

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

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Practice Points

- The etiology of primary localized cutaneous nodular amyloidosis (PLCNA) is thought to be due to a local plasmacytoma.
- Patients with PLCNA are at risk for progression to systemic amyloidosis and therefore should be screened regularly.
- Lesions associated with PLCNA may lead to functional impairment and discomfort.

Primary localized cutaneous nodular amyloidosis (PLCNA) is a rare disorder that manifests as the cutaneous formation of nodules composed of light-chain amyloid. Although the type of amyloid deposit is similar to primary systemic amyloidosis, there seems to be little, if any, crossover between the 2 diseases. Because reports of PLCNA are sparse, there is no established protocol for treating this disease. This case report presents a 42-year-old man with a visually striking presentation of PLCNA on both feet with some of the lesions possibly being secondary to trauma, a rare phenomenon. The lesions had been present for more than 4 years, and there were no signs or symptoms of systemic amyloidosis. The lesions responded well to a combination of complete curettage followed by CO₂ laser ablation. Primary

localized cutaneous nodular amyloidosis is rare and difficult to treat, with high rates of recurrence and a concern for progression to systemic amyloidosis. The diagnosis, workup, treatment, and monitoring of PLCNA also are discussed.

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Case Report

A 42-year-old man presented to the clinic for treatment of large growths on the bottom of both feet of more than 4 years' duration. The patient reported the nodules were becoming painful during physical exercise and he was interested in having them removed. He noted that some of the growths seemed to occur at sites of prior blisters due to normal outdoor activity.

On examination, numerous soft, pink to yellow, waxy-appearing nodules were noted to project from the sides and bottoms of multiple toes on both feet (Figure 1). The nodules were not tender to palpation and were not friable or fissured. There also was a 5×3-cm soft, pink, waxy plaque located on the arch of the plantar aspect of each foot. A biopsy stained positive for deeply eosinophilic homogeneous material infiltrating the entire depth of the dermis to the subcutis; on closer examination, an infiltrate composed of plasma cells was noted. The sample also stained positive with Congo red, indicating cutaneous amyloidosis (Figure 2). Furthermore,

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Figure 1. Large amyloid nodule on the fifth toe of the right foot with smaller nodules at the base of the first 3 toes.

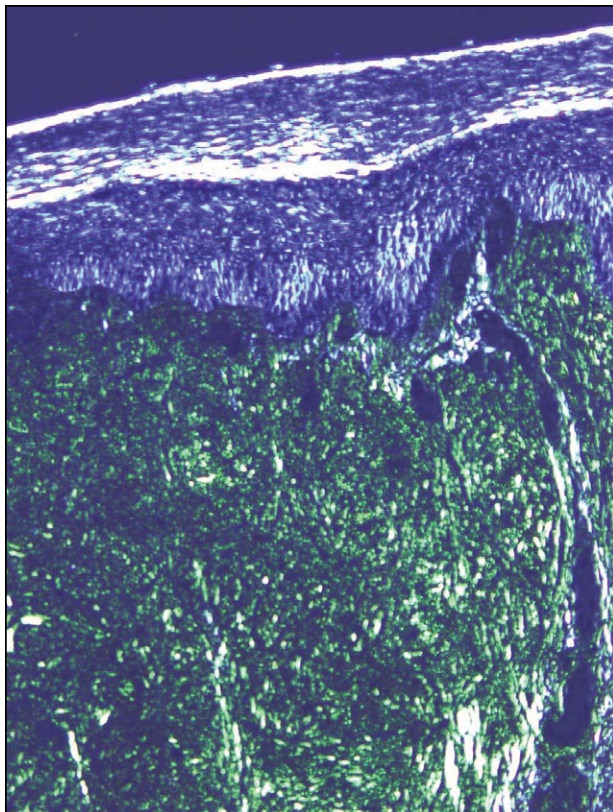


Figure 2. Congo red stain of the biopsy demonstrated apple green birefringence under polarized light, clearly indicating amyloid deposition through the base of the sample (original magnification $\times 100$).

immunohistochemistry revealed the deposition of immunoglobulin κ (Figure 3A) and λ light chains (Figures 3B). Electron microscopy showed typical amyloid deposits; under high magnification the

