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CASE REPORT

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A case of pulmonary transthyretin amyloidosis with concurrent mycobacterial tuberculosis infection

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Abstract

Amyloidosis is a pathological deposition disease that causes a spectrum of organ dysfunction. Pulmonary involvement is generally associated with immunoglobulin light chain type (AL) amyloid. Transthyretin (ATTR) amyloid build up in the lung is thought to be a senile disease observed usually as a finding at autopsy. We describe a case of pulmonary ATTR amyloidosis with concurrent mycobacterial tuberculosis infection.

KEYWORDS

amyloidosis, ante-mortem, *Mycobacterium tuberculosis*, pulmonary, transthyretin

INTRODUCTION

Amyloidosis is a condition caused by extracellular deposition of abnormally folded proteins that precipitates organ dysfunction.[1] These misfolded proteins resemble pathologic linear structured β-pleated sheets rather than its physiologic tertiary structure.[1] The major types of amyloidosis depend on the precursor protein and include immunoglobulin light chain (AL), transthyretin (ATTR), and serum amyloid A (AA). AL amyloidosis is the most commonly diagnosed type (55%), followed by ATTR amyloidosis (20%) and AA amyloidosis (8%).[2]

Each amyloid type presents as a different spectrum of organ involvement and disease manifestations. Whilst the most common organ site is of cardiac origin, amyloid deposition in the lungs can occur.[3] Pulmonary involvement is usually attributed to AL amyloid type, with ATTR amyloid thought to be a senile disease observed usually as a finding at autopsy.[4–7] Chronic inflammation from mycobacterial infections is generally associated with AA amyloidosis.[8] To our knowledge, we report the first case of pulmonary ATTR amyloidosis from Australia.

CASE REPORT

An 86-year-old male presented with dyspnoea, fevers and decompensated congestive cardiac failure.

The patient was a retired furniture businessman with no overt endemic risk factors for tuberculosis. He was an ex-smoker (3 pack year history) with no known occupational exposures. Past history included cardiac ATTR amyloidosis diagnosed with technetium-99 m pyrophosphate scintigraphy (PYP) 1 year prior treated with tafamidis. It also included prostate cancer with extensive bone and lymph node metastasis managed expectantly, with androgen deprivation therapy ceased a year prior due to side effects. Prostate specific antigen levels remained suppressed without active treatment.

Cardiac complications included congestive cardiac failure, atrial fibrillation (treated with apixaban) and ventricular tachycardia (implantable cardioverter defibrillator in situ). Echocardiogram revealed normal left ventricular size with mild global systolic dysfunction and severe concentric left ventricular hypertrophy with apical sparing strain pattern consistent with known cardiac amyloid. There was no family history of amyloidosis.

The patient presented with 1 day history of dyspnoea, fevers and anorexia. There were no other localizing infective symptoms except for a mild non-productive cough. He was noted to be sarcopaenic with initial observations; temperature of 38.5°C, blood pressure 98/54 mmHg, heart rate 60 beats per minute (paced rhythm), respiratory rate 28 breaths per minute and oxygen saturation 97% on room air. Blood analysis revealed haemoglobin 93 g/L (125–175 g/L), white cell count 3.3 $\times 10^9$/L (4.0–11.0 $\times 10^9$/L), lymphocytes 0.4 $\times 10^9$/L (1.0–4.0 $\times 10^9$/L), platelets 99 $\times 10^9$/L (150–450 $\times 10^9$/L) and C-reactive protein 85 mg/L (<5 mg/L). Chest x-ray identified right lower lobe consolidation. Pancytopaenia was thought to be in setting of sepsis and the patient was treated with intravenous ceftriaxone for presumed pneumonia.

After 4 days, there were persistent fevers and development of moderate hypoxia (oxygen saturation 85% on room air and 95% on 2 L/minute oxygen via nasal prongs). Due to worsening clinical state, an urgent chest computed tomography (CT) demonstrated a new micronodular pattern throughout both lung fields which was not present 1 year prior (Figure 1). The widespread pulmonary nodules measured up to 5 mm with most below 1 mm in size. Additionally, there was a dense triangular area of mass-like consolidation in the right lung base and bilateral small pleural effusions (Figure 1).

Primary differentials included miliary tuberculosis, other atypical infection, pulmonary amyloidosis and lymphoma. Metastatic prostate spread to the lung was thought to be unlikely given the imaging appearance. Further CT of the brain, abdomen and pelvis did not identify any new process.

