Atypical Lichen Myxedematosus with an Interstitial Granulomatous Pattern; A Difficult Case in Making Diagnosis

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ABSTRACT:

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Lichen myxedematosus (LM) is characterized by multiple discrete papules with shiny surface and area of induration caused by mucin deposition. There are 3 subtypes including the generalized papular and scleroderma form or scleromyxedema, the localized papular form, and the atypical or intermediate form. Histological characteristics can be classical mucin deposition or rare interstitial granuloma annulare variant. The authors report an atypical case of LM with an interstitial granuloma histologic pattern which was rare and difficult to make a diagnosis.

Key words: Atypical lichen myxedematosus, scleromyxedema, interstitial granulomatous

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บทคัดย่อ:

ชนิดา อึ้งอักษรไพโรจน์ พรรณแข มไหสวริยะ โรคไลเคนมิกซิดีมาโตซุส ชนิดไม่ปกติ (ATYPICAL LICHEN MYXEDEMATOSUS) ที่มีลักษณะทางพยาธิวิทยาเป็นแบบแกรนูโลมา ซึ่งยากต่อการวินิจฉัย

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ภาควิชาตจวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล กรุงเทพมหานคร ประเทศไทย

โรคไลเคนมิกซิดีมาโตซุส (Lichen myxedematosus) เป็นโรคที่มีลักษณะทางคลินิกคือ มีตุ่มมันวาวหลายตุ่ม อยู่ร่วมกันเป็นกลุ่ม บนผิวหนังแข็ง สาเหตุเกิดจากการสะสมของสารมิวซิน ภายใต้ผิวหนังบริเวณนั้น โดยโรคนี้สามารถแบ่งออกได้เป็น 3 ชนิด คือ แบบกระจายทั่วไป หรือ สเคลอโรมิกซิดีมา (scleromyxedema), แบบเฉพาะที่ และแบบไม่ปกติ ลักษณะทางพยาธิวิทยาที่พบปกติทั่วไปคือ มีสารมิวซินสะสมภายในชั้นผิวหนังแท้ และน้อยมากที่จะพบลักษณะทางพยาธิวิทยาแบบแกรนูโลมา คณะผู้รายงานพบว่าผู้ป่วยรายนี้มีโรคไลเคนมิกซิดีมาโตซุส ชนิดไม่ปกติ ร่วมกับมีลักษณะทางพยาธิวิทยาเป็นแบบแกรนูโลมา ซึ่งพบได้น้อยมาก และยากต่อการวินิจฉัย

คำสำคัญ: โรคไลเคนมิกซิดีมาโตซุสชนิดไม่ปกติ, สเคลอโรมิกซิดีมา, ลักษณะทางพยาธิวิทยาแบบแกรนูโลมา

Introduction

Lichen myxedematosus (LM) was formerly referred as "generalized localized" myxedema. The disease is characterized by multiple discrete papules with shiny surface and areas of induration caused by mucin deposition. The etiology of mucin accumulation in the dermis is still unclear. One of the hypotheses suggests the role of circulating cytokines such as IL-1, TNF-alpha and TGF-beta, and their ability to stimulate glycosaminoglycan synthesis and fibroblast proliferation in the skin.[1] Rongioletti divided LM into 3 subtypes, which are the generalized papular and sclerodermoid form or scleromyxedema, the localized papular form, and the atypical or intermediate form (**Figure1**).[2,3] Scleromyxedema, also known as generalized and sclerodermoid LM, is a chronic disease affecting the middle-aged adults in their fifties to sixties with no significant gender predominance.[4] Cutaneous manifestations in scleromyxedema are generalized sclerodermoid eruption with multiple, firm, 1 to 3 mm flesh-colored papules, involving all parts of the body, including the face. The disease is often accompanied by monoclonal gammopathy. Extracutaneous manifestations such as neurologic dysfunction, arthralgia, cardiac abnormalities, myositis, esophageal dysfunction may be present.[4] In the localized form of LM, sclerotic features, systemic involvement, and monoclonal gammopathy are absent. This form

is also divided into 4 subtypes.[2,3] Firstly, a discrete papular form is characterized by a chronic, symmetrical eruption of small papules, involving the limbs and trunk. Secondly, in acral persistent papular mucinosis, the lesions are localized on the dorsum of the hands and extensor surface of the distal forearms. Thirdly, cutaneous mucinosis of infancy occurs in infants with opalescent papules located on the upper arms and the trunk. Lastly, in a pure nodular form, the lesions present with nodules on the trunk and extremities without papules. Additionally, the atypical form of LM lies in between scleromyxedema and the localized form, thereby making it difficult to diagnosis. Moreover, it can be categorized into 3 subtypes; (1) scleromyxedema without monoclonal gammopathy, (2) localized forms with monoclonal gammopathy and/or systemic symptoms, and (3) not well-delineated cases.[2,3] Several cases were reported with different systemic involvement such as neurologic dysfunction, cardiac or hematologic abnormalities.[5-11]

