

CLINICAL REPORT

Ultrastructural Demonstration of a Relationship between Acquired Cutis Laxa and Monoclonal Gammopathy

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Acquired cutis laxa is an uncommon disorder sometimes associated with monoclonal gammopathy and multiple myeloma, although the mechanism of this link is unclear. We report here a case of a 34-year-old man with generalized acquired cutis laxa and monoclonal light chain disease with renal and neurological involvement. Electron microscopy examination of a skin sample revealed shortened and fragmented elastic fibres in the reticular dermis and normal collagen bundles. Immunogold labelling revealed anti-lambda antibodies closely bound to the microfibrillar component of elastic fibres, thus supporting a causal relationship between monoclonal gammopathy and the changes in skin elasticity. Key words: monoclonal gammopathy; cutis laxa; myeloma; elastolysis; electron microscopy.

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Cutis laxa is an uncommon disorder in which the skin hangs loosely in folds, leading to a prematurely aged appearance. It can be inherited or acquired, generalized or localized. Acquired cutis laxa may occur after inflammatory skin diseases (e.g. systemic lupus erythematosus, erythema multiforme, allergic reaction to penicillin, urticaria, sarcoidosis) (1, 2), and can be associated with internal diseases (e.g. lymphoma, myeloma, nephrotic syndrome, α -1-antitrypsin deficiency, Wilson's disease) (3–8). Several cases of localized or generalized cutis laxa associated with monoclonal gammopathy or myeloma have been published (5–8), but the mechanism of cutis laxa associated with monoclonal gammopathy is unclear. In cases associated with amyloidosis, elastolysis probably results from a direct effect of amyloid deposits on elastic fibres (9); in post-inflammatory elastolysis, the release of elastolytic enzymes and phagocytosis of damaged elastic fibres are believed to be causative.

We report here a case of a man who had generalized acquired cutis laxa and monoclonal light chain disease, with renal and neurological involvement. Ultrastruc-

tural investigations of his skin demonstrated binding of IgG monoclonal paraproteins to the elastic fibres, providing further evidence of a link between monoclonal gammopathy and the occurrence of acquired cutis laxa.

CASE REPORT

A 34-year-old man developed laxity and wrinkling of the skin, starting on the eyelids. He was embarrassed by the loss of elasticity of his palpebral skin, which was responsible for conjunctival irritation. The loss of elasticity spread slowly and after 2 years involved almost all of his skin (Fig. 1). Questioning revealed no inflammatory lesions prior to the onset of skin laxity. Apart from white nails with no lunula and the generalized skin laxity, cutaneous examination was normal, as was oral examination. Symmetrical peripheral sensory neuropathy of both lower and upper limbs was found, but mobility was unaffected. Physical examination was otherwise normal.

Routine blood testing (including red cell, white cell and platelet counts, serum calcium, proteins and albumin, serum creatinine and urea, and liver function tests) was normal, except for serum protein electrophoresis, which showed a monoclonal band in the gamma region (3.3 g/l), identified as IgG lambda on immunofixation. Serum IgA and IgG levels were within the normal range (1.9 g/l and 9.9 g/l, respectively). There was a slightly increased level of IgM (1.8 g/l). Lambda light chains were increased in the serum (44 mg/l) and the urine (0.022 mg/day), and non-selective glomerular proteinuria (3.6 g/day) was evidenced. Renal biopsy was consistent with light chain disease, with no amyloid deposits. Bone marrow examination was normal, with less than 5% mature plasma cells. No autoantibodies (antinuclear, rheumatoid factors, anti-myelin-associated glycoprotein (MAG) and anti-Hu) were found. Electromyography confirmed conduction disorders, disclosing slowing of motor and sensory conduction in the lower limbs, which was less reduced in the upper limbs. Pulmonary function and alpha-1 antitrypsin levels were normal, as were serum copper and ceruloplasmin levels.

