Acquired Cutis Laxa Associated With Multiple Myeloma

Anjeli Gupta, BS; Thomas N. Helm, MD

GOAL

To recognize cutis laxa as a possible manifestation of multiple myeloma

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the clinical features of cutis laxa.
2. Explain the possible etiologies of cutis laxa.
3. Describe an algorithm for evaluating patients with suspected cutis laxa.

CME Test on page 110.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: January 2002.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. The Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1.0 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This activity has been planned and produced in accordance with ACCME Essentials.

Cutis laxa is an uncommon condition characterized by loose and redundant skin. Biopsy results are positive for a reduction in or an absence of elastic fibers in the dermis. Cutis laxa is acquired or congenital. The acquired form is either a generalized insidious form (type I) or a form associated with prior inflammation (type II). Cardiovascular, pulmonary, gastrointestinal, and urologic complications may occur. In the past, cutis laxa was associated with plasma cell dyscrasia. We report on a characteristic case of cutis laxa to alert clinicians to this uncommon manifestation of multiple myeloma.

Cutis laxa results from injury to cutaneous elastic fibers.[1-3] The skin is loose, has redundant folds, and is soft to the touch. Fine wrinkling may be evident, and there is decreased recoil of the skin. Under an electron microscope, granular degeneration of elastic fibers is visible. Microfibrils remain normal, but elastin in skeletal fibrils is diminished.

Congenital cutis laxa is usually inherited as an autosomal-recessive condition.[1] The X-linked recessive form of cutis laxa is thought to result from deficiency in lysyl oxidase and is classified as type IX Ehlers-Danlos syndrome. Acquired cutis laxa may occur as a generalized insidious loss of elastic fibers beginning in adulthood (type I). Development of an urticarial or nondescript, erythematous, and papular vesicular eruption sometimes precedes the onset of generalized cutis laxa. Type II cutis laxa (Marshall syndrome) is most often encountered in females of African or South American descent. Development of inflammatory skin lesions is followed by localized loss of elasticity.

Both congenital and acquired cutis laxa may be associated with internal abnormalities including

Ms. Gupta is a medical student at the State University of New York at Buffalo School of Medicine. Dr. Helm is Clinical Associate Professor of Dermatology at the State University of New York at Buffalo.

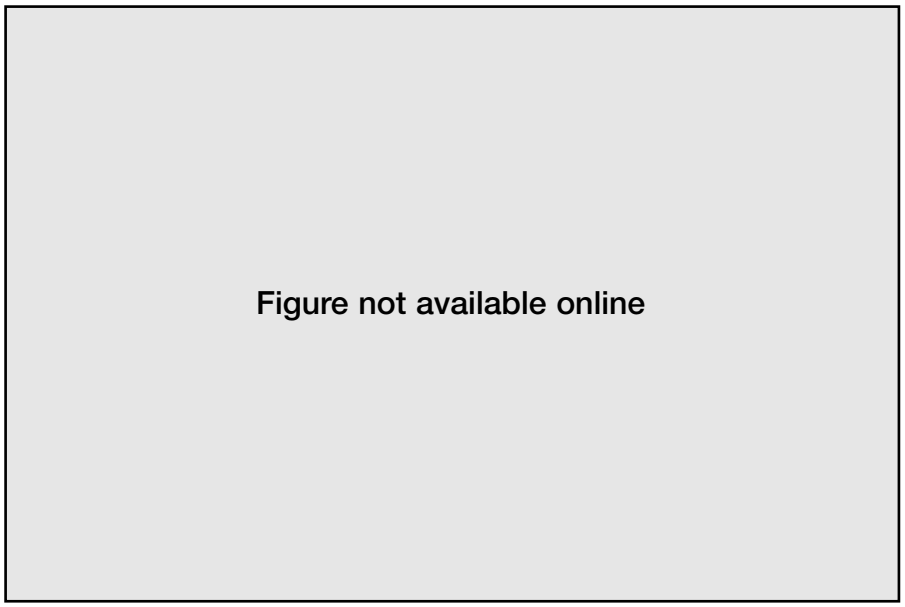

Figure 1. Redundant skin on the chin and neck.

