Generalized Acquired Cutis Laxa Associated With Multiple Myeloma With Biphenotypic IgG-λ and IgA-κ Gammopathy Following Treatment of a Nodal Plasmacytoma

H. Douglas New, MD; Jeffrey P. Callen, MD

Background: Cutis laxa is a rare dermatosis that can be inherited or acquired. The acquired form is rare and has been associated with various conditions, including multiple myeloma, monoclonal gammopathy of undetermined significance, and heavy chain deposition disease.

Observations: We describe a 48-year-old man who developed generalized cutis laxa over a 4-year duration. There were no preceding skin changes except for a history of erythematous plaques with granuloma annulare–like features on his buttocks and lateral hips. He underwent treatment of an axillary lymph node plasmacytoma with surgery and radiation 4 years prior to his cutaneous changes and had been clinically monitored with a diagnosis of monoclonal gammopathy of unknown significance (MGUS). Cutaneous manifestations prompted a systemic evaluation demonstrating a persistent monoclonal IgG-λ M-spike on immunofixation electrophoresis and lytic bone lesions. He was later found to have biphenotypic IgG-λ and IgA-κ multiple myeloma.

Conclusions: Multiple myeloma, plasma cell dyscrasia, and heavy-chain deposition disease have been very rarely reported to be associated with acquired cutis laxa (ACL). Findings in our patient support the hypothesis that paraproteinemia is a cause of ACL through immunologic destruction of elastic fibers manifesting as granuloma annulare–like plaques. Evaluation for an underlying gammopathy is essential for the workup of a patient with new-onset ACL.

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Cutis laxa (CL) is a rare dermatosis resulting in loose, wrinkled, redundant skin secondary to defects in dermal elastic tissue. When involving the face, patients classically have a “bloodhound-like” or “hound dog–like” appearance. Extracutaneous manifestations may also occur, including pulmonary emphysema, diverticulae of the gastrointestinal tract or genitourinary tract, and cardiovascular defects. Cutis laxa may be inherited or acquired with acquired cutis laxa (ACL) having a later onset of disease, and more generalized involvement and is related to various different etiologies including medications, inflammatory diseases, infections, and hematologic disorders.

We describe a 48-year-old man who developed ACL and granuloma annulare (GA)-like lesions as a paraneoplastic manifestation of early myeloma years after being treated for a lymph node plasmacytoma.

See also pages 331 and 342

A 48-year-old man was referred for evaluation of “recalcitrant” GA. At the time of referral, we noted a 4-year history of gradually developing loose, wrinkled skin of his face, chest, upper back, lateral hips, buttocks, and proximal upper extremities. There were no preceding cutaneous changes on his face and upper body; however, he developed asymptomatic erythematous plaques with GA-like features on his buttocks and hips. Eight years earlier, a nodal plasmacytoma was surgically excised from his left axilla. He received local radiation therapy at that time and was clinically monitored by an oncologist for the working diagnosis of monoclonal gammopathy of unknown significance (MGUS).

His medical history was otherwise unremarkable, and his medications included oral acitretin, 25 mg/d, and daily oral multivitamins: oral vitamin E, 400 IU; oral vitamin D, 2000 IU; omega-3 fish oil, 2000 mg; and B-complex vitamin supplements. Acitretin was added by the referring dermatologist 1 month prior to his ini-
tial presentation to us without improvement of his skin disease. His family history was unremarkable.

Physical examination demonstrated a healthy-appearing man who appeared older than his stated age. He had loose, sagging skin on the face and neck along with wrinkled, lax skin on the chest, upper back, proximal upper extremities, and the lateral aspects of his hips (Figure 1 and Figure 2). Granuloma annulare–like erythematous, nonscaly plaques were noted on his lower back, buttocks, and lateral hips in association with increased wrinkling (Figure 3).

METHODS

Findings from two 4-mm punch biopsy specimens of the patient’s left hip and upper back revealed a normal epidermis and dermoeidermal junction with few lymphocytes and histiocytes around superficial blood vessels and interstitially in the upper dermis. A marked decrease in elastic fibers with elasto-
phagocytosis by epitheloid cells and giant cells were observed (Figure 4 and Figure 5). Results from periodic acid–Schiff and giemsa stains were unremarkable. No evidence of amyloid was seen with crystal violet. No alteration of collagen or increased mucin deposition was appreciated. Initially, the biopsy specimen involving his left hip had been diagnosed as GA and that from his upper back as mid-dermal elastolysis. Further review of the specimens concluded that both biopsy specimens

Table 1. Summary of Acquired Cutis Laxa (ACL) Associated With Plasma Cell Dyscrasias

