Acquired Cutis Laxa With an Interstitial Granulomatous Reaction Associated With IgG Lambda Monoclonal Gammopathy

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Abstract: Acquired cutis laxa (ACL) is a rare connective tissue disorder that affects the skin elastic fibers, resulting in the loss of elasticity. In 50% of cases, this condition is associated with other diseases, particularly plasma-cell dyscrasias. This report describes a case of ACL with unusual clinical and histopathological characteristics. A 29-year-old man presented with diffuse erythematous plaques that had first appeared 5 months previously. Examination revealed multiple flaccid erythematous plaques on his trunk, neck, and skinfolds. Immunophenotyping of bone marrow aspirate revealed 7% of monoclonal plasma cells with lambda light chain expression. Skin biopsy histology revealed foci of interstitial granulomatous reaction. Weigert stain showed a loss of elastic fibers in the dermis, areas with thickened fibers and elastophagocytosis. Immunohistochemistry was positive for CD68. The cutaneous findings enabled an early diagnosis of IgG lambda monoclonal gammopathy to be made. Microscopic examination revealed an interstitial granulomatous reaction and severe alterations in the elastic fibers that varied in intensity in the different biopsies. Curiously, little has been mentioned in the literature regarding the presence of an interstitial granulomatous reaction in ACL. It is our belief that this reaction is secondary to the degenerative process of the elastic fibers.

Key Words: acquired cutis laxa, IgG lambda monoclonal gammopathy, interstitial granulomatous disease

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CASE REPORT

A 29-year-old male patient, looking older than his chronological age, presented with erythematous, mildly infiltrated papules and plaques on his trunk that had first appeared 5 months previously, associated with flaccidity of the face, axillae, groin, and neck. The patient reported that the lesions initially appear as erythematous papules and plaques that progressed to flaccid lesions maintaining the erythematous borders. He had no previous infections or skin lesions before the present disease and denied having used any medication. There was no history of any similar skin disease in his family. His paternal grandmother had recently been diagnosed with multiple myeloma; however, she had no similar skin condition.

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Dermatological Examination

The skin on the face was flaccid and droopy. The patient's neck was completely flaccid and droopy without erythema, and pendulous folds of lax skin were seen in the axillae, surrounded by erythematous skin (Fig. 1A). Erythematous plaques and papules were noted on the front of the chest and back (Fig. 1B), some of them compressible and others without loss of elasticity. In the abdomen, the lesions were larger, compressible but less erythematous (Fig. 1C). There was an extensive, erythematous, and intensely wrinkled lesion in the inguinocrural folds (Fig. 1D). There were no lesions on the distal extremities, the elasticity of the skin being normal in these areas. Initial routine laboratory test findings were normal. Serum and urine protein immunofixation showed the presence of isolated lambda monoclonal protein in the urine and a biclonal pattern with the presence of 2 IgG lambda monoclonal proteins in the serum. Immunophenotyping of bone marrow cells showed 7% of monoclonal plasma cells expressing lambda light chain. Serology for *Borrelia burgdorferi* was nonreactive, as was serology for antinuclear antibodies. Alpha 1-antitrypsin levels were within the normal range. Skeleton and skull x-rays were normal, as was tomography of the chest and abdomen. Echocardiography showed a large left atrium, with no changes in the overall contractile function. Endoscopy identified a hiatus hernia. A hyperplastic colon polyp was found at sigmoidoscopy and colonoscopy.

Evolution

Eight months after diagnosis, the patient came back with significant deterioration of the skin lesions. In addition, he informed us that he had developed nephrotic syndrome and acute renal failure requiring dialysis. Bortezomib, dexamethasone, and thalidomide were introduced. Two months later, the patient came back and showed no improvement of his dermatological lesions. Therefore, the patient was diagnosed with IgG lambda monoclonal gammopathy associated with ACL, in accordance with the current criteria defined by the Myeloma Working Group.[1]

