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Long-Term Efficacy of Treatment with Intravenous Immunoglobulin in Scleromyxedema

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ABSTRACT Scleromyxedema or generalized lichen myxedematosus is a rare depositional disorder. Diagnostic criteria encompass a generalized papular and sclerodermoid eruption, monoclonal gammopathy (paraproteinemia), most often with G-lambda type immunoglobulin, a characteristic microscopic triad (mucin deposition, fibroblast proliferation, fibrosis), and absence of thyroid disease. Many internal manifestations of scleromyxedema have been described to date, leading to high mortality and morbidity. Because the disease is rare, the etiology is not fully understood and there is a lack of well-designed studies, so no optimal treatment exists so far. This paper reports the follow-up on a patient in 5.5-year remission after successful intravenous immunoglobulin therapy 10.5 years since initial diagnosis.

KEYWORDS: scleromyxedema, mucinoses, therapy, intravenous immunoglobulin

INTRODUCTION

Scleromyxedema is a rare depositional disorder and one of the three subtypes of lichen myxedematous (1). The other two are localized and atypical forms. The prevalence is the same for both sexes and mainly affects adults in their fifties or sixties (2,3). Diagnostic criteria encompass a generalized papular and sclerodermoid eruption, monoclonal gammopathy (paraproteinemia) most often with G-lambda type immunoglobulin, a characteristic microscopic triad (mucin deposition, fibroblast proliferation, fibrosis), and absence of thyroid disease (2,3). Skin features are numerous, widespread, firm, and waxy 2-3 mm papules in symmetrical distribution, most commonly located on the head, neck, dorsum of the hands and forearms, the upper trunk, and thighs (4). Non-tender subcutaneous nodules occur rarely (5). Additionally, the skin of the face, trunk, and distal extremities is thickened, consequently leading to microstomy and decreased articular mobility (4). Many internal manifestations of scleromyxedema have been described to date, including cardiovascular, neurological, rheumatological, muscular, pulmonary, renal, gastrointestinal, and ophthalmological (1,2). According to the literature, they occur in 70-77% of cases, and morbidity and mortality are therefore high (3). Possible occurrence of multiple myeloma in 10% of patients has also been described (6). Scleromyxedema can mimic systemic scleroderma (7). The etiopathogenesis has not yet been fully explained; however, it is known that serum from the patient enhances the proliferation of dermal fibroblasts and that a yet unspecified factor in it is probably responsible, rather than not purified

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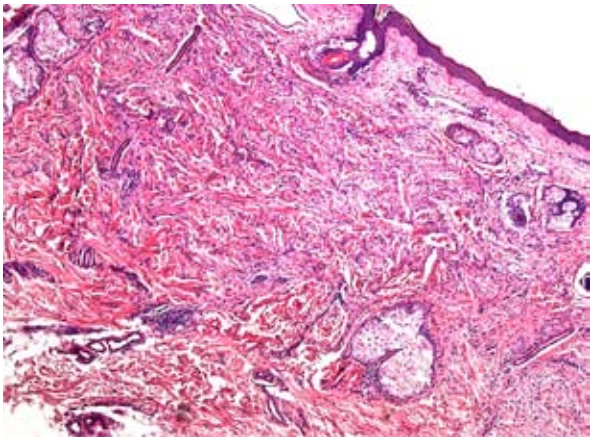

Figure 1. Histopathological analysis of punch biopsy revealed normal epidermis with dermal proliferation of fibroblasts and increased interstitial mucin.

immunoglobulin. Mucin and increased collagen depositions take place in the dermis (1). Because the disease is rare, the etiology is not fully understood and there is a lack of well-designed studies, no optimal treatment exists to date. Relying on case reports and case series, the European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin supports the use of intravenous immunoglobulin (IVIg) as the first-line therapy because it is effective and safe (5). However, it should be emphasized that many other therapeutic options and drug combinations are sometimes used with varying efficiency, for example melphalan, autologous stem-cell transplantation, thalidomide, systemic glucocorticoids, retinoids (isotretinoin, acitretin), hydroxychloroquine, cyclosporine, cyclophosphamide, methotrexate, 2-chlorodeoxyadenosine, interferon alfa-2b, plasmapheresis, electron-beam therapy, bortezomib, and extracorporeal photopheresis (1,5).

