



Case Letter

Systemic amyloidosis: The skin as a clue of an unexpected diagnosis



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Dear Editors,

A 36-year-old woman with a 10-year-history of Sjögren's syndrome was referred with a 5-year-history of skin lesions and a histological diagnosis of morphea (Fig. 1A). Although she was treated with phototherapy, methotrexate, and mycophenolate mofetil, the skin lesions progressed. On examination, the patient had slightly painful, irregular-sized, and hard-elastic nodules in the groin and multiple well-demarcated, yellowish plaques on the arms, abdomen, and trunk (Fig. 1B). Hematoxylin and eosin staining of a new skin biopsy revealed a suspicious amorphous eosinophilic material throughout the dermis. The diagnosis of amyloidosis was confirmed by apple-green birefringence on polarization and positive staining for Congo red and Thioflavin-T (Fig. 2A-C).

To distinguish cutaneous from systemic disease, a surgical biopsy of the abdominal fat pad was performed. Amyloid deposition around the hypodermic vessels was observed, and systemic amyloidosis (SA) was confirmed. To explore other organs or tissue involvement, several studies were carried out. Laboratory tests showed increased lambda light chains (LC) serum and urine values. Peripheral blood cytometry evidenced a clonal plasmocytare population CD38+, CD138+, and CD19-. Bone marrow biopsy revealed 7% of plasma cells with LC predominance, with negative Congo red staining. The 24-hour urine test, echocardiogram, and b-type natriuretic peptide plasma levels ruled out renal and cardiac involvement.

To identify the type of SA, a tissue immunohistochemistry for amyloid A amyloidosis was performed, and the result was negative. Immunohistochemistry for LC amyloid was not available in our country. Therefore, amyloidosis due to Sjögren's syndrome was ruled out and the diagnosis of SA LC amyloidosis with multifocal cutaneous involvement was made.

Based on the diagnosis, the patient was administered bortezomib 1.3 mg/m², cyclophosphamide 500 mg, and dexamethasone 40 mg, and both cutaneous manifestations and laboratory abnormalities resolved. One year later, the patient developed new skin lesions and serum LC increased (23.20 mg/L), so she was started

on lenalidomide. She evolved with resolution of skin and hematological findings and is still undergoing longitudinal follow-up.

Amyloidoses are a large group of diseases in which deposits of abnormally folded proteins with fibrillar ultrastructure infiltrate extracellular spaces of affected organs (Kelsey et al., 2016). These conditions can present as localized or systemic disease. SA is characterized by the deposition of fibrils composed of low-molecular-weight subunits of a variety of proteins. It is classified according to the protein involved into 36 different types (Sipe et al., 2016). Its clinical features depend on the spectrum and severity of the involved organs. The kidney (70%) and heart (60%) are the more commonly compromised organs. Skin involvement is present in 40% of patients and usually presents as purpura, waxy thickening, plaques, nodules, or macroglossia. These cutaneous findings result from the deposition of amyloid within the skin and blood vessels and should be differentiated from primary localized cutaneous amyloidosis, scleromyxedema, xanthomatosis, histiocytosis, mastocytosis, hypodermitis, lymphomas, and morphea, as in this case.

An SA diagnosis requires histologic demonstration of amyloid deposition. In cutaneous localized forms, the biopsy must be obtained from the lesions. However, to demonstrate systemic disease, other biopsies of clinically uninvolved sites, such as subcutaneous fat, minor salivary glands, rectal mucosa, or dysfunctional organs (e.g., kidney, nerve), must be carried out. The most recommended procedures are fine-needle aspiration or surgical biopsy of subcutaneous tissue, which are safe and have >70% of sensitivity for diagnosing SA (Obici et al., 2005). The sensitivity of minor salivary glands, rectal mucosa, or dysfunctional organ biopsies are 61%, 85%, and 90% to 100%, respectively.

Furthermore, amyloid type identification and systemic involvement evaluation should be done to classify each case and offer adequate treatment. This could be performed by immunohistochemistry or laser microdissection and tandem mass spectrometry analysis of the congophilic areas of the biopsy (Winter et al., 2017). The latter technique can identify the type of amyloid with >98% specificity and sensitivity (Sipe et al., 2016). Unfortunately, this technique is not available in our country.

