Scleromyxedema in a Patient With Thyroid Disease: An Atypical Case or a Case for Revised Criteria?

Ezra Hazan, MD; Thomas D. Griffin Jr, MD; Serge A. Jabbour, MD; Matthew S. Keller, MD

PRACTICE **POINTS**

- Scleromyxedema (SM) is progressive disease of unknown etiology with unpredictable behavior.
- Systemic manifestations associated with SM can cause serious morbidity and mortality.
- Intravenous immunoglobulin is the most effective treatment modality in SM.
- The presence of thyroid disease should not preclude the diagnosis of SM.

Lichen myxedematosus (LM), commonly referred to as papular mucinosis, is a rare papular eruption defined by mucin deposition in the dermis. Scleromyxedema (SM) is a generalized papular and sclerodermoid form of LM. It is a progressive disease of unknown etiology with systemic manifestations that cause serious morbidity and mortality. Current criteria list thyroid dysfunction as an exclusion for the diagnosis of SM. Cases of LM associated with thyroid dysfunction have been defined as atypical. We describe a patient with uncontrolled hypothyroidism due to Hashimoto thyroiditis who subsequently developed a diffuse papular eruption with systemic signs and symptoms attributable to SM. Diagnostic workup, including laboratory studies and histologic specimens from the skin and muscle, were consistent with SM. Furthermore, our patient responded clinically to intravenous immunoglobulin (IVIg) and lenalidomide. We discuss the diagnostic criteria, differential diagnoses, and diagnostic challenges associated with LM in association with thyroid dysfunction. We propose that the presence of thyroid disease should not preclude the diagnosis of SM. Finally, we add to the case reports and series of successful treatments of SM with IVIg and lenalidomide.

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Scleromyxedema (SM) is a generalized papular and sclerodermoid form of lichen myxedematosus (LM), commonly referred to as papular mucinosis. It is a rare progressive disease of unknown etiology with systemic manifestations that cause serious morbidity and mortality. Diagnostic criteria were initially created by Montgomery and Underwood[1] in 1953 and revised by Rongioletti and Rebora[2] in 2001 as follows: (1) generalized papular and sclerodermoid eruption; (2) histologic triad of mucin deposition, fibroblast proliferation, and fibrosis; (3) monoclonal gammopathy; and (4) absence of thyroid disease. There are several reports of LM in association with hypothyroidism, most of which can be characterized as atypical.[3-8] We present a case of SM in a patient with Hashimoto thyroiditis and propose that the presence of thyroid disease should not preclude the diagnosis of SM.

Case Report

A 44-year-old woman presented with a progressive eruption of thickened skin and papules spanning many months. The papules ranged from flesh colored to erythematous and covered more than 80% of the body surface area, most notably involving the face, neck, ears, arms, chest, abdomen, and thighs (Figures 1A and 2A). Review of systems was notable for pruritus, muscle pain but no weakness, dysphagia, and constipation. Her medical history included childhood atopic dermatitis and Hashimoto thyroiditis. Hypothyroidism was diagnosed with support of a thyroid ultrasound and thyroid peroxidase antibodies. It was treated with oral levothyroxine for 2 years prior to

All from Thomas Jefferson University Hospital, Philadelphia, Pennsylvania. Drs. Hazan, Griffin, and Keller are from the Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College. Dr. Jabbour is from the Division of Endocrinology, Diabetes and Metabolic Diseases.
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Correspondence: Ezra Hazan, MD, 833 Chestnut St, Ste 740, Philadelphia, PA 19107 (ezra.hazan@jefferson.edu).

