Seminars in Cutaneous Medicine and Surgery

Lichen Myxedematosus (Papular Mucinosis): New Concepts and Perspectives for an Old Disease

Franco Rongioletti, MD

Lichen myxedematosus (LM) is an idiopathic cutaneous mucinosis; its classification dates back to 1953, when Montgomery and Underwood distinguished 4 types of LM. In the literature, the terms LM, papular mucinosis, and scleromyxedema often have been used indiscriminately as synonyms, but most reported cases of LM or papular mucinosis without indication of the subtype appear in fact to be cases of scleromyxedema. Actually, LM includes 2 clinicopathologic subsets: a generalized papular and sclerodermoid form (the only one which should be called scleromyxedema) with systemic, even lethal, manifestations and a localized form, which does not run a disabling course. The localized form is subdivided into 4 subtypes: (1) a discrete papular form involving any site; (2) acral persistent papular mucinosis involving only the extensor surface of the hands and wrists; (3) papular mucinosis of infancy, a pediatric variant of the discrete form or the acral form of persistent papular mucinosis; and (4) nodular form. A third group of atypical or intermediate forms, not meeting the criteria for either scleromyxedema or the localized form, includes cases of (1) scleromyxedema without monoclonal gammopathy, (2) localized forms with monoclonal gammopathy and/or systemic symptoms, (3) localized forms with mixed features of the subtypes, and (4) not well-specified cases.

KEYWORDS mucin, scleromyxedema, lichen myxedematosus, papular mucinosis

Lichen myxedematosus (LM) is a chronic idiopathic disorder characterized by lichenoid papules, nodules and/or plaques caused by dermal mucin deposition and a variable degree of fibrosis in the absence of thyroid disease.[1] Although the first descriptions of LM were attributed to Dubreuilh in 1906 and Reitman in 1908, it was not until the review of Montgomery and Underwood in 1953 that the disease was distinguished from scleroderma and generalized myxedema and that different clinical patterns were recognized.[2] A year later, Gottron and his colleagues gave the name scleromyxedema to the generalized and sclerotic form. The association of a monoclonal gammopathy with scleromyxedema was first described in 1963.

Actually, LM includes 2 clinicopathologic subsets[1]: (1) a generalized papular and sclerodermoid form (also called scleromyxedema) with a monoclonal gammopathy and systemic, even lethal, manifestations and (2) a localized papular form which does not run a disabling course. Making a distinction between these forms is important because there are differences in prognosis and therapeutic approach. Occasionally, patients with LM have overlapping or atypical features and fall between scleromyxedema and localized LM (atypical forms; Table 1).

Epidemiology and Pathogenesis

The generalized and sclerodermoid form of LM is termed scleromyxedema. It is an uncommon disease. Scleromyxedema affects middle-aged adults of both sexes equally. The localized form appears to be seen less frequently, but its prevalence is probably underestimated. The pathogenesis of LM is unknown. The significance of the monoclonal gammopathy in patients with scleromyxedema is still debated. Paraprotein levels do not correlate with either the extent or the progression of the disease. However, although serum from patients with scleromyxedema enhanced fibroblast proliferation in vitro, an immunoglobulin purified from the paraprotein-containing serum failed to do so, suggesting a pathogenetic role for circulating factors other than the paraprotein. Clinical remission of scleromyxedema following autologous stem cell transplantation points to the bone marrow

Dermatology Section, Department of Endocrinological and Metabolic Diseases, Universiyy of Genoa, Genoa, Italy.
Address reprint requests to Franco Rongioletti, Clinica Dermatologica, viale Benedetto XV,7 16132, Genova, Italy. E-mail: frongioletti@libero.it

 1085-5629/06/$-see front matter
doi:10.1016/j.sder.2006.04.001

Table 1 Clinicopathologic Subsets of Lichen Myxedematosus (Papular Mucinosis)