Once a tissue diagnosis of amyloidosis has been established, confirmation of LC disease requires demonstration of plasma cell

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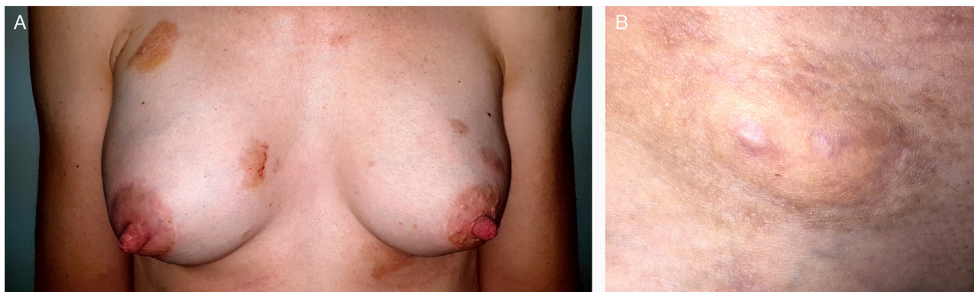


Fig. 1. (A) Well-demarcated, yellowish plaques with tendency to bleed with minimal trauma on the trunk. (B) Rounded, skin-colored, slightly painful nodules on the groin.

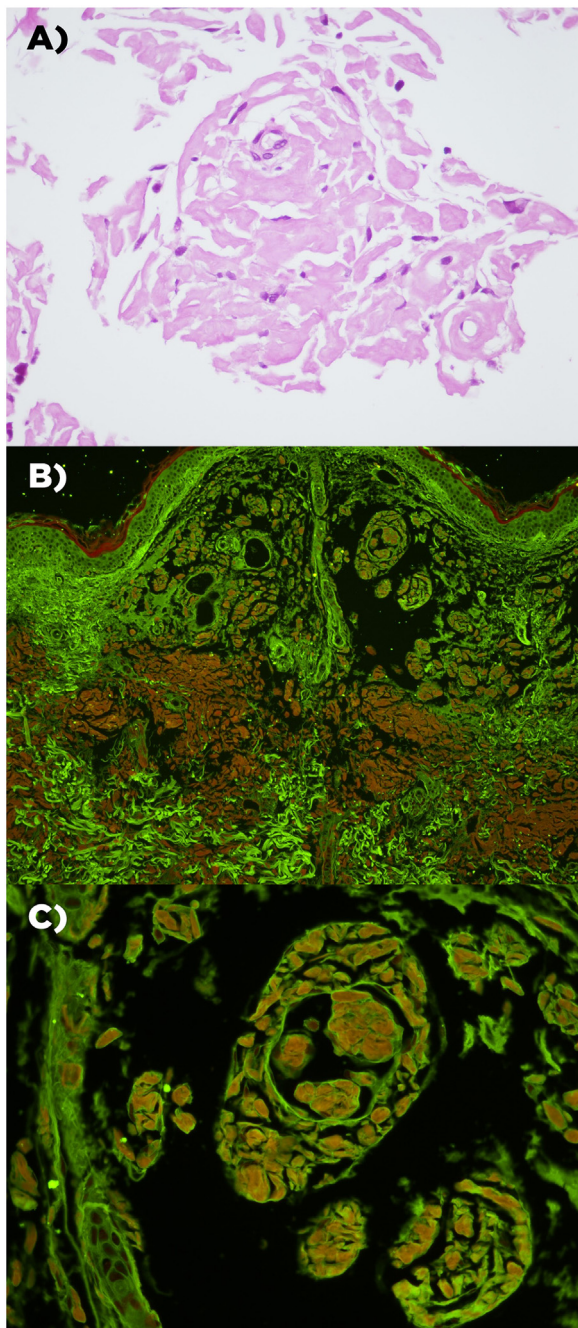


Fig. 2. (A) Eosinophilic, amorphous substance, arranged around superficial and deep vessels (hematoxylin and eosin; 40×). (B) Congo red imparting a green birefringence under polarized light (10×), and (C) Congo red imparting a green birefringence under polarized light (40×).

dyscrasia by bone marrow biopsy with a predominance of λ - or κ -plasma cells or the presence of a monoclonal LC in the serum or urine (Obici et al., 2005).

Treatment of the different types of amyloidosis usually varies with the cause of the disease. The treatment of choice for LC amyloidosis is stem cell transplantation, but it is possible only for a minority of patients (Gertz et al., 2013). For those patients who are not transplant eligible, the standard of care is bortezomib-based chemotherapy. For very frail patients, oral therapy with melphalan and dexamethasone could be appropriate (Winter et al., 2017).

Daratumumab is an anti-CD38 monoclonal antibody. Case reports and retrospective studies have described the safety and efficacy of this treatment in patients with relapsed or refractory LC amyloidosis (Winter et al., 2017).

Conflicts of interest

None.

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Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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