

Case Report

Multiple myeloma with primary systemic amyloidosis affecting cutaneous, gastro intestinal and cardio-vascular system

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ABSTRACT

Amyloidosis refers to a group of disorders characterized by extracellular deposition of protein fibrils. Primary systemic amyloidosis is commonly due to an underlying plasma cell dyscrasia. Infiltrative amyloid cardiomyopathy is a rare cause of predominantly diastolic myocardial disease. Restrictive cardiomyopathy is the main finding in cardiac amyloidosis and results from the replacement of normal myocardial contractile elements by infiltration and interstitial deposits of amyloid, leading to alterations in cellular metabolism, calcium transport, receptor regulation, and cellular edema. Injury can also occur from circulating light chains in the absence of amyloid fibril formation. Cardiac amyloidosis should be considered in any patient presenting with congestive heart failure, preserved systolic function, and a discrepancy between a low QRS voltage on electrocardiography and an apparent left ventricular hypertrophy on sonogram. The pattern of left ventricular diastolic dysfunction changes during the course of amyloidosis and the classically described restrictive physiology occurs only in advanced stages of the disease. This is a case report where an unusual extensive cutaneous and cardiac involvement provided the sign of widespread systemic deposition of amyloid protein which eventually led to the diagnosis of multiple myeloma.

Keywords: Cutaneous Amyloidosis, Diastolic dysfunction, Multiple Myeloma, Restrictive cardiomyopathy

INTRODUCTION

Amyloidosis is the term used to describe abnormal deposition of a protein-rich substance (insoluble and proteolysis resistant) in the skin or other organs.¹ The composition of such amyloid substances, in addition to fibrils, although formed by different types of proteins and carbohydrates presents some common aspects: they bind to Congo red dye, having a reddish coloration in normal light or birefringent green coloration under polarized light. They also bind to thioflavin, becoming strongly fluorescent and conferring a peculiar aspect to histological sections.² Tissue infiltration by these amyloid

deposits occurs in a localized or systemic manner. When localized, there is only cutaneous involvement and when systemic, it may be primary or secondary.¹ The primary systemic form is related to hidden dyscrasia or multiple myeloma, while the secondary form arises from complications of chronic inflammatory processes like rheumatoid arthritis, osteomyelitis, scleroderma, Hansen's disease and tuberculosis, among others.²

Amyloidosis comprises a unique group of diseases that share in common the extracellular deposition of insoluble fibrillar proteins in organs and tissues. Cardiovascular amyloidosis can be primary, a part of systemic

amyloidosis, or a result of chronic systemic diseases elsewhere in the body. The most common presentations are congestive heart failure- mainly a restrictive infiltrative pattern- and conduction system disturbances. Recent developments in imaging techniques and extra-cardiac tissue sampling have minimized the need for invasive endomyocardial biopsy for amyloidosis. Despite advances in treatment, the prognosis for patients with amyloidosis is still poor and depends on the underlying disease type.³

CASE REPORT

A 58-year-old normotensive, non-diabetic male presented with multiple raised non pruritic hyper pigmented lesions initially on the forehead, periorbital region, and chin (figure 1) for 6 months which was insidious in onset and progressive. Associated with dysphagia for solids relieved on taking liquids and exertional breathlessness which progressed over 3 months with recent onset fatigue.

