Nodular amyloidosis in a patient with systemic scleroderma

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Abstract

Primary cutaneous amyloidosis may be characterized as macular amyloidosis, lichenoid amyloidosis, or nodular amyloidosis. Nodular amyloidosis results from the deposition of immunoglobulin light chains and may rarely be associated with systemic amyloidosis. We report an unusual case of a patient with systemic scleroderma who developed primary cutaneous nodular amyloidosis on the left lower leg. The diagnosis was confirmed with a skin biopsy with Congo red staining and a novel technique using a laser microdissection and mass spectrometry-based proteomic analysis method for amyloid protein characterization. A work-up for systemic amyloidosis was negative and the patient improved symptomatically with wound care. Patients with primary cutaneous nodular amyloidosis should be followed clinically over time for the possible development of systemic amyloidosis, although the risk of disease progression is likely low.

Keywords: nodular amyloidosis, scleroderma

Introduction

Primary cutaneous amyloidosis may be classified as macular amyloidosis, lichenoid amyloidosis, or nodular amyloidosis [1]. Macular and lichenoid amyloidosis are relatively common and are related to trauma to the skin, thereby resulting in keratin-derived amyloid deposits in the upper dermis. Unlike macular and lichenoid amyloidosis, nodular amyloidosis involves the deposition of immunoglobulin light chain amyloid protein in the dermis and subcutis [1-3]. Nodular amyloidosis is the rarest of the cutaneous amyloidosis subtypes [1]. We report a case of primary cutaneous nodular amyloidosis occurring in a woman with a history of systemic scleroderma.

Case Synopsis

A woman in her 60s with a past medical history significant for systemic scleroderma was referred to the dermatology clinic for evaluation of left lower leg nodules of several year's duration that were previously clinically diagnosed as calcinosis cutis without biopsy confirmation. One of the nodules ulcerated and resulted in significant pain, so the patient's rheumatologist requested a referral. The patient was diagnosed with systemic scleroderma 15 years prior to her dermatology consultation visit. The systemic manifestations of her scleroderma included interstitial lung disease with pulmonary hypertension, esophageal dysmotility, and Raynaud phenomenon. A review of her prior laboratory evaluation demonstrated a positive high titer antinuclear antibody (ANA) of 1:2560 with a discrete speckled (anti-centromere antibody) pattern, positive anti-scleroderma (SCL)-70 antibody, and positive ribonucleoprotein (RNP) antibody. She was followed by the rheumatology department and was being treated with mycophenolate mofetil 1000mg twice daily with overall adequate control of her systemic scleroderma symptoms.

Physical examination revealed the presence of three large, erythematous, edematous nodules with overlying crust on the left lower leg (**Figure 1**). The nodule on her left medial lower leg was ulcerated (**Figure 1**). In addition, the patient was noted to have sclerotic skin on her bilateral arms and legs, numerous matted telangiectasias on the face, and

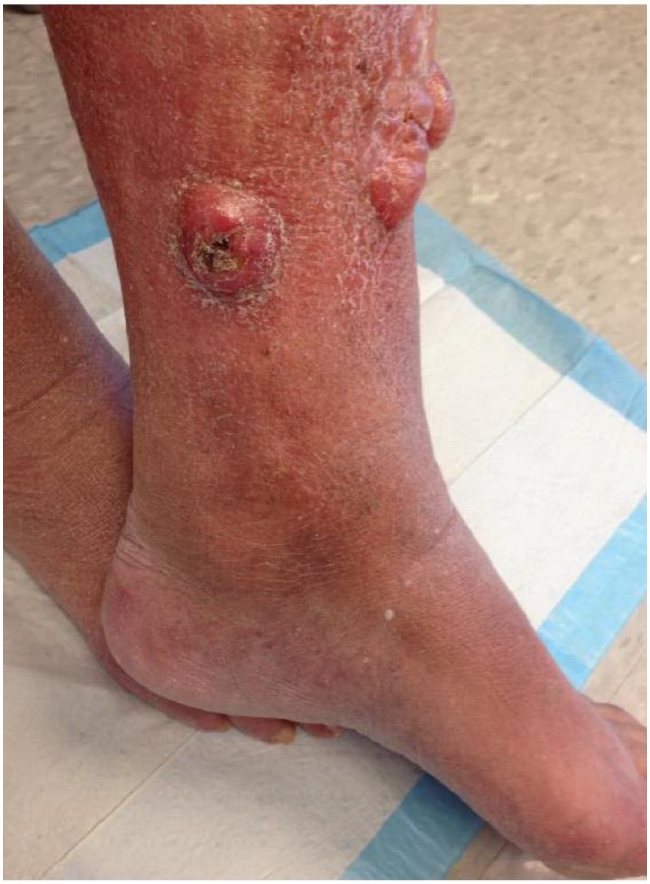

Figure 1. *Clinical photograph of three left lower leg nodules consisting of erythematous, boggy, nodules with overlying crust. The left medial lower leg nodule ulcerated and resulted in significant pain.*

capillary loops visible on the proximal nailfolds with nail dermoscopy, all of which were consistent with her history of systemic scleroderma.

