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An unusual presentation of scleromyxedema as inflammatory myopathy

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Scleromyxedema is a rare cutaneous mucinosis with frequent extracutaneous manifestations. Myopathy in scleromyxedema is a poorly recognized syndrome among neurologists and can mimic idiopathic and connective tissue disease-associated inflammatory myopathy. Diagnosis is suspected by the characterization of the skin lesions and clinched by skin and muscle biopsies. Here, we report a patient with scleromyxedema and myopathy with the characteristic histopathological feature of mucin deposition in skin biopsy. Her muscle biopsy showed a picture consistent with scleromyxedema myopathy with vacuolar and inflammatory changes. The association with paraproteinemia, propensity to life-threatening central nervous system disease and good response to intravenous immunoglobulin necessitate the accurate diagnosis of this condition.

Key words: scleromyxedema, monoclonal gammopathy, inflammatory myopathy, vacuolar myopathy, scleroderma

Abbreviations

IVIg: Intravenous immunoglobulin
MRC: Medical Research Council

Introduction

Scleromyxedema is a rare cutaneous mucinosis characterized by dermal mucin deposition and fibroblast proliferation. This disease commonly affects middle-aged people and shows no sex predilection (1). An increased production of mucin and hyaluronic acid in scleromyxedema is presumed to result from cytokine-mediated fibroblast stimulation, possibly from an abnormal plasma cell clone (2). The diagnosis is established by satisfying the criteria of (i) generalized papular and sclerodermoid eruption, (ii) mucin deposition, fibroblast proliferation, and fibrosis in skin histopathology, (iii) monoclonal gammopathy and (iv) absence of thyroid dysfunction (3).

Extracutaneous manifestations including nervous system involvement are frequent and potentially life-threatening. Neurological syndrome manifests as encephalopathy, neuropathies, stroke, seizures, acute psychosis or rarely coma ('dermato-neuro syndrome') (1). Myopathy and dysphagia are the other common presentations which are apparent in up to 50% patients (4, 5). These symptoms in combination with cutaneous lesions raise the alternate diagnostic possibilities of systemic sclerosis-associated myositis, dermatomyositis, and myxedema. The diagnosis of scleromyxedema can be missed in this setting owing to the rarity of the disease. Herein, we discuss the case of a lady who presented with dysphagia and myopathy with the typical skin lesions of scleromyxedema.

Case report

A 38-year-old woman presented with a two-year history of progressive symmetric proximal lower and upper limb weakness. She gradually developed dysphagia to solids, hypophonic nasal speech and neck weakness with severe weight loss. One year prior to the onset of the weakness, she had noted painless nodular skin lesions on her fingers, face and trunk with diffuse skin thickening for which she was seen by a dermatologist. She underwent skin biopsy and was prescribed topical treatment,

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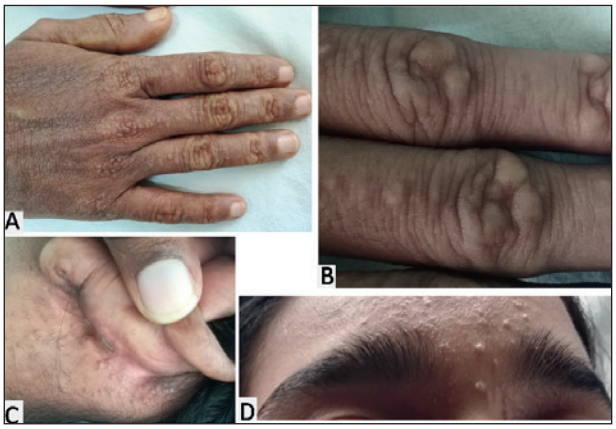

Figure 1. Indurated and hyperpigmented skin of dorsum of hand with multiple non-erythematous, closely-placed, dome-shaped, firm, papular and nodular lesions with a waxy appearance (A). The characteristic "doughnut sign" (B) with an elevated rim of thickened skin and central depression over the interphalangeal joints. Papular lesions involving the post-auricular region (C) and forehead (D).

but was then lost to follow up. At presentation to our center, she was ambulant but needed considerable help for rising and climbing.

On examination, she was emaciated and had induration of the skin of her hands, forearms, neck, upper trunk, and thighs. She had multiple non-erythematous, closely-placed, dome-shaped, papular and nodular waxy lesions over the dorsum of the hands, post-auricular region and between the eyebrows (Fig. 1). The mobility of the fingers was restricted suggesting sclerodactyly. There were no telangiectasias or calcinosis. Neurological examination showed symmetric palatal and tongue weakness with tongue atrophy. Symmetric weakness of neck flexors (Medical Research Council (MRC) scale 2/5), triceps (2/5), biceps (4/5), hip flexors (4/5) and quadriceps (3/5) was noted. Deep tendon reflexes and sensory examination were normal.