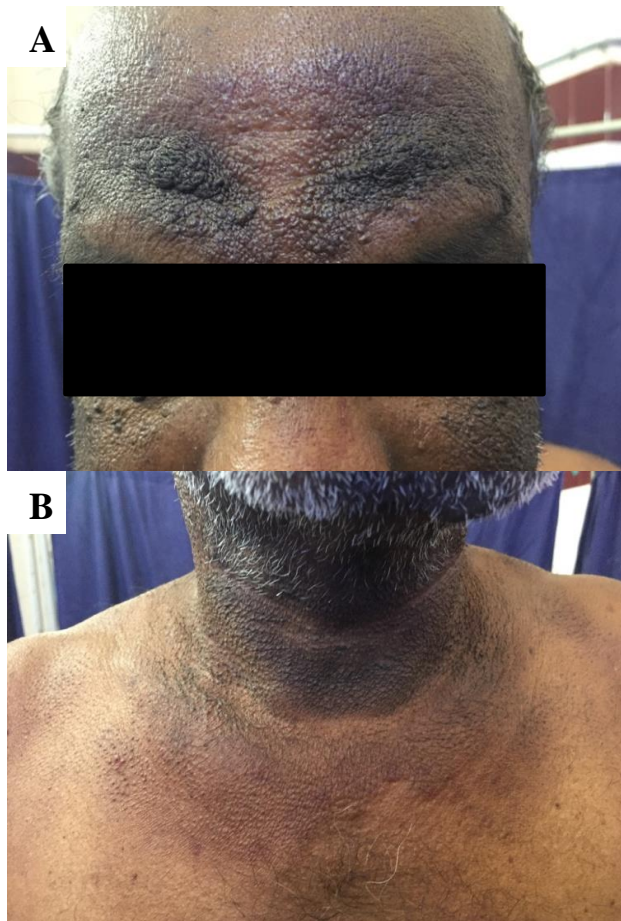


Figure 1: (A): Hyper pigmented velvety plaque, (B): Shiny papules over forehead, periorbital region and around neck.

On general examination he was pale and had macroglossia with dental indentations on the lateral borders of the tongue. No icterus, cyanosis, clubbing or

lymphadenopathy. Systemic examination was within normal limits.

Punch biopsy from forehead and chin was performed which showed homogenous eosinophilic deposits in dermal-epidermal junction (Figure 2A) and eosinophilic deposits seen around eccrine coils in dermis (Figure 2B) suggestive of cutaneous amyloidosis.

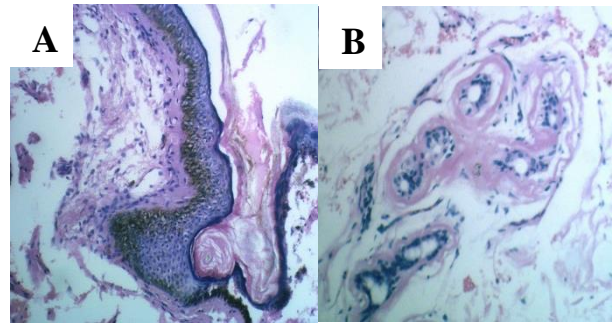


Figure 2: (A): Homogenous eosinophilic deposits in dermal-epidermal junction, (B): Eosinophilic deposits seen around eccrine coils in dermis.

Barium swallow was normal. Upper GI scopy showed superficial ulcerations and inflamed mucosa in the antrum (Figure 3).



Figure 3: Superficial ulcerations and inflamed mucosa in the antrum.

Biopsy from 2nd part of duodenum and antrum showed eosinophilic homogenous deposits replacing lamina propria (Figure 4A) and perivascular eosinophilic deposit (Figure 4B) suggestive of gastrointestinal amyloidosis.

Electrocardiography showed normal sinus rhythm and low voltage in precordial leads (Figure 5). Echocardiography revealed concentric left ventricular hypertrophy with grade II diastolic dysfunction. Radiological evaluation of skeleton showed single lytic lesion in skull (Figure 6).

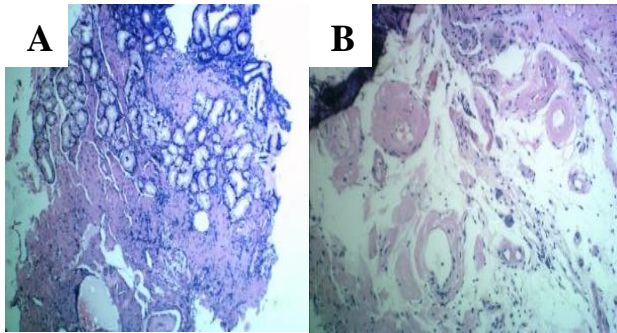


Figure 4: (A) Eosinophilic homogenous deposits replacing lamina propria antrum, (B): Perivascular eosinophilic deposit.

