

Suspected cardiac toxicity to intravenous immunoglobulin used for treatment of scleromyxedema

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ABSTRACT

Scleromyxedema is a rare, generalized form of lichen myxedematosus, which may be associated with systemic involvement and can be fatal. The therapeutic options available provide partial or inconsistent response and are associated with significant adverse effects. We report a case of scleromyxedema with cardiac involvement, treated with low-dose intravenous immunoglobulin, with almost complete clearing of the skin lesions. The patient died after three cycles of treatment, possibly due to myocardial infarction.

Key Words: Cardiac toxicity, Intravenous immunoglobulin, Scleromyxedema

INTRODUCTION

Lichen myxedematosus is a rare skin disease characterized by the deposition of acid glycosaminoglycans in the dermis, leading to the formation of numerous lichenoid papules, causing thickening and hardening of the skin. The generalized form is called scleromyxedema, in which diffuse thickening of the skin underlies the papules. The tumorous variant is very rare. Scleromyxedema may be associated with systemic involvement and can be fatal. The various therapeutic options available have only partial efficacy and are often associated with toxic side effects. We report a case of scleromyxedema treated with intravenous immunoglobulin (IVIg), with almost complete clearing of the skin lesions but with suspected cardiac toxicity to IVIg.

CASE HISTORY

A 40-year-old man, a manual laborer, presented with diffuse thickening, darkening, and pruritus of the skin since 6 months. Cutaneous examination revealed widespread and symmetric, waxy, firm, skin-colored and hyperpigmented papules, 2 to 4 mm in diameter, closely set over the whole of the face, ears, trunk, and limbs, coalescing to form plaques

on the forearms, thighs, dorsa of the hands and fingers and flexures. The skin underlying the papules showed diffuse thickening but was not bound down. Infiltration, furrowing, and tumor formation of the skin of the face, indurated thickening of the ears, and superciliary madarosis produced a leonine facies. Opening of the mouth was restricted. He was unable to flex or extend his fingers and toes due to pain and stiffness. Other systems were clinically normal. A diagnosis of scleromyxedema was made.

Hemogram, urine analysis, serum biochemistry, thyroid function tests, serum calcium, X-rays of chest and skull were all normal. Tests for hepatitis B, HIV 1 and 2, and antinuclear antibodies were negative. Bone marrow aspiration cytology did not show a significant increase in plasma cells. Serum lipid profile showed slight hyperlipidemia. Total cholesterol was 242 mg/dL (desirable <200); triglycerides, 191 mg/dL (optimal <150); HDL cholesterol, 47 mg/dL (desirable 60 and above); and LDL cholesterol, 147 mg/dL (optimal <100).

Serum immunoglobulin estimation showed normal levels of IgA, IgM, and IgE. Serum IgG was 29.45 g/L (normal 7-16). Serum electrophoresis revealed a restricted band in the

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gamma region. Immunofixation revealed IgG lambda light chains.

Skin biopsies from the forehead and chest confirmed the diagnosis. There was proliferation of stellate and spindle-shaped fibroblasts; and thick bundles of collagen with plenty of mucin in between, which stained positively with Alcian blue at pH 2.5.

Examination of the eye showed no ocular involvement. During cardiology consultation, ECG revealed a short PR interval and mild sinus tachycardia. Findings from echocardiography were within normal limits.

Treatment was started with 0.4 g/kg of IVIg in divided doses, every 4 weeks. He was given one vial of 2.5 g of IVIg daily for four consecutive days (10 g per cycle).

The patient was reviewed after 1 month when he returned for the second cycle of IVIg. Pruritus and tightness of the skin were significantly reduced. He could flex his fingers and toes without pain. The skin was less indurated and more mobile. When he came for the third cycle, the skin was almost completely normal. The plaques had flattened and softened and the thickness had subsided. The skin was more mobile and he could open his mouth fully. No side effects were noted. He was not on any other drugs. He was discharged after the third cycle, with advice to come for the next cycle after 4 weeks.

