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Primary Systemic Amyloidosis and the Dermatologist

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Abstract

Primary systemic amyloidosis is a rare disorder characterized by multi-systemic homogenous hyaline amyloid material. We report a case of 68 years old male presented with generalized weakness, fatigue, anorexia and impaired taste sensation. Muco-cutaneous lesions like, macroglossia with bullous haemorrhagic lesions, peri-orbital purpura, and nail changes were present. He had no cardiomegaly, hepatomegaly, splenomegaly or renal involvement. His skiagram chest showed minimal left sided pleural effusion which had no pus cells despite high protein content. The diagnosis was established on the basis of classical cutaneous lesions. Diagnosis was confirmed by tongue biopsy using Haematoxylin and Eosin staining and crystal violet staining. Polarized microscopy was not done because of unavailability. We report this case because of the sheer rare presentation and diagnosis is considered in dermatologist's differentials. This case report suggests that skin lesions may provide a clue for an early diagnosis of systemic amyloidosis, which lengthens the survival period of the patient.

Introduction

Primary systemic amyloidosis is a plasma cell dyscrasia of unknown cause. The systemic form is sub-classified as primary, secondary, familial and amyloidosis associated with multiple myeloma [1]. The accepted nomenclature is AX, where A represents amyloidosis and X indicates type of protein in the fibrils, AL is for light chains, AA for secondary amyloidosis (in

chronic infectious and inflammatory diseases) while AF indicates familial amyloidosis. Systemic amyloidosis affects both sexes with male preponderance; onset usually begins in the sixth decade. The kidneys are most frequently affected organ (80%), followed by the heart (40%). Carpel tunnel syndrome is present in 25% of cases, sensory neuropathy (18%), postural hypotension (16%) are the other common manifestations. Specific mucocutaneous lesions occur in 29% to 40% of cases which gives an early indication of the existence of an underlying plasma cell dyscrasia [2,3]. No satisfactory treatment for systemic amyloidosis has been discovered. In this article, we report this case because of rare presentation, without plasma cell dyscrasia and no renal, cardiac or hepatic involvement. Presence of macroglossia and typical mucocutaneous lesions help the dermatologist to reach the diagnosis at an early stage and when the initiation of therapy starts before the onset of organ failure, survival may be prolonged.

Case Report

A 68 year old male presented in medical outpatients department of Era's Lucknow medical college hospital with complaints of anorexia, generalized weakness, impaired taste sensation and progressive weight loss of approximately 10 kg in the last year. There was no other systemic complaint or history of any other chronic illness in the past. Family history was insignificant. On examination he had normal vital parameters and blood pressure was 140/70 mmHg with no postural hypotension. There was mild pallor and pedal oedema. The systemic examination did not reveal any abnormality. In view of presence of peri-orbital pigmentation and lesions present in oral cavity he was referred to seek dermatologist consultation. On dermatological examination peri-orbital pigmentation was found to be purpuric lesion around the eyelids (**fig. 1**). Ecchymotic lesions were also present over the lips, and on buccal mucosa (**fig. 2**). There was ecchymoses at the site of venipuncture. The tongue was diffusely enlarged, firm, fissured and haemorrhagic bulla was present on the surface. Teeth indentation marks were present around its lateral border. Multiple shiny smooth, firm yellowish papules up to 0.5cm in size were present on the retro-auricular area and over eyelids. Nail changes were present, longitudinal striations, crumbling, brittleness, ragged cuticle and partial onycholysis were present (**fig. 3**).



