



Case report

Primary systemic amyloidosis: A rare cause for pleural effusion



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A B S T R A C T

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Pleural effusion is a common problem dealt by most of the practicing clinicians. Some causes for pleural effusion are less often considered as a differential diagnosis owing to its rarity. Here we report a case of renal amyloidosis on alternate day haemodialysis for about two months time presenting with left sided pleural effusion. On evaluation this turned out to be a case of amyloidosis on thoracoscopic pleural biopsy suggesting the possibility of Primary systemic amyloidosis.

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Case report

A forty two year old lady was referred to us from the department of nephrology with dyspnoea and left sided pleuritic chest pain of one week duration. She was managed in the nephrology ward as a case of synpneumonic effusion with antibiotics and other supportive measures. She was an established case of renal amyloidosis and was being worked up as a prospective transplant case. She was detected to have hypertension in the past and also gave history of preeclampsia and frequent foetal loss. She was thoroughly worked up for the evidence of collagen vascular disease which were negative. She had proteinuria, hypothyroidism and hypertension. Her renal biopsy revealed mild mesangial cellularity, Congo red positive eosinophil material in the glomeruli, tubular atrophy, interstitial inflammation and thickened vessel wall and this was reported as consistent with renal amyloidosis.

There was evidence of massive left side pleural effusion with mediastinal shift on digital Chest X-ray Fig. 1. Thoracentesis was done and it initially drained straw coloured fluid which later on turned to hemorrhagic fluid on subsequent aspirations. She did not have oliguria, haematuria. There was history of loss of appetite, exertional dyspnoea and orthopnoea for last two weeks. Two of her maternal uncles had chronic kidney disease, details of which were not known. Her renal functions gradually worsened over a period of eight years and she was diagnosed as stage V Chronic Kidney disease. She was initiated on haemodialysis since last two weeks and an alternate day schedule was planned. Pleural fluids study showed low ADA, exudative effusion with a total count of 300 cells/mm³ with 79% lymphocytes.

The pleural fluid cytology did not reveal any malignant cells. She was subjected to repeated thoracentesis, alternate day haemodialysis and blood transfusions on top of broad spectrum antibiotics. Her Mantoux was non reactive. She was also on weekly doses of erythropoietin, antihypertensives, oral soda bicarbonate, diuretics and iron supplements. She was on thyroxine replacement following thyroidectomy for last fifteen years. Blood investigations during admission showed Hb-8.4 gm%, TC-6000 cells/mm³, DC-P76L24, ESR-90 mm/h. Her renal function values were S.Creatinine-13.1, Urea-155 mg%. Serum Potassium was 4.1 meq/L. Her total protein was 5.9 gm% with albumin 3 gm%. Her serum electrophoresis did not reveal any abnormal paraprotein. Her skeletal survey also was normal.

She had worsening dyspnoea while she was in the nephrology ward and was shifted to our side and was subjected to a thoracoscopy. Under conscious sedation and local anaesthesia, single port Thoracoscopy was performed by the Jacobs's technique. Pleural space was entered after draining around one litre of hemorrhagic fluid under controlled suction. Lung collapsed partially and few adhesions could be seen. Parietal Pleura revealed sheets of yellow granular nodules Fig. 2. Biopsy was taken and haemostasis attained. Histopathology of the nodule showed evidence of Congo red positive abundant amyloid material Fig. 3. Intercostal tube drainage was put. Her CT chest taken prior to Thoracoscopy showed massive pleural effusion on the left with minimal effusion in the right side shown by white bold arrows in Fig. 4.

Her post thoracoscopic chest X-ray PA showed evidence of cardiomegaly and bilateral costophrenic blunting supporting the pre procedural CT evidence of bilateral effusion Fig. 5.

In view of her gross cardiomegaly a cardiology consultation was taken and the echocardiogram done subsequently did not reveal any evidence of pericardial effusion or cardiac amyloidosis. Hence she was managed conservatively with intercostal tube drainage, diuretics, hydrolazine, cilnidipine, weekly erythropoietin, paren

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Fig. 1. Chest X-ray showing left massive effusion.