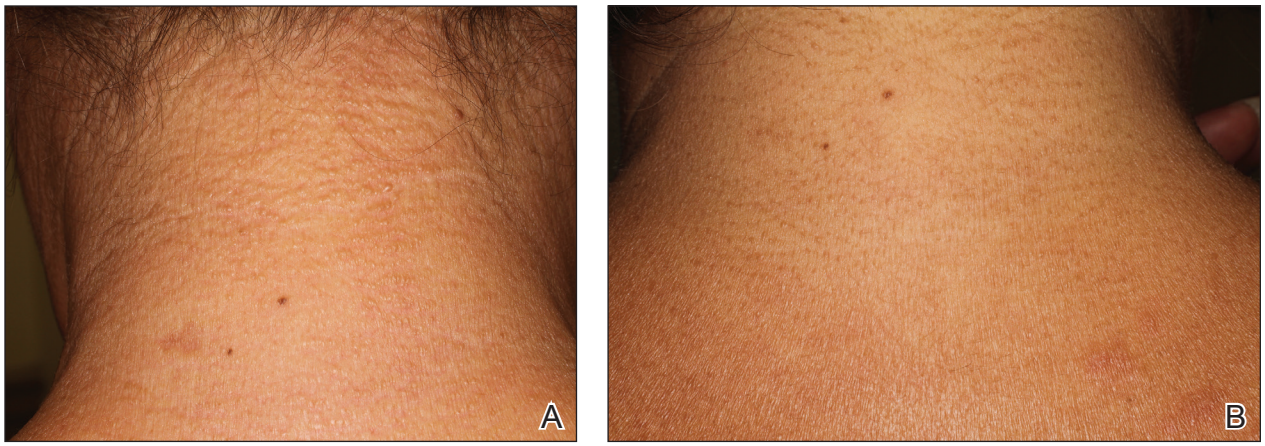

FIGURE 1. A, Posterior neck at initial presentation showing 1- to 3-mm papules ranging from flesh colored to erythematous. B, Resolution of the skin eruption after treatment with intravenous immunoglobulin and lenalidomide.

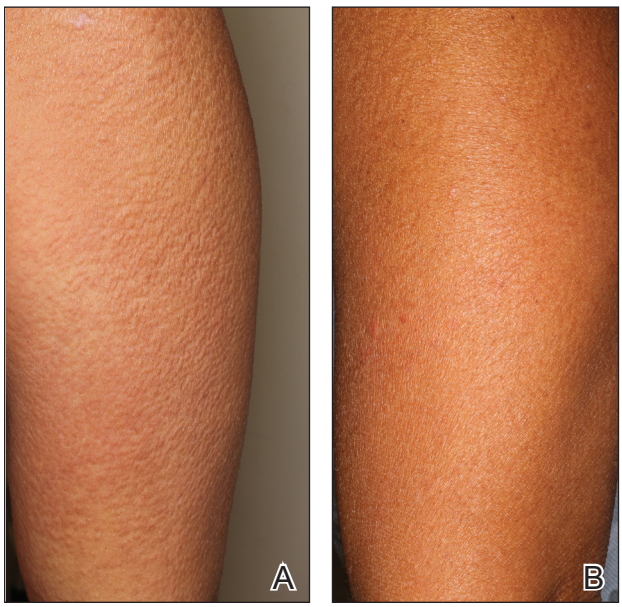

FIGURE 2. A, Left upper arm at initial presentation showing 1- to 3-mm papules ranging from flesh colored to erythematous. B, Resolution of the skin eruption after treatment with intravenous immunoglobulin and lenalidomide.

the skin eruption. Thyroid biopsy was not performed. Her thyroid-stimulating hormone levels notably fluctuated in the year prior to presentation despite close clinical and laboratory monitoring by an endocrinologist. Laboratory results are summarized in Table 1. Both skin and muscle[9] biopsies were consistent with SM (Figure 3) and are summarized in Table 1.

Shortly after presentation to our clinic the patient developed acute concerns of confusion and muscle weakness. She was admitted for further inpatient management due to concern for dermato-neuro syndrome, a rare but potentially fatal decline in neurological status that can progress to coma and death, rather than myxedema coma.