Given ongoing fevers and hypoxia he proceeded to have a bronchoscopy in the context of consolidation and diffuse nodular changes. Endoscopic assessment showed inflamed endobronchial mucosa. There was no endobronchial lesion or overt secretions. Broncho-alveolar lavage (BAL) of the right middle lobe and right lower lobe was conducted. Additionally, transbronchial biopsy of the right lower lobe mass like consolidation was sent for histopathology. His observations remained stable after the procedure with an ongoing mild oxygen requirement (oxygen saturation 94% on 2 L/minute oxygen via nasal prongs).

BAL differential cell count was lymphocyte predominant. Cytology was negative for malignancy, flow cytometry did not identify any abnormal lymphoid population and microscopy was non-diagnostic. Tuberculosis polymerase chain reaction (TB-PCR) was positive for fully-sensitive mycobacterium tuberculosis complex. Standard tuberculosis treatment was commenced (rifampicin, isoniazid, pyrazinamide, ethambutol and pyridoxine).

Histopathology from transbronchial biopsy revealed small fragments of alveolar lung tissue with thickened septate showing amorphous eosinophilic material. There was no significant associated lymphoplasmacytic infiltrate and no granulomatous reaction. Congo red stain was positive with birefringence under polarized light consistent with amyloidosis, showing patchy interstitial deposition with some droplet like deposits (Figure 2). Immunohistochemistry revealed strong positive staining for transthyretin confirming ATTR amyloidosis (senile/wild type) (Figure 2).

Serum protein electrophoresis revealed no paraprotein bands and serum free light chains were within normal limits – kappa free light chain 17 mg/L (7–22 mg/L), lambda free light chain 18 mg/L (8–27 mg/L), kappa/lambda ratio 0.94 (0.31–1.56).

The patient deteriorated over a few weeks from mycobacterium tuberculosis and cardiac ATTR amyloidosis despite treatment. A decision was made to provide supportive palliative care.

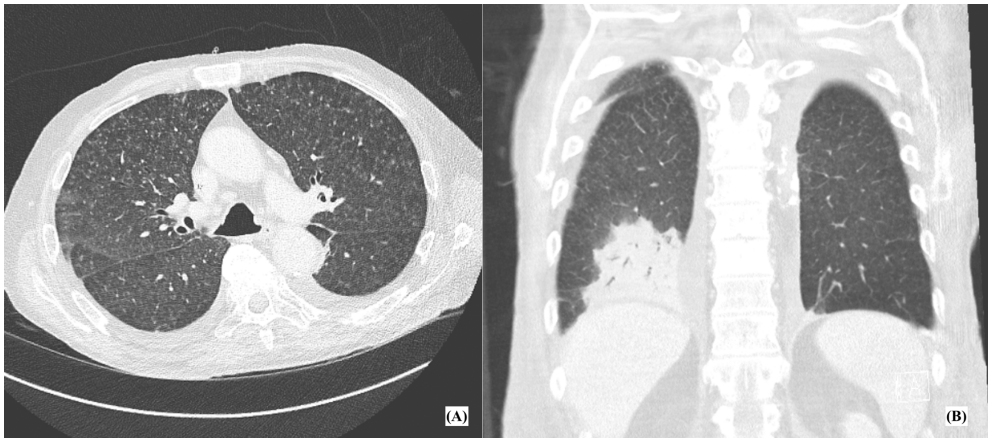

FIGURE 1 Chest computed tomography showing: (A) bilateral diffuse 'miliary' micronodular pattern; (B) dense triangular area of consolidation in the right lung base and background diffuse micronodular disease.

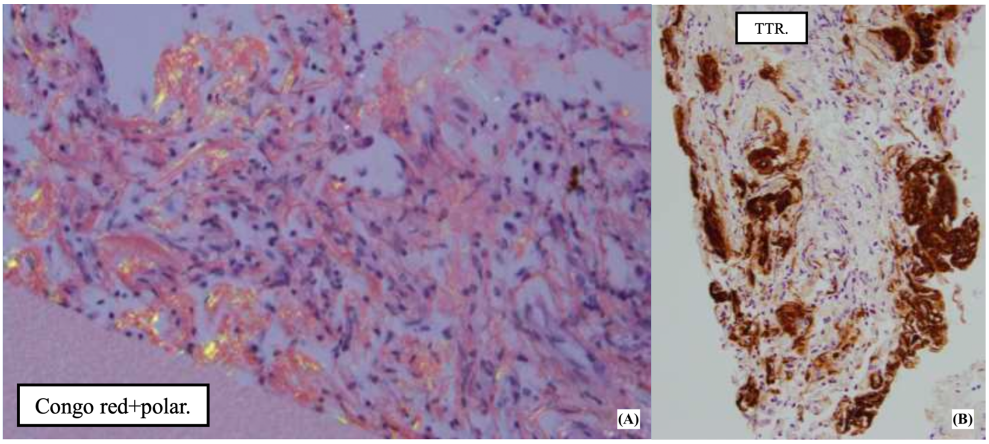

FIGURE 2 Histopathological examination of transbronchial biopsy. (A) Cross-section of alveolar lung tissue with thickened septate showing amorphous eosinophilic material and Congo red stain positive with birefringence under polarized light. (B) Immunohistochemistry strong positive staining for transthyretin (TTR).