Fig 1

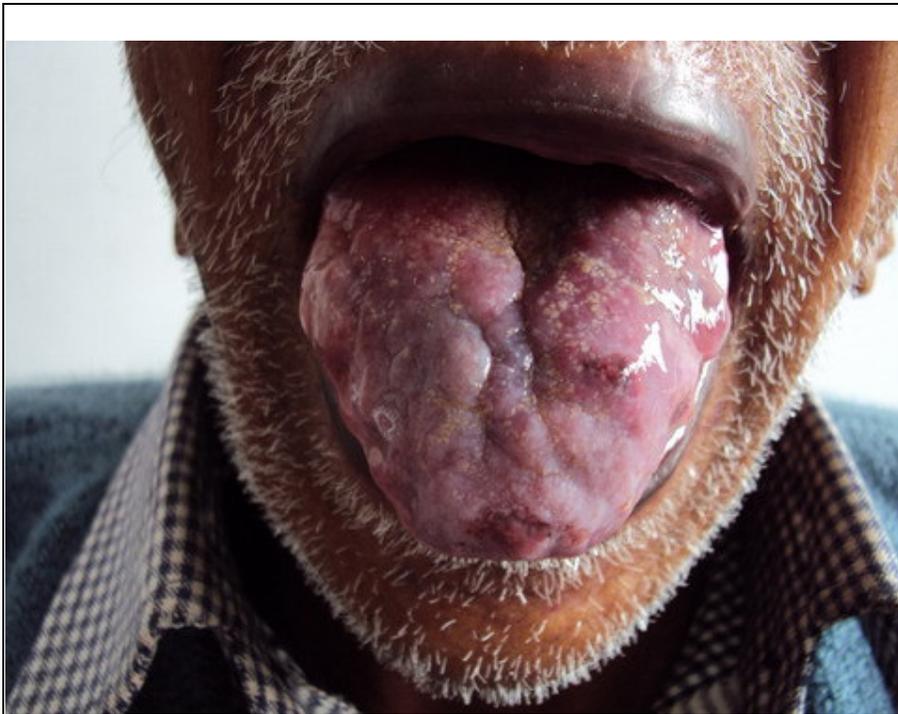


Fig 2

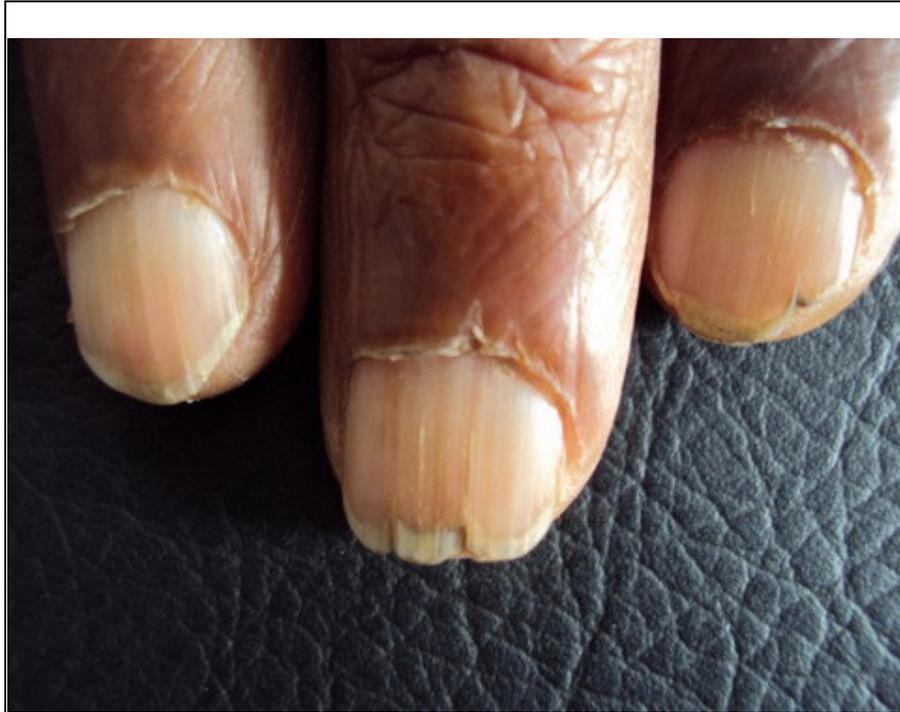
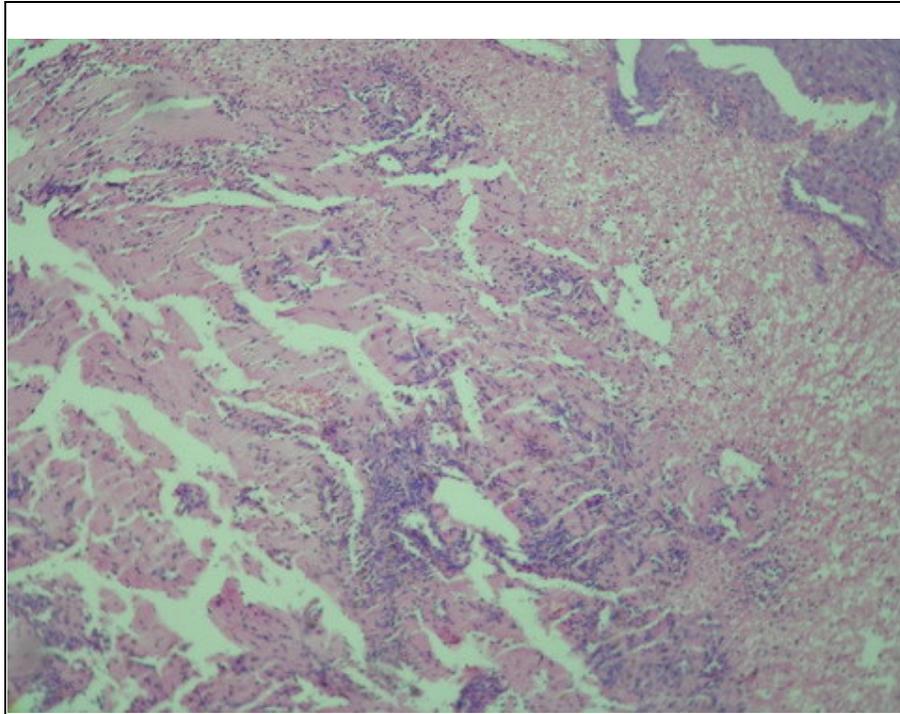


Fig 3

On investigations, Hb was 8gm%, ESR was 56 mm at first hour. Urine showed albumin1+ with no Bence Jones proteins. Serum and urine electrophoresis was normal. All other hematological and biochemical reports including coagulation profile were normal. The x-ray chest showed minimal pleural effusion on left side which when aspirated showed protein content 3.5gm/dl with no pus cells and was sterile on culture. RA factor, ANA and anti ds DNA were negative. Bone marrow examination was also normal. ECG and 2D Echo were normal. Abdominal ultrasound did not reveal any abnormality. No pathology was demonstrated in bone survey.

