Primary Localized Cutaneous Nodular Amyloidosis and CREST Syndrome: A Case Report and Review of the Literature

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Primary localized cutaneous nodular amyloidosis (PLCNA) is a form of primary localized cutaneous amyloidosis (PLCA) that presents as yellowish waxy nodules on the extremities, face, trunk, or genitalia. We report the case of a patient with PLCNA and CREST (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) syndrome. A diagnosis of her extensive PLCNA was made after biopsy specimens from the bilateral shins stained positive for amyloid extending from the superficial papillary dermis to the subcutis. Results of a workup were negative for paraproteinemia or signs of systemic amyloidosis and have remained so after 8 years of follow-up. We present a review of the literature describing the presentation and histopathology of the varying forms of amyloidosis.

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Figure 1. Yellow, waxy, well-circumscribed nodules ranging in size from 1 to 4 cm on the lateral surface of the right lower leg.
Serum protein electrophoresis, urine protein electrophoresis, free serum k, free serum λ, complete blood count, glucose, and renal function values all were within reference range. Liver function values were slightly elevated, likely due to a fatty liver. Antinuclear and anticentromere antibodies were positive in the remote past in the setting of the diagnosis of CREST syndrome. Echocardiogram results did not reveal an infiltrative process. Findings from a computed tomographic scan of the chest did not reveal any pulmonary fibrosis. Oncologic studies to evaluate for systemic involvement of amyloidosis included a skeletal survey, which did not reveal any evidence of osteolytic lesions. In addition, a bone marrow biopsy revealed normocellular bone marrow and no evidence of plasma cell dyscrasia. Treatment was initiated with a pulsed dye laser every 6 weeks at varying intensities, which seemed to improve her symptoms of tenderness at the lesion sites. After 8 years of follow-up, she has not developed any evidence of systemic involvement.

Comment

Amyloidosis may be classified as either systemic or localized to a particular organ, such as the skin. Systemic amyloidosis may be further classified into a primary type associated with plasma cell dyscrasia, myeloma associated, and a secondary type associated with a variety of chronic diseases (ie, inflammatory bowel disease, rheumatoid arthritis, Hodgkin disease, some solid nonlymphoid tumors). Finally, there is the rare autosomal dominant–inherited familial amyloidosis and hemodialysis-related amyloidosis, both systemic forms. The primary type of systemic amyloidosis can involve the gastrointestinal tract, heart, tongue, muscles, nerves, and skin. Cutaneous manifestations of primary amyloidosis are common, occurring in 29% to 40% of cases, but are rare in secondary systemic amyloidosis. Cutaneous and systemic involvement of myeloma-associated amyloidosis is similar to the primary type.

Primary localized cutaneous amyloidosis (PLCA) presents with deposition of amyloid material in the skin, without evidence of systemic involvement. It is a condition characterized by extracellular protein deposition and classified according to clinical and histologic features of the amyloid deposits. Macular amyloidosis classically presents as pruritic, small, dusky brown–pigmented or gray-pigmented macules, with a characteristic rippled appearance. These macules are often symmetrically distributed on the upper back, extremities, chest, or buttocks. Lichen amyloidosis often is described as persistent pruritic hyperkeratotic papules initially localized to the shins. These discrete papules may then coalesce into plaques, with spread to the thighs, ankles, dorsum of the foot, abdomen, chest, or calves. Macular and lichen amyloidosis often have been regarded as variants of the same process because both may be present in the same individual.
Primary localized cutaneous nodular amyloidosis (PLCNA), the most unusual form of PLCA (seen in our patient), commonly presents as single or, more rarely, multiple yellowish waxy nodules, generally located on the extremities, face, trunk, or genitalia, with sizes varying from several millimeters to several centimeters. Clinically, cutaneous manifestations of PLCNA are identical to those associated with plasma cell dyscrasia–related primary systemic amyloidosis.10

Histologically, macular and lichen amyloidosis are associated with deposition of amyloid in the papillary dermis. PLCNA, however, is characterized by amyloid deposition in the dermis, blood vessels, and subcutis.11 Based on histology and the coexistence of macular and lichen amyloidosis in the same individual, it seems that PLCNA may be regarded as a distinct entity from the other 2 variants.

Most patients with PLCNA will follow a benign course over many years without any development of systemic involvement. However, some patients have paraproteinemia and later develop systemic amyloidosis.12,13 An original study by Brownstein and Helwig12 in 1970 revealed PLCNA that progressed to systemic amyloidosis in 5 of 10 patients (a progression rate of 50%). However, a later study by Woollons and Black14 estimated progression of PLCNA to systemic amyloidosis to be 7% after only 1 of 15 patients with PLCNA developed systemic involvement. Our patient had 8 years of multiple lesions of PLCNA without evidence of paraproteinemia or systemic amyloidosis.

