

Received: 2016.07.20
Accepted: 2016.09.14
Published: 2016.11.22

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 874-879
DOI: 10.12659/AJCR.900682

Hereditary Amyloidosis with Recurrent Lung Infiltrates

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 51
Final Diagnosis: Familial amyloidotic polyneuropathy with lung involvement
Symptoms: Cough • dyspnea • lethargy
Medication: Diflunisal
Clinical Procedure: Fiberoptic bronchoscopy with trans-bronchial biopsy
Specialty: Pulmonary Medicine

Objective: Rare co-existence of disease or patholog
Background: Amyloidosis is a protein conformational disorder characterized by extracellular deposition of amyloid fibrils in extracellular tissue. Lung involvement is most commonly caused by secondary AL amyloidosis. The familial autosomal-dominant senile transthyretin (ATTR) disease manifests mainly as polyneuropathy and restrictive cardiomyopathy denoting the name familial amyloidotic polyneuropathy (FAP). Rarely, this form manifests with clinical and radiologically relevant respiratory tract symptoms and lung involvement.

Case Report: A 51-year-old male former smoker presented with progressive lower-extremity weakness of several months' duration. He was ultimately diagnosed with chronic demyelinating polyneuropathy and treated with intravenous immunoglobulin therapy. Subsequently, he was admitted with heart failure symptoms and pulmonary infiltrates and his echocardiogram showed a 'myocardial speckled pattern', prompting an endomyocardial biopsy, which showed transthyretin amyloid deposition. He was started on diflunisal. Additionally, serial radiographic imaging of his chest over 3 different admissions for cough, dyspnea, hypoxemia, and lethargy demonstrated recurrent pulmonary infiltrates. A fiberoptic bronchoscopy with trans-bronchial biopsies revealed amyloid deposition in the lung tissue.





Conclusions: The clinical presentation of recurrent or persistent pulmonary symptoms and fleeting infiltrates on imaging in a patient with familial amyloidotic polyneuropathy is not common; when present, it should raise the suspicion of respiratory tract involvement.

MeSH Keywords: MeSH: Amyloid Neuropathies, Familial • Amyloidosis, Familial • Pulmonary Alveoli

Units of measurement: K/CU MM – cubic millimeter; pg/m – picogram/milliliter; ng/mL – nanogram/milliliter; mmHg – millimeter mercury; F – Fahrenheit

Abbreviations: AL – immunoglobulin light-chain; AA – secondary amyloid; ATTR – amyloidogenic transthyretin; SSA – senile systemic amyloidosis; FAP – familial amyloidotic polyneuropathy; CT – computed tomography

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/900682>

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Background

Amyloidosis is a pathologic deposition of insoluble proteins in different tissues in the body. Amyloidosis is majorly categorized into: 1) immunoglobulin light-chain (AL), 2) secondary (AA), 3) hereditary or senile transthyretin (ATTR), and 4) dialysis-associated disease. Transthyretin is the precursor protein in both familial amyloidotic polyneuropathy and systemic amyloidosis (SSA), but these 2 are distinct diseases. Different TTR variants have been discovered, the most common of which is mutation Val30Met (V30M).

Familial amyloidotic polyneuropathy ATTR V30M is an insidious disease that fully presents its end stage in approximately 10 years. It is well-described to involve the heart, kidneys, gastrointestinal tract, eyes, and peripheral and autonomic nervous system. The clinical and pathological changes seen in lung disease in FAP have been rarely described due to its delayed presentation.

