Systemic Amyloidosis: Unusual Presentation Mistaken for a Recurrent Scabies Infection

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Practice Points

- Primary systemic amyloid light chain amyloidosis can present with varied and unusual initial symptoms, making diagnosis difficult without high clinical suspicion.
- Patients suspected or proven to have amyloid light chain amyloidosis must undergo diagnostic workup for multiple myeloma in an expeditious fashion.

We report the case of a 63-year-old woman with a history of undifferentiated connective-tissue disease, polyarthritis, and bilateral carpal tunnel syndrome who presented with generalized pruritus and erythematous and excoriated papules on the trunk and extremities. Empiric scabies treatment was unsuccessful. Patch testing and T-cell receptor gene rearrangement studies were unremarkable. The patient was found to have mild interstitial lung disease and hypogammaglobulinemia. Eventually a diagnosis of primary systemic amyloidosis was made after she developed frank lingual hypertrophy despite normal initial serum protein electrophoresis and negative abdominal fat pad aspiration. Diagnosis was confirmed with lingual biopsy. This case demonstrates an unusual presentation of primary systemic amyloidosis consisting of arthritis and intense debilitating pruritus without primary skin lesions for a full year prior to diagnosis of multiple myeloma. The patient responded to treatment with chemotherapy and corticosteroids.

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Case Report

A 63-year-old woman presented with worsening generalized pruritus and rash of 5 months' duration. Her medical history was remarkable for polyarthritis with periarticular demineralization on radiographs, mild interstitial lung disease, and positive antinuclear antibodies, leading to a diagnosis of undifferentiated connective-tissue disease. The patient also reported carpal tunnel syndrome, degenerative joint disease, osteoporosis, and chronic sinusitis. Her medications included hydroxychloroquine, clobetasol, doxepin, risedronate, fexofenadine, calcitonin, and nabumetone. Biopsies performed prior to dermatology consultation were consistent with eczematous dermatitis; however, the patient did not respond to treatment with topical tacrolimus, clobetasol, oral doxepin, or prednisone. A review of systems was negative for fever, chills, night sweats, weight loss, and new or worsening joint pain.

Physical examination revealed scattered, excoriated, erythematous papules on the trunk and extremities without primary lesions. The differential diagnosis included scabies, chronic allergic contact

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dermatitis, prurigo, and dermatitis herpetiformis. Despite a lack of clear burrows, the patient was treated with 2 courses of permethrin cream 5% for presumed scabies.

Two weeks later, the patient was found to have mild exfoliative erythroderma with excoriated, erythematous, 2- to 3-mm papules on the chest, back, abdomen, and extremities following a course of trimethoprim-sulfamethoxazole (TMP-SMX) administered by her primary care physician for an abscess on the right flank. Darier sign was negative and no burrows were appreciated. A review of systems was unremarkable. The differential diagnosis was expanded to include a drug reaction to TMP-SMX as well as erythroderma related to her connective-tissue disease or secondary to underlying eczema. Antinuclear antibodies were negative, despite a positive result in the past. The creatine kinase level was within reference range, but the serum aldolase level was mildly elevated at 8.7 U/L (reference range, 1.5–8.1 U/L). SS-A (Sjögren syndrome antigen A)/Ro and SS-B (Sjögren syndrome antigen B)/La antibodies were not detected. After discontinuation of TMP-SMX, the patient was re-treated for scabies with permethrin and ivermectin due to prior success. Despite noting subjective improvement of the erythema and pruritus, she continued to exhibit almost 90% body surface area involvement with hyperpigmentation, lichenification, and excoriations without primary lesions.

The possibility of a diffuse lymphomatous or paraneoplastic process was considered; however, a repeat biopsy from the left upper arm was indicative of subacute eczematous dermatitis. T-cell receptor gene rearrangement tissue studies were negative and patch testing was unremarkable. Serum protein electrophoresis revealed mild hypogammaglobulinemia without a monoclonal spike and slightly elevated α_1- and α_2-globulin levels consistent with inflammation. Urine protein electrophoresis was within reference range. Immunologic studies revealed low absolute CD3, CD4, CD8, and CD19 cell counts with a mild increase in the CD4:CD8 cell ratio. After consultation with the allergy and immunology department, the patient was diagnosed with an allergic reaction to hydroxychloroquine, which was subsequently discontinued. She was started on a 1-month prednisone taper and empiric treatment 3 times weekly with narrowband UVB light therapy for pruritus.

