case report

Systemic amyloidosis presenting as mucocutaneous bullous lesions

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A 65-year-old male presented with hemorrhagic bullous skin lesions with purpura and ecchymoses. There was increased skin fragility with a strongly positive Nikolsky sign. Histopathology of the skin revealed large amounts of amyloid deposits in the dermis with a positive Congo Red staining around the dermal vessels. Examination and tests in this patient also revealed anemia, hepatomegaly, infiltrative cardiomyopathy, polyneuropathy and immunoglobulin λ deposition, favoring a diagnosis of primary amyloidosis (AL type). The present case is reported in view of the rarity of the bullous variant of primary systemic amyloidosis as well as presence of mucosal lesions and a positive Nikolsky sign.

The amyloidoses are a heterogenous group of disorders characterized by deposition of various types of extracellular fibrillar proteins, which have in common a typical green birefringence in polarized light after Congo red staining of the involved tissue specimen.[1] Amyloidoses may be divided into the systemic, localized and the heredofamilial types. Immunohistology allows the identification of the types of amyloid based on the composition of the fibrillar protein.[2] We describe a case of primary systemic amyloidosis with multiorgan involvement who presented with extensive mucocutaneous bullous lesions with a strongly positive Nikolsky sign.

CASE

A 65-year-old non-diabetic, normotensive farmer presented with a 6-month history of a progressively worsening bullous skin eruption. Clinical evaluation of the patient revealed a history of dysphagia, anorexia, hoarseness of voice, paresthesias in the hands and feet, and dyspnea and postural hypotension of nearly the same duration. There was no history of a similar eruption in the past. There was no history of intake of any drug and family history was non-contributory. On general physical examination, the patient had pallor. Auscultation of the chest revealed decreased breath sounds in the right lower chest. The patient also had hepatomegaly and hypothenar and thenar muscle wasting of both hands.

Cutaneous examination revealed multiple large hemorrhagic bullae intermingled with non-palpable purpura, ecchymoses, erosions and waxy plaques predominantly involving the neck, trunk, axillae, lower limbs and hands (Figure 1, 2). Hemorrhagic bullae and ecchymotic plaques were present on both upper eyelids (Figure 3). Yellowish-white milium-like papules were observed on the back. The skin was tender to the touch and substantially fragile as revealed by strongly positive Nikolsky sign. Purpuric and ecchymotic lesions were present on the tongue and hard palate. The patient's tongue was firm on palpation. Longitudinal ridging was present in all the fingernails.

The complete blood count revealed a hemoglobin of 9.1 g/dL and an erythrocyte sedimentation rate of 60 mm (first hour reading by Westergen method). Platelet count, clotting time, bleeding time, prothrombin and activated partial thromboplastin times were within normal limits. Liver function tests and kidney function tests were also within normal limits. Twenty-four hour urinary protein was 0.54 g/L (total volume 1.3 L), while urine for Bence-Jones proteins was negative. Serum and urine protein electrophoresis was negative. Bone marrow examination was normal. A collagen vascular profile of the patient did not reveal any abnormality.

An electrocardiogram showed decreased voltages in all standard leads. A chest x-ray showed right-sided pleural effusion while radiographic examination of the skull and pelvis did not reveal any lytic bone lesion. Ultrasonographic examination of the abdomen and pelvis revealed hepatomegaly (17.7 cm). On echocardiog-

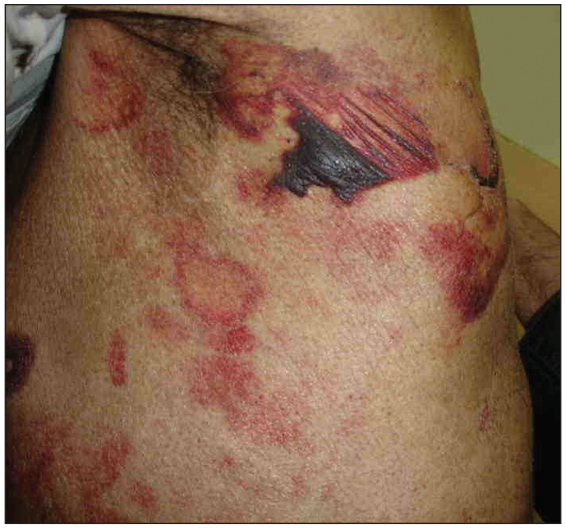

Figure 1. Hemorrhagic blister with ecchymoses and erosions on the trunk.

