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Authors

Mullangi, Samyukta
Granter, Scott R
Laubach, Jacob P
et al.

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Case report

Scleromyxedema with histology resembling granuloma annulare

Samyukta Mullangi, BS¹, Scott R Granter, MD², Jacob P Laubach, MD, MPP³, Adam D Lipworth, MD⁴

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¹Harvard Medical School, Boston, MA

²Department of Pathology, Brigham and Women's Hospital, Boston, MA

³Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

⁴Department of Dermatology, Brigham and Women's Hospital, Boston, MA

Correspondence:

Adam D Lipworth
Department of Dermatology
Brigham and Women's Hospital
221 Longwood Ave, Boston, MA 02115
Email: alipworth@bics.bwh.harvard.edu
P: 617-732-4918, F: 617-582-6060

Abstract

Scleromyxedema is a generalized and progressive fibromucinous disorder associated with substantial cutaneous and systemic morbidity. The diagnosis is often challenging, as is management. We present here a patient with scleromyxedema with atypical, granuloma annulare-like histology, which contributed to delayed diagnosis and management, including a delayed workup for multiple myeloma. Ultimately, the patient did well with appropriate therapy, but his presentation illustrates the importance of more widespread familiarity among dermatologists and dermatopathologists with this variant of scleromyxedema.

Keywords: scleromyxedema, granuloma annulare

Introduction

Scleromyxedema is a rare cutaneous fibromucinous disorder that is closely associated with monoclonal gammopathy. Patients present with a generalized papular and sclerodermoid eruption that progresses to diffuse skin induration and sclerosis, with significant deformity and loss of joint mobility. Histology demonstrates extensive dermal mucin deposition between thickened collagen bundles, with an increased number of large, stellate fibroblasts. Patients may also develop systemic manifestations, which can be highly morbid and difficult to treat, including proximal myopathy, inflammatory polyarthritis, esophageal dysfunction, neurologic dysfunction, and occasionally, hematologic disorders; the condition is not often amenable to treatment.

The origin and exact pathogenesis of scleromyxedema remain a mystery. The diagnosis can be challenging, and requires careful integration of clinical, histologic, and laboratory data. Herein we describe a patient with scleromyxedema, whose diagnosis was particularly challenging because of atypical, granuloma annulare-like histology. This variant has only rarely been described previously and it remains obscure and poorly recognized. Increased awareness of this scleromyxedema variant with GA-like histology can facilitate timelier diagnosis and early intervention, greatly impacting patient function and quality of life.

Case synopsis

A 57-year-old man presented with one year of a progressive eruption that started with generalized erythema and pruritus several weeks after starting a new fish oil supplement. The rash progressed over months, despite stopping that supplement and his only two other medications, atorvastatin and olmesartan. A seven-day course of prednisone had no effect.

Initial workup revealed normal electrolytes, urinalysis, quantitative immunoglobulin levels, and complement levels. He had normal liver and thyroid function, and a negative anti-nuclear antibody serology, rheumatoid factor, and Ehrlichia antibody screen. Lyme Western blot was equivocal, and a subsequent three-week course of doxycycline had no effect.

Over the next several months, he developed increasing skin thickening, associated with hand swelling and bilateral digital anesthesia, prompting nerve conduction studies, which were unrevealing. A skin biopsy several months prior to his presentation to our clinic demonstrated a palisaded granulomatous dermatitis with central necrobiosis, interpreted as most consistent with granuloma annulare. He was therefore treated for presumptive GA with topical steroids under occlusion and narrow-band UVB phototherapy.

He presented to our clinic after experiencing no benefit from steroids and phototherapy. At presentation, he had diffuse erythema and cutaneous thickening with infiltrated red-brown papules, especially on the upper extremities and thighs (Figures 1-3). There were infiltrated, broad skin folds over his extensor elbows and knees, and on his flanks with abdominal flexion (Figures 2 and 4).



Figure 1. (Crossed arms): Diffuse generalized erythema and skin-thickening, studded with firm waxy papules. **Figure 2.** (Lower extremities): Diffuse generalized erythema and skin-thickening, with markedly accentuated and lax skin folds over the extensor surfaces, including the knees. **Figure 3.** (Right forearm): Right forearm demonstrates the infiltrated firm coalescent waxy papules that covered much of his cutaneous surface. **Figure 4.** (Right elbow): Right elbow demonstrating the marked accentuation of lax skin folds over the extensor surfaces.

