Primary Systemic (Amyloid Light-Chain) Amyloidosis Masquerading as Pseudoxanthoma Elasticum Recognizing a Novel Clinicopathological Pattern

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rimary systemic (amyloid light-chain [AL]) amyloidosis has a variety of cutaneous manifestations. In this case, we present a novel clinicopathological pattern of AL amyloidosis.

Report of a Case

A woman in her 50s was referred for dermatological consultation regarding a 7-year history of an asymptomatic cutaneous eruption involving the neck, bilateral antecubital fossae, and bilateral canthi. She had been recently diagnosed as having primary systemic (AL) amyloidosis.

Her course of AL amyloidosis began with the detection of a vulvar mass in 2004 during a routine Papanicolaou smear examination. A biopsy of this mass at that time was interpreted as cutaneous amyloidosis. Subsequently, renal function testing, results from repeated evaluations of her urine protein electrophoresis and serum protein electrophoresis were consistently within reference range, and she remained free of symptoms suggestive of systemic amyloidosis.

In 2006, the patient developed cutaneous involvement of the neck and antecubital fossae. These lesions began as discrete, skin-colored to yellow cobblestoned plaques to the neck and bilateral antecubital fossa. Although clinical similar to pseudoxanthoma elasticum (PXE), the skin changes were found to be due to amyloid deposition primarily around the pilosebaceous unit but also within the papillary and reticular dermis. Previous reports of PXE-like plaques in AL amyloidosis have been reported as part of a very rare entity termed amyloid elastosis. However, our case demonstrates several important clinical and pathological differences from this entity. Most notably, there was no dermal elastic fiber involvement, limited cutaneous and systemic involvement, and a fairly indolent course with better response to treatment.
The original vulvar biopsy specimen showing presence of dermal amyloid deposits from 2004 was reviewed. Additional immunohistochemical analysis revealed CD138 positivity in small clusters of interstitial plasma cells. These plasma cells showed λ chain restriction, findings that were compatible with the diagnosis of AL amyloidosis. The patient initiated treatment with chemotherapy consisting of bortezomib, cyclophosphamide, and dexamethasone with excellent response as demonstrated by a decline in serum-free λ chain levels to 224.5 mg/L after 3 monthly cycles and resolution of macroglossia.

Because the patient’s pseudoxanthoma elasticum (PXE)-like plaques persisted, a dermatological consultation was sought. The examination revealed skin-colored to yellow papules coalescing into plaques with a cobblestone-like surface that extended circumferentially around the neck with a predilection for the anterior surface (Figure 1A). There were similar, though less prominent, plaques affecting the bilateral antecubital fossae (Figure 1B). She was also noted to have faint clusters of skin-colored papules distributed around the medial canthi bilaterally. There was no evidence of petechiae or periorbital purpura. She denied a tendency for bruising or systemic symptoms, including weight loss or malaise. There were no other areas of cutaneous involvement. The clinical appearance of the lesions on the neck and antecubital fossa was strikingly similar to PXE. However, there was a lack of yellow papules on mucosal surfaces, and ophthalmological consultation revealed a lack of angioid streaks in the eyes.

Three biopsies of plaques from the neck were performed to microscopically analyze these changes. Interestingly, examination of all biopsy specimens revealed no features of PXE. Instead, in 2 of the specimens, amorphous eosinophilic amyloid deposited around a pilosebaceous unit (hematoxylin-eosin, original magnification ×50). B, High-power image of deposits of amyloid in the dermis. Amorphous eosinophilic amyloid deposited around a pilosebaceous unit (hematoxylin-eosin, original magnification ×200). C, Deposits of amyloid in the dermis. Congo red stained positive for amyloid deposits (original magnification ×100).

Three biopsies of plaques from the neck were performed to microscopically analyze these changes. Interestingly, examination of all biopsy specimens revealed no features of PXE. Instead, in 2 of the specimens, amorphous eosinophilic material (amyloid) was found to have accumulated, predominantly around pilosebaceous units (Figure 2A and B). However, the peripilosebaceous area was not the only site of amyloid deposition, as globular focal deposits were also seen.
in papillary and deep reticular dermis. The deposits stained strongly positive for Congo red (Figure 2C) and demonstrated positive apple-green birefringence on polarized microscopy. Both hematoxylin-eosin- and Verhoeff–van Giesen–stained slides showed normal dermal elastic fibers because they showed no thickening, truncation, or fragmentation. The dermal elastic fibers were not encased or coated by amyloid. No perivascular deposits of amyloid were present, and plasma cells were not seen. Von Kossa staining was negative for calcium deposits. Immunohistochemical studies for λ and κ light chains revealed positivity for both within the amyloid deposits. Keratin stains (AE1/AE3 and pan-cytokeratin) were negative for amyloid deposits.

### Discussion

We report a new clinicopathological entity of amyloid deposition surrounding mainly pilosebaceous units but notably sparing elastic fibers, giving rise to a clinical picture remarkably reminiscent of PXE. To our knowledge, this is the reported first case of AL amyloidosis with cutaneous manifestations similar to PXE based on clinical morphologic characteristics and distribution, but with distinct histopathological findings.