PATHOLOGY FINDINGS

Initially, 3 biopsies were taken from compressible erythematous lesions. A slight edema and minimal perivascular lymphocytic infiltration were observed in the superficial dermis in both biopsies (Fig. 2A). Areas of interstitial granulomatous reaction with elongated histiocytes and epithelioid cells distributed among the collagen fibers were seen, mainly in 1 of the biopsies (Fig. 2B). Rare giant cells with 2–3 nuclei, showing elastophagocytosis were also found. There was no sign of elastosis, vasculitis, and neutrophilic or eosinophilic infiltration. Weigert staining showed a loss and fragmentation

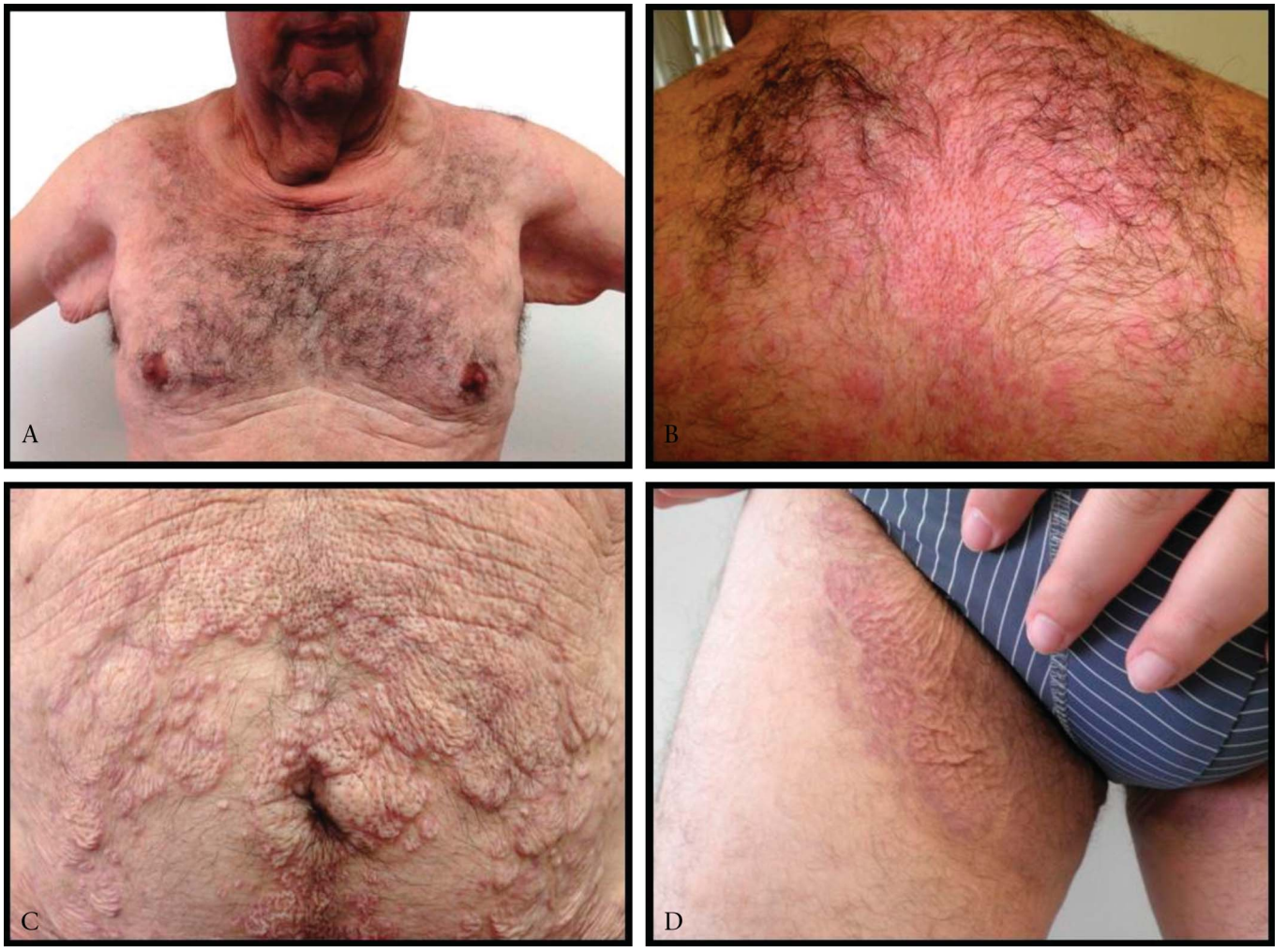

FIGURE 1. A, Patient's neck completely flaccid and droopy without erythema; pendulous folds of lax skin in the axillae. B, Erythematous plaques and papules on the back, some of them compressible and others without loss of elasticity. C, The lesions are larger, compressible but less erythematous on the abdomen. D, An erythematous wrinkled plaque in the groin.

of elastic fibers (Fig. 2C) throughout the entire thickness of the dermis alongside with small areas of thick, fragmented elastic fibers. With this staining, the elastophagocytosis was better demonstrated (Fig. 2D). In one of the biopsies, in which the granulomatous reaction was much less extensive, the alterations in the elastic fibers were much less marked. Later, a biopsy was performed on a noncompressible erythematous lesion, revealing slight edema, minor alterations of elastic fibers, and rare vessels with mild perivascular lymphocytic infiltration; only a small