The histopathological examination of the biopsy taken from the lesion on the tongue revealed homogenous eosinophilic amorphous material and infiltration with lymphocytes seen on haematoxylin and eosin staining (**fig. 4**) and revealed metachromatic staining on crystal violet. Polarized microscopy was not done because of unavailability.

**Fig 4**

Discussion

Amyloidoses are protein conformation disorders, in which different soluble proteins aggregate as extracellular insoluble fibrils. In immunoglobulin light chain amyloidosis (AL), monoclonal light chains undergo conformational changes leading to their aggregation into amyloid fibrils that can deposit in virtually every organ, with the exception of parenchymal brain tissue [4]. This process causes organ dysfunction and, if it is not halted by therapy, it leads to patient's death. Median survival of primary systemic amyloidosis without myeloma is up to 14.7 months. Unusual longevity for 19 years have been reported with combined melphalan, prednisolone and colchicine treatment and is the longest reported in literature [5]. Non specific presentation delays 1-2 years in reaching the diagnosis.

In our case, the presenting symptoms are fatigue, weight loss, breathlessness, reduced taste perception and mucocutaneous presentations. Impaired taste perception is a frequently unnoticed sensory impairment in primary systemic amyloidosis [6].

Clinically evident mucocutaneous involvement in primary systemic amyloidosis is an early pointer. Oral manifestations have been reported in 39% of patients with amyloidosis [7]. Amyloidosis deposition in the tongue of multiple myeloma occurs frequently and can result in macroglossia, which is the most common oral finding [7,8,9]. An enlarged tongue resulting in apertognathia and tooth indentations along the lateral border can be the first clinical sign of amyloidosis [10,11,12].

In our case, tongue of the patient is enlarged, firm, fissured and hemorrhagic bulla were present on its surface. Teeth indentations were present along the lateral border of tongue.

Amyloid infiltration of vessel wall causes capillary fragility, which bleeds on minor trauma or even spontaneously. Purpura, ecchymoses and petechiae occur commonly in the skin and mucous membranes due to intracutaneous haemorrhage. In our case, peri-orbital purpura and ecchymotic lesions were present on lips and on buccal mucosa. Ecchymoses was present at the site of veni-puncture. Purpuric lesions with normal platelet count and normal coagulation profile should suggest the possibility of capillary fragility. Senile purpura which also comes in differentials, is also due to capillary fragility but is commonly seen on extremities and rarely involve the peri-orbital and over the lips and buccal mucosa.

Nail dystrophy is not unusual in systemic amyloidosis. In our case longitudinal ridging, ragged cuticles and splitting of nails was present. There are reported instances of nail dystrophy seeing the only feature at presentation [13,14].

Biopsy is the definitive investigation for amyloidosis. Fine-needle fat-pad biopsy and rectal biopsy have both been hailed as the investigation of choice, each giving positive results in 80-90 percent of cases [15,16,17]. Haematoxylin and eosin staining suggests the possibility of amyloidosis but Congo red staining confirms the diagnosis. Skin biopsy characteristically shows diffuse amyloid deposition in the form of nodules and plaques. There may be amyloid infiltration of blood-vessel walls, around individual fat cells, and in pilo-sebaceous units.

The clinical diagnosis was confirmed by tongue biopsy on H & E stain, the specimen revealed homogenous eosinophilic aggregates and infiltration with lymphocytes and metachromatic stain with crystal violet.

The prognosis for AL amyloidosis is poor, with death usually resulting from cardiac or renal failure. The mean survival from diagnosis is approximately 15 months [7]. Treatment is aimed at decreasing amyloid production and deposition and promoting lysis of deposits. Current treatment options include oral melphalan with or without prednisone, as well as stem-cell harvest and transfer, with intravenous melphalan or other chemotherapeutic agents. Supportive measures include symptomatic treatment for organ impairment, such as diuretics for cardiac impairment, or hemodialysis in the case of renal failure. Stem-cell harvest and transfer, after the use of either melphalan or other chemotherapeutic agents, has also been shown to improve survival. [18]

The case of systemic amyloidosis is presented because of its rare occurrence and in this case no other organ was involved and only mucocutaneous findings help in reaching the diagnosis which was confirmed by tongue biopsy. Clinically evident mucocutaneous involvement in primary systemic amyloidosis is an early pointer and this condition is considered in

the dermatologist's differential. So, early diagnosis and initiation of therapy before the onset of organ failure is essential to lengthen the survival period.

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