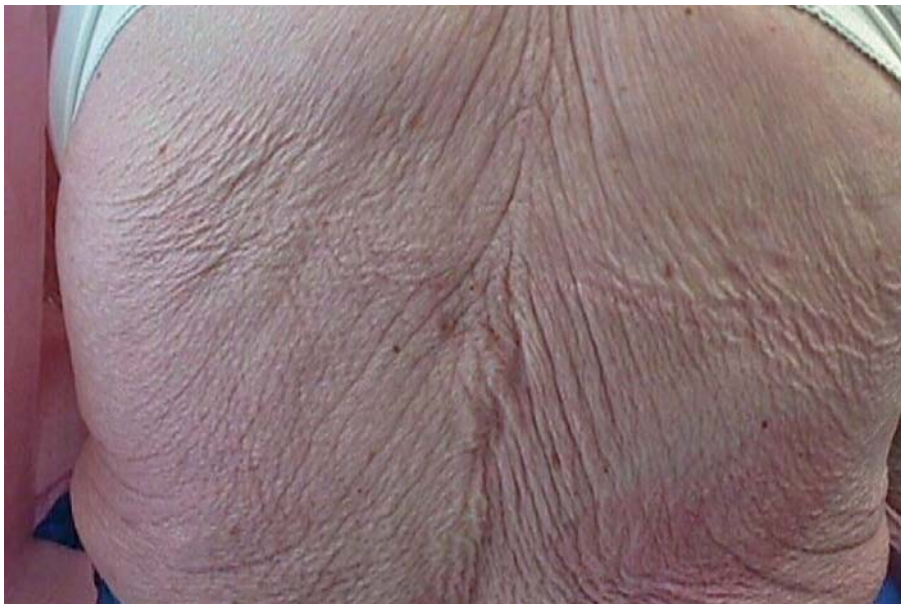

Figure 2. Loose redundant skin on the back in areas that have not received significant sun exposure.

diverticula of the gastrointestinal tract and bladder, rectal prolapse, pulmonary manifestations (eg, emphysema, pulmonary fibrosis), inguinal or hiatal hernias, and vascular abnormalities. Cardiomegaly, congestive heart failure, pulmonary stenosis, and aortic dilatation may occur. Uncommon associations with cutis laxa include multiple myeloma, other plasma cell dyscrasias,[4-7] amyloidosis, penicillamine therapy, and a reaction to penicillin or isoniazid therapy. Middermal elastolysis results from intense ultraviolet radiation exposure and also may be considered a form of cutis laxa; an unusual localized acral variant has been noted.[8]

Case Report

A 62-year-old woman with a history of multiple myeloma presented for evaluation of age-related changes. Diagnosis of the disease had been made 5 years earlier; present results of bone-marrow aspirate were positive for immunoglobulin G (IgG) multiple myeloma. A bone-marrow smear included 40% plasma cells, but lytic lesions were not evident on a bone scan.

Treatment began with vincristine, melphalan, doxorubicin, cyclophosphamide, and prednisone therapy, and the patient improved markedly. She received interferon, granulocyte-macrophage colony-

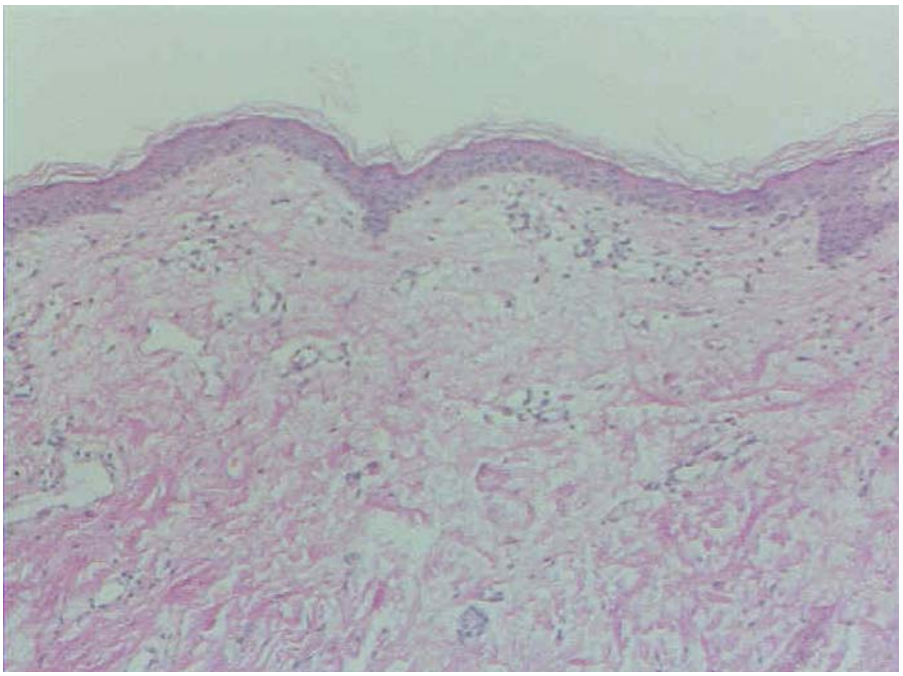

Figure 3. Unremarkable skin (H&E, original magnification ×20).