Two weeks after the third cycle of IVIg, his wife informed us about his sudden death following an acute onset of chest discomfort while walking, possibly a myocardial infarction.

DISCUSSION

Scleromyxedema is a chronic disabling condition that shows little tendency for spontaneous remission. The majority of patients have an IgG paraproteinemia. In some cases, plasma cell dyscrasia is identified on bone marrow biopsy. Although primarily a skin disorder, extracutaneous manifestations due to restrictive disease are also observed in other organs such as muscles, joints, lung, esophagus, kidney, eye; and the central nervous system.^[1] Cardiovascular abnormalities may occur in up to 10% of cases.^[2] Cardiac failure and cardiomyopathy,^[2] dyspnea, and hypertension,^[3] due to deposits of mucin have been reported.

The exact pathogenesis of scleromyxedema is unknown. It is thought that the paraprotein acts as an autoantibody, which directly stimulates fibroblast proliferation and mucin

deposition. Other circulating factors may also stimulate fibroblast activity, leading to hyaluronic acid synthesis, possibly mediated through prostaglandins.^[4]

Treatment of scleromyxedema remains a challenge. There are no controlled studies of treatment. Significant toxicity, including death, has been associated with some of the therapeutic regimens. The most frequently used drug is melphalan. However, problems with the long-term use of melphalan were observed in the recent Mayo clinic review of 26 patients.^[5] There were 9 deaths in the treated group, with no deaths in the untreated group. Other therapies include cyclophosphamide alone or with prednisolone, cyclosporine, glucocorticoids, oral retinoids, plasmapheresis, topical betamethasone and dimethyl sulfoxide, extracorporeal photochemotherapy, electron-beam therapy, thalidomide, interferon alpha, PUVA, hydroxychloroquine, and stem cell transplantation. Toxic drugs should be limited to patients who are disfigured, disabled, or very ill.^[1]

IVIg is increasingly being used to treat many inflammatory and autoimmune conditions, including those associated with a paraprotein, such as chronic inflammatory demyelinating polyneuropathy. The dose ranges from 0.4 g/kg/month to 2 g/kg every 2 weeks. The guidelines suggest that a dosage of 2 g/kg every 3 to 4 weeks is most likely to produce beneficial results.^[6] IVIg is expensive; and due to financial constraints, we initiated treatment with a low dose of 0.4 g/kg. However, the skin lesions showed a very good response to this dose.

The immunomodulatory effect of IVIg is mediated either through the FC portion of IgG or the antigen binding site and variable region of the antibody molecule. It could be that IVIg might reduce the production of, or inhibit the action of, a putative circulating factor that exerts a stimulatory effect on fibroblasts.^[7] Seven publications report a total of 13 patients with scleromyxedema treated with IVIg, 2 g/kg over 5 days, the majority as monotherapy.^[8] Improvement in cutaneous and systemic manifestations of the disease was observed in all patients within a period of 6 months and could be maintained in 11 of the 13 patients with IVIg maintenance therapy. Successful therapy of the tumorous variant with five 5-day monthly courses has been reported. After a further five courses in the following year, there was complete clearance, which was sustained without any therapy for 1 year, till the time of publication.^[9]

IVIg may be associated with minor and major side effects. Many of them occur in patients with underlying risk factors or diseases that predispose to such side effects.^[8] Myocardial infarction has been reported after the first cycle

of IVIg in patients with known cardiac risk factors such as hypertension, diabetes mellitus, and coronary artery disease. Hyperviscosity seems to play a role by favoring the occlusion of blood vessels that are already narrowed by atherosclerotic plaques.^[10]

Our patient had mild hyperlipidemia and ECG abnormalities. IVIg is known to induce thromboembolic episodes by increasing the viscosity of blood. Although his death could be due to preexisting cardiac involvement, the role of IVIg in precipitating or hastening death cannot be excluded. We suggest that though our patient's signs and symptoms improved dramatically, IVIg should be used with caution in patients with underlying risk factors.

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