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Case Report Open Access

Scleromyxedema associated with ankylosing spondylitis treated successfully with cyclosporine and high dose corticosteroids

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Scleromyxedema (SM) is a rare disorder which initially presents with waxy skin stiffness and maculopapular lesions. It also has non-dermatologic manifestations, such as serum paraproteinemia and myopathies, and is sometimes associated with other autoimmune disorders. A 52-year-old man was referred for treatment because of torso-dominant skin stiffness. He also had a neglected history of bilateral inflammatory back pain and chronic *Helicobacter pylori*-negative gastritis. Skin histopathology confirmed a diagnosis of SM. A grade 4 bilateral sacroilitis and a positive *human leukocyte antigen B27* led to the patient also being diagnosed with ankylosing spondylitis (AS). Upon further analysis, monoclonal gammopathy of immunoglobulin (Ig) G/kappa (lower than 3 g/dl) and a normal percentage of plasma cells in his bone marrow aspiration sample were discovered. Due to the patient's IgA deficiency, intravenous immunoglobulin (IVIG) could not be used to treat his SM; due to his positive tuberculin skin test (25 mm) and history of gastritis, anti-tumor necrosis factor alpha and non-steroid anti-inflammatory drugs were also withheld. The patient received a drug regimen of cyclosporine (3mg/kg/day) and high-dose prednisolone (0.5mg/kg/day) which successfully controlled both his SM and AS disorders. In this paper, we report a previously unreported case of SM-associated gammopathy and AS. We also show the efficacy of cyclosporine and high-dose prednisolone in the treatment of both of these conditions.

Keywords: ankylosing spondylitis, cyclosporine, prednisolone, scleromyxedema.

Introduction

Scleromyxedema (SM) is a rare chronic disorder characterized by skin stiffness and waxy maculopapular lesions. Histologists suggested a classic triad for the diagnosis of this disorder: dermal mucin deposition, fibroblast hyperplasia, and fibrosis [1]. Serum paraproteinemia is a condition present in 83% of cases, mainly with the immunoglobulin G (IgG) lambda subtype [2]. Extra-cutaneous manifestations develop among a small number of patients in the form of dysphagia and various myopathies. SM can involve both the upper and lower esophagus with symptoms ranging from aspiration to dysphagia and dyspepsia. The muscles can also be involved with inflammatory or non-inflammatory myopathies; this has a prevalence of approximately 20% [3]. Previous case reports have demonstrated an association between SM and other autoimmune disorders such as systemic lupus erythematosus (SLE), seronegative arthritis, and autoimmune polyendocrine syndrome (APS) type II.

In this article we report a patient with skin stiffness and inflammatory back pain. The patient was diagnosed with SM based on skin histopathology reports and with ankylosing spondylitis (AS) from positive physical, radiographic, and serologic findings. We also report the challenges faced in treating this patient, who responded dramatically to cyclosporine and high-dose prednisolone.

Case presentation

A 52-year-old man with skin stiffness was referred to our outpatient systemic sclerosis clinic. Symptoms had initially begun 6 months earlier in the torso and proximal limbs and had rapidly progressed to the distal segments. Skin stiffness was not associated with any new onset signs or symptoms of systemic sclerosis (including Raynaud's phenomenon). The patient reported a neglected inflammatory bilateral buttock pain from 20 years before which had not been appropriately treated. The patient did not regularly use any particular medication. He had a positive history of *Helicobacter pylori* (*H. pylori*) negative chronic gastritis, which had been diagnosed 2 years earlier by upper endoscopy. He did not report any current or former history of smoking,

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nor did he report any specific positive family history.

