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# Perianal purpuric plaques revealing an amyloid light-chain amyloidosis: case report and review of the literature

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## Abstract

Systemic immunoglobulin light chain amyloidosis is the most common and severe type of amyloidosis. There is an abnormal fibrillary protein deposition in tissues that leads to progressive and irreversible organ dysfunction. The most commonly affected organs are kidney and heart. Although rare, cutaneous manifestations may be the first clinical sign of the disease and usually present as hemorrhagic lesions, such as purpura, petechiae, and ecchymosis. We present a 71-year-old man that presented to our department because of exuberant purpuric plaques in the anogenital area as the first manifestation of an amyloid light-chain (AL) amyloidosis. The multi-organ involvement in addition to rapid clinical deterioration precipitated the patient's death four months later.

*Keywords: amyloidosis, cutaneous manifestations, purpura*

## Introduction

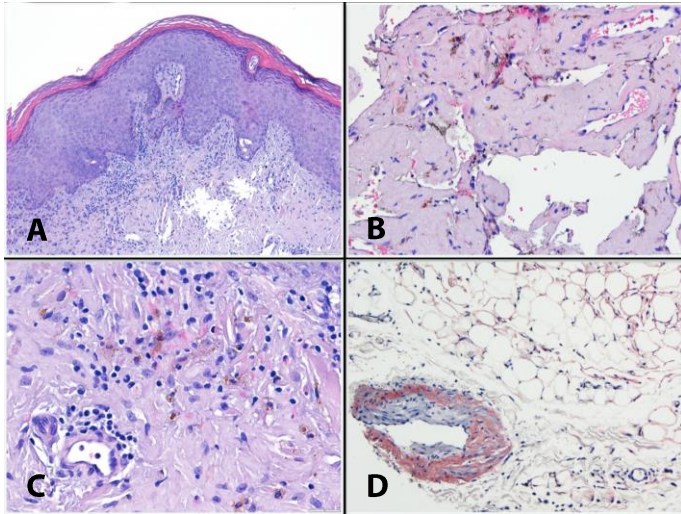
Amyloidosis comprises a group of rare diseases caused by misfolding and aggregation of abnormal autologous proteins with extracellular deposition as amyloid fibrils [1-5]. These disorders can present as limited cutaneous or systemic diseases [3, 5]. The precursor protein that causes the buildup of abnormal amyloid fibrils determines the classification of the disease [3]. Systemic immunoglobulin light chain amyloidosis is the most common and severe type, usually presenting with systemic manifestations [1-4].

## Case Synopsis

A 71-year-old man, otherwise healthy, was referred to the department of dermatology for purpuric lesions evolving over the last year. He had exuberant perianal purpuric plaques and hemorrhagic blisters of the buttocks and inguinal areas. There was also a stony consistency of the buttocks and thighs, with enlargement of this area (**Figure 1**). Owing to a suspicion for amyloidosis, a skin biopsy was performed. Extensive deposits of homogeneous, hyaline material were observed diffusely in the dermis, vascular walls, and the subcutis (**Figure 2**). Congo-red staining revealed apple-green birefringence under polarized light, consistent with amyloid (**Figure 3**). Immunohistochemical typing of amyloid was compatible with AL amyloidosis. The patient presented with proteinuria and a substantial elevation of cardiac markers, troponin and brain natriuretic protein (BNP). Electrocardiography



**Figure 1.** Skin involvement by AL amyloidosis. Note the plaque-like ecchymotic lesions in flexural areas.



**Figure 2.** Hyaline deposits in the superficial dermis (A, H&E, 40x; B, H&E, 200x), and deep dermis with cracking artefact (C, H&E, 100x); Congo-red staining in a subcutaneous small vessel wall (D, 100x). Note the recent and ancient hemorrhagic features of the dermis (B, C).

showed low QRS voltage and poor R-wave progression. Echocardiographic study revealed moderate-to-severe left atrial enlargement and severe concentric left ventricular hypertrophy with preserved systolic function.

During the hospitalization, the patient complained of asthenia and myalgia that rapidly evolved to tetraparesis, consistent with a systemic disease. In this setting, the clinical deterioration was fast and precluded the performance of an electromyography. The patient died four months later without initiating targeted treatment and no autopsy was performed.

## Case Discussion

AL amyloidosis has an estimated incidence of three to five patients per million per year [6]. The mean age of diagnosis is 65 years and it is slightly more frequent in men [2, 6].

AL amyloidosis is characterized by the abnormal production of fibrillary proteins composed of intact or fragments of monoclonal immunoglobulin light chains, produced by plasma cells [2, 3]. It may be associated with plasma cell dyscrasia, multiple myeloma and Waldenström macroglobulinemia [3]. Abnormal fibrillary proteins can deposit in every organ except for parenchymal brain tissue, leading

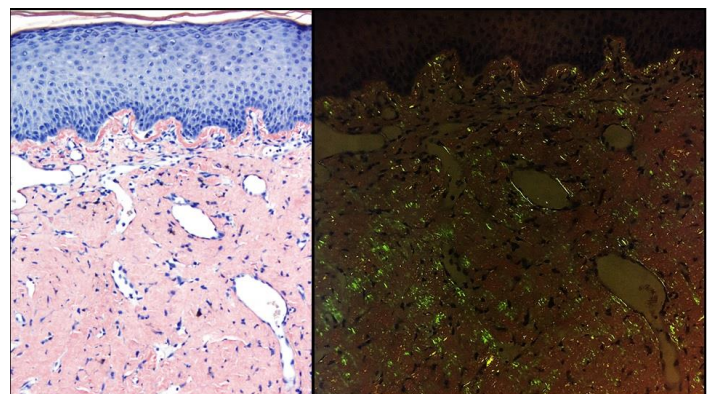
to progressive and irreversible organ dysfunction [2, 3, 7].

