

Primary systemic amyloidosis with skin and cardiac involvement: a case report

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Abstract

Primary systemic amyloidosis is characterized by the deposition of insoluble monoclonal immunoglobulin light chains in various tissues and is usually associated with an underlying plasma cell dyscrasia. In the early stage of the disease, dermatological findings can be the only manifestation, as opposed to organ involvement in the later stages. A dermatologist can diagnose amyloidosis early with a skin biopsy stained with Congo red dye and other appropriate investigations. This case report describes a female patient with primary systemic amyloidosis confirmed histologically from a skin biopsy. When the diagnosis was established, cardiac involvement and monoclonal gammopathy were already present. Treatment with bortezomib and dexamethasone was initiated; due to side effects, the treatment was later switched to lenalidomide, which was better tolerated.

Keywords: AL amyloidosis, pinch purpura, amyloid, monoclonal gammopathy, amyloid cardiomyopathy

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Introduction

The amyloidoses are a group of rare disorders characterized by the deposition of extracellular fibrils in different tissues and organs (1). Primary systemic amyloidosis (AL amyloidosis), which is usually associated with an underlying plasma cell dyscrasia, involves the deposition of insoluble monoclonal immunoglobulin light chains in the skin, muscles, connective tissues, blood vessel walls, peripheral nerves, heart, kidneys, gastro-intestinal tract, and lungs (2).

The global incidence of amyloidosis is estimated at up to nine cases per million per year, with AL amyloidosis the most prevalent type in developed countries. The disease is usually diagnosed later in life, around the age of 65 years (1, 3).

Case report

A 70-year-old woman presented with a 2.5-year history of recurrent periorbital edema and purpuric macules, which resembled a hematoma, on her face, neck, and upper body. The lesions and facial edema occurred suddenly and disappeared spontaneously in less than one month. In addition to her skin changes, the patient complained of fatigue, obstipation, and unintentional weight loss (7 kg in the preceding 3 years).

Her medical history revealed that her skin symptoms had started three months prior following the implantation of a pacemaker due to sinus node disease. She had also been examined by a hematologist because of benign monoclonal IgG gammopathy with light kappa chains predominating. Therefore, a bone marrow biopsy was performed in 2013, which ruled out multiple myeloma. Other chronic diseases in her medical history included congestive heart failure and depression. The patient's family history was negative for dermatologic diseases. Her brother had been diagnosed with multiple myeloma.

The physical examination showed symmetrical periorbital edema with purpura, which also presented on her neck and the anterior portion of her upper body (Fig. 1). The partial regression

of some of the lesions was observed as yellow, waxy, minimally infiltrated plaques (Fig. 2).



Figure 1 | Symmetrical periorbital edema with purpura.



Figure 2 | Purpura on the neck and yellow, waxy, minimally infiltrated plaques.

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A skin biopsy showed eosinophilic hyaline deposits in the epidermis, dermis, and interstitium after hematoxylin and eosin staining (Fig. 3). After staining with Congo red, the sample showed diffuse amyloid apple-green deposits when viewed under polarized light (Fig. 4). Immunohistochemical staining revealed positive light kappa chains, while lambda chains, transthyretin, and amyloid A were negative (Fig. 5). The diagnosis of primary systemic amyloidosis was confirmed.

Extensive laboratory testing indicated that the complete blood count with differential, electrolytes, liver function, and kidney function were all normal. Cardiac enzymes showed normal creatinine kinase and myoglobin levels with slightly elevated troponin I and NT-proBNP levels. Thyroid hormones were within normal ranges. Electrophoresis and immunofixation of the serum and urine showed traces of monoclonal IgG kappa. Proteinuria was 0.7 g/24 h. Fecal occult blood tests were negative. Coagulation tests were not impaired: factor X was slightly reduced (0.61).

A chest X-ray showed an enlarged left ventricle. An echocardiogram revealed concentric thickening of the left ventricle with a normal ejection fraction and infiltrative cardiomyopathy; this is consistent with cardiac involvement in amyloidosis. Abdominal and renal ultrasounds were within the normal ranges. Electromyography showed no impairment of the lower motor neuron.

Based on these findings, the patient was again referred to a hematologist, who recommended chemotherapy with bortezomib and dexamethasone. Side effects developed after the second cycle of chemotherapy, including fatigue, pretibial edema, and neuropathy (her leg pain and constipation worsened). After the therapy was switched to lenalidomide, which was better tolerated, there was a partial regression of her skin and systemic pathology.

Discussion

Primary systemic amyloidosis has a multitude of clinical presentations (4). Early in the disease course, non-specific complaints such as weakness, fatigue, and weight loss dominate and are commonly reported, which was also the case with the patient described here. Skin lesions may also be an early—and sometimes the only—feature of primary amyloidosis until organ failure occurs later in the disease course.

Spontaneous skin and mucous membrane lesions, which include purpura, petechiae, and ecchymoses, may occur on the eyelids, axillae, umbilicus, and even the anogenital area. Periorbital purpura can sometimes be induced by vagal maneuvers. Pathophysiologically, these skin findings appear because of clotting factor deficiencies (such as lowered factor X in the case described here) and fragile venules. Other skin findings, such as smooth, waxy, yellowish nodules, plaques, and scleroderma-like changes, which are usually found on the face, buccal mucosa, and flexor surfaces, are the result of amyloid deposits in the dermis. Uncommon presentations of AL amyloidosis can include alopecia and nail dystrophy (5–7).

Extracutaneous manifestations of AL amyloidosis include dysfunction of the heart and kidneys, liver (rarely), intestines, and neurological system (8). The predilection for specific organs and the mechanisms by which the amyloid fibrils are deposited are still poorly understood (4).

Cardiac involvement in AL amyloidosis is around 60%, with the most profound manifestation being right heart failure. Patients may also present with apparent acute coronary syndrome, arrhythmias, and high-grade conduction diseases that require pacemaker

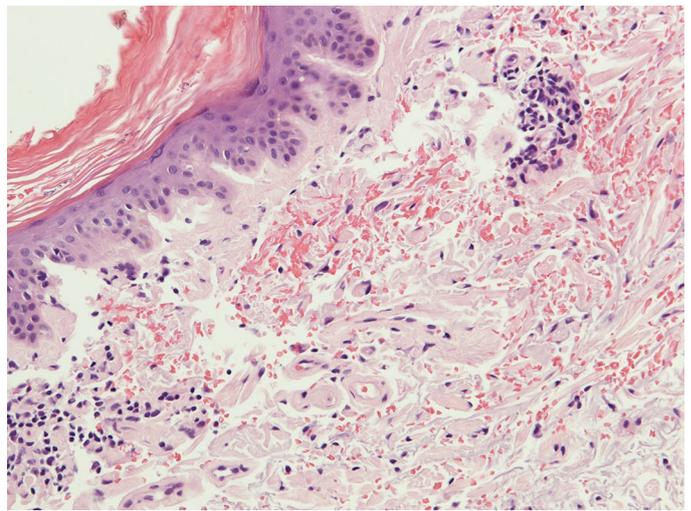


Figure 3 | Hematoxylin and eosin staining. The deposition of pale eosinophilic, amorphous material around blood vessels and throughout the dermis. Note the red cell extravasation.

