

Scleromyxoedema: Clinical Follow-up After Successful Treatment with High-dose Immunoglobulins Reveals Different Long-term Outcomes

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Scleromyxoedema is a rare skin disease characterized by generalized papular sclerodermoid eruptions. Patients typically show clusters of itching and lichenoid pinpoint papules on the hands, forearms, neck, face, upper trunk and thighs (1, 2). The scleroderma-like diffuse thickening of the skin with hyperpigmentation leads to sclerodactyly and reduced mobility of the mouth and joints (3). In addition to cutaneous signs, extracutaneous involvement, such as arthralgia, myalgia, gastro-intestinal problems (dysphagia, reflux) and lung, renal and neurological involvements are known (2, 4). Histological examination reveals diffuse depositions of mucin in the papillary and mid-reticular dermis, and increased numbers of irregular fibroblasts and inflammatory cells (3, 5). Scleromyxoedema responds poorly to conventional immunosuppressive therapy and various therapeutic options, including corticosteroids, retinoids, cyclosporine, cyclophosphamide, thalidomide, melphalan, extracorporeal photopheresis (ECP), plasmapheresis, psoralen plus ultraviolet A (PUVA) and stem cell transplantation have been described (4, 6, 7). High-dose intravenous immunoglobulins (IVIG) have been shown to treat scleromyxoedema effectively. We report here the

clinical follow-up on 3 patients with scleromyxoedema after successful IVIG therapy.

CASE REPORT

The patients first presented in our immunological outpatients department between March 2005 and April 2008. They were diagnosed with scleromyxoedema in June 2000 (patient 1), June 1999 (patient 2) and November 1996 (patient 3), at the age of 49, 57 and 59 years, respectively. All patients presented with similar skin and systemic symptoms.

Patient 1 initially noticed an erythematous induration and a papular eruption on her forehead. In due course these lesions extended to involve her face, neck, shoulders, forearms and legs. She developed problems in opening her mouth fully as well as in moving her hands and wrists (Fig. 1a). Patient 2 presented with massive skin-coloured to erythematous, monomorphic, tiny and nearly confluent papular eruptions over the whole body, and several almost pea-sized erythematous nodules on her forehead. She also had huge wrinkles on her bottom and a strongly indurated, thickened waxy skin, especially on her face, fingers and toes, which resulted in limited mobility of the affected joints. As in patient 1, her mouth opening was limited. Furthermore, she reported breathing problems and reduced physical fitness. Patient 3 also presented with reduced physical fitness, limited mobility of her face, arms and hands, and erythematous eruptions that had progressed over several years. In addition, she reported muscle ache and hair loss.

Skin biopsies were performed and revealed the typical histological findings of scleromyxoedema in all 3 patients. Laboratory examinations, including full blood count, blood morphology and thyroid functions, were normal, serum immunoelectrophoresis revealed an IgG-lambda paraproteinaemia in all three cases. Since all 3 patients had received multiple previous treatments, including ECP, cyclophosphamide, melphalan, prednisolone, PUVA, UVA1 and thalidomide (Table I), without therapeutic effect, we decided to start IVIG therapy. The patients received IVIG at a dose of 2 g/kg bodyweight in 4-week intervals. After initiation of IVIG treatment, all 3 showed a noticeable improvement in skin symptoms after the first course of IVIG. They reported improved mobility of the joints and hands, as well as remarkable softening of the skin. During the course of IVIG therapy none of the patients experienced any severe side-effects.

There was a considerable improvement after the first cycle of IVIG treatment and a further decrease in symptoms was noticed during the following cycles. Since all patients responded well to IVIG therapy, treatment was discontinued after reaching complete response. This decision



Fig. 1. (a) This patient showed strong induration of the skin and lichenoid papular eruptions before initiation of intravenous immunoglobulin (IVIG) therapy. (b) Complete response after the first treatment period (43 cycles). (c) Recurrence of papular eruptions and skin induration after interruption of IVIG therapy for 8 months. (d) Softening of the skin and reduction of papular eruptions after re-initiation of IVIG therapy.

Table I. Patient characteristics

Pat. no./age (years)/sex	First diagnosis month/year	Pre-treatment	IVIG cycles <i>n</i>
1/60/F	06/2000	ECP, cyclophosphamide, melphalan + steroids, PUVA	59 in total, 43 during the first treatment period
2/70/F	06/1999	ECP, melphalan + steroids, PUVA, UVA ₁	39 in total, 26 during the first treatment period
3/75/F	11/1996	ECP, endoxane, melphalan, thalidomide	16 in total

IVIG: intravenous immunoglobulins; ECP: extracorporeal photopheresis; PUVA: psoralen plus ultraviolet A; UVA: ultraviolet A.

was based on several cases reporting no recurrence of disease activity after termination of IVIG therapy (4, 6, 8). Treatment was stopped after 43 cycles (patient 1), 26 cycles (patient 2) and 16 cycles (patient 3), respectively. After discontinuation of IVIG all patients underwent further clinical follow-up every 3 months.

One patient remained disease-free for 2 years until today. The other two patients experienced a relapse. The patients were stable for 5 or 8 months, respectively, after cessation of IVIG treatment, but then new clinical symptoms resembling the first appearance of disease occurred.

We decided to re-initiate IVIG therapy at an early stage of recurrent disease, and both patients responded well, showing rapid re-improvement of symptoms after the first cycle. To date, they are without any symptoms under continuous IVIG treatment.

DISCUSSION

Scleromyxoedema is a chronic disease, which strongly impairs affected patients and does not show spontaneous remission. The exact pathophysiology of scleromyxoedema remains unclear and treatment is challenging. Most of the frequently-used drugs have severe side-effects, such as bone marrow depression for melphalan and cyclophosphamide or teratogenic potential, as well as irreversible peripheral neuropathy for thalidomide or Cushing's syndrome and osteoporosis for corticosteroids.

Only a few side-effects, in combination with good efficacy, have been reported for the use of IVIG as a treatment for several autoimmune diseases (9). There are several reports of successful IVIG therapy for scleromyxoedema, and different authors describe a long-term state with no residual disease of several months up to 3 years after the end of IVIG treatment (6, 8). However, these reports of long-term remission without relapse after cessation of successful IVIG therapy are now being challenged by the fact that 2 of our 3 patients clearly showed a clinical relapse within the first 8 months of follow-up after the end of IVIG therapy.

Altogether, these observations indicate that there are different possible outcomes of IVIG therapy, as this therapy might lead to a complete remission of scleromyxoedema, as in pemphigus vulgaris (10), or to a relapsing course. Nevertheless, one has to take into account that IVIG therapy is relatively new and that the follow-up

periods are thus limited. To make a definite statement one has to await the results of long-term clinical follow-up. In addition, our report shows that after re-initiation of IVIG therapy no lower response-rates, as well as an immediate response, are noticed, indicating that there is no risk of loss of response to IVIG therapy after interruption of treatment.

We conclude that after effective IVIG therapy of scleromyxoedema there might be either long-term response or relapse on long-term clinical follow-up. However, in the latter case the disease can easily be controlled again by re-initiation of IVIG treatment.

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