Clinicopathologic Subsets of Lichen Myxedematosus
Generalized papular and sclerodermoid (scleromyxedema)
Localized:
Discrete lichen myxedematosus*
Acral persistent papular mucinosis*
Cutaneous mucinosis of infancy
Nodular type
Atypical forms

*May affect HIV-infected patients.

as a source of these circulating factors. The development of scleromyxedema following a cutaneous granulomatous reaction after intradermal hyaluronic gel injections may also suggest a type of human adjuvant disease.[3]

Clinical Features

Scleromyxedema

In scleromyxedema, there is a widespread symmetric eruption of 2 to 3 mm, firm, waxy, closely spaced papules. The most common sites of involvement are the hands, forearms, head and neck region (Fig. 1), upper trunk, and thighs. Papules often are arranged in a strikingly linear array; the surrounding skin is shiny and indurated, ie, sclerodermoid in appearance. The glabela typically is involved with deep longitudinal furrowing (Fig. 2). Erythema, edema, and a brownish discoloration also may be seen in the involved areas; pruritus is not rare. The mucous membranes and scalp are spared. As the condition progresses, erythematous and infiltrated plaques may appear with skin stiffening, sclerodactyly and decreased motility of the mouth and joints. On the proximal interphalangeal joints, a central depression surrounded by an elevated rim (due to the skin thickening) can be seen and is referred to as the "doughnut sign." Telangiectasias and calcinosis are always absent.

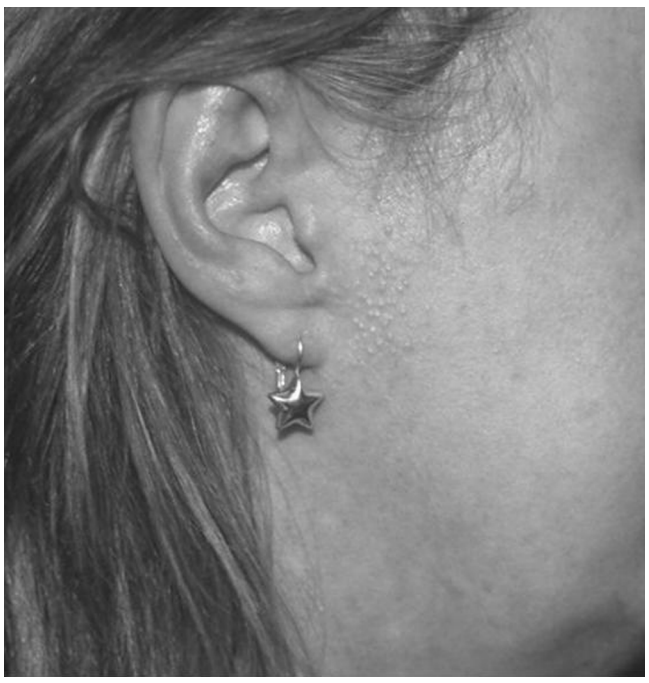

Figure 1 Papules on indurated skin in scleromyxedema. (A color version of this figure is available online.)

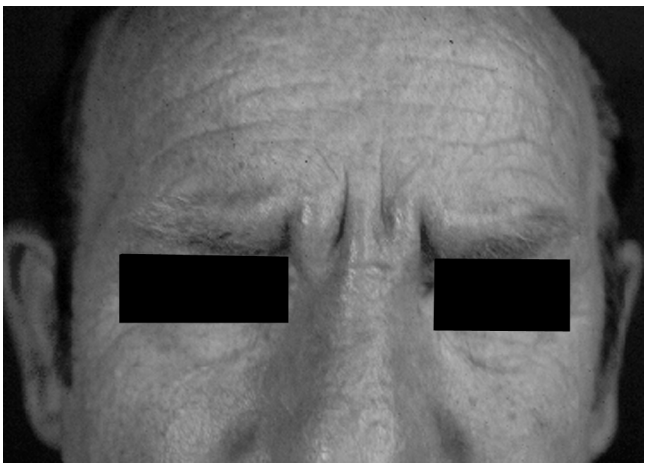

Figure 2 Deep longitudinal furrows on the glabela in scleromyxedema. (A color version of this figure is available online.)