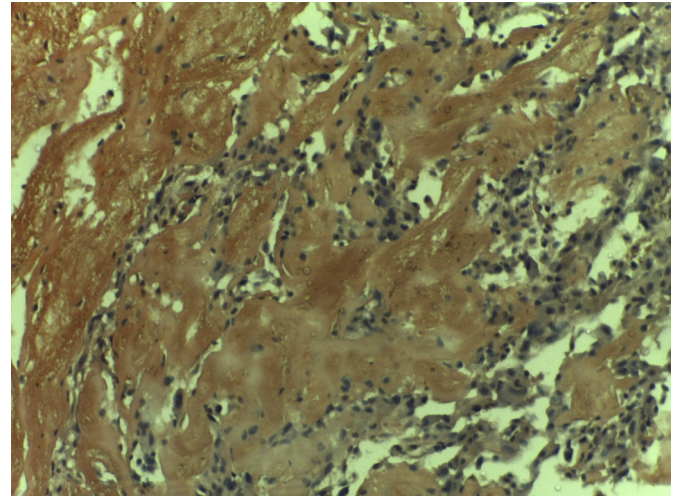


Fig. 3. Congo red staining positive material.

teral iron supplementation, alternate day haemodialysis, and oral sodabarbonate. She continued to have drainage which made pleurodesis not possible and during the course of her stay in the pulmonary medicine unit she started developing more effusion on the right side [Fig. 6](#).

Hence she was presumed to have primary systemic amyloidosis with possibly bilateral pleural deposits on the basis of thoracoscopic biopsy on the left side and renal amyloid diagnosed on renal biopsy. She was transferred back to the parent nephrology unit for a combination therapy of Bortezomib, Lenalidomide and dexamethasone along with hemodialysis. Other agents tried with varying

success in stem cell transplant ineligible primary systemic amyloidosis patients includes antimetabolites like cyclophosphamide, vincristine, adriamycin or proteasome inhibitors and immunomodulatory agents which includes bortezomib, melphalan, colchicine, thalidomide and pomalidomide.

Discussion

Amyloidosis is a rare disorder with a potential for multisystem involvement, characterized by extracellular deposition of different proteins as insoluble beta pleated sheets resulting in disruption of the function of the organ affected. Amyloidosis had been classified over the years based on the site of deposition and presence or absence of other diseases [1]. The term “Generalized” or “Systemic” had been used to describe deposition in multiple anatomic sites and “localized” used to describe deposition in one anatomic site. The term “secondary” used to describe patients with coexistent

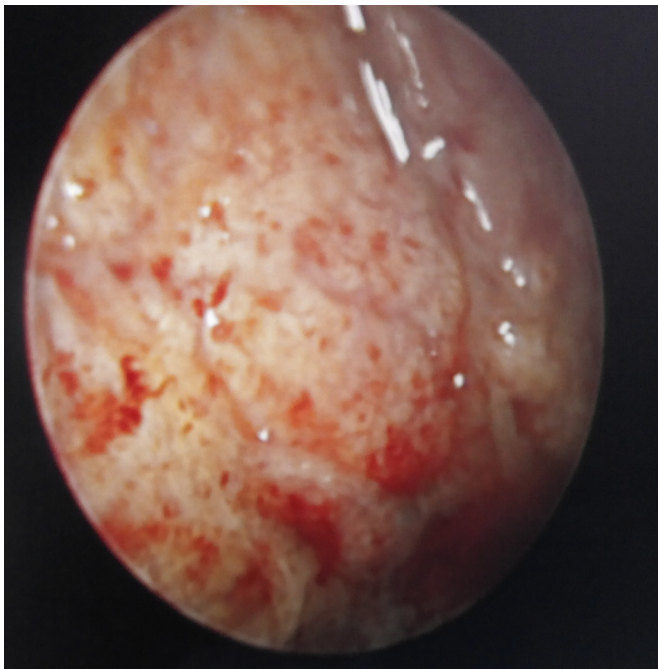


Fig. 2. Thoracoscopic view of amyloid deposits.

