Pathol. Oncol. Res. (2009) 15:133–136
DOI 10.1007/s12253-008-9066-4

ORIGINAL PAPER

Idiopathic Systemic Amyloidosis Primarily Affecting the Lungs with Fatal Pulmonary Haemorrhage due to Vascular Involvement

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Received: 8 April 2008 / Accepted: 16 May 2008 / Published online: 14 June 2008

Abstract A patient who presented with dyspnea and suspected interstitial pulmonary fibrosis suffered a fatal pulmonary haemorrhage with no feasible cause for bleeding. Autopsy revealed abundant amyloid deposits in both lungs with a diffuse alveolar septal distribution pattern. Amyloid was also found in the cardiac interstitium and in many vessel walls. Considering the affected organs and the histological characteristics, the deposits were regarded as light chain-type. Amyloidosis, which is generally an uncommon disease, very rarely affects the lung predominantly. Haemorrhagic diathesis is a known complication in amyloidosis patients, although fatal haemorrhage is rare and has not yet been reported solely of pulmonary origin. This report describes an uncommon case of idiopathic systemic amyloidosis mainly manifesting in the lungs. The diagnosis was established after fatal pulmonary haemorrhage caused by vessel impairment due to additional vascular amyloid deposits.

Keywords Amyloidosis · Haemorrhage · Pulmonary

Introduction

Amyloidosis is a rare disease characterized by the extracellular accumulation of insoluble fibrillar proteins due to the formation of beta-pleated structures in various organs. These amyloid fibrils may derive from a variety of precursor proteins, frequently serum amyloid A protein (AA) or monoclonal immunoglobulin light chains (AL). It can be an inherited or acquired condition and take a lethal course or simply be an incidental finding. Amyloidosis may be classified as systemic or localized, as well as primary (idiopathic) or secondary (reactive). Approximately 75% of primary amyloidosis cases demonstrate fibrils derived from the variable region of lambda light chains and systemic AL-amyloidosis is the most common systemic type accounting for more than 60% of cases [1], estimated to affect 5–12 people per million per year. [2] Pulmonary manifestation is possible in all types but mostly occurs in systemic AL amyloidosis, although the lung is rarely the predominantly affected organ [3].

Haemorrhagic diathesis in patients with amyloidosis is a recognised complication usually due to deficiencies of clotting factors [4], whereas fatal haemorrhage is a rare event [5]. Less frequently, haemorrhage has been reported as a result of vascular fragility caused by amyloid deposits in blood vessel walls. Common sights of bleeding include the gastro-intestinal tract and the skin [6].

We report an unusual case of primary systemic amyloidosis mainly affecting the lungs with widespread vascular involvement and deposits in the heart. The diagnosis was established post mortem after massive pulmonary haemorrhage with fatal outcome due to vascular amyloid deposits.

Clinical History

A 70-year-old female patient without relevant familial or social history presented with recurring pleural effusions and

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stress dyspnea. Pulmonary radiologic findings were interpreted as sarcoidosis (stage two) and fibrosing lung disease. Histological verification by biopsy was refused by the patient. One month after a pleural tap the patient suffered a massive pulmonary haemorrhage with no feasible source of bleeding by bronchoscopy. Shortly afterwards she succumbed to the substantial blood loss. Autopsy with subsequent histological examination was performed, revealing pulmonary, cardiac and widespread vascular amyloidosis. Next to an extensive pulmonary haemorrhage, an erosive gastritis was identified with additional recent bleeding. An underlying disease was not evident. This form was classified as idiopathic systemic amyloidosis, with pronounced diffuse alveolar septal, pleural, cardiac and vascular involvement, resulting in fatal pulmonary haemorrhage.

Materials and Methods

Tissue was obtained during autopsy, fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin as well as Congo red. Positive Congo red staining was diagnosed by eosinophilia in normal light microscopy and by green birefringence in polarized light microscopy. Pre-treatment with potassium permanganate, which causes loss of congophilia in AA amyloid was performed according to Wright [7].