<table>
<thead>
<tr>
<th>Source</th>
<th>Sex, Age, y</th>
<th>Site(s) of Cutis Laxa</th>
<th>Associated Findings</th>
<th>Skin Biopsy Finding</th>
<th>SPEP, UPEP, or IFE</th>
<th>Bone Marrow Evaluation</th>
<th>Treatment and Outcome</th>
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<tbody>
<tr>
<td>Turner et al⁹</td>
<td>M/29</td>
<td>Face, neck, shoulders, upper extremities</td>
<td>Urticarial vasculitis with LCV and immune complex mediated glomerulonephritis</td>
<td>LCV with perivascular neutrophilic infiltrate with extravasated RBCs, fibrin deposition and perivascular karyorrhexis Marked loss of elastic fibers in zones of LCV Fragmentation and granulation of dermal elastic fibers DIF and IIF were negative</td>
<td>IgA myeloma involving kidneys</td>
<td>IgA myeloma</td>
<td>High-dose pulse methylprednisolone and cyclophosphamide urticaria persisted; patient became hemodialysis dependent and died of his disease</td>
</tr>
<tr>
<td>Scott et al⁹</td>
<td>F/44</td>
<td>Face, neck, axillae, wrists, abdomen</td>
<td>Started following penicillin hypersensitivity reaction Extensive colonic diverticulae, bladder and rectal prolapse, loss of support of eyelids, palate, and uvula Panacinar emphysema, uterine and vaginal prolapse, rectocoele, hiatal hernia, colonic diverticulae Airway obstruction, pulmonary restriction, and hypotension followed episodic “puffiness” of eyelids Loss of elasticity of lungs, bladder, and rectum</td>
<td>Aspirate: 58% immature plasma cells confirming diagnosis of myeloma</td>
<td>Prednisone, melphalan, cyclophosphamide; patient became bedridden over the following 18 mo and died after endotracheal tube was removed</td>
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<tr>
<td>Cho et al¹⁰</td>
<td>F/46</td>
<td>Face, neck, trunk, extremities</td>
<td>Began after penicillin hypersensitivity reaction with marked facial and neck edema Panacinar emphysema, uterine and vaginal prolapse, rectocoele, hiatal hernia, colonic diverticulae Airway obstruction, pulmonary restriction, and hypotension followed episodic “puffiness” of eyelids Loss of elasticity of lungs, bladder, and rectum</td>
<td>Skin biopsy finding consistent with CL DIF: IgG bound to dermal elastic fibers</td>
<td>Aspirate revealed 58% plasma cells confirming diagnosis of myeloma</td>
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<td></td>
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<tr>
<td>Ting et al¹¹</td>
<td>F/45</td>
<td>Entire body with more severity on face, neck, axillae, and perineum</td>
<td>Absence of elastic fibers in the upper dermis and marked diminished amount in deep dermis DIF: negative Fragmented dermal elastic fibers DIF: negative</td>
<td>Aspirate showed 57% immature plasma cells confirming diagnosis of myeloma</td>
<td>Treatment and outcome not discussed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCarty et al¹²</td>
<td>M/62</td>
<td>Face, neck, trunk, and extremities</td>
<td>Exercise intolerance and fatigue Lytic vertebral lesions</td>
<td>SPEP: monoclonal lgG proteinemia 60% Plasma cells in bone marrow aspirate confirming myeloma</td>
<td>Melphalan and prednisone initially. Developed spontaneous bilateral humeral fractures requiring surgery and radiation therapy. Then treatment with doxorubicin, vincristine, and dexamethasone was initiated; serum immunoglobulin levels declined. Skin disease continued to progress</td>
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<tr>
<td>Gupta and Helm¹³</td>
<td>F/82</td>
<td>Face, neck, chest, back</td>
<td>Had a 5-γ history of IgG myeloma prior to development of CL Loss of elastic fibers: no inflammatory infiltrate noted</td>
<td>Aspirate consistent with IgG multiple myeloma with 40% plasma cells</td>
<td>Treatment and outcome not discussed</td>
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(continued)
were more suggestive of dermal elastolysis consistent with ACL rather than GA.

Findings from a complete blood cell count, including differential, hepatic function panel, basic metabolic panel, fasting lipid profile, thyroid panel, anti-Ro/SSA antibody, anti-La/SSB antibody, antinuclear antibody, anti-double-stranded DNA antibody, serum ceruloplasmin, serum copper level, serum β-2 microglobulin, erythrocyte sedimentation rate, and echocardiogram were negative for disease or were within reference range. Serum levels of IgG, IgA, IgM, albumin, total protein, α1-globulin, α2-globulin, γ-globulin, and total globulin were also within reference range, and serum protein electrophoresis (SPEP).

