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

Erika M. Summers, MD; Christina G. Kendrick, MD

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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Case Report

A 61-year-old woman presented with an 8×9-mm brown papule with eccentric erythema on the left shin. Prior medical history included CREST (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) syndrome (diagnosed one year prior), hypertension, type 2 diabetes mellitus, and fatty liver. Results of the initial biopsy of the nodule on the left shin revealed macular and lichen amyloidosis with involvement of the papillary dermis. The biopsy specimen stained positive for amyloid on fluorescence microscopy. Clinically, the lesions did not appear consistent with lichen amyloidosis but rather appeared more like nodular amyloidosis. Over the course of the following 3 years, more than 20 yellow waxy nodules on the bilateral lower extremities, ranging in size from 1 to 4 cm, subsequently developed (Figure 1). Repeat punch biopsies of the nodules on the bilateral shins were performed 3 years after the initial cutaneous biopsy. Focal aggregates of plasma cells were identified (Figure 2). The biopsy specimen stained positive for amyloid extending from the superficial papillary dermis to the subcutis, consistent with nodular amyloidosis (Figure 3). Immunohistochemistry showed a ratio of kappa- to lambda-positive cells of approximately 10 to 1, indicative of a light chain–restricted infiltrate.

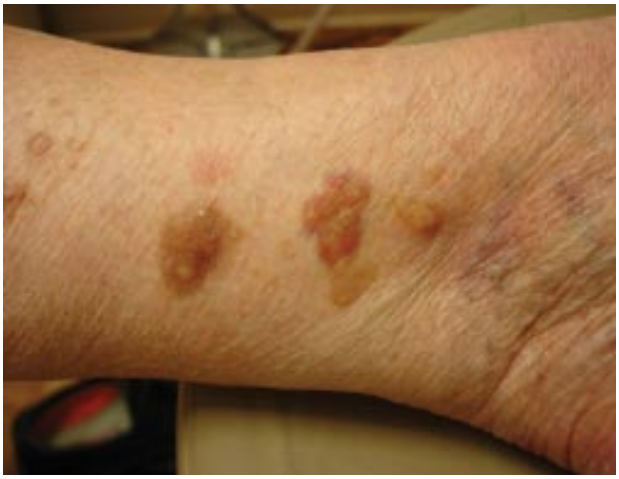

Figure 1. Yellow, waxy, well-circumscribed nodules ranging in size from 1 to 4 cm on the lateral surface of the right lower leg.

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Dr. Summers is from the Department of Internal Medicine and Dr. Kendrick is from the Department of Dermatology, both at Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, Massachusetts.

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Correspondence: Erika M. Summers, MD, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (esummers@bidmc.harvard.edu).

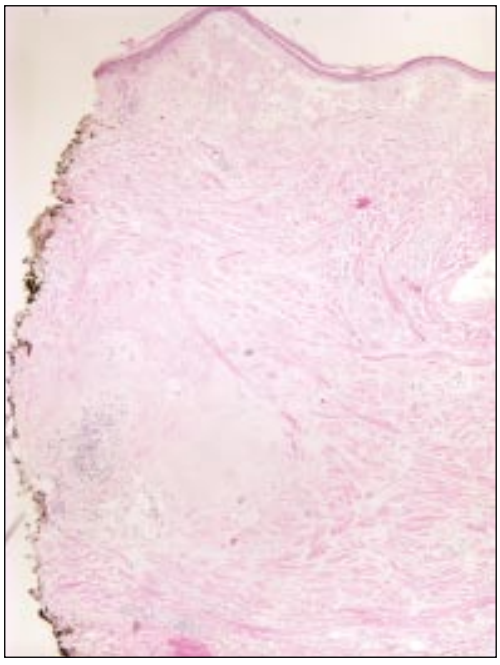

Figure 2. Focal aggregates of plasma cells noted superficially to a dense deposit of amyloid (H&E, original magnification ×20).

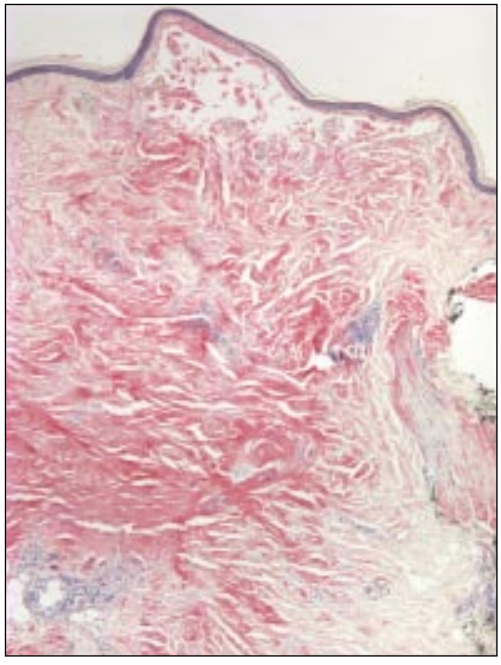

Figure 3. Dense deposits of amyloid extending from the superficial papillary dermis to the subcutis (Congo red, original magnification ×40).

Serum protein electrophoresis, urine protein electrophoresis, free serum κ, 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).[1-4] 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.[1,2] Cutaneous manifestations of primary amyloidosis are common, occurring in 29% to 40% of cases, but are rare in secondary systemic amyloidosis.[1,3,5-7] 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.[1] 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.[1,8] Macular and lichen amyloidosis often have been regarded as variants of the same process because both may be present in the same individual.[9]

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.[1,12,13] An original study by Brownstein and Helwig[12] 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 Black[14] 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 al[16] 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-Masoliver[15] discussed the occurrence of macular amyloidosis in a woman with CREST syndrome. Ogiyama et al[17] 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, β_2-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] Huilgol et al[26] 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]

Clinical Classifications of Amyloidosis With Cutaneous Involvement and Associated Amyloid Fibril Proteins

Clinical Classification	Cutaneous Involvement	Amyloid Fibril Protein
Systemic Amyloidosis		
Primary	Yes; also gastrointestinal tract, heart, tongue, muscles, nerves	AL
Myeloma associated	Yes; similar to primary type	AL
Secondary	Rarely; often involves liver, spleen, kidney, adrenal glands	AA
Heredofamilial (familial amyloidosis, Mediterranean fever, Muckle-Wells syndrome)	Yes	AA
Hemodialysis related	No	β_2-Microglobulin
Localized Amyloidosis		
Macular	Yes; upper back, extremities, chest, buttocks	Keratin
Lichen	Yes; shins, thighs, ankles, dorsum of the foot, abdomen, chest, calves	Keratin
Nodular	Yes; extremities, face, trunk, genitalia	AL

Abbreviations: AL, amyloid L; AA, amyloid A.

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.[1,14] Variable success has been seen with surgical excision, dermabrasion, electrodesiccation and curettage, cryotherapy, and laser therapy, often with recurrence of the lesions.[28-30]

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