

CASE STUDY

Primary diffuse alveolar septal amyloidosis with multiple cysts and calcification

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ABSTRACT: We report an extremely rare case of primary diffuse alveolar septal amyloidosis associated with multiple cysts and calcification. Development of multiple cysts may have resulted from fragile alveolar walls, as a consequence of amyloid deposition both on alveolar walls and around capillaries.

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Diffuse alveolar septal amyloidosis localized exclusively to the lung is extremely rare. We present a case of diffuse alveolar septal amyloidosis associated with multiple cysts and calcification.

Case report

A 54 year old woman presented with dizziness when she visited an otorhinolaryngologist in March 1989. She was diagnosed as having Ménière's syndrome and corticosteroids were initiated leading to rapid improvement. She was referred to our hospital in April 1989 for further evaluation of abnormal chest shadows when she was asymptomatic. The patient's past medical history revealed that she had been treated for pulmonary tuberculosis with para-aminosalicylic acid (PAS) and streptomycin for 1 yr at the age of 16 yrs. She had undergone a total hysterectomy for uterine myoma at the age of 50 yrs. She had never smoked. On physical examinations, no evidence of respiratory distress, hepatosplenomegaly, or macroglossia were disclosed.

Laboratory examination revealed a total leucocyte count of 6.2×10^9 cells·L⁻¹ with a normal differential, and haemoglobin of 146 g·L⁻¹. Erythrocyte sedimentation rate (ESR) was 10 mm·h⁻¹. Urinalysis was normal, with negative Bence Jones protein. Blood biochemical examination were normal. A tuberculin skin test was positive (15 mm transverse diameter). Measurement of serum immunoglobulins revealed a slightly increased immunoglobulin G (IgG) of 15.9 g·L⁻¹ and normal levels of immunoglobulin A and M (IgA and IgM) (3.28 and 1.46 g·L⁻¹, respectively). The following data were negative: C reactive protein, rheumatoid factor, antinuclear factor, anti-SS-A antibody, anti-SS-B antibody, parathyroid hormone. An electrocardiogram was normal. Sputum was negative for acid-fast bacilli.

Pulmonary function tests revealed normal forced vital

capacity (FVC) of 2.49 L (105% of predicted), reduced forced expiratory volume in one second (FEV₁) of 1.61 L (65% pred), increased forced expiratory flow at 50% VC/25% VC (FEF₅₀/FEF₂₅) ratio of 4.0, a mildly increased residual volume/total lung capacity (RV/TLC) of 41%, and mild reduction in carbon monoxide transfer factor (78% pred). Blood gas analysis was within normal limits arterial carbon dioxide tension (P_{a,CO_2}) 5.2 kPa (39.1 mmHg), arterial oxygen tension (P_{a,O_2}) 10.7 kPa (80.0 mmHg), and mildly increased alveolar to arterial oxygen tension difference $P_{(A-a),O_2}$ of 3.2 kPa (24 mmHg).

Histological examinations of gastric mucosa obtained by gastroendoscopy were normal. Chest roentgenogram showed diffuse reticulonodular shadows and a fine stippled appearance in the middle and lower lungs (fig. 1).

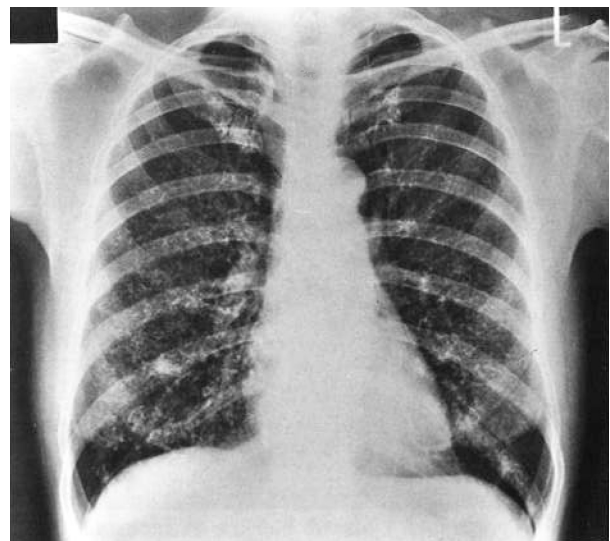


Fig. 1. – Chest radiograph demonstrating diffuse reticulonodular shadows and fine stippled appearance in the middle and lower lungs.