TABLE 1. Workup at Presentation in Our Patient With Scleromyxedema

Test	Result
Serum protein electrophoresis, g/dL	0.3-M spike with IgG λ chain (reference range, 0.5–1.4)
Creatine kinase, U/L	1212 (reference range, 30–170)
Aldolase, U/L	12.8 (reference range, <7.5)
Thyroid peroxidase antibody, IU/mL	632 (reference range, <35)
Thyroid-stimulating hormone, uU/mL	0.03 to 419 (reference range, 0.3–4.35)
Free triiodothyronine (FT_3), pg/mL	1.5 (reference range, 2.3–4.2)
Free thyroxine (FT_4), ng/dL	0.51 (reference range, 0.8–2.8)
Complete blood cell count, comprehensive metabolic panel, erythrocyte sedimentation rate, C-reactive protein, peripheral blood smear, hepatitis panel, flow cytometry, autoimmune antibody panel, human immunodeficiency virus 1 and 2, and free κ/λ ratio were all within reference range/nonreactive. Bone scan; computed tomography of chest, abdomen, and pelvis; and colonoscopy were unrevealing.	
Skin biopsy	Increased fibroblasts and increased mucin accumulation in the dermis
Muscle biopsy	Vacuolar myopathy with empty vacuoles

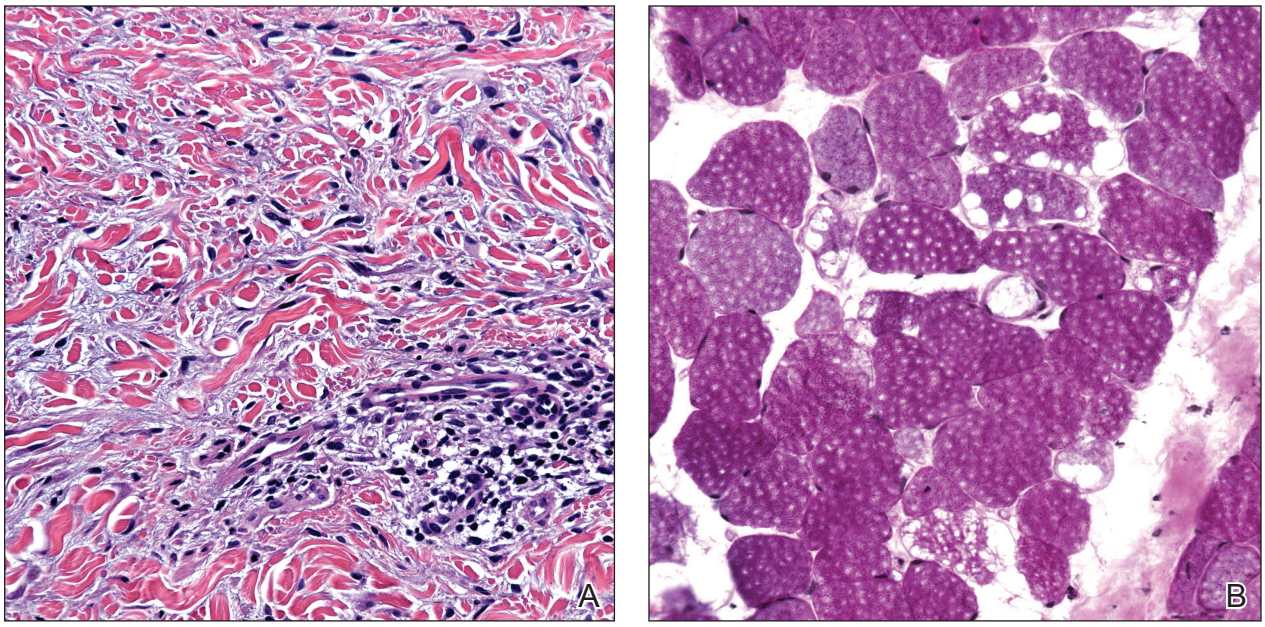

FIGURE 3. A, Increased number of fibroblasts and mucin deposition splayed between collagen bundles (H&E, original magnification ×400). B, Large, empty, cytoplasmic vacuoles with marked variation in muscle fiber size and paucity of inflammation and necrosis (periodic acid–Schiff, original magnification ×20).

On admission, a thyroid function test showed subclinical hypothyroidism with a thyroid-stimulating hormone level of 6.35 uU/mL (reference range, 0.3–4.35 uU/mL) and free thyroxine (FT_4) level of 1.5 ng/dL (reference range, 0.8–2.8 ng/dL). While hospitalized she was started on intravenous levothyroxine, systemic steroids, and a course of intravenous immunoglobulin (IVIg) treatment consisting of 2 g/kg divided over 5 days. On this regimen, her mental status quickly returned to baseline and other symptoms improved, including the skin eruption (Figures 1B and 2B). She has been maintained on lenalidomide 25 mg/d for the first 3 weeks of each month as well as monthly IVIg infusions. Her thyroid levels have persistently fluctuated despite intramuscular levothyroxine dosing, but her skin has remained clear with continued SM-directed therapy.

