Primary Systemic Amyloidosis


Abstract
We report here a case of a 35-year-old male who presented with multi-system disease, which on evaluation was found to be due to primary systemic amyloidosis. We present the myriad manifestations of this uncommon disease entity.

Introduction
Due to the prevalence of chronic systemic diseases, particularly chronic infections such as tuberculosis, secondary amyloidosis is not infrequently encountered in our country. On the other hand, primary systemic amyloidosis is relatively uncommon. We present here the case of a young male with primary systemic amyloidosis, with the intention of demonstrating the classical presentation and discussing the investigational approach to this uncommon entity. It is also intended to reiterate to the practicing physician, that primary systemic amyloidosis should always be considered in the differential diagnosis of multi-system disease.

Case Report
A 35-year-old man presented with increasing breathlessness, pedal edema, easy fatigability and weight loss since 4 years. He also had easy bruising on minor skin trauma. There was difficulty in protrusion of the tongue, swallowing and constipation. Macroglossia precluded carcinoma of the tongue, but FNAC for malignancy was negative. There was no history of alcohol or tobacco intake, parasthesias, light-headedness, sweating abnormalities or impotence.

On examination we had a young man, with a pulse 90/min and BP 100/80 mm Hg. There was mild pallor, minimal pedal edema and an elevated jugular venous pressure. There was no evidence of pericardial tamponade. The patient had a peculiar pattern of peri-orbital ecchymoses (Fig. 1) and multiple erythematous skin papules with a purpuric rash over the anterior chest wall (Fig. 2). The examination also revealed alopecia and macroglossia with tooth indentations (Fig. 3). The nails were brittle and had longitudinal fissures (Fig. 4). On cardiovascular system examination, there was evidence of cardiomegaly and a gallop rhythm. Auscultation over the lung fields revealed bilateral fine basal crackles. Per abdomen examination revealed mild non-tender hepatomegaly. Neurological examination was unremarkable.

On investigations, he had an Hb of 12.5 gm%; WBC count was 5500/cmm with 37% lymphocytes, reticulocyte count was 1.5%. Urine examination was normal; with a 24-hour urine examination negative for albumin and urinary Bence Jones proteins were absent. Liver and kidney function tests were normal. ECG showed low voltages and the echocardiography revealed gross concentric left ventricular hypertrophy with pericardial effusion.

Serum protein electrophoresis showed total proteins of 5.4gm% (normal 6.6-8.3gm%), albumin 3.1gm% (normal 3.5-5gm%) and globulin 2.3 (normal 1.3-3.2gm%). On electrophoresis alpha 1 globulin was 0.3gm%, alpha 2 globulin was 1.0gm%, beta globulin 0.5gm% and gamma globulin was 0.5gm%. Bone marrow aspirate revealed erythroid hyperplasia with plasmacytosis. Serum ANA and double stranded DNA were negative.

The clinical profile favored a disease with multi-system involvement, with predominant affection of the skin and heart. A subcutaneous abdominal fat biopsy was done. The slides appeared normal on routine staining, but polarizing microscopy of Congo Red stained slides showed an apple-green birefringence, suggestive of amyloidosis. The bone marrow biopsy slide was retrieved and was sent for immunohistochemical staining for kappa and lambda light chains. The test was reported positive for lambda light chains both in the plasma cells as well as extra-cellularly, confirming the diagnosis of primary (AL) systemic amyloidosis. There was obvious involvement of the skin and the heart. The non-tender hepatomegaly suggested liver involvement. However, since a liver biopsy would not have contributed further to the diagnosis, it was deferred.

Thus with the diagnosis of primary systemic amyloidosis, the patient was put on Melphalan 0.15 mg/kg/day in two divided doses and Prednisolone 0.8 mg/kg/day in 4 divided doses for seven days and the cycle repeated after 6 weeks.
He showed remarkable improvement with substantial reduction of exercise intolerance, and is still under treatment.