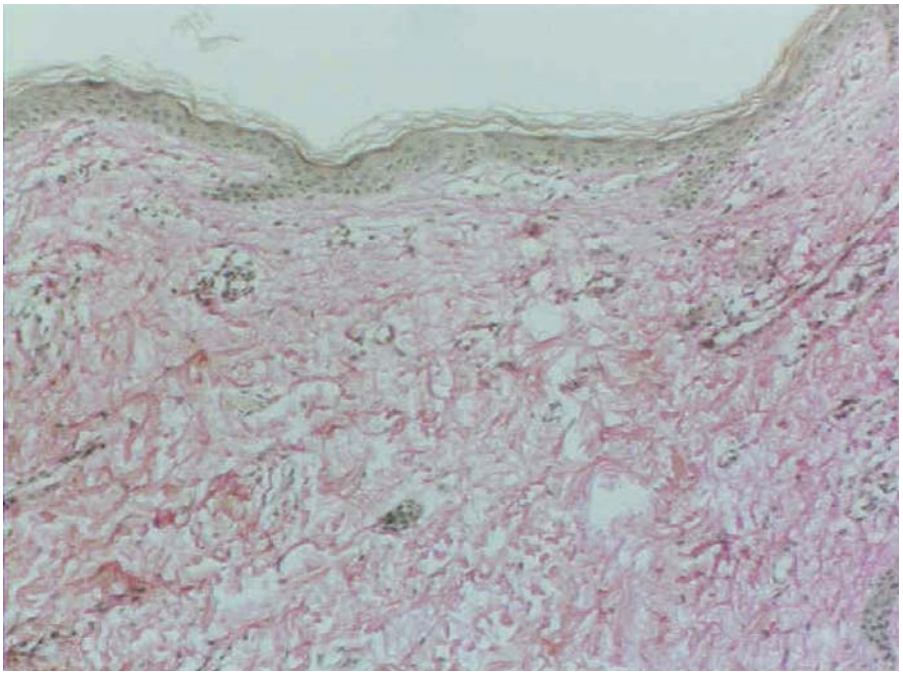

Figure 4. Results of a biopsy taken from the back were positive for loss of elastic fibers but negative for other abnormalities (Verhoeff elastic tissue stain and van Gieson stain, original magnification ×20).

stimulating factor, thalidomide, and occasional dexamethasone pulse therapy. At presentation, she was taking prednisone 50 mg every other day and thalidomide 100 mg daily, with the thalidomide gradually being increased to a total of 400 mg daily.

Family history included malignant melanoma in the patient's brother and father. Evident on physical examination of the patient was marked skin laxity with redundant folds on the face, neck, chest, and back. She denied any prior inflammatory skin disorder or exanthema. Non–sun-exposed sites were involved (Figures 1 and 2). Biopsy results were positive for loss of elastic fibers but negative for inflammatory infiltrate (Figures 3 and 4). Results of serum protein electrophoresis showed raised levels of human gamma globulin (1.98 g/dL; reference range, 0.5–1.4 g/dL) and β_2-microglobulin (2.3 mg/L; reference range, 0.3–1.9 mg/L).

Recommended Algorithm for Evaluation of Patients Suspected of Having Acquired Cutis Laxa

Evaluation	Findings
Biopsy taken from lax-skin site	Elastic fibers reduced or absent
Systemic involvement	Diverticula of gastrointestinal tract and bladder, rectal prolapse, pulmonary manifestations (eg, emphysema, pulmonary fibrosis), inguinal or hiatal hernias, vascular and cardiovascular abnormalities
Prior inflammation	Urticarial lesions, papular erythema
Duration and severity of ultraviolet radiation exposure	Skin laxity
Serum copper level	Decrease corresponds to abnormal lysyl oxidase activity and abnormal elastin synthesis
Amyloidosis	Apple-green birefringence; deposition of Congo-red staining material
Serum elastase inhibitor level	Decreased α_1-antitrypsin

Consider Other Underlying Causes

- Medication use—isoniazid, minocycline, penicillamine, penicillin
- Evaluate for plasma cell dyscrasia
- Evaluate for underlying multiple myeloma
  - —Determine if patient has bone pain (pain in back or ribs is most common)
  - —Perform complete blood cell count for serum calcium level, erythrocyte sedimentation rate, and presence of anemia
  - —Perform serum protein electrophoresis, immunofixation electrophoresis
  - —Perform bone radiography; perform urine analysis for Bence Jones proteins
  - —Perform blood smear test for rouleau formation

Homogenous bands to IgG and the κ region were evident on immunofixation electrophoresis. Results of urine monoprotein analysis showed monoclonal κ light chains, and results of monoclonal protein serum analysis showed raised levels of κ (3340 mg/dL; reference range, 534–1267 mg/dL) and IgG (8040 mg/dL; reference range, 717–1411 mg/dL). Erythrocyte sedimentation rate, serum copper level, and ceruloplasmin level were all unremarkable. On review of systems, no rectal or vaginal prolapse problems, emphysema, or cardiac problems were detected.