At 4 months' follow-up, there was remarkable improvement in pruritus and erythema, and physical examination revealed only a few mild excoriations on the right arm as well as generalized hyperpigmentation secondary to light therapy. At this follow-up visit, the patient was prescribed low-dose hydroxychloroquine for treatment of an arthritic flare. Approximately 1 month later the patient reported swelling of the tongue and noted that she could see "ridges from her teeth" on the tongue. Substantial diffuse edema of the tongue and clear tooth-shaped grooves were visible along the lateral edges of the tongue (Figure 1). Lymphadenopathy was not appreciated and there was no enlargement of the parotid gland. The differential diagnoses associated with her macroglossia included lymphoma, sarcoidosis, and amyloidosis. An abdominal fat aspiration biopsy was negative for amyloid and magnetic resonance imaging of the tongue was unremarkable. The patient reported difficulty swallowing and had developed substantial swelling of the submandibular lymph nodes. Despite the negative fat aspiration biopsy, a diagnosis of amyloidosis still was strongly suspected. A biopsy of the tongue was performed, which definitively demonstrated extensive amyloid deposits (Figures 2–4). Hemoglobin, white blood cell count, platelet count, creatinine, total protein, albumin, parathyroid hormone, and uric acid levels were within reference range; however, her calcium level was elevated at 10.5 mg/dL (reference range, 8.8–10.0 mg/dL).

An oncologic workup, which included serum protein electrophoresis and immunofixation, showed no evidence of paraproteinemia. The following results were reported: serum IgG, 637 mg/dL (reference range, 700–1700 mg/dL); IgA, 56 mg/dL (reference range, 70–350 mg/dL); IgM, 67 mg/dL (reference range, 50–300 mg/dL). Serum free light chain analysis revealed free κ light chain levels of 8.1 mg/L (reference range, 3.3–19.4 mg/dL), and free λ light chain levels of 637.5 mg/L (reference range, 5.71–26.3 mg/dL), yielding an abnormal κ:λ ratio

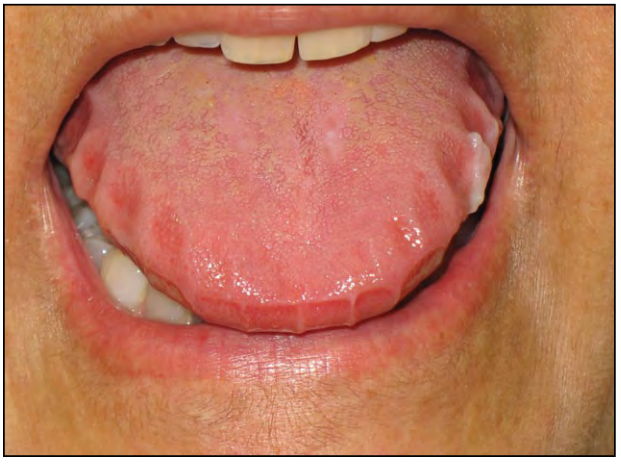

Figure 1. Diffuse edema and clear tooth-shaped grooves along the lateral edges of the tongue.

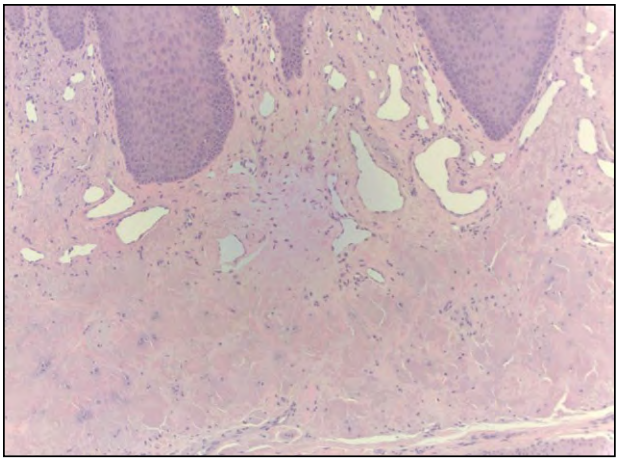

Figure 2. Biopsy of the tongue showed amyloid deposits characterized by a waxy appearance (H&E, original magnification ×10).