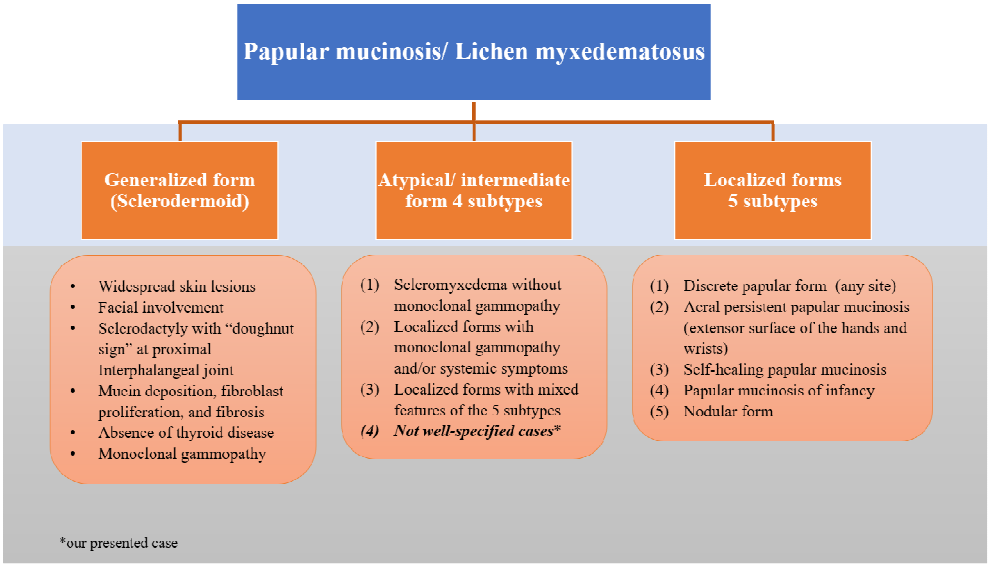

Figure 1. Types of Lichen myxedematosus

Classic histological findings in scleromyxedema comprised of a characteristic triad, including a diffuse deposit of mucin in the upper and mid reticular dermis, associated with increased collagen deposition and marked proliferation of irregularly arranged fibroblasts.[12] In localized form, mucin accumulates in the dermis but fibroblast proliferation is variable.[3] An interstitial granuloma annulare - like pattern has been reported in several patients with

generalized form of scleromyxedema or localized LM.[13-20]

Hereby, the authors present the case of an atypical form of LM with the interstitial granulomatous histologic presentation.

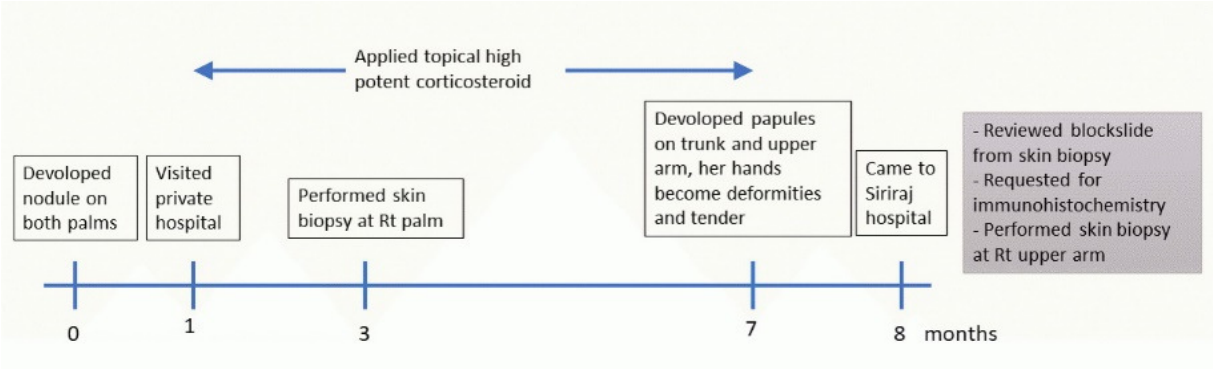

Figure 2. Diagram showing disease progression and management

Case report

A 75-year-old woman presented with an eight-month history of bilateral multiple erythematous nodules on both hands. These lesions were painless and not itchy.