A 4mm punch biopsy of the skin of the left medial lower leg nodule was performed. This biopsy showed chronic inflammation consisting of lymphocytes and plasma cells, neovascularization within the dermis, and areas of dermal amorphous eosinophilic material as seen in **Figure 2A**. Congo red staining examined with a polarized microscope was positive for the classic apple green birefringence consistent with the presence of amyloid protein (**Figure 2A**). In order to confirm a diagnosis of nodular amyloidosis, a laser microdissection and mass spectrometry-based proteomic analysis method was performed by Mayo Clinic laboratories, which revealed an immunoglobulin light chain amyloid protein [8, 9]. To evaluate for possible systemic amyloidosis, a screening laboratory work-up was ordered. A serum protein electrophoresis and urine protein electrophoresis were negative for a monoclonal protein. A complete blood count with differential and a comprehensive metabolic panel showed that serum creatinine (0.7mg/dL), white blood cell count (5.5×10^9/L), and hemoglobin (12.6g/dL) values were within normal limits. Overall, the diagnosis was most consistent with primary cutaneous nodular amyloidosis on the left lower leg since there was no evidence of systemic amyloidosis. The patient was treated conservatively with wound care with a foam dressing over the ulceration on the left medial lower leg and she wore compression stockings daily, resulting in improvement of her ulceration. The patient was offered and declined laser treatment or excision of the nodules as the pain associated with the ulceration was most bothersome to her rather than the cosmetic appearance of the nodules.

Case Discussion

Primary cutaneous nodular amyloidosis presents with tan, yellow, or erythematous, often boggy, nodules and is most commonly located on the lower extremities, head, trunk, or genitals [1, 4]. A biopsy is required to diagnose cutaneous amyloidosis to evaluate for the amyloid protein with Congo red staining. Additionally, in our immunosuppressed patient with systemic scleroderma, a biopsy was done to evaluate for possible involvement of cutaneous scleroderma or calcinosis cutis, infection, or malignancy.

Given that both cutaneous scleroderma and nodular amyloidosis may result in amorphous, eosinophilic dermal material in a skin biospy, we sought to utilize additional testing to confirm a diagnosis of nodular amyloidosis in our patient. Therefore, we characterized the amyloid protein using the laser microdissection and mass spectrometry-based proteomic analysis method performed by Mayo Clinic laboratories. This method was developed because the clinical management of amyloidosis generally is based on the underlying etiology, so the specific protein present is very important to both diagnosis and clinical management [5, 6]. This