Repeat biopsies from the right forearm and abdomen were submitted for histologic examination; while awaiting those results, a serum protein electrophoresis revealed an IgG-lambda monoclonal gammopathy, with a spike at a level of 0.26 mg/dL. He subsequently underwent bone marrow evaluation and was ultimately diagnosed with monoclonal gammopathy of undetermined significance (MGUS).

Histologic findings from two biopsies on the day of presentation to our institution demonstrates interstitial histiocytes infiltrating through dermal collagen, in a plaque-like distribution in some areas (Figures 5-6), most suggestive of a granuloma annulare (GA)-like reaction. High power H&E reveals the presence of eosinophils within the histiocytic infiltrate (Figure 6). Colloidal iron stains reveals abundant mucin (Figures 7-8)

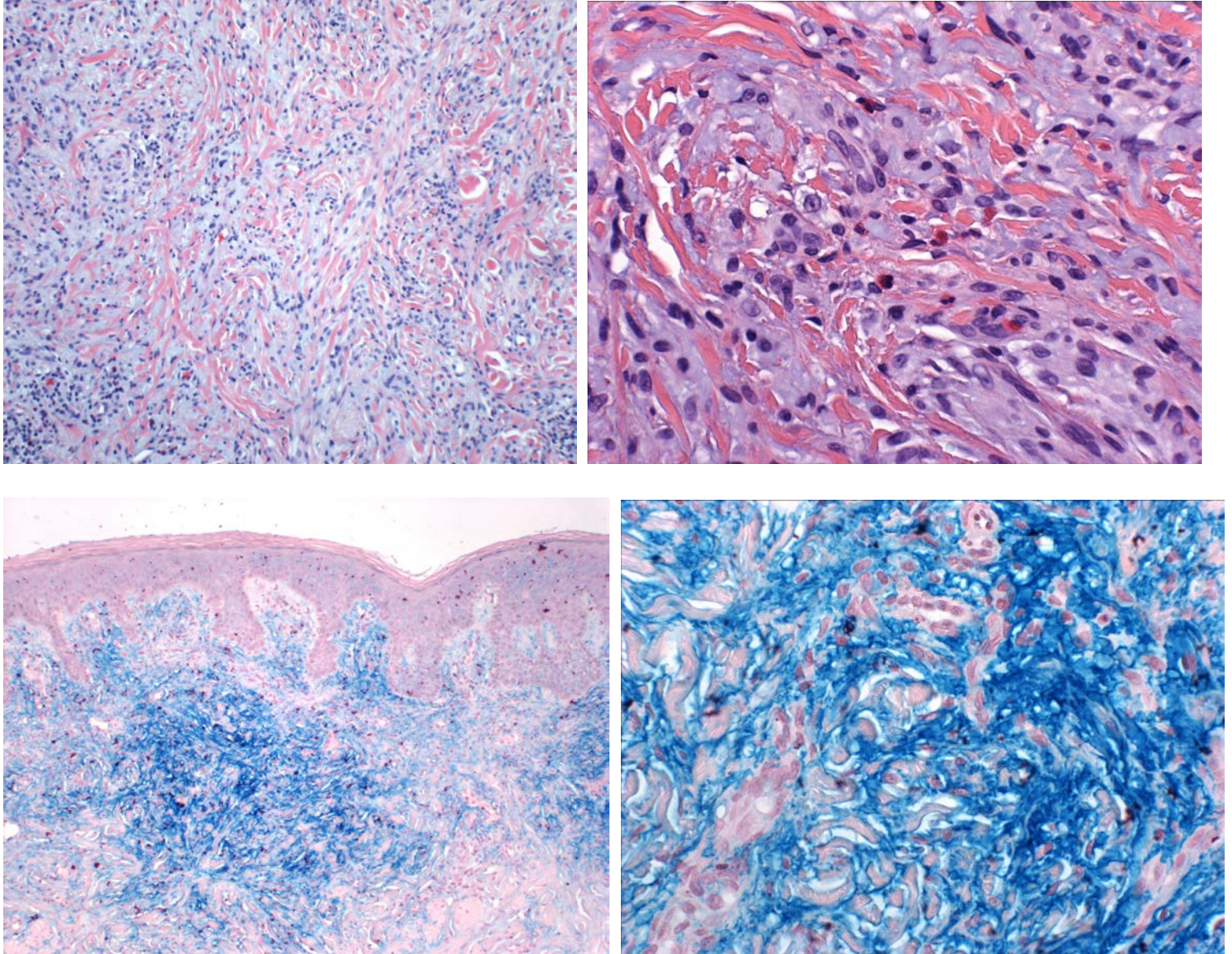


Figure 5. (Low Power H&E—100X): Numerous histiocytes are seen percolating through dermal collagen. **Figure 6.** (High power H&E — 400X): Interstitial granuloma annulare-like histiocytic infiltrate, with associated eosinophils. **Figure 7.** (Low power colloidal iron stain—100X): Abundant dermal mucin is demonstrated by colloidal iron stain. **Figure 8.** (High power Colloidal iron stain — 400X): Abundant dermal mucin.

