. Over time, the patient experienced progressive dyspnea, dysphagia to solid foods, non-hematogenous vomiting after meals, extension of skin thickening to the face and peri-oral folds, fatigue, and myalgia. Two years ago, laboratory findings revealed positive ANA (titer of 9.4) and positive Anti-scl-70 by enzyme immunoassay, and high-resolution computed tomography (HRCT) of lungs showed irregular reticulation, thickening of interlobular septa with honeycombing view, and traction bronchiectasis in posterior inferior of both hemi-thoraxes, suggestive of interstitial lung disease, probably non-specific interstitial pneumonia (NSIP). As a result, she was prescribed prednisolone (5 mg twice a day) and Cellcept (500 mg four times a day). The patient's allergy history, family history, and psychosocial history were not significant.

Upon arrival at the Emergency Department, the patient's vital signs were stable, with a blood pressure of 100/65 mmHg, regular pulse rate of 82 beats per minute, respiratory rate of 18 breaths per minute, SpO2 of 96%, and body temperature of 36.8°C. Physical examination demonstrated skin induration and thickening of the fingers of both hands, extending proximal to the metacarpophalangeal joints, as well as involvement of the toes and face with peri-oral folds (Figure 1). The skin overlying her upper limbs appeared shiny, tight, hairless, and showed signs of paresthesia. Inspiratory crackles were noted upon auscultation of the lungs. The patient's arms, limbs, fingers, and toes appeared elongated and slender (Figure 1).

Due to the suspicion of Marfan syndrome, specific tests for Marfan syndrome were conducted. The patient exhibited arachnodactyly, positive thumb sign, positive wrist sign, pectus carinatum (Figure 2), and an increased arm span to height ratio (>1.05; =1.1). Total systemic score was six based on the revised Ghent nosology.[9] However ophthalmoscopic examination for assessing ectopia lentis, and genetic studies were yet to be done for a confirmed diagnosis of Marfan syndrome. Moreover, undeveloped secondary sexual characteristics were found during the examination (Figure 2).

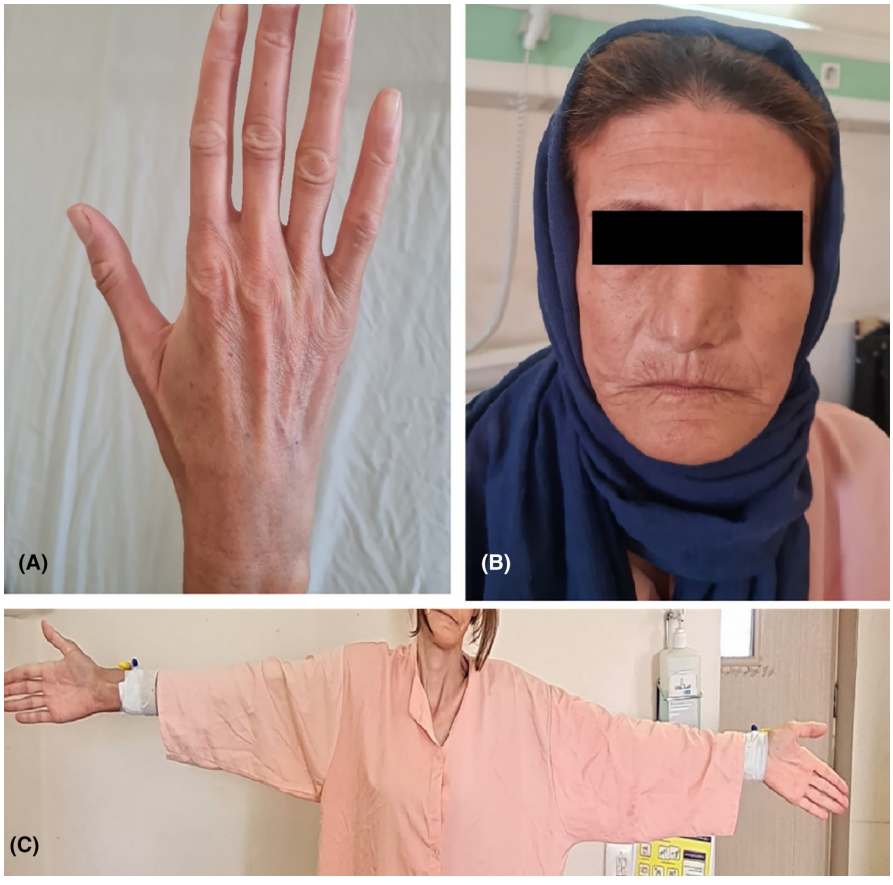

FIGURE 1 (A) Elongated and slender fingers, (B) peri-oral folds, and (C) elongated arms.