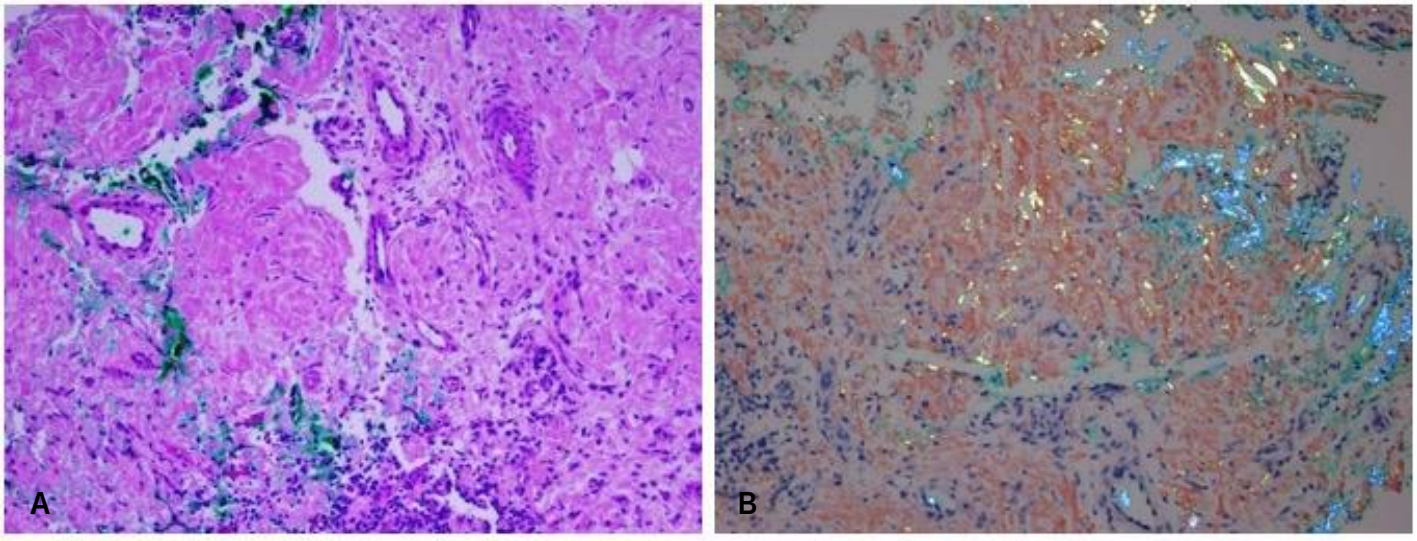

Figure 2. ***A)*** *Skin biopsy demonstrating the presence of dermal amorphous eosinophilic material and a background of chronic inflammation with lymphocytes and plasma cells and neovascularization. H&E, 20×.* ***B****) Positive Congo red staining visualized under polarized light showing apple-green birefringence located within the dermal amorphous, 20×.*

method has 98-100% specificity in identifying the correct amyloid protein [5, 6].

The laser microdissection and mass spectrometry-based proteomic analysis method involves the following: paraffin sections are stained with Congo red, amyloid protein is identified and then microdissected with a very low power laser into 2-4 microdissections per sample; the microdissected fragments are digested with trypsin, separated by liquid chromatography, and analyzed by mass spectrometry; finally a list of identified proteins is generated [5, 6]. The patient's amyloid characterization was consistent with a light chain amyloidosis as seen in nodular amyloidosis [5, 6]. We propose that this methodology may be particularly useful in patients such as ours' when the diagnosis of nodular amyloidosis is not entirely clear.

Interestingly, the majority of case reports documenting cutaneous nodular amyloidosis in association with autoimmunity are with Sjogren syndrome [3, 7]. There have been few reports of cutaneous amyloidsis, including macular and lichenoid subtypes, and only two previous case reports of nodular amyloidosis specifically in systemic scleroderma [8-12]. Thus, this patient case may highlight a possible association for dermatologists to observe in patients with systemic scleroderma. Logically, autoimmune diseases may cause plasma cell dyscrasia in the skin that produce excessive immunoglobulins and cause local amyloid deposition [1, 7]. Nevertheless, the relationship between cutaneous amyloidosis and autoimmune disease has not been well-described and warrants further study.

The treatment of cutaneous nodular amyloidosis is challenging. If there is an underyling systemic amyloidosis, a referral to a hematology/oncology consultant should be placed for further treatment. A work-up for systemic amyloidosis should be done. Light chain systemic amyloidosis may relate to a malignant or benign monoclonal gammopathy, so a screening work-up should include complete blood cell count with differential, complete metabolic panel, serum protein electrophoresis, and urine protein electrophoresis. Most cases of cutaneous nodular amyloidosis are treated with either supportive wound care as in our patient, excision, or laser therapy. Excision is often only temporarily effective because the plasma cells in the dermis often remain and result in disease recurrence [13]. Both carbon dioxide laser and pulsed-dye laser have been utilized to treat cutaneous nodular amyloidosis, but just as with excision, may result in disease recurrence [14, 15].

The ultimate clinical challenge in patients with nodular amyloidosis is to determine the risk of nodular amyloidosis progressing to systemic amyloidosis since these appear similar histologically and proteomically. As stated previously, predominantly immunoglobulin light chain amyloid

protein is concerning for primary systemic amyloidosis and this is important to consider for monitoring purposes as well as for treatment. In a patient with an autoimmune disease who may be immunosuppressed, underlying hematologic malignancy is an important consideration. There is conflicting literature on this subject. Most patients with primary cutaneous nodular amyloidosis will follow a benign course. The first published report on the cutaneous amyloidoses reported a high incidence of 5 out of 10 patients with progression to systemic amyloidosis [16]. A long term follow-up study published on 15 patients seen from 1968-1999 with nodular amyloidosis showed one patient with progression to systemic amyloidosis at a rate of 7% [17]. The patient did not progress until 23 years after his initial diagnosis. A second long term follow up study of 16 cases from 1971-2001 was performed and also demonstrated one patient with progression to systemic amyloidosis [18]. This patient had a monoclonal gammopathy determined by serum protein electrophoresis at the time of diagnosis. Moreover, a recent review was published regarding organ-limited light chain amyloidosis and the risk of progression to systemic amyloidosis [19]. This study included patients with cutaneous, limited light chain amyloidosis. The results demonstrated that overall survival for patients with organ-limited light chain amyloidosis is 90% at 5 years, which is quite favorable in contrast to those patients with systemic light chain amyloidosis [19]. These authors suggest that the rate of progression from limited organ involvement is rare. Essentially, clinical monitoring in patients with cutaneous nodular amyloidosis is recommended to detect progression to systemic amyloidosis over time, but the risk of this occurring is likely low.