Upon examination, pulse and respiratory rates were 84 and 18 per minute, respectively, and blood pressure was 130/85 mmHg. Dermatologic examination revealed skin stiffness with doughnut signs over the proximal interphalangeal joints of both hands (Fig. 1B). Since there is no specific score to evaluate skin stiffness and its changes in SM, the modified Rodnan skin score (mRSS) was used with this patient and found to be 35, with the highest scores in the torso and proximal parts. Upon musculoskeletal examination, dorsal kyphosis and increased lumbar and cervical lordosis was found (Fig. 1A). The Schober's test result was 3 cm with a mean tragus-to-wall of 18 cm, a mean neck rotation of 35 degrees, maximal intermalleolar distance of 115 cm, and a mean lateral flexion of 13 cm with a Bath Ankylosing Spondylitis Metrologic Index (BASMI) of 5. The shoulders and hips were limited in all directions, which seemed to be related to the patient's severe skin stiffness. Other examinations were unremarkable.

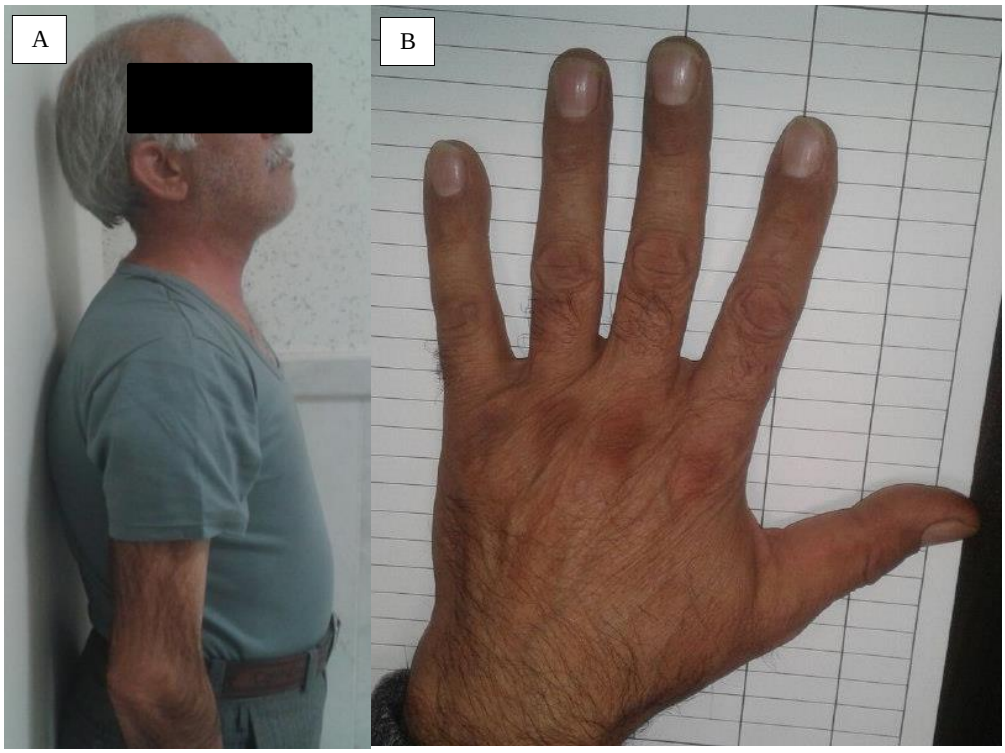

Fig. 1. A) Lateral image of the patients, showing severe dorsal kyphosis in addition to lumbar and cervical lordosis. B) A typical "doughnut sign" is evident over the proximal interphalanges joints, in which the skin rim is elevated and the central part is depressed.

Laboratory data showed normal results in the patient's complete blood count, repeated fasting blood sugar (FBS), postprandial blood sugar, hemoglobin A1C, lipid profile, serum creatinine, electrolytes concentration, liver function tests, and urine analysis. The thyroid stimulating hormone, parathyroid hormone, and 25 hydroxyvitamin D levels were all within normal range. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were 30 mm per hour and 14 mg/dl (upper limit of normal 6 mg/dl), respectively. Serum protein electrophoresis (SPE) indicated the albumin concentration was 3.7 g/dl (4.0-4.8) and the gamma protein concentration was 1.4 g/dl (0.8-1.4) with M protein. In serum protein immunotyping, monoclonal gammopathy of immunoglobulin (Ig) G/kappa was detected. Fluorescence anti-nuclear antibody (FANA), anti-topoisomerase I antibody, anti-centromere antibody, and anti-RNA polymerase III antibody were all negative. The patient was positive for human leukocyte antigene-B27 (HLA-B27). He also had IgA deficiency with a level of 13 mg/ml (70-200) and normal IgG and IgM levels. Viral markers were negative, but he had a positive tuberculin skin test (TST) of 25 mm. Muscle enzymes were normal.