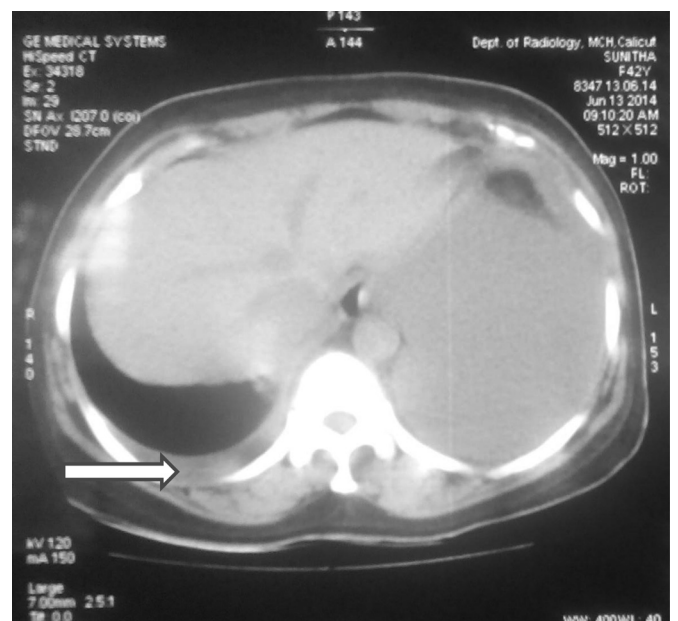


Fig. 4. CT chest showing (L) sided massive effusion and right sided minimal effusion (Bold arrow).

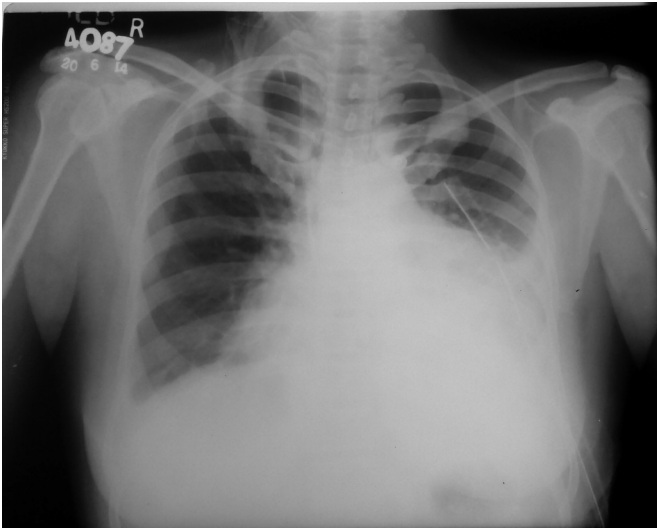


Fig. 5. Post thoracoscopy chest X-ray PA.

disease like multiple myeloma and “primary” for patients with no such coexistent disease [2]. In our patient there was evidence of involvement of two organ systems and there was no evidence of any other co-existent diseases.

The most common cause of the respiratory amyloid disease is secondary to systemic AL Amyloidosis which accounts for up to 80% of pulmonary amyloid [3]. Moreover, it has been reported that 88% of patients with systemic amyloid have pulmonary disease [4].

Nomenclature Committee of the International Society of Amyloidosis 2010 recommends identification of an amyloid fibril protein in tissue deposits which exhibit affinity for Congo red and green birefringence when viewed by polarization microscopy [5,6]. Furthermore, the protein must have been unambiguously characterized by protein sequence analysis (DNA sequencing in the case of familial diseases). To date, there are twenty seven known extracellular fibril proteins identified in humans. Amyloid derived from immunoglobulin light-chain protein (AL disease) is most frequently involved in manifestations in the lung in both systemic and localized forms of the disease. Protein sequencing analysis was not attempted in our case.

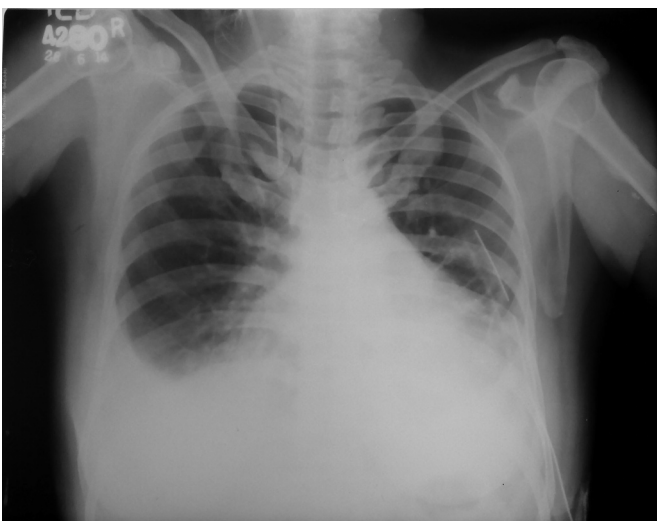


Fig. 6. Right effusion with ICD on left side.