Case Report

A 51-year-old-male former smoker (30 pack-years) with bilateral carpal tunnel syndrome and prior cervical and lumbar spinal fusion surgeries was referred from an outside facility to our Neurology Department for progressive bilateral lower extremity weakness, pain, and paresthesia of 3 months' duration, but during the last month prior to his presentation he was not able to walk with his cane like he used to and required full assistance to ambulate. These symptoms were also associated with bowel and bladder incontinence. Concomitant symptoms were ongoing fatigue, weight loss, malaise, backache, and lower extremity edema. He denied cough, dyspnea, fever, or night sweats. Family history was significant for lung cancer in his father. His physical examination disclosed a fully alert, oriented but anxious middle-age man with a blood pressure of 138/89 mmHg, pulse rate of 101 beats per minute, respiratory rate of 14 breaths per minute, temperature 97.5°F (15°C) and an oxygen saturation on room air of 97%. His cardiovascular, respiratory, and abdominal examination were unremarkable. His neurological examination was remarkable for bilateral lower extremity weakness as follows: distal ankle 1/5, lower extremity 1/5, and proximal hip 0/5; sensation in both lower extremities L4-L5 levels up to knee decreased, T12 level decreased, T11 level preserved, and S3-S5 decreased. Rectal tone was absent. Deep tendon reflexes: 1+ bilateral upper extremities and bilateral knee and Achilles tendon reflexes were absent. He had normal flexor plantar reflex bilaterally. The lower extremities were also notable for pitting edema. Initial laboratory testing was unremarkable. A magnetic resonance imaging study of the cervical and lumbo-sacral spine did not show evidence of spinal cord canal stenosis or compression. An electromyography

study was consistent with a severe, chronic sensorimotor neuropathy with both axonal and demyelinating features suggestive of inflammatory neuropathy. He was treated with intravenous immunoglobulin and then subsequently discharged to an acute rehabilitation facility.

A week after discharge, he was readmitted to our hospital with lethargy, fever, hypotension, and hypoxia. He denied sick contacts or occupational exposures. On arrival, he was afebrile and normotensive. His lung examination revealed bibasilar decreased breath sounds and inspiratory crackles more prominent on the left. There was bilateral lower extremity edema and chronic skin discoloration. His laboratory examination was notable for leukocytosis of 13.8 K/CU MM, troponin I elevation to 2.65 ng/mL (peak), BNP 563 pg/mL, arterial blood gas pH 7.46 pCO₂ 40 mmHg paO₂ 61 mmHg O₂ Sat 94% on continuous positive airway pressure of 8 cmH₂O and FiO₂ of 0.40. The electrocardiogram showed non-ST segment elevation myocardial infarction and the initial impression was demand ischemia secondary to hypoxemia. A chest x-ray showed bilateral upper and lower lobe airspace opacities. A computer tomography (CT) scan of the chest showed bilateral diffuse ground glass opacities in the upper lobes, lingula and left lower lobe consolidations, and a small right pleural effusion (Figure 1). He was treated with supplemental oxygen and broad-spectrum antibiotics for healthcare-associated pneumonia.

A 2D-echocardiogram was remarkable for a reduced left ventricular ejection fraction of 45%, inferior wall hypokinesis, mildly reduced right ventricular function, and a 'speckled myocardium'. The left heart cardiac catheterization showed non-obstructive coronary artery disease. A cardiac magnetic resonance image showed possible amyloidosis, which was confirmed with a right ventricle endomyocardial biopsy demonstrating transthyretin (TTR)-type amyloid deposition. Liquid chromatography tandem mass spectrometry was performed and detected an amino acid sequence abnormality in the TTR protein (Thr60Ala) strongly suggestive of hereditary TTR amyloidosis. He was started on diflunisal and referred to an amyloidosis program at a local specialty hospital.

Two months later, during a routine follow-up office visit, he reported a 3-day history of non-productive cough and exertional dyspnea. His oxygen saturation on room air was 89%. He was afebrile. A repeat non-contrast chest CT scan showed improvement of the bilateral upper lobe ground glass opacities, persistence of the lingular and left lower lobe consolidations, and a new right lower lobe airspace disease (Figure 2). A bronchoscopy with trans-bronchial biopsy was scheduled, but on the day of the procedure his chest x-ray showed unexpected interval improvement or resolution of the bilateral lower lobe and lingular infiltrates (Figure 3). The procedure was canceled.