**DISCUSSION**

Amyloidosis is a heterogeneous group of diseases associated with the common pathological process of extracellular protein deposition in various organs, leading to organ dysfunction and death. In 1838, Mathias Schleiden, a German botanist, coined the term ‘amyloid’ for the amylaceous constituents of plants. In 1854, Rudolf Virchow, adopted the term to describe abnormal extra-cellular material that he encountered in the liver during autopsy. Virchow described its reaction with iodine and sulfuric acid, which, at the time, was a marker for starch; thus, the term amyloid or starch-like is used. Divry and associates recognized that the amyloid deposits showed apple-green birefringence when specimens stained with Congo red were viewed under polarized light. This observation remains the *sine qua non* of the diagnosis of amyloidosis.

Many different types of proteins are known to form amyloid and cause a heterogeneous array of clinical conditions. The unifying aspect of this condition is the common structural entity resulting from the assembly of primary beta structure protein units, 5-10 nm wide, forming non-branching insoluble fibrils. Several factors contribute to amyloid assembly. Any mutation that sufficiently decreases protein stability, favors the formation of a partially folded state under physiological conditions. This condition exposes other key sequence elements that decrease solubility, promote aggregation and ultimately promote amyloid formation.

Systemic amyloidosis has been classified into three-primary (AL), familial (ATTR, AApO-A-I and others) and secondary (AA). Primary AL amyloidosis is associated with deposition of immunoglobulin light chains (kappa, lambda) in the extra-cellular tissue (hence the name AL). It is usually found in association with multiple myeloma (20%) or with plasma cell dyscrasias (80%). Clinical manifestations are diverse, and at presentation, there is usually involvement of multiple organ systems, the kidney and heart being most commonly involved. Physical examination may reveal a palpable liver and spleen, peripheral edema, orthostatic hypotension, ecchymosis and purpura. Vascular infiltrates result in easy bruising, which is typically seen around the
eyes, as seen in our patient, producing the “raccoon-eyed” appearance, classical of amyloidosis. There may be evidence of alopecia and nails show dystrophic changes. Macroglossia is another classical feature, seen in 20% of patients. The tongue is usually enlarged and stiff, and is frequently rimmed by indentations of the teeth. Although the central nervous system is almost always spared, there is frequent involvement of the peripheral and autonomic nervous system, with a predominantly sensory painful neuropathy commonly seen. Cardiac involvement causes symptoms related to congestive heart failure; with echocardiography showing concentric left ventricular hypertrophy. In contrast ATTR amyloidosis is usually associated with conduction abnormalities of the heart.3

The close association of AL amyloidosis with plasma cell dyscrasias has lead to the use of similar regimes, as used for multiple myeloma. In a trial of three regimen, Kyle et al4 found that objective response and survival benefits were best with a combination of Melphalan and Prednisolone, as compared to Colchicine alone, and Colchicine with Prednisolone. A treatment protocol consisting of 0.15mg/kg/day of Melphalan in two divided doses for 7 days with Prednisolone 0.8mg/kg/day in four divided doses for 7 days has been recommended. Symptomatic therapy aimed at heart failure, renal and other organ system dysfunction must be continued.

The prognosis in patients with primary systemic amyloidosis remains poor, particularly if left untreated. Overall survival at the time of diagnosis is 1-2 years. In a study conducted by Patel et al5, in 25 patients of AL amyloidosis, it was found that right ventricular dilatation, was associated with a mean survival of only 4 months. Survival is grave when there is multi-system involvement.

Our patient had multi-system involvement. However he has survived through six cycles of Melphalan/Prednisolone has not shown overt deterioration since the time of institution of therapy and is alive and well 10 months from the time of diagnosis.

Acknowledgements

We duly acknowledge Dr A K Deshpande, Professor and Head, Department of Medicine and Dr. G B Daver, The Dean, Grant Medical College and Sir JJ Group of Hospitals, for permitting us to publish this case report.

References