For electron microscopy small probes from paraffin wax embedded material were deparaffinised in xylene for at least 3 h, re-hydrated in a graded series of ethyl alcohol (100%, 90%, 70%, 50%, 30%) and finally transferred in pure water, followed by a 1 h treatment in an aqueous solution of 1% OsO_4 at room temperature. After a regressive series of ethyl alcohol as described above the probes were embedded in Durcupan ACM (Fluka, Germany). Thin sections were prepared with a Reichert Jung Ultracut E (Leica Instruments, UK) and mounted on formvar coated nickel grids (Polysciences, USA). Subsequently the grids were counterstained with uranyl acetate and lead citrate. Ultrastructural investigations were performed with a Zeiss EM 109 (Zeiss, Germany). Micrographs were taken on ILFORD PAN F 50 negative film and digitalized with a Nikon ED 9000 film scanner (Nikon, Japan).

Results

Except for slightly elevated inflammation parameters (C-reactive protein, leukocyte count and erythrocyte sedimentation rate), the clinical routine laboratory work-up was without pathological findings. Radiologic findings consisted of interstitial and micronodal opacities in both lungs with prominent hilar lymph nodes and extensive right-sided pleural effusion. Cytology of the pleural fluid revealed a high cell count with some atypical cells. Micro-organisms could not be detected histologically, or by cell culture.

Autopsy revealed very firm lungs with nodules varying from 0.5 to 1 cm in diameter localized pleural, as well as parenchymal, distributed randomly in all lobes. The nodules were of waxy, gritty consistency, and yellow-tan Fig. 1A,B). Some areas, particularly the lingula and the lower mid lobe, showed friable masses bonding to the pleural surface (Fig. 1C). On histological examination all lobes as well as the pleura demonstrated interstitial, amorphous, frequently micronodular, eosinophilic deposits, sometimes with calcifications (Fig. 1D). A perivascular pattern was common, with deposits in the arterial walls as well. The deposits exhibited only few interspersed macrophages and were often nearly acellular. The Congo red stain identified these structures as amyloid (Fig. 2A) without sensitivity to potassium permanganate pre-treatment. The heart and hilar lymph nodes also displayed interstitial amyloid deposits, as did the examined vessels in the heart, liver (Fig. 2B), kidneys, spleen and stomach. Amyloid was not detectable in the brain or the cerebral vessels. At the ultrastructural level macrophages containing amyloid deposits in different stages of degradation were visible (Fig. 2C). Finally degradation process of internalized amyloid leads to the so called laminated bodies shown in Fig. 2D.

Further notable autopsy findings consisted of massive left sided diffuse pulmonary haemorrhage and erosive gastritis with recent bleeding.

Discussion

Amyloidosis is generally considered an uncommon disease and the lung is rarely the predominantly affected organ [3]. Renal involvement dominates the clinical course of systemic amyloidosis, with renal failure being the most common cause of death [8]. Gastrointestinal disorders, hepatosplenomegaly, amyloid cardiomyopathy, neuropathy and macroglossia are additional prevalent features reported in AL amyloidosis [8]. Virtually any tissue except the brain can be involved in this form, and non-specific symptoms are common. Lung manifestation is possible in all types of amyloidosis and may be detected in 35–90% of primary amyloidosis, while being extremely rare in secondary forms [9]. Hereditary amyloidosis also does not show prominent lung involvement [9]. Three different distribution patterns may be distinguished in amyloidosis of the respiratory system. Tracheobronchial amyloidosis is uncommon and has been associated with tracheobronchopathia osteoplastica. Parenchymal amyloidosis can be divided into a solitary/multiple nodular form and a diffuse