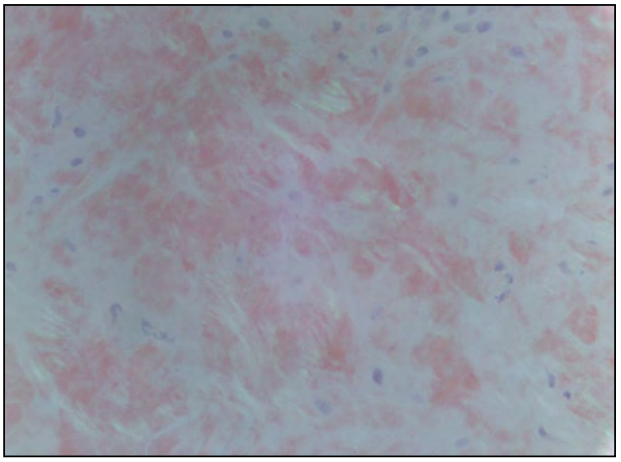

Figure 4. Orange to apple green birefringence on Congo red staining under polarized light (original magnification ×40).

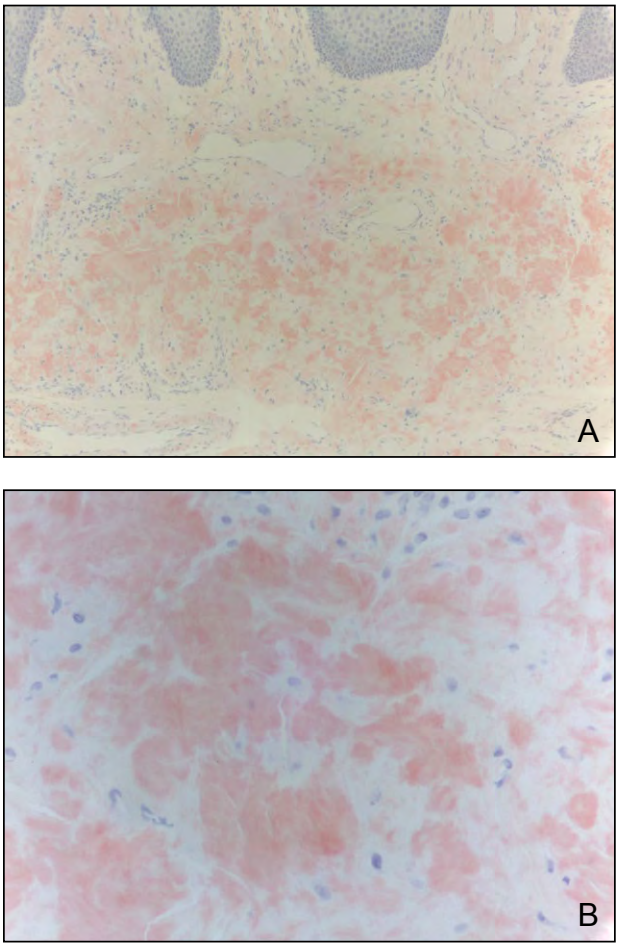

Figure 3. Positive Congo red stain showing orange deposits of amyloid on low- and high-power view (A and B)(original magnifications ×10 and ×40, respectively).

of 0.013 mg/dL (reference range, 0.26–1.65 mg/dL). Bone marrow biopsy revealed a λ-restricted plasmacytosis, with 30% of the examined cells staining for λ light chain positivity. Immunohistochemical staining of a tongue biopsy was positive for λ light chains. The clinical features of macroglossia, bilateral carpal tunnel syndrome, and diffuse pruritus along with increased λ light chains were constant with the diagnosis of primary amyloid light chain (AL) amyloidosis secondary to λ light chain myeloma. Fortunately, there were no lytic bone lesions. After 4 cycles of lenalidomide and dexamethasone the disease was found to be in remission.