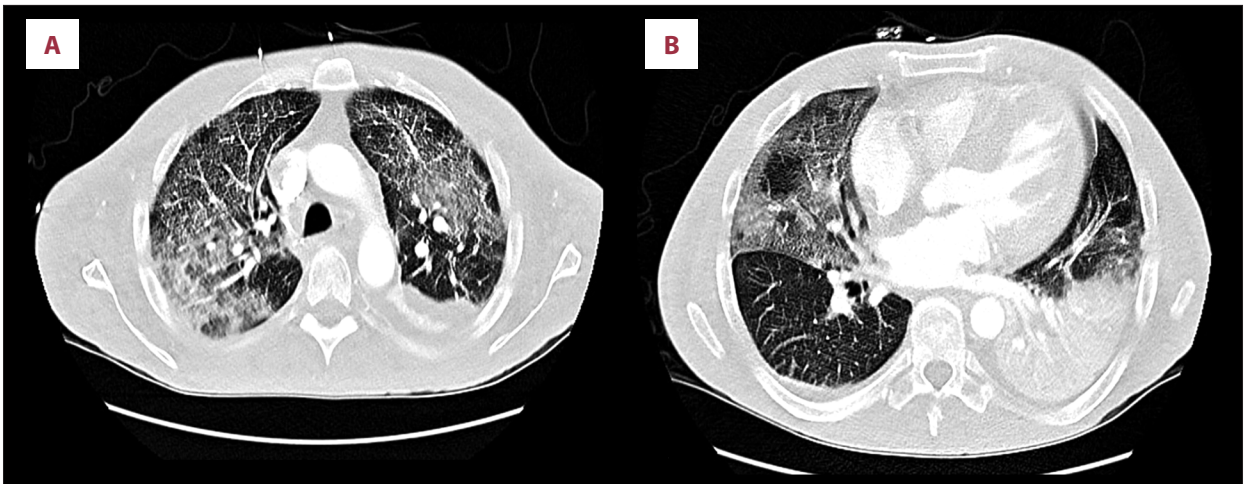


Figure 1. Axial chest CT scan images at different levels. Bilateral upper-lobe ground glass opacities (A) and right upper-lobe ground glass opacities with lingular and left lower-lobe consolidations (B).

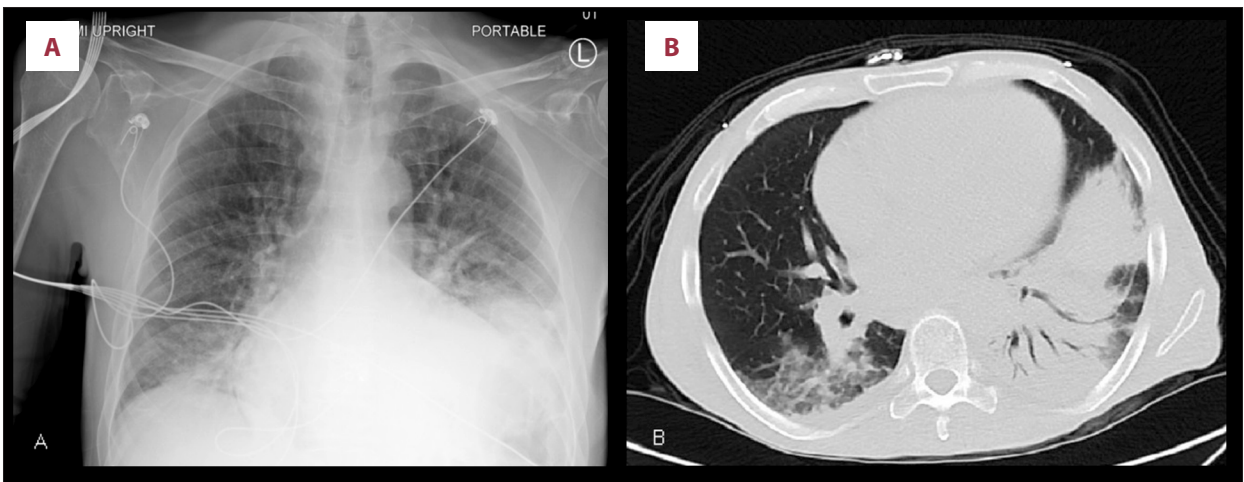


Figure 2. Portable chest x-ray and axial chest CT scan images. Bilateral interstitial and airspace opacities in the upper and most notable in the lower lung zone (A). Improved aeration of the right upper lobe with persistent lingular and left lower-lobe infiltrates (Figure 1) and evolving right lower-lobe infiltrate (B).



