Managing scleromyxedema with intravenous immunoglobulin: acute worsening of scleromyxedema with biclonal gammopathy

I. Manousaridis, C. Loeser, S. Goerdt, and J. C. Hassel

ABSTRACT

Scleromyxedema is a rare chronic cutaneous mucinosis usually associated with a monoclonal gammopathy and underlying systemic disease. The etiology of the disease is not known. There are no standard treatments and response to various therapeutic modalities varies. We report a case of refractory scleromyxedema in a 63-year-old man with a biclonal IgG and IgM λ-gammopathy. The patient was successfully managed with intravenous immunoglobulin.

KEY WORDS

scleromyxedema, intravenous immunoglobulin

Introduction

Scleromyxedema is a chronic idiopathic disorder characterized by extensive mucin deposition and fibrosis, which typically affects middle-aged adults. Criteria for the diagnosis of scleromyxedema are a generalized papular eruption of a sclerodermoid character, characteristic histological features, including mucin deposition, fibroblast proliferation, and fibrosis, the presence of a monoclonal gammopathy, and the absence of thyroid disease (1). The clinical features include diffusely thickened skin on the face, on the trunk, and at the distal extremities, leading to decreased motility of the mouth and joints, as well as numerous firm, waxy, linearly arranged papules measuring 2 to 3 mm in a widespread symmetrical distribution pattern, most commonly on the hands, forearms, head and neck region, upper trunk, and thighs (2). Patients with scleromyxedema can also have a number of internal manifestations: muscular, neurological, rheumatologic, pulmonary, renal, and cardiovascular (1). No causal therapy is known. Cases limited to skin are initially treated with local retinoids and PUVA therapy, whereas in more extensive disease systemic treatments with glucocorticoids, cyclophosphamide, plasmapheresis, melphalan, thalidomide, chloroquin, extracorporeal photophoresis, intravenous immunoglobulin, and autologous stem cell transplantation have been tried with variable success (3, 4).

Case report

A 63-year-old Caucasian male patient presented with an acute worsening of his general condition, myalgias, fever, lethargy, and malaise, and was admitted to the hospital. The patient had been suffering from a scleromyxedema associated with a biclonal IgG and IgM λ-gammopathy for 3 years (Fig. 1). The patient

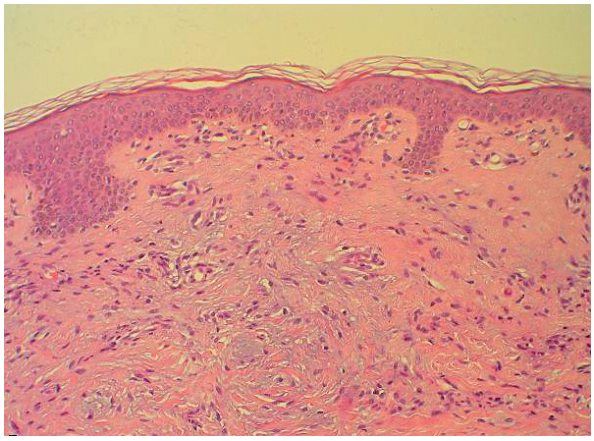


Figure 1. Baseline histological findings: Thinned epidermis, prominent deposits of mucin in the upper part of the dermis accompanied by widespread proliferation of fibroblasts. (a. hematoxylin stain, b. alcian blue stain, ×40).