Scleromyxedema almost always is associated with paraproteinemia. The monoclonal gammopathy is usually IgG with γ light chains. Although a mild plasmacytosis may be found in the bone marrow, scleromyxedema progresses to multiple myeloma in less than 10% of cases. Patients with scleromyxedema can have a number of internal manifestations, ie, muscular, neurologic, rheumatologic, pulmonary, renal, and cardiovascular. Dysphagia, proximal muscle weakness caused by myositis, disturbances of the central nervous system (dermato-neuro syndrome) leading to psychosis, convulsions and encephalopathy with unexplained coma,[4] peripheral neuropathy, arthropathies, carpal tunnel syndrome, restrictive or obstructive lung disease, and a scleroderma-like renal disease may accompany or follow the cutaneous manifestations.

Localized LM

In localized LM, the patients exhibit small, firm, waxy papules (or nodules and plaques produced by the confluence of papules) confined to only a few sites (usually the upper and lower limbs and trunk) without sclerotic features, paraproteinemia, systemic involvement or thyroid disease. Localized LM is subdivided into four subtypes: (1) a discrete papular form, (2) acral persistent papular mucinosis, (3) cutaneous mucinosis of infancy, and (4) a pure nodular form. Moreover, localized LM may be observed in association with HIV infection, exposure to toxic oil or L-tryptophan, and hepatitis C virus infection.

Discrete LM is characterized by a chronic eruption of 2- to 5-mm papules, numbering from just a few to hundreds and involving the limbs and trunk (Fig. 3) in a symmetric pattern.[5] The affected skin is not indurated, and the face is

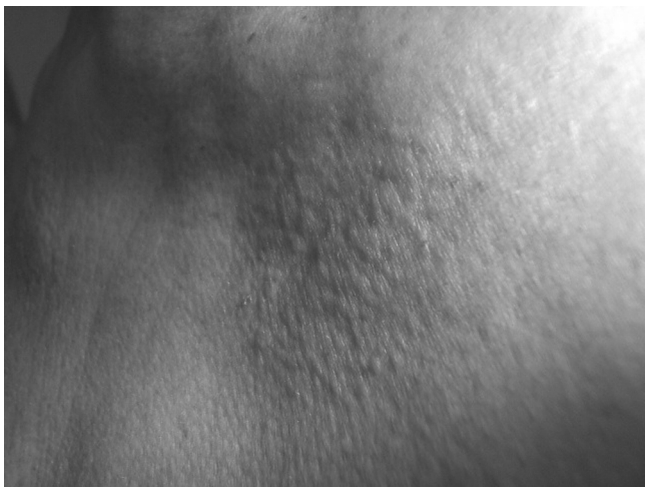

Figure 3 Papules without induration in localized LM (discrete type). (A color version of this figure is available online.)

spared. The lesions progress slowly without systemic involvement. However, they rarely resolve spontaneously. Progression to scleromyxedema has never been really proven.

In acral persistent papular mucinosis, first described in 1986,[6] multiple ivory to flesh-colored papules develop exclusively on the back of the hands and extensor surface of the distal forearms (Fig. 4). Twenty cases of this entity have been convincingly reported with a preponderance of female (3:1), whereas some other cases described under this label do not fit the defined diagnostic criteria.[7] The lesions persist without systemic manifestations.

In cutaneous mucinosis of infancy (syn. papular mucinosis of infancy), first described by Lum in 1980, firm opalescent papules appear on the upper arms (especially the elbows) and the trunk.[8] There are neither systemic symptoms nor spontaneous resolution. Of the handful of patients described to date, at least 2 have had a congenital linear variant, which might be better categorized as an example of a mucinous nevus.