CASE REPORT

In February 2009, a 64-year-old retired truck driver and former chain smoker presented to the doctor's office for the first time at the age of 54 with a 1-year history of gradual thickening and stiffening of the skin over the upper extremities, trunk, and face. He also complained of bumps on the cheeks, first noticed 10 months ago, due to which he had undergone several excisions at the Otorhinolaryngology Department one week prior to the examination. The patient was otherwise healthy with no significant medical history. Examination of the skin of the cheeks, forehead, and dorsum of the hands showed diffuse thickening with a waxy texture and erythema. Infiltration and furrowing produced leonine facies. The skin of the back was infiltrated, and longitudinal folds could be noticed. Opening of the mouth was restricted, and the patient had sclerodactyly 2. Other systems were clinically normal. The presentation raised suspicion of scleromyxedema. Histopathological analysis of a punch biopsy confirmed the diagnosis. WE also observed normal epidermis with dermal proliferation of fibroblasts and increased interstitial mucin). Extended laboratory results were within normal ranges, including complete blood count with a differential, comprehensive metabolic panel, urine analysis, and thyroid examination. Monoclonal gammopathy on serum protein electrophoresis was initially absent. Tumor markers were negative as well. We carried out the investigations listed below to further exclude any

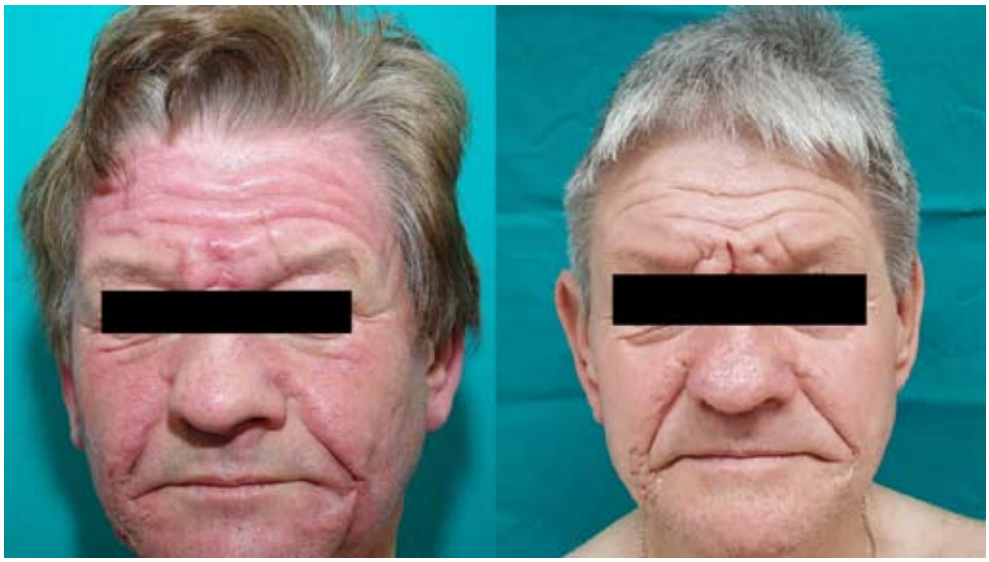

Figure 2. (a) Scleromyxedema: typical leonine facies with erythematous skin. (b) The same patient 10.5 years after the initial diagnosis. Minimally indurated skin of the face can be seen, with less prominent longitudinal wrinkles of the forehead.