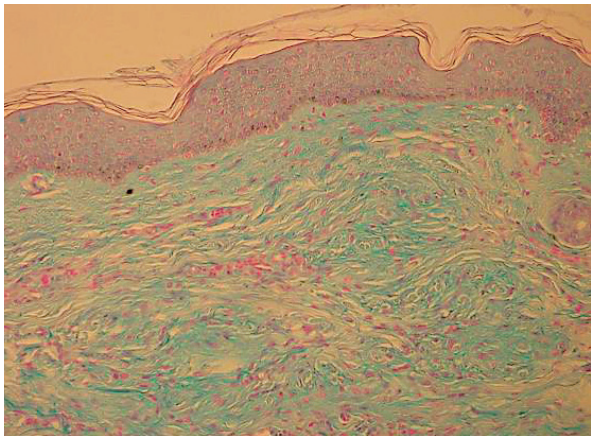
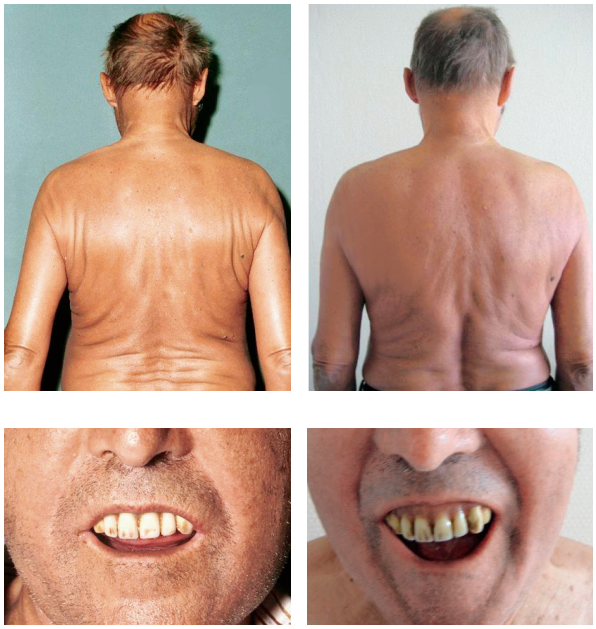


Figure 2. Skin thickness measured by 20 MHz sonography. (HC: hydroxychloroquine, CP: cyclophosphamide pulse, ECP: extracorporeal photophoresis, IVIG: intravenous immunoglobulin).



Figures 3–5. Clinical appearance directly prior to initiation of IVIg and after six cycles of IVIg: Skin thickness decreased, papules cleared, mouth opening increased.

had been treated with various modalities, including UVA1 phototherapy, hydroxychloroquine (initially 600 mg daily, successively 200 mg daily) for 2 months, 6 cycles of a cyclophosphamide pulse therapy (750 mg/m^2), hydroxychloroquine revision (200 mg daily) for 12 months, and 21 cycles of an extracorporeal photophoresis over the course of 15 months (Fig. 2). A temporary amelioration had been achieved after the cyclophosphamide pulse therapy, which, however, had to be discontinued due to intolerance.

On examination, the skin was diffusely thickened and hyperpigmented. The massively thickened skin in the face and at the knees, elbows, and fingers resulted in decreased articular motility and microstomy. Waxy, yellowish, sclerotic papules were arranged linearly on the neck, elbows, forehead, and behind the ears. Axillary hair was absent. The cardiological and neurological status was normal despite lethargy and signs of depression. A bone marrow biopsy revealed no abnormalities. Laboratory investigations, including urine analysis, hemogram, blood glucose, renal and

Table 1. Reports of the use of IVIg in the management of scleromyxedema.