Varying forms of PLCA have been uncommonly associated with autoimmune connective tissue disorders, including primary biliary cirrhosis, systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, and rheumatoid arthritis.15 A review of the literature by Yoneyama et al16 demonstrated 14 cases of PLCNA associated with Sjögren syndrome. To our knowledge, an association of PLCNA and systemic sclerosis, including the CREST variant of limited cutaneous systemic sclerosis, has not yet been reported. However, reports have associated scleroderma with other forms of PLCA. For example, Azon-Masoliver15 discussed the occurrence of macular amyloidosis in a woman with CREST syndrome. Ogiyama et al17 described PLCA in 6 of 66 patients with progressive systemic sclerosis. These lesions were described as having a rippled appearance on the upper backs of patients, most consistent with the macular subtype of PLCA.17

Most lesions associated with secondary amyloidosis and heredofamilial syndromes consist of amyloid fibrils composed of the amyloid A protein AA.18 The AA type of amyloid is not composed of immunoglobulin but is instead derived from an acute phase reactant that is increased in certain inflammatory states. Another amyloid fibril protein, β2-microglobulin, has been associated with the amyloid fibrils of chronic hemodialysis-related amyloidosis.19

Primary localized cutaneous nodular amyloidosis is characterized by the formation of amyloid fibrils that consist of immunoglobulin light chains, referred to as the amyloid L (AL) type, which is the same type of amyloid fibril protein seen in primary systemic amyloidosis and myeloma-associated systemic amyloidosis. Immunohistochemistry staining has demonstrated the presence of either κ or λ light chains or both in dermal deposits of PLCNA.20,21 Unfortunately, the mechanism by which plasma cells locally secrete amyloid is unknown.22,23 The histopathology of PLCNA is similar to primary systemic amyloidosis, with the exception of a more prominent plasma cell infiltrate in PLCNA.12,24 Our patient had both κ and λ light chains present on immunohistochemistry, typical of PLCNA.

As opposed to PLCNA, macular and lichen amyloidosis are derived from keratin, formed by the conversion of degenerated epidermal cells into amyloid within the papillary dermis.25 Huiligol et al26 showed that all 7 of their frozen sections of either macular or lichen amyloidosis were successfully labeled with antikeratin antibodies. Interestingly, macular amyloidosis often is called frictional amyloidosis because chronic friction of the epidermis has been associated with formation of this condition.27 The Table demonstrates the amyloid fibril proteins associated with the varying clinical classifications of amyloidosis.

Local and remote recurrence of PLCNA have been difficult to treat. Variable success has been seen with surgical excision, dermabrasion, electrodesiccation and curettage, cryotherapy, and laser therapy, often with recurrence of the lesions.28-30

**Conclusion**

Primary localized cutaneous amyloidosis, presenting with deposition of amyloid material in the skin, without evidence of systemic involvement, has been classified as macular, lichen, and nodular forms. It has been uncommonly associated with autoimmune connective tissue disorders, including primary biliary cirrhosis, systemic lupus erythematosus, Sjögren syndrome, systemic sclerosis, and rheumatoid arthritis.15 The most unusual form of PLCA is PLCNA and typically presents as single or, more rarely, multiple yellowish waxy nodules on the extremities, face, trunk, or genitalia. Our patient is unusual in that she had an extensive number of nodular lesions and had underlying CREST syndrome. PLCNA is characterized by deposition of AL in the dermis, blood vessels, and subcutis produced by local plasma cell aggregates.11
Patients with cutaneous amyloidosis need to be followed for development of systemic symptoms, as some patients have been reported to develop multiple myeloma years later.\textsuperscript{1,14} Variable success has been seen with surgical excision, dermabrasion, electrodesiccation and curettage, cryotherapy, and laser therapy, often with recurrence of the lesions.\textsuperscript{28-30}

**REFERENCES**


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<thead>
<tr>
<th>Clinical Classification</th>
<th>Cutaneous Involvement</th>
<th>Amyloid Fibril Protein</th>
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<tbody>
<tr>
<td><strong>Systemic Amyloidosis</strong></td>
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<tr>
<td>Primary</td>
<td>Yes; also gastrointestinal tract, heart, tongue, muscles, nerves</td>
<td>AL</td>
</tr>
<tr>
<td>Myeloma associated</td>
<td>Yes; similar to primary type</td>
<td>AL</td>
</tr>
<tr>
<td>Secondary</td>
<td>Rarely; often involves liver, spleen, kidney, adrenal glands</td>
<td>AA</td>
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<tr>
<td>Heredofamilial</td>
<td>Yes</td>
<td>AA</td>
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<td>(familial amyloidosis, Mediterranean fever, Muckle-Wells syndrome)</td>
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<tr>
<td>Hemodialysis related</td>
<td>No</td>
<td>β2-Microglobulin</td>
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<td><strong>Localized Amyloidosis</strong></td>
<td></td>
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<tr>
<td>Macular</td>
<td>Yes; upper back, extremities, chest, buttocks</td>
<td>Keratin</td>
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<tr>
<td>Lichen</td>
<td>Yes; shins, thighs, ankles, dorsum of the foot, abdomen, chest, calves</td>
<td>Keratin</td>
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<td>Nodular</td>
<td>Yes; extremities, face, trunk, genitalia</td>
<td>AL</td>
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Abbreviations: AL, amyloid L; AA, amyloid A.