Conclusion

In summary, this patient case represents a noteworthy presentation of nodular amyloidosis occurring in a patient with systemic scleroderma. In addition to Congo red staining, the laser microdissection and mass spectrometry-based proteomic analysis method may be useful in differentiating amorphous eosinophilic dermal material related to scleroderma or amyloidosis. Treatment of primary cutaneous nodular amyloidosis is challenging. Patients with nodular amyloidosis should be worked-up for systemic amyloidosis. The risk of progression to systemic amyloidosis is likely low, however clinical monitoring may be beneficial.

References

1. Love WE, Miedler JD, Smith MK, et al. The spectrum of primary cutaneous nodular amyloidosis: Two illustrative cases. *J Am Acad Dermatol*. 2008;58(2 Suppl):S33-5. [PMID: 18191697].
2. Inazumi T, Hakuno M, Yamada H, et al. Characterization of the amyloid fibril from primary localized cutaneous nodular amyloidosis associated with Sjogren's syndrome. *Dermatology*. 1994;189(2):125-8. [PMID: 8075437].
3. Kitajima Y, Seno J, Aoki S, et al. Nodular primary cutaneous amyloidosis. Isolation and characterization of amyloid fibrils. *Arch Dermatol*. 1986;122(12):1425-30. [PMID: 3789778].
4. Kim WB, Chang MC, Limacher JJ, Shaw JC. Nodular Amyloidosis of the Penis: A Case Demonstrating Keratinocyte Origin. *JAMA dermatology*. 2015;151(8):910-2. [PMID: 25946373].
5. Theis JD, Dasari S, Vrana JA, et al. Shotgun-proteomics-based clinical testing for diagnosis and classification of amyloidosis. *J Mass Spectrom*. 2013;48(10):1067-77. [PMID: 24130009].
6. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;114(24):4957-9. [PMID: 19797517].
7. Yoneyama K, Tochigi N, Oikawa A, et al. Primary localized cutaneous nodular amyloidosis in a patient with Sjogren's syndrome: a review of the literature. *J Dermatol*. 2005;32(2):120-3. [PMID: 15906542].
8. Kikuchi N, Sakai E, Nishibu A, et al. Primary localized cutaneous amyloidosis in patients with scleroderma. *Acta Derm Venereol*. 2010;90(3):326-7. [PMID: 20526567].
9. Ogiyama Y, Hayashi Y, Kou C, et al. Cutaneous amyloidosis in patients with progressive systemic sclerosis. *Cutis*. 1996;57(1):28-32. [PMID: 8620682].
10. Looi LM. Primary localised cutaneous amyloidosis in Malaysians. *Australas J Dermatol*. 1991;32(1):39-44. [PMID: 1930004].
11. Summers EM, Kendrick CG. Primary localized cutaneous nodular amyloidosis and CREST syndrome: a case report and review of the literature. *Cutis*. 2008;82(1):55-9. [PMID: 18712025].
12. Shiman M, Ricotti C, Miteva M, et al. Primary localized cutaneous nodular amyloidosis associated with CREST (calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) syndrome. *Int J Dermatol*. 2010;49(2):229-30. [PMID: 20465653].
13. Vestey JP, Tidman MJ, McLaren KM. Primary nodular cutaneous amyloidosis--long-term follow-up and treatment. *Clin Exp Dermatol*. 1994;19(2):159-62. [PMID: 8050149].
14. Truhan AP, Garden JM, Roenigk HH, Jr. Nodular primary localized cutaneous amyloidosis: immunohistochemical evaluation and treatment with the carbon dioxide laser. *J Am Acad Dermatol*.

1986;14(6):1058-62. [PMID: 3088070].

15. Alster TS, Manaloto RM. Nodular amyloidosis treated with a pulsed dye laser. *Dermatol Surg*. 1999;25(2):133-5. [PMID: 10037520].
16. Brownstein MH, Helwig EB. The cutaneous amyloidoses. I. Localized forms. *Arch Dermatol*. 1970;102(1):8-19. [PMID: 4100068].
17. Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long-term follow-up study. *Br J Dermatol*. 2001;145(1):105-9. [PMID: 11453916].
18. Moon AO, Calamia KT, Walsh JS. Nodular amyloidosis: review and long-term follow-up of 16 cases. *Arch Dermatol*. 2003;139(9):1157-9. [PMID: 12975157].
19. Mahmood S, Bridoux F, Venner CP, et al. Natural history and outcomes in localised immunoglobulin light-chain amyloidosis: a long-term observational study. *Lancet Haematol*. 2015;2(6):e241-50. [PMID: 26688234].