Number of patients	Clinical background	Dosis of IVIg	Combination therapy	Response assessment	References
Full dose protocols					
1	tumorous scleromyxedema	1,5 g/kg body weight, once monthly	melphalan and oral glucocorticoids	regression of tumorous lesions, improvement of mobility	Wojas-Pelc A et al, 2005 (7)
1	skin restricted scleromyxedema	2 g/kg body weight, once monthly	__	regression of skin lesions	Majeski C et al, 2005 (8)
2	scleromyxedema, associated with IgG-λ paraproteinemia	2 g/kg body weight, once monthly	__	decrease in skin induration, increase in mobility	Lister RK et al, 2006 (6)
1	scleromyxedema with dermatoneuro-syndrome	2 g/kg body weight, once monthly	__	regression of skin lesions, improvement of neurological symptoms	Gholam P et al, 2007 (9)
8	skin restricted scleromyxedema	2 g/kg body weight, once monthly	__	regression of skin lesions	Blum M et al, 2008 (10)
1	scleromyxedema with cutaneous, gastrointestinal, hematologic, and neurologic involvement	2 g/kg body weight, once monthly	oral thalidomide	regression of skin lesions, improvement of systemic symptoms	Efthimiou P et al, 2008 (11)
Low dose protocols					
1	scleromyxedema, associated with monoclonal gammopathy	0,5 g/kg body weight, once monthly	__	objectified criteria (increase in freedom of movement of upper extremities, width of mouth opening and reduction of sclerodactyly)	Körber A et al, 2007 (14)
1	skin restricted scleromyxedema	0,4 g/kg body weight, once monthly	__	absolute cleaning of skin lesions	Binitha MP et al, 2008 (12)
1	scleroderma with dermatoneuro-syndrome	0,4 g/kg body weight, once monthly	__	regression of skin lesions	Rey JB et al, 2009 (13)
1	skin restricted scleromyxedema	0,5 g/kg body weight, once monthly	__	regression of skin lesions	Lopez L et al, 2009 (15)

liver function tests, and serology monitoring, did not reveal an infectious state.

The patient was managed with intravenous immunoglobulin (IVIg) 2 g/kg BM administered over 2 days once monthly for 6 months, after the patient had failed to respond to peroral methylprednisolone alone (60 mg initially, gradually tapered over 3 weeks). The IVIg at the beginning led to an improvement of his general condition, including lethargy and depressive symptoms, within a few days. The continuation of IVIg once monthly induced a reduction of skin thickness (Figs. 2–5) and an increase in articular motility. The mouth opening improved (Fig. 5) in particular, and it was then possible to have new dentures made for him. Hence, quality of life improved significantly for the patient. The therapy was tolerated very well and no side effects occurred.

Discussion

The current uses of IVIg in dermatology have recently been reviewed (5) and, although the mode of action is not fully understood, a number of immunomodulatory mechanisms have been postulated, including functional blockade of Fc receptors on splenic macrophages, inhibition of complement mediated damage, modulation of the production of cytokines and cytokine antagonists, neutralization of circulating autoantibodies by antiidiotype antibodies in IVIg, neutralization of pathogens involved in the cause of autoimmune disease, blockade of CD95 (Fas ligand) and hence inhibition of apoptosis (6).

In the literature there have been sporadic reports on the successful application of IVIg in scleromyxedema cases (Table 1). In most cases, high-dose protocols of IVIg (most commonly 2 g/kg body weight, once monthly) were applied (6–11). Low-dose protocols (0.4–0.5 g/kg body weight, once monthly) have been applied with comparably good results as well (12–15). IVIg therapy proved to be effective in patients that failed to respond to other modalities such as hydroxychloroquine, UVA1 phototherapy and isotretinoin (8), as well as extracorporeal photophoresis (ECP), cyclophosphamide, and melphalane (9). IVIg not only improved the skin lesions, but it also resulted in an improvement of systemic manifestations if other organs were involved (11). Especially in cases of neurological involvement, the contribution of IVIg to the successful management of patients has been reported to be significant (9, 11, 13).

In conclusion, in our patient and in line with previous reported experience, the administration of IVIg proved to be a highly effective and well-tolerated alternative in the case of scleromyxedema refractory to other first-line modalities. Especially in acute worsening of the clinical condition with neurological symptoms, IVIg might be considered a first-choice treatment. Moreover, it should be noted that the skin thickness in the ultrasound examination after each therapeutic regimen correlated with the clinical response to the corresponding modality. Therefore ultrasound emerges as an attractive tool for objectifying the level of clinical response to treatments in scleromyxedema and other skin mucinoses.

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