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Case Report

Therapy resistant idiopathic scleredema: an underlying pathology not always present

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Abstract

Scleredema is a rare connective tissue disorder of unknown pathogenesis. Three types of scleredema have been described, based on its association with postinfection, monoclonal gammopathy and diabetes mellitus. We report herein a case of scleredema which the diagnosis didn't get specified. The patient was followed regularly for 13 years and did not respond to various combinations of immunosuppressants and psoralen plus ultraviolet A therapy. Treatment of scleredema is quite difficult and of limited success. At present, there is no proved treatment for this disease.

Keywords: Scleredema, methotrexate, PUVA

Introduction

Scleredema is a rare condition of unknown pathogenesis. It is characterized by diffuse, symmetric, non-pitting edema and thickening of the skin. Three types of scleredema have been described; infection, paraprotein and diabetes related types (1, 2). Hereby we present a patient with a 13-year history of scleredema, yet with no identified type, who did not respond to various immunosuppressants and psoralen plus ultraviolet A (PUVA) therapy.

Case Presentation

A 21-year-old man was admitted to the hospital with only one-week history of thickening of the skin of face, neck, shoulders, upper arms and upper back in 2001. He had no history of infection or underlying illness before symptoms.

Physical examination showed woody, nonpitting, hard induration of the skin involving neck, shoulders, upper arms, upper part of his back and face. Other systemic examination was normal. The full blood count, serum fasting glucose levels, serum protein electrophoresis and common immunological tests were within normal limits. The skin biopsy from the medial side of the right forearm revealed perivascular lymphocytic infiltration and perifollicular fibrosis with no evidence of deposition in the dermis. Systemic sclerosis was excluded with normal manometric test of the esophagus, pulmonary functioning tests with diffusing capacity of the lungs for carbon monoxide (DLCO), echocardiographic tests, chest X-ray. According to clinical and laboratory findings he was diagnosed as scleredema. Systemic corticosteroids, D-penicillamine, methotrexate, hydroxychloroquine, colchicine therapies were given during follow up. Informed consent form was filled before the treatment.

In 2011, after 10 years from his first admission, he was hospitalized to evaluate current clinical condition. Under immunosuppressive treatment his skin involvement found to be unchanged. He was re-evaluated for the presence of systemic connective tissue diseases, diabetes mellitus and monoclonal gammopathy. No abnormality was found after extensive investigation including high-resolution computed tomography (HRCT) imaging of the lungs. Skin biopsy from adjacent to left scapula repeated after 10 years showed fibrosis around skin appendices and enlarged collagen bundles. According to the results he was again diagnosed as scleredema. Because of no change in skin involvement under immunosuppressive treatment, he underwent and well-tolerated PUVA radiation therapy between September and December 2011. There wasn't sufficient response to this therapy. With a 10-year history, perhaps the disease wasn't in active period anymore and that might be the reason of poor response.

In January 2012, methotrexate was again started because he complained of skin thickening getting worse, although clinical examination and laboratory tests showed no difference.

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In his last visit in June 2014, physical examination remained basically the same, the full blood count, serum chemistry profiles (including fasting glucose levels, serum protein electrophoresis, and immunoglobulin studies), common immunological tests, pulmonary functioning tests, and echocardiographic tests were still within normal limits. Although we planned to make a bone marrow aspiration and biopsy in order to completely exclude paraproteinemia, the patient didn't accept.

After 13 years of follow up, the etiology didn't get specified. In 2014, the patient was not diabetic. He did not have a hematologic disease. He had no complication due to scleredema.

Discussion

Scleredema is characterized by diffuse, symmetric, non-pitting edema and thickening of the skin. It typically begins on the neck and spreads to the shoulders, upper part of the trunk and sometimes the face. The pathogenesis is not known, although the increased expression of type 1 collagen-producing fibroblasts in the skin of affected individuals has been demonstrated. The disease occurs at all ages and the female to male ratio is about 2:1 (1). However, in patients associated with diabetes, it occurs predominantly in men (1, 3).

