

Pleural amyloidosis with recurrent pleural effusion and pulmonary embolism

A case report

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Abstract

Rational: Clinical and radiologic manifestations of pleural amyloidosis are non-specific. And it can easily be missed or misdiagnosed. Meanwhile, few studies document amyloidosis presenting with pulmonary infarcts at the same time. Hereby, we report a case of immunoglobulin light chain amyloidosis (AL) pleural amyloidosis with pulmonary embolism rarely reported.

Patient concerns: A 66-year-old male patient who suffered recurrent pleural effusion for more than 6 months and coughed for 2 months was admitted to hospital for clear diagnosis and treatment. He was previously engaged in a job which exposed him to dust and talcum powder for a long time. He underwent right thoracentesis and anti-infective treatment before admission. The patient's cough and shortness of breath were slightly relieved. He still experienced pleural effusion and had symptoms of cough and shortness of breath.

Diagnosis: Chest X-ray demonstrated bilateral pleural effusion. Chest computed tomography (CT) angiography demonstrated left lower pulmonary embolism. The thoracoscopy showed hyperaemia and black tissue of the parietal pleura, which were biopsied. The pathological diagnosis was amyloidosis. The final diagnosis of this patient was AL pleural amyloidosis and left lower pulmonary embolism.

Intervention: During the hospitalization, the patient underwent thoracentesis several times without any conclusive diagnosis. After the diagnosis of pleural amyloidosis, the patient was repeatedly advised to undergo bone marrow biopsy and pleurodesis which the patient refused. For pulmonary embolism, Nadroparin calcium combined Warfarin were administered as anticoagulative therapy.

Outcomes: The pulmonary embolism resolved 13 days after the anticoagulant therapy. The patient refused treatment for pleural effusion and requested for discharge. At the time of discharge, shortness of breath was relieved, and the pleural effusion had decreased. The patient was lost to follow-up.

Lessons: Amyloidosis is a rare disease which can be ignored by many clinicians. It needs to be diagnosed promptly since the prognosis of amyloidosis is poor. Clinicians must improve relevant understandings of this kind of disease so as not to delay the diagnosis and treatment. We must be alert to the occurrence of embolic disease among amyloidosis patients. Last but not least, we should also think of the possibility of amyloidosis in patients with pulmonary embolism and recurrent pleural effusion.

Abbreviations: AL amyloidosis = immunoglobulin light chain amyloidosis, CT = computed tomography, LDH = lactate dehydrogenase, MTB = *Mycobacterium tuberculosis*, RIF = rifampicin.

Keywords: amyloidosis, pleural effusion, thoracentesis, thoracoscope

1. Introduction

Amyloidosis is an unusual disease caused by the extracellular deposition of amyloid substance in various organ or tissues, which

is more common in kidney, liver, gastrointestinal, nervous system, and skin. However, reports about amyloid involvement of the pleural amyloidosis with intractable pleural effusion are scarce.^[1] The most frequent types of amyloidosis are the immunoglobulin light chain (AL) amyloidosis and the serum amyloid A. The former is associated with plasma cell dyscrasia, while the latter results from longstanding chronic infectious diseases.^[2] Clinical and radiologic manifestations of pleural amyloidosis are non-specific. And it can easily be missed or misdiagnosed. Meanwhile, few studies document amyloidosis presenting with pulmonary infarcts at the same time. Hereby, we report a case of AL pleural amyloidosis with pulmonary embolism rarely reported.

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2. Consent

The clinical and imaging data were obtained with the patient's consent for purpose of scientific research publication.

3. Methods section

The Ethics Committee of Guangdong Provincial Hospital of Chinese and Western Medicine had approved this study.

4. Case presentation

A 66-year-old male patient who suffered recurrent pleural effusion for more than 6 months and coughed for 2 months was admitted to hospital for clear diagnosis and treatment. He was previously engaged in a job which exposed him to dust and talcum powder for a long time.

He underwent right thoracentesis and anti-infective treatment before admission. The patient's cough and shortness of breath were slightly relieved. He still experienced pleural effusion and had symptoms of cough and shortness of breath.

On physical examination, the patients' blood pressure was 110/80mm Hg and SaO₂ was 96%. Respiratory rate was 18 times per minute. Heart rate was 87 times per minute. Temperature was 36.8°C. There was decreased breath sound at right lung base. There was no edema in lower limbs. Laboratory examinations revealed that complete blood count and serological data, including the C-reactive protein level and procalcitonin level, was within the normal range. Laboratory tests related to the immune system were also negative. The comprehensive metabolic panel, including total protein, liver function tests, showed pro-BNP of 1211pg/mL, D-dimer of 4.85ug/mL, total protein of 47.1g/L, albumin of 31.9g/L, globulin of 15.2g/L, serum troponin I of 0.002ng/mL. Echocardiography indicated diastolic dysfunction. Chest X-ray taken at the time of admission demonstrated bilateral pleural effusion. There was much pleural effusion on the right side. During the hospitalization, the patient underwent thoracentesis 3 times on right side while 1 time on left side. The 1st thoracentesis which is performed on day 1 of admission drained egg-yellow effusion (Fig. 1). The biochemical examination showed lymphocyte count of 98%, monocyte count of 2%, glucose of 6.88mmol/L, total protein 37.8g/L, lactate dehydrogenase (LDH) of 96mmol/L, adenosine deaminase of 5.1U/L. The subsequent 2 thoracentesis also presented as egg-yellow effusion. The biochemical result were suggestive of exudative effusions for both of them. Cultures were also negative. Cytological examination of all pleural effusion samples revealed mesothelial cells and numerous lymphocytes without cancer cells.

For this patient with repeated pleural effusions, we considered the possibility of pneumonia effusion, or tuberculosis, or tumor?

Initial treatment was mainly based on anti-infective therapy in the early hospital stay. Levofloxacin was selected as antibiotics. However, we found that pleural effusion did not decrease but increased after a dynamic observation of pleural fluid using doppler ultrasound examination. As a result, we suspended the use of levofloxacin on day 14 of admission. Other diagnosis was suggested. In order to find the diagnosis, thoracoscope (day 5), GeneXpert *Mycobacterium tuberculosis* (MTB)/rifampicin (RIF) test on pleural effusion (day 13) and chest CT angiography (day 15) were all performed during early hospitalization. GeneXpert MTB/RIF test on pleural effusion was negative. Chest CT angiography demonstrated left lower pulmonary embolism (Fig. 2). The thoracoscopy showed hyperaemia and black tissue of the parietal pleura, that were biopsied. The specimen was submitted for cytopathologic valuation. Paraffin electron microscopy of pleural biopsy was consistent with pleural amyloidosis (Fig. 3). The lesion was mainly comprised of amyloid deposition. