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Jayanta Das**

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Introduction: Primary systemic amyloidosis arises from clonal B cell disorder and may be associated with myeloma or lymphoma. Amyloid deposition can occur in any organ in the body as well as skin lesions. Both sexes are affected by this disease, with onset most commonly in the sixth decade or after.

Case Report: A 26-year-old female was presented with gradually changing quality of voice, diffuse pigmentation all over body and lymphadenopathy in upper cervical group. Biopsy of a lymph node showed follicular hyperplasia with a few discrete large cells. Over a period of time, she developed purpuric rash over extremities and periorbital area, respiratory distress and heart failure. Echocardiography revealed cardiac amyloidosis and rectal biopsy with Congo red staining was positive for amyloidosis. Skin biopsy from hyperpigmented lesion of right forearm was also suggestive of amyloidosis and bone marrow examination showed plasma cell dyscrasia with a small M-band in serum protein electrophoresis. Finally, it was diagnosed a case of primary systemic amyloidosis.

Conclusion: We report a primary systemic amyloidosis with an early age presentation.



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CASE REPORT

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Keywords: Primary systemic amyloidosis, Heart failure, Skin rash, Plasma cell disorder

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INTRODUCTION

Primary systemic amyloidosis (AL amyloidosis) arises from clonal B cell disorder and may be associated with myeloma or lymphoma. Plasma-cell clones produced immunoglobulin light chains or fragments of light chains that form extracellular amyloid fibrils. Amyloid deposition can occur in any organ in the body, causing features such as congestive cardiac failure, renal failure and hepatosplenomegaly as well as skin lesions. Both sexes are affected by this disease, with onset most commonly in the sixth decade or after. Although recent advances in therapy are encouraging, the prognosis for primary amyloidosis remains poor.

CASE REPORT

A 26-year-old female admitted in June 2010 with hoarseness of voice, diffuse pigmentation all over body

and lymphadenopathy in upper cervical group of lymph nodes for last one year. It was of insidious in onset and was progressive in nature. Detailed history taking did not reveal any history of fever, joint pain, joint swelling, bone pain or any other constitutional symptoms. Physical examination showed only upper cervical lymphadenopathy, diffuse skin pigmentation with thickening of skin of upper limb. There was no history of Raynaud's phenomenon and the tongue was thick but of normal size. Differential diagnosis of collagen vascular disease, malignancy with paraneoplastic syndrome, tuberculosis and lupoid proteinosis were made. Routine blood tests and thyroid profile, Antinuclear antibody (ANA), double-stranded deoxyribonucleic acid (ds DNA), Rheumatoid factor (RF), hepatitis B surface antigen (HBsAg), Anti-hepatitis C virus (Anti-HCV) antibody and human immunodeficiency virus (HIV) antigen were within normal limit. Mantoux (with 10 U tuberculin) was positive with 21 mm induration and erythema. Chest X-ray (posterior-anterior view) showed perihilar lymphadenopathy. Contrast enhanced computer tomography of thorax confirmed the X-ray findings but failed to specify the nature of the lesions better than chest X-Ray. Biopsy from the cervical lymph node showed follicular hyperplasia with few discrete large cells and CD 15, CD30 and BCL2 were advised, but the patient sought discharge from hospital for personal reason without undergoing these investigations.

In February 2011, she got readmitted with complaints of respiratory distress, bilateral swelling of feet, and a few purpuric skin rashes over extremities and face. These lesions resolved spontaneously and similar purpuric rash in periorbital region appeared (Figure 1). She also reported pain and tingling sensation in the distal parts of all four limbs and the skin pigmentation has increased remarkably. Physical examination revealed persistence of upper cervical lymphadenopathy, bilateral pitting pedal edema with engorged and pulsatile neck veins and gallop rhythm, orthopnea, decreased vocal resonance and breath sound over lower zone of right lung.

Considering the new features suggestive of heart failure, skin rash and pigmentation a new set of differentials was considered in addition to the previous ones including the possibility of primary systemic amyloidosis.

Laboratory workup revealed leukocytosis with a positive urine culture of *Klebsiella pneumoniae*. Chest X-ray showed persistence of perihilar lymphadenopathy with right sided pleural effusion. Pleural fluid study was transudative. Serological tests encompassing viral markers and autoimmune profile were negative. Abdominal ultrasonography did not reveal any significant findings. Nerve conduction study was suggestive of entrapment neuropathy of right median nerve at wrist joint and bilateral peroneal neuropathy.

Echocardiography (Figure 2) revealed increased ventricular wall thickness with ground glass appearance of myocardium, restrictive left ventricular filling pattern

and moderate pericardial effusion posteriorly with borderline left ventricular systolic function and thickened mitral and tricuspid valves. These features were strongly suggestive of cardiac amyloidosis.

Rectal biopsy with Congo red staining revealed orangophilia in amorphous deposits around the blood vessels, suggestive of amyloidosis. Skin biopsy was also consistent with amyloidosis (Figures 3 and 4).

Bone marrow examination revealed 15% plasma cell and suggestive of plasma cell dyscrasia (Figure 5), with M band in serum protein electrophoresis. Twenty-four hour urinary protein was 440 mg without any light chain on electrophoresis.



Figure 1: Periorbital ecchymoses in the patient (raccoon eye sign).

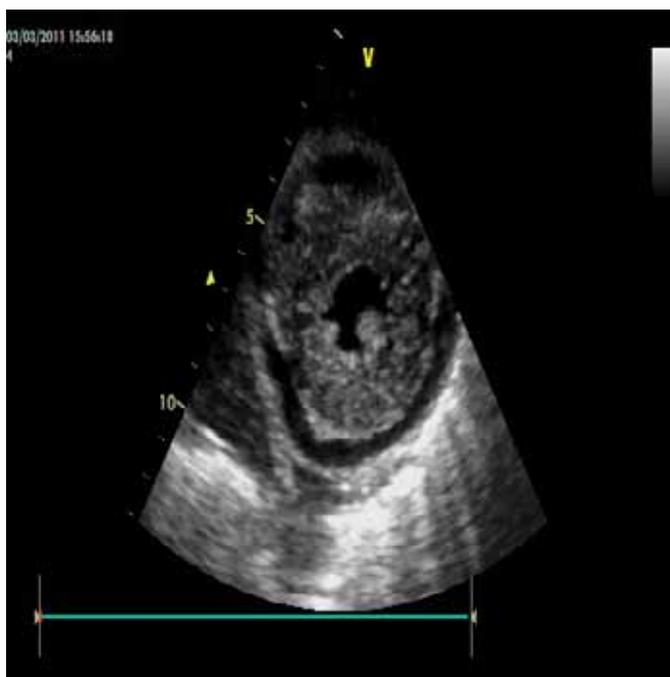


Figure 2: Echocardiography showing ground glass appearance suggestive of cardiac amyloidosis.

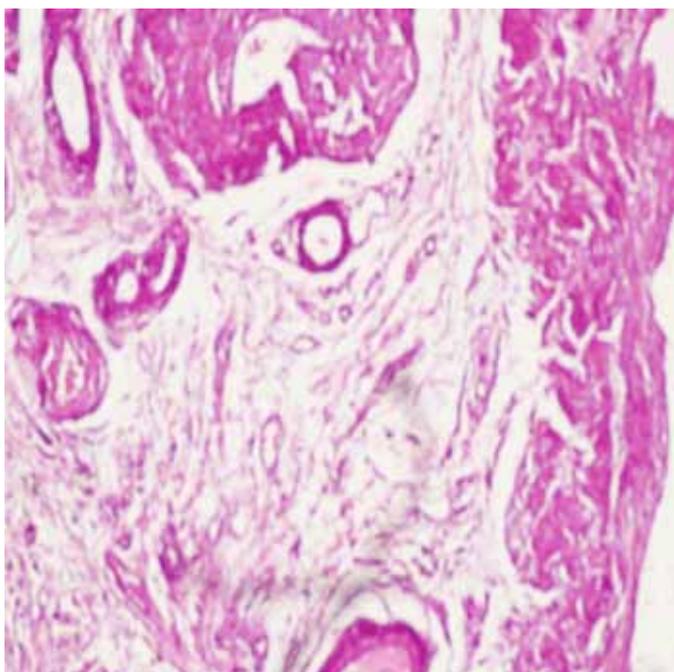


Figure 3: Rectal biopsy showing edematous sub mucosa and deposition of amorphous eosinophilic material predominantly around the blood vessels.

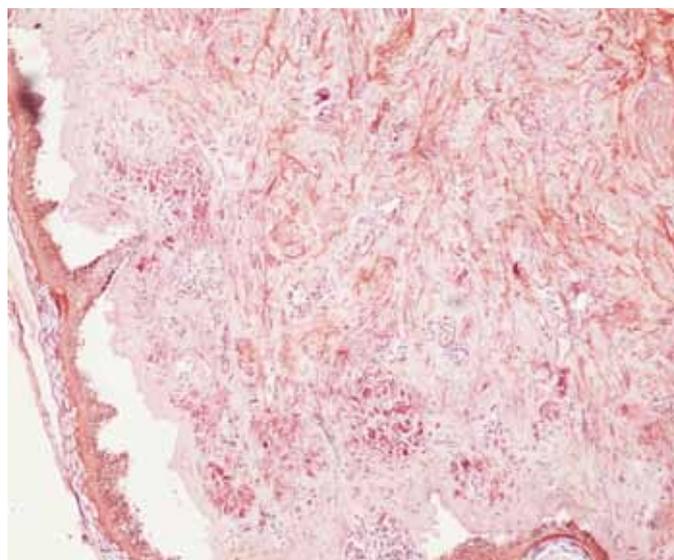


Figure 4: Skin biopsy showing deposition of amorphous material suggestive of primary systemic amyloidosis.

A final diagnosis of primary systemic amyloidosis was made. The patient was treated with pulse dexamethasone and cyclophosphamide and daily thalidomide. Patient tolerated the drugs well and was discharged with a plan of bone marrow transplant.

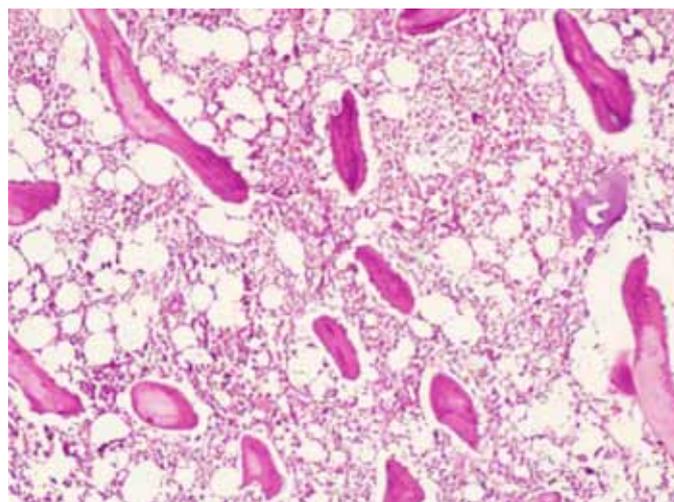


Figure 5: Bone marrow of the patient.

DISCUSSION

Amyloidosis is the term for diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. These diseases are a subset of a growing group of disorders attributed to misfolding of proteins. Polypeptide chain gets folded to form a secondary structure of the protein molecule. Helical structure and pleated structure are two important secondary structures of protein molecule. The amyloid protein has a beta-pleated sheet structure, which makes it highly insoluble and resistant to proteolytic digestion and hence difficult to remove from the tissues [1]. About 25 different proteins are known to produce amyloid fibrils in human, most of them are constituents of plasma. These normally soluble precursor proteins, due to some unknown reason, get misfolded and forms a beta-pleated sheet structure and becomes amyloid. Inherited amyloidosis is due to mutation in certain precursor protein, which makes them susceptible to misfolding. In case of primary systemic amyloidosis, the amyloid is derived from monoclonal immunoglobulin light chain and is called AL amyloid where L stands for light chain of immunoglobulin molecule. In case of secondary amyloidosis, which is associated with many chronic inflammatory diseases, amyloid fibrils are derived from cleavage fragment of the circulating acute phase reactant serum amyloid A protein (SAA), hence this type is called AA amyloid. Serum amyloid A protein is synthesized in liver during inflammation [2]. In localized cutaneous amyloidosis, amyloid is derived from keratin released from apoptotic keratinocytes [3]. The possible reason that many diverse conditions are associated with amyloidosis is each of these conditions results in excessive production of proteins that are prone to misfolding [2]. In multiple

myeloma-associated AL amyloidosis, precursor light chains of immunoglobulin (Bence Jones protein) are produced in large quantity by malignant plasma cell clone and can be detected in serum or urine by electrophoresis. Multiple myeloma is a malignancy of plasma cell. Amyloidosis develops in about 15% of patients of myelomatosis [1]. Majority of patients of AL amyloidosis do not have obvious B cell/plasma cell neoplasm hence they are idiopathic amyloidosis. These patients might have underlying B cell dyscrasia in which production of abnormal protein, rather than production of tumor masses, is the only clinically apparent manifestation [2]. Although different types of amyloid are associated with distinct clinical picture, all amyloid share a certain common features such as amorphous eosinophilic appearance on light microscopy in hematoxylin and eosin staining, bright green fluorescence observed under polarized light after Congo red staining, beta-pleated structure on X-ray crystallography, deposition of amyloid in tissues leads to distortion of tissue architecture, organ enlargement (organomegaly) and organ dysfunction. Amyloid deposition can occur in any organ. Primary systemic amyloidosis is known for highly varied clinical manifestation [4].

The mean age of presentation of primary systemic amyloidosis is 50 years, but this case presented at 26 years of age which is really unusual presentation. In literature we found a case report of unusual presentation at 39 years who first developed cutaneous reactions at 18 years age [5]. No other case report of unusual age presentation has been reported.

Cutaneous involvement is seen in 40% patients with AL amyloidosis. Cutaneous manifestation depends upon the site of amyloid deposited. Amyloid deposition in superficial dermis produces shiny waxy translucent papules and common sites for predilection are eyelids, retroauricular areas, neck and axilla. Amyloid deposited around pilosebaceous unit leads to the destruction of hair, producing alopecia. Diffuse infiltration of scalp skin results in the thickening of skin which gets thrown into longitudinal folds resembling cutis verticis gyrata. Diffuse infiltration of large area of skin may simulate scleroderma. Infiltration of nail matrix by amyloid may produce ridging; splitting and brittleness of nail plate [2].

Prognosis in AL amyloidosis is poor and major causes of death are cardiac and renal failure. The amyloid infiltration of vessel wall causes capillary wall fragility, which leads to purpura and ecchymosis after a minor trauma or even spontaneously. Periorbital area is one of the common sites of expression of purpura, as evident in this case. The capillary fragility may be demonstrated by pinching the skin. Purpuric lesions with normal platelet count and normal coagulation profile should suggest the possibility of capillary fragility. Amyloid deposition in tongue leads to macroglossia. Tongue is diffusely enlarged and firm and there may be tooth indentation along its lateral border. Amyloidosis is the most common

cause of macroglossia in adults [1]. Macroglossia if severe might lead to dysphagia. Macroglossia was present in our patient. Hepatomegaly occurs in 50% patients and splenomegaly in 10% patients. Cardiac involvement leads to conduction defects, arrhythmias, congestive cardiac failure and may account for 40% of deaths. Cardiac involvement in terms of cardiac amyloidosis with features of congestive heart failure was present in this case. Carpal tunnel syndrome is seen in up to 25% of patients of primary systemic amyloidosis as was present in our patient [1]. Amyloid infiltration might occur in peripheral nerves leading to thickening of nerves and resulting neuropathy often mimicking Hansen's disease. Renal involvement presenting with proteinuria and renal failure, is one of the bad prognostic indicators.

Our patient had plasma cell dyscrasia and M band in serum protein electrophoresis. The diagnosis was confirmed by demonstration of amyloid in rectal biopsy and skin biopsy. Clinically, it is difficult to distinguish primary, secondary or familial form of amyloidosis. Immunohistochemical staining using commercially available antisera is useful for classifying the type of amyloid deposited in tissues [6]. Biopsy is very important for the diagnosis. Hematoxylin and eosin staining suggests the possibility of amyloidosis but Congo red staining confirms the diagnosis. Congo red staining results in a brick red color of amyloid when seen under ordinary light and under polarized light shows classical green birefringence. Unfortunately, polarized microscopy is not easily available in developing country like India. In systemic amyloidosis, amyloid deposits are seen in dermis, subcutaneous tissue and blood vessels, whereas in localized cutaneous amyloidosis, deposits are seen only in papillary dermis; subcutaneous tissues and blood vessels are not involved. Tuberculosis is definitely a common entity in India, and we also considered it among one of the differentials but in this case it is unlikely to be a case of tuberculosis because: though it is a chronic disease it is unusual to be such a prolong course of disease as the disease started a year before presentation and it took another 9–10 months to diagnose the case, lymph node biopsy was not suggestive of tuberculosis so cannot be explained under one umbrella. Echocardiography was very much suggestive of amyloidosis, bone marrow aspiration shows 15% plasma cell, serum protein electrophoresis shows M band and rectal and skin biopsy median survival of patients with myeloma-associated amyloidosis is five months and for patients with primary systemic amyloidosis is 2.1 years [1]. Prognosis depends upon the extent of involvement. Treatment of amyloidosis is aimed at reducing the supply of precursor proteins [3]. In AL amyloidosis, the precursor is immunoglobulin light chain produced by B lymphocytes/plasma cells hence treatment with cytotoxic agents like melphalan and prednisolone that reduces plasma cell proliferation is useful [3]. Chemotherapy will be useful only when precursors are supplied by plasma cells like AL amyloidosis.

CONCLUSIONS

We report a primary systemic amyloidosis with an early age presentation.

Author Contributions

Arghya Chattopadhyay – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content , Final approval of the version to be published

Shatarupa Dutta – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Amitava Majumdar – Substantial contributions to conception and design, Drafting the article, revising it critically for important intellectual content , Final approval of the version to be published

Jayanta Das – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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