Primary Cutaneous Nodular Amyloidosis: Case Report and Review of the Literature

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The estimated time to complete this activity is 1 hour.

GOAL

To understand primary cutaneous nodular amyloidosis (PCNA) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, you will be able to:

1. Recognize the clinical presentation of PCNA.
2. Discuss the pathophysiology of PCNA.
3. Distinguish primary systemic amyloidosis from PCNA based on clinical and laboratory findings.

INTENDED AUDIENCE

This CME activity is designed for dermatologists and general practitioners.

CME Test and Instructions on page 107.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: July 2009.

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Primary cutaneous nodular amyloidosis (PCNA) is a rare form of primary cutaneous amyloidosis. It presents as waxy yellow-red nodules that are located preferentially on the lower extremities, face, scalp, and genitals. Recognition of this condition is of particular importance, as primary systemic amyloidosis can have a similar cutaneous presentation. We report a case of PCNA in a 52-year-old woman with systemic lupus erythematosus (SLE) and Sjögren syndrome (SS). We discuss the need to evaluate for systemic disease and provide a concise review of the literature

focusing on clinical presentation, disease associations, and management.

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Case Report

A 52-year-old woman with a medical history of well-controlled systemic lupus erythematosus (SLE) and Sjögren syndrome (SS)(both diagnosed approximately 2 decades prior) was evaluated in the dermatology clinic for progressively enlarging asymptomatic papules and plaques of the lower extremities. She denied systemic concerns. Her medical history also included osteoporosis, fibromyalgia, seizure disorder (epilepsy), anxiety, and depression. At the time of presentation, her medications included hydroxychloroquine sulfate, conjugated estrogens/medroxyprogesterone acetate, alendronate sodium, topiramate, and cyclosporine ophthalmic emulsion 0.05%. On physical examination, the patient had multiple 1-mm yellow papules coalescing into a 1-cm, yellow-pink, asymmetric plaque on the right thigh. She also had a 3-cm, well-defined, yellow, firm plaque on her left calf (Figure 1).

Punch biopsy specimens from each plaque demonstrated a slightly orthokeratotic hyperkeratotic stratum corneum with an effaced epidermis overlying a dermal nodular homogeneous collection of an eosinophilic material with a cracked appearance (Figure 2). Bennhold Congo red staining was positive for amyloid (Figure 3). Further diagnostic workup including a complete blood cell count, comprehensive metabolic panel, chest radiography, electrocardiography, urinalysis, serum protein electrophoresis, and urine protein electrophoresis were normal with no findings suggestive of systemic amyloidosis. The patient had a positive antinuclear antibody titer (1:160, speckled pattern) and was positive for double-stranded DNA as well as SS-A (Sjögren syndrome antigen A) and SS-B (Sjögren syndrome antigen B) antibodies attributed to her known SLE and SS.

Comment

Primary cutaneous nodular amyloidosis (PCNA) is a rare form of primary cutaneous amyloidosis.[1] This condition occurs in both males and females, with an average age of onset of 60 years, but the age of onset can be highly variable.[2] There is no known predilection for any ethnic group, though reports of this disease appear in the American, Asian, and European literature. Prevalence of PCNA has not been defined but is likely very low, with approximately 50 cases reported in the medical literature.[3] Among the reported cases, patients typically present with a solitary cluster of waxy yellow-red nodules that are located preferentially on the lower extremities, face, scalp, and genitals, similar to the cutaneous presentation of primary systemic amyloidosis. Occasionally, the lesions can be bullous or atrophic.[4,5]

Amyloidosis is a disorder defined by an abnormal extracellular deposition of various host-synthesized proteins configured as beta-pleated sheets, a tertiary protein structure that is abnormal in human tissue.[6] It is categorized as either primary cutaneous amyloidosis or systemic amyloidosis. Primary cutaneous amyloidosis differs from systemic amyloidosis in that the deposits are exclusively localized to the skin without involvement of internal organs.[7] There are 3 subtypes of primary cutaneous amyloidosis: lichenoid, macular, and nodular. Lichenoid amyloidosis presents with discrete, highly pruritic, brownish red papules that typically occur on the lower legs. Macular amyloidosis also is pruritic and presents with