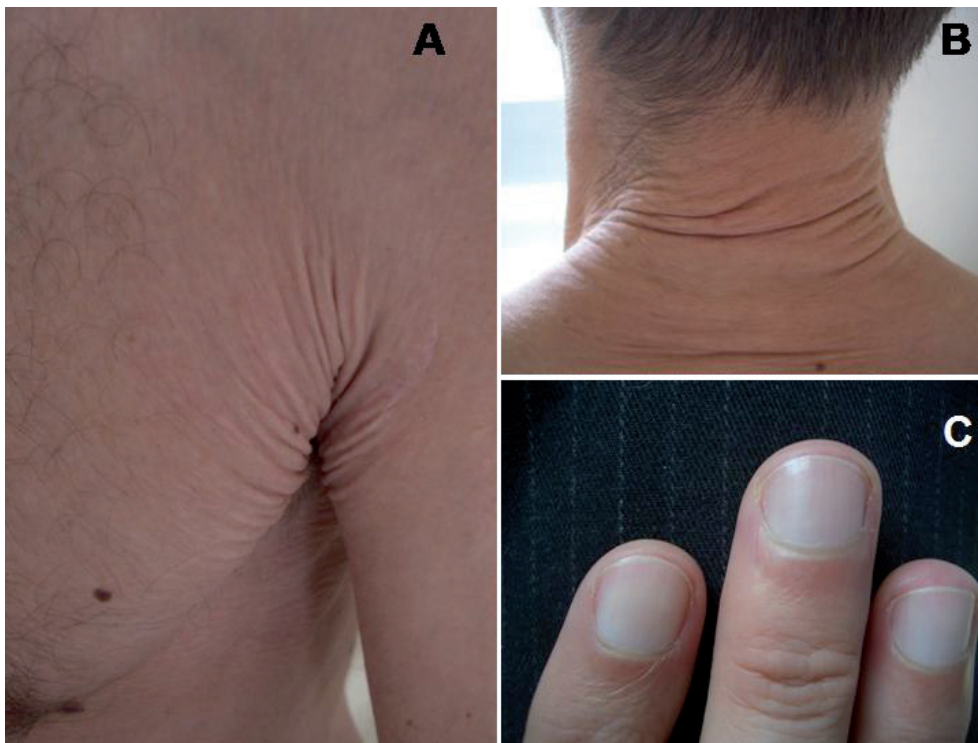


Fig. 1. Acquired cutis laxa with abnormal laxity and wrinkling of the skin in: (A) the axillary fold; and (B) the neck. (C) Absence of lunula was responsible for white nails.

Histopathology of a skin biopsy showed no abnormalities on haematoxylin-and-eosin-safran staining. However, there were marked abnormalities of the elastic network, including reduction in elastic fibres, which were fragmented, shortened and clumped on orcein staining (Fig. 2). Electron microscopy of a skin sample revealed that the elastic fibres were shortened and fragmented, with an abundant microfibrillar component, contrasting with normal collagen bundles in the reticular dermis. Immunogold labelling revealed that anti-lambda antibodies were bound to the microfibrillar component of elastic fibres (Fig. 3). The same technique was applied to a skin biopsy from a control patient with no cutis laxa but with monoclonal gammopathy.

DISCUSSION

This is the first report demonstrating binding of monoclonal gammopathy to elastic fibres using electron microscopy, thus providing further evidence of a causal relationship between monoclonal paraprotein and the development of acquired cutis laxa.

A few cases of acquired cutis laxa have been reported to be associated with monoclonal gammopathy and multiple myeloma (4–8). In these cases, as in our own, no correlation was observed between the level of monoclonal paraprotein in the serum and the severity of the acquired cutis laxa. In cases of myeloma associated with amyloidosis, elastolysis was thought to be due to