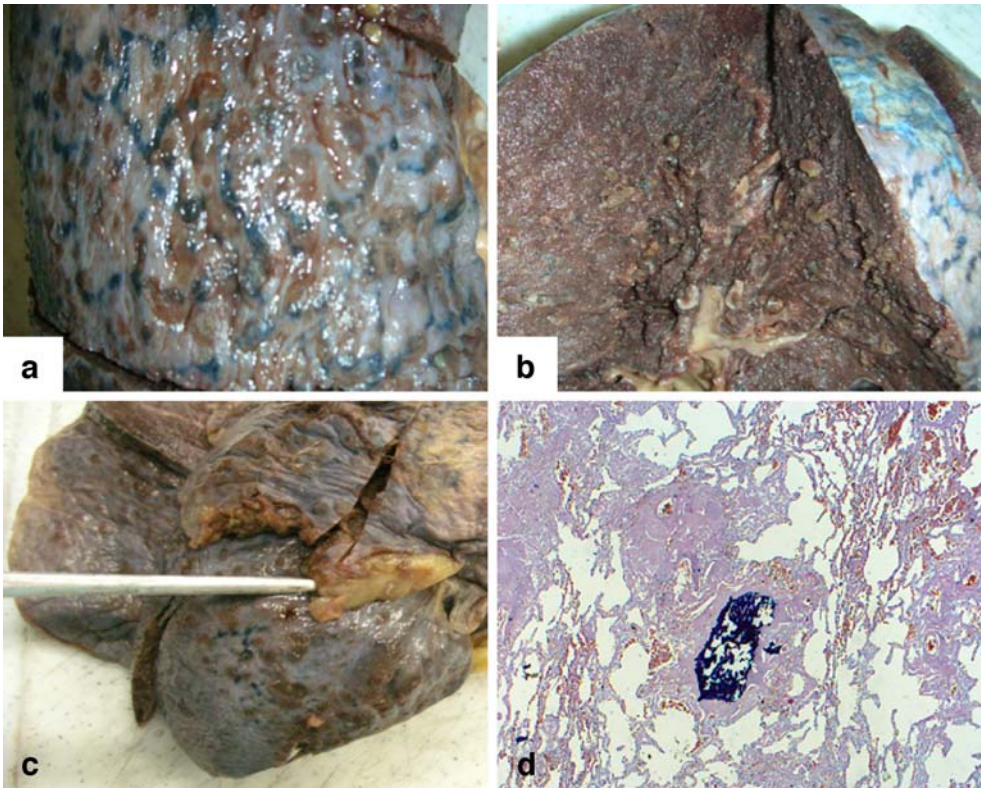

Fig. 1 **A** nodular pleural surface. **B** lung section with waxy, yellow-tan nodules. **C** friable masses bonding to the lingula. **D** alveolar-septal, amorphous, micronodular, eosinophilic deposits, with calcifications (hematoxylin–eosin, original magnification 2×*g*)

alveolar septal form. Tracheobronchial and parenchymal nodular types are usually localized. In contrast diffuse pulmonary involvement has usually been reported in association with systemic amyloidosis [9] and is the most frequently detected lung amyloidosis [1], although only presenting as a major manifestation in less than 10% [3]. By immunohistochemistry, amyloidosis can be classified as reactive (AA type), primary idiopathic (AL type) or

