IVIG Treatment in Scleromyxedema: Do Histologic Variants Influence Outcomes?

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Scleromyxedema is a rare, chronic cutaneous mucinosis characterized clinically by diffuse indurated plaques, numerous waxy papules, and potential for systemic involvement, including neurological, pulmonary, and gastrointestinal complications. It can significantly impact the clinical course and patient prognosis [1].

Histologically, scleromyxedema typically manifests in two main forms. The classic form, the most common variant, is characterized by dense mucin deposition within the dermis, an increase in fibroblasts, and thickened collagen. The granuloma annulare-like variant, accounting for approximately 23% of cases, mimics granuloma annulare and is characterized by interstitial granulomatous infiltration and, in some cases, palisaded granulomas within the dermis. This unusual variant presents a significant diagnostic challenge due to its overlap with other granulomatous conditions, potentially causing diagnostic delays [2].

The lack of standardized treatment regimens makes managing scleromyxedema complex. Intravenous immunoglobulin (IVIG) has emerged as a leading therapeutic option, demonstrating efficacy in controlling both cutaneous and systemic manifestations. Other options include systemic steroids, thalidomide, retinoids, and melphalan [3].

These cases underscore the challenges of recognizing the clinical and histologic variability of scleromyxedema, which may lead to a delay in the diagnosis. Early diagnosis is critical given the potential for systemic involvement (neurological, gastrointestinal, and muscular) and the association of scleromyxedema with monoclonal gammopathy of undetermined significance (MGUS), which might progress to multiple myeloma. Consequently, timely hematologic evaluation and ongoing surveillance are warranted.

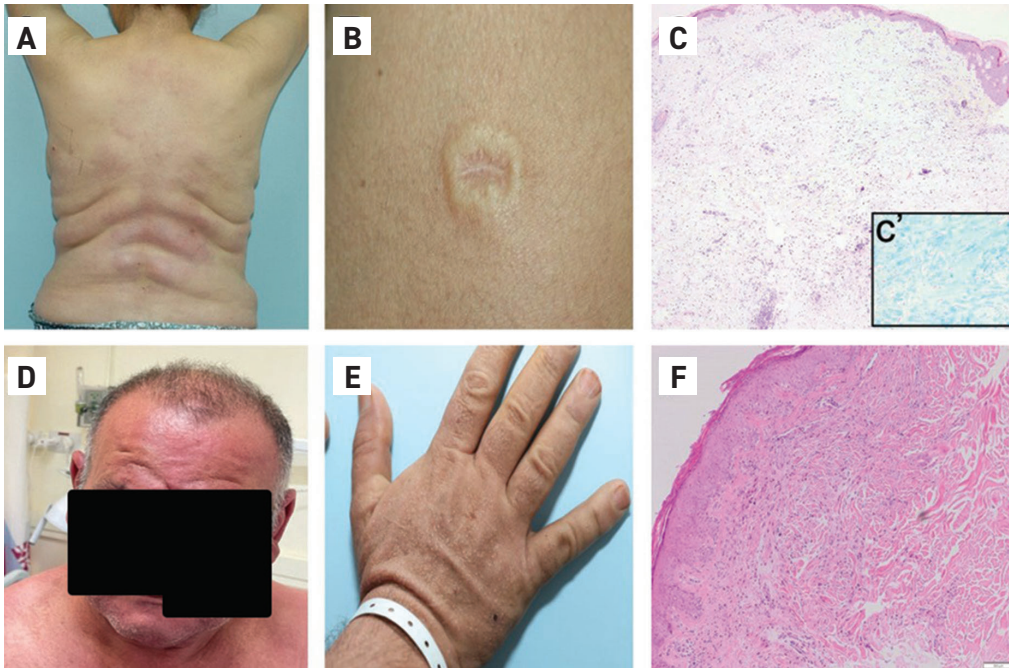
PATIENT DESCRIPTION

CASE 1: CLASSIC VARIANT

A 71-year-old female presented with a several-month history of a widespread rash, progressive muscle weakness, difficulty swallowing, and joint pain. On examination, the patient presented with diffuse waxy papules and plaques on the head, trunk, and extremities, accompanied by the Shar-Pei Sign and the Doughnut Sign [Figures 1A, 1B]. Laboratory evaluation revealed normal thyroid function tests and elevated free light chains. A bone marrow biopsy confirmed MGUS. Gastric evaluation demonstrated gastritis and duodenitis, while a neurological assessment indicated inflammatory myopathy.

A skin biopsy showed abundant mucin deposition throughout the full thickness of the dermis, located between collagen bundles. There was an increased number of fibroblasts, with a mononuclear inflammatory infiltrate located both perivascularly and between the vessels, composed primarily of CD3-positive T lymphocytes and CD138-positive plasma cells. These findings are consistent with scleromyxedema [4,5] [Figure 1C]. Initial treatment with oral corticosteroids and PUVA therapy was attempted but yielded minimal improvement in cutaneous symptoms. Given the limited response and considering the safety profile, IVIG was selected as the next-line treatment. The patient received monthly IVIG at a dose of 2 g/kg, which led to substantial improvement in both cutaneous and systemic symptoms over 30 treatment cycles. Subsequently, remission was maintained when the

Figure 1. [A] Shar-pei sign on the trunk; **[B]** doughnut sign; **[C]** extensive mucin deposition throughout the dermis between collagen fibers with numerous fibroblasts; **[D]** Leonine facies **[E]** indurated skin-colored papules on the dorsal hands; **[F]** thickened collagen fibers within the papillary dermis, interspersed with mucin and numerous fibroblasts and histiocytes



treatment interval was extended to every 2 months. Cutaneous improvement was assessed qualitatively through serial photography and clinical examinations because there is no standardized severity scoring tools for scleromyxedema.