Skin biopsy was performed and showed a thickened dermis with swollen collagen bundles extending to the deep dermis and subcutaneous fat (Fig. 2A). There was focal mucin deposition among the collagen bundles with hyperplasia of the fibroblast cells (Fig. 2B). Mild infiltration of lymphocytes in the upper dermis was also

seen (Fig. 2C). The overlying dermis was atrophic with basal pigmentation. Mucin deposition was confirmed by Periodic acid–Schiff (PAS) stain. The skin biopsy was compatible with a diagnosis of SM. To investigate the probable malignant origin of M protein in SPE, bone marrow aspiration was done, and the results showed normocellular erythroid hyperplasia with a normal percentage of plasma cells. Grade IV bilateral sacroilitis was observed in plain radiography, which was in favor of a long-standing non-treated AS (Fig. 3A). Confusingly, the lumbar and thoracic spine radiography did not show syndesmophytes or bamboo spine (Fig. 3B, 3C). Radiography of the shoulders and hips was unremarkable. The chest X-ray and lung high-resolution computed tomography (HRCT) were normal despite the positive TST. Consequently, a diagnosis of SM and AS was made.

According to the literature review, intravenous immunoglobulin (IVIG) is the drug of choice for SM treatment; therefore, we checked the patient's serum IgA level to eliminate the chance of infusion anaphylaxis reaction. Due to the patient's IgA deficiency, this treatment was not begun [4, 5]. Non-steroidal anti-inflammatory drugs (NSAIDs) were not used to treat the patient's AS because of the patient's history of intolerance resulting from his chronic *H. pylori* negative gastritis [6]. Anti-tumor necrosis factor (anti-TNF) agents were also eschewed based on the patient's positive TST and lack of evidence in SM treatment [7]. In addition, the efficacy of high-dose corticosteroids and cyclosporine has previously been shown in several case reports [8-10]. Therefore, high-dose prednisolone (0.5 mg/kg/day), cyclosporine (3 mg/kg/day), alendronate 70 mg/week, isoniazid 300 mg/day, and pyridoxine (10 mg/day) were started. After 6 months of follow up, the BASMI diminished to 3.3 and mRSS diminished to 21; this result was evaluated as a positive response to treatment. Cyclosporine was tolerated without any evidence of nephrotoxicity or electrolyte disturbance, and prednisolone was gradually tapered to 15 mg per day.

Discussion

SM has previously been reported in association with other rheumatic diseases, but never with AS. In this case report, we have shown the efficacy of cyclosporine and high-dose prednisolone in the treatment of both of these conditions.

The association of SM with myopathies has also been previously reported. David et al. presented a case of myopathy in an SM patient and reviewed the clinical manifestations of nine similar cases [11]. The patient showed symmetrically reduced proximal muscle forces with elevated serum levels of specific muscle enzymes. Electromyography (EMG) findings were compatible with inflammatory myositis, and muscle biopsies revealed diffuse scattered degeneration of both types of fibers in addition to diffuse vacuolar degeneration, acute and chronic inflammatory cells with mild fibrosis.