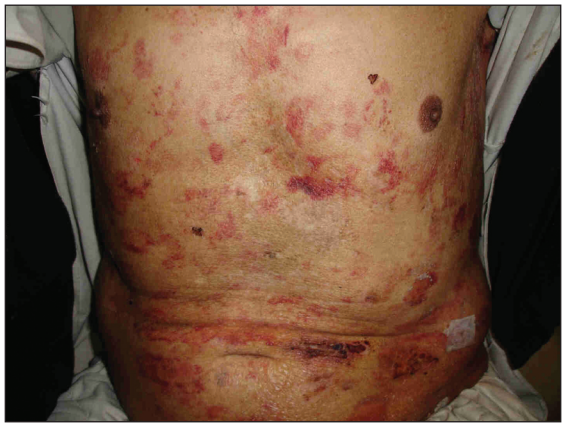

Figure 2. Ecchymoses and erosions on abdomen.

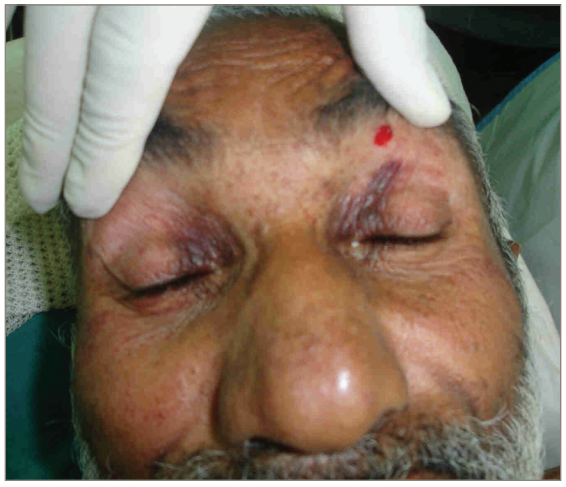

Figure 3. Ecchymotic patches on upper eyelids.

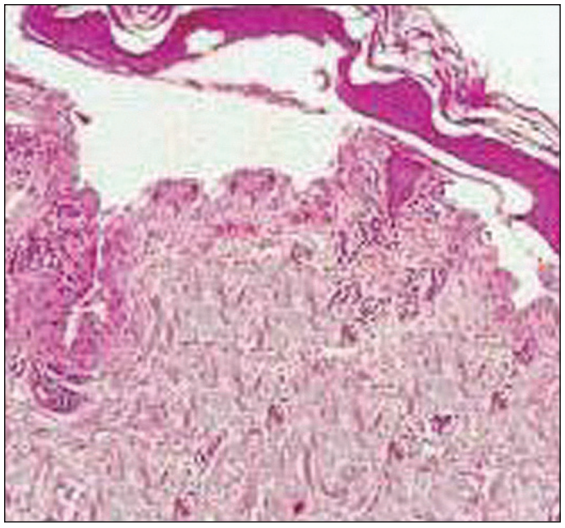

Figure 4. Subepidermal blister on hematoxylin and eosin stain (×100).

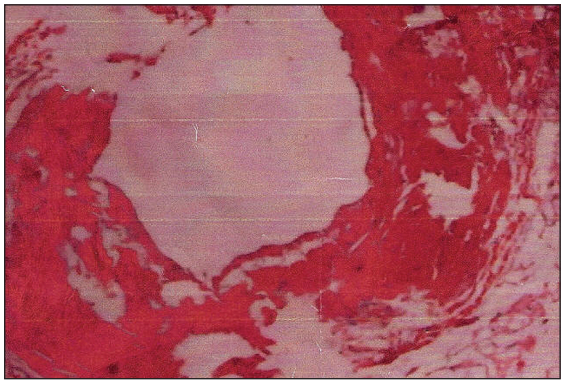

Figure 5. Positive Congo red staining of cutaneous amyloid deposits.

raphy, infiltrative cardiomyopathy with grade I diastolic dysfunction with normal left ventricular systolic function was seen. Nerve conduction studies showed polyneuropathy (axonal more than demyelinating type). Fiber optic laryngoscopy revealed bullous lesions on the vocal cords while upper gastrointestinal endoscopy revealed several erosions in the upper-third of esophagus.

Histopathological examination of a skin biopsy specimen showed an atrophic epidermis with large amounts of an amorphous eosinophilic material deposited in the dermis and subcutis. The blisters were pauci-inflammatory and subepidermal (Figure 4). The amorphous deposits were positive for Congo-red staining with apple-green birefringence under polarized light and surrounded the dermal vessels in a cuff-like manner (Figure 5). Direct immunofluorescence examination of the skin

biopsy specimen performed to rule out an immunobullous disorder, was negative. Abdominal fat pad and rectal biopsies were also done and were positive for Congo-red staining. Immunohistochemical staining showed positive staining for immunoglobulin λ light chain.

