PRIMARY SYSTEMIC AMYLOIDOSIS WITH BULLOUS LESIONS
A Case Report

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Summary

Primary systemic amyloidosis with bullous lesions associated with multiple myeloma is described in an adult patient. The response to therapy with melphalan and prednisolone had been quite encouraging. The patient was well when seen more than 2 years after the initial diagnosis. Details are presented.

KEY WORDS: Amyloidoses, plasma cells, Bence Jones proteins melphalan.

Introduction

Amyloidosis was probably first noted in 17th century by Bonet, who described a patient with a liver abscess, whose enormous spleen contained innumerbale 'white stones'. This probably was the 'sago spleen' of amyloidosis. The first case report of amyloidosis is generally credited to Wild in 1886[1]. A case in whom findings were compatible with multiple myeloma and amyloidosis was presented in 1872 by Adams[2]. In 1903, Weber[3] also described a patient with myeloma and amyloidosis.

Amyloidosis is a pathologic disorder of extracellular deposition of amorphous proteinaceous material in organs throughout the body with resultant impairement of organ function. The disease is commonly classified as being primary (when without antecedent or coexisting disease), secondary (when associated with chronic infection or inflammatory disease states), myeloma-associated, heredo-familial and localised. Typically primary amyloidosis involves tongue, heart, GIT, skeletal and smooth muscles, skin and nerves. The skin lesions are present in 20% to 30% of patients[4,5]. Common cutaneous findings are waxy papules, nodules, purpura, sclerodermoid indurations and diffuse alopecia. A characteristic waxy appearance of the skin is classically described. Although erosions and ulcerations caused by cutaneous fragility are known to occur in systemic amyloidosis[6], intact bullae have not been reported often[7] and the microscopic descriptions are still less common[8,9]. Bullae may also occur in the poikilodermatous form of localised cutaneous amyloidosis[10] and in amyloidosis involving the oral mucosa[8,11].

We present a rare case of primary systemic amyloidosis with multiple intact cutaneous bullae.

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Case Summary

A 45 years old male patient was admitted to the Dermatology ward of Postgraduate Institute of Medical Education and Research, Chandigarh, with the chief complaints of recurrent vesiculo-bullous, sometimes haemorrhagic eruptions on the palms and soles and ruddiness of the face for two and a half years. Difficulty in speech, swallowing and restricted movements of the tongue and hoarseness of voice had been present for 2 years and these were worsening. Breathlessness on exertion and mild pain in the chest was present for 1½ years. Generalised swelling of the body, more so of the legs and feet were present for one year. There was no family history of similar skin problem.

Examination revealed a moderately built and nourished individual with generalised swelling of the body and pitting oedema of legs and feet.

The skin all over the body, especially on the face and periorbital regions was thick, oedematous and ruddy. Multiple discrete waxy polygonal papules, varying in size from 2-4 mm were present all over the body particularly over buttocks, thighs, nape of the neck and back. Macular purpuric areas were present on the distal parts of the body, maximally on the dorsal aspects of the hands and legs. Erosions, crusts and hypopigmented scars were present on extremities at many places. Thick roofed, moderately tense bullae varying in size from 1 mm to 2 cm, containing serous or serosanguinous fluid were present discretely scattered over the arms, legs, feet, palms and soles. The underlying skin was normal with no inflammatory halo around these vesicles and bullae. The bullae persisted for many days before rupturing and then healed gradually leaving behind discolouration. Tourniquet test was normal. Normal amount of rubbing of the skin did not produce bullae or petechiae. Soles showed hyperkeratosis and fissures. Nails were thin, discolored, ridged and atrophic.

A firm, non-tender and non-mobile swelling measuring 4 × 2.5 cm on the parietal region of the skull was detected on examination. Submandibular glands were enlarged on both sides. Tongue was enlarged, thick and rounded, very firm, pale red, coated and could only be protruded partially. There were prominent impressions of teeth on the edge of the tongue. Angular stomatitis was present. There was hepatosplenomegaly. Cardiovascular, neurological and respiratory systems were essentially normal.

Investigations revealed normal blood cell count and haemoglobin. ESR was 45 mm in 1st hr by Westergren method. Heavy proteinuria was detected. Total serum proteins were 4.8 g, albumin 2.0 g and globulin 2.8 g with A/G ratio of 0.7. Serum cholesterol was 320 mg percent. Serum electrophoresis revealed a dense narrow zone in β-γ region α-2 component was also prominent. Bone marrow aspriate revealed 33% plasma cells, many of which were in clumps.

Skin biopsy and biopsy from the tongue showed amyloid deposits. (Fig 1).

Rectal biopsy did not reveal any abnormality.

X-ray chest, skull and abdomen did not reveal any abnormality. Pulmonary function tests were normal. 24 hr urine protein was 1.5 gms (normal 0.1 gm). Urine electrophoresis did not reveal Bence–Jones proteins. Porphyrin levels in urine and blood were normal. Direct immunofluorescence of the bullae was negative. All other investigations on blood, stools and urine including serum electrolytes, urea, serum creatinine, uric acid, bilirubin, alkaline phosphatase, transaminases, LE cell, and ANF were negative.

