

CONCISE REPORT

Intravenous immunoglobulins control scleromyxoedema

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Background: Scleromyxoedema is a variant of papular mucinosis affecting the skin and internal organs. The different therapeutic approaches proposed for scleromyxoedema are still unsatisfactory. Intravenous immunoglobulin (IVIg) has been successfully employed in the treatment of connective tissue diseases and vasculitides.

Patients: The successful treatment of three cases of scleromyxoedema with IVIg is reported here.

Conclusions: The relatively low risk of the drug and the high effectiveness seen in three patients suggest that IVIg is a new treatment potentially useful in scleromyxoedema.

Scleromyxoedema is a variant of papular mucinosis affecting the skin and sometimes internal organs.¹ In the skin, deposition of a mucinous substance is found, and fibroblasts are activated to produce an excessive amount of mucopolysaccharides and collagen fibres. Scleromyxoedema is often associated with plasmacytoma, leukaemia, lymphoma, myeloma, and other diseases.^{2,3} Frequently, scleromyxoedema is associated with paraproteinaemia and is described as monoclonal gammopathy.^{4,5} Scleromyxoedema is a chronic

condition and rarely improves spontaneously.⁶ The therapeutic approach to it is still disappointing and mortality is high. Different treatments have been suggested, with discrepant results (table 1).

Intravenous immunoglobulin (IVIg) has been successfully employed in the treatment of connective tissue diseases, vasculitides,⁷ and recently proposed for the treatment of scleromyxoedema⁸ (table 2). This evidence led us to use IVIg in the treatment of three patients with scleromyxoedema. The successful results and the relatively low risk of the drug confirm IVIg as a new potential treatment for scleromyxoedema.

CASE REPORTS

Case 1

In June 1997 a 74 year old man, a smoker (40 cigarettes/day), complained of a Raynaud's phenomenon, of a painful swelling of the wrists, metacarpophalangeal joints, ankles, and metatarsophalangeal joints that greatly limited the range of motion. Blood and urine laboratory investigations were

Abbreviations: IL, interleukin; IVIg, intravenous immunoglobulin; TNF, tumour necrosis factor

Table 1 Different kinds of treatments in scleromyxoedema

Author	No of patients	Treatment	Results	References
Tschenja, Chagj	1	Interferon α	Cutaneous improvement but not changes in systemic manifestations	<i>J Am Acad Dermatol</i> 1999;40:303–7
Ellot, Dooley	1	Surgical intervention	Cutaneous results only in one patient	<i>Ann Plast Surg</i> 1998;436–9.
Shoenlamb, Lipsker	2	Tp plasmacytoma	Cutaneous improvement in scleromyxoedema associated with plasmacytoma in two patients	<i>Ann Dermatol Venereol</i> 1997;124:228–32
Krajnc	1	Cyclosporin A	Cutaneous results but not in the arthralgia in one patient	<i>Wien Klin Wochenschr</i> 1997;109:960–3
Devis, Sanal	1	2-Chlorodeoxyadenosine (purine analogue)	Good result in one patient	<i>J Am Acad Dermatol</i> 1996;35:288–90
Craig, Putterman	1	Cyclophosphamide	Cutaneous improvement in a case of scleromyxoedema associated with a multiple periorbital myxoma, myalgias, and deep venous thrombosis	<i>J Am Acad Dermatol</i> 1996;34:928–30
Dineen, Dicken	26	Alkylating agents, melphalan	Good results in the short term but significant toxicity with long term use in 26 patients	<i>J Am Acad Dermatol</i> 1995;33:37–43
Cosgarea, Cos	1	Mucopolysaccharides (thiomucase)		<i>Ann Dermatol Venereol</i> 1994;121:159–61
Catala, Lopez-Aldeg	1	Cyclophosphamide and corticosteroids	Good results in myopathy in a patient with scleromyxoedema	<i>Rev Clin Esp</i> 1993;193:119–21
Shirren, Betke	1	Chlorambucil and PUVA	Little benefit to the skin in a case of scleromyxoedema	<i>Hautarzt</i> 1992;43:152–7
Bonnetblanc, Bedane	1	Topical betamethasone, dimethylsulphoxide	Cutaneous results in one patient	<i>Arch Dermatol</i> 1991;127:733–4
Berkson, Lazarus	1	Photochemotherapy		<i>J Am Acad Dermatol</i> 1991;25:854–7
Hiler, Savoy	1	Isotretinoin	A little improvement in a case of scleromyxoedema with myopathy	<i>J Am Acad Dermatol</i> 1991;24:854–7
Keong, Asaka	1	Plasmapheresis immunosuppression	Good results in the short time	<i>J Am Acad Dermatol</i> 1990;22:842–4