DISCUSSION

ATTR amyloidosis is classified as either from variations (mutations) in the transthyretin gene (mut-ATTR) or acquired wild-type form (wt-ATTR). Clinical disease classically affects cardiac and nerve tissue. Musculoskeletal symptoms such as carpal tunnel syndrome and lumbar spinal canal stenosis are known early presentations that precede cardiac involvement,[9,10] however our case of wild type ATTR amyloidosis lacked these.

Amyloidosis is classically diagnosed from tissue biopsy showing positive Congo red stain with birefringence under polarized light.[11] Further subtyping for ATTR can be done by either immunohistochemistry or mass spectrometry. Mass spectrometry is the most definitive way to identify the subtype of amyloid present in biopsy specimens.[11] In comparison, immunohistochemistry has a specificity of 92%–100% for ATTR amyloid and is more widely accessible.[12,13] Our diagnosis of Pulmonary ATTR amyloidosis was found on immunohistochemistry and may have been confirmed via mass spectrometry but this was not available.

Pulmonary ATTR amyloidosis has been identified in several autopsy studies.[4–7] These are generally reported as incidental alveolar deposits in asymptomatic cases. Ante-mortem diagnosis of systemic pulmonary ATTR amyloidosis is rare.[14–16] Only two out of 16 ante-mortem cases of pulmonary amyloidosis were reported by Yamada et al.[14] to be wild-type ATTR over a 19-year period at two Japanese cardiovascular and respiratory centres. A study from the Mayo Clinic identified 28 ante-mortem cases of pulmonary ATTR amyloidosis over a 15-year period.[15]

A rare feature of this case was the diagnosis of pulmonary tuberculosis. The patient had no endemic risk factors for mycobacterium tuberculosis and was not immunocompromised. Secondary AA amyloidosis is well described in chronic inflammatory states including mycobacterium tuberculosis.[8] This generally occurs more frequently in those from developing countries.

Radiological assessment of pulmonary amyloidosis demonstrates a wide spectrum of features including consolidation, nodules, pleural effusions, calcified granulomas, septal thickening, and cysts.[3,5,15] The most common radiological finding in pulmonary ATTR amyloidosis is small, diffuse, bilateral nodules.[15] In this case, the micronodular pattern displayed on chest CT was a new finding on review of interval scans over 4 years. Typically, a 'miliary' nodular pattern has a differential list including infection (tuberculosis, histoplasmosis, mycoplasma, nocardia, and blastomycosis), inflammatory disorders (sarcoidosis, pulmonary eosinophilia, hypersensitivity pneumonitis, malignancy (primary and metastases) and pneumoconiosis.[17] Pulmonary ATTR amyloidosis can also present as an isolated nodular deposit without cardiac or systemic involvement.[16]

Pulmonary ATTR amyloidosis is thought to be a senile disease with an unclear clinical significance. Previous autopsy studies have suggested cardiac disease as the most common cause of death in patients with pulmonary amyloidosis.[5] Eggleston et al.[15] found that patients who died in their follow up period had symptomatic nodular parenchymal disease with a prognosis of less than 2 years. Given our case involved concurrent mycobacterial tuberculosis infection the finding of pulmonary ATTR amyloidosis was thought unlikely to be the cause of deterioration.

There is no established causal links between pulmonary ATTR amyloidosis and tuberculosis infection. This case raises the possibility of clinicians needing to keep tuberculosis in consideration in patients with cardiac ATTR amyloidosis. Further reports are needed to explore whether there is a role of wild type pulmonary ATTR amyloidosis increasing risk of mycobacterium tuberculosis infection. To our knowledge, this is the first Australian report of an ante-mortem finding of pulmonary ATTR amyloidosis with further cases required to establish its clinical significance.

AUTHOR CONTRIBUTIONS

H.S.: Key writing and editing. **A.M.**, **J.S.**, **R.C.**, **P.H.**: Substantial contributions to the conception and design of

the work. **H.W.**: Drafting the work or revising it critically for important intellectual content and final approval.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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