Case Report

A patient presented to our office with a circumscribed, pink nodule localized to the left angle of the mouth (Figure 1). Upon our initial evaluation of the patient, we considered angular cheilitis or basal cell carcinoma, and a shave biopsy was subsequently performed. The biopsy results revealed an amorphous, dull, pink material extending through the thickness of the reticular dermis with many associated plasma cells arranged in a perivascular and interstitial distribution (Figure 2). Additionally, the dermal material was positive on Congo red staining, and immunoperoxidase-stained sections revealed a marked predominance of Lambda over Kappa light chains (Figures 3, 4).

Discussion

The term “amyloid” was first introduced into medicine by Virchow in 1853. In general, amyloidosis refers to the abnormal tissue deposition of misfolded β-sheet fibrillar protein known as amyloid. However, amyloid is not a single protein, but rather a broad term used to describe one of the many types of amyloid proteins that may become abnormally deposited in tissues (Table 1). Amyloid deposits display a characteristic apple-green birefringence after being stained with Congo red and viewed under polarized light microscopy. The misfolded proteins arise from specific precursor proteins, which help us to classify amyloidosis based on the individual protein chemical compositions (Table 1).

Amyloidosis itself is not necessarily a disease, but rather a manifestation of several underlying disease processes. There are numerous forms of amyloidosis, which consist of various primary and secondary manifestations. Likewise, amyloidosis may present in a wide variety of clinical settings, and it is important for any practitioner to be able to identify this disease process and its appropriate management.

Localized cutaneous amyloidosis is of particular importance to dermatologists and may be further sub-classified as either primary cutaneous amyloidosis or secondary cutaneous amyloidosis. Primary cutaneous amyloidosis may present as one of three types: macular amyloidosis, papular/lichenoid amyloidosis, or nodular amyloidosis. However, macular
and papular amyloidosis may also be present simultaneously in what is referred to as biphagic amyloidosis. Secondary cutaneous amyloidosis refers to amyloid deposition seen in association with basal cell carcinomas, Bowen’s disease, other cutaneous tumors, and following PUVA therapy. Both macular and lichenoid amyloidosis, in addition to secondary localized cutaneous amyloidosis, result from the abnormal misfolding and deposition of keratin protein.6 Familial forms of both disorders may be associated with RET oncogene mutations.

Nodular amyloidosis is perhaps one of the rarest forms of amyloidosis. It presents as either single or multiple waxy nodules or plaques that most commonly affect the trunk or extremities. Nodular amyloidosis may present as a primary cutaneous disorder, but it may also present as a cutaneous manifestation of primary systemic amyloidosis associated with plasma-cell dyscrasias, such as multiple myeloma. Nodular amyloidosis is particularly associated with immunoglobulin γ light-chain deposition, which is believed to be secreted by an infiltrate of plasma cells.2 The presence of nodular amyloidosis confers an approximate 7% risk of progression to systemic involvement. In a study of 16 patients with nodular amyloidosis without systemic involvement, one patient was noted to have a serum monoclonal IgGκ protein upon initial evaluation and subsequently developed symptoms of systemic amyloidosis within one year.5 Thus, it is important to delineate the etiology in all cases of nodular amyloidosis, as it may be indicative of underlying malignancy. Approximately 25% of patients with primary systemic amyloidosis have cutaneous manifestations, which present as waxy, translucent or purpuric papules, nodules, and plaques localized to the palms and volar aspect of the fingertips. Additionally, the face, neck, and scalp may be involved. Signs and symptoms of systemic involvement may be evident, and patients may present with nephrotic syndrome, autonomic and sensory neuropathies, and congestive heart failure. Other signs and symptoms may include:

- Left ventricular hypertrophy
- Low-voltage QRS complex
- Urinary immunoglobulin light chains
- Renal failure

The majority of cases of systemic amyloidosis occur as a result of plasma-cell dyscrasias, including but not limited to multiple myeloma and monoclonal gamopathy of undetermined significance (MGUS), which account for approximately 30% of these cases.6 Treatment options for cutaneous amyloidosis are limited, and there are few randomized controlled trials involving the treatment of this disease. First-line treatments include topical steroids under occlusive dressings and intralesional steroid injections. However, dermabrasion, shave excision, and curettage with cautery have been used successfully in some cases.3 Systemic amyloidosis with cutaneous manifestations requires a multidisciplinary approach to treatment, possibly involving systemic chemotherapy with melphalan. Thus, the treatment options will vary depending on the underlying cause.

**Conclusion**

This case highlights the important role that dermatologists play in diagnosis and management of cutaneous manifestations of both localized and systemic disease.

**References**


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### Table 1. Amyloid Proteins and Clinical Syndromes1

<table>
<thead>
<tr>
<th>Precursor Protein</th>
<th>Amyloid Protein</th>
<th>Clinical Syndrome</th>
</tr>
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<tbody>
<tr>
<td>Immunoglobulin light chain</td>
<td>AL</td>
<td>Primary systemic amyloidosis (plasma-cell dyscrasia and multiple myeloma)</td>
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<tr>
<td></td>
<td></td>
<td>Primary cutaneous nodular amyloidosis</td>
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<tr>
<td>Transthyretin</td>
<td>ATTR</td>
<td>Senile systemic amyloidosis</td>
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<tr>
<td>Cytokeratin (CK5)</td>
<td>AK</td>
<td>Primary cutaneous lichenoid and macular amyloidosis</td>
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<tr>
<td>β₂-microglobulin</td>
<td>Aβ₂,M</td>
<td>Chronic hemodialysis</td>
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<tr>
<td>Aβ precursor protein (AβPP)</td>
<td>Aβ</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>ACal</td>
<td>Medullary carcinoma of the thyroid</td>
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**Table 1. Amyloid Proteins and Clinical Syndromes**

1 The extensor surfaces of the extremities may also be affected. Both macular and papular amyloidosis may be associated with autoimmune connective-tissue disorders, such as systemic lupus erythematosus, scleroderma, and dermatomyositis.1 Familial forms of both disorders may be associated with RET oncogene mutations.

The macular, lichenoid, and biphagic forms of amyloidosis are characterized by amyloid deposition limited to the papillary dermis and may present as yellowish or brownish macules, papules, or plaques. Additionally, a lymphohistiocytic perivascular infiltrate may be appreciated on histopathology.2 In contrast, primary cutaneous nodular amyloidosis is characterized by amyloid deposition in the dermis, subcutis, and even the vessel walls.1,3 Additionally, a perivascular infiltrate of plasma cells may be appreciated on histopathology.1 There is much variability among the different cutaneous forms of amyloidosis, and clinical presentation alone is unlikely to provide a definitive diagnosis. Pruritus is a common symptom associated with cutaneous amyloidosis; however, it is not always present.

Lichenoid or papular amyloidosis is the most common type of primary cutaneous amyloidosis. It presents as firm, scaly, skin-colored or hyperpigmented papules that coalesce into plaques with a rigid appearance. It most commonly affects the extensor surfaces of the extremities. Macular amyloidosis usually presents in early adulthood, affecting women more often than men. It presents as hyperpigmented papules that coalesce into a “rippled” appearance and most commonly affects the scapular region of the upper back. Frequently, this occurs after persistent rubbing of the area with either brushes or towels and has been subclassified as “friction amyloidosis.”1 The extensor surfaces of the extremities may also be affected. Both macular and papular amyloidosis may be associated with autoimmune connective-tissue disorders, such as systemic lupus erythematosus, scleroderma, and dermatomyositis.1 Familial forms of both disorders may be associated with RET oncogene mutations.

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**Conclusion**

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