Table 2 The result of our cases and those previously published are reported

	Scleromyxoedema: response to high dose intravenous immunoglobulin (hdIVIg). <i>J Am Acad Dermatol</i> 2000;43:403-8	Our cases
Number patients	2	3
Dose	2 g/kg/5 days every month	2 g/kg/5 days every month
Side effects	None	None
Variables considered	Only cutaneous improvement (skin scores)	Cutaneous and systemic improvement
Results	In the first patient skin scores reduced over a three month period, but after one year his skin score returned to baseline In the second patient skin scores reduced over three months and the patient's improvement was still maintained after 10 months	In the first and second cases, significant improvement of the skin thickening was seen, and in the third case the symptoms of encephalopathy also improved. In all cases, the beneficial results were long lasting

normal except for mild positivity of rheumatoid factor. In the serum paraproteins were found as a monoclonal gammopathy (IgG monoclonal λ), with normal urine electrophoresis. During the winter the erythema worsened and small vesicles and a levelled skin wrinkle appeared on his face, the skin became more stretched, thickened and hardened, spreading to the chest wall, abdomen, thighs, and prepuce. Eyelids and lips were affected, reducing his ability to open his eyes and mouth (microstomia) (fig 1). A skin biopsy showed a hypercellular derma with the presence of histiocytes and fibrocytes around thickened collagen fibres. Mucin stain was not performed. Immunofluorescent stains were negative for immunoglobulin, C3, C1q, and fibrinogen. This pattern was suggestive of a sclerodermatoid lesion in a early inflammatory phase. In March 1998 treatment was started with prednisone, D-penicillamine, and a calcium antagonist. D-Penicillamine was continued for a month, but it was ineffective.

In April 1998 papules appeared on his forehead, ears, neck, shoulder, hands, and feet. Relevant laboratory findings were normal. The patient started treatment with cyclosporin (100 mg/day), which produced a slight improvement, but it was stopped after five months because of a systemic blood pressure increase. In November 1998 he attended the outpatient clinic of our department. Plasmapheresis (once a week for one month and two times a week for another month) was stopped shortly after the start of a headache. Small papules and thickening of the face, larger sebaceous nodules on the skin, monoclonal gammopathy, and hepatosplenomegaly prompted the

diagnosis of scleromyxoedema. The bone marrow biopsy confirmed a monoclonal gammopathy of undetermined significance. Melphalan (2 mg/day) produced a mild but brief improvement but was stopped owing to leucopenia. In February 1999 IVIg was started (Sandoglobulin-Novartis 2 g/kg/5 days every month). After 15 days' treatment with IVIg, skin tightening and erythema disappeared, the skin turned soft and elastic, and the joint recovered the range of motion (fig 2). After two years' follow up the patient is still receiving treatment and the disease is controlled; no side effects have occurred.

Case 2

In April 1998 in the outpatient clinic of the Institute of Rheumatology of the University of Padova a 32 year old woman, a non-smoker, was observed with an eight month onset of cutaneous thickening and papules on her face, neck, arms, and forearms, the dorsal surface of the hands, periumbilical area, and back. Laboratory findings were negative except for a monoclonal IgG λ chain with negative Bence-Jones proteinuria. Technetium-99 oesophageal scanning, respiratory function tests, a chest x ray examination, and ECG were normal. Scleromyxoedema was suspected and confirmed by mucin tests on a skin biopsy. Plasma exchange (once a week and later on two or three times/month) and prednisone 50 mg/day (later gradually withdrawn) led, after the first three months, to an improvement of the skin. During the following months, the disease activity increased and the cutaneous manifestation worsened. In October 1998 isotretinoid was added (0.5



Figure 1 Patient 1 before the IVIg treatment (November 1998) showing characteristic skin lesion of scleromyxoedema. Papules can be seen on the ears and the forehead, and the face skin is thickened and hardened, reducing the ability to open the eyes and the mouth. Reproduced with permission of the patient.



Figure 2 Patient 1 after one month of IVIg treatment (March 1999). The characteristic skin lesions have disappeared. The skin of the face is softer and fewer papules are visible on the forehead. Reproduced with permission of the patient.

mg/kg/day) but then withdrawn because of lack tolerance and absence of improvement. In December 1998 the patient complained of chest pain. An echocardiogram showed a slight thickening of the pericardium and minimal pericardial effusion. The pain disappeared after the steroid dose was increased to 15 mg/day.