Six to eight weeks later, he was readmitted to the hospital with recurrent symptoms of cough with brownish sputum production, fevers, hypoxemia, malaise, and fatigue but no dyspnea. He appeared chronically ill, but without respiratory distress. A respiratory multiplex polymerase chain reaction test was negative. His chest imaging demonstrated a new right lower lobe infiltrate and residual left lower lobe airspace disease (Figure 4). A fiberoptic bronchoscopy revealed normal endobronchial anatomy and no growth from the broncho-alveolar

Figure 3. PA chest x-ray on inspiration. Significant interval improvement of bilateral airspace disease more evident at the left mid- and right lower-lung zones (Figure 2) and left hemi-diaphragm elevation.

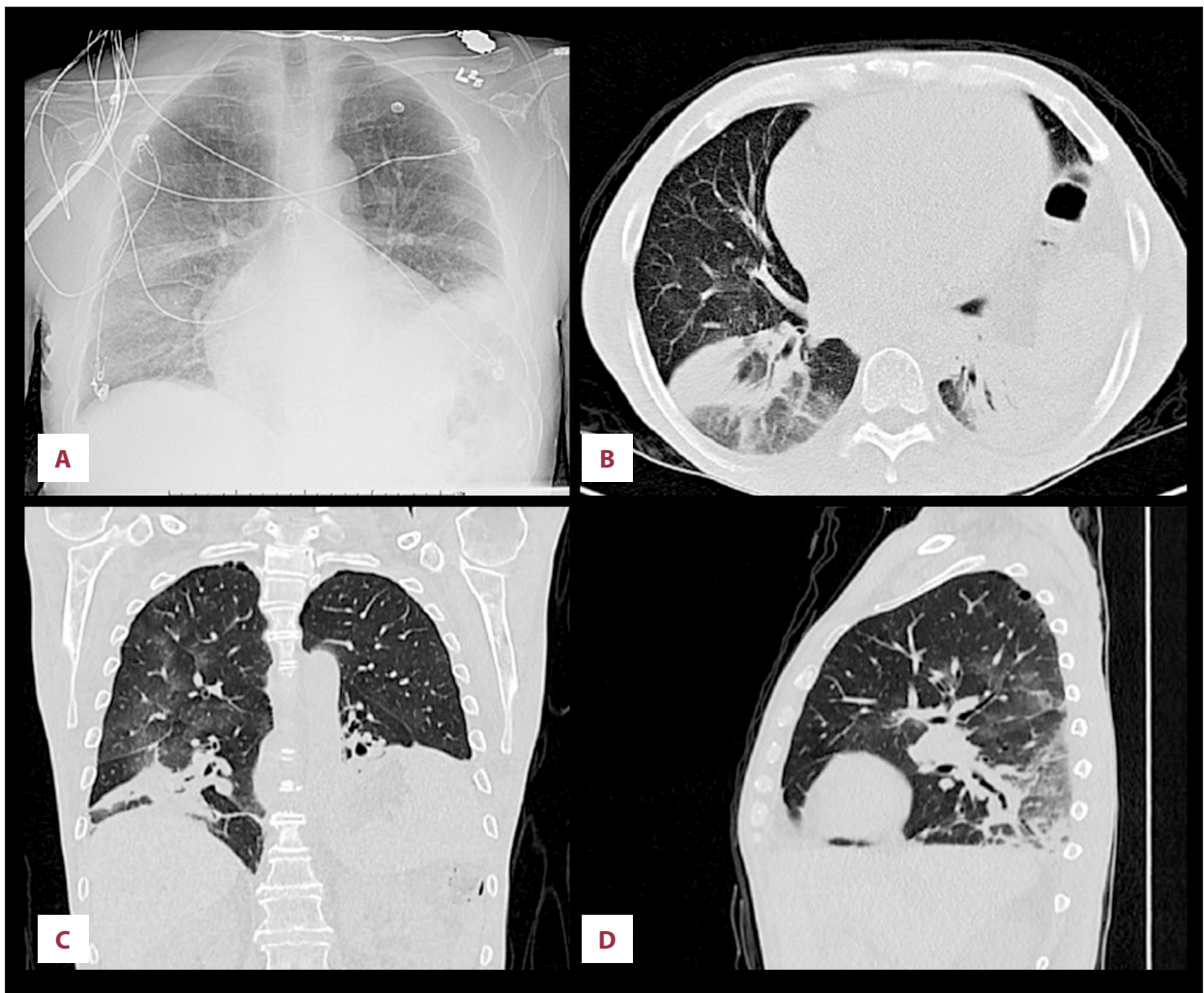
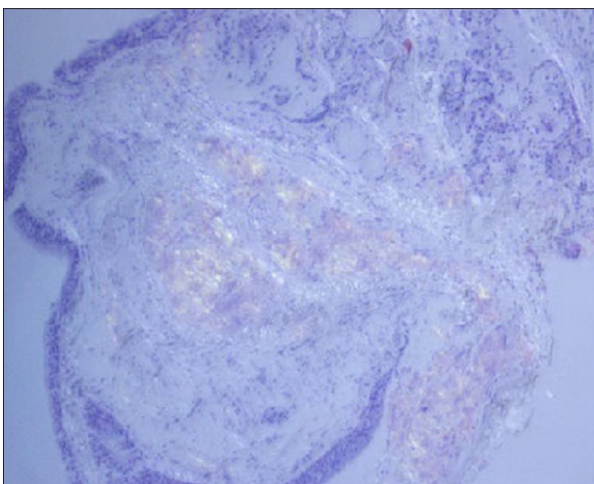