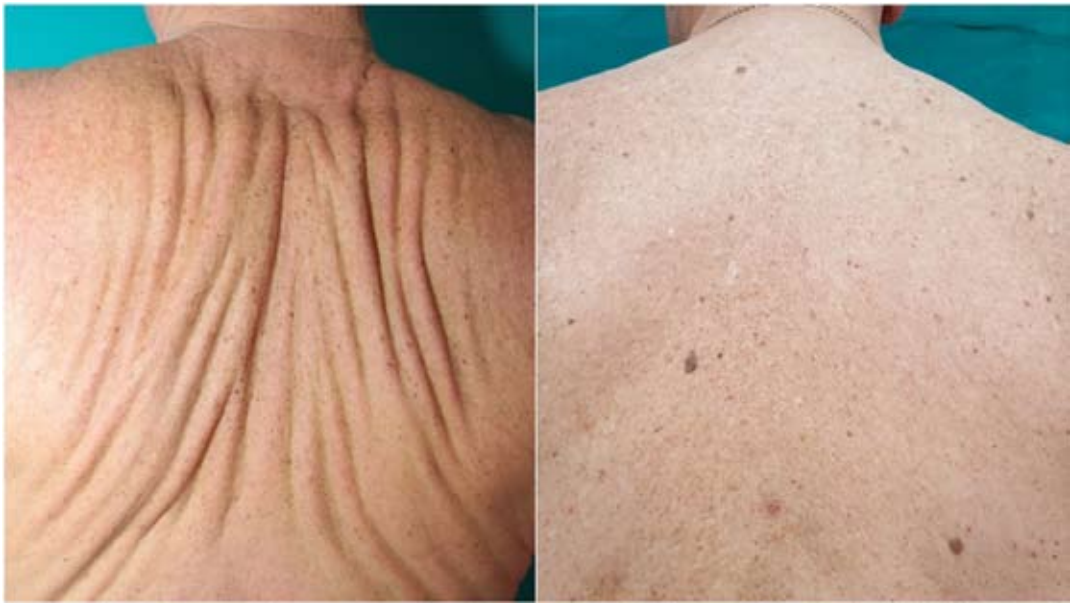

Figure 3. (a) Longitudinal folds on the back, also known as a Shar-Pei sign. The photo was taken on the patient's first visit to the doctors' office. (b) The same patient in August 2019. Indurated skin had completely disappeared.

systemic involvement of the disease. Abdominal ultrasound showed markedly hyperechogenic liver, most likely because of fibrotic parenchyma. Due to changes in ECG (left heart axis, low R tooth from V1 to V3, negative T wave and left anterior hemiblock) along with detailed cardiac diagnostics, single-vessel coronary artery disease was identified and a prescription of acetylsalicylic acid, ramipril, and bisoprolol was introduced. Chest X-ray, esophageal passage X-ray, and spirometry were without significant deviations from the normal range.

When the entire diagnostic process was completed, we introduced monotherapy with high dose IVIg in the dose of 2 g/kg bodyweight, administered over 4 consecutive days (45 g/day) once monthly. Initially, the patient received 6 cycles of IVIg, and gradual clinical improvement was observed after each of them but full regression was not achieved. The disease noticeably progressed approximately every 3 months, which was first observed 4 months after the last of these 6 cycles when monoclonal IgG type lambda in serum immunofixation electrophoresis was also detected

Figure 4. (a) Induration of the dorsal parts of the hands before initiating therapy with intravenous immunoglobulin. (b) Improvement of erythema and edema after successful treatment can be observed.

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for the first time, but further investigations excluded hematological disorders. With each reappearance of the skin changes, we reintroduced IVIg following the same dosing scheme as before, i.e. one cycle of 2 mg/kg divided over 4 consecutive days. In January 2014, a few months after the patients' retirement, the dermatologists decided to repeat regular dosing, this time every six weeks, with the usage of the same scheme as previously. Almost complete clinical remission was achieved after four cycles – erythema in the nasolabial folds could be observed, with minimally indurated skin on the face and upper extremities. The patient was able to fully open his mouth. In total, the patient received 21 IVIg cycles over 5 years.