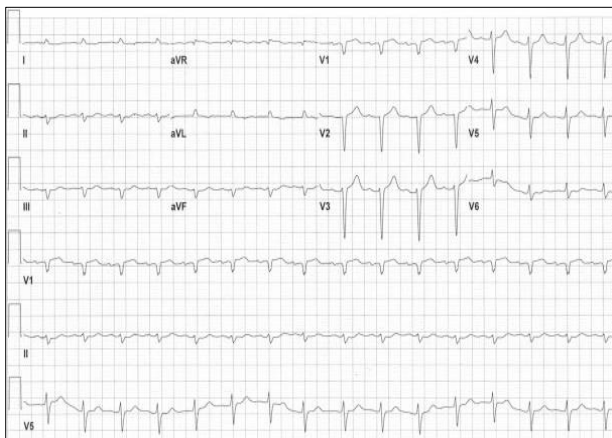


Figure 5: Normal sinus rhythm and low voltage in precordial leads.



Figure 6: Single lytic lesion of skull.

In view of primary systemic amyloidosis an underlying plasma cell dyscrasia was looked for. Investigations revealed normocytic normochromic anemia, 24hr urine proteins and serum calcium were normal. Skull X Ray revealed an isolated lytic lesion, Bence Jones proteins were negative with hemoglobin 9.9g/dL, hematocrit 32.6% with normocytic normochromic picture in peripheral blood smear. SPEP revealed M Band.

Subsequent Bone marrow aspiration and biopsy revealed 65% atypical plasmacytosis (Figure 7). In the bone marrow biopsy, a discrete plasma cell mass displaced normal marrow fat cells and hematopoietic elements consistent with diagnosis of multiple myeloma.

Patient was started on chemotherapy with Inj Bortezomib 2mg s/c once weekly, T. Linalidomide 25mg once daily and T. Dexamethasone 40mg once daily. After 6 months of chemotherapy patient improved symptomatically.

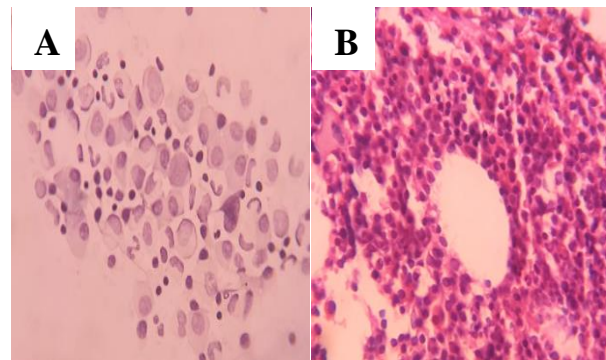


Figure 5: (A) Bone marrow imprint revealed numerous plasma cells, (B) Plasma cells accounted for >65% and Marrow partly replaced by sheets of plasma cells.

DISCUSSION

The prevalence of amyloidosis associated with multiple myeloma varies from 13% to 26%.⁴ Among the patients with multiple myeloma, 15% may develop some form of amyloidosis.^{1,3}

The sequential analysis of amino acids demonstrated that in systemic amyloidosis associated with multiple myeloma, fibrils are composed of an AL protein (light chain amyloidosis protein), which in turn is composed of variable immunoglobulin light chain (amino terminal), intact light chain, or both.¹

The most common cutaneous signs include: petechiae, purpura and ecchymosis. Such signs occur spontaneously following trauma and are due to amyloid infiltration in the vascular walls.⁵ Other lesions may be seen, such as: plaques, papules and nodules; serous, smooth and shiny, amber or skin colored, non pruriginous, and they may be hemorrhagic.