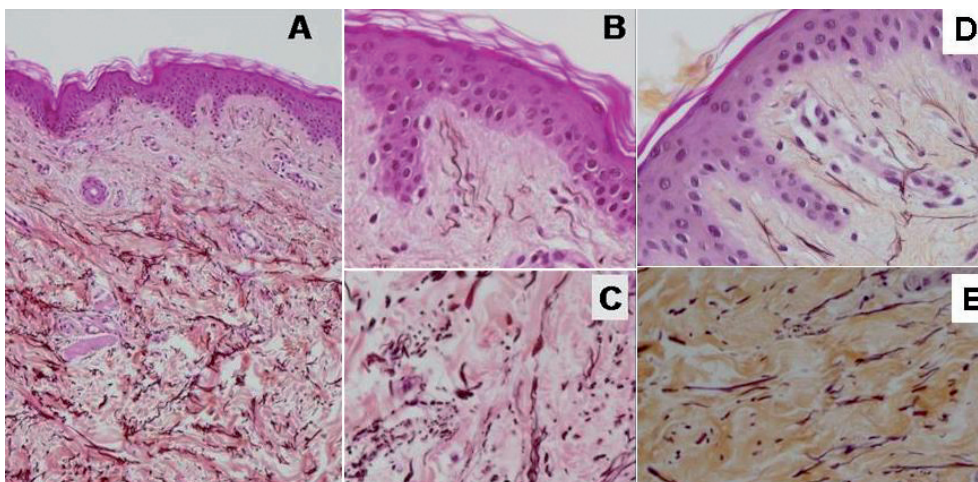


Fig. 2. Skin biopsy (orcein staining). (A, B and C) Marked fragmentation of elastic fibres, which appear shortened and clumped. (D and E) Normal appearance of elastic network in a control. Original magnifications: A ($\times 10$), B and D ($\times 40$), C and E ($\times 20$).

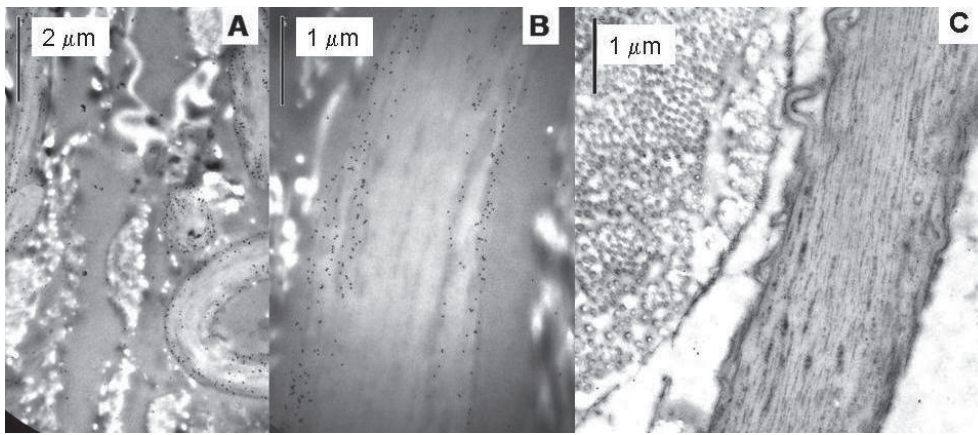


Fig. 3. Post-embedding immunogold labelling showing IgG binding to microfibrillar component of elastic fibres (A and B: patient), contrasting with the absence of binding in a control (C).

direct destruction of elastic fibres by amyloid deposits (9). Other mechanisms have also been discussed, including allergic hypersensitivity reaction and inflammatory cell effects (macrophages and neutrophils) (2). When performed, electron microscopy showed degenerative changes in elastic fibres and electron-dense amorphous or granular aggregates in the vicinity of the elastic fibres (10). A causal link between monoclonal paraprotein and acquired cutis laxa has also been suggested, as direct immunofluorescence revealed slight deposition of IgG around elastic fibres of the dermis in 4 cases (6–8). However, no antibodies were highlighted by immunofluorescence skin studies in most cases of cutis laxa with myeloma (3, 11). The demonstration of monoclonal antibodies bound to elastic fibres in the present case does not definitely prove causality in the occurrence of elastolysis. Monoclonal gammopathy is frequent in the general population, and acquired cutis laxa is very rare. The association may therefore occur by chance and the passive fixation of the monoclonal antibody would thus not be responsible for the development of elastolysis, which could alternatively be explained by a genetic polymorphism in one of the component of elastic fibres (fibulin-5 or elastin) (12). However, the fixation seemed to be very specific to elastic fibres in our case. We believe that the monoclonal paraprotein binding to elastic fibres was the primary event and that this may have triggered complement activation, leading to elastolysis. An alternative hypothesis is impairment of the maturation and assembly of elastic fibres consecutively to the binding of monoclonal immunoglobulin to fibulin-5 (12).

The authors declare no conflict of interest.

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