area with few epithelioid cells was observed. Alcian blue staining did not reveal mucoid deposits. Immunohistochemistry revealed that the few lymphocytes present in the biopsies were CD3+, CD4+, CD5+, CD7+, CD8+, UCHL-1+, and CD20−. The infiltrate was predominantly constituted of CD68 + cells.

DISCUSSION

Acquired cutis laxa (ACL) is a rare disorder that affects the elastic fibers and results in flaccidity of the skin producing wrinkled and pendulous lesions.[2,3] The dermatological pattern of the current case was extremely exuberant, disseminated, and varied, with intensely wrinkled or pendulous lesions, erythematous compressible lesions, and erythematous noncompressible lesions. The early lesions were erythematous, but the erythema gradually disappeared in the central areas with loosening or wrinkling of the lesions. Interestingly, the lesions of ACL are not always described as being erythematous.[2–8] Notwithstanding, there are few reports describing erythematous lesions associated with flaccid lesions.[9–11]

Alterations in elastic fibers may also occur systemically.[2] Of all the systemic abnormalities that have been reported to occur in the elastic tissue in ACL,[2] only hiatus hernia and left atrial dilatation were found in this patient.

In some cases of ACL, there is a history of inflammatory diseases, autoimmune diseases, and hematological neoplasms. The use of certain drugs and the presence of infectious processes have also been implicated.[3–5] However, the patient had no history of inflammatory diseases, and the diagnosis of monoclonal gammopathy was only made after