Serum creatinine phosphokinase was elevated (685 U/L, normal 26-192 U/L) and thyroid function tests were normal. Electromyography showed myopathic potentials with fibrillations and positive sharp waves. Peripheral nerve conduction study showed symmetrically reduced peroneal nerve compound muscle action potentials recording from extensor digitorum brevis muscles, with normal pickup from tibialis anterior muscles and inelicitable F waves from peroneal nerves. Rest of the motor and sensory conduction parameters were normal. Serum antinuclear antigen and extractable nuclear antigens were negative. Immunofixation electrophoresis showed monoclonal bands in IgG and lambda regions. Bone marrow biopsy ruled out plasma cell proliferation.

Skin biopsy from left forearm was reviewed which showed fibrosis of dermis with thick collagen bundles, loss and fragmentation of elastic fibers, and colloidal iron-positive acid mucin deposition (Fig. 2A-C). Muscle biopsy from left quadriceps showed loss of fascicular architecture with endomysial fibrosis and adipose tissue infiltration. Many myofibers exhibited large cytoplasmic vacuoles that failed to stain with periodic acid-Schiff, Oil red O and mucin stains (colloidal iron, Alcian blue and toluidine blue). However, acid mucin deposition was noted in the endomysial and perimysial connective tissue along with chronic inflammatory cell infiltrate (Fig. 2D-I). These histopathological features were consistent with vacuolar and inflammatory myopathy associated with scleromyxedema.

She was initiated on monthly intravenous immunoglobulin (IVIg) at 2 g/kg and oral prednisolone (1 mg/kg). After 3 months of therapy, she had nearly 50% improvement of muscle power with proximal limb power improving to MRC grade 4+ and neck flexion improving to grade 3. She had subjective improvement in swallowing, but no objective change was noted in the swallow assessment or palatal and tongue excursion. Skin lesions over the face and hands improved but did not completely disappear. She is currently maintained on oral thalidomide and prednisolone.

Discussion

We have described a rare case of scleromyxedema-associated myopathy which can present as a close differential diagnosis of idiopathic inflammatory myopathy. When the dominant presentation is extracutaneous, as in our patient, diagnostic labelling can be tenuous.

The characteristic skin lesions of scleromyxedema are non-pruritic, flat-topped, waxy, firm papules affecting the distal forearms, neck, and face, sparing the palm and mucous membranes. Typically, the skin is indurated with reduced mobility of jaw and extremities (6). The cutaneous lesions mimic localized scleroderma, systemic sclerosis, scleredema, nephrogenic systemic fibrosis, and lichen myxoedematosus. The diagnosis is clinched by skin biopsy which characteristically demonstrates dermal mucin accumulation, increased collagen deposition, and fibroblast proliferation (7).

The diagnosis becomes challenging when the dominant presentation is proximal limb-girdle and bulbar weakness as in our patient. In the absence of skin lesions, the diagnostic considerations would include myopathies such as oculopharyngeal myopathy, myotonic dystrophy and inflammatory myopathy, neuromuscular junction disorders and anterior horn cell disease (8). Skin lesions would prompt the consideration of systemic sclerosis as-