Figure 4. Portable chest x-ray and lung windows of a single chest CT showing elevation of the left hemi-diaphragm and increased left basilar opacity and prominent markings in the right mid- and lower-lung zones (A). Axial view of the CT scan showing bilateral new right and persistent left lower-lobes consolidations (B). Coronal view with evidence of mild apical emphysema, patchy ground glass opacities, and bilateral lower lobe consolidations (C). A right lower-lobe infiltrate, ground glass opacities, and bronchiectasis are evident in the sagittal view (D).



lavage fluid that was cultured for bacteria, fungi, virus, and mycobacteria. Cytology was negative for malignant cells. Trans-bronchial biopsy specimens from the superior segment of the right lower lobe showed non-specific chronic inflammation and the classic birefringence on Congo red stain (Figure 5).

After the patient was diagnosed with cardiac amyloidosis, he was referred to a specialized amyloidosis center, but he was unable to enroll for any therapy. In the interim, he was readmitted to our hospital a number of times; the most important re-admission was after a left comminuted intertrochanteric

Figure 5. Trans-bronchial biopsy specimen of the right lower lobe showing focal patchy positivity for amyloid. (Congo red stain ×200).

fracture. Subsequently, his overall functional status rapidly declined, preventing him from actively participate in a full rehabilitation program. His condition was significantly limited by shortness of breath despite maximal medical therapy for heart failure. During his last admission to the hospital, the palliative care team was consulted. The patient wished to stay home for as long possible and home hospice care was arranged given his overall poor prognosis.

Discussion

Amyloidosis is a protein conformational disorder characterized by extracellular deposition of amyloid fibrils in extracellular tissue. It can be hereditary or acquired, localized or systemic, and has the potential to infiltrate virtually all organ systems [1]. The patterns of respiratory system involvement are: nodular, trachea-bronchial, diffuse alveolar septal, affecting lymph nodes or with pleural effusions. The histological classification is based on its fibril protein: 1) immunoglobulin light-chain (AL), 2) secondary (AA), 3) hereditary or senile transthyretin (ATTR), and 4) dialysis-associated disease. Pathologically, respiratory involvement occurs in 50% of patients and is usually with AL amyloidosis. Hereditary amyloidosis is a rare autosomal dominant disease with a prevalence of less than 1 in 100,000 people in the United States. There is variability in the penetrance of this disease; hence, family history may not be very reliable [2].

Prominent lung manifestation is not a recognized feature of ATTR [3]. Transthyretin, a 4-unit polymer involved in thyroxine and retinol transport in the serum, is a mutual precursor protein in 2 distinct types of systemic amyloidosis: familial amyloidotic polyneuropathy (FAP) and senile systemic amyloidosis (SSA). About 101 point mutations have been discovered in patients with FAP. Among the mutated types of TTR, ATTR V30M is the most common. Variant types of TTR amyloid were not found in patients with SSA, which implies that the wild-type TTR can produce amyloid *de novo*. The familial autosomal-dominant ATTR disease manifests mainly as polyneuropathy and restrictive cardiomyopathy, which has a particularly late onset in adulthood. High mortality is often seen with cardiac disease.

