Acquired Cutis Laxa Associated With Heavy Chain Deposition Disease Involving Dermal Elastic Fibers

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Heavy chain deposition disease (HCDD) is a form of plasma cell dyscrasia characterized by uncontrolled production and tissue deposition of abnormal immunoglobulin (Ig) heavy chains. These deposits disrupt kidney function and result in the clinical findings of nephrotic syndrome, hypertension, and microhematuria and, in advanced disease, can result in emphysema, hiatal hernias, and cutis laxa. The truncated heavy chains in this disorder typically share deletions in the heavy chain constant domain 1 (CH1) starting after the leader sequence and involving the antigen-binding domains, i.e., the complementarity-determining regions (CDRs). There have been a few reports of intact CDRs with deletions in both CH1 and CH2. The CH1 is required for normal assembly of the Ig molecule. Heavy chains lacking CH1 are unable to bind to chaperone protein heavy chain binding protein, which retains the nascent heavy chain within the endoplasmic reticulum of the plasma cell for binding to light chain. Once the light chains and heavy chains are paired, the newly synthesized Ig molecule normally enters the secretory pathway for cellular release into the circulation. In HCDD, mutated free heavy chains lacking CH1 are secreted and deposited in various tissues of the body. As in the case of light chain deposition disease, it is thought that tissue binding results not from antigen-specific binding, but from altered chemical properties of the mutated heavy chain that govern its solubility, glycosylation, and charge, thereby enhancing aggregation and affinity for extracellular matrix proteins.

One of the major depots of the heavy chain is the kidney, where heavy chains typically deposit diffusely in the glomerular, tubular, and vascular basement membranes leading to nodular glomerulosclerosis. Diagnosis of the disease by immunofluorescence techniques is made when there is intense linear staining for a single Ig heavy chain (IgG, IgM, or IgA), with negative staining for both κ and λ light chains.

While the heavy chain has also been detected in muscle and skin, it is unclear if such deposition typically results in disease. Herein we describe the development of acquired cutis laxa in a patient with HCDD and hypocomplementemia. In addition, we report the distribution of heavy chain deposits on the surfaces of dermal elastic fibers with codeposites of complement components C1q and C3, suggesting that aggregated γ heavy chains can activate complement by the classic pathway, leading to a complement-mediated mechanism of elastic fiber degradation.

Report of a Case

A woman in her 60s first presented with nephrotic syndrome and renal insufficiency. Analysis of renal biopsy
specimens revealed the presence of nodular glomerulosclerosis with extensive deposition of Ig γ heavy chains and absence of light chains. Electron microscopy identified granular electron-dense deposits in the same distribution, consistent with renal HCDD. She was treated with pulse dexamethasone for a year, with resultant diminution of heavy chain deposition in a follow-up renal biopsy. The following year, she became increasingly short of breath, and computed tomography scans of the chest and abdomen revealed extensive emphysema requiring home oxygen administration, despite only a 20 pack-year smoking history, as well as an incidental inguinal hernia.

Over the next few months, she developed increasing lower extremity edema, and a third renal biopsy performed at the beginning of the next year showed a relapse of HCDD. Two months later, during an admission for worsening renal function, the dermatology service was called to evaluate her skin. She was noted to have “hound-dog” facies with lax, hypoelastic skin encompassing her face, neck, and arms. She reported the gradual development of these skin changes over the prior 10 to 12 years, correlating with the time renal involvement was first diagnosed. Her skin appeared much more aged than that of her sisters, who were 7 and 9 years younger (Figure 1A). Laboratory studies were remarkable for a decreased C3 level of 61.6 mg/dL (reference range, 83-177 mg/dL) and normal C4, CH50, and α1-antitrypsin levels. Surprisingly, histopathologic analysis of the biopsy specimens taken from the upper, proximal inner arm showed normal-appearing skin (Figure 1B). Orcein staining of the specimen revealed normal-appearing distribution and structure of elastic fibers (Figure 1C), even when compared with a normal skin sample taken from her inner arm.

Despite the unremarkable histopathologic findings, direct immunofluorescence of the skin biopsy specimens showed extensive γ heavy chain deposition, specifically surrounding fragmented elastic fibers, in addition to involvement of sweat glands and arterial walls (Figure 2A-D). Moreover, complement components C1q and C3c were detected in a similar distribution, suggesting that the heavy chain deposition was capable of activating complement through the classic pathway (Figure 2E and F). Similar codeposits of γ heavy chain, C1q, and C3c had been found in her renal biopsy specimens. Immunofluorescence studies of the kidney biopsy specimens showed that the γ heavy chain was of the IgG1 subclass and had loss
of immunoreactivity for CH1, with normal immunoreactivity for CH2 and CH3. In both kidney and skin, there was no detectable IgA, IgM, κ light chain or λ light chain deposition.