Nodular LM is characterized by multiple nodules on the limbs and trunk, with a mild or absent papular component. Localized LM in patients with HIV has been described in 14 HIV-positive men, both homosexuals and drug-abusers. Twelve of them developed the discrete form on the limbs and trunk, and 2 had acral persistent papular mucinosis. All became infected with HIV before the onset of LM. Most of them had hypergammaglobulinemia and only two had a paraproteinemia. None had visceral involvement due to mucin deposition.[9]

Localized LM in "Toxic" Syndromes

Multiple papules caused by mucin deposition with a clinical appearance similar to discrete LM also have been described in the setting of toxic oil syndrome and L-tryptophan-associated eosinophilia–myalgia syndrome. Although unrelated epidemiologically, toxic oil syndrome caused by the ingestion of adulterated rapeseed oil in Spain and L-tryptophan-associated eosinophilia–myalgia related to a contaminant of L-tryptophan-containing products share in common some clinical features, including constitutional symptoms, peripheral eosinophilia, and skin changes. The latter consist of a mucinous papular eruption, hyperpigmentation, and a sclerodermoid appearance.[10] The mucinous papules develop on the limbs 1 to 5 months after the onset of the illness and subside slowly after discontinuation of the toxic substance.

Localized LM and Hepatitis C Infection

An association of LM with chronic hepatitis due to hepatitis C infection has been reported,[11] especially from Japan,[12] and this relationship needs to be confirmed by more extensive studies.

Atypical Forms of LM

Some patients with LM have atypical features or features intermediate between scleromyxedema and localized LM.[1] This category includes patients with (1) scleromyxedema without monoclonal gammopathy, (2) localized forms with monoclonal gammopathy and/or systemic symptoms, and (3) not well-delineated cases.

Pathology

Scleromyxedema is characterized by a triad of microscopic features that includes[13] (1) a diffuse deposit of mucin in the upper and mid-reticular dermis, (2) an increase in collagen

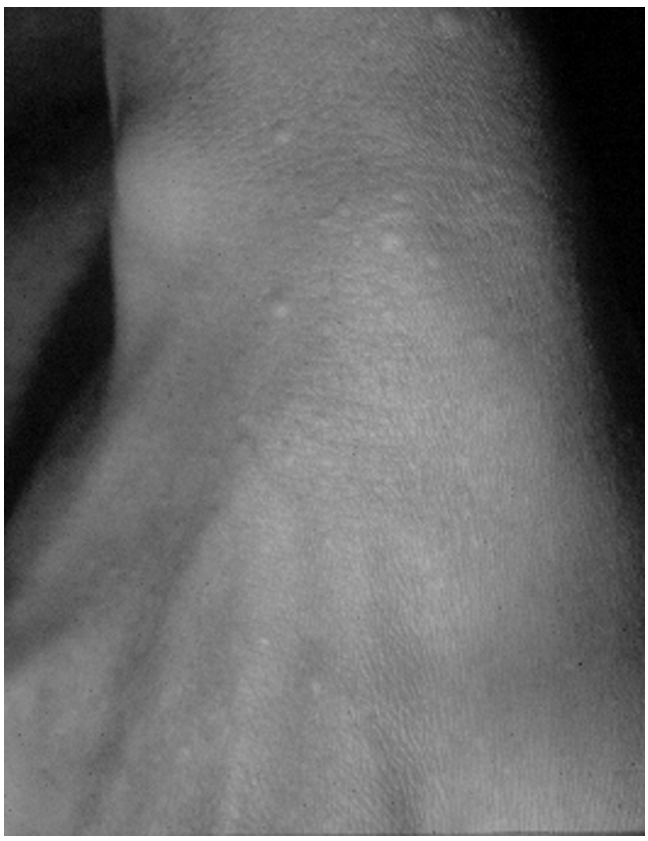

Figure 4 Acral persistent popular mucinosis. (A color version of this figure is available online.)