CASE 2: GRANULOMA ANNULARE-LIKE VARIANT

A 61-year-old male presented with an 8-month history of progressive, erythematous, indurated plaques that started on the dorsum of his hands and later spread to the scalp and trunk. He reported significant pruritus but denied systemic symptoms. Examination revealed erythematous plaques distributed symmetrically along with firm, infiltrated papules. Dermatologic signs included the Shar Pei sign and Leonine Facies [Figure 1D,1E].

Laboratory workup revealed elevated monoclonal lambda chains. A punch biopsy showed thickening of collagen fibers and an increased number of fibroblasts and histiocytes scattered in an interstitial pattern. Immunostaining was positive for CD68 and CD163, and negative for CD138. There were few perivascular lymphocytes. Elastic staining was markedly reduced. PAS and Ziehl–Neelsen stains were negative, findings that consistent with scleromyxedema. [4,5] [Figure 1F]. Differential diagnoses, including interstitial granuloma annulare and necrobiotic xanthogranuloma, were considered. Additional immunohistochemical stains for CD20, PAS, and Ziehl–Neelsen were negative, thus excluding infectious lymphoproliferative or other granulomatous diseases. The patient had previously received PUVA and oral corticosteroids without significant benefit. Due to persistent cutaneous symptoms, monthly IVIG therapy at a dose of 2 g/kg was initiated. This treatment resulted in gradual improvement of erythema and induration. However, the disease relapsed when the treatment intervals were extended to every 2 months, necessitating a return to monthly therapy.

Cutaneous improvement was assessed qualitatively in both cases through serial photography and clinical examinations because there is no standardized severity scoring tools for scleromyxedema. In both cases, no adverse effects were observed during IVIG therapy. IgA levels were assessed before treatment, while complete blood count and renal function tests were monitored throughout the treatment period.

COMMENT

Scleromyxedema is a rare, chronic disease that can be disabling and presents challenges in diagnosis

and management due to its rarity and variability. Diagnosis requires a combination of clinical presentation, histopathologic findings, and laboratory investigations, particularly to confirm the presence of monoclonal gammopathy. Characteristic dermatologic manifestations include symmetric eruptions of small, waxy, firm papules, often giving the skin a shiny, indurated appearance [1].

Histologically, scleromyxedema has two main patterns: the classic type and the granuloma annulare-like type. The latter is less common, presenting in approximately 23% of cases.

Despite the positive outcomes associated with IVIG treatment, previous studies did not differentiate outcomes based on histologic subtypes.

Rongioletti et al. [5] found consistent IVIG responses among 34 patients, including those with the granuloma annulare-like variant, though specific outcome percentages were not provided. Additional case reports and retrospective analyses have demonstrated clinical improvement following IVIG, even in patients unresponsive to corticosteroids. Notably, reductions in skin thickening have been observed using the modified Rodnan score. However, relapses are frequently reported after treatment discontinuation, highlighting the potential need for maintenance therapy. Most of the available literature does not distinguish between histologic subtypes. A systematic review by Haber et al. [3] reported clinical improvement in over 80% of patients treated with IVIG, though relapses were common when therapy was discontinued, or intervals extended.

Our case reports address this gap by evaluating IVIG treatment outcomes in two patients with distinct histologic subtypes of scleromyxedema, followed over a long-term period. In our observation, both histologic variants responded well to IVIG therapy. The classic variant achieved sustained remission and successfully transitioned to a two-month treatment interval. In contrast, the granuloma annulare-like variant relapsed when the interval was extended and required continued monthly IVIG to maintain remission. Notably, conclusions regarding comparative efficacy or optimal dosing intervals can't be drawn based on these individual cases. To further establish our observation that IVIG may be equally effective across different histologic variants, large-scale prospective controlled studies are warranted. However, these are extremely challenging in this rare disease. Additional reports may help to elucidate whether classic and granuloma annulare-like variants share similar outcomes.

Scleromyxedema is strongly associated with MGUS, although a direct causal relationship has not been established. Early recognition of the disease is important because it may offer an opportunity to identify systemic complications (neurological, gastrointestinal, or muscular) at an early stage, although it does not alter management. Furthermore, recognizing the association with MGUS allows for appropriate hematologic evaluation and long-term monitoring for potential progression to multiple myeloma.

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Capsule

Bandage biomarkers from wounds

Wang et al. designed a wearable device, iCares, for optimized collection of the slowly released wound fluid and sensing of reactive oxygen and nitrogen species, pH, and temperature. In diabetic mice, the sensors detected changes in these factors during skin wound infection that resolved with antibiotic treatment. In a cohort of 20 human patients with chronic wounds, the iCares multiparameter sensor measurements were paired with a machine learning algorithm to classify wound severity and the potential for healing. Further development of this in situ analysis could provide an objective evaluation of wound status to inform treatment decisions in chronic wounds.

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