Comment

Classification—Lichen myxedematosus is differentiated into localized and generalized forms. The former is limited to the skin and lacks monoclonal gammopathy. The latter, also known as SM, is associated with monoclonal gammopathy and systemic symptoms. *Atypical LM* is an umbrella term for intermediate cases.

Clinical Presentation—Skin manifestations of SM are described as 1- to 3-mm, firm, waxy, dome-shaped papules that commonly affect the hands, forearms, face, neck, trunk, and thighs. The surrounding skin may be reddish brown and edematous with evidence of skin thickening. Extracutaneous manifestations in SM are numerous and unpredictable. Any organ system can be involved, but gastrointestinal, rheumatologic, pulmonary, and cardiovascular complications are most common.[10] A comprehensive multidisciplinary evaluation is necessary based on clinical symptoms and laboratory findings.

Management—Many treatments have been proposed for SM in case reports and case series. Prior treatments have had little success. Most recently, in one of the largest case series on SM, Rongioletti et al[10] demonstrated IVIg to be a safe and effective treatment modality.

Differential Diagnosis—An important differential diagnosis is generalized myxedema, which is seen in longstanding hypothyroidism and may present with cutaneous mucinosis and systemic symptoms that resemble SM. Hypothyroid myxedema is associated with a widespread slowing of the body's metabolic processes and deposition of mucin in various organs, including the skin, creating a generalized nonpitting edema. Classic clinical signs include macroglossia, periorbital puffiness, thick lips, and acral swelling. The skin tends to be cold, dry, and pale. Hair is characterized as being coarse, dry, and brittle with diffuse partial alopecia. Histologically, there is hyperkeratosis with follicular plugging and diffuse mucin and edema splaying between collagen fibers spanning the entire dermis.[11] In contradistinction with SM, there is no fibroblast proliferation. The treatment is thyroid replacement therapy. Hyperthyroidism has distinct clinical and histologic changes. Clinically, there is moist and smooth skin with soft, fine, and sometimes alopecic hair. Graves disease, the most common cause of hyperthyroidism, is further characterized by Graves ophthalmopathy and pretibial myxedema, or pink to brown, raised, firm, indurated,

TABLE 2. Summary of Case Reports That Potentially Describe LM Associated With Hypothyroidism

Reference (Year)	Clinical Presentation	Skin Histology	Monoclonal Spike	Systemic Symptoms	Treatment	Outcome	Presumed Diagnosis
Archibald and Calvert[3] (1977)	Recurrent transient ischemic attacks; grouped lichenoid papules on extremities	Mucin in upper dermis; fibroplasia	IgG κ chain	Lethargy, poverty of thought	Thyroxine and coumadin	Resolved CNS; unknown skin outcome	Atypical LM; possibly scleromyxedema
Schaeffer et al[4] (1983)	Hashimoto thyroiditis with cool dry skin; papules on extremities; no skin thickening	Diffuse mucin in lower dermis; no fibroplasia	No	None	UVB/thyroxine	Resolved	Atypical thyroid dermopathy
Martin-Ezquerra et al[5] (2006)	Papules on abdomen; subclinical hypothyroidism	Mucin; mild fibroplasia	No	None	Thyroxine	Resolved	Atypical thyroid dermopathy
Volpato et al[6] (2010)	Large annular plaques; subclinical hypothyroidism	Inflammation, diffuse mucin; no fibroplasia	No	Fatigue, arthralgia	Thyroxine	Resolved systemic symptoms; skin persisted	Atypical LM
Macnab and Kenny[7] (2013)	Generalized papular eruption; subclinical hypothyroidism	Mucin; fibroplasia	IgG λ chain	CNS	Intravenous immunoglobulin	Resolved skin and CNS; thyroid uncontrolled	Scleromyxedema
Shenoy et al[8] (2019)	Progressive cutaneous thickening	Increased mucin, fibroblasts; perivascular mixed inflammation	Delayed spike in IgG λ chain	None	Intravenous immunoglobulin	Cleared but recurred when dose was decreased	Scleromyxedema
	Diffuse waxy papules	Palisading lymphocytes and histiocytes around mucin	None	Rheumatoid arthritis	Systemic steroids	Responded to systemic steroids but recurred with cessation of therapy	LM