Three types of scleredema have been described; Type 1 is the classic type, associated with febrile illness, usually streptococcal infections. Other infections related with scleredema include influenza, measles, mumps, chickenpox, and cytomegalovirus. Most cases resolve completely in several months to two years. Approximately half of scleredema patients match type 1 (1, 2). Type 2 has a slow progression of symptoms with no apparent underlying illness. These patients have increased risk of monoclonal gammopathy or multiple myeloma. One-fourth of scleredema cases match Type 2 (1-3). Type 3 scleredema is associated with insulin-dependent diabetes mellitus and makes up about one-fifth of the patients (1, 3, 4). Third type tends to have a slowly progressive, nonresolving course. Our case was not Type 1 or Type 3. He didn't have a hematologic disease yet so we couldn't diagnosed him as Type 2 scleredema as well. Dziadzio et al. (5) showed that median interval between the diagnosis of scleredema and the detection of paraprotein was 2.5 to 6.9 years. Although the observation period for our patient isn't short, we will continue to follow him with yearly for potential progression to gammopathy.

Eosinophilic fasciitis, scleroderma, scleromyxedema, amyloidosis, lymphedema, cellulitis, dermatomyositis and other forms of edema and mucin deposition which should be considered in the differential diagnosis were excluded in our case.

Scleredema is rather a benign disease as was the case with our patient. Limited range of motion due to skin thickening is the main complication. Others such as restrictive lung disease, cardiac dysfunction, dysarthria, dysphagia, skin infections, and poor wound healing are rarely seen.

Biopsy is not always necessary for the diagnosis of scleredema (6). Biopsy of skin shows normal epidermis and no inflammation in dermis. The dermis gets thickened; the collagen bundles appear swollen and are characteristically separated from each other by wide spaces. The subcutaneous tissue is also involved with fat being replaced by coarse collagen bundles. Our case showed similar biopsy results with fibrosis around skin appendices and enlarged collagen bundles which on two were performed on 2001 and 2011.

There is no consensual treatment for scleredema (6). Because the disease is self-limited in type 1, therapy is not necessary. In patients with monoclonal gammopathy or multiple myeloma, the disease can resolve with the treatment of the underlying disease. Some type 3 patients appear to improve with better glycemic control. Numerous other therapies including cyclosporin, methotrexate, high-dose penicillin, corticosteroids, prostaglandin E1, D-penicillamine, intralesional hyaluronidase, systemic photochemotherapy with PUVA, bath-PUVA, UVA-1 phototherapy, electron-beam radiotherapy, and extracorporeal photopheresis have been tried in case reports or small case series which ended with limited effect (1, 2, 6-10). Prognosis is largely dependent on the underlying etiology. In our case, the patient was given D-penicillamine, methotrexate, hydroxychloroquine, colchicine, and corticosteroid therapies and because of no change in skin involvement, he underwent PUVA therapy.

In summary, we report the case of a patient with a 13-year history of scleredema. He showed a slow progression and did not respond to immunosuppressive agents and PUVA therapy. Although there was no objective clinical evidence for active disease, methotrexate was again started because he complained of skin thickening getting worse and noted that he felt better under methotrexate therapy.

In conclusion, in literature scleredema has been reported with various infections, paraproteinemia or diabetes mellitus (1-4). Nevertheless this pathology may also be idiopathic, as in our case. However, it should be kept in mind that monoclonal hypergammaglobulinemia may occur even years after the diagnosis of scleredema (3, 5), and follow up should go on indefinitely. On the other hand, scleredema can be considered as a benign disease. Limitation in movement secondary to thickening of the skin is the main problem. Systemic involvement may occur rarely and has to be screened in order to prevent mortality and morbidity.

Treatment of scleredema is quite difficult and of limited success. At present, there is no proved treatment for this disease.

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