Immunofixation electrophoresis (IFE) revealed a stable monoclonal IgG-λ M-spike (0.5 g/dL vs 0.4 g/dL when evaluated the previous year). One year prior to his presentation, the patient had elevations of serum κ free light chain (FLC) level (118 mg/L; reference range, 3.3-19.4 mg/L) and serum λ FLC level (79.3 mg/L; reference range, 5.7-26.3 mg/L).

A bone marrow biopsy was performed, revealing 10% plasma cells. A skeletal survey was also performed, revealing multiple lucent bone lesions, less than 5 mm in size, in the patient’s skull along cent bone lesions, less than 5 mm in size, in the patient’s skull along

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<tr>
<td>Yoneda et al13</td>
<td>M/71</td>
<td>Both thumbs with lax skin</td>
<td>Lumbar back pain, paresthesias of right leg, night sweats; EKG with atrial fibrillation</td>
<td>Fingertip biopsy: reduced elastic fibers with fragmentation</td>
<td>SPEP: monoclonal IgG-κ; UPEP: large amount of Bence Jones κ proteins</td>
<td>Aspirate with immature plasma cells (no further details)</td>
<td>Cyclophosphamide; decrease in serum Igκ κ and urine Bence Jones protein; skin lesions persisted; rectal biopsy indicated no amyloidosis</td>
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<td>Yoneda et al14</td>
<td>M/62</td>
<td>Acral sites on fingertips and soles of feet</td>
<td>Hepatomegaly; osteolytic lesions of both femurs; diffuse osteoporosis; renal insufficiency; hypercalcemia</td>
<td>Fingerpont biopsy: fragmentation and reduction of elastic fibers</td>
<td>Elevated serum IgG 16.9 g/L (RR, 7.5-18 g/L) SPEP: monoclonal IgG-κ; UPEP: Bence Jones κ proteins</td>
<td>Aspirate with numerous immature plasma cells (no further details)</td>
<td>Cyclophosphamide and prednisolone; decrease in serum monoclonal Igκ κ and urine Bence Jones protein; cutaneous lesions progressed; amyloidosis involving the liver, kidneys and entire intestine led to death from chronic intestinal pseudo-obstruction and renal failure</td>
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<tr>
<td>Appiah et al16</td>
<td>F/64</td>
<td>Axillae, medial thighs, eyelids, labia majora with flesh-colored papules with loose, wrinkled skin of fingertips</td>
<td>None discussed</td>
<td>Axillary, lip and thigh biopsy: nodular amyloid deposits with decrease and clumping of elastic fibers in dermis</td>
<td>SPEP and UPEP with prominent homogeneous band in mid-γ region IFE: κ FLCs</td>
<td>Biopsy of bone marrow: 25%-30% plasma cells with κ light chain restrictions; amyloid deposits in bone marrow staining for κ light chains</td>
<td>Treatment and outcome not discussed</td>
</tr>
<tr>
<td>Dicker et al17</td>
<td>F/59</td>
<td>Axillae, medial thighs, labia majora with flesh-colored papules with loose, wrinkled skin of fingertips</td>
<td>Acralized ACL with tender tense areas of “puffiness” of fingertips resolved leaving lax skin on fingertips on her thumbs and second and third fingers bilaterally</td>
<td>Tongue swelling leading to airway obstruction; history of carpel tunnel syndrome; hypothyroidism Elliptical biopsy right index finger: Amyloid deposition in dermis; elastic fibers not assessed owing to amount of amyloid deposition</td>
<td>SPEP: monoclonal band UPEP: Bence Jones proteins</td>
<td>Biopsy of bone marrow: plasma cell dyscrasia; did not meet criteria for diagnosis of myeloma</td>
<td>Cycles of C-VAMP; after 2 cycles of C-VAMP laxity of skin improved as did the size of her tongue; patient considering bone marrow transplant at time of publication</td>
</tr>
<tr>
<td>This article</td>
<td>M/48</td>
<td>Face, neck, upper trunk, axillae, proximal upper extremities, lateral hips, lower back, and buttocks</td>
<td>Erythematous nonscaly papules and plaques on patient’s lower back and buttocks; multiple lucent bone lesions in skull and ribs; skin lesions developed 4 years after treatment for lymph node plasmacytoma of left axilla Findings from left hip and upper back biopsy specimens: normal epidermis and dermoepidermal junction, marked decrease in elastic fibers with elastophagocytosis; crystal violet negative for amyloid</td>
<td>Findings from left hip and upper back biopsy specimens: normal epidermis and dermoepidermal junction, marked decrease in elastic fibers with elastophagocytosis; crystal violet negative for amyloid IFE: monoclonal IgG-λ M-spike (stable compared with level 1 year prior)</td>
<td>Bone marrow biopsy with 10% plasma cells</td>
<td>Subsequently, diagnosed as having Bence Jones protein; skin improved as did the size of her tongue; patient considering bone marrow transplant at time of publication Lenalidomide, 25 mg/d orally, dexamethasone, 40 mg/wk; oral pamidronate monthly and aspirin, 81 mg. During 5 mo of therapy, patient had stable hematologic markers, skeletal disease; skin laxity gradually progressive</td>
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Abbreviations: CL, cutis laxa; C-VAMP, cyclophosphamide, vincristine, Adriamycin, and methylprednisolone; DIF, direct immunofluorescence; EKG, electrocardiogram; FLC, free light chain; IFE, immunofixation electrophoresis; LCV, leukocytoclastic vasculitis; RBC, red blood cell; RR, reference range; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.
The pattern of elastic fiber destruction with engulfment by phagocytes can be a nonspecific finding but is characteristic of elastolytic giant cell granuloma, which occurs on sun-damaged areas in contrast to our patient. However, a papular variant with 2- to 3-mm skin-colored papules occurring on the chest, neck, back, and shoulders of a 43-year-old woman was recently described in association with an IgG-A gammopathy.17