Table 2 Diagnostic Criteria of Lichen Myxedematosus (Papular Mucinosis)

Diagnostic Criteria of Lichen Myxedematosus	
Scleromyxedema	Localized lichen myxedematosus
Generalized papular and sclerodermoid eruption	Papular eruption (or nodules and/or plaques due to confluence of papules)
Microscopic triad (mucin deposition, fibroblast proliferation, fibrosis)	Mucin deposition with variable fibroblast proliferation
Monoclonal gammopathy	Absence of monoclonal gammopathy
Absence of thyroid disorder	Absence of thyroid disorder

deposition, and (3) a marked proliferation of irregularly arranged fibroblasts.

The epidermis may be normal or thinned by the presence of the underlying mucin and fibrosis, the hair follicles may be atrophic, and a slight perivascular, superficial, lymphoplasmacytic infiltrate is often present. The elastic fibers are fragmented and decreased in number. Mucin may fill the walls of myocardial blood vessels as well as the interstitium of the kidney, pancreas, adrenal glands and nerves.

In the localized forms the changes are less characteristic. Mucin accumulates in the upper- and mid-reticular dermis, fibroblast proliferation is variable, and fibrosis is not marked and may even be absent. In acral persistent papular mucinosis, mucin accumulates focally in the upper reticular dermis (sparing a subepidermal zone) and fibroblasts are not increased in number.

Differential Diagnosis

Histologic examination of the skin helps to distinguish localized LM from several papular eruptions that have a similar appearance, such as granuloma annulare, lichen amyloidosus, lichen planus and other lichenoid eruptions, and eruptive collagenoma. Scleromyxedema should be distinguished mainly from systemic scleroderma and scleredema. The presence of papules, especially in linear arrays, is a very helpful clinical sign in scleromyxedema. Another important differential diagnosis is with nephrogenic fibrosing dermopathy that is seen in patients with serious renal dysfunction in the absence of face involvement (commonly seen in scleromyxedema) and paraproteinemia.[14] Criteria for diagnosing scleromyxedema versus localized LM are summarized in Table 2.

Treatment

In general, the treatment of scleromyxedema is disappointing. In the United States, melphalan has been the therapy of choice, targeting the plasma cell dyscrasia. This alkylating agent can result in some clinical improvement, but it has also been implicated in 30% of the deaths secondary to its induction of hematologic malignancies and septic complications.[15] Other chemotherapeutic agents have been tried, such as cyclophosphamide, methotrexate, chlorambucil, and 2-chlorodesoxyadenosine, but with no better results and similar side effects. Systemic corticosteroids are also often used with variable, but temporary, results. A complete and durable response to high-dose dexamethasone has been recently suggested.[16]

The use of intralesional and topical corticosteroids has met with limited success. Topical and intralesional hyaluronidase, electron-beam radiation, extracorporeal photochemotherapy, plasmapheresis, PUVA, retinoids, dermabrasion, and topical dimethyl sulfoxide have all produced some improvement without treating the underlying disease. Granulocyte colony-stimulating factor proved beneficial in one patient with idiopathic neutropenia, as did cyclosporine in a second patient. Interferon alfa has led to paradoxical effects, both improving and worsening LM.[17] High-dose intravenous immunoglobulins,[18] autologous stem cell transplantation both alone or associated with high-dose melphalan,[19] and thalidomide[20] may represent promising therapies. In addition, spontaneous improvement and clinical resolution, even after 15 years, have been described. The use of potentially toxic drugs should be limited to patients who are disfigured, disabled, or very ill. Dysarthria and a flu-like illness may herald coma, and the patient should be promptly admitted to hospital for close observation.