Comment

The amyloidoses constitute a large group of diseases that may be localized or systemic as well as rapidly lethal or incidental. The primary pathology uniting these varied entities lies in the misfolding of extracellular proteins generating insoluble toxic aggregates.[1]

A full discussion of the amyloidoses is beyond the scope of this article; instead we focus on AL amyloidosis, which is a clonal plasma cell dyscrasia in the bone marrow related to multiple myeloma, which produces amyloidogenic immunoglobulins, usually of the λ light chain isotype.[2,3]

Abnormal protein deposition occurs in the heart, kidneys, lungs, liver, spleen, gastrointestinal tract, skin, joints, lymph nodes, soft tissues, and peripheral nervous system, but not the central nervous system.[4,5] Mucocutaneous lesions (eg, macroglossia, waxy lichenoid papules, subcutaneous nodules, purpura) may be present.[6] Periocular pinch purpura may occur due to amyloid deposition that weakens blood vessels and causes them to be easily ruptured by trauma. Fatigue and weight loss are common presenting symptoms of AL amyloidosis, and pruritus

often is present.[7] Renal AL amyloidosis manifests as proteinuria, often resulting in nephrotic syndrome.[3] Cardiac amyloidosis can manifest as progressive congestive heart failure, which may present rapidly and may be associated with asymptomatic electrocardiographic abnormalities.[3]

Amyloid light chain amyloidosis must be histologically confirmed. Congo red–stained amyloid can be seen as amorphous deposits with light pink coloration when viewed under regular light; however, scant deposits easily can be missed. Sensitivity is increased with uncompensated double-polarized light under which the stained deposits appear to glow with apple green birefringence against a black background.[8] In AL amyloidosis, a fine-needle aspiration of abdominal fat generally is considered an acceptable alternative to more invasive biopsies in the majority of patients, though fat aspiration may be less specific than biopsy of the tongue or myocardium.[2,8] Because AL amyloidosis is the most common type of systemic amyloid deposition in the United States, a search for an underlying plasma cell dyscrasia is imperative and can be done using immunofixation electrophoresis of serum and urine,[3] though these tests were negative in our patient. Today immunofixation electrophoresis often is combined with measurement of the serum κ to λ free light chain ratio to improve sensitivity in screening.[9,10] A bone marrow biopsy with immunohistochemical staining to detect κ and λ light chains also may be performed.[4] If there is no evidence of a plasma cell dyscrasia, consideration should be given to another form of amyloidosis[3] (eg, hereditary amyloidosis) determined via genetic testing.[2]

The goal of therapy in systemic AL amyloidosis is to reduce or stop the production of monoclonal light chains by reducing or eliminating clonal plasma cells.[4] The treatment of AL amyloidosis, therefore, involves the same chemotherapeutic agents for multiple myeloma. Treatments include melphalan alone or in combination with prednisone; autologous stem cell transplantation, which generally is utilized in patients with fewer comorbidities[4,11,12]; lenalidomide in combination with dexamethasone[13]; and bortezomib.[3]

Polyarthritis resembling rheumatoid arthritis with AL amyloidosis only rarely occurs as the initial manifestation of multiple myeloma.[14,15] Interestingly, Zilko and Dawkins[16] described a case of dermatomyositis with hypogammaglobulinemia occurring in the setting of AL amyloidosis. Reyes et al[17] described a case of sclerodermalike illness with carpal tunnel syndrome, hypogammaglobulinemia, and positive antinuclear antibodies as the presenting manifestations of AL amyloidosis associated with multiple myeloma, with polyarthritis that responded to low-dose prednisone and hydroxychloroquine, as seen in our patient. Isaac et al[18] found that chloroquine substantially attenuated amyloid fibril formation using an in vitro model, but others have found that chloroquine enhanced amyloid β protein accumulation, suggesting that the type of protein is important.[19,20] Hypogammaglobulinemia is not a rare initial manifestation of multiple myeloma, occurring in 9% in one series (N=869); however, amyloid arthropathy only rarely has predated the diagnosis of myeloma.[21,22]

Conclusion

In our patient, the diagnosis of AL amyloidosis was demonstrated by positive λ light chains on tongue biopsy, elevated serum free λ light chains, and λ-restricted bone marrow plasmacytosis, which manifested as pruritus, macroglossia, polyarthritis, and bilateral carpal tunnel syndrome. Our case is unusual for the confluence of autoimmune features (ie, polyarthritis, sarcoidosislike lung disease), hypogammaglobulinemia, primary AL amyloidosis, and multiple myeloma that initially was difficult to detect. It is imperative for physicians to revisit the diagnosis if treatment fails, even if the patient is on the treatment regimen that should improve the condition at hand.

