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SYSTEMIC AMYLOIDOSIS PRESENTED WITH PERSISTENT COUGH : A CASE REPORT AND REVIEW OF LITERATURE

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Summary

A 64-year-old male presented with persistent cough, anorexia and profound weight loss over 6 months which was unresponsive to all antibiotics, cough suppressant and even steroid. Ultrasound detected diffuse mesenteric and omental infiltration, histologically diagnosis was consistent with amyloidosis and finally confirmed by congo stain. There was no kidney involvement. Although cough improved with treatment, he died of persistent hypoalbuminaemia and hypotension which was non responsive to treatment.

Key words: systemic amyloidosis; immunoglobulin light chain-derived amyloidosis (AL); respiratory amyloidosis; coughs

Introduction

Amyloidosis is a group of acquired and hereditary disorders characterized by the extracellular deposition of insoluble proteins. Descriptive terms such as primary amyloidosis, secondary amyloidosis, and others (eg, senile amyloidosis), are no longer recommended[1]. About twenty-three different fibril proteins are described in human amyloidosis with variable clinical features. Chemical classification of amyloid is the current standard. Systemic amyloidosis is classified into four major forms: immunoglobulin light chain-derived (AL), reactive (AA), dialysis-related (beta2M) and hereditary transthyretin (ATTR) type[2,3]. Although it is usually seen in a systemic form10-20% of cases can be localized. In both systemic and localized forms of the disease, respiratory tract can be involved [4]. Localized respiratory tract amyloidosis mostly affects the trachea and the bronchi. Chest X-rays are not sensitive to detect these lesions. Systemic amyloidosis often involves lung parenchyma and the pleura. Open lung biopsy or pleural biopsy should be performed for the diagnosis.

The symptoms and signs of primary amyloidosis are due to amyloid infiltration and subsequent malfunction of the infiltrated organ (e.g. nephritic syndrome and renal failure, cardiomyopathy and cardiac conduction defects, Alzheimer's disease, intestinal malabsorption and pseudo-obstruction, carpal tunnel syndrome, macroglossia, peripheral neuropathy, end organ insufficiency of endocrine glands respiratory failure, capillary damage with echymosis) [5].

The primary diagnosis of amyloidosis is based on clinical suspicion with corroboration provided by detection of a monoclonal gammopathy on serum protein electrophoresis and microscopic examination of abdominal fat pad aspirates. In systemic disease, rectal or gingival biopsies show a sensitivity of about 80%, bone marrow biopsy about 50%, and abdominal fat aspiration between 70-80%. The latter is a simple and reliable method for diagnosing systemic amyloidosis [6,7].

The final diagnosis of amyloidosis rests on demonstrating Congo red-positive deposits on any of affected organs. Immunohistochemical analysis of amyloid protein on tissue deposits is necessary to make classification of the disease and DNA testing is also useful in a hereditary form [8]. We report a case of systemic amyloidosis (AL) presented with persistent cough and profound weight loss.

Case record

A 64-year-old Bangladeshi businessman presented with persistent dry cough for one year associated with anorexia, weight loss (6 kg) and intermittent vomiting over 6 months in August 2006. He was non diabetic but known hypertensive, there was no history of fever, chest pain, haemoptysis, wheezing, tuberculosis or exposure to it, bronchial asthma or symptoms related to bowel and bladder. There was no risk factor for human immunodeficiency virus (HIV) infection. Meanwhile he was tried with

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almost all sorts of antibiotics, bronchodilators and cough suppressants empirically without any help. He was a past smoker. His past medical and drug history was unremarkable.

Physical examination revealed that the temperature was 37.2°C, the pulse 80/min, respirations 18/min and blood pressure 105/70 mm Hg. He was cachectic. No significant finding like peripheral edema, digital clubbing, cyanosis, lympadenopathy, visceromegaly, skin lesion, chest abnormality or cardiac murmur was detected.

