PRIMARY SYSTEMIC AMYLOIDOSIS

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A 45-year-old male had nephrotic syndrome of 2 years duration and multiple, asymptomatic, small, yellowish papules on eyelids, nasolabial folds and perioral region since 6 months. He also had progressive weakness, fatigue, breathlessness and joint pains. His voice was hoarse. Macroglossia and beaded vocal cords were present. There was a history of exsanguinating bleeding following a kidney biopsy done 6 months earlier. Proteinuria was present, but Bence-Jones proteins were absent. Skin biopsy of lesional skin showed an eosinophilic, amorphous, fissured mass distending the dermal papillae and around blood vessels and appendages. Congo red stain was negative for amyloid, but crystal violet stain demonstrated amyloid in lesional as well as normal appearing skin. Electron microscopy confirmed the same. The patient deteriorated quickly and succumbed to gross haematemesis.

Key Word : Amyloidosis

Introduction

Primary systemic amyloidosis is a rare disorder characterized by the multisystemic deposition of a homogeneous, hyaline amyloid material. Wilks, in 1856, was the first to lucidly describe primary systemic amyloidosis.[1] Primary systemic amyloidosis represents a plasma cell dyscrasia[2] and may be associated with multiple myeloma. Amyloid filaments have as their major protein component either an intact L chain or the amino - terminal fragment of an L chain or both.[1]

Case Report

A 45-year-old male presented with multiple small, asymptomatic periorificial facial lesions and a low, husky quality of voice of 6 months duration. Two years earlier the patient had been diagnosed as having nephrotic syndrome for which he had been on steroids on and off, without much amelioration of his condition. Six months earlier, the patient had an episode of exsanguinating retroperitoneal bleeding following kidney biopsy and necessitating transfusion of 40 units of blood. In spite of 2 exploratory laparotomies the cause of bleeding was inexplicable at that time as no bleeders were found and the patient's coagulation profile was normal. The patient gave a history of steadily increasing weakness, fatigue, breathlessness and joint pains involving mainly the small joints of both the hands since 6 months. There were no other systemic complaints or history of any chronic illness in the past.

On examination the vital parameters were normal and blood pressure 150/80 mm of Hg. Pallor and oedema feet were present. Multiple shiny, smooth, firm, skin to yellowish papules upto 0.5 cm in size were present on the eyelids, lips, nasolabial folds and periorally (Fig. 1).

A few lesions coalesced to form plaques and some were pedunculated. There was no purpura elicited with trauma. However, ecchymoses were

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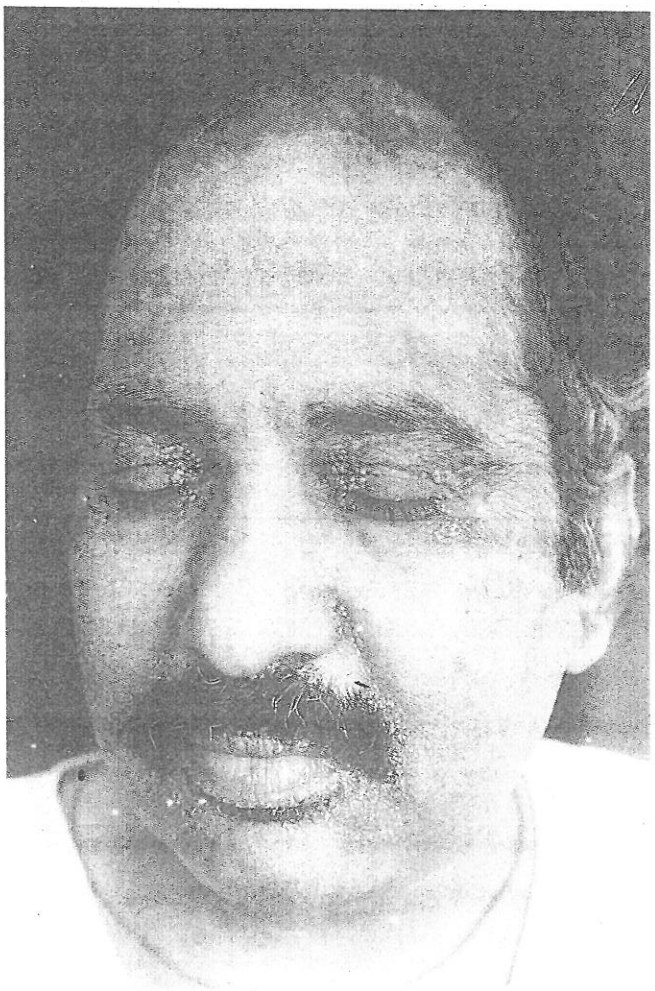

Fig. 1. Waxy papules seen around eyes, mouth and in nasolabial grooves

present over sites of venepuncture. Sclerodactyly of fingers was present. The tongue was enlarged, smooth, indented by teeth and red waxy papules studded its surface (Fig. 2). Indirect laryngoscopy

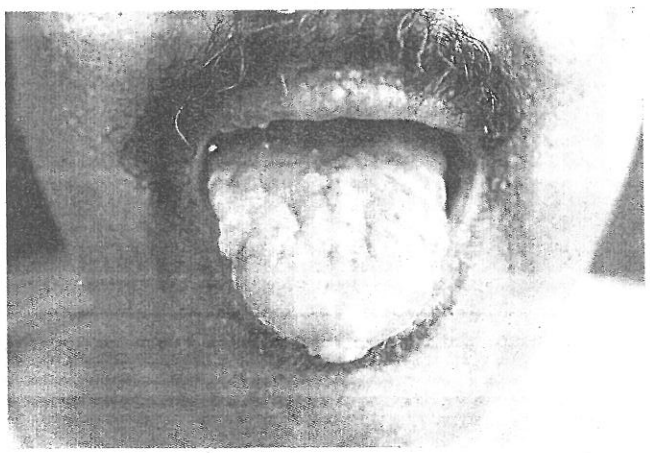

Fig. 2. Papules on the lips and studding the surface of the enlarged tongue

revealed similiar lesions on the voc cords, giving them a beaded appearenc There was free fluid found per abdome Liver and spleen were not palpable a other systems were normal. presumptive diagnosis of primary system amyloidosis was entertained.