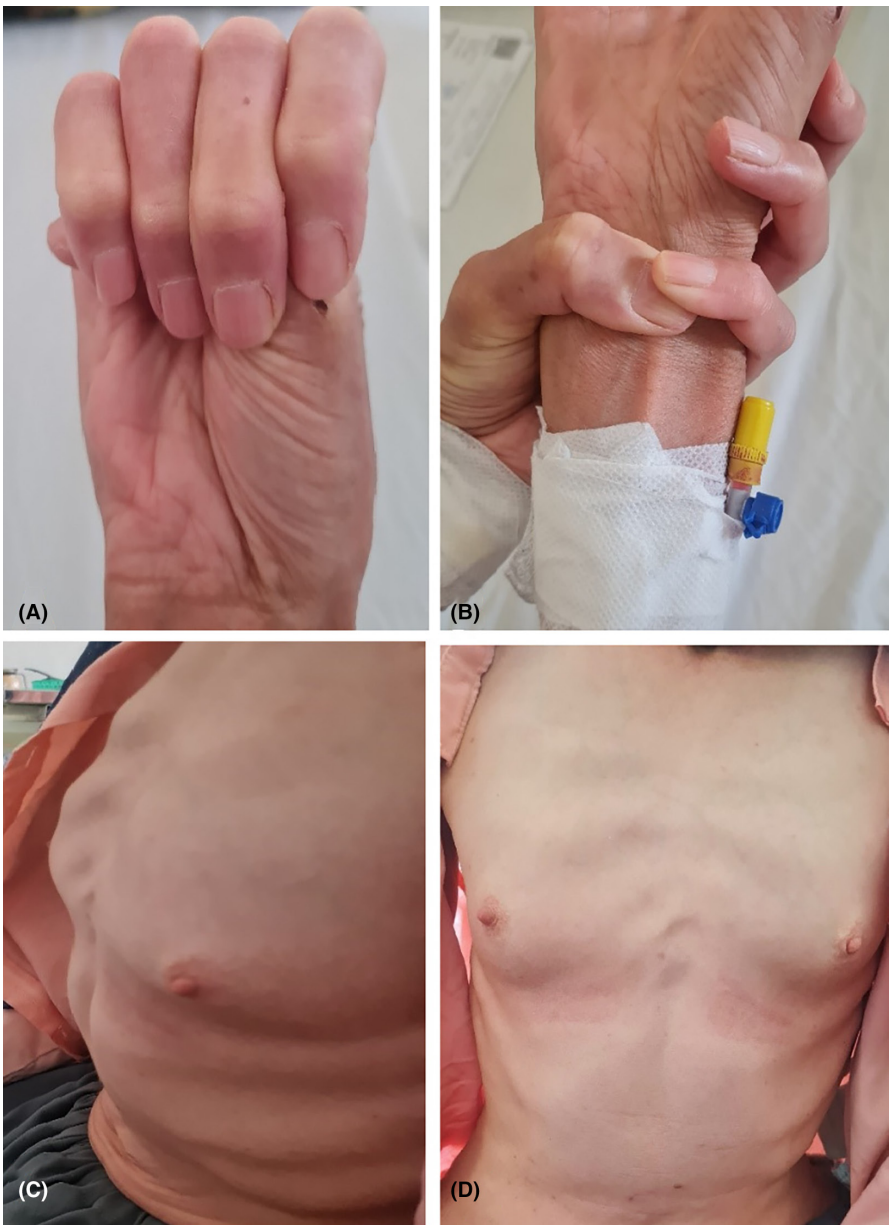

FIGURE 2 (A) Positive thumb sign. (B) Positive wrist sign. (C) Pectus carinatum. (D) Undeveloped secondary sexual characteristics.

Paraclinical examination revealed telangiectasia at the fundus of the stomach during endoscopic examination, along with grade 2 reflux esophagitis. The chest X-ray of the patient showed dilated aortic root, which was confirmed by 2D echocardiography (dilated ascending aorta measuring 41 mm in diameter), accompanied by mild mitral regurgitation and moderate tricuspid regurgitation. Abdomen and pelvis computed tomography didn't detect uterus and ovaries between urinary bladder and rectum (Figure 3).

Our patient received treatment for scleroderma and its complications including prednisolone, mycophenolate mofetil (Cellcept), PPI therapy with pantoprazole, ferrous sulfate, and beta-blocker (bisoprolol), and her health status was improving. She was counseled for gynecological assessments and starting HRT (hormone replacement therapy), but she has yet to decide.

