Acquired cutis laxa from heavy chain deposition disease

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Kidney International (2022) **102,** 1432–1433; https://doi.org/10.1016/j.kint.2022.08.035

A 35-year-old woman presented with fatigue, nausea, marked lower-limb edema, and hypertension (180/100 mm Hg). Blood tests showed kidney failure (serum creatinine: 10 mg/dl), and urinalysis demonstrated heavy proteinuria (10 g/d) with microscopic hematuria. Her serum C3 level was low (0.75 g/l; N > 0.9). Serum immunoblot analysis identified a truncated monoclonal γ4 heavy chain with deletion of the CH1 domain. The patient looked much older than her age, with inelastic and sagging skin on her face, neck, axillae, and groin areas (Figure 1). Kidney biopsy showed nodular glomerulosclerosis (Supplementary Figure S1) with linear deposits of gamma heavy chain and C3 along tubular and glomerular basement membranes, without staining for kappa or lambda light chains. Electron microscopy revealed finely granular electron-dense deposits in the mesangium and along the inner aspect of the glomerular basement membrane. A skin biopsy revealed linear deposition of gamma 4 heavy chain, C1Q, and C4D along dermic elastic fibers (Supplementary Figure S2).

Heavy chain deposition disease is a rare condition defined by linear tissue deposition of a truncated monoclonal immunoglobulin heavy chain, secreted by an abnormal B-cell clone. These pathogenic heavy chains exhibit a deletion of the first constant domain (CH1) that is required for assembly of the whole immunoglobulin molecule. Monoclonal mutated heavy chains lacking CH1 are freely secreted by clonal plasma cells and are deposited in various organs and tissues including the kidneys and skin. Despite the rarity of both conditions, the peculiar association between cutis laxa and heavy chain deposition disease has been highlighted. Cutis laxa is an inherited or acquired condition resulting from alterations of the dermal elastic fibers. The skin looks loose and redundant, especially in the neck, axilla, and groin, with an accentuation of facial folds giving a prematurely aged appearance. Acquired cutis laxa in the context of plasma cell dyscrasia is thought to derive from dermal inflammatory reaction secondary to complement activation by the truncated monoclonal γ heavy chain deposited along elastic fibers, resulting in elastolysis.

The patient received 6 courses of bortezomib-dexamethasone-cyclophosphamide, which resulted in complete hematologic response and normalization of the serum C3 level. She remained dialysis-dependent, and chemotherapy had no effect on skin involvement. Unfortunately, she was found dead at home while investigations were being made for autologous stem cell transplantation.

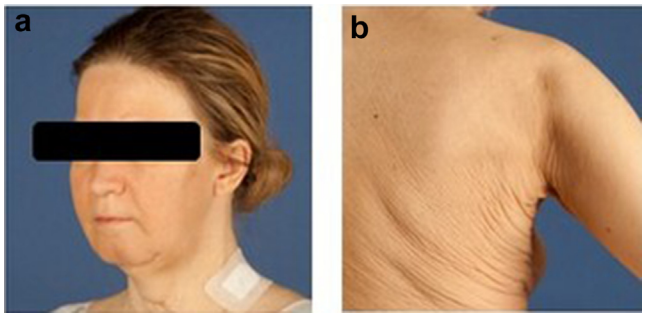

Figure 1 | Pictures of the patient, showing premature aging, with sagging skin in the (a) chin and (b) axilla.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Kidney biopsy: (**A**) Silver staining (original magnification x200) showing nodular glomerulosclerosis with mesangial proliferation, endocapillary hypercellularity, and double contours. (**B**) Electron microscopy (original magnification x3000) revealing deposition of electron-dense finely granular materiel linearly along the glomerular basement membrane and in the mesangium.

Figure S2. Skin biopsy: (**A**) Immunofluorescence study (original magnification x200) showing linear deposits of γ heavy chain on the elastic fibers of the superficial dermis and the epithelial basement membranes, with negative staining for (**B**) kappa and (**C**) lambda light chains. Analysis of γ heavy chain subclasses demonstrated negative staining for (**D**) γ1, (**E**) γ2, and (**F**) γ3 heavy chains, and positive staining for only (**G**) γ4. No significant staining was observed with (**H**) anti-CH1 antibody by contrast with (**I**) anti-CH2 antibody, indicating deletion of the first constant domain (CH1). Light microscopic examination of the same skin biopsy also showed (**J**) Congo red-positive deposits (original magnification x200) showing (**K**) apple-green birefringence under polarized light, located in the middle and deep dermis. (**L**) By immunofluorescence (original magnification x200), amyloid deposits stained with anti-lambda LC antibody. Staining for kappa LC was negative (not shown).