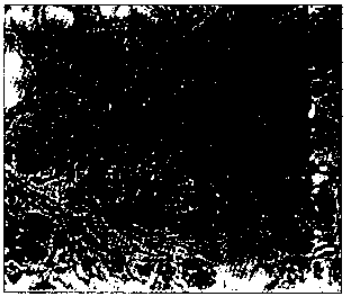

Fig 1 : Microscopic examination of omental tissue

Laboratory investigations revealed that Hb% -14.50 gm /dl ESR100 mm in 1st hour, blood count and blood glucose were normal. Renal functions, Liver enzymes, Serum electrolytes, calcium including phosphate were normal. S, albumin was, 3.30 gm/dl. Chest X-ray showed mild cardiomegaly and clear lung fields. Tuberculin test was negative. CT scan of chest, bronchoscopy, lung/pleural biopsy was not done in this patient. HBsAg, anti HCV, HIV and VDRL were non reactive .USG of abdomen reported as diffuse mesenteric and omental infiltration; with minimal ascites. Echo cardiography showed mild concentric left ventricular hypertrophy, enlarged left atrium and aortic root, aortic regurgitation, (grade 1) mitral regurgitation (grade 1), trivial TR and no evidence of pulmonary hypertension. Endoscopy of upper and lower GIT including hepatobiliary scintigraphy was normal.

FNAC from omental fat reported that smear showed mainly locules of mature adipocytes with spindle cells, degenerated cells, lymphocytes, reactive mesothelial cells and histiocytes. Neither granuloma nor any cytological evidence of malignancy was seen. Laparotomy was done, biopsy of omental tissue and omental lymph node showed dense extra cellular deposition of eosinophilic hyaline material which was present around blood vessels, interlobar septae and around lobules of fat. The lymph nodal architecture was completely replaced by eosinophilic materials. Congo stain showed a strong apple green birefringens. Diagnosis was consistent with Amyloidoma. (Fig-1)

Urinary Bence jones protein was absent. Bone marrow showed mild hypercellularity, moderate megaloblastic changes but no plasma cells excess (07%). Urine electrophoresis showed no monoclonal light chain or protein. Serum protein electrophoresis showed presence of M band in gamma globulin region (albumin -3.07 gm/ l alpha1-o.21 alpha2 o.65 beta o.77 gamma + M protein 2.80 gm /dl). (Fig-2).

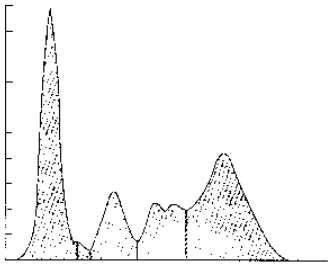

Fig 2 : Serum protein Electrophoresis report

Final diagnosis of systemic amyloidosis immunoglobulin light chain derived (AL) was made.

He was treated with 4 cycles of chemotherapy [Melphalan (12 mg /day, day 1-4) and prednisolone (80 mg /day, day 1-4] (pulse therapy to repeat every 4 weeks). His cough disappeared and weight improved. In mid November 2006 his clinical and blood profiles was reevaluated and found normal except ESR 100 mm in 1st hour.

In August 2007, he experienced, abdominal discomfort, leg swelling in spite of taking the drugs. Investigations were repeated including tumor markers. His CT of whole abdomen revealed amyloid involvement of the omentum, mesentery, peritoneum, bilateral perinephric spaces, gall bladder and urinary bladder wall, massive ascites, minimal pericardial and pleural effusion. After having no clinical response and no change in serum free light chain, treatment regimen was changed to thalidomide 200-300 mg/day and prednisolone 60 mg/day. Initially his ascites disappeared and wellbeing improved; in the following months he experienced frequent episodes of diarrhea, severe anorexia and persistent hypotension (70/40 mm of Hg) and hypoalbuminaemia. At one stage his hypotension could not be reversed and he expired in August 2008.

Discussion

The diagnostic criterion of systemic amyloidosis immunoglobulin light chain (AL) is met in this case. In normal adults, immunoglobulin with kappa light chains outnumbers those with lambda light chains i,e, kappa:lambda is 2:1. In amyloidosis the ratio of kappa:lambda light chains is 1:3 [9]. Because AL is a plasma cell dyscrasia, it is not surprising that some patients with AL have overt associated multiple myeloma where the light chain-secreting plasma cells are a part of a frankly malignant clone[10]. If multiple myeloma is not present at the diagnosis of AL, it is unlikely to develop[11]. Excess lambda light chain in serum electrophoresis with absent plasma cell excess in bone marow was observed in our patient.