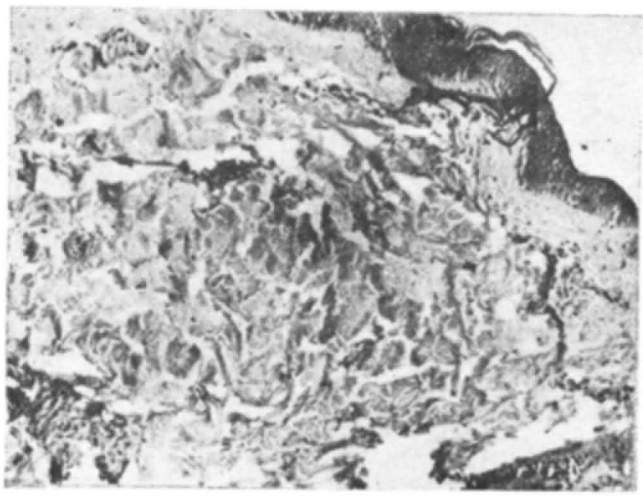

Fig. 1

Epidermis is separated from dermis by a thin band of collagen. Minimal lymphocytic cell reaction. Homogeneous fissured masses of amyloid in the upper dermis. (H & E × 44)

In the hospital, the patient was managed with tablet lasix (Frusemide) 100 mg on alternate days, melphalan, in the dosage of 0.25 mg/kg/day and prednisolone 2 mg/kg/day, for 4 days every month. Ten such courses were given. The improvement was partial. Skin lesions improved and swelling of the tongue reduced so that it could be protruded more easily. The initial proteinuria which had disappeared, reappeared. Serum electrophoresis revealed normal pattern. Urinary Bence-Jones proteins remained absent. Raised serum cholesterol levels persisted. Bone marrow aspiration revealed normocellular bone marrow with 2% plasma cells. Patient was well when seen last; two years after the initial diagnosis.

Discussion

Primary amyloidosis is a progressive disorder in which mesenchymal tissue, rather than parenchymal organs are involved. Macroglossia is a featurc in about 40% of the cases and was present in our patient. Primary amyloidosis and amyloidosis associated with multiple myeloma occurred more often in men than in women and both types are rare under the age of 40 years[4]. The other associated syndromes reported are carpal-tunnel syndrome, nephrotic syndrome, congestive heart failure, sprue, peripheral neuropathy and orthostatic hypotension.

One of the classic manifestations of primary systemic amyloidosis is purpura, which is attributed to the fragility of dermal blood vessels caused by amyloid deposition within their walls[12]. Our patient demonstrated this, and also bullae, which can be again attributed to the fragility of the amyloid laden dermal blood vessels and connective tissue as a result of minor trauma. Haemorrhagic dissection through the amyloid deposits may result in extension of the bullae. The diagnosis requires deposits of amyloid in the dermis and dermal cleft formation through these deposits. The level of bullous separation tends to be well below the basal lamina[10,13].

The histopathological picture was of a subpapillary bulla, at a much deeper plane of separation than seen in prophyria cutanea tarda or epidermolysis bullosa both of which could be considered in the histopathological diagnosis. PAS positive perivascular deposits were observed which confirmed the diagnosis. The etiolgy of amyloidosis is unknown. It has long been known that amyloid can form in response to some prolonged antigenic stimulation. The relation of Bence-

Jones protein to amyloid was first postulated by Magnus Levy[14]. Osserman et al[15] and Glenner et al[16] have emphasized the association and similarity of Bence-Jones proteins and amyloid. Gafni et al[17] have postulated that in case of primary systemic amyloidosis with multiple myeloma, plasma cells synthesise myeloma proteins and fibroblasts produce the amyloid indicating a certain relationship with one another. Thus a single stimulus can cause alteration in the metabolism of both cells resulting in the synthesis of an abnormal product in either cell. The frequent findings of abnormal numbers or forms of plasma in cells the bone marrow, presence of monoclonal serum and/or urine proteins in most patients[18] and the recognition that amyloid fibrils may be derived from immunoglobulin light chain fragments[16,19,20] suggests that the disease represents an abnormality of immune system[21].

There is no satisfactory treatment for primary amyloidosis. Alkylating agents or immuno-suppressive drugs may prove beneficial in patients with demonstrable Bence-Jones proteins by suppressing either light chain production or overactivity of the reticulo endothelial cell system. The alkylating agent melphalan has received maximum attention because of its effectiveness in multiple myeloma therapy, though melphalan itself is myelotoxic and leukemogenic[22,23].

Our patient improved considerably after 10 doses of melphalan and prednisolone. Macroglossia and mobility of the tongue improved. The voice became less husky and more clear. Pedal oedema reduced considerably. Plasma cells concentration in the bone marrow reduced to 2 per cent. The electrophoretic pattern of serum proteins reverted to normal. The 24 hour total urinary proteins remained unaltered, because no reversal of the amyloid deposition in the kidneys is expected. The renal function parameters of urea, creatinine, uric acid also remained the same. The size, frequency and severity of bullous lesions reduced considerably.

Average survival after diagnosis in most series has been reported to be 1-3 years, renal failure being the major cause of early death. Long-term survival has been reported in some cases[24,27]. Some serious complications of amyloidosis e.g. nephrosis and hepato-splenomegaly may improve with therapy. In such situations trial with melphalan and prednisolone may be indicated. Prognosis of the disease in general is poor.

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