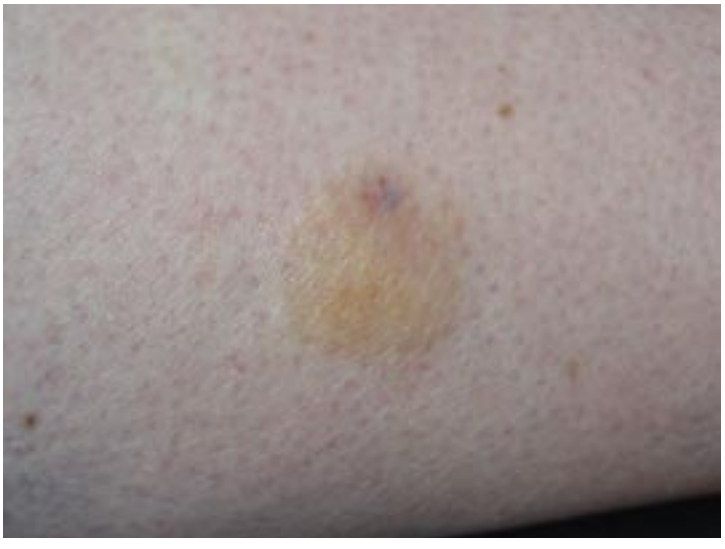

Figure 1. A 3-cm, well-defined, yellow, firm plaque on the left calf diagnosed as primary cutaneous nodular amyloidosis.

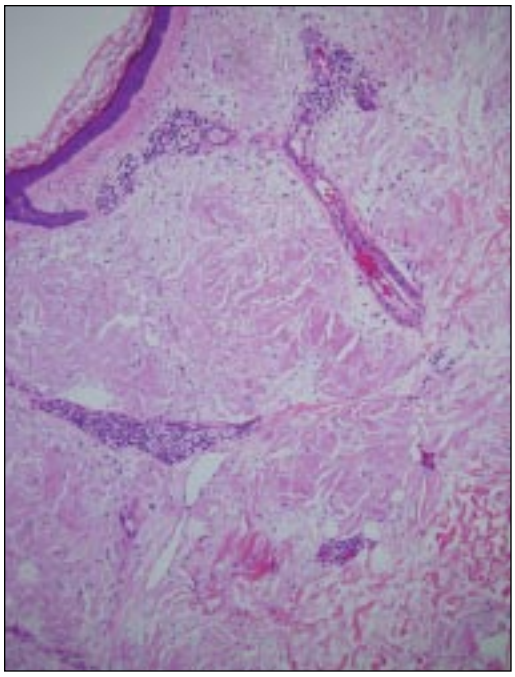

Figure 2. A biopsy specimen from a plaque on the patient's left calf demonstrated a slightly orthokeratotic hyperkeratotic stratum corneum with an effaced epidermis overlying a dermal nodular homogeneous collection of eosinophilic material with a cracked appearance (H&E, original magnification ×10).

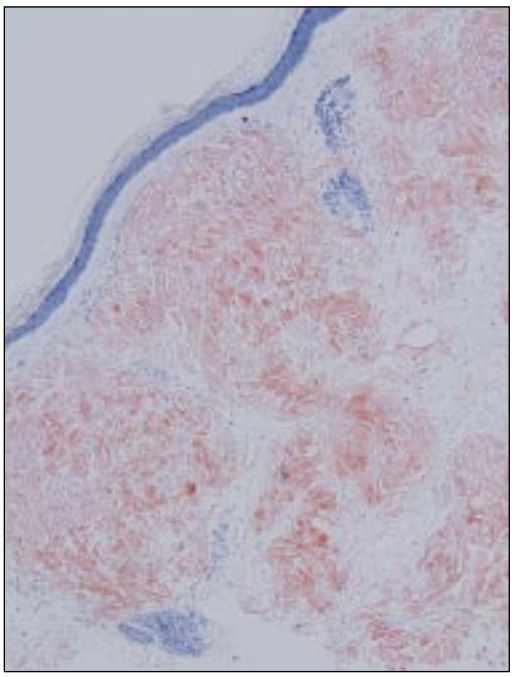

Figure 3. Bennhold Congo red staining of a biopsy specimen from a plaque on the patient's left calf was positive for amyloid (original magnification ×10).

gray-brown, reticulated, macular lesions occurring principally on the upper back.[8]

Systemic amyloidosis is divided into 3 subtypes, each with specific amyloid fibril precursor proteins, such as transthyretin, β_2-microglobulin, apolipoprotein A-I, and gelsolin: primary systemic amyloidosis, secondary systemic amyloidosis, and hereditary amyloidosis.[9] The precursor protein of primary systemic amyloidosis is a monoclonal immunoglobulin light chain (AL [amyloid light chain]), either λ or κ, associated with a B lymphocyte monoclonal proliferation or plasma cell dyscrasia. Secondary systemic amyloidosis is unique, as it is characterized by extracellular tissue deposition of fibrils that are composed of acute phase reactants (AA [amyloid associated]). Rheumatoid arthritis and chronic inflammatory bowel disease, particularly Crohn disease, are the most common causes of secondary systemic amyloidosis in Western Europe and the United States.[10] While up to 40% of cases of primary systemic amyloidosis manifest as cutaneous nodularlike plaques,[11] there are typically no cutaneous findings in secondary systemic amyloidosis.[8] The cutaneous nodules of primary systemic amyloidosis may appear clinically and histologically similar to PCNA. Unlike the keratin-derived amyloid deposits in the other forms of primary cutaneous amyloidosis, the amyloid deposits in both primary systemic amyloidosis and PCNA are derived from monoclonal immunoglobulin light chains.[1,8]