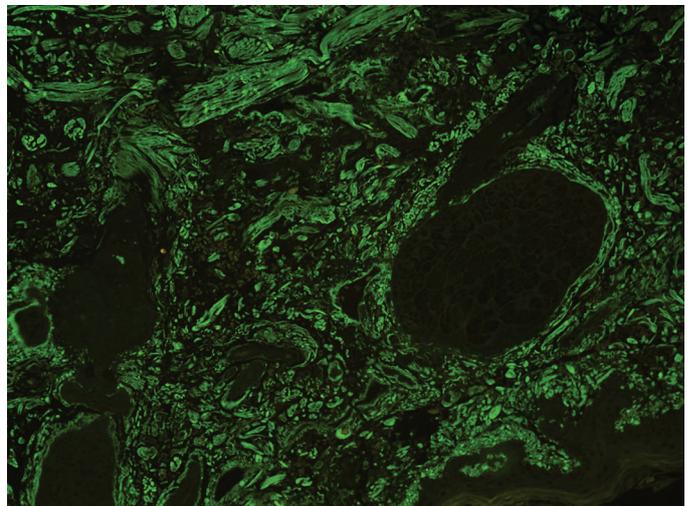


Figure 4 | Congo red staining viewed with polarized light revealed amyloid deposits with typical apple-green birefringence in the dermis.

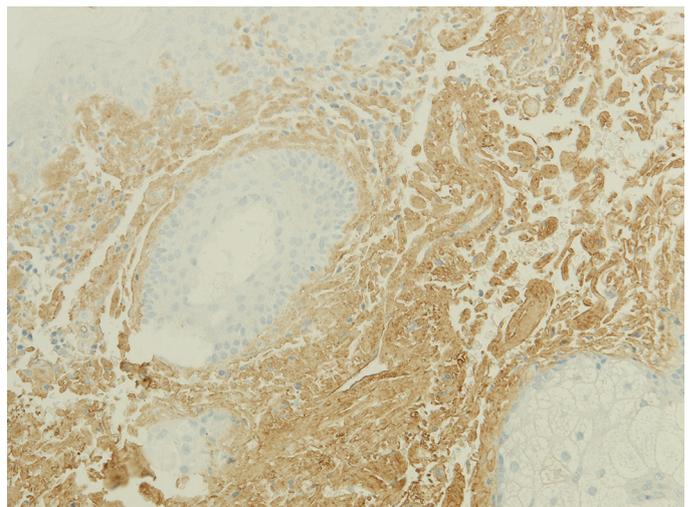


Figure 5 | Positive immunohistochemical staining of amyloid deposits for kappa light chains.

implantation. Renal involvement can range from asymptomatic proteinuria to nephrotic syndrome and end-stage renal disease. Peripheral, autonomic, and central nervous system involvement, such as carpal tunnel syndrome, bowel and bladder dysfunction, or dementia, is often present. Amyloid deposits can also lead to organ enlargement, such as hepatomegaly or macroglossia (8, 9).

The diagnosis of AL amyloidosis is made by staining a bioptic sample of skin or another affected organ tissue with Congo red dye and viewing it under a polarizing microscope. The typical histological findings are amyloid apple-green birefringent deposits. After establishing a histological diagnosis, plasma cell dyscrasia and other hematologic disorders associated with AL amyloidosis should be ruled out by serum and urine immunofixation electrophoresis and a bone marrow biopsy (10). The degree of end organ damage is assessed by imaging and extended laboratory measurements. Congestive heart failure is confirmed by echocardiography and increased NT-proBNP, which appears to be the best prognostic factor in AL amyloidosis (11). The most favorable prognosis has been observed in patients suffering from amyloid neuropathy without cardiac or renal involvement (12). Survival rates vary: patients presenting without cardiac involvement have a median survival of close to 2 years, while the median survival of those with cardiomyopathies is as low as 4 months (9).

Depending on the patient's age, overall performance status, and organ involvement, several treatment strategies are available (13). High dose melphalan and stem cell support may be beneficial and offer longer survival, but the majority of patients are not suitable for this treatment plan due to cardiomyopathy and other comorbidities (14). A selective proteasome inhibitor, bortezomib,

has been used with encouraging results in the treatment of AL amyloidosis. With or without dexamethasone, bortezomib induces significant hematologic and organ responses. Despite its efficacy, several side effects have been observed, including neurotoxicity, fatigue, peripheral edema, constipation, and the exacerbation of postural hypotension (13, 15). These symptoms are, in most cases, dose-dependent and diminish after discontinuing treatment. Significant symptomatic improvement of neurotoxicity was observed in some patients when switching the therapy to lenalidomide; this was the case for the patient described here also (16).