REFERENCES

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med*. 2003;349:583-596.
2. Obici L, Perfetti V, Palladini G, et al. Clinical aspects of systemic amyloid diseases. *Biochim Biophys Acta*. 2005;1753:11-22.
3. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. *N Engl J Med*. 1997;337:898-909.
4. Comenzo RL. Primary systemic amyloidosis. *Curr Treat Options Oncol*. 2000;1:83-89.
5. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol*. 2005;79:319-328.
6. Black MM, Upjohn E, Albert S. Amyloidosis. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. Vol 1. 2nd ed. Philadelphia, PA: Mosby-Elsevier; 2008: 623-631.
7. Schreml S, Szeimies RM, Vogt T, et al. Cutaneous amyloidoses and systemic amyloidoses with cutaneous involvement. *Eur J Dermatol*. 2010;20:152-160.
8. Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N Engl J Med*. 2002;346:1786-1791.

9. Fulton RB, Fernando SL. Serum free light chain assay reduces the need for serum and urine immunofixation electrophoresis in the evaluation of monoclonal gammopathy. *Ann Clin Biochem*. 2009;46(pt 5):407-412.
10. Bakker AJ, Bierma-Ram A, Elderman-van der Werf C, et al. Screening for M-proteinemia: serum protein electrophoresis and free light chains compared. *Clin Chem Lab Med*. 2009;47:1507-1511.
11. Music E, Piette W. Cutaneous amyloidosis: similar, but different. *Am J Med*. 2010;123:423-425.
12. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med*. 1997;336:1202-1207.
13. Gertz MA, Zeldenrust SR. Treatment of immunoglobulin light chain amyloidosis. *Curr Hematol Malig Rep*. 2009;4:91-98.
14. Alpay N, Artim-Esen B, Kamali S, et al. Amyloid arthropathy mimicking seronegative rheumatoid arthritis in multiple myeloma: case reports and review of the literature. *Amyloid*. 2009;16:226-231.
15. Katoh N, Tazawa K, Ishii W, et al. Systemic AL amyloidosis mimicking rheumatoid arthritis. *Intern Med*. 2008;47:1133-1138.
16. Zilko PJ, Dawkins RL. Amyloidosis associated with dermatomyositis and features of multiple myeloma. the progression of amyloidosis associated with corticosteroid and cytotoxic drug therapy. *Am J Med*. 1975;59:448-452.
17. Reyes CM, Rudinskaya A, Kloss R, et al. Scleroderma-like illness as a presenting feature of multiple myeloma and amyloidosis. *J Clin Rheumatol*. 2008;14:161-165.
18. Isaac J, Kerby JD, Russell WJ, et al. In vitro modulation of AL-amyloid formation by human mesangial cells exposed to amyloidogenic light chains. *Amyloid*. 1998;5:238-246.
19. Urmoneit B, Prikulis I, Wihl G, et al. Cerebrovascular smooth muscle cells internalize Alzheimer amyloid beta protein via a lipoprotein pathway: implications for cerebral amyloid angiopathy. *Lab Invest*. 1997;77:157-166.
20. Fukatsu R, Tsuzuki K, Takamaru Y, et al. Biological characteristics of amyloid precursor protein and Alzheimer's disease [in Japanese]. *Rinsho Byori*. 1996;44:213-224.
21. Kyle RA. Multiple myeloma: review of 869 cases. *Mayo Clin Proc*. 1975;50:29-40.
22. Hamza S, Landolsi F, Sahli H, et al. Light chain multiple myeloma revealed by an amyloid arthropathy. a report of two cases [in French]. *Rev Med Interne*. 2004;25:390-394.