To determine whether the γ heavy chains were depositing specifically on elastic fibers, we performed electron microscopy. A coating of granular electron-dense deposits was found on the surfaces of fragmented elastic fibers in the dermis, with sparing of the adjacent collagen fibers (Figure 3), correlating with the distribution noted by immunofluorescence. Furthermore, both immunofluorescence and electron microscopy effectively demonstrated fragmentation and fraying of individual elastic fibers, which was not discernible histologically using Orcein stain. During the patient’s hospitalization, a serum protein and urine protein electrophoresis detected monoclonal IgG-κ proteins, and a bone-marrow biopsy revealed 10% plasma cells with κ light chain restriction. These findings were consistent with an evolving low-grade plasma cell neoplasm. The patient was discharged on a regimen of bortezomib and pulse dexamethasone, with subsequent improvement of her nephrotic syndrome and resolution of her acute kidney injury.

Discussion

Acquired cutis laxa is a rare disorder with insidious onset typically occurring in adulthood. Most cases of acquired cutis laxa
result from a prior inflammatory insult (eTable in the Supplement). To our knowledge, this is only the fourth reported case of acquired cutis laxa resulting from HCDD, as summarized in the Table.4-6 Prior studies have observed heavy chain deposition in the dermis of patients with HCDD around connective tissue fibers, blood vessels, and sweat glands, with only 1 other case mentioning heavy chain deposition involving elastic fibers.7 In our case, complement components C1q and C3c were also detected in a similar distribution as the y heavy chain on the surfaces of individual elastic fibers, suggesting that heavy chain deposition is sufficient to cause complement activation. This mechanism is consistent with the known activation of complement on CH2, which was not deleted in this patient.8 Therefore, we propose a mechanism of complement-mediated elastic fiber degradation in our patient with HCDD. Elastic fibers likely undergo destruction via heavy chain deposition on their surfaces, which causes activation of the classic pathway of complement and release of chemotactins C3a and C5a that recruit leukocytes. We hypothesize that subsequent release of proteases and elastases by leukocytes and/or local fibroblasts may promote elastic fiber destruction.

Interestingly, our patient was found to have a monoclonal IgG-κ paraprotein in her serum later in her course, consistent with an evolving low-grade plasma cell neoplasm. The production of both free heavy chain and IgG-κ suggested evolution of the plasma cell disorder to a biclonal gammopathy. Without gene sequencing of the plasma cells in the marrow, it is not possible to determine if the 2 clones (free heavy chain and IgG-κ) are related or what percentage of neoplastic plasma cells may be pure heavy chain producers. Approximately 25% of patients with HCDD subsequently develop multiple myeloma.9 Of note, multiple myeloma has also been associated with acquired cutis laxa, although the mechanisms are unclear. The absence of light chain deposits in the skin of our patient argue against a role for κ light chain deposition in this case. The development of cutis laxa may be a cutaneous manifestation of the secretory activity of HCDD. Although intriguing to speculate, it is unclear whether it also may be a cutaneous clue to impending transformation to multiple myeloma, since the 3 other published cases did not provide follow-up information regarding potential evolution to myeloma.4-6

This case highlights that mild abnormalities in elastic fibers are difficult to detect by histochemical staining. Thus, failure to demonstrate elastic fiber abnormalities by light microscopy does not exclude a clinical diagnosis of cutis laxa. Heavy chains were detected in the kidney and skin of our patient because related symptoms prompted targeted biopsies; however, it is likely that organ involvement was more generalized, since our patient was also afflicted with other known disorders of the structural integrity of elastic tissue, namely pulmonary emphysema and hiatal hernia. Associations of HCDD with emphysema and hiatal hernia have been reported previously.7 It is unclear what properties of the heavy chain in this patient mediated the affinity for elastic tissue and resultant cutis laxa. Studies of more patients with HCDD and cutis laxa are needed to determine the optimal therapy, especially in the early stages of the hematologic disorder.

### Conclusions

This report is the first to our knowledge to demonstrate deposition of y heavy chain and complement components on the surfaces of dermal elastic fibers in HCDD. We hypothesize a mechanism of elastic tissue destruction by complement fixation, activation of the complement cascade, resulting immune activation, and release of elastases into the dermal microenvironment. Based on our findings and other reports, we propose that heavy chain deposition in the skin can serve as a marker of the secretory activity of plasma cells in HCDD.

