Scleromyxedema Without Monoclonal Gammopathy Treated with Intravenous Immunoglobulins

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Received: January 3, 2019
Accepted: March 15, 2021

ABSTRACT Scleromyxedema is a generalized cutaneous mucinosis that may cause internal damage. This condition is frequently associated with monoclonal gammopathy. However, its physiopathological implications remains uncertain. The natural development of scleromyxedema is unpredictable and may lead to potentially fatal complications. Although there is no standardized treatment, intravenous immunoglobulins are considered the best method for treating scleromyxedema. The effects of this method of treatment on this condition are not well known, and it could be argued that intravenous immunoglobulins interact with the monoclonal gammopathy. This paper describes a case of scleromyxedema without associated monoclonal gammopathy that was treated effectively using monthly courses of treatment with intravenous immunoglobulins.

KEY WORDS: scleromyxedema, monoclonal gammopathy, intravenous immunoglobulins

INTRODUCTION

Papular mucinosis (or scleromyxedema) is a generalized mucinosis that is characterized by a generalized scleroderma eruption with firm, monomorphic papules predominantly on the side of the neck, the glabella, the hands, and behind the ears. The majority of scleromyxedema cases are combined with monoclonal gammopathy and systemic manifestations (1,2). There is still no standardized treatment for scleromyxedema, although several studies have examined intravenous immunoglobulins and their place in the first line of treatment (3,4). The effects of intravenous immunoglobulins and, notably, their role in associated monoclonal gammopathies are not well known. This paper describes a case of scleromyxedema without associated monoclonal gammopathy that was treated effectively with intravenous immunoglobulins.

CASE REPORT

A 59-year-old woman without notable medical history had been presenting with firm, monomorphic, millimeter-sized and asymptomatic papules for four weeks. These were initially localized on the neck but progressively extended to the chest, behind the ears, and to the glabella (Figure 1). This was also associated with significant edemas in all four limbs, with sclerotic eruption.

Clinical examination also showed bilateral carpal tunnel syndrome.

Standard biological tests found no abnormalities. No monoclonal gammopathy was discovered. Serum protein electrophoresis showed only a lowered level of gamma globulins at 4.8 g/L (normal levels 8.0-13.5 g/L); serum protein immunoelectrophoresis showed an abnormal outline of immunoglobulins with no