The patient’s cutaneous changes prompted further systemic investigation leading to the diagnosis of early myeloma, which could improve his overall survival. It is theoretically possible that use of immunosuppressive agents may improve his gammopathy and decrease the progression of his cutaneous changes; however, the likelihood is very low given the outcomes of prior reported cases.

The exact pathogenesis of ACL is unclear. In the setting of myeloma, amyloid light chains are produced by plasma cells and are deposited in various organs leading to end-organ failure. Three of the cases14-16 reviewed did show evidence of amyloid deposition with reduction and fragmentation of elastic fibers, and the patient described by Dicker et al16 with localized acrolocalized ACL had so much dermal amyloid deposition that elastic fibers could not be evaluated. In addition to amyloid deposition, immunoglobulin-heavy chain deposition has also been reported with ACL (Table 2).3,4,18 Unfortunately, we could not assess immunoglobulin deposition owing to lack of tissue. This hypothesis could be the basis for the cell-mediated destruction of elastic fibers in the gammopathy-associated cases of cutis laxa and the case of papular

Our patient’s cutaneous laxity distribution is consistent with descriptions of prior cases. In contrast to prior reports, this is the first case, to our knowledge, of ACL due to myeloma associated with the clinical presentation of GA-like plaques. It is also interesting to note that the face and upper body had only isolated skin laxity without preceding plaques. Histologic examination of the erythematous lesions showed marked elastolysis with elastophagocytosis by giant cells and lacked evidence of amyloid deposition.

Acquired cutis laxa manifests as localized or generalized laxity and has been associated with inflammatory dermatoses (ie, urticaria, dermatitis herpetiformis, sarcoidosis, amyloidosis, systemic lupus erythematosus, erythema multiform), medication use (ie, penicillamine, penicillin, isoniazid), hypersensitivity reaction to insect bites and related to an underlying hematologic disorder (ie, multiple myeloma, lymphoma, immunoglobulin heavy-chain deposition disease, plasma cell dyscrasia).1-4

Acquired cutis laxa has also been reported in patients following cutaneous mastocytosis, Sweet syndrome in pediatric patients (Marshall syndrome), and interstitial granulomatous dermatitis.3,7 At least 10 patients have been described in the literature as having ACL associated with multiple myeloma (Table 1).8-16

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elastolytic giant cell granuloma recently described. However, it is difficult (if not impossible) to determine if the immune deposits are the primary event or a normal response to repair and “clean up” damaged tissue.

In conclusion, ACL is a very rare entity described in the literature, and cases related to monoclonal gammapathy are even scarcer. We believe our case supports the theory that myeloma-associated immunoglobulin deposition on elastic fibers triggers a cell-mediated immune response leading to their destruction phagocytosis. In our patient, this resulted in decreased skin laxity and the development of plaques with a clinical presentation strikingly resembling GA. Clinicians should be aware of this association and evaluate for the presence of a gammapathy with immunofixation electrophoresis when a patient presents with ACL and/or GA-like plaques with histologic characteristics resembling the so-called elastolytic giant cell granuloma.

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REFERENCES