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Table. Summary of Clinical and Immunopathologic Characteristics of Acquired CL Occurring in Association With HCDD

<table>
<thead>
<tr>
<th>Source, Patient Sex/Age, y</th>
<th>Duration of HCDD at CL Diagnosis</th>
<th>IgG Heavy Chain Subtype</th>
<th>Serum Complement Levels</th>
<th>Histology</th>
<th>DIF</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrington et al,6 F/38</td>
<td>Concurrent diagnosis, but lax skin noted a few years prior in axilla</td>
<td>Not determined</td>
<td>C3 and C4 within normal limits</td>
<td>Marked reduction of dermal elastic fibers</td>
<td>Deposition of IgG along the fibers of connective tissue in dermal papillae</td>
<td>Not performed</td>
</tr>
<tr>
<td>Rott et al,4 F/73</td>
<td>Skin findings not discussed</td>
<td>Not determined</td>
<td>C3 and C4 decreased</td>
<td>PAS-positive material in reticular dermis</td>
<td>IgG deposits in dermis, arteriolar walls, connective tissue fibers, eccrine glands</td>
<td>Splitting of collagen fibers, no IgG deposits</td>
</tr>
<tr>
<td>Tan et al,7 M/50</td>
<td>4 years</td>
<td>IgG4</td>
<td>Not mentioned</td>
<td>Loss of elastic fibers in superficial and deep dermis</td>
<td>IgG deposits near elastic fibers, arteriolar walls, and lumen</td>
<td>Fragmented and clumped elastic fibers</td>
</tr>
<tr>
<td>Present patient, F/68</td>
<td>12 years, but with skin changes noted approximately 10 years prior</td>
<td>IgG1</td>
<td>C3 decreased, C4 within normal limits</td>
<td>Elastic fibers within normal limits</td>
<td>IgG, C1q, and C3c deposits on elastic fibers, arteriolar walls, eccrine glands</td>
<td>Granular electron-dense deposits on surfaces of elastic fibers of dermis, adjacent collagen fibers spared</td>
</tr>
</tbody>
</table>

Abbreviations: CL, cutis laxa; DIF, direct immunofluorescence; EM, electron microscopy; HCDD, heavy chain deposition disease; PAS, periodic acid-Schiff stain.
Depilation was widely performed in ancient Rome and was considered a class identifier. A clean-shaven person symbolized civilization and progress, whereas a beard was regarded as a mark of slavery and barbarism. Besides the use of razors with curved tweezers (forcipes aduncae), chemical depilatory agents were very popular. In the famous treatise on Cosmetics, written in the second century AD by Crito of Heraclea, chief physician of the Roman Emperor Trajan, a chemical depilatory recipe was mentioned that contained yellow orpinum, quicklime, Selinus earth, and fine meal (starch). Chemical depilatories were named psilotron, from the Greek psilo, to strip, or acilia, from the Latin acies/accer, meaning sharp edge, reflecting thus the mixture’s extreme causticity. Other chemical depilatories were also used in form of paste, based on resins, essential oils, and caustics.\(^1\)

However, in the first century AD, Pliny the Elder (AD 23-79), the distinguished Roman philosopher, medical author, and naturalist, provided a recipe for depilation based on torpedo fish, a group of electric rays capable of producing an electric discharge ranging from 30 to 50 V depending on the species and approaching the 220 V in the case of *Torpedo occidentalis*. The electric discharges of torpedo fish were highly appreciated among ancient physicians, prescribed mainly for epilepsy, gout, headache, prolapsed anus, and as antiaphrodisiac. In his treatise entitled *Natural History*, Pliny dedicates a chapter entitled “Methods of Removing Superfluous Hair—Depilatories.” About the various depilatory formulas that he describes, containing blood, gall and liver of the tuna, and ashes of burnt crabs, he suggests: “Depilatories are prepared...by brains of the torpedo applied with alum on the sixteenth day of the moon.”\(^2\)

Our current knowledge on torpedo fish supports that a dead one has a prolonged and variable electrical activity, emitting electricity up to 9 hours.\(^3\) How far Pliny and his contemporaries realized the electrical discharges, of which to some extent they were cognizant, does not appear clearly in ancient texts. However, they were familiar with the electrical phenomena, which in Pliny’s case found an application in depilation, being thus a precursor of modern electrical depilation or electrolysis.

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