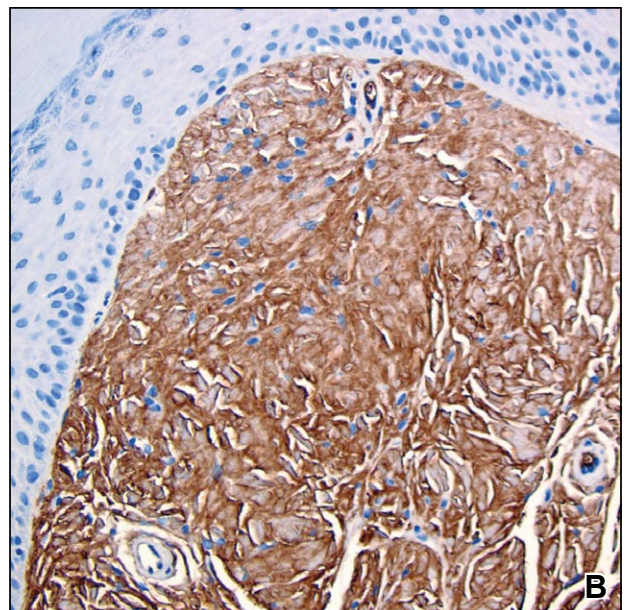
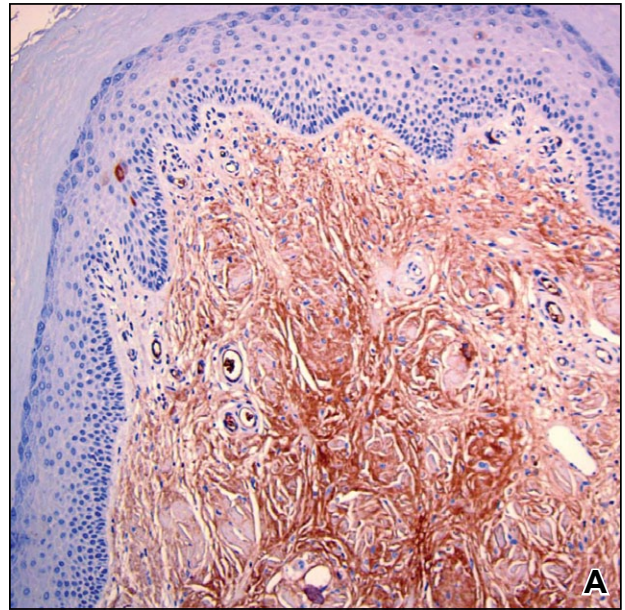


Figure 3. Deposition of immunoglobulin κ (A) and λ (B) light chains throughout the dermis (original magnifications $\times 100$ and $\times 100$, respectively).

typical amyloid fibrils were seen adjacent to thicker collagen fibers (Figure 4).

A thorough review of systems was conducted. The patient reported no additional abnormalities. A workup was initiated to rule out systemic involvement of amyloidosis. Serum protein electrophoresis, urine protein electrophoresis, complete blood cell count with differential, liver-associated enzymes, creatinine levels, urinalysis, electrocardiogram, and chest radiograph results were normal. Based on these findings and the histologic characteristics of the skin

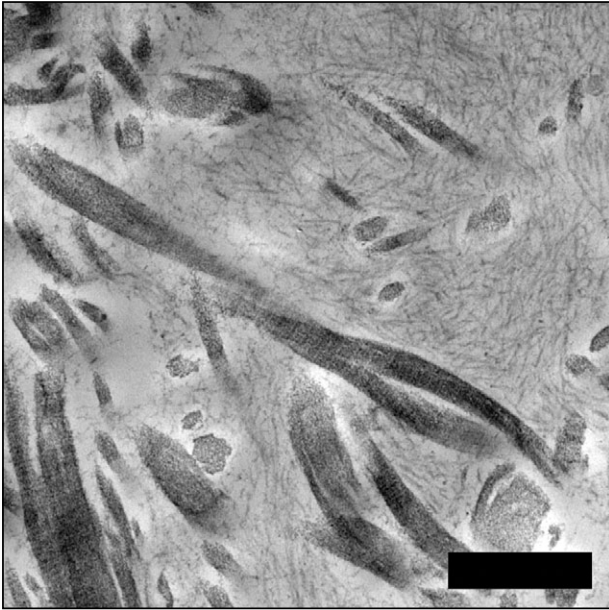


Figure 4. Electron microscopy demonstrated typical amyloid fibrils adjacent to thicker collagen fibers. Reference bar denotes 500-nm width.



Figure 5. Nodules on the right foot 6 months after treatment with curettage and CO₂ laser ablation.

lesions, a diagnosis of primary localized cutaneous nodular amyloidosis (PLCNA) was made.

The patient underwent a series of procedures to remove and reduce the nodules, including shave excision of 4 lesions, intralesional injection to another lesion (0.3 mL of triamcinolone acetate at a concentration of 40 mg/mL), and curettage followed by CO₂ laser ablation of all lesions on the right foot (Figure 5).

