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Research Article

Scleroderma Associated with Monoclonal Gammopathy of Undetermined Significance

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Abstract

A 53-year-old female presented with itchiness in her back. She has a 5 years history of tightness of the skin on her face, neck, and torso bilaterally. She did not have other symptoms suggestive of systemic sclerosis (scleroderma), and her rheumatologic workup was negative. Skin biopsy showed increased dermal mucin confirming a diagnosis of scleredema. Further workup with serum protein electrophoresis (SPEP) showed an M-spike, confirming the diagnosis of monoclonal gammopathy of undetermined significance MGUS as the underlying pathology.

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1. Introduction

This is a case of a rare connective tissue disorder characterized by the accumulation of collagen and aminoglycans in the dermis (1). The skin manifestations mimic scleroderma (systemic sclerosis); however, scleredema spares hands and feet (2). Scleredema can be associated with paraproteinemia and diabetes (3–5) and requires specialist investigation and management. Gammopathies can be an underlying cause of scleredema; therefore, early diagnosis can aid in prompt treatment.

In this case report, we present an example of the importance of a multidisciplinary approach to diagnose patients with rare connective tissue diseases. Rheumatologists should involve dermatologists and other specialists in diagnosing cases that present with subtle symptoms like skin tightness/itchiness even in the setting of seronegativity.

For instance, this patient's condition was initially confused with scleroderma (systemic sclerosis). In addition, this case report presents a successful diagnosis of MGUS as a result of a meticulous search for an underlying cause of scleredema. It is worth mentioning that this patient has a family history of MGUS and multiple myeloma (MM) in her father and mother, which might point to a familial link to her condition.

2. Case Presentation

A 53-year-old female presented to a dermatologist with itching in the left back area. She was nondiabetic and did not have any chronic conditions. Relevant to this history, the patient stated that her skin had been changing for the past 5 years. She noticed progressive tightness of the skin of her face, neck, and arms. For a while, she thought it was "tight muscles or fascia." It worsened over the years and she also noticed involvement of her torso and legs. Three years prior to her presentation she went to the emergency room for a separate issue (choked on a fishbone), where physician suspected that she had scleroderma. Therefore, she was referred to a rheumatologist for further workup.

Initially, based on her skin examination, the rheumatologist suspected scleroderma. However, she tested negative for dsDNA, Smith, ANA IgG, SSB, SCL, centromere, RNA polymerase III, Jo 1, CCP, ANA by hep 2, U1 RNP, RNP 70, Ro 52, Ro 60, SSB, rheumatoid factor, anticardiolipin IgM/IgG, beta-2 glycoprotein IgM/IgG, Antithyroglobulin IgG, and thyroid peroxidase IgG. Therefore, the rheumatologist informed the patient that her blood tests are negative for scleroderma.

Eventually, she visited the dermatologist for skin screening and itchiness on her back. She reported night sweats due to menopause but denied any weight changes, fever, or chills. She also denied dry eyes, dry mouth, joint pain, muscle aches, migraine headaches, changes in vision, and any history of blood clots or miscarriages. She described a history of intermittent acid reflux aggravated by certain foods and relieved by calcium carbonate (antacid). On examination, she was a well-appearing Caucasian female, with infiltrative thickening of the skin on the torso, neck, and arms (Figure **1**). Her hands, fingers, and feet are spared. Upon inquiry, she denied skin infection before these skin changes. The examination was negative for malar rash, parotid enlargement, Raynaud's phenomenon, sclerodactyly, telangiectasia, calcinosis, nasal and digital ulcerations, alopecia, nail changes, genital ulcers, or joint swelling. The oropharynx was clear, without ulcerations, and the mucous membranes were moist without oral telangiectasias. There was no palpable lymphadenopathy. No tenderness

or synovitis was noted on the examination of the metacarpophalangeal, proximal-interphalangeal, distal-interphalangeal, metatarsal-phalangeal joints, ankles, and wrists bilaterally. She was able to make tight fists bilaterally. She had preserved range of motion in both shoulders, wrists, and elbows. Based on the distribution of skin involvement, the dermatologist suspected scleredema rather than scleroderma. A 4mm punch biopsy on the left mid-forearm was performed to establish the diagnosis (Figure **2**). The biopsy results showed increased dermal mucin, and a sparse perivascular chronic inflammatory infiltrate. The overlying epidermis appeared uninvolved with orthokeratosis. Colloidal iron stain highlighted the dermal mucin. Periodic acid Schiff with diastase (PAS-D) stain was negative for fungal hyphae. CD34 immunostaining showed retained expression within the dermis. These distinctive histological features were consistent with scleredema.