Our patient had marked involvement of the heart, nervous system, and lungs with recurrent symptoms of cough, dyspnea, and lethargy, which is a described manifestation in the diffuse-alveolar septal pattern. The cases reported in the literature of symptomatic pulmonary involvement in familial amyloidosis are limited. Most of the cases reported have been during autopsy. During our patient's first re-admission, his clinical presentation was more consistent with either acute heart failure exacerbation and/or pneumonia, and he was managed as such.

We did not have an initial impression of amyloidosis involving the lung until after he was diagnosed with cardiac amyloidosis and had recurrent waxing and waning pulmonary infiltrates, which did not improve with antibiotic therapy. As suggested by Ueda et al., it is possible that patients with ATTR amyloidosis do not manifest any symptoms of respiratory tract involvement because their disease is more localized to the nervous and cardiac systems, and it is not until the disease has been present for a number of years that some evidence of lung involvement is evident. Their study also suggested that age plays a role in the amyloid deposition of patients with ATTR disease [4]. We arrived at the diagnosis of amyloid deposition in the lung after a bronchoscopy-guided trans-bronchial biopsy. Additionally, in this particular case, the patient's major symptoms and complaints were predominantly related to the respiratory tract and cardiovascular systems. This makes it particularly difficult to manage when there is no definite medical therapy for ATTR other than supportive care and conventional management of heart failure, including diuretics, which should be used with caution as patients with cardiac amyloidosis already have a restrictive cardiac physiology with already low end-diastolic volumes. Diuretics can further decrease the preload and, in turn, cardiac output. Ultimately, liver transplantation is indicated.

As described in this case, ATTR amyloidosis patients can have the history of carpal tunnel syndrome and this can precede the onset of cardiac involvement for up to a decade. Diagnosis of cardiac amyloidosis is suggestive when imaging reveals a picture of infiltrative cardiomyopathy. Medical therapy for ATTR amyloidosis is lacking. Diflunisal has been shown to delay the progression of neurological deterioration in patients with ATTR, but the effect on cardiac disease is unknown. Other drugs like tafamidis, which is approved in Europe and Japan, have also been shown to reduce neurological decline. This medication is not approved to be used in the United States. Liver transplantation has been considered the best treatment for patients with FAP since both wild- and variant-type TTR amyloids are produced in the liver. Transplantation provides the recipient a source of the normal gene variant of transthyretin. Long-term outcomes of liver transplantation for mutant ATTR indicate that neuropathy and organ impairment are usually irreversible. Five-year survival rates in 1 study were 100% and 59% for V30M and non-V30M ATTR, respectively, with death, primarily caused by cardiac problems and sepsis [5]. When transplantation is performed in the early stage of disease, increased post-operative survival is expected with FAP. However, the occurrence of cardiac amyloid deposition has been reported in some transplanted patients [6]. Additionally, it may be important to thoroughly assess for any potential lung involvement in transplant candidates, including chest imaging and pulmonary function tests, as there have been cases in which cardiac amyloidosis recurs and might also involve the respiratory

system itself. Finally, it is not clear whether identifying lung involvement would change the management or approach to a particular patient; however, it is important to take into consideration that the disease can also manifest in such way and thus a high index of suspicion for lung involvement should be raised when a patient with FAP disease presents with cough, hypoxemia, and fleeting pulmonary infiltrates.

Conclusions

Hereditary amyloidosis predominantly manifests with heart and nervous system involvement. In previous studies, an association between aging and FAP amyloidosis involving the

lung has been suggested; however, most of these patients do not survive long enough to have florid respiratory symptoms suggestive of lung amyloid deposition. Liver transplantation has been the most promising therapy for increased survival in patients with FAP, but disease can recur. Symptomatic lung disease is very rare and it has only been described in a few cases. Patients with ATTR who present with respiratory symptoms and recurrent pulmonary infiltrates should raise the suspicion of respiratory system involvement.

Disclosure statement

None of the authors have anything to disclose.

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