They affect mainly the eyelids, lips, tongue, oral mucosa, neck, axillae, umbilical scar and retro auricular, inguinal and anogenital regions.¹ Bullous lesions are rare.⁶

Some less frequent cutaneous alterations are: jaundice, paleness, hyperpigmentation, infiltrate similar to scleroderma, alopecia areata or universal, nail dystrophies, cutis laxa and lesions similar to cutis verticis girata in the scalp.¹

In primary systemic amyloidosis, the deposit occurs predominantly in tissues such as in the gastrointestinal tract, smooth and skeletal muscles, carpal connection, nerves and skin. In contrast, in the secondary systemic form the amyloid deposition takes place above all in parenchymatous organs: liver, spleen, kidneys and adrenal glands.¹

The amyloid deposits in the gastrointestinal tract may result in a variety of manifestations: abdominal pain, dysphagia, altered movements. Spleen and liver are present in 10% and 25% of cases, respectively.⁴ The tongue may be affected with macroglossia in 20% of cases, and there may be ulcerations, fissures, hemorrhages and teeth marks laterally.⁴ The heart may be involved in 25% to 40% of cases and the kidneys in 30 to 50%, which are determinants of prognosis.⁴

Clinical evidence of cardiac involvement occurs in up to 50% of patients with AL amyloidosis but only in 10% of individuals with AA amyloidosis and less than 5% with familial syndromes.⁷ It is important to emphasize that although only 10% of the patients with multiple myeloma develop systemic light-chain amyloid disease, their prognosis is very poor, especially in the presence of cardiac amyloidosis. Because cardiac involvement in amyloidosis is associated with a rapidly progressive course and high mortality, a rapid and accurate diagnosis is essential to aid in the selection of therapy.

Amyloid depositions occur mainly in the interstitium of contractile myocardium but may also involve the pericardium, the endocardium (resulting in valvular leaflet thickening),⁵ and the conduction system (giving rise to abnormalities in impulse formation, impulse conduction, stress-precipitated syncope, atrial fibrillation, and sudden cardiac death).⁸

The diagnosis of cardiac amyloidosis can be ascertained by either (i) a positive biopsy from a non-cardiac tissue in addition to sonographic evidence of amyloidosis, which includes a mean LV wall thickness of greater than 12mm in the absence of other causes of LV hypertrophy, or (ii) an endomyocardial biopsy illustrating amyloid deposition in addition to laboratory and clinical evidence of organ involvement. In patients with cardiac involvement, endomyocardial biopsy is a relatively safe procedure in experienced hands with 100% sensitivity in diagnosis of cardiac amyloidosis.⁹ Untreated patients with AL amyloidosis and heart failure have a median survival of 6-9 months.¹⁰ In summary a cardiac screening in all patients with multiple myeloma should include at least an ECG and complete cardiac sonography. Sonographic findings in cardiac amyloidosis are not specific for this disease because they can also be present in other disease states.

Multiple myeloma is a bone marrow plasmocyte dyscrasia diagnosed when there is more than 10% plasmocytes in the bone marrow or a plasmocytoma and

at least one of the following findings: 1) monoclonal serum protein; 2) monoclonal urine protein; 3) lytic bone lesions.¹¹

The prognosis of amyloidosis associated with multiple myeloma is unfavorable, with between 12 and 15 months mean survival rate.⁴ It depends on patient response to therapy and the extension of the disease. It is very important to make the earliest possible diagnosis, and always investigate multiple myeloma, especially in cases of systemic amyloidosis in patients considered suspect after the anatomic-pathological test used in this case.

CONCLUSION

In patients with primary systemic Amyloidosis, an extensive cutaneous and cardiac involvement must prompt to look for Multiple Myeloma as one of the common etiology. Early identification and management will improve the patient survival and cure multiple myeloma.

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