Nodular amyloidosis is a protein deposition disorder that is important to recognize in the clinical setting. Identification and differentiation from primary systemic amyloidosis, which has an identical cutaneous presentation, but serious systemic implications, is of particular significance. Our case report highlights two patients who presented with isolated involvement of the plantar surface and ungual phalanges, each with concomitant tinea pedis. Recognition and diagnosis of cutaneous amyloidosis enables discrimination from systemic disease, and if found, prompt institution of appropriate treatment. (J Am Podiatr Med Assoc 104(5): 544-547, 2014)

Nodular amyloidosis is an abnormal protein deposition disorder. Along with lichen and macular amyloid, it forms the group of disorders known as primary cutaneous amyloidosis, and is least common of the three. Amyloidoses in general are classified as disorders of aberrant protein deposition, where proteins assume an abnormal tertiary β pleated sheet conformation rather than the α helical form common in normal tissues. All primary cutaneous amyloidoses are composed of a conserved amyloid P component and amyloid ground substance, and a unique protein amyloid fibril, by which the subtype of amyloid can be delineated. While lichen and macular amyloid are composed of an epidermal keratin–derived amyloid fibril, are purely cutaneous, and commonly result from trauma; nodular amyloid is composed of amyloid light chains derived from plasma cells, may progress to systemic amyloidosis, and has only rarely been associated with trauma. Nodular amyloidosis is especially relevant to the clinician given reports of progression to systemic amyloidosis, with most recent reviews indicating that development of systemic disease occurs in 7% of patients. The most common published locations are legs, followed by head, trunk, arms, and genitalia. Moon et al reported similar findings in a review of 16 patients with nodular amyloidosis, finding a preferentially acral distribution of skin lesions. The lesions are often insidious in onset and growth pattern, and may not be the patient’s chief complaint unless located in an area of cosmetic concern. Often these nodules are asymptomatic, but pruritus, tenderness, and pain have also been reported with these nodules. The fibrillar component of nodular amyloidosis derives from amyloid light chains—often of the λ subtype—rather than epidermal keratins. This is suspected to result from a localized plasma cell dyscrasia.

Establishing a diagnosis of cutaneous nodular amyloidosis is important for several reasons. These patients require periodic evaluation in the event of progression to systemic amyloidosis. Equally important is that approximately 40% of patients with primary systemic amyloidosis will have cutaneous findings that are clinically and histologically indistinguishable from primary cutaneous amyloidosis. Primary systemic amyloidosis also results from deposition of light chain derived amyloid. Rather than local proliferations of plasma cells, however, primary systemic amyloidosis is usually associated with myeloproliferative conditions, and thus deposition of amyloid is found not only in the skin, but various other organs, such as the heart, gastrointestinal tract, liver, kidneys, and in the peripheral nervous system. Early diagnosis and treatment are essential in these cases.
The association between nodular amyloidosis and systemic amyloidosis is one of particular significance, but nodular amyloidosis has been found in other conditions as well. Sjögren’s syndrome seems to be the most common, with an associated incidence as high as 25%.\(^\text{10-12}\) Although this may represent an overestimate due to a reporting bias, the association between the two cannot be dismissed.

Once the diagnosis of nodular amyloidosis is established, work-up to rule out systemic amyloidosis should be initiated and should include a complete blood count, comprehensive metabolic panel, serum protein electrophoresis, and urine protein electrophoresis, which should be completed at each annual visit. Specific imaging studies, bone marrow biopsies, and other diagnostic work-up can be considered as the clinical situation warrants.\(^\text{6,7,13}\)

There is no established standard of care for treatment of individual lesions of cutaneous nodular amyloidosis. Due to deposition of amyloid from the dermis into or beyond the subcutaneous fat,\(^\text{1}\) complete removal with scarring, or incomplete removal with recurrence are common complications. This must be taken into account when choosing the appropriate treatment. Surgical excision, CO\(_2\) laser, pulsed dye laser, dermabrasion, electrodessication and curettage, cryotherapy, intralesional steroids, topical and systemic retinoids, and localized radiation have all been reported with varying degrees of success.\(^\text{1,3,4}\)