3 | DISCUSSION

Systemic sclerosis (SSc) is a chronic autoimmune disease that remains to be an important challenge for clinicians. The primary characteristic of SSc is the gradual development of fibrosis caused by the excessive accumulation of extracellular matrix components in various tissues and organs. SSc is characterized by vascular injury, inflammation, and the presence of particular autoantibodies. Skin and internal organs like the heart, kidneys, lungs, musculoskeletal system, and gastrointestinal tract are all impacted by systemic sclerosis.[10] Multiple disease-specific autoantibodies are present in SSc; these autoantibodies are associated with different disease types and also serve to predict the prognosis. Patients with dcSSc are more susceptible to the presence of autoantibodies

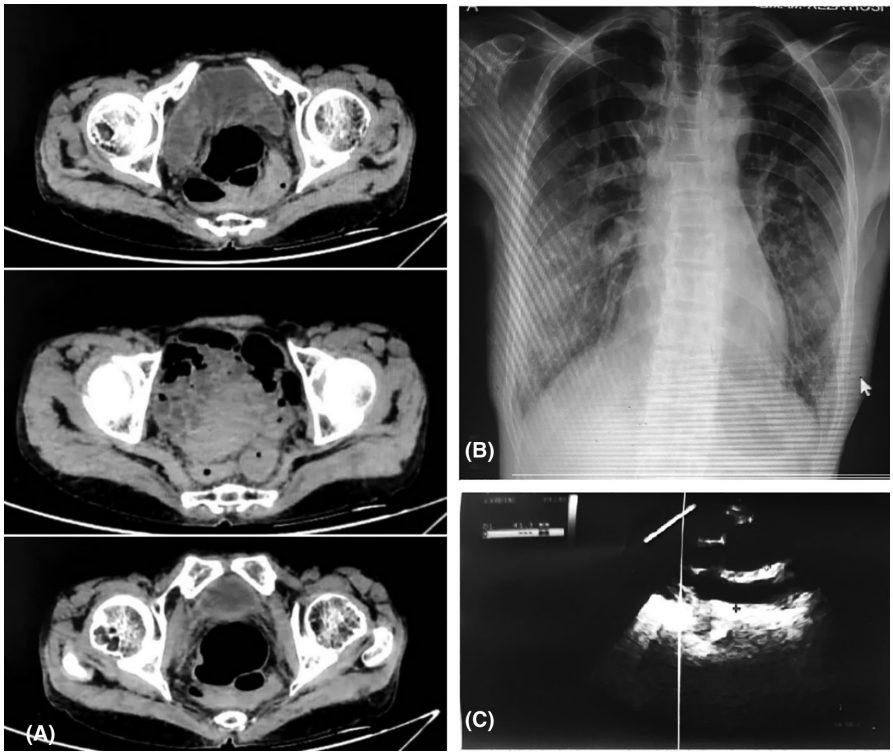

FIGURE 3 (A) Abdominal and pelvic CT scan didn't identify uterus and ovaries; (B) aortic root dilation in CXR; and (C) 2D echocardiography measured ascending aorta 41 mm in diameter.

targeting topoisomerase I (Topo I, ATA, and Scl-70), which have been linked to the development of pulmonary complications, digital ulcers, and the advancement of hand disability, as in the case we presented.[11] Marfan syndrome, an autosomal dominant condition, is a connective tissue disorder. Individuals with Marfan syndrome often have tall stature, long limbs, and flexible joints. They may also experience various complications, such as cardiovascular problems (such as aortic aneurysms and mitral valve prolapse), skeletal abnormalities (such as scoliosis and pectus excavatum), and ocular issues (such as lens dislocation and myopia), all caused by mutations in fibrillin-1 (FBN-1), the principal component of extracellular microfibrils. The gene FBN1 is situated at chromosome 15q-21.1. Fibrillin-1 is the major protein found in extracellular microfibrils and is believed to assist in the development and maintenance of elastic fibers. In addition to compromising tissue integrity, fibrillin-1 mutations disrupt local TGFβ signaling, as demonstrated by Marfan syndrome mouse models.[12,13] Our patient exhibited notable physical attributes that are commonly associated with Marfan syndrome. She nearly met the clinical diagnostic criteria outlined in the 2010 revised Ghent nosology for MFS. However, genetic testing and an ocular examination were not yet performed.