The patient's haemoglobin was lo Urine showed 3+ albumin and casts Bence-Jones proteins were absent. Seru protein and lipoprotein electrophores were normal. Stool showed the presenc of occult blood in 3 consecutive sample RA test, ANF and anti ds DNA wer negative. ECG showed sinus tachycardia Abdominal ultrasound showed n enlargement of kidney, liver or spleen Kidney biopsy (done 6 months earlier had shown a minimal lesion glomerulopathy with negativ immunofluorescence and negativ staining for amyloid. Skin biopsy take from lesional skin showed the presence o an eosinophilic, amorphous, fissure mass distending the dermal papilla (Fig 3). Similiar material was also note

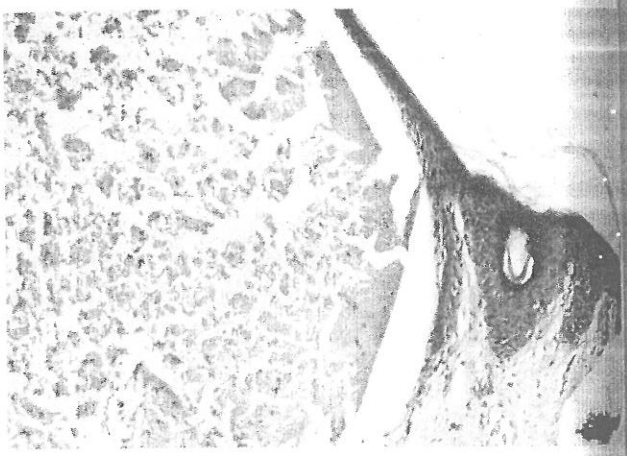

Fig. 3. Amorphous, eosinophilic amyloid material distending a dermal papilla (H & Ex100)

around blood vessels and appendage from lesional skin as well as from a biops taken from apparentely normal skin o

forearm. This material was weakly PAS positive, but staining with congo red failed to show apple-green birefringence on repeated sections. However a crystal violet stain showed a positive eosinophilic staining of the amyloid. Electron microscopy showed the presence of straight, non-branching, non-anastomosing, often irregularly arranged filaments, suggestive of amyloid filaments (Fig. 4).

Fig. 4. Straight, non-branching disorderly arranged amyloid filaments (electron microscopy x 60,000)

The patient was on treatment for nephrotic syndorme with salt restricted diet, diuretics, prednisolone and azathioprine. While his investigations were on, his condition steadily deteriorated. He developed severe muscle weakness, giddiness and later haematemesis to which he succumbed.

Comments

With the clinical presentation of classical mucocutaneous lesions, nephrotic syndrome and post renal biopsy bleeding, a diagnosis of primary systemic amyloidosis was entertained. Bleeding or haematuria following renal biopsy has been known to occur more frequently in patients with amyloidosis as compared to patients without amyloidosis. Widespread loss of vascular integrity because of infiltration with amyloid along with other factors like deficiency of vitamin K, factor X, increased antithrombin activity and increased fibrinolysis, all contribute to the bleeding.[1]

Involvement of the kidneys is extremely common in patients with amyloidosis. Amyloid is first deposited in the mesangium of the glomerulus and later extends along the basement membrane. The degree of proteinuria in the nephrotic syndrome does not correlate well with the extent of amyloid deposition in the kidneys.[3] This may explain why amyloid was not demonstrated on a kidney biopsy done 6 months earlier, even though the patient had gross proteinuria.

Hoarseness or change of voice to a weak, high-pitched or deep husky sound often alerts the physician to the possibility of amyloidosis. Macroglossia can be extremely impressive, however it can be sometimes difficult to decide whether the tongue is enlarged or not. Increased firmness of the tongue, enlargment of the sub-mandibular structures and dental indentations are helpful in determining the presence of macroglossia.

The straightforward confirmation of the evident clinical diagnosis by histopathology proved difficult as repeated congo red stains failed to show the classical green birefringence. The negative congo red test could have been

due to technical errors, too thin sections or excess formalin fixation which is known to alter the staining properties of amyloid. For a better positivity yield, staining of frozen.fixed material, rectal and subcutaneous fat biopsy and a battery of different stains are recommended.[4] Crystal violet, a metachromatic stain and electron microscopy which is the most specific diagnostic method, helped in establishing the diagnosis in this patient.

Kyle and Greipp have seen several cases in whom the results of staining of tissue with congo red or the metachromatic stains were negative, yet electron microscopy revealed the typical amyloid fibrils. A third class of stains, the cotton dyes, Pagoda Red, RIT Scarlet No. 5 and RIT Cardinal Red No. 9 which are simple, bright, long lasting and specific for amyloid, can also be used.[5]

This patient survived for 2 years following onset of symptoms. The median survival of patients with nephrotic syndrome has been reported to be around 17 months. Melphalan has been used with occasional success in some patients with nephrotic syndrome. Other drugs like prednisolone, colchicine and DMSO have been tried. The unsatisfactory nature of the available treatment modalities is reflected in the poor prognosis of patients.

Acknowledgement

We express our thanks to Dr Vana Shetty of Foundation for Medical Research, Worli, Bombay-400 018 for electron microscopic studies.

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