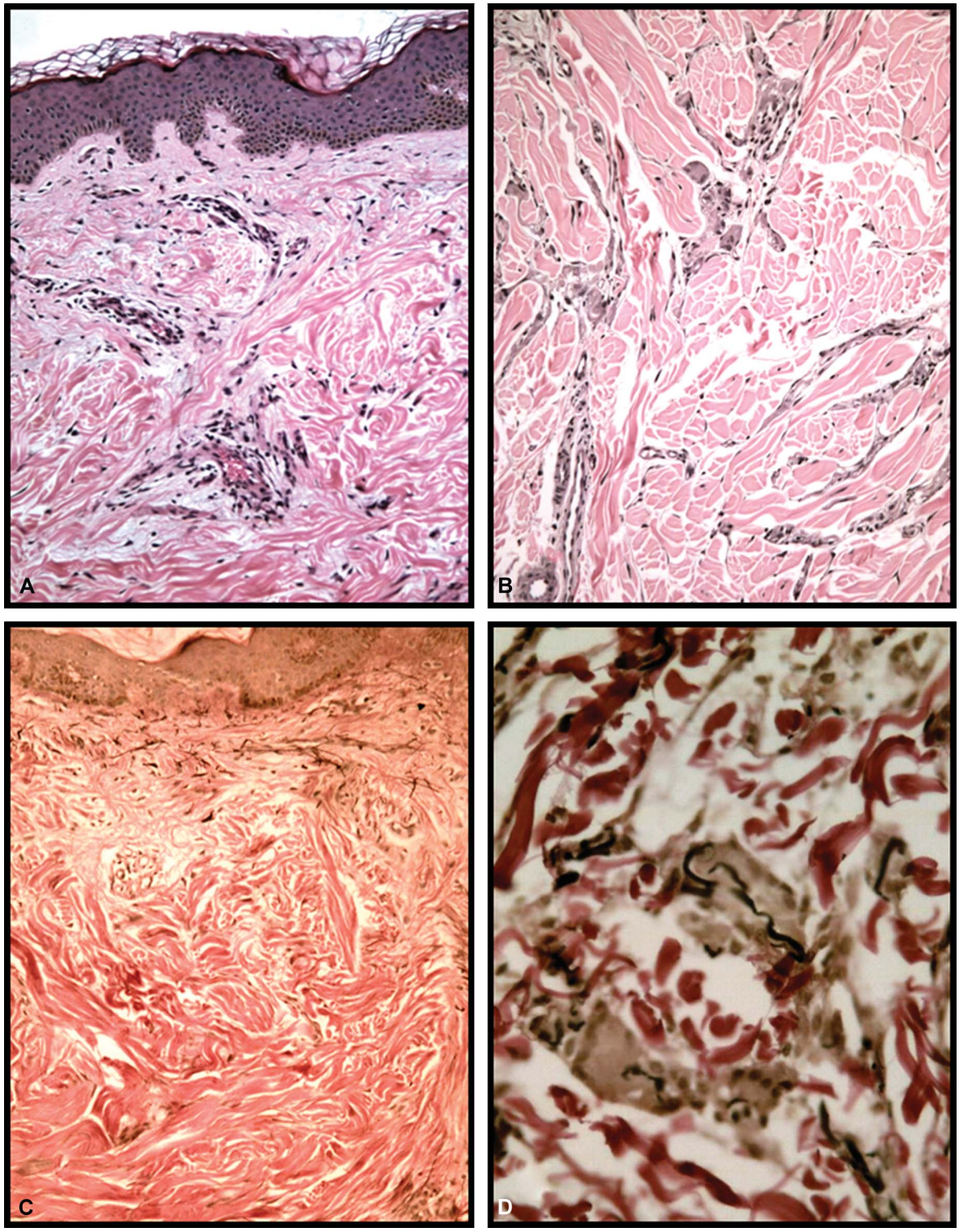

FIGURE 2. A, Mild perivascular lymphocytic infiltration in the superficial dermis (hematoxylin and eosin, original magnification ×100). B, Interstitial granulomatous reaction (hematoxylin and eosin, original magnification ×160). C, Diffuse loss of elastic fibers in the dermis (Weigert stain, original magnification ×100). D, Elastic fiber within a giant cell (Weigert stain, original magnification ×320).

the diagnosis of cutis laxa. The concomitant existence of monoclonal gammopathies with ACL has been well documented in the literature.[4–7,9] The possibilities of a cutaneous reaction to the use of D-penicillamine and isoniazid, *Borrelia burgdorferi* infection or alpha 1-antitrypsin deficiency as referred in the literature[2,3] were all discarded. Thus, this case presents a monoclonal gammopathy of undetermined significance. Different from what was reported in the literature, the disease appeared at a very early age. It is known that this condition is much more common in older people, generally over age 70, but it can be found even in young adults.[1] As an outlier patient, he was tested twice. Serum protein electrophoresis and immunofixation have confirmed that he had a real monoclonal gammopathy. This condition represents a premalignant plasma cell–proliferative disorder associated with a life-long risk of progression to multiple myeloma.[1] Curiously, the patient's grandmother had been diagnosed with multiple myeloma; however, there was no association with ACL.

