# Classic features of primary systemic amyloidosis (AL amyloidosis) leading to diagnosis of plasma cell myeloma

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## Abstract

The diagnosis of primary systemic amyloidosis, also known as AL (amyloid light-chain) amyloidosis, is often delayed owing to its nonspecific manifestations as well as its rarity. A 64-year-old woman presented with an eight-month history of significant weight loss, anemia, fatigue, and progressive painful cutaneous lesions on her hands, lips, back, perianal, and vulvar area that were originally treated unsuccessfully with antimalarials and systemic corticosteroids. Histopathological examination revealed an amorphous dermis with pale pink material that demonstrated positive birefringence with Congo red staining. Subsequently, the patient underwent a bone marrow biopsy, which uncovered a plasma cell myeloma, the source of her amyloidogenic protein production.

*Keywords: primary systemic amyloidosis, amyloid light-chain, AL amyloidosis, plasma cell myeloma*

## Introduction

Primary systemic amyloidosis, also known as immunoglobulin light chain (AL) amyloidosis, is caused by clonal plasma cells that produce misfolded, amyloidogenic light-chains, which deposit systemically resulting in organ dysfunction. Although AL amyloidosis is the most common type of amyloidosis, the incidence of systemic AL amyloidosis is rare, estimated at 8.9 per million annually [1]. Cutaneous symptoms manifest in 30-40% of patients with primary systemic amyloidosis and can provide the first diagnostic clues in

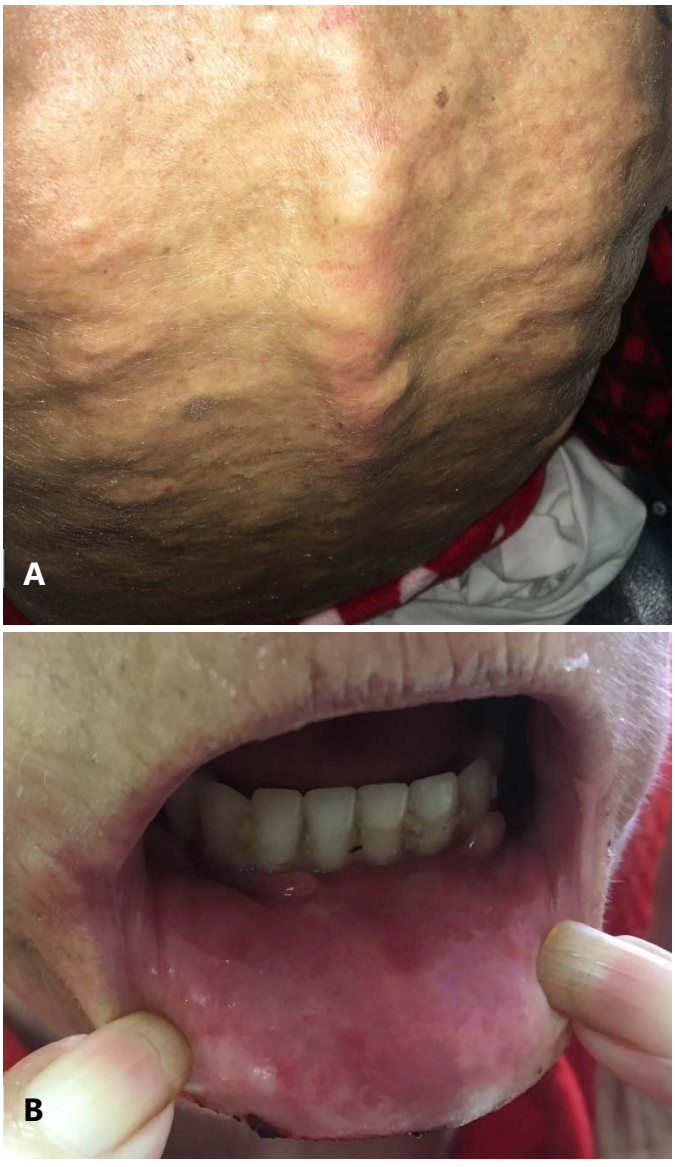


**Figure 1**. ***A)*** *Diffuse skin-colored palpable firm nodules on the back.* ***B)*** *Pink firm pedunculated papules on lower labial mucosa. Lower lips are grossly hypertrophied and filled by palpable infiltrative plaques.*