Primary cutaneous nodular amyloidosis is thought to occur because of a localized plasma cell dyscrasia from which a monoclonal population of plasma cells generates the amyloid protein.[2] Gene rearrangement studies have confirmed clonality of the amyloid-producing plasma cells in the skin but without such cells present in the bone marrow. Some authors have defined PCNA as an extramedullary plasmacytoma in which amyloid fibrils are produced locally by plasma cells.[12]

The clinical differential diagnosis of PCNA is substantial and includes entities such as lymphoma cutis, pseudolymphoma, pretibial myxedema, cutaneous sarcoidosis, granuloma annulare, reticulohistiocytoma and multicentric reticulohistiocytosis, and granuloma faciale. Many of these conditions have indurated papules or nodules as their clinical presentation but all have distinguishing features when compared to PCNA. Lymphoma cutis encompasses various B and T cell non-Hodgkin lymphomas with presentations varying from typically erythematous solitary nodules to ulcerating tumors. Pseudolymphoma presents similar to lymphoma cutis but is differentiated by histopathologic criteria and a benign clinical course.[13] Pretibial

myxedema presents as erythematous to flesh-colored, sometimes purple-brown or yellowish, waxy, indurated nodules or plaques that characteristically have a peau d'orange appearance.[14] Cutaneous sarcoidosis most commonly manifests as papules and plaques that often are red-brown. Papules may be flat-topped in appearance. Sarcoid lesions are fairly symmetric in distribution and favor the face, lips, neck, upper trunk, and extremities. Granuloma annulare usually presents with asymptomatic annular plaques that may be flesh colored, pink, or violaceous. Upon close inspection, the plaques are comprised of individual small papules measuring a few millimeters in diameter. Reticulohistiocytoma can present as a single, asymptomatic, yellow to red nodule (giant cell type). Multicentric reticulohistiocytosis is characterized by cutaneous and mucous membrane reticulohistiocytomas and severe arthropathy. Lesions range in size from a few millimeters to 2 cm and are flesh colored to red, brown, or yellow. Small papules characteristically align along the periungual regions, resulting in a characteristic coral bead appearance.[13] Granuloma faciale usually presents as a solitary, asymptomatic, smooth, red-brown to violaceous plaque on the face.[15]

The evaluation for suspected primary cutaneous amyloidosis should begin with a punch biopsy of a representative lesion. Histology is characterized by a diffuse homogeneous eosinophilic deposit in the dermis, subcutis, and perivascular tissue, along with interspersed plasma cells (Figure 2). Staining of the eosinophilic deposits elicits a positive reaction to Bennhold Congo red stain (Figure 3), which exhibits apple green birefringence under polarized light. Thioflavine T also will stain the amyloid deposits (intense yellow-green fluorescence) as well as crystal violet (purple).[1,9]

The histopathologic differential diagnosis of nodular amyloidosis includes erythropoietic protoporphyria, lipoid proteinosis, colloid milium, and gouty tophi, all presenting with large eosinophilic deposits in the dermis. The clinical presentation of these disorders differs from PCNA and differentiation is not difficult in the context of the patient. Erythropoietic protoporphyria is a genetic disorder arising from defective activity of ferrochelatase, a final enzyme of heme biosynthesis. Accumulated excess of its substrate, protoporphyrin, can cause a distinctive cutaneous photosensitivity with hepatobiliary disease. Histology demonstrates marked eosinophilic homogenization and thickening of the blood vessels in the papillary dermis.[8] Lipoid proteinosis is a rare, recessively inherited disorder characterized by deposition of hyalinelike material in the skin, larynx, and other organs that leads to hoarseness from early infancy and protean manifestations.[16] Histologically, it is characterized by deposition of periodic acid–Schiff positive, diastase-resistant, basement membrane thickening at the dermoepidermal junction, surrounding blood vessels and adnexal epithelia. There also is deposition or accumulation of hyaline material in the dermis.[17] Colloid milium is a rare cutaneous disorder characterized by translucent papules occurring on sun-exposed regions, including the face, neck, and dorsal aspects of the hands and back.[18] Colloid milium shows cleaved, homogeneous, eosinophilic material occupying the dermal papillae with routine hematoxylin and eosin staining.[19] Staining for colloid milium is similar to PCNA but can be distinguished by electron microscopy and its clinical scenario.[20] The key histologic feature of gouty tophi is the deposition of amorphous material within the dermis and subcutis. These deposits contain needle-like clefts that represent dissolved urate crystals and are surrounded by an infiltrate composed of histiocytes, multinucleate giant cells, and lymphocytes. When preserved with ethanol-based fixatives, the crystals can be examined with a polarizing filter. The needle-shaped crystals vary from yellow to blue when the polarizing filter is turned, meaning they exhibit negative birefringence.[13]