In April 1999 all treatments were stopped for one month and in May 1999 IVIg (Sandoglobulin-Novartis 2 g/kg/5 days every month) was started and steroid was tapered to 5 mg/day. After the second infusion of IVIg the papules were less prominent and the skin became softer. After six months of treatment the cutaneous involvement vanished completely and the skin appeared normal. The patient did not continue with the treatment and after three years of follow up continues to do well.

Case 3

A 41 year old woman was first seen in 1978 in the Department of Dermatology, Warsaw Medical School because of widespread erythematous and papular skin lesions affecting mainly the face and the limbs. On the arms, the small perifollicular papules had a linear arrangement. Within a few years, the skin became thickened, folded, and pendulous. The general condition was satisfactory and no visceral, bone and muscle changes were disclosed. Skin biopsy showed fibroblast proliferation with mucin deposits between concentric bundles of collagen fibres. Hypergammaglobulinaemia (34.6%) and monoclonal protein IgG λ were detected, with no Bence-Jones proteinuria. A bone marrow examination showed an increase in plasmacyte number (6.4%, with 0.4% paraplasmyocytes) and lymphoplasmoid cells (0.4%). Melphalan was ineffective. After the onset of encephalitis, she was treated with acyclovir (although herpesvirus infection was not established) and dexamethasone, which did not control the disease. After introduction in 1994 of IVIg (Sandoglobulin-Novartis 2 g/kg/5 days every month), the fever and the symptoms of encephalopathy disappeared, within four weeks the cutaneous involvement was cleared, and did not reappear during three years of follow up. Monoclonal antibodies were no longer detectable and the patient resumed her normal activity.

DISCUSSION

The remission of disease in our patients clearly shows that IVIg may block the disease evolution and also cause the skin to recover. The results confirm the efficacy of IVIg on skin involvement already observed in systemic sclerosis⁹ and in two previous cases of scleromyxoedema.⁸ The IVIg effect on scleromyxoedema might have been fortuitous. However, in our patients the improvement of skin symptoms correlated with the time of IVIg administration.

In the first and second patients, significant improvement of the skin thickening was seen, and in the third patient symptoms of encephalopathy also improved. In all cases, the beneficial results were long lasting. Thus in two cases the treatment led to a complete resolution of the disease while in the other case IVIg treatment was necessary to control the disease. The encouraging results obtained in our three cases mimic the good results obtained previously in other rheumatic diseases such as dermatomyositis, Still's disease, systemic lupus erythematosus, and vasculitides.⁶⁻¹⁰ In autoimmune diseases, IVIg treatment may have additional effects, such as the modulation of immunological reactivity and of inflammatory reactions with different mechanisms of action. However, it is difficult to speculate on the mechanism that led to the improvement of our patients. In fact, the available concentrated IgG preparations contain a vast library of antibodies reacting with thousands of determinants, and among these, many antibodies have an anti-idiotypic specificity. These anti-idiotypic antibodies can neutralise an autoantibody by

forming an idiotype-anti-idiotype dimer. Anti-idiotypic antibodies may bind and down regulate the B cell receptor for antigen, may eventually bind to T cells regulating their function, and may have an immunomodulatory action by FcR blockade.⁶

Cytokines derived from macrophages or activated T cells can exert a direct cytotoxic effect on many tissues. IVIg contains specific high affinity antibodies against interleukins (IL1 α and IL6) and tumour necrosis factor α (TNF α), thus suppressing the continuing immune response in different disorders. IVIg also down regulates the production of IL2, IL2R, IL3, IL6, IL10, TNF β , and granulocyte-monocyte colony stimulating factor.^{6 11}

Acceleration of the rate of IgG catabolism is the most likely explanation for the beneficial action of high doses of exogenous IgG in antibody mediated autoimmune diseases. Recently it has been recently shown that FcRn is a protective receptor that prevents the catabolism of IgG. In a state of hypergammaglobulinaemia, this receptor is presumably saturated, permitting the degradation of IgG to occur in proportion to its total concentration in plasma.¹² The IVIg treatment induced, without any side effects, a complete remission of scleromyxoedema in two patients and controlled the disease by long term treatment in the third. Thus IVIg may be considered a wise therapeutic approach, which may prevent evolution of the disease and assure a good quality and longer expectation of life.

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