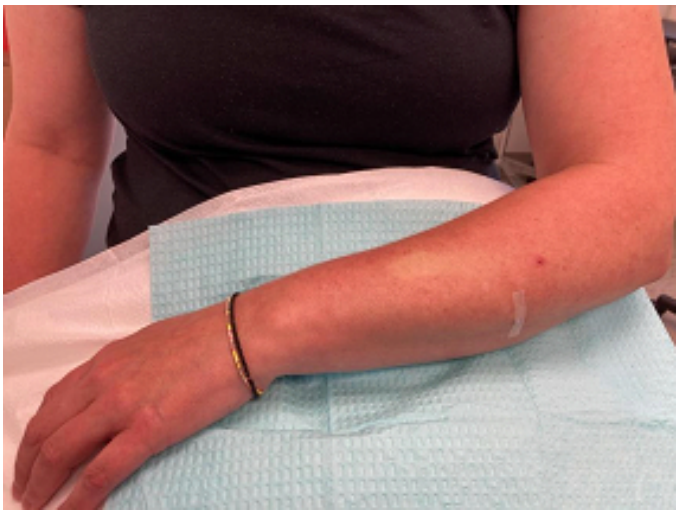

Figure 1: Left-arm skin thickness.

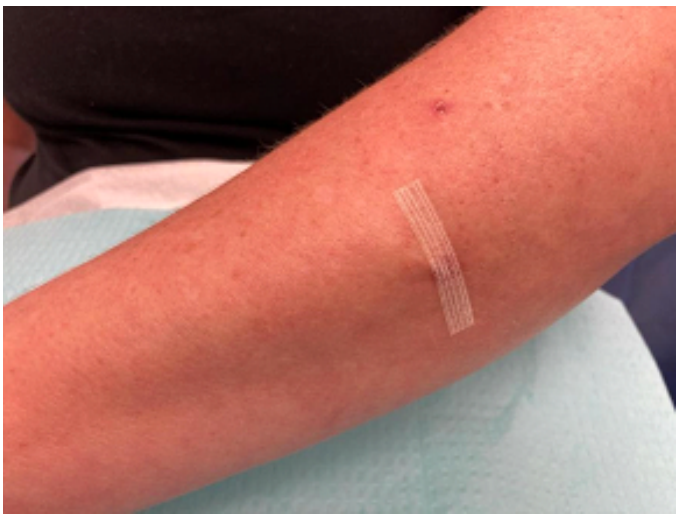

Figure 2: Left-arm punch biopsy site.

This diagnosis prompted further workup by the primary care physician for possible underlying and associated conditions. Her investigations were negative for diabetes, thyroid disease, other collagen storage diseases, and liver disease. However, the workup revealed an M-spike of 0.6 on SPEP, which led to the diagnosis of MGUS. Therefore, a diagnosis of scleredema secondary to monoclonal gammopathy of undetermined significance was made. Interestingly, the patient has a strong family history of MGUS and MM with both her mother and father diagnosed with MM. Therefore, this patient also represents a case of inherited susceptibility to MM. The patient underwent further workup with a hematologist which confirmed IgG Kappa MGUS. The studies showed a free kappa light chain of 36.6, free lambda chain of 11.1 with a ratio of 3.3. Her immunoglobulin levels were - IgA 41, IgG 1268, and IgM 81. These results confirmed that she had a low risk (IgG subtype, serum M protein <1.5g/dl with FLC ratio <8) with no myeloma-defining events at this time. Her MGUS was classified as low-risk according to the Mayo Clinic Criteria (6). She was also evaluated for MM and was found to have a low-risk IgG-subtype MGUS with only a 5-7% chance of evolving to malignant plasma cell dyscrasia at 20 years.

Differential diagnosis**:** Scleroderma was the most important differential diagnosis for this patient. Initially, she was suspected of having scleroderma rather than scleredema. Contrary to scleroderma, scleredema spares the distal extremities including hands, fingers, and feet (7–9).

Scleromyxedema, a mimicking condition, displays a sclerodermiform papular eruption and histopathologic mucin deposition in the upper and mid dermis (2,10,11,12). Unlike scleredema, it causes fibroblast proliferation and fibrosis (2). Similar to scleredema, scleromyxedema is associated with systemic disorders like paraproteinemia (usually Ig) (2,8,11) but not thyroid disease (2,8,10,12).