Clinical manifestations vary according to organ involvement [5, 7]. Although non-specific, asthenia and dyspnea are common presenting symptoms, thus contributing to a delay in the diagnosis [2].

Albeit rare, periorbital purpura, macroglossia, and submandibular gland swelling may evoke the diagnosis of amyloidosis [2, 3, 7]. Purpura, petechiae, and ecchymosis may represent the first clinical signs of the disease and are frequently distributed periorbitally, in flexural areas, and at sites of trauma [2, 3].

Cardiac involvement is present in up to 90% of the patients with AL amyloidosis [2]. Heart disease is considered a poor prognostic factor, accounting for 75% of deaths, commonly related to heart failure and arrhythmia [2]. Echocardiogram is the main diagnostic procedure to confirm amyloid cardiomyopathy, but since findings are non-specific, it may lead to misdiagnosis [6, 7]. N-terminal pro-natriuretic peptide type B (NT-proBNP) and troponin are used to assess severity of heart dysfunction [1, 5, 7]. Moreover, NT-proBNP seems to rise before clinical and imaging changes, allowing earlier diagnosis and probably influencing patient prognosis and survival [7]. According to previous studies, BNP is preferred in patients with renal involvement owing to differences in the metabolism of the markers [1, 5].

The kidney is affected in about two thirds of the patients at the time of diagnosis [1, 2, 4]. Initially, it



**Figure 3.** Congo-red staining (A, H&E, 200x) with apple-green birefringence under polarized light (B, H&E, 200x) in the superficial dermis.

manifests as albuminuria with development of nephrotic syndrome and decreased glomerular filtration rate in 20-to-45% of the cases [2, 7].

Peripheral nerve involvement may also be present in 20% of the patients with painful and slowly progressing peripheral polyneuropathy [2].

Since clinical manifestations are shared with other pathologies and often occur in advanced stages of the disease, this contributes to a delay in the diagnosis. Almost 40% of the affected patients remain undiagnosed for one year after the initial symptoms [5, 6].

The diagnosis relies on the presence of extracellular Congo red positive deposits with apple green birefringence under polarized light [2]. Non-invasive abdominal fat, minor salivary gland, and rectal mucosa biopsies should be considered in the initial study [2, 4]. The biopsy of other organs (kidney, heart) should be considered only when clinical suspicion persists, to avoid unnecessary complications [2, 4]. The presence of serum or urine paraprotein is not sufficient to confirm the diagnosis in elderly patients, since monoclonal gammopathies are frequent in this age group [2]. Our patient displayed features of plasma cell dyscrasia and the diagnosis of AL amyloidosis was based on histologic and immunohistochemical demonstration of amyloid deposits.

Immunohistochemistry on paraffin-embedded tissue sections and immunofluorescence microscopy on frozen sections are common diagnostic methods to identify the type of amyloid involved before starting specific treatment [1, 2, 4, 6]. Recent studies suggest that laser capture mass spectroscopic proteome analysis may be the gold standard for typing the amyloid protein subunit, but it is not already available in most centers [4-6]. The identification of the involved amyloid is crucial since chemotherapy and stem cell transplantation are only indicated in AL amyloidosis [6].

Treatment varies according to the patient's risk [1, 5, 7]. Autologous stem cell transplantation is the best option in low-risk patients [1, 5]. Intermediate-risk individuals are good candidates for chemotherapy, including conventional treatment with melphalan

and dexamethasone or bortezomib-based regimens [1, 2, 5, 7]. For high-risk patients, usually owing to advanced cardiac disease, available treatment options seem to marginally influence median survival ranges, even with bortezomib-based regimens [1]. Recently, novel therapies are being tested in advanced stage and refractory patients, including the proteasome inhibitors ixazomib and carfilzomib, the anti-plasma cell antibody daratumumab, and the immunostimulatory monoclonal antibody elotuzumab [1, 5].

The prognosis of patients with AL amyloidosis is influenced by the hematological response to treatment, the extension and grade of organ attainment, and the severity of cardiac dysfunction [2, 3, 5, 7]. Bone marrow plasma cell (BMPC) infiltration has also an independent impact on patient survival [2, 7]. Previous studies suggest that a BMPC infiltration higher than 10% is associated with poorer prognosis whereas very low levels correlate with better prognosis, independently of the cardiac staging of the disease [2, 5, 7]. AL amyloidosis patients have a median survival between 1 to 2 years, with high-risk patients having only 3 to 7 months of expected lifetime, similar to the course of our patient [1, 3, 4].

## Conclusion

The diagnosis of AL amyloidosis should be considered in every patient presenting with nephrotic range proteinuria and cardiomyopathy with preserved ejection fraction, especially in the presence of unusual purpuric plaques in flexural areas. Clinicians should be aware that cutaneous lesions may be the first manifestation of AL amyloidosis, as in the present case. Therefore, accurate diagnosis of skin AL amyloidosis may be relevant for the adequate management of patients. Moreover, this case report reinforces that skin can be used to biopsy in order to confirm the diagnosis of multisystem disorders with cutaneous manifestations, such as amyloidosis. Since late stage disease is associated with a poorer prognosis, it is crucial to diagnose this condition early to provide adequate treatment and ultimately increase patient survival.

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