Initial systemic evaluation for patients with suspected PCNA includes a complete blood cell count, comprehensive metabolic panel, chest radiography, electrocardiography, urinalysis, serum protein electrophoresis, and urine protein electrophoresis.[21] This testing is essential, as up to 40% of patients with primary systemic amyloidosis can present with cutaneous findings identical to PCNA, often early in the disease course.[11] Additionally, PCNA has been observed to progress to systemic amyloidosis in 7% of individuals, necessitating continuous follow-up and laboratory evaluation.[1] Clinical features suggestive of systemic amyloidosis include nephrotic syndrome with renal insufficiency, restrictive cardiomyopathy, peripheral neuropathy, hepatomegaly with elevated liver function tests, macroglossia, periorbital purpura, lytic bone lesions, and more than 30% plasma cells on bone marrow examination.[22] Iodine-123–labeled serum amyloid P component scintigraphy is another test that can be used to evaluate patients with suspected systemic involvement. Serum amyloid P component is present in all amyloid deposits and scanning shows distribution of amyloid within all organs; thus it can be used for diagnosing, locating, and monitoring the extent of systemic amyloidosis.[23] Serum amyloid P component scintigraphy is expensive and many patients and physicians prefer to monitor for

signs of systemic involvement without this testing. However, a nuclear medicine study revealed 90% sensitivity and 93% specificity for serum amyloid P component scintigraphy for systemic AL amyloidosis.[24] Physicians and patients can assess if the expense is worth the potential diagnostic information.

Sjögren syndrome should be considered in any patient with PCNA. Meijer et al[25] found 16 published cases of an association between SS and PCNA, representing approximately 25% of the reported cases of PCNA. The pathogenesis of amyloid deposition in SS may be secondary to lymphocytic proliferation that affects the exocrine glands, specifically the lacrimal and salivary glands. This proliferation may cause unidentified local factors to alter the immunoglobulin light chain's conformation, leading to fibril formation and ultimately PCNA.[26] As many cases of SS occur in patients with PCNA, Meijer et al[25] hypothesized that the combination of amyloid and SS is a distinct disease entity reflecting a particular and benign part of the polymorphic spectrum of lymphoproliferative diseases related to SS. This combination could be called SS-associated localized nodular amyloidosis.[25]

While SS is the most common disease associated with PCNA, other disease associations have been reported. A recent case report described PCNA in a patient with CREST (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) syndrome.[27] Other autoimmune disorders, such as primary biliary cirrhosis, SLE, rheumatoid arthritis, and systemic sclerosis, also have been linked to PCNA as well as the lichenoid and macular subtypes of primary cutaneous amyloidosis.[28]

Recommendations on the treatment of PCNA are highly variable because there are no consistently effective therapies. Cryotherapy, electrodesiccation and curettage, intralesional steroid injection, surgical excision, localized radiation, and CO_2 laser therapy all have been employed, but the rate of local recurrence for all of the modalities is quite high.[1] Because of the lack of effectiveness of treatment options, physicians should focus on monitoring for progression to systemic amyloidosis. Systemic evaluation should be performed at least yearly and when clinically indicated.

Conclusion

Primary cutaneous nodular amyloidosis is a rare cutaneous amyloidosis that presents with a solitary cluster of waxy nodules. It is clinically and histologically similar to primary systemic amyloidosis, as the amyloid deposits in both are derived from monoclonal immunoglobulin light chains, thereby eliciting the need to further investigate to confirm the diagnosis. Various treatments have been described and physicians and patients should discuss the treatment that is in the patient's best interest, mindful of the high recurrence rate. A possible link between SS and PCNA has been speculated, and while the evidence has some merit, no definitive explanation of this phenomenon has been solidified. Primary cutaneous nodular amyloidosis is generally benign, but there have been reports of PCNA progressing to systemic amyloidosis. While clinicians should be aware of this possibility, the overall prognosis of PCNA is promising.

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