In the context of his clinical findings and the newly discovered monoclonal gammopathy, the patient was diagnosed with scleromyxedema with GA-like histology and started on therapy with intravenous immune globulin (IVIG) at 0.5gm/kg daily for four consecutive days per month. Within the first two cycles, he had markedly improved mobility and resolution of erythema, edema, and pruritus. He has experienced near complete resolution of his generalized papules and cutaneous sclerosis at the time of this writing, six months after initiation of therapy.

Discussion

Scleromyxedema is a rare chronic fibromucinous disorder, also known as generalized lichen myxedematosus [1]. It is characterized by a generalized papular and sclerodermoid eruption, with mucin deposition, fibroblast proliferation, and fibrosis.

Unlike the localized papular form of lichen myxedematosus, scleromyxedema is closely associated with monoclonal gammopathy [2].

As in our patient, scleromyxedema causes papules and widespread sclerosis, with edema, induration, and erythema, predominantly affecting the face, hands, trunk, and thighs. Pruritus is common. Proximal interphalangeal joints may exhibit a central depression surrounded by an elevated rim on the extended proximal interphalangeal joint, the so-called ‘doughnut sign.’ Deep furrowing is also typically evident on the back, called “Shar-Pei sign,” and over the extensor surfaces of elbows and knees, as in our patient. Deep furrows and confluent papules on the glabella and chin in severe cases may produce leonine facies. There can be some clinical overlap with the shiny taut skin and resultant decreased joint mobility of scleroderma, but telangiectasias and calcinosis are not features of scleromyxedema.

Systemic manifestations may include proximal muscle weakness, peripheral neuropathy and central nervous system disturbances, arthralgias, carpal tunnel syndrome, restrictive or obstructive lung disease, dysphagia and nasal regurgitation, renal disease, and vasculopathy including mucinous deposition in the coronary artery walls [3]. Scleromyxedema is associated with Raynaud syndrome and other rheumatologic diseases.

Monoclonal gammopathy, which is most often the IgG-lambda sub-type, is a diagnostic criterion for scleromyxedema [4]. However, the pathogenic role of this gammopathy is uncertain, since paraprotein levels do not correlate with either the extent or the progression of the disease. The monoclonal gammopathy progresses to multiple myeloma in only about 10% of patients [3, 5]. Scleromyxedema has been associated with several other hematologic malignancies, including Hodgkin’s and non-Hodgkin’s lymphoma, Waldenström’s macroglobulinemia, and lymphocytic leukemias [5].

Biopsy of scleromyxedema typically reveals marked mucin deposition in the papillary dermis, in association with increased numbers of fibroblasts and haphazardly arranged collagen bundles [6].

The treatment of scleromyxedema is difficult and prognosis is guarded. A variety of approaches have been taken in the treatment of scleromyxedema, including extracorporeal photochemotherapy [7], electron beam radiation [8], intravenous immune globulin [9-11], interferon alpha [12, 13], corticosteroids [14], thalidomide [15-17], bortezomib [18-20], and autologous stem cell transplant [21-23]. Of note, our patient had failed treatment for presumed GA with narrow-band UVB (NB-UVB) phototherapy, even though other phototherapy modalities, PUVA and UVA-1, have been successful in treating scleromyxedema and other sclerosing diseases [24]. Our patient’s lack of response to NB-UVB is consistent with prior reports of UVB as an ineffective phototherapeutic modality for scleromyxedema [25], likely because UVB energy, unlike UVA energy, does not penetrate skin deeply enough to impact the deep cutaneous focus of scleromyxedema pathology.

The rapid and sustained improvement with IVIG noted in reports [26] on IVIG led us to choose IVIG shortly after diagnosing our patient with scleromyxedema. After failing therapy directed at GA for nearly a year, our patient experienced rapid and prolonged improvement with IVIG, further supporting the diagnosis of scleromyxedema.

A GA-like histologic pattern of scleromyxedema has been described twice previously in the literature (Table 1) [26, 27]. One of the reports speculated a reactive phenomenon similar to the cutaneous granulomatous response sometimes observed in the setting of systemic lymphoma [27]. In this context, the eosinophils noted in our patient’s biopsies, although of unknown significance and not characteristic of scleromyxedema or GA histology, may be a reflection of the condition’s reactive nature.

