Systemic Amyloidosis: Unusual Presentation Mistaken for a Recurrent Scabies Infection

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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.

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, risdropronate, 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
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, erthematous, 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% improvement in pruritus and erythema, and physical examination revealed only a few mild excoriations along the lateral edges of the tongue. 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, 15–120 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.

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 α1- and α2-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. Figure 1. Diffuse edema and clear tooth-shaped grooves along the lateral edges of the tongue.
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

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

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).

Figure 4. Orange to apple green birefringence on Congo red staining under polarized light (original magnification ×40).
often is present. Renal AL amyloidosis manifests as proteinuria, often resulting in nephrotic syndrome. 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, 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.9 If there is no evidence of a plasma cell dyscrasia, consideration should be given to another form of amyloidosis1 (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 comorbidities4,11,12; lenalidomide in combination with dexamethasone13; and bortezomib.1

Polyarthritis resembling rheumatoid arthritis with AL amyloidosis only rarely occurs as the initial manifestation of multiple myeloma.14,15 Interestingly, Zilko and Dawkins16 described a case of dermatomyositis with hypogammaglobulinemia occurring in the setting of AL amyloidosis. Reyes et al17 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 al18 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