In addition to FBN-1's association with Marfan syndrome, there is strong evidence of the impact of this gene on other connective tissue disorders such as systemic sclerosis. Most fibroblast cell strains taken from patients with Marfan syndrome have shown a significant decrease in microfibrils, as demonstrated using a monoclonal antibody (mAb) that targets fibrillin 1, as compared to control cell strains; In a study conducted by D. Wallis et al. to investigate the association between fibrillin 1–containing microfibrils and systemic sclerosis, they demonstrated that SSc fibroblasts showed a distinct structure of microfibrils containing fibrillin 1 by utilizing a fibrillin 1 mAb for IF visualization, and electron microscopy identified ultrastructural abnormalities and diminished quantities of microfibrils produced by every strain of SSc cells.[14] Furthermore, systemic sclerosis has been associated with FBN1 haplotypes and single nucleotide polymorphisms[4] and in the Tight skin mouse (Tsk) model, the replication of the FBN1 gene leads to the development of a condition that resembles systemic sclerosis (SSc).[5] As previously stated, SSc is characterized by the production of autoantibodies against a variety of autoantigens; therefore, it is conceivable that the discharge of microfibril fragments could provoke the immune system in a genetically vulnerable host, resulting in the production of autoantibodies.[14]

It's noteworthy to mention that dysregulation of TGF-β signaling and the interaction of fibrillin-1 with TGF-β play critical roles in the manifestation of both MFS and SSc. However, the outcomes differ due to the distinct effects on structural integrity and tissue fibrosis in these conditions. In MFS, there is an ineffective binding of the mutant fibrillin-1 protein to the small latent complex (SLC) of transforming growth factor-beta (TGF-β), which results in

the release of active TGF-β. Consequently, there is excessive activation of TGF-β signaling, which plays a role in the distinctive traits of MFS, such as enlargement of the aorta and skeletal abnormalities. Conversely, in SSc, a particular mutation in the fibrillin-1 gene known as Tsk Fbn1 results in the synthesis of an enlarged fibrillin-1 protein that closely mimics latent TGF-β binding protein (LTBP). The Tsk fibrillin-1 protein, resulting from a mutation, functions in a way that enhances its activity and leads to an abnormal buildup of microfibrils and tissue fibrosis. This occurs by elevating the levels of latent TGF-β in the large latent complex (LLC). Consequently, this results in the excessive production of extracellular matrix (ECM) elements, specifically collagen and fibronectin, which ultimately contributes to the formation of tissue fibrosis in SSc.[7,15,16]

Another important point in the presented patient is the primary amenorrhea and the absence of ovarian and uterine structures in the abdominal and pelvic CT scan. According to our latest search, no definite and established genetic connection between connective tissue disorders and agenesis of the uterus and ovaries has been found. However, there have been some reported cases of co-occurrence of Ehlers–Danlos syndrome (a type of connective tissue disorder) and MRKH (Mayer–Rokitansky–Küster–Hauser) syndrome, characterized by agenesis of the uterus, cervix, and upper vagina, with the manifestation of primary amenorrhea with 46 XX karyotype and normal development of external genitalia.[17,18] Additionally, an interesting case report of ascending aortic dissection in a young girl with MRKH syndrome has recently been reported, which may indicate a potential association between these syndromes.[19] Additional studies are required to elucidate the underlying genetic factors, molecular mechanisms, and clinical associations between connective tissue disorders, agenesis of the uterus and ovaries, and other related conditions. Understanding these connections can contribute to improved diagnosis, management, and potential therapeutic interventions for individuals affected by these syndromes.

4 | CONCLUSION

Systemic sclerosis (SSc) is a multisystem auto-immune disease that is classified among connective tissue disorders. In this paper, we presented a forty-eight-year-old woman with systemic sclerosis, primary infertility because of uterous agenesia, and clinical findings in favor of Marfan syndrome. It seems that the simultaneity and association of two connective tissue diseases, including Marfan syndrome and systemic sclerosis, where the first is associated with the loosening of the subcutaneous tissue and the second with its tightening, is a very interesting and controversial paradox at the same time. This rare syndromic concomitancy in this patient will be helpful in finding possible genetic etiologies by conducting studies in the future.

AUTHOR CONTRIBUTIONS

Aliasghar Ebrahimi: Supervision; writing – review and editing. **Padideh Panahi:** Investigation; writing – review and editing. **Sepideh Tahsini Tekantapeh:** Conceptualization; investigation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors have declared that no competing interests exist.

DATA AVAILABILITY STATEMENT

The patient details are available in the electronic medical records and can be made available from the authors on request.

ETHICS STATEMENT

The patient provided written informed consent to allow for her deidentified medical information to be used in this publication.

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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