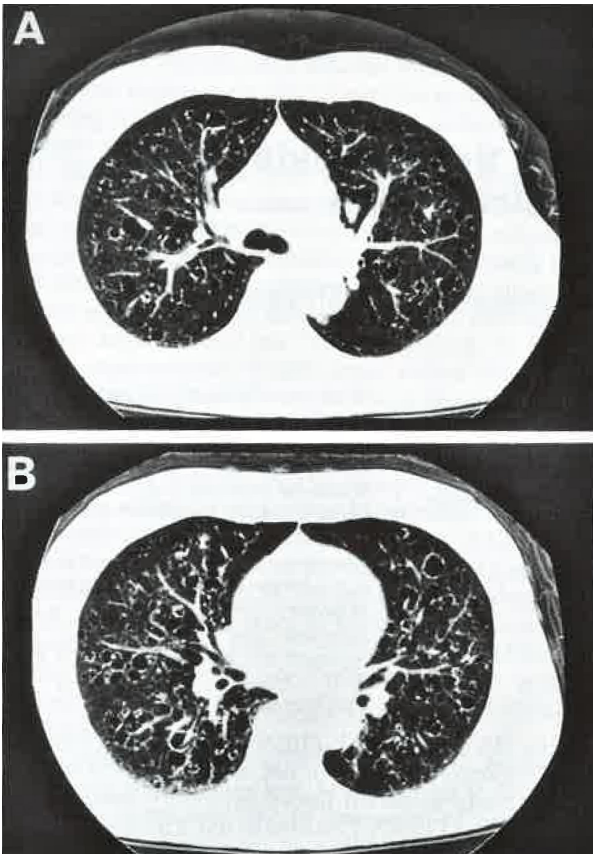


Fig. 2. - Chest computed tomography at: A) carinal level; and B) lower lobe. Multiple cysts are located mainly over the hilar and central zone and high density areas are seen around the cysts.

These findings had progressed slowly during the last 4 yrs. The fine stippled calcification was more prominently demonstrated by chest tomography (CT). Furthermore, chest CT scan showed multiple cystic lesions of various size up to 1.5 cm. The cysts were located mainly over the

hilar and central zone, and high density areas were seen around the cysts (fig. 2).

The major tracheobronchial airways appeared entirely normal by bronchofibrescopy. There was no bleeding tendency, spontaneously or during the transbronchial lung biopsies. Histological examinations of the biopsies revealed focal thickening of alveolar septa and amorphous eosinophilic material and small nodules of deposits in the wall of small vessels. There were destructive changes of the alveolar wall, dilatation of alveolar ducts, and interstitial infiltration with lymphocytes and plasma cells (fig. 3a). Calcifications were present in several lesions of amyloid deposits (fig. 3b).

On staining with Congo red, this material was positive (fig. 3c), and there was apple-green birefringence when examined under polarized light. The birefringence was resistant to potassium permanganate treatment. Immunoperoxidase staining was strongly positive for λ light chains but not for κ light chains, IgG, IgA and IgM heavy chains and anti-AA antibody. Biopsy specimens from stomach and bone marrow were negative for amyloid deposits. The bone marrow aspiration disclosed no evidence of proliferation of atypical plasmacytes or lymphocytes. A ^{99m}Tc -diphosphate bone scan showed intense radioactivity in the middle and lower lung fields but not in extrathoracic areas (fig. 4). From these findings the diagnosis of primary diffuse alveolar septal amyloidosis was made.

A careful search for a predisposing cause for secondary amyloidosis disclosed no evidence of a chronic infectious process (tuberculosis, syphilis, bronchiectasis), an inflammatory disease (rheumatoid arthritis, systemic lupus erythematosus, Behçet's disease), or a familial or personal history of periodic fever, Hodgkin's disease or other neoplastic disease (normal results of gastroscopy, pelvic and renal ultrasonography and urinary cytology). The patient has been free of respiratory symptoms without any treatment, and there were no remarkable changes of chest roentgenograms during 2 yrs of follow-up.