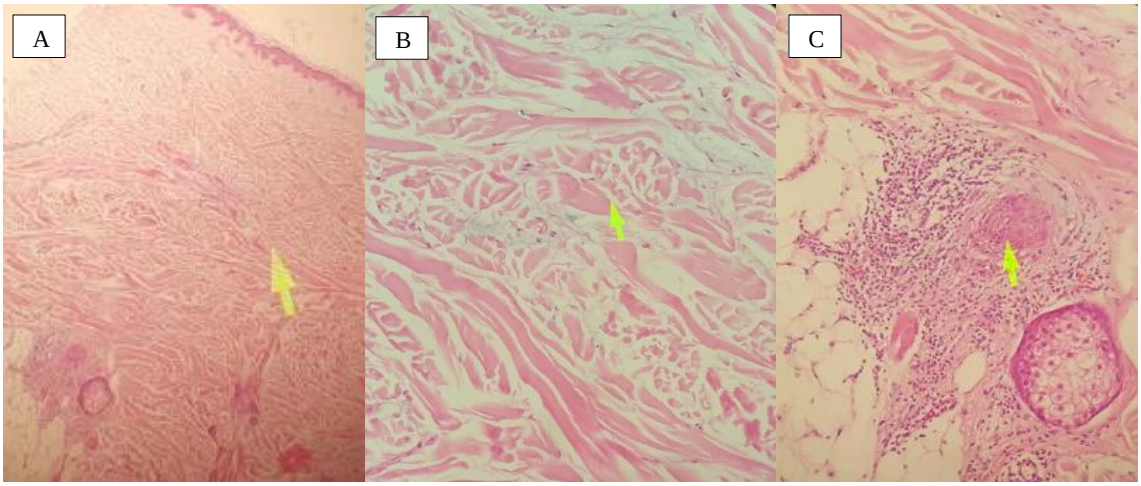

Fig. 2. Patient skin biopsy samples. A. Low magnification image showing thickened swollen collagen bundles extending to the deep dermis, as well as subcutaneous fat and normal epithelium. B. High magnification image showing thick collagen bundles separated by semi-clear spaces. Fibroblast cells are clearly seen in the sample with elongated nuclei in the upper right of the figure. C. High magnification image showing infiltration of the mononuclear inflammatory cells and proliferation of fibroblast cells (upper right). The yellow arrows do not point to any specific feature, and are related to the microscope.