Treatment**:** Scleredema has been linked to monoclonal paraproteinemia (MGUS) and MM (5,8,13,14). About 25% of patients with scleredema are found to have paraproteinemias such as MGUS (most common), myeloma, and amyloidosis (5,8,13). The appropriate management for MGUS-related cases remain questionable with inconsistent outcomes. Treatments include immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), intravenous immunoglobulins (IVIG), and dermatologic treatments such as phototherapy and corticosteroids (4,15,16). It is unclear as to what is the appropriate treatment option for patients of scleredema secondary to MGUS, who would otherwise not require treatment given low-risk disease with no myeloma defining events (primary treatment for scleredema versus myeloma treatment). There are toxicities associated with myeloma

monotherapies, making this option less appealing, especially in this patient's case because she has a low risk of evolving to MM.

The patient in this case report had a normal range of motion of her joints and no significant limitations from her skin disease. Therefore, methotrexate and phototherapy were not

recommended. However, they can be considered in the future if required as per references (17).

Outcome and Follow-up: The patient in this case report had low-risk MGUS with a slight chance of ever evolving to MM. As such, given this unique case, she will undergo regular monitoring for paraproteinemia.

The patient follow-up plan comprises a multidisciplinary approach with a dermatologist, hematologist, and rheumatologist. She will be monitored for the evolution of MM. Like other patients with low-risk MGUS, this patient will be followed up with a periodic serum protein electrophoresis (6,9). It is performed at six months and subsequently every 2-3 years if the results remain steady and no symptoms point toward plasma cell malignancy (6).

Although the patient's skin involvement is quite extensive, it has not led to significant disability. She has good mobility in her shoulders. However, physical therapy was recommended to prevent future disability.

3. Discussion

Cutaneous mucinosis, a group of connective tissue disorders, is characterized by increased proliferation and deposition of acid glycosaminoglycan (mainly hyaluronic acid) in the upper and mid reticular dermis (2,18). It does not involve the epidermis, deep dermis, or subcutis (1,3).

Primary mucinosis, also known as degenerative or inflammatory mucinosis, is characterized by increased deposition of mucin as the main histologic feature (8,18). It is divided into two groups, dermal and follicular types (8,18). The dermal type comprises, among others, scleredema, dysthyroid mucinosis, papular-nodular mucinosis associated with lupus erythematosus, and cutaneous mucinosis of infancy (8,18). The follicular type can be found in follicular mucinosis (pinkus) and urticaria-like follicular mucinosis (8,18).

In secondary mucinosis, mucin deposition is not the main finding (18). It involves conditions like mycosis fungoides, spongiotic dermatitis, basal cell carcinoma, squamous cell carcinoma, warts, scleroderma, lupus erythematosus, dermatomyositis, granuloma

annulare, acanthosis nigricans, lymphoma, lupus erythematosus, hypertrophic lichen planus, lichen striatus and sarcoidosis (18).

Scleredema presents with thickening and tightening of the skin (19). The initial course is characterized by the involvement of the skin in the neck and then it extends over the torso and arms symmetrically (19). Contrary to scleroderma, scleredema spares the distal extremities, including hands and feet, and causes non-pitting edema which can be associated with erythema and peau d'orange (2). Initially, the skin looks doughy and progresses over time into a woody induration (5,8).

Scleredema is classified into three groups. Type I accounts for the majority of the cases (55%). It is acute, develops after a febrile infection, is usually caused by *Streptococcus pyogenes* or viral infection and self-resolves in weeks to months (3,4). Type II is a slowly progressive disorder associated with paraproteinemia (25% of cases) (2). Finally, type III is called scleredema adultorum of Buschke or diabeticorum and it occurs in patients with diabetes (2,3,17,19,20, 21).

The pathophysiology of scleredema is not well understood. However, it is known that serum factors like immunoglobulins and cytokines increase the synthesis of glycosaminoglycans (2,5,8,13,18,22). It is thought that the persistent stimulation of the collagen by antigens from scleredema produces monoclonal immunoglobulins (5). However, no immunoglobulins are found in negative direct immunofluorescence of the involved skin (5,21). A negative ANA result will support the differentiation of diagnoses such as scleredema, scleromyxedema, and systemic sclerosis (1,3,8).

The onset of scleredema might not be noticed by patients and it will be identified by treating physicians (17). The confirmation of the diagnosis of scleredema should be done by performing a tissue biopsy (4,5,20,23). Histopathologic findings include mucin deposits between collagen bundles in the dermis.

Monoclonal gammopathy of undetermined significance is an asymptomatic premalignant condition that can precede MM. The risk progression to MM is approximately 1% per year. (6,15). Some of the risk factors to develop MGUS include age, race, and hereditary factors (6,15). Individuals whose parents had MGUS are at a high risk of developing MGUS, especially, first-degree children (6,15).

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Ethical Considerations

Ethical clearance was obtained from the research ethical committee (REC), Faculty ofMedicine, Alneelain University. Written consent was taken from the patient.

Competing Interests

The authors declare that they have no competing interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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