Table 1. Characteristics of reported scleromyxedema patients with granuloma annulare-like histology

	Study		
	Stetsenko, et al., 2008[27]	Rongioletti, et al., 2010[26]	Mullangi, et al., 2014*
Demographics			
Age	56	76	57
Sex	Male	Male	Male
Race	Caucasian	Caucasian	Caucasian
Clinical features			
Time Until Diagnosis	2 years	1 year	1 year
Symptoms			
Pruritus	Yes	ND	Yes
Joint pain/dysesthesia	ND	Yes	Yes
Cutaneous Morphology			
Generalized erythema	Yes	ND	Yes

Indurated papules	Yes Generalized, sparing upper chest, neck, forehead	Yes Glabella, forearms, periauricular	Yes Forearms, thighs, legs, abdomen, scalp, forehead
Sclerodermoid thickening	Yes	Yes	Yes
Functional loss	Yes Sclerodactyly, microstomia, joint contractures	Yes Sclerodactyly, microstomia, joint contractures	Yes Hand and wrist edema with dysesthesia and decreased mobility
Calcinosis and telangiectasia	ND	Absent	Absent
Other cutaneous features	General hyperpigmentation	Accentuated skin folds	Accentuated skin folds
Systemic features	Difficulty swallowing, esophageal dysmotility, weight loss, pulmonary obstruction and decreased diffusing lung capacity	Absent	Absent
Laboratory findings			
Monoclonal gammopathy	Ig-G kappa	Ig-G lambda	Ig-G lambda
Bone marrow biopsy	Monoclonal plasma cell population		Normocellular
Anti-nuclear antibodies	ANA 1:160	ANA-not reported. Negative anti-Scl70 and anti-centromere	Negative ANA
Histologic findings			
Abundant mucin	Yes-- patchy	Yes	Yes-- extensive
Histiocytic infiltrate	Band-like infiltrate in papillary and mid reticular dermis; loose granulomas among collagen fibers	Perivascular and interstitial infiltrate; loose granulomas among collagen fibers	Forearm: Band-like infiltrate Abdomen: Interstitial GA-like infiltrate
Immunohistochemistry	CD68 +; factor XIIIa +	CD68+	CD163 +
Associated infiltrate	Dermal scant chronic inflammatory infiltrate	CD3+ lymphocytes	Dermal chronic inflammatory infiltrate with eosinophils
Elastic fiber abnormalities	ND	Normal elastic tissue	Increased elastic fibers in 1 of 2 biopsies
Dense collagen bundles, fibroblast proliferation	Absent	Absent	Absent
Therapy			
Ineffective treatments	Clofazimine, dapsone, mycophenolate mofetil, prednisone, PUVA, topical steroids	None	Topical steroids, doxycycline, NB-UVB
Effective treatments	Dexamethasone + thalidomide	IVIg	IVIg
Response to therapy	Limited	Excellent, rapid	Excellent, rapid

*Current report

Abbreviations:

NB-UVB: Narrowband Ultraviolet-B

PUVA: Psoralen + Ultraviolet-A

IVIg: Intravenous immunoglobulin

ANA: Antinuclear antibodies

GA: Granuloma Annulare

ND: not discussed

In the prior two reports, as in our patient, the unusual GA-like histologic pattern resulted in diagnostic and therapeutic delay despite the relatively typical clinical findings of scleromyxedema. In all three patients, the classic clinical features of scleromyxedema, including sclerodermoid skin thickening, diffuse skin-colored waxy papules, and a monoclonal gammopathy ultimately resulted in a diagnosis of scleromyxedema, despite the atypical histology. In all three patients, therapy directed at the underlying paraproteinemia ultimately resulted in clinical improvement; our patient has maintained his near complete response for over one year since shifting therapy to a modality specifically intended for paraproteinemia-associated scleromyxedema.

Conclusion

In this case, we have described a patient presenting with MGUS and scleromyxedema, whose diagnosis was delayed owing to histology suggestive of interstitial granuloma annulare. Ultimately, he did very well with treatment that is used for more traditional scleromyxedema, after failing various treatments directed at GA. This report adds to the very small body of literature on this poorly recognized variant of scleromyxedema. Greater familiarity with this GA-like histologic pattern in some patients with scleromyxedema is likely to facilitate the diagnosis of this disease. Given the availability of reasonable management options for this variant of scleromyxedema, early diagnosis enables more appropriate and timely therapy, with potential to substantially improve patient function and comfort, as it has for our patient.

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