The median age of patients with AL seen at the Mayo Clinic was 62 years. And only 1% was younger than age 40 years[12]. Two-thirds of the patients with AL are men, our patient was a male and age of above 60 years. In a report from Mayo Clinic[12] all patients (n-13) diagnosed with amyloidosis and malabsorption syndrome who had been seen from 1960 through 1998, the most common sign was weight loss with a median loss of 30 pounds (range, 2 to 134 pounds) and hypotension or orthostatic changes. The median time from symptom onset to diagnosis was 7 months. Weight loss was one of the key sign and malabsorption was a late symptom in our patient. Almost one year time elapsed for confirmation of diagnosis.

Cough in this patient might be due to amyloidosis with pulmonary involvement. CT scan of chest could be helpful in evaluation. Patchy shadows, nodules, pleural effusion, pleural thickening and intrathoracic adenopathy are often seen on CT scan. Bronchoscopic findings of tracheobronchial amyloidosis are narrowing of airway lumen, noduler, 'tumor like' or 'bubble like' masses, with missing or vague cartilaginous rings. Open lung biopsy or pleural biopsy should have been performed for the diagnosis [4].

Hypoalbuminaemia and hypotension is a very vexing feature in AL which is multifactorial-cytokine effect, cardiac failure malabsorption[12]. We also observed both of these clinical symptoms and biochemical change. On physical examination, purpura, hepatomegaly, splenomegaly, lymphadenopathy, and macroglossia were seen in 15%, 24%, 5%, 3%, and 9%, respectively. These physical findings were generally nonspecific and did not consistently raise suspicion of amyloidosis[3]. We did not noticed any one of those sign in our patient. In AL, the most frequently affected organ is the kidney. Dysfunction of the kidney is the presenting problem in one-third to one-half of patients with amyloidosis[13]. If amyloid does not involve the kidney at presentation, it is rare for it to occur during the follow-up period; only 2% of patients with amyloid develop renal involvement after presentation.11 In amyloidosis liver may not be enlarged. We also observed these facts. In patients of amyloidosis with cardiac involvement, the reduced stroke volume due to diastolic dysfunction produces systolic hypotension[14, 15]. Hypotension may also occur as a consequence of autonomic failure. The cause of death in most patients with amyloidosis is cardiac, either progressive cardiomyopathy with heart failure or sudden death due to ventricular arrhythmia[16]. Our patient also died of cardiac dysfunction and malabsorption. The aim of management is to support the function of affected organs and to prevent further amyloid deposition through treatment of primary cause[4]. Prognosis depends on the causative condition and the extent of kidney involvement. These patients never die of liver failure. One study reported that the median survival of primary amyloidosis is 13 months. Only 7% survived for 5 years or more, only1% were alive at 10 years[17]. Our patient also died within 30 months from the onset of symptoms.

Conclusion

Systemic amyloidosis is a multi-system disease, involving renal, cardiovascular, gastrointestinal, respiratory & nervous system and nervous systems. The symptoms and signs are due to amyloid infiltration. The constellation of anorexia, weight loss, persistent cough even with clear chest X-ray, multi valvular cardiac abnormality and absence of coronary disease in elderly should raise the suspicion of systemic amyloidosis though a rare clinical entity. The diagnosis of amyloidosis is based on clinical suspision but the final diagnosis rests on demonstrating Congo red-positive deposits on any of affected organs. The cause of death in most patients is cardiac dysfunction. Amyloidosis had been considered to be an incurable disease but during the past one decade several therapeutic approaches have been employed with diverse pathogenetic backgrounds: intravenous large dose of melphalan

accompanied by autologous peripheral blood stem cell transplantation for AL amyloidosis, high dose of thalidomide and steroid for seconday amyloidosis and liver transplantation for hereditary ATTR type amyloidosis.

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