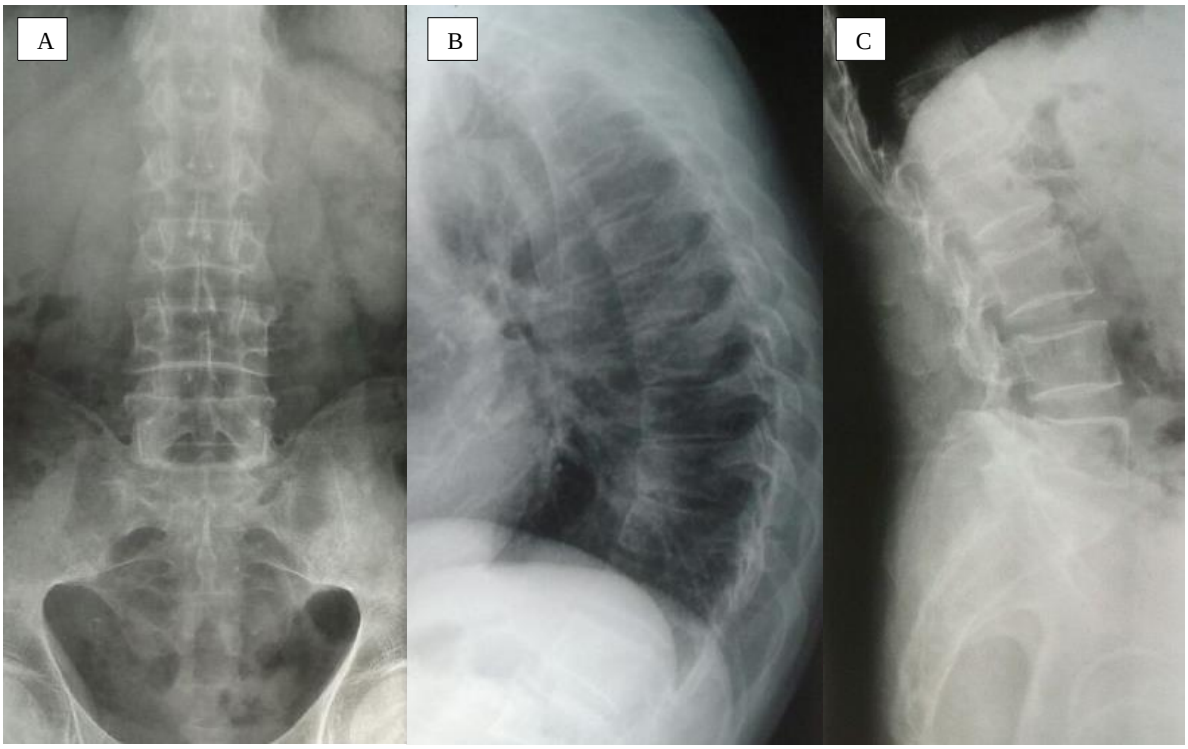

Fig. 3. A) Antero-posterior view of sacroiliac joint which shows complete bilateral fusion (sacroilitis grade 4), B) Lateral view of thoracic spine with severe kyphosis and a few anterior syndesmophytes, C) Lateral view of lumbar spine

The vacuolization was also confirmed by electron microscopy examinations. According to their review of literature, all previous cases had proximal or distal dysphagia, myopathy patterns in EMG, and muscle enzyme elevation. Based on muscle biopsy results, half of the muscles had inflammatory myopathy. In another study conducted on 19 patients with SM in the rheumatology department of Mayo Clinic, dysphagia was reported in 8 cases, proximal muscle weakness in 5 cases, and inflammatory myopathy in 3 cases [3]. Another report also refers to the association of SM with seronegative polyarthritis and myopathy [12].

The association of SM with lupus erythematosus (systemic and cutaneous types) has previously been reported. Sonntag et al. reported two cases of SM and subacute cutaneous LE (SCLE), in which SM had appeared years after SCLE, having possibly been induced by exposure to sunlight [13]. They also reviewed previous cases of SLE associated with SM; they found that the disease was significantly more common among men, with a male to female ratio of 18:13, as opposed to SLE which classically has a ratio of 1:9. Another recently published case study reported a patient with SM and APS type II defined by Addison's disease, autoimmune thyroiditis, and type I diabetes [14].

The association of SM and malignancies has previously been reported. Chan *et al.* reported a case of thymic carcinoma with SM. They also reviewed previous cases in which SM was the para-neoplastic manifestation. In the present case, the history, physical examination, laboratory examination, chest HRCT, and bone marrow aspiration did not show any evidence of malignancy. The patient was followed for 6 months after treatment and did not develop any signs or symptoms indicating occult cancer.

Due to the high prevalence of AS, there are many case reports and case series that report its association with other autoimmune/autoinflammatory disorders; therefore, we will not explain it here in detail. However, the association of AS and SM has not been previously reported. The serum level of IgA is highly challenging and different in AS patients compared to the normal population; we encountered patients presenting with both elevated and deficient IgA serum levels. Cowling *et al.* showed that the serum IgA level is elevated among patients with active disease, and this level is strongly associated with the patient's ESR level. However, this is not true for IgG and IgE, which reinforce the effect of microbial activities in AS [15]. Surprisingly, IgA deficiency has also been reported in AS patients with poorer prognoses [16, 17]. Therefore,

it seems that the selective IgA deficiency in our patient is probably associated with AS.

Our patient was a case of SM in a long-standing non-treated auto-inflammatory disease. Based on the patient's response to treatment, it seems that cyclosporine and high-dose prednisolone can be candidates for the treatment of SM. Surprisingly, this patient showed a significant change in BASMI following the administration of high-dose prednisolone. To the best of our knowledge, this is the first case report of SM and AS association.

Conflicts of interest

The authors declare no conflicts of interest.

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