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Pulmonary AL amyloidosis and multiple myeloma presenting as cough with diffuse pulmonary opacities

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Abstract

Amyloidosis is an uncommon multisystem disease that can affect many organs. However, interstitial lung involvement is very rare. A 68-year-old man presented with long-standing dyspnoea and productive cough. After extensive investigation, including two non-diagnostic bronchoscopies, a surgical lung biopsy demonstrated pulmonary amyloidosis. A bone marrow biopsy confirmed multiple myeloma. The patient was treated with chemotherapy and an autologous stem cell transplant.

Introduction

Amyloidosis is an uncommon disease characterized by deposition of misfolded protein fibrils in various organs. Its most common subtype, AL amyloidosis, often portends a poor prognosis, due to damaging renal and cardiac effects. Whilst light chains can deposit in any organ, interstitial lung involvement is very rare.

Case Report

A 68-year-old retired business consultant and bookkeeper presented with six months of slowly progressive exertional dyspnoea and productive cough. His medical history included ischaemic heart disease with previous coronary artery stenting, hypertension, type 2 diabetes mellitus, and *Legionella pneumophila* and culture-negative community-acquired pneumonia, 10 and 20 years prior, respectively. He was a reformed smoker with a 22-pack-year history. There were no relevant environmental or occupational exposures and no family history of pulmonary, connective tissue, or haematological disease.

Respiratory examination was normal. Peripheral arterial oxygen saturation breathing room air was 97%.

Laboratory investigations revealed a haemoglobin level of 151 g/L, white cell count of 7.80 $\times$ 10^9/L, platelet count of 199 $\times$ 10^9/L, and peripheral eosinophil count 0.1 $\times$ 10^9/L. His renal function was normal (creatinine 74 μmol/L), and electrolytes were unremarkable, including a calcium level of 2.48 mmol/L. Liver function tests, coagulation studies, C-reactive protein, and viral serology were also not deranged. There was a mildly elevated antinuclear antibody level of 1:160 with a homogeneous pattern, while other autoimmune tests, specifically rheumatoid factor, extractable nuclear antigen, anti-double-stranded DNA, antineutrophil cytoplasmic antibody, and angiotensin-converting enzyme levels were not elevated. Immunoglobulin (Ig) levels were normal, including IgE (6 kU/L) and IgD (69 mg/L). No pathogens were isolated on sputum microbiological and mycobacterial cultures.

A chest X-ray demonstrated bilateral interstitial infiltrates. A computed tomography (CT) of the chest demonstrated diffuse ground glass and nodular pulmonary infiltrate and nodular consolidation throughout both lungs, with more confluent consolidation in the left hilum, lingular and right middle lobes, and patchy infiltrates in the upper lobes bilaterally. There was mildly enlarged mediastinal, hilar, and axillary lymphadenopathy (Fig. 1). These changes remained stable on CT imaging over three