Comment

Cutaneous amyloidosis is a rare disease with 3 clinically and histologically distinct variations: macular, lichenoid, and nodular. In all of these subtypes, extracellular amyloid deposits are present in the skin due to nonfunctional β -pleated sheets.¹

Macular and lichenoid amyloidoses commonly are grouped together, as they both have a keratin derivative constituting their amyloid deposits and neither extends below the papillary dermis. These 2 diseases commonly are copresent and may be considered the same disease with slightly different clinical presentations.² Both also are thought to arise secondary to trauma in the epidermis,^{2,3} and there have been reports of these conditions coexisting with various autoimmune diseases.⁴⁻⁶

Nodular amyloidosis is the rarest of the 3 subtypes, with fewer than 100 cases reported in the literature.^{7,8}

There are 2 major factors that differentiate nodular amyloidosis from macular and lichenoid amyloidoses. First, a nodular amyloid is composed of light-chain immunoglobulins (ie, AL amyloid) derived from a monoclonal expansion of plasma cells.⁷⁻⁹ Second, the amyloid of nodular amyloidosis infiltrates the entire dermis, from the papillary dermis to the subcutis. Cutaneous nodular amyloidosis seems to occur most commonly on the legs, feet, face, trunk, and genitalia.² Although lichen amyloidosis is the only type that has been specifically associated with the Köbner phenomenon,¹⁰ it appears that nodular amyloidosis also can occur at sites of prior trauma,^{1,11} which may have been true in our case, as the patient noted a correlation between sites of prior blisters and formation of some of the amyloid nodules; however, we cannot be certain that there was no subclinical accumulation of amyloid material in the feet that predisposed these areas to blister formation, followed by further accumulation of amyloid that formed the nodules. Nodular amyloidosis does share one feature with macular and lichenoid amyloidosis, namely that it is potentially linked to autoimmune diseases, specifically Sjögren syndrome¹²⁻¹⁵; however, there is no clear evidence to indicate if nodular amyloidosis causes Sjögren syndrome or vice versa. Reports of nodular amyloidosis associated with other autoimmune diseases such as CREST (scleroderma

characterized by calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, telangiectasia) syndrome² and primary biliary cirrhosis¹⁴ have been sparse, but Sjögren syndrome appears to be the only one related on a frequent basis at the present time.¹²⁻¹⁴

Similar to primary cutaneous amyloidosis, systemic amyloidosis can cause cutaneous symptoms and must be ruled out when evaluating a patient with cutaneous amyloidosis. Systemic amyloidosis, either primary or secondary, is a rapidly fatal disease characterized by the deposition of amyloid within various organs of the body. Primary systemic amyloidosis results from myeloma or other plasma cell dyscrasias that release large quantities of light-chain immunoglobulins into the circulation. Secondary systemic amyloidosis is caused by inflammatory conditions (eg, rheumatoid arthritis, inflammatory bowel disease, chronic infection, Hodgkin lymphoma) that can release various immunoglobulins into the systemic circulation.¹⁶ Although skin lesions are common in primary systemic amyloidosis and are virtually indistinguishable both clinically and histologically from the AL amyloid of PLCNA, cutaneous lesions rarely are found in secondary systemic amyloidosis and are of the AA (amyloid A) amyloid

type.¹⁶⁻¹⁹ The various cutaneous amyloidoses are compared in the Table.

The differential diagnosis for macular and lichenoid amyloidoses should include xanthoma, perforating collagen disorders, PLCNA, lichen planus, and mycosis fungoides. When considering PLCNA as the diagnosis, the physician also should consider systemic amyloidosis, squamous cell carcinoma, verruca vulgaris, adnexal tumors, and keloids or hypertrophic scarring in the differential. Skin findings in cutaneous amyloidoses may appear similar to these conditions; therefore, a biopsy to determine the correct etiology may be warranted.

Of serious concern to patients with PLCNA and their caregivers is the possibility of its progression to systemic amyloidosis. In 1970, Brownstein and Helwig¹⁸ determined that the risk for progression was 50% based on a cohort of 10 patients; however, on reviewing the data from this report more thoroughly, we determined it is possible that some of the patients who were diagnosed with PLCNA that progressed to systemic disease during the study actually had systemic amyloidosis from the beginning and then developed cutaneous lesions. Other studies have provided evidence for a lower rate of progression to systemic amyloidosis. Woollons and Black¹⁷