The patient went to a private hospital and was diagnosed with allergic contact dermatitis. She was, in turn, prescribed with a high potency topical corticosteroid. The lesions did not respond to the topical treatment. A skin biopsy was then done at a nodule on the right palm. Nevertheless, the diagnosis was still inconclusive.

Seven months later, she developed more multiple skin-colored nodules on both upper arms, neck, upper back and chest. Also, both hands were swollen and tender. In addition, flexion contracture of the fingers was observed on both sides. No other systemic symptoms were shown. Eventually, the patient decided to come to Siriraj hospital. The timeline was shown in **figure 2**.

On the physical examination, ill-defined, indurated plaques with multiple waxy, skin-colored flat-top papules on top were observed at neck, upper back, chest, and both upper arms (**Figure 3**). Both hands showed symmetrical, multiple erythematous papules and nodules mainly on the palmar sites. The surrounding skin showed scleroderma-like induration with flexion deformities and sclerodactyly (**Figure 4**). Other physical examinations were unremarkable.

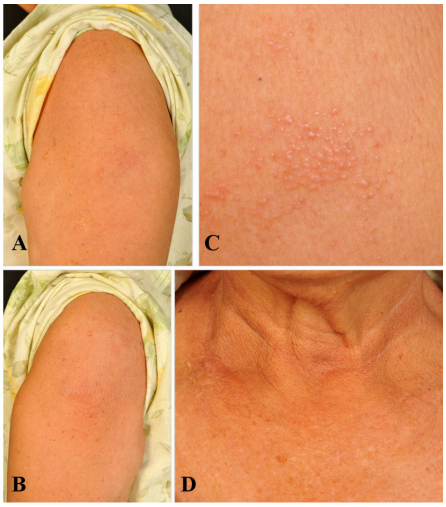

Figure 3. Ill-defined, indurated plaques with multiple waxy, skin-colored flat-top papules on **A**, **B**; both upper arms, and **D**; upper chest, **C**; magnified view of **A**.

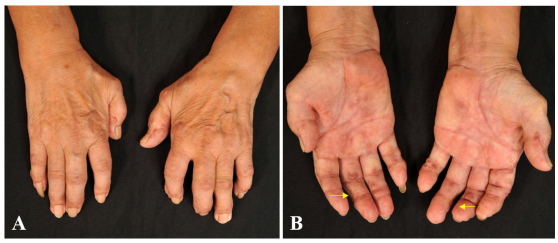

Figure 4. Both hands showed scleroderma-like induration with multiple erythematous papules and nodules on top; **A**, dorsum; **B**, palmar. Sclerodactyly was presented (arrow).

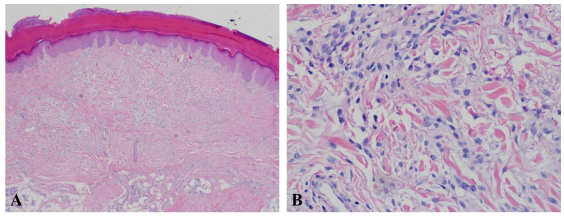

Figure 5. Histological finding from right palm; **A**, increased dermal mucin in the upper reticular dermis; **B**, superficial perivascular lymphocytic infiltrate and interstitial infiltrate of histiocytes (hematoxylin-eosin stain; **A** x 4, **B** x 40 original magnification).

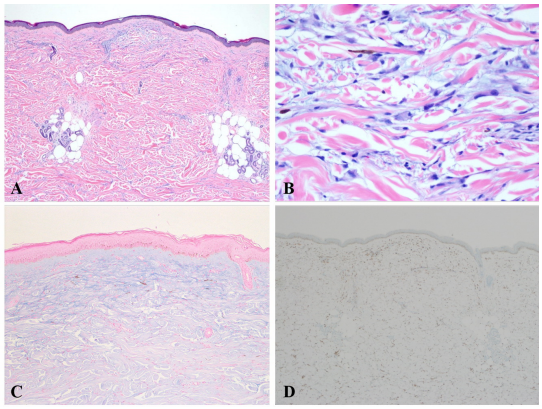

Figure 6. Histological finding from right upper arm; **A**, Focal aggregation of histiocytes in upper dermis "Granuloma annulare - like" pattern in upper dermis; **B**, diffuse infiltration of histiocytes and mucin deposition throughout the whole thickness of dermis; **C**, positive mucin in Alcian blue pH 2.5; **D**, the mononuclear cell marked with CD 163 (hematoxylin-eosin stain; **A, C** and **D** x 4, **B** x 40 original magnification).