Pulmonary presentations

1. Tracheobronchial amyloidosis: nodular or diffuse submucosal involvement
2. Diffuse alveolar-septal: presents as interstitial lung disease
3. Single or multiple parenchymal nodules: peripheral, subpleural and could be bilateral
4. Mediastinal adenopathy with egg shell or popcorn calcification
5. Pleural effusion: unilateral or bilateral. Could be transudative or exudative.

Amyloid deposition is widespread in AL disease, although only specific organs may be clinically involved. Patients may present primarily with respiratory symptoms that warrant pulmonary workup leading to the diagnosis of amyloidosis [1,7]. Symptoms of pulmonary amyloidosis are very non-specific and hence require a high degree of clinical suspicion. Amyloid nodules in the lung parenchyma are most often asymptomatic and are usually incidental findings on imaging studies. These nodules tend to calcify, and sometimes they may cavitate. Diffuse alveolar-septal amyloidosis related to systemic AL disease may present with interstitial lung disease pattern or even more frightening symptoms of haemoptysis due to dissection of pulmonary arteries infiltrated by amyloid protein deposits or massive pulmonary embolism related to thrombosis of inferior vena cava [8]. Mediastinal or hilar adenopathy is less common than extrathoracic adenopathy in patients with systemic AL disease. They can cause luminal narrowing of the airways and thus may lead to post-obstructive atelectasis and/or pneumonia. However, these patients may sometimes present with cervical nodes that may enlarge, become tender and can mimic sarcoidosis. Johns Hopkins Hospital examined the association of cardiac and pulmonary amyloid infiltration in autopsy data from 26 patients with systemic AL disease. Pulmonary amyloid deposition was not found in the absence of cardiac disease [4,9]. Hence if pulmonary amyloid is suspected it is imperative that one should be looking for its presence within the myocardium. However this dictum could not be proved in our case with echocardiographic evaluation which is supposed to have specific appearance in case of myocardial infiltrative disease. Beta-2 microglobulin fibril precursor protein related systemic amyloidosis is reported in chronic renal impairment patients on long term dialysis and with periarticular involvement. Our patient was started on renal dialysis only two months back and she did not have any features to suggest joint involvement.

Pleural effusion

Pleural effusions in patients with amyloidosis which is a rare cause for massive effusion can cause dyspnoea and may require repeated thoracentesis to relieve symptoms as was the situation in our case which finally required intercostal tube drainage for dyspnoea management. One of the first reports of amyloid-associated pleural effusion included five patients by Kavuru et al. [10]. These authors found that pleural effusions in the majority of their patients (60% in their series) were believed to be related to either congestive heart disease or nephrotic syndrome, and only 40% of pleural effusions were “idiopathic”. Despite this they found that even those patients with transudative effusions had pleural infiltration with amyloid on biopsy, as what has happened in our case also. Direct amyloid infiltration of the parietal pleura was responsible for large recurrent pleural effusions.

Large, recurrent effusions can also occur in the setting of co-existent significant cardiac dysfunction and pleural amyloid. Their claim was supported by thoracoscopic descriptions of pleural studding and histological evidence of amyloid infiltrating pleural surfaces on biopsy [10]. Although uncommon, pleural effusions in

patients with Primary pulmonary amyloidosis can be hemorrhagic [11]. In our case the effusion was uniformly hemorrhagic.

Chylous effusions occur in patients with extensive amyloid burden due to direct infiltration of mediastinal nodes by amyloid rather than by mechanical obstruction [12]. Patients with nephrotic syndrome and serum albumin levels <2.5 gm/dL do not frequently manifest pleural effusion in the absence of congestive heart failure. Thoracoscopic view reveals amyloid deposits studding the parietal pleural surface, supporting the diagnostic utility of even closed needle pleural biopsies in centres not having thoracoscopic facilities. Hence transudative massive pleural effusion in established cases of renal amyloidosis merits evaluation with pleural biopsy.

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