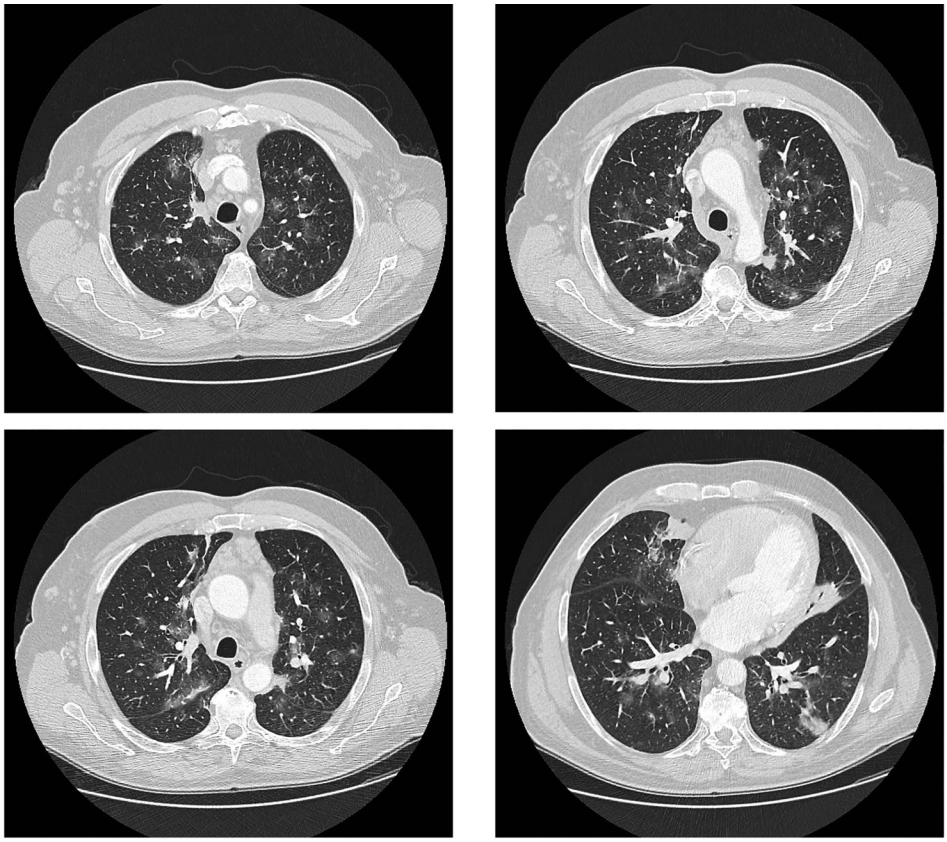

Figure 1. Computed tomography (CT) of the chest at presentation.

months, despite the administration of oral antibiotics directed at standard community-acquired pathogens.

Pulmonary function tests revealed a mild obstructive ventilatory defect: forced expiratory volume in 1 sec (FEV_1) 1.91 L/71%, forced vital capacity (FVC) 2.98 L/81%, FEV_1/FVC 64% with no bronchodilator reversibility, and normal diffusing capacity of the lung for carbon monoxide (DLCO) 72%.

Right middle lobe bronchoalveolar lavage (BAL) did not demonstrate cytological evidence of malignancy or culture any pathogens. The BAL differential cell count showed 73% macrophages, 25% lymphocytes, and 2% neutrophils. Endoscopic bronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) of a mildly enlarged 11R node demonstrated benign lymphoid tissue. Left upper lobe (LUL) transbronchial biopsies were non-diagnostic. As the aetiology of the interstitial lung disease remained elusive, he was referred for surgical lung biopsy (SLB).

Histopathology of the LUL resection revealed variably dense, diffuse, and nodular plasma cell infiltrates, associated with amyloid deposits showing apple green birefringence in Congo red stain (Fig. 2). A subsequent bone marrow biopsy demonstrated an increased plasma cell population (12% on aspirate and 20–25% on trephine). The marrow was normocellular and there was no evidence of amyloid deposition at the biopsy site. Serum paraprotein (IgD kappa) was elevated at 11 g/L, and kappa and lambda free light chains elevated at 323 and 988 mg/L, respectively. The kappa/lambda ratio was normal, 0.33. 18-Fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET) scan did not demonstrate any areas of focal skeletal FDG uptake and there was no FDG-avid lymphadenopathy. There was widespread pulmonary parenchymal ground-glass opacity with areas of more confluent consolidation in the upper lobes with moderate FDG uptake [maximum standardised uptake value (SUVmax) 2.9]. Cardiac magnetic resonance imaging (MRI) demonstrated normal systolic function, mild septal hypertrophy, and no evidence of amyloid deposition.

He was thus diagnosed with pulmonary AL amyloidosis and multiple myeloma. Treatment involved six cycles of bortezomib, cyclophosphamide, and dexamethasone, after which he underwent autologous stem cell transplant. Almost 10 months post-transplant, he remains well with no progression of symptoms, stable lung function, and a promising trajectory of respiratory and haematological