Localized LM does not require therapy, and a wait-and-see approach is recommended. Topical corticosteroids may be of some benefit. One patient with associated HIV infection had complete remission after treatment with oral isotretinoin. Pimecrolimus gave relief in another case.[5] However, spontaneous resolution may occur,[21] even in the setting of HIV-associated cases.[9]

References

1. Rongioletti F, Rebora A: Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. J Am Acad Dermatol 44:273-281, 2001
2. Montgomery H, Underwood LJ: Lichen myxedematosus; differentiation from cutaneous myxedemas or mucoid states. J Invest Dermatol 20:213-236, 1953
3. Rongioletti F, Cattarini G, Sottofattori E, et al: Granulomatous reaction after intradermal injections of hyaluronic acid gel. Arch Dermatol 139: 815-816, 2003
4. Rongioletti F, Hazini A, Rebora A: Coma associated with scleromyxedema and interferon alfa therapy. Full recovery after steroids and cyclophosphamide combined with plasmapheresis. Br J Dermatol 144: 1283-1284, 2001
5. Sulis DJ, Harford R, O,Neil JT: Discrete papular form of lichen myxedematosus: a case report and review of the literature. Cutis 75:105-112, 2005
6. Rongioletti F, Rebora A, Crovato F: Acral persistent papular mucinosis: a new entity. Arch Dermatol 122:1237-1239, 1986

7. Harris JE, Purcell SM, Griffin TD: Acral persistent papular mucinosis. J Am Acad Dermatol 51:982-988, 2004
8. Podda M, Rongioletti F, Greiner D, et al: Cutaneous mucinosis of infancy: is it a real entity or the paediatric form of lichen myxoedematosus (papular mucinosis)? Br J Dermatol 144:590-593, 2001
9. Rongioletti F, Ghigliotti G, De Marchi R, et al: Cutaneous mucinoses and HIV infection. Br J Dermatol 139:1077-1080, 1998
10. Rongioletti F, Rebora A: Cutaneous toxic mucinoses. J Am Acad Dermatol 26:789-790, 1992
11. Rongioletti F, Rebora A: Worsening of lichen myxedematosus during interferon alfa-2a therapy for chronic active hepatitis C. J Am Acad Dermatol 38:760-761, 1998
12. Banno H, Takama H, Nitta Y, et al: Lichen myxedematosus associated with chronic hepatitis C. Int J Dermatol 39:212-214, 2000
13. Rongioletti F, Rebora A: Cutaneous mucinoses: microscopic criteria for diagnosis. Am J Dermatopathol 23:257-267, 2001
14. Cowper ES, Su LD, Bhawan J, et al: Nephrogenic fibrosing dermopathy. Am J Dermatopathol 23:383-93, 2001
15. Dinneen AM, Dicken CH: Scleromyxedema. J Am Acad Dermatol 33: 37-43, 1995
16. Horn KB, Horn MA, Swan J, et al: A complete and durable clinical response to high-dose dexamethasone in a patient with scleromyxedema. J Am Acad Dermatol 51:S120-S123, 2004
17. Rongioletti F, Rebora A: Paradoxical effect of interferon alfa on lichen myxedematosus. J Am Acad Dermatol 43:730, 2000
18. Lister RK, Jolles S, Whittaker S, et al: Scleromyxedema: response to high-dose intravenous immunoglobulin (hdIVIg). J Am Acad Dermatol 43:403-408, 2000
19. Lacy MQ, Hogan WJ, Gertz MA, et al: Successful treatment of scleromyxedema with autologous peripheral blood stem cell transplantation. Arch Dermatol 141:1277-1282, 2005
20. Sansbury JC, Cocuroccia B, Jorizzo JL, et al: Treatment of recalcitrant scleromyxedema with thalidomide in 3 patients. J Am Acad Dermatol 51:126-131, 2004
21. Kwon OS, Moon SE, Kim JA, Cho KH: Lichen myxedematosus with rapid spontaneous regression. Br J Dermatol 136:295-296, 1997