From April 2014 to the present the patient was regularly monitored and required no additional cycles of IVIg. He is currently in clinical remission 10.5 years after initial diagnosis and has not been receiving therapy for the last 5.5 years. The last follow-up evaluation was performed in August 2019 when a punch biopsy from the same site as the first time was repeated and revealed non-specific histological findings without dermal mucin deposits on special staining with alcian blue. Widespread laboratory tests were completely normal. Serum protein electrophoresis showed still present IgG lambda paraproteinemia, as was suspected. On repeated abdominal ultrasound examination, liver echogenicity was normal as were all other structures, with the exception of bladder with walls of uneven contractures and a moderately enlarged hypo echogenic prostate. Since 2015, the patient has been undergoing regular check-ups by urologists for benign prostatic hyperplasia and persistent microscopic hematuria.

DISCUSSION

The patient presented herein was followed-up for a period of 10.5 years. He had characteristic skin findings and ultimately fulfilled all four criteria for diagnosing scleromyxedema, the pathophysiology of which is still under debate. As no stable clinical improvement was observed until few months after his retirement as truck driver, we think ultraviolet exposure had a role in disease pathogenesis, but there are case reports in which UVA-1 and PUVA phototherapy have led to improvement of the disease. However, our theory may be supported by a case report written by Kirchberger MC *et al.* where scleromyxedema in a young woman first expressed itself after holidays in Egypt as erythema strictly limited to photoexposed sites, initially clinically and pathologically evaluated as dermatitis solaris and eventually properly diagnosed once fully expressed (7). No other anamnestic data except smoking stand out in our patient. As for systemic manifestations, cardiovascular problems may be due to the disease itself, in which case mucin deposition in the heart vessels should be demonstrated, or the overall coincidence can be only incidental. Ultrasound liver changes vanished over the years, and there was no mention of co-occurrence of liver fibrosis in the literature reviewed. The same applies to benign prostatic hyperplasia.

Many possible treatments have been mentioned to date, all with their own advantages and disadvantages. This case report confirms IVIg can be an effective and safe therapy for long-term control of scleromyxedema. In total, our patient received 21 IVIg cycles from 2010 to 2014. According to the literature, some authors discontinued IVIg therapy after reaching complete response and reintroduced it in case of a relapse without noticeable lower response rates, which is what we did in the case presented here. Others advocate an approach with long-term maintenance dosing spaced out to every two months, but this may be uneconomical (3,8). According to the European Dermatology Forum S1-guideline, the use of IVIg is initially recommended over a period of six months. If no improvement is observed during this time, treatment should be discontinued (5). Different therapeutic regimens are used, most commonly full doses or 2 g/kg once every 4 weeks, divided over 4-5 consecutive days (3-5). This was the approach chosen in our case. A minority of clinicians opt for the low dose protocol, i.e. 0.4-0.5 g/kg once monthly, with similar outcomes (4). The mechanism of action of IVIg is still under debate, with blockage of the Fc receptor leading to non-functional phagocytic cells or immunomodulatory action including neutralization of circulating autoantibodies by anti-idiotype antibodies as two of the hypotheses (3,6). Another hypothesis claims alternation of metalloproteinases is important, resulting in alternation of matrix collagen (6). IVIg improves both cutaneous and extracutaneous manifestations, which can also be observed in the case presented above with normalization of liver echogenicity. Side-effects are usually mild and self-limiting. There may, however, be rare but serious side-effects, for example anaphylaxis, acute renal failure, deep venous thrombosis, pulmonary embolism, stroke, arrhythmia, aseptic meningitis, hemolytic anemia, myocardial ischemia, and transfusion-related acute lung injury (5,6,9). Their incidence may be reduced by the following measures: performing an early assessment of risk factors, infusing at a slow rate, premedicating, and switching from intravenous to subcutaneous immunoglobulin (9). The patient presented above tolerated the therapy well.

CONCLUSION

In summary, our patient was followed for a period of 10.5 years and has currently been in clinical remission for 5.5 years after cessation of IVIg, which is to our knowledge among the longest reported disease-free periods. Namely, in the largest retrospective study of 30 patients with scleromyxedema by Rangioletti *et al.*, one of the patients was monitored for a maximum of 11 years (3). Moreover, there was also histological response in our case. The paraprotein is still detectable as was expected from the findings reported so far, however, it should be emphasized that there was a delay in its appearance. The relapse rate is high after discontinuation of therapy, so regular follow-up of the patient once per year is required.

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