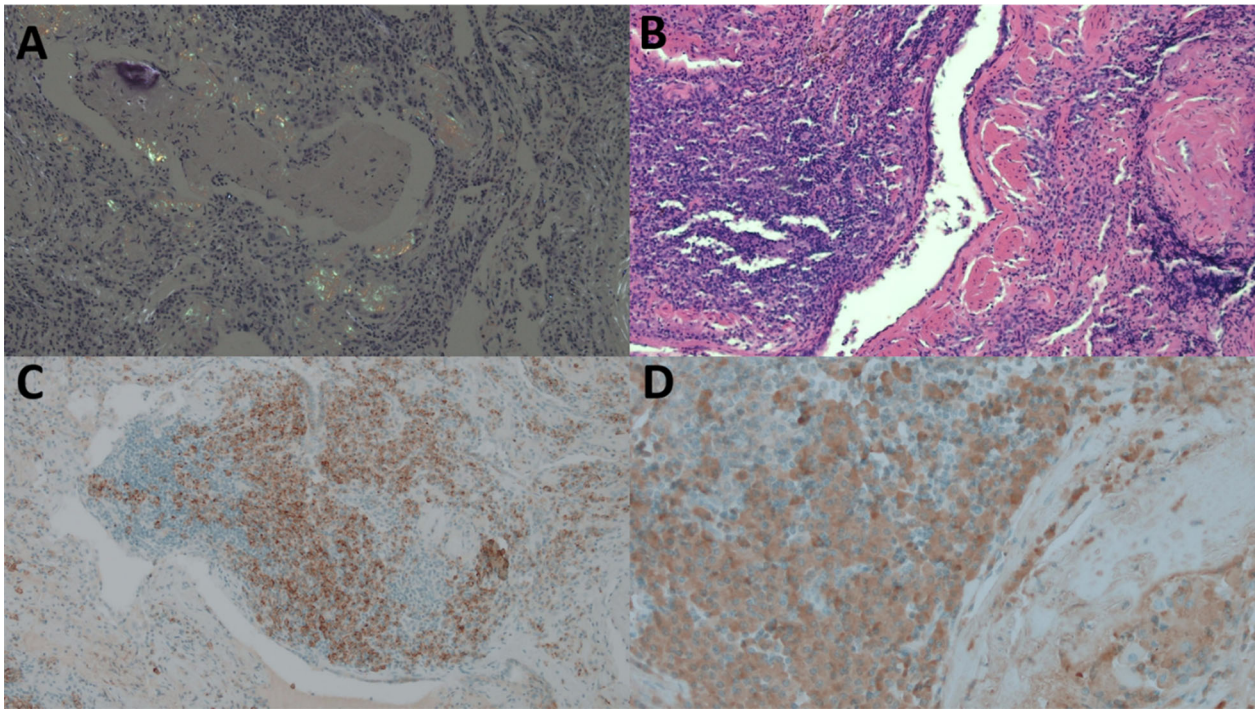

Figure 2. Surgical lung biopsy. (A) Apple green birefringence on Congo red stain confirming the presence of amyloid deposits. (B) Pulmonary parenchyma with variable diffuse and nodular plasma cell infiltrate and deposits of amorphous eosinophilic material consistent with amyloid deposition. (C) Immunohistochemistry stain for CD138 confirming plasma cell population. (D) Immunohistochemistry for kappa light chain suggesting kappa restriction.

disease. Serial CT imaging approximately six months post-diagnosis showed no progressive chest changes.

Discussion

Amyloidosis is rare, with an estimated international incidence of 10 cases per 1 million [1]. It can cause severe end-organ damage and, for most patients, morbidity and mortality are attributable to severe cardiac or renal disease.

The differential diagnosis for diffuse interstitial pulmonary infiltrates is broad, with pulmonary infections, pulmonary oedema, idiopathic fibrosing lung disease, occupational lung disease, and sarcoidosis amongst the common causes. Pulmonary amyloidosis is uncommon and, when present, may be nodular, alveolar, or tracheobronchial. The most frequent localized nodular pattern presents as amyloid nodules and is usually asymptomatic. Tracheobronchial pulmonary amyloid generally spares the lung parenchyma, and is not associated with myeloma. The diffuse interstitial variant of pulmonary amyloidosis is the rarest form [2]. As in this case, the clinical manifestations are respiratory symptoms due to diffuse parenchymal involvement, in particular dyspnoea and cough. There are only a few patients in whom interstitial pulmonary amyloidosis has been described in the literature, and these are associated with haematological disorders, including multiple myeloma [3]. Isolated pulmonary AL amyloidosis without systemic manifestation and myeloma is also described in the context of low-grade B non-Hodgkin lymphoma and on occasions in context of autoimmune disorders [4]. Although the disease rarity precludes high-level data to guide treatment, therapy is usually directed at the underlying myeloma.

In this case, pulmonary AL amyloidosis was only detected after histological examination of an SLB specimen. There were little data in the initial diagnostic workup to suggest an underlying haematological condition, chest radiology was non-specific, and bronchoscopy with transbronchial biopsies and EBUS TBNA of hilar nodes was non-diagnostic.

This case highlights the importance of obtaining sufficiently large histological specimens when the diagnosis remains elusive, with either SLB or transbronchial cryobiopsy [5] and the need to consider haematological causes for diffuse lung disease.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

All authors contributed substantially to this submission. All authors contributed to the conception, acquisition, analysis, and interpretation of the work; drafting and revision of the work; and final approval of the version to the published.

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