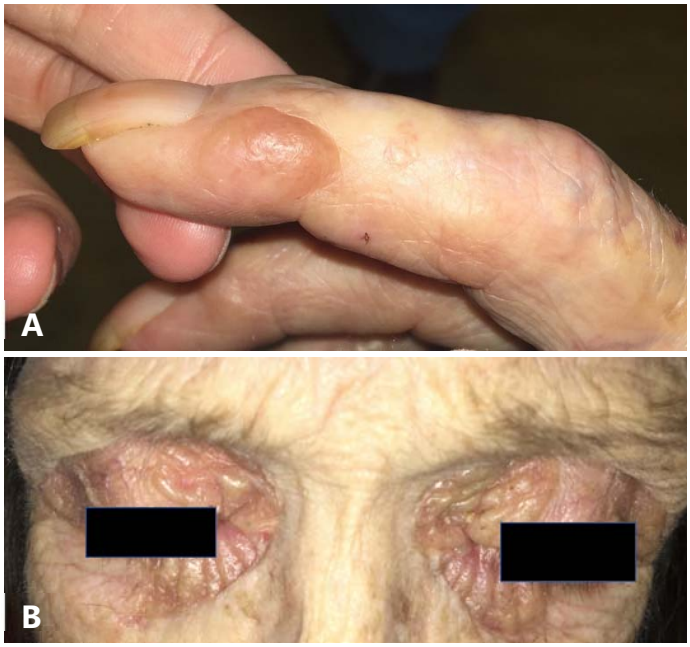


**Figure 2**. ***A)*** *Skin colored to yellow firm plaques on lateral aspects of fingers.* ***B)*** *Yellow papules coalescing into plaques on upper and lower eyelids.*

discovering an underlying systemic pathophysiology [2].

## Case Synopsis

A 64- year-old woman, with an eight-month history of significant weight loss, anemia, fatigue, and progressive painful cutaneous lesions on her hands, lips, back, and perianal and vulvar areas was admitted for syncope and work up of hematologic malignancy. Her past medical history included coronary artery disease and carpal tunnel surgery performed five years prior to admission. A dermatology consultation was requested for her skin lesions. Lesions originally began on two fingers on the patient's right hand and several more very painful, enlarging and hardened plaques subsequently developed on the lower lips, vulva, perianal region, abdomen, and back. The patient reported having taken oral prednisone 5mg daily and hydroxychloroquine 200mg twice daily for two years for a diagnosis of "autoimmune inflammation."

On physical examination, the patient had numerous yellow-to-skin-colored indurated plaques and nodules on the upper eyelids, upper back, right index and third lateral fingers, abdomen, and vulvar and perianal regions (**Figures 1-3**). Our patient also had 12-50mm firm infiltrative plaques on the lower lip with yellow papules on the labial mucosae (**Figure 1B)**. These lesions covered a total body surface area greater than 10%. Also noted were 30-60mm ecchymotic patches on the arms, hands, and upper thighs.

A 4mm punch biopsy was performed on the indurated plaque on the lower lip, along with a shave biopsy on a softer plaque on the right index finger. Microscopic findings displayed compact orthokeratosis overlying a hypocellular and amorphous dermis in which pale pink material appeared to have replaced a majority of the dermal