Review of the English-language literature on MEDLINE demonstrated 3 cases that mentioned PXE-like appearance as part of a constellation of cutaneous findings found in amyloid elastosis. A total of 5 cases of this entity have been reported; the other 2 cases featured other distinct cutaneous findings but an absence of cutaneous PXE-like plaques. Winkelman et al first defined this entity in 1985 based on the finding of striking, disseminated amyloid-coated elastic fibers in visceral, vascular, and subcutaneous sites. Discrete yellow-brown dermal papules and nodules ranging from 3 mm to 2 cm affected the trunk, extremities, neck, groin, and axillae. Sepp et al described a second case of amyloid elastosis that predominantly affected the vasculature. Their patient displayed cutaneous signs consisting of sclerodermatous facial appearance, poikidermatous and livedo reticularis–like changes of the trunk, cordlike thickening of temporal vessels, PXE-like changes of the neck, and Raynaud phenomenon. Furthermore, the patient underwent amputation of the right lower limb following thrombosis, and subsequent histopathological examination of the tissue revealed extensive amyloid deposition within blood vessels and surrounding elastic fibers. Vecchietti et al highlighted a case of amyloid elastosis successfully treated by hematopoietic cell transplantation. The patient presented with yellow, discrete macules, and patches on the neck, axillae, submammary region, and abdominal folds. There were also orange palmar discoloration and white granular gingival changes. Bocquier et al described a unique case presenting with classic cutaneous findings, such as periorbital purpura and macroglossia, but also coupled with the novel finding of a white plaque around the urethral meatus. Marchand et al highlighted a case of intensely pruritic, skin-colored papules disseminated to cutaneous and mucosal surfaces. These cases are summarized in the eTable 1 in the Supplement.

### Table. Differences Between Amyloid Elastosis and Pseudoxanthoma Elasticum (PXE)-like Plaques of Amyloid Light-Chain (AL) Amyloidosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Amyloid Elastosis</th>
<th>PXE-like Plaques</th>
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<tbody>
<tr>
<td>Cutaneous findings</td>
<td>Varied: yellow-brown macules, discrete papules and nodules, sclerodermoid changes, cordlike thickening of superficial blood vessels, poikidermatous changes</td>
<td>Skin-colored to yellow cobblestoned plaques resembling “plucked chicken skin”</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Severe pruritus reported</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Sites of involvement</td>
<td>Diffuse</td>
<td>Localized</td>
</tr>
<tr>
<td></td>
<td>Skin folds (neck, axillae, submammary, abdominal folds), extremities, trunk, mucosa (gingiva, lips), penis</td>
<td>Neck, antecubital fossa</td>
</tr>
<tr>
<td>Systemic involvement</td>
<td>Extensive (eg, pulmonary, renal, cardiac, hepatic)</td>
<td>Limited (eg, carpal tunnel syndrome, macroglossia, mild transient renal dysfunction, bone marrow with 20% plasma cells)</td>
</tr>
<tr>
<td>Pathologic characteristics</td>
<td>Striking massive amyloid deposition encasing elastic fibers</td>
<td>No elastic fiber involvement, mainly peri pilosebaceous</td>
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<tr>
<td>Course of amyloidosis</td>
<td>Aggressive; often leading to death from end-organ involvement</td>
<td>Indolent</td>
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There are several clinical and histopathological features that distinguish our case from previous reports of amyloid elastosis. Most important, all 5 cases of amyloid elastosis were distinguished by the hallmark histopathological finding of abnormal elastic fibers encased with amyloid deposits, a feature notably absent in our case. Furthermore, those 5 cases featured generalized cutaneous findings and extensive systemic involvement. Three cases resulted in end-organ failure and death. However, our case featured plaques that were localized to sites classically associated with PXE, a comparatively indolent course, and limited extent of systemic involvement. These differences are summarized in the Table.

Classically recognized features of AL amyloidosis include petechiae, hemorrhage, and pinch purpura typically in a peri-orbital, intertriginous, or disseminated distribution. In addition, waxy, smooth papules and nodules that are often hyperpigmented and in a periorificial, flexural, or anogenital distribution are also commonly seen. Rare cutaneous manifestations of primary systemic amyloidosis include sclero-derma-like infiltration of the fingers, chronic paronychia with palmodigital erythematous swelling and induration, diffuse nonscarring or scarring alopecia, cutis verticis gyrata, nail dystrophy, mucosal and cutaneous bullae with possible diffuse hemorrhagic involvement, and cutis laxa. Our case was unique and distinctive from the known presentations of AL amyloidosis because the patient presented with papules and plaques involving the neck and antecubital fossae that were similar to those of PXE, but confirmed histopathologically to be the result of amyloid deposits that did not encase elastic fibers.
Conclusions

This case represents a unique clinicopathological pattern of AL amyloidosis. In fact, this cutaneous finding was one of the presenting signs of systemic disease. Disseminated accumulation of amyloid around elastic fibers has sometimes accompanied an aggressive course of amyloidosis, as evidenced by 3 reports of lethal outcome. Further study is required to determine if any prognostic significance is associated with the differentiation of PXE-like plaques with normal elastic fibers from amyloid elastosis. Recognition of this unique cutaneous presentation of AL amyloidosis could be instrumental in the early detection and rapid treatment of this severe multisystem disease.

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REFERENCES