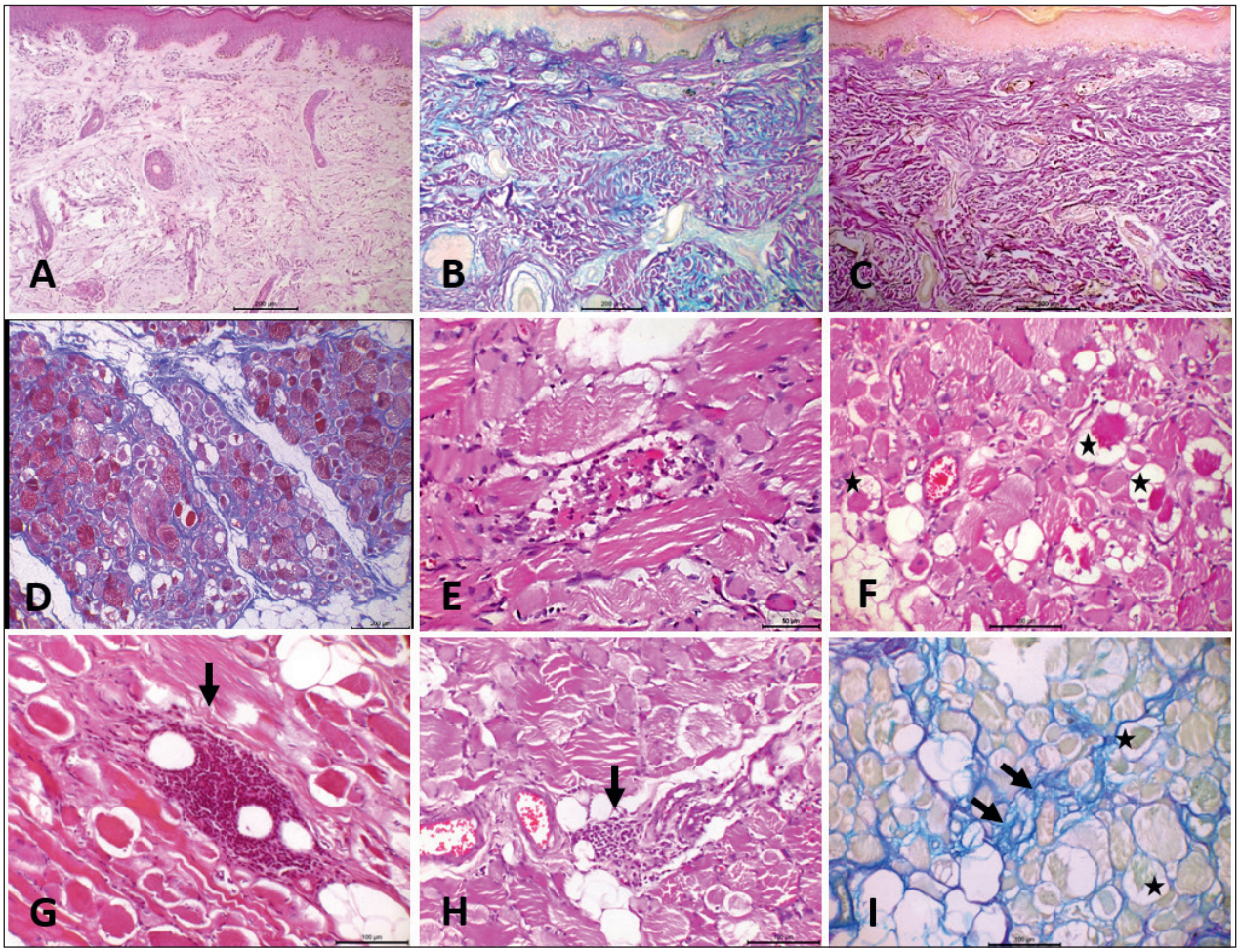

Figure 2. Skin biopsy shows dermal fibrosis with thick collagen bundles (A) separated by acid mucin (B) and associated with loss and fragmentation of elastic fibres (C). Left quadriceps muscle biopsy shows myopathic features like endomysial fibrosis (D), rounded fibers and myophagocytosis (E) with presence of intracytoplasmic vacuoles (F, *). In addition, focal endomysial (G, arrow) and perimysial (H, arrow) lymphocytic infiltration is also evident. Colloidal iron stain shows interstitial acid mucin deposition (I, arrow) without highlighting any vacuoles in myofibres (I, *). [A,E,F,G,H: Hematoxylin and Eosin; B,I: Colloidal iron; C: Verhoff van Gieson; D: Masson's trichrome. Magnification = Scale Bar A-D:200µm; F-I:100µm; E:50µm].

sociated myositis and dermatomyositis (9). The diagnosis in this situation was clinched by the accurate characterization of the skin lesions. The distribution of skin lesions in the mid-back and posterior auricular region differentiates scleromyxedema from scleroderma (5). The lesions also lack the distinctive distribution, erythema, and photosensitivity of dermatomyositis rash (4). In scleromyxedema, dysphagia results from oesophageal hypomotility and hoarseness (9) and recurrent aspiration from decreased laryngeal and vocal cord mobility (10).

Muscle pathology in scleromyxedema myopathy commonly reveals vacuolar degeneration of myofibres (11) and inflammatory myopathy (12) either in isolation or in combination (4). Other associated findings include varying degree of myophagocytosis, necrosis, regeneration, fiber splitting and internalization of nuclei. Despite the myofibres exhibiting large vacuoles, it is a rarity to demonstrate mucin deposition in skeletal muscle (11). The absence of deposits inside vacuoles has been reported in dermatomyositis, sarcotubular myopathy and scleromyxedema associated myopathy (4).

The treatment for scleromyxedema is impeded by the lack of clarity regarding the pathogenesis. The two successful modalities include immunotherapy and treatment directed against the paraproteinemia. They provide symptom control and limit progression, but the disease tends to relapse on cessation of therapy. The treatment of choice for cutaneous and extracutaneous disease is high

dose IVIg (6, 13) which usually provides excellent improvement. Long-term therapy is often required to sustain remission.

Second line therapy includes thalidomide with corticosteroids, but the response to steroid is usually partial (1). In severe and refractory cases, autologous hematopoietic stem cell transplantation, bortezomib, and melphalan have been tried (13). Mortality results from severe extracutaneous disease such as dermato-neuro syndrome, mucinous cardiomyopathy, and hematological malignancy (1).

In conclusion, scleromyxedema-associated myopathy is a rare disease which can masquerade as idiopathic and connective tissue disease-associated inflammatory myopathies. The clinical characterization of the skin lesions is key in suspecting the diagnosis. Though aggressive therapy provides disease control, the prognosis remains guarded due to the systemic complications and high relapse rate.

Conflict of interest

The Authors declare to have no conflict of interest.

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