Keeping the above-mentioned constellation of clinical and laboratory parameters in mind, a diagnosis of primary systemic amyloidosis (AL amyloidosis) was entertained. The patient was put on intravenous dexamethasone pulse therapy (40 mg per day for three consecutive days every four weeks) in combination with daily oral colchicine (0.5 mg three times a day). Although dexamethasone is usually used for four consecutive days, we used it for only three days every four weeks so as to prevent fluid retention. After the 12th week (third pulse) cutaneous lesions started resolving and the Nikolsky sign was negative. After moderate improvement in cutaneous lesions, the patient was referred to medical oncology for further management.

DISCUSSION

Amyloidosis is a generic term that denotes extracellular deposition of a proteinaceous substance composed of one of a family of biochemically unrelated proteins, usually associated with considerable tissue dysfunction.[1] The amyloid deposits show an apple-green birefringence when specimens stained with Congo red are viewed under polarized light and demonstrate a non-branching fibrillar structure under the electron microscope.[2-4]

Amyloidoses used to be classified clinicopathologically as systemic amyloidosis (primary and myeloma associated or secondary), cutaneous amyloidosis (macular, lichen, nodular) and heredofamilial amyloidosis. However, it now tends to be classified on the basis of characterization of the fibril proteins.[5] Fibrils in primary and myeloma associated systemic amyloidosis are composed of immunoglobulin protein AL; it occurs in a setting of multiple myeloma or plasma cell dyscrasia. In secondary systemic amyloidosis, the fibrils are composed of a non-immunoglobulin protein termed protein AA, occurring in association with a variety of disease states-chronic inflammatory disorders (e.g., rheumatoid arthritis, ankylosing spondylitis), chronic infections (e.g., tuberculosis, lepromatous leprosy), hereditary diseases (e.g., epidermolysis bullosa of dystrophic and acquista types), malignant conditions (e.g., Hodgkin disease, non-lymphoid tumors) and various dermatoses (e.g., psoriasis, acne conglobata).[6] Skin lesions are found in about 40% of patients of systemic AL amyloidosis and rarely in patients with AA systemic amyloidosis. Commonly seen cutaneous manifestations include petechiae, purpura, ecchymoses, waxy papules and nodules.[7-9]

Bullous lesions as a presenting clinical feature of amyloidosis are very rare. There is usually associated multiorgan involvement. The blisters occur due to intra-dermal splitting within the amyloid deposits. The contents of the blisters are often hemorrhagic because of intracutaneous hemorrhage due to infiltration of blood vessel walls by amyloid deposits, which is also responsible for other cutaneous features like purpura and ecchymoses.[10-14] Acquired factor X deficiency, as seen in about 14% of patients with amyloidosis, may also contribute to the presentation of hemorrhagic bullae along with purpura and ecchymoses.[15]

In our patient, bullae along with purpura and ecchymoses were the presenting complaints. It was only after hospitalization and investigations were conducted that involvement of other organs was detected. Our patient also had mucosal lesions; only one patient with mucosal lesions has been previously described.[14] Although serum and urine electrophoresis was negative, characteristic mucocutaneous lesions with multiorgan involvement, positive Congo-red staining in the skin, rectal and abdominal fat pad biopsies along with a positive immunostaining for immunoglobulin λ were all in favor of primary systemic amyloidosis (AL amyloidosis). In addition, history and examination revealed no cause of secondary amyloidosis in our patient nor was there evidence of any heredofamilial syndrome. A strongly positive Nikolsky sign was also present in our patient, in which epidermal separation was subepidermal, as revealed by histopathological examination. Although classically associated with pemphigus, toxic epidermal necrolysis and staphylococcal scalded skin syndrome, Nikolsky sign has also been described in several other disorders; in our patient being due to subepidermal deposition of amyloid (pseudo-Nikolsky sign).[16,17] Prognosis in primary and myeloma associated systemic amyloidosis is poor, the major cause of death being cardiac and renal failure. Cardiac involvement especially indicates a very poor prognosis.[18]

The treatment of amyloidosis is often unsatisfactory and is directed toward the affected organ and the specific type of the disease.[18] Various chemotherapeutic agents (for example, melphalan) as well as colchicine, thalidomide and dexamethasone have been used with variable response rates.[18,19] Cardiac and renal transplantation can prolong survival.[20]

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