Variations of Cutaneous Amyloidosis

Type of Amyloidosis	Amyloid Type	Cutaneous Involvement	Associated Diseases
Macular amyloidosis	Keratin derivative	Papillary dermis and above	Trauma, Sjögren syndrome, systemic sclerosis, idiopathic conditions, other autoimmune diseases
Lichenoid amyloidosis	Keratin derivative	Papillary dermis and above	Trauma, Sjögren syndrome, systemic sclerosis, idiopathic conditions, other autoimmune diseases
Nodular amyloidosis	AL amyloid	Reticular dermis and above	Sjögren syndrome, idiopathic conditions, possibly trauma
Primary systemic amyloidosis	AL amyloid	Reticular dermis and above	Myeloma, plasma cell dyscrasias
Secondary systemic amyloidosis	AA amyloid	Rare cutaneous involvement	Rheumatoid arthritis, inflammatory bowel disease, Hodgkin lymphoma, chronic infection, celiac disease, other chronic inflammatory conditions

Abbreviations: AL, amyloid light chain; AA, amyloid A.

looked retrospectively at 15 cases of PLCNA and found only 1 case that progressed to systemic amyloidosis, thus determining a rate of 7%. Northcutt and Vanover²⁰ took a similar retrospective approach and determined a progression rate of 15%; however, this analysis included the original Brownstein and Helwig¹⁸ study, thus adding 5 patients who may have had systemic amyloidosis from the start. As a result, the true rate of progression of the 47 cases analyzed by Northcutt and Vanover²⁰ is anywhere between 4% and 15%.

Due to the paucity of reported cases of PLCNA, a prospective study that can accurately determine the true rate of progression of PLCNA to systemic amyloidosis is unlikely to be conducted; however, given the data available and the understanding that PLCNA appears to be local clonal plasmacytoma,^{16,21,22} the true rate of progression likely is quite low. Although there are no formal guidelines for monitoring patients with PLCNA, it is appropriate to assess patients for progression to systemic amyloidosis indefinitely on a regular basis. Follow-up assessment should include a full history and physical examination, along with an electrocardiogram, complete blood cell count, serum creatinine level, serum liver-associated enzyme levels, serum protein electrophoresis, and urine protein electrophoresis. An abdominal wall fat pad biopsy may be performed to rule out systemic disease.²³ If the history, physical examination, and all ancillary tests are normal, patients can be reassured that they do not currently exhibit any signs or symptoms of systemic amyloidosis. Any indication of systemic disease requires immediate attention, as it is rapidly progressive.

Although PLCNA appears to confer a relatively low risk to the patient's health, the associated lesions can be cosmetically disturbing and sometimes become painful or irritated. Our patient experienced pain from the growths on his feet that limited his running. For these lifestyle reasons as well as cosmetic concerns, patients commonly will seek treatment to have the lesions removed. However, the lesions of PLCNA are difficult to treat and often recur after treatment.¹⁷ Several treatment modalities have been employed, including dermabrasion, laser therapy,²⁴ surgical excision, shave excision,¹⁵ dimethylsulfoxide injections, triamcinolone acetate injections, and cryosurgery. If koebnerization appears to play a role in the development of a patient's lesions, the best way to prevent new lesions from arising is to avoid trauma to the affected areas. Our patient did not experience nodule formation at other sites of trauma on his body, but he noticed that they sometimes occurred at prior sites of blisters on his feet. The avoidance of trauma to the lower extremities

may be difficult for some patients, especially those who are active and wish to remain active.

The treatments that seem to have the most success all include physical removal of the affected tissue followed by a procedure to ablate the surface of the wound. Physicians have attempted shave excision followed by dermabrasion,²⁵ curettage and cautery,⁷ excision followed by dermabrasion and CO₂ laser treatment,^{16,26,27} and excision with split-thickness skin grafting,²⁸ all with excellent results and no recurrence within a year. Other modalities such as cryotherapy, triamcinolone injections, and CO₂ laser treatment alone have not been shown to be beneficial.⁷ In fact, triamcinolone injections alone have been reported to increase the amount of amyloid deposition and therefore have not been recommended for treatment²⁶; however, our patient did not experience any worsening of his amyloid nodules after intralesional triamcinolone injections. In our patient, the combination of complete curettage followed by CO₂ laser ablation appeared to be effective and prevented recurrence of the lesions. However, the lesions that were not completely curetted due to concerns of poor wound healing did not respond as well (Figure 5). As a result, we recommend that our technique of complete curettage and CO₂ ablation be considered as a treatment option.

Conclusion

Primary localized cutaneous nodular amyloidosis is a rare disease that causes cosmetic and functional impairment, leading most patients to seek treatment. Understanding how to correctly diagnose and treat this condition as well as monitor the patient for progression to systemic disease is important in attaining excellent results for these patients.

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