Comment

Acquired cutis laxa may present without an obvious underlying cause or may be associated with prior inflammation. Several studies have linked cutis laxa with plasma cell dyscrasia or multiple myeloma.[3,4,9] Our patient's skin condition coincided with her diagnosis of multiple melanoma. A clear association between cutis laxa and the treatment our patient received for multiple myeloma has not been established.

The etiology of cutis laxa is unknown, but a decrease in serum elastase inhibitors (eg, α_1-antitrypsin)

is thought to be a factor.[2] Elastase activity is increased in fibroblasts of patients with acquired cutis laxa.[2] Elastolysis also may result from increased fibroblast matrix metalloproteinase (MMP) activity.[10] In some studies, MMP1, MMP3, and MMP9 were found to have increased levels of messenger RNA activity. MMP1 and MMP3 degrade elastin.

Another possible factor in elastolysis is copper metabolism. Lysyl oxidase is a copper-dependent enzyme necessary for elastic fiber synthesis.[11] Linear polypeptides connected by desmosines contribute to the formation of elastin.[12,13] A decrease in serum copper level affects lysyl oxidase activity and therefore may affect elastic fiber synthesis (our patient's serum copper level was normal).

Immunologic factors also may play a role in elastolysis. Immunoglobulins may induce elastolysis by complement fixation. IgG may bind to dermal elastic fibers and lead to complement fixation and subsequent elastic fiber degradation. We suspect that our patient may have had a unique protein that, when combined with elastic fibers, caused complement fixation and elastolysis. Immunoglobulin A deposits are found in some patients with blepharochalasis.[14]

A possible algorithm for evaluating cutis laxa is outlined in the Table. Although the exact nature of the association between cutis laxa and multiple myeloma is unclear, clinicians should be alert to this uncommon association because identification of cutis laxa may point to underlying plasma cell dyscrasia.

REFERENCES

1. Koch SE, Williams ML. Acquired cutis laxa: case report and review of disorders of elastolysis. *Pediatr Dermatol.* 1985;2:282-288.
2. Bouloc A, Godeau G, Zeller J, et al. Increased fibroblast elastase activity in acquired cutis laxa. *Dermatology.* 1999;198:346-350.
3. Nikko A, Dunnigan M, Black A, et al. Acquired cutis laxa associated with a plasma-cell dyscrasia. *Am J Dermatopathol.* 1996;18:533-537.
4. Yoneda K, Kanoh T, Nomura S, et al. Elastolytic cutaneous lesions in myeloma-associated amyloidosis. *Arch Dermatol.* 1990;126:657-660.
5. Ting HC, Foo MH, Wang F. Acquired cutis laxa associated with multiple myeloma. *Br J Dermatol.* 1984;110:373-387.
6. Scott MA, Kauh YC, Lunscombe HA. Acquired cutis laxa associated with multiple myeloma. *Arch Dermatol.* 1976;112:853-855.
7. Cho SY, Maguire RF. Multiple myeloma associated with acquired cutis laxa. *Cutis.* 1980;26:209-211.
8. Martin L, Requera L, Yus ES, et al. Acral localized acquired cutis laxa. *Br J Dermatol.* 1996;134:973-976.
9. McCarty MJ, Davidson JM, Cardone JS, et al. Cutis laxa acquisita associated with multiple myeloma: a case report and review of the literature. *Cutis.* 1996;57:267-270.
10. Hatamochi A, Kuroda K, Shinkai H, et al. Regulation of matrix metalloproteinase (MMP) expression in cutis laxa fibroblasts: upregulation of MMP1, MMP3, and MMP9 genes but not of the MMP2 gene. *Br J Dermatol.* 1998;138:757-762.
11. Holbrook KA, Byers PH. Structural abnormalities in the dermal collagen and elastic matrix from the skin of patients with inherited connective tissue disorders. *J Invest Dermatol.* 1982;79(suppl 1):7S-16S.
12. Hatamochi A, Wada T, Takeda K, et al. Collagen metabolism in cutis laxa fibroblasts: increased collagenase gene expression associated with unaltered expression of type I and type III collagen. *J Invest Dermatol.* 1991;97:483-487.
13. Uitto J, Ryhanen L, Abraham P, et al. Elastin in diseases. *J Invest Dermatol.* 1982;79(suppl 1):160S-168S.
14. Grassegger A, Romani N, Fritsch P, et al. Immunoglobulin A (IgA) deposits in lesional skin of a patient with blepharochalasis. *Br J Dermatol.* 1996;135:791-795.