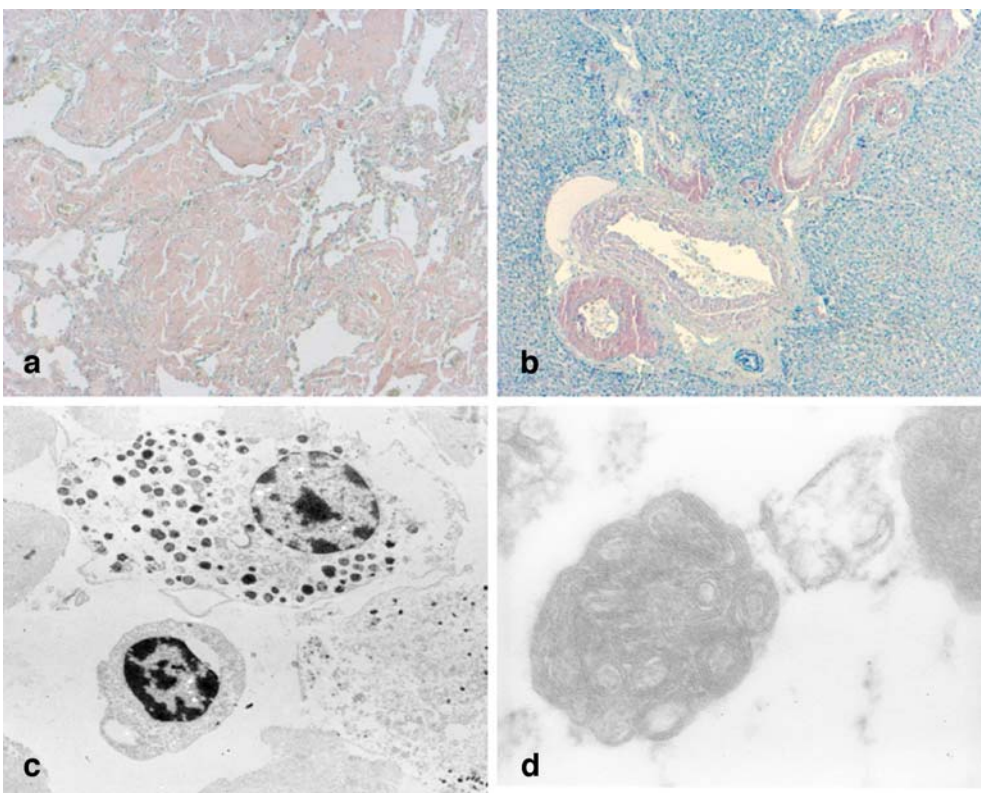

Fig. 2 **A** alveolar-septal, nearly acellular, eosinophilic, amorphous deposits (Congo red, original magnification 4×*g*). **B** hepatic vascular amyloid deposits (Congo red, original magnification 4×*g*). **C** macrophages containing amyloid deposits in different stages of degradation (electron microscopy original magnification 3,000×*g*). **D** final degradation process of internalized amyloid (electron microscopy original magnification 85,000×*g*)

transthyretin-related (ATTR type). Few reports of AA amyloidosis affecting the lung exist, although fibril typing was generally imperfect or sequencing revealed AL amyloid [1]. ATTR pulmonary amyloidosis may occur in senile systemic amyloidosis although its clinical significance is questionable. Therefore in most situations respiratory amyloidosis will be of the AL type, manifesting primarily as the diffuse parenchymal form with involvement of other organ systems. Overall, pulmonary amyloidosis occurs in up to 28% of AL amyloidosis patients and does not affect survival [10].

Diffuse pulmonary amyloidosis rarely manifests clinically but typically presents with progressive dyspnea [9]. Respiratory function tests may point towards a restrictive pathology with impaired gas exchange, which to some extent also might be due to frequently co-existing cardiac amyloidosis [9], thereby complicating diagnosis. Persistent pleural effusions have been reported in 5.5% of patients and are commonly associated with cardiac amyloidosis, however amyloid induced pleural dysfunction is also possible, presenting with effusions refractory to diuretics and requiring repeated drainage or pleurodesis [10].

Diffuse pulmonary amyloidosis may be mistaken clinically as pulmonary oedema or fibrosis, demonstrating a diffuse retioculonodular pattern radiologically, possibly also mimicking interstitial lung disease. In most AL amyloidosis patients there is substantial histologic cardiac involvement with restrictive cardiomyopathy as the presenting feature in up to one third of cases, and ultimately the cause of death in one half [1]. Although microscopic pulmonary amyloid deposits are universally present, in most patients dyspnoe is secondary to cardiac involvement [1].

Bleeding diathesis is a recognised complication in patients with amyloidosis, although fatal haemorrhage is rare [5]. The pathogenesis may be related to coagulation deficits or thrombocytopenia due to malignancy induced bone marrow depletion. Mumford et al. reported that in most patients with AL amyloidosis coagulation abnormalities can be explained by either impaired fibrin polymerisation or reduction of factor X activity [6]. In patients with other types of amyloidosis, acquired haemostatic defects are rare. Many cases with bleeding manifestations despite absence of coagulopathy exist, suggesting amyloid infiltration of vessels, leading to increased fragility [5]. Unusual reports of bleeding incidents associated with amyloidosis include subconjunctival haemorage [11], macroscopic haematuria [5], hemoptysis [5], vaginal bleeding [12], haemopericardium [12] and mediastinal haemorrhage [13]. More common forms consist of cutaneous and gastrointestinal tract bleedings [6]. One case of fatal bronchopulmonary haemorage due to unrecognised amyloidosis has been reported [14].

The case described here presented clinically and radiologically as an interstitial lung disease without further classification due to refusal of biopsy. Systemic amyloidosis with an uncommon distribution, mainly affecting the lungs and blood vessels was diagnosed post mortem after fatal pulmonary haemorrhage. Considering the pattern and unverifiable loss of congophilia after potassium permanganate pre-treatment, the deposits were regarded as AL-type. Spontaneous haemorrhage of virtually any organ in the absence of a feasible cause may be due to amyloid angiopathy. Fatal haemorrhage, however, is a rare occurrence and has not been reported solely of pulmonary origin.

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