At histopathology, alterations of varying degrees were found in the elastic fibers from the 4 lesions examined; these alterations being mild in the noncompressible and erythematous lesion that appear to represent an initial lesion. On the other hand, the magnitude of the interstitial granulomatous reaction varied in the different biopsies. The reaction was found to be present largely in the areas in which there was a greater destruction of the elastic fibers and it was minimal in one of the biopsies. Microscopic examination revealed an interstitial granulomatous reaction and severe alterations in the elastic fibers that varied in intensity in the different biopsies. According to these observations, it is our belief that this reaction is secondary to the degenerative process of the elastic fibers. Xanthomas and a related condition necrobiotic xanthogranuloma can be associated with monoclonal gammopathy. Notwithstanding the histological patterns of these entities are different from those of the interstitial granulomatous reaction observed in the present case.[12,13]

Curiously, the presence of an interstitial granulomatous reaction in ACL has not been well emphasized in the literature. According to Nanko et al,[11] the manifestations of this disease vary in accordance with the stage and severity of the condition, suggesting 4 stages of progression. They reported a predominance of macrophages in stage 3, associated with phagocytosis and elastic tissue depletion. On the other hand, Kim and Klein[6] found vacuolated macrophages with an interstitial arrangement in the dermis. Evaluation of the present case leads us to believe that lesions progress individually, with different stages being present simultaneously, resulting in a great variation in the morphology of the lesions. The lesions began with an intense erythema and progressed into compressible, wrinkled, or pendulous lesions. The dermatological and histopathological characteristics of this particular case are similar to that described by Lucas et al[14] who considered it to represent an example of interstitial granulomatous dermatitis (IGD) that had progressed to ACL. Initially, that patient presented with an erythematous lesion and 2 years later with a sagging, wrinkled lesion. IGD was first described in 1993 in association with subcutaneous linear cords and arthritis.[15] In the present case, histology showed an interstitial granulomatous reaction associated with intense alterations in the elastic tissue, with no symptoms of arthritis and no linear cord lesions; hence, this did not constitute a case of IGD. There has been no reference to elastic tissue disease in patients with this disorder. It seems more likely that the case reported by Lucas et al[14] represented different stages of the same disease, that is, ACL.

The principal differential diagnoses in ACL include granulomatous slack skin (GSS) and middermal elastolysis. GSS is also a rare condition that usually affects the axillary and inguinal regions.[16,17] In the current case, the skin lesions were disseminated and varied compared with those found in GSS. On the other hand, in GSS, there is a dense lymphocytic infiltration with well-organized and isolated granulomas with very large giant cells containing >10 nuclei; indeed, up to 40 nuclei may be present in addition to lymphocyte phagocytosis. The disease referred to as middermal elastolysis involves the selective loss of elastic fibers in the middle dermis and may present elastophagocytosis. In the present case, phagocytosis of elastic fibers was seen; however, the loss of elastic fibers was not restricted to the middle dermis, and the skin lesions were different and much larger (Table 1).

This is a case of ACL with varied clinical and histopathological characteristics, in association with IgG lambda monoclonal gammopathy. This also highlights the need to include ACL in the differential diagnosis for interstitial granulomatous diseases.

TABLE 1. Differential Diagnosis of Acquired Cutis Laxa, Granulomatous Slack Skin, and Middermal Elastolysis[2,6,14,15]

	Acquired Cutis Laxa	Granulomatous Slack Skin	Middermal Elastolysis
Skin lesions	Erythematous, pendulous and wrinkled lesions	Pendulous lax skin	Lesions with fine wrinkling
Altered elastic fibers	In all dermis	In all dermis	Only in middermis
Elastophagocytosis	Present	Present	Present
Cellular infiltration	Rare or absent	Lymphocytic dense and diffuse	Mild lymphocytic/histiocytic
Granulomas	Rarely present	Present. Giant cells with >40 nuclei	Absent
Systemic lesions of the elastic tissue	Possible	Absent	Absent
Associated diseases	Multiple myeloma, SLE	HL, mycosis fungoides	Autoimmune diseases, arthritis

HL, Hodgkin lymphoma; SLE, systemic lupus erythematosus.

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