Acta Dermatovenerol Croat
2021;29(1):51-53

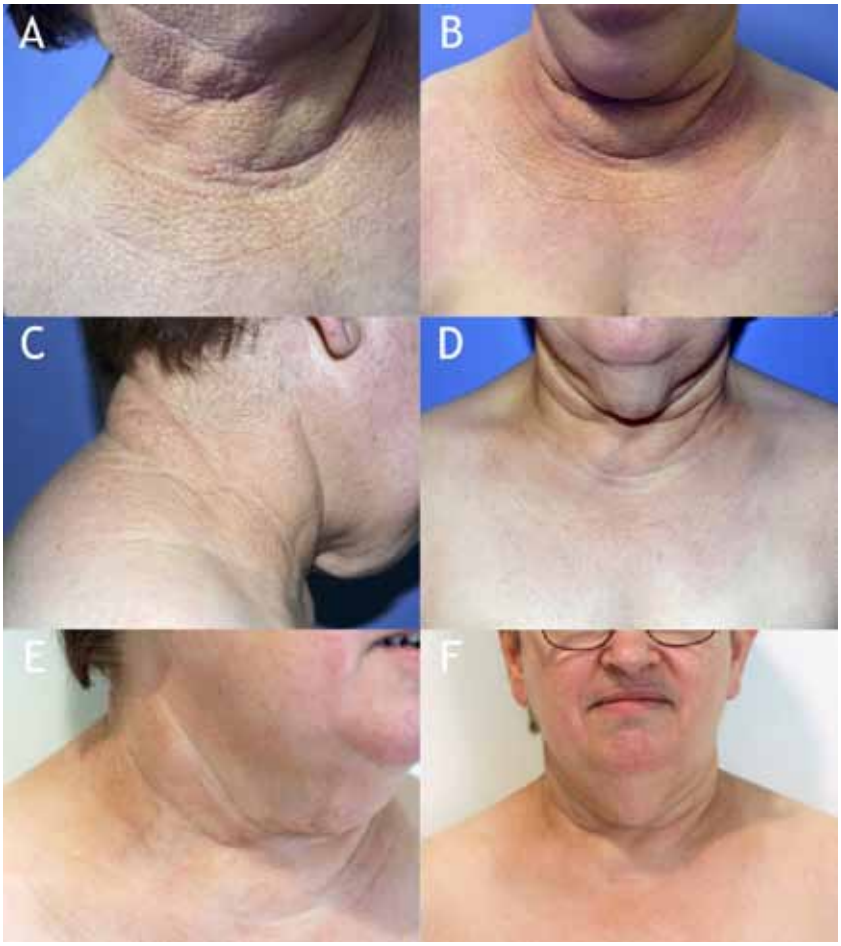

Figure 1. Evolution after five courses of treatment with intravenous immunoglobulins. (a, b) Edemas of the neck and face with sclerosis eruption and firm, millimeter-sized papules on the neck and chest before any treatment. (c, d) After two courses of treatment with intravenous immunoglobulins: clear reduction of edemas, some persistent discreet papules on the side of the neck. (e, f) After five courses of treatment with intravenous immunoglobulins: disappearance of edemas and papules, only the scleroderma eruption on the side of the neck remains. The patient was treated with a total of six monthly courses of treatment with intravenous immunoglobulins.

qualitative atypicality; immunoglobulins IgA and IgG were slightly reduced at 0.82 g/L (normal values 0.84-4.99 g/L) and 5.3 g/L (normal values 6.1-16.2 g/L), respectively, while kappa and lambda light chain quantity was normal, with a normal kappa/lambda ratio. There was no proteinuria and no dysthyroidism.

Histological analysis of the cutaneous retro-auricular biopsy discovered dermal mucinosis without sclerosis and with light chronic inflammation. PET scan showed no metabolic anomaly leading to a primitive neoplasia.

The patient underwent electroneuromyography (ENMG) due to the neuropathic pain, which gave a clinical confirmation of the diagnosis of bilateral carpal tunnel syndrome.

Monthly treatment courses with intravenous immunoglobulins for five days at a dose of 2 g/kg per week were started. Clinical improvement with a reduction in the number of papules and a clear reduction in edemas was observed from the first treatment with immunoglobulins. After three courses of treatment, the papules on the chest and retro-auricular area had almost disappeared and there was no longer sclerosis or paresthesia of the upper limbs. Minor edemas in the lower limbs remained. The drips were well tolerated.

DISCUSSION

Our case shows the success of intravenous immunoglobulins in treating scleromyxedema without associated gammopathy.

The physiopathology of the disease is not well understood. The principle hypothesis rests on the role of circulating cytokines, such as interleukin 1, TNF, and TGF-β, which stimulate the synthesis of glycosaminoglycans and the growth of fibroblasts (1).

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There has also been progress in determining the physiopathological role of monoclonal gammopathy. Cokonis Georgakis *et al.* suggested that the monoclonal gamma globulins may act as antibodies that promote fibroblast growth and hyperproduction of mucins (5).

Berger *et al.* also mentioned the role of monoclonal gammopathy in the physiopathology of dermatoneuro syndrome (a potentially fatal complication of scleromyxedema) through induced hyperviscosity (6).

Little is known about how intravenous immunoglobulins work, although their effects are certainly multifactorial. Samuelsson *et al.* used murine models of autoimmune thrombocythemia to show that the protective effect of intravenous immunoglobulins is mediated by their capacity to induce the expression of FcγRIIB inhibitory receptors on effector cells. This effect was mediated by the Fc portion of immunoglobulins. In fact, it was achieved by administering only the monomeric Fc-fragment-induced protection, in contrast with the equimolar administration of the Fab portion (7).

Other immunological mechanisms have also been used to explain the antifibrotic action of immunoglobulins: neutralization of circulating antibodies, reduction in the production of profibrotic factors such as TGF-β, endothelin-1, and connective TGF, modulation of metalloprotein activity, inhibition of the complement reaction, and fibrotic cascade (8,9).

83.2% of scleromyxedema cases are linked with monoclonal gammopathy (2). The effect of immunoglobulins on these monoclonal gammopathies is unknown.

A prospective Italian study, which included eight patients with associated monoclonal gammopathy who were treated with immunoglobulins, did not demonstrate any link between the rate of gamma globulins in the blood and the severity of the disease or treatment. A modest reduction in the level of gamma globulin in the blood was observed in just one patient (10). In another multi-center study which included 30 patients, of which 27 had monoclonal gammopathy, Rongioletti *et al.* observed that immunoglobulin treatment slightly reduced the levels of gamma globulins in the blood in just one patient. These results reinforce the hypothesis that the effects of immunoglobulins do not interfere with monoclonal gammopathy.(4)

There are some publications on scleromyxedema without associated gammopathies treated successfully with just thalidomide or combined with corticoids, or ciclosporin or even methotrexate and corticoids, but there are very few publications on scleromyxedema without monoclonal gammopathy treated successfully using intravenous immunoglobulins.

To our knowledge, we report the first French case of scleromyxedema without monoclonal gammopathy treated successfully using intravenous immunoglobulins. Our observations support the hypotheses that, on the one hand, monoclonal gammopathy does not interfere with the physiopathology of the disease and, on the other hand, that the effects of intravenous immunoglobulins do not interfere with monoclonal gammopathy.

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