Abbreviations: LM, lichen myxedematosus; CNS, central nervous system.

asymmetric plaques most commonly affecting the shins. Histologically there is increased mucin in the lower to mid dermis without fibroblast proliferation. The epidermis can be hyperkeratotic, which will clinically correlate with verrucous lesions.[12]

Hypothyroid encephalopathy is a rare disorder that can cause a change in mental status. It is a steroid-responsive autoimmune process characterized by encephalopathy that is associated with cognitive impairment and psychiatric features. It is a diagnosis of exclusion and should be suspected in women with a history of autoimmune disease, especially antithyroid peroxidase antibodies, a negative infectious workup, and encephalitis with behavioral changes. Although typically highly responsive to systemic steroids, IVIg also has shown efficacy.[13]

Presence of Thyroid Disease—According to a PubMed search of articles indexed for MEDLINE using the terms *scleromyxedema* and *lichen myxedematosus*, there are 7 cases in the literature that potentially describe LM associated with hypothyroidism (Table 2).[3-8] The majority of these cases lack monoclonal gammopathy; improved with thyroid replacement therapy; or had severely atypical clinical presentations, rendering them cases of atypical LM or atypical thyroid dermopathy.[3-6] Macnab and Kenny[7] presented a case of subclinical hypothyroidism with a generalized papular eruption, monoclonal gammopathy, and consistent histologic changes that responded to IVIg therapy. These findings are suggestive of SM, but limited to the current diagnostic criteria, the patient was diagnosed with atypical LM.[7] Shenoy et al[8] described 2 cases of LM with hypothyroidism. One patient had biopsy-proven SM that was responsive to IVIg as well as Hashimoto thyroiditis with delayed onset of monoclonal gammopathy. The second patient had a medical history of hypothyroidism and Hodgkin lymphoma with active rheumatoid arthritis and biopsy-proven LM that was responsive to systemic steroids.[8]

Current literature states that thyroid disorder precludes the diagnosis of SM. However, historic literature would suggest otherwise. Because of inconsistent reports and theories regarding the pathogenesis of various sclerodermoid and mucin deposition diseases, in 1953 Montgomery and Underwood[1] sought to differentiate LM from scleroderma and generalized myxedema. They stressed clinical appearance and proposed diagnostic criteria for LM as generalized papular mucinosis in which "[n]o relation to disturbance of the thyroid or other endocrine glands is apparent," whereas generalized myxedema was defined as a "[t]rue cutaneous myxedema, with diffuse edema and the usual commonly recognized changes" in patients with endocrine abnormalities.[1] With this classification, the authors made a clear distinction between mucinosis caused by thyroid abnormalities and LM, which is not caused by a thyroid disorder. Since this original description was published, associations with monoclonal gammopathy and fibroblast proliferation have been made, ultimately culminating into the current 2001 criteria that incorporate the absence of thyroid disease.[2]

Conclusion

We believe our case is consistent with the classification initially proposed by Montgomery and Underwood[1] and is strengthened with the more recent associations with monoclonal gammopathy and specific histopathologic findings. Although there is no definitive way to rule out myxedema coma or Hashimoto encephalopathy to describe our patient's transient neurologic decline, her clinical symptoms, laboratory findings, and biopsy results all supported the diagnosis of SM. Furthermore, her response to SM-directed therapy, despite fluctuating thyroid function test results, also supported the diagnosis. In the setting of cutaneous mucinosis with conflicting findings for hypothyroid myxedema, LM should be ruled out. Given the features presented in this report and others, diagnostic criteria should allow for SM and thyroid dysfunction to be concurrent diagnoses. Most importantly, we believe it is essential to identify and diagnose SM in a timely manner to facilitate SM-directed therapy, namely IVIg, to potentially minimize the disease's notable morbidity and mortality.

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