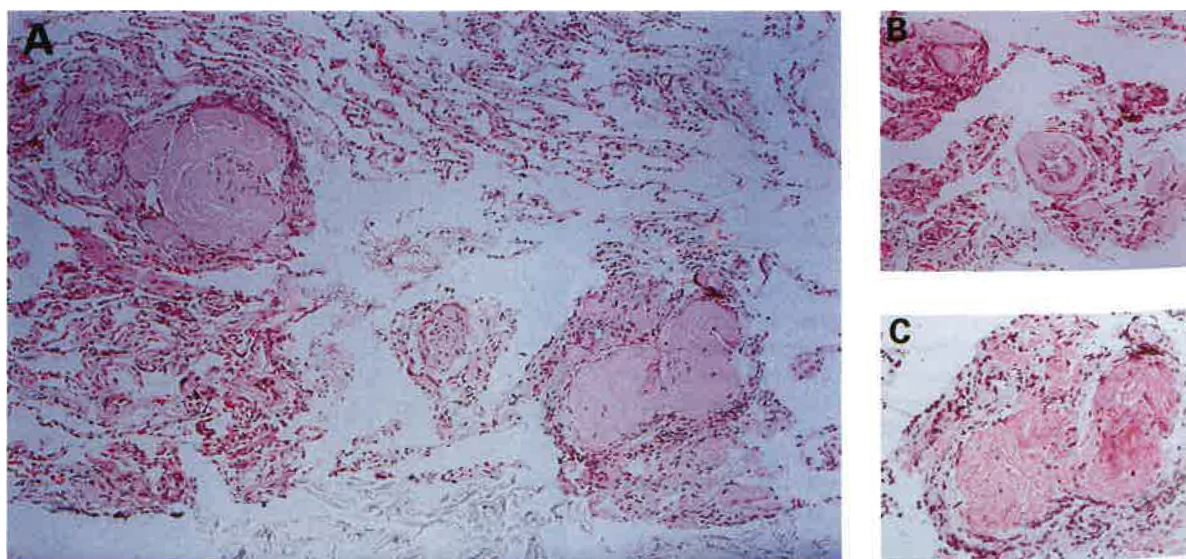


Fig. 3. - Specimens obtained from transbronchial biopsies. A) Histological examination of haematoxylin and eosin stained sections revealed focal thickening of alveolar septa and the wall of small vessels with an amorphous eosinophilic material. (Original magnification $\times 200$). B) Calcifications are presented in several lesions of amyloid deposits. C) This material shows positive for Congo red staining.



Fig. 4. — A ^{99m}Tc -diphosphorite bone scan, showing intense radioactivity in the middle and lower lung fields but not in extrathoracic areas.

Discussion

Pulmonary amyloidosis occurs as a localized process restricted to the lung (primary pulmonary amyloidosis), or as part of a systemic involvement. Isolated pulmonary amyloidosis may be subdivided into the following groups: tracheobronchial, nodular parenchymal, diffuse parenchymal (interstitial/diffuse alveolar septal), and senile [1].

Diffuse alveolar septal amyloidosis is by far the most uncommon type, and usually occurs in association with primary systemic amyloidosis or multiple myeloma [1–4]. Hui *et al.* [4] reported that 6 out of 48 cases with primary pulmonary amyloidosis showed a diffuse interstitial parenchymal pattern.

Amyloidosis can be separated into AL (light chain related) and AA (protein AA) amyloidosis on the basis of the biochemistry of amyloid fibrils. AL is generally found either in primary amyloidosis or in association with multiple myeloma, whereas protein AA is the major constituent of secondary amyloidosis [5]. The present case was diagnosed as having primary amyloidosis because AL was found in the lungs, and there was no evidence of an underlying disease predisposing to secondary amyloidosis.

Ossification and/or calcification is seen in 29% of the nodules with amyloidosis on chest radiographic films and bone scintigrams, and these findings are considered diagnostic [6].

Multiple cystic spaces were the characteristic radiological findings on CT scans in the present case. All cysts had a distinct thin wall and were located in the peripheral lung zone. These findings are not consistent with diffuse bronchiectasis, which have a thick wall and are located in more central parts of the bronchi.

The mildly reduced FEV₁ and subnormal $P(A-a)O_2$ may

be attributed to small airway narrowing, loss of pulmonary elastic recoil forces and loss of capillary bed secondary to cystic parenchymal changes, as observed in lymphangioleiomyomatosis (LAM) [7].

This patient had never smoked and there was no evidence of underlying disease predisposing to cystic lesions. The association between pulmonary amyloidosis and cyst formation is not clear. There are three possible mechanisms involved in cyst formation with amyloidosis. One mechanism is narrowing of the airway with extensive inflammatory cell infiltration, leading to the check valve mechanism [8]. A second mechanism is increased fragility and disruption of the alveolar walls as a result of amyloid deposits on alveolar wall [9]. The third mechanism is ischaemia leading to destruction of alveolar walls as a result of amyloid deposition around capillaries and within the interstitial tissue, ultimately obliterating alveolar capillaries [9].

We are unable to exclude the possibility of the first mechanism because the material obtained from transbronchial biopsy was insufficient to examine the airways. Since the histological findings of parenchymal involvement were restricted to vascular walls and alveolar septa, the second and third mechanisms might be responsible for cyst formation. Calcifications occur frequently in patients with primary amyloidosis, but cyst formation is a rare complication.

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