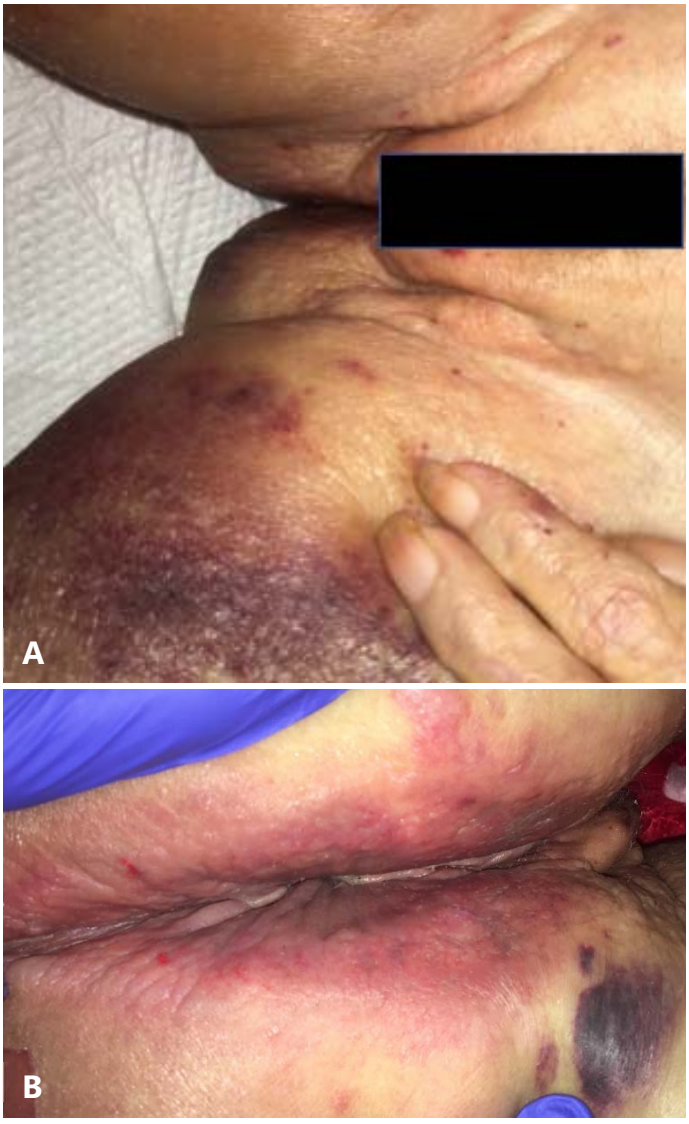


**Figure 3**. ***A)*** *Discrete firm papules infiltrating edge of labia majora and large ecchymotic plaques on upper inner thighs.* ***B)*** *Firm plaques with erythema infiltrating entire perirectal region.*

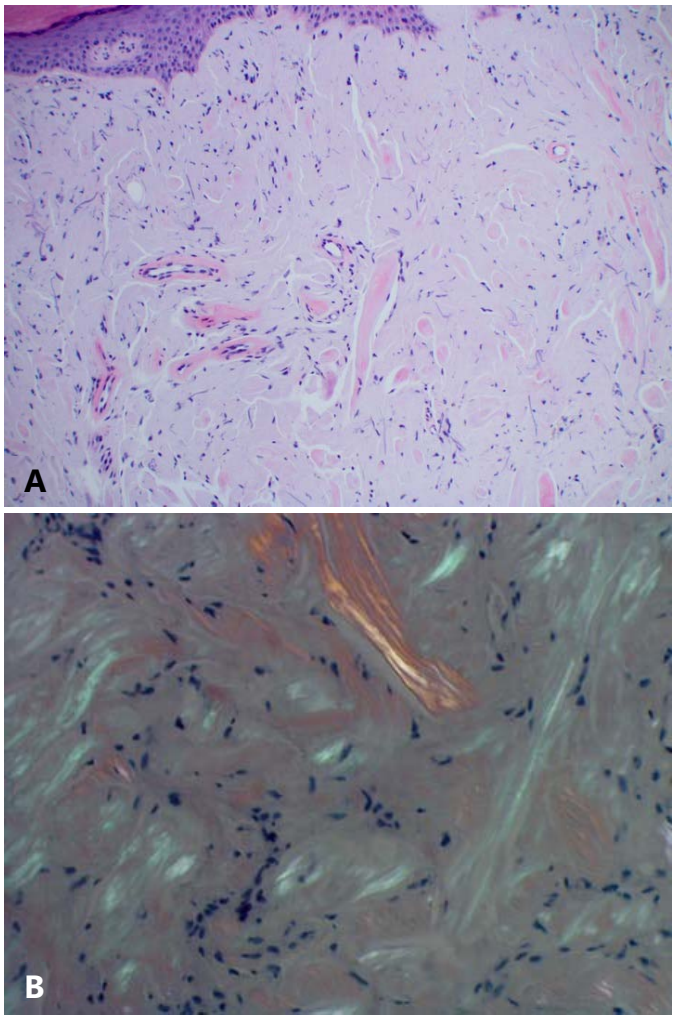


**Figure 4**. ***A)*** *Hypocellular dermis in which hyalinized pale pink amorphous material appears to have replaced a majority of dermal collagen. Vascular structures have retained perivascular collagenous deposits. H&E, 10×.* ***B)*** *Shave biopsy from the lower lip with Congo red stain highlighting positive birefringence in the thick hyaline material deposited within the dermis, 20×.*

collagen (**Figure 4A)**. Perivascular collagenous deposits were also noted (**Figure 4A)**. Congo red stain demonstrated weak but positive birefringence in the thick hyaline material deposited within the dermis (**Figure 4B)**. Based on these findings, the patient underwent a bone marrow biopsy, which showed an infiltration of the marrow with a monoclonal population of plasma cells, comprising 57% of the total cells. Flow cytometric analysis of aspirated bone marrow revealed a distinct plasma cell population with an intracytoplasmic lambda light chain restriction.