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The skin biopsy from the nodule at the right palm which was done from another hospital was reinspected. The section showed superficial perivascular lymphocytic infiltrate and interstitial infiltrate of mononuclear cells in the dermis and subcutaneous fat septum (**Figure 5**). There was increased dermal mucin in the upper reticular dermis. The histopathological findings suggested the interstitial granuloma annulare. Given the clinical history of multiple shiny, skin-colored papules and nodules on both arms and hands, we suspected it was scleromyxedema. Therefore, skin biopsy was repeated at the papule on the right upper arm and immunohistochemistry for Alcian blue pH 2.5, CD163, AE1/AE3, CD1a and factor XIIIa was used to confirm the diagnosis. The immunostaining demonstrated that the mononuclear cells stained positive for CD 163 and factor XIIIa, but negative to AE1/AE2 and CD1a. The upper reticular dermis was highlighted with Alcian blue pH 2.5. These stainings suggested histiocytic differentiation of the mononuclear cells and were compatible with granuloma annulare. The section from the skin biopsy at the papule on the right upper arm, which was 5 months after the first skin biopsy, revealed similar in pattern and staining (Figure 6). Dermal mucin was increased and stained positive with Alcian blue pH 2.5. There was a diffused infiltration of mononuclear cells throughout the entire dermis, these cells stained positive for CD 163, factor XIIIa and negative to AE1/AE2 and CD1a.

Laboratory analysis was sent to screen systemic involvement and showed normal complete blood count, liver function test and thyroid function test. Serum protein electrophoresis, immunofixation electrophoresis and immunoglobulin free light chain assays could not detect any monoclonal gammopathy.

The patient was diagnosed as an atypical form of LM with the interstitial granulomatous histologic variant. Since the patient was suffered from sclerodactyly, we decided to give her oral chloroquine 250 mg per day and methotrexate 7.5 mg weekly, together with the rehabilitation for sclerodactyly and routine clinical follow ups for the further systemic symptom.

Discussion

The authors hereby present the case of atypical LM type 4 (not well-delineated cases). She firstly developed with discrete papular lesions on both palms. This presentation distinguished from acral persistent popular mucinosis form of LM, which localized lesion appeared at the dorsum of the hands and extensor surface of the distal forearms. Later, multiple papules and nodules at the trunk, both upper arms and palms appeared altogether with limited lichenoid sclerodermoid plaques on the upper part of the body and sclerodactyly without monoclonal gammopathy. The clinical

findings of sclerodactyly and sclerodermoid changes of both hands can be seen in both limited form and diffused form of scleroderma. However, the presence of a multiple waxy nodulopapular eruption on the trunk, upper arms and palms are almost never involved in scleroderma.[21] The patient has no facial involvement. The skin hardening was limited on the nodulopapular area. Moreover, no calcinosis cutis, esophageal dysmotility, nor telangiectasia were found in our patient.

The histological finding of the interstitial granulomatous pattern makes the disease more difficult to diagnose. The diagnosis of granuloma annulare would be without a doubt if the patient presented with only skin-colored papules. However, the clinical findings of sclerodactyly and sclerodermoid changes of both hands are unlikely to occur in granuloma annulare. In contrast, the interstitial granulomatous pattern has been reported in several patients with generalized form of scleromyxedema or localized LM.[13-20] Most of the cases were accompanied by sclerodactyly and sclerodermoid skin manifestation, which was similar to our patient. All the report cases showed at least a monoclonal gammopathy. It has been suggested that granulomatous inflammation is a reactive response to the monoclonal gammopathy.[15] However, this hypothesis could not be explained in our patient who lacks monoclonal gammopathy. Since the time to diagnosis is 8 months for this patient that was shorter than the other reported cases, further systemic involvement and monoclonal gammopathy need to be followed up.

There is no specific guideline for the treatment of scleromyxedema. Rather, multiple modalities such as intravenous immunoglobulin, corticosteroids, chemotherapeutic agents, thalidomide, chloroquine, radiotherapy, and autologous stem cell transplantation were reported with variable outcomes.[4] For localized LM, the clinical course is usually spontaneous resolution.[2] Due to the limited data on atypical scleromyxedema, the prognosis is unpredictable. Therefore, further clinical follow up is necessary.

Conclusion

An unusual presentation of scleromyxedema can be presented with an unusual histological finding, as in the present case. The diagnosis is considered difficult. Clinical correlation is an important key to diagnosis this distinctive variation. Due to the unknown prognosis for atypical LM, the main treatment is to follow up for further systemic involvement.

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Potential conflicts of interest

None.

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