Conclusion

In AL amyloidosis, the deposition of immunoglobulin light chains can occur in any organ, causing dysfunction. Dermatological findings, which can occur in up to 40% of patients, are well recognized and can be the only manifestation in the early stages of the disease. Thus, the dermatologist must include AL amyloidosis in the differential diagnosis in a proper clinical setting. With an appropriate investigation and a skin biopsy stained with Congo red, the diagnosis can be established. Various therapeutic regimens are available; however, the prognosis still remains poor (5, 17).

References

- Real de Asúa D, Costa R, Galván JM, Filigheddu MT, Trujillo D, Cadiñanos J. Systemic AA amyloidosis: epidemiology, diagnosis, and management. *Clin Epidemiol.* 2014;6:369–77.
- Hayman SR, Bailey RJ, Jalal SM, Ahmann GJ, Dispenzieri A, Gertz MA, et al. Translocations involving the immunoglobulin heavy-chain locus are possible early genetic events in patients with primary systemic amyloidosis. *Blood.* 2001;98:2266–8.
- Desport E, Bridoux F, Sirac C, Delbes S, Bender S, Fernandez B, et al. AL amyloidosis. *Orphanet J Rare Dis* [internet]. 2012 [cited 2017 August 3];7:54 Available from: <https://orjrd.biomedcentral.com/articles/10.1186/1750-1172-7-54>.
- Abraham RS, Geyer SM, Price-Troska TL, Allmer C, Kyle RA, Gertz MA, et al. Immunoglobulin light chain variable (V) region genes influence clinical presentation and outcome in light chain-associated amyloidosis (AL). *Blood.* 2003;101:3801–8.
- Silverstein, SR. Primary, systemic amyloidosis and the dermatologist: where classic skin lesions may provide the clue for early diagnosis. *Dermatol Online J* [internet]. 2005 [cited 3 August 2017];11:5. Available from: <http://escholarship.org/uc/item/4kp758ow>.
- Wheeler GE, Barrows GH. Alopecia universalis: a manifestation of occult amyloidosis and multiple myeloma. *Arch Dermatol.* 1981;117:815–6.
- Breathnach SM, Wilkinson JD, Black MM. Systemic amyloidosis with an underlying lymphoproliferative disorder. *Clin Exp Dermatol.* 1979;4:495–9.
- Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. *Arch Intern Med.* 2006;166:1805–13.
- Bejar D, Colombo PC, Latif F, Yuzefpolskaya M. Infiltrative cardiomyopathies. *Clin Med Insights Cardiol.* 2015;9:29–38.
- Sancharawala, V. Light-chain (AL) amyloidosis: diagnosis and treatment. *Clin J Am Soc Nephrol.* 2006;1:1331–41.
- Palladini G, Campana C, Klersy C, Balduini A, Vadacca G, Perfetti V, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation.* 2003;107:2440–5.
- Gertz MA, Kyle RA. Primary systemic amyloidosis—a diagnostic primer. *Mayo Clin Proc.* 1989;64:1505–19.
- Kastritis E, Anagnostopoulos A, Roussou M, Toumanidis S, Pamboukas C, Miggou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. *Haematologica.* 2007;92:1351–8.
- Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBORd) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood.* 2012;119:4391–4.
- Kastritis E, Wechalekar AD, Dimopoulos MA, Merlini G, Hawkins PN, Perfetti V, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. *J Clin Oncol.* 2010;28:1031–7.
- Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, et al. Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature. *Cancer.* 2007;110:1042–9.
- Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol.* 1988;18:1–16.