Hematology investigations demonstrated anemia, an abnormal kappa-to-lambda ratio of 0 (reference 0.26-1.65), and remarkably elevated free kappa light chain of 29.96mg/L (reference 3.3-19.4mg/L) and free lambda light chain of 9466mg/L (reference 5.7-26.3mg/L). No M spike was detected on serum protein electrophoresis. The patient's other blood tests did not show deterioration in renal or hepatic function. However, she was found to have nephrotic range proteinuria of 2.4g/day (normal range <150mg/day). Radiographic results, including a bone survey, were negative. Echocardiography and electrocardiogram findings were also normal. Calcium was within normal limits.

Based on our patient's clinical findings, biopsy, and hematological results, a diagnosis of primary systemic amyloidosis resulting from plasma cell myeloma was made. She was started on the CyBorD chemotherapy regimen consisting of: cyclophosphamide 900mg/m$^2$ on day 1, bortezomib 1.3mg/m$^2$ SQ on days 1, 4, 8, 11, and dexamethasone 40mg PO days 1, 4, 8, 11. The patient was discharged on day 11 of her chemotherapy regimen and returned to her local hematologist/ oncologist for the remainder of therapy. The patient was lost to follow up.

## Case Discussion

In primary systemic amyloidosis, a population of clonal plasma cells produce monoclonal light chains that form fibrils with a ß-pleated sheet configuration that are then deposited in various tissues. Immunoglobulin light chain amyloidosis can occur alone or in association with multiple myeloma, Waldenström macroglobulinemia, or non-Hodgkin lymphoma [3, 4]. Cutaneous involvement occurs in approximately 30%-40% of systemic AL amyloidosis patients, usually presenting as purpuric to skin colored, waxy papules, plaques, and nodules affecting the scalp, face, flexural areas, genitalia, and periorbital regions [2]. The infiltration of amyloid into superficial blood vessels often presents as non-traumatic purpura and ecchymosis, particularly on the face, particularly the periorbital regions. Bilateral periorbital ecchymosis or "raccoon eyes" is highly characteristic and should raise suspicion for amyloidosis [5]. There have also been case reports of AL amyloidosis causing bullous and hemorrhagic

lesions, cutis laxa, scalp lesions resembling cutis verticis gyrata, nail dystrophies, alopecia, and scleroderma-like infiltrative plaques [6-12]. Patients with AL amyloidosis present with a wide range of associated symptoms, including weight loss, fatigue, syncope, peripheral edema, peripheral neuropathy, carpal tunnel syndrome, and cutaneous symptoms.

For a patient with suspected AL amyloidosis, initial evaluation includes a fat pad aspirate or rectal biopsy, bone marrow biopsy, and workup for light chain abnormalities [13]. Routine workup for light chain abnormalities includes ratio analysis of serum free light chain and serum protein electrophoresis with immunofixation. Hematoxylin and eosin-stained sections from the biopsy should demonstrate amorphous, eosinophilic masses characteristic of amyloid deposition. With Congo red stain, amyloid deposits show a characteristic apple green birefringence under polarized light [13]. Persistent Congo-red positivity after treatment with potassium permanganate is specific for AL amyloidosis [14].

Primary systemic amyloidosis without treatment has a median survival of approximately 12 months [15]. Treatment designs are aimed at eliminating light chain production and typically utilize cytotoxic agents such as mephalan, bortezomib, and cyclophosphamide [16]. Despite improvements in treatment prognosis is poor in general.

Diagnosis of this disease is often delayed owing to its nonspecific manifestations as well as its rarity. Cutaneous presentations of primary systemic amyloidosis have been misdiagnosed as scleroderma, squamous cell carcinoma, or other conditions [9, 17, 18]. In the case of our patient, the infiltrative yellow plaques on the eyelids initially raised suspicion for necrobiotic xanthogranuloma and other xanthomatous disorders in the initial differential diagnosis. However, the diffuse nature of the mucocutaneous amyloid deposition pointed to a possible underlying systemic infiltrative process. The hematological workup included bone marrow biopsy, which then confirmed monoclonality with restriction of free lambda light chains.

## Conclusion

This case demonstrates the classical cutaneous manifestations of primary systemic amyloidosis, particularly the generalized infiltrative plaques and ecchymosis. It highlights the inconspicuous nature of plasma cell dyscrasia and the importance of initiating appropriate malignancy work up in a time-sensitive fashion upon recognition of these cutaneous findings.

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