**Case 1**

A 63-year-old man presented to the dermatology clinic at Geisinger Medical Center for evaluation of thickened areas on his left distal arch of several months duration. He had a past medical history significant for various cardiac problems including Wolff-Parkinson-White syndrome, atrial fibrillation and atrial flutter, paroxysmal ventricular tachycardia, and also had history pertinent for adenomatous colon polyps. The patient initially felt the areas on his feet were blisters, and had tried various moisturizers without success. He noted a tight sensation when wearing shoes, but otherwise expressed no discomfort.

On physical exam the patient had a pseudovesicular plaque on the left distal arch and the base of the second and third toes on the left foot. Red to violaceous papules and plaques were observed at the base of the right first, fourth, and fifth toes, as well as the distal right arch (Fig. 1). He also had prominent yellow keratotic debris underneath his toenails with overlying nail thickening and dystrophy. There was a fine white moccasin distribution of scaling circumferentially on the acral rim of the soles bilaterally. Potassium hydroxide (KOH) slide preparation of a scraping from the roof of a true vesicle was positive for fungal hyphae. Biopsy of one of the violaceous plaques was positive for fungal hyphae overlying a deposition of amorphous thioflavin-T-positive material in the dermis (Figs. 2 and 3), consistent with nodular amyloid and concurrent tinea pedis. The patient was treated with econazole for tinea pedis and initial work-up by hematology-oncology for systemic amyloidosis (complete blood count, basic metabolic profile, serum and urine protein electrophoresis) was negative. A bone marrow biopsy was suggested for...
further evaluation, but the patient declined and he was subsequently lost to follow-up.

Case 2

A 67-year-old man followed in our dermatology clinic for a history of basal cell carcinoma and premalignant skin change presented with a 6-month history of asymptomatic red plaques on the arches of both feet. His medical history was significant for benign prostate hypertrophy, neurogenic bladder, hypertension, and osteoarthritis. The patient expressed concern over the etiology of the areas on his feet but was not bothered by them symptomatically and had attempted no previous treatment.

On examination the patient displayed prominent smooth red to pink plaques on the arches of both feet bilaterally (Fig. 4). He also had fine scaling along the acral margins of both feet in a classic moccasin distribution. Potassium hydroxide examination of this area was positive for fungal hyphae. A biopsy of one of the plaques demonstrated fungal hyphae in the stratum corneum with underlying nodular dermal deposits of pink thioflavin-T–positive material consistent with a diagnosis of nodular amyloidosis and concomitant tinea pedis. Serum protein electrophoresis, urine protein electrophoresis, and Bence-Jones proteins were within normal limits.

Discussion

Cutaneous nodular amyloidosis, a rarely encountered cutaneous deposition disorder, can occasionally signify serious underlying systemic disease, and is therefore important to recognize in the clinical setting. We report two cases of nodular amyloidosis localized to the plantar surface in elderly men. Our cases correspond to previously published reports as a disorder that is not often associated with systemic disease, is localized to acral surfaces, and found in individuals in their sixth to seventh decade of life. Interestingly, both of our cases were associated with concomitant tinea pedis. The first patient, in particular, had dermatophyte in the stratum corneum overlying the nodular deposits of amyloid in the dermis. This may be purely serendipitous, as occult tinea infection has a reported incidence of 3.8% to as high as 31% in certain geographic regions, or this may represent a previously unreported association between unknown factors of nodular amyloid, creating a permissive environment for tinea colonization and infection. There are no case reports to date that address a causal or otherwise adventitious relationship between nodular amyloidosis and tinea pedis.

Conclusions

In conclusion, we recognize the need to increase awareness of this dermatologic condition, which, given its predisposition for the distal legs and feet, may initially present to a podiatrist for diagnosis and management. Recognition and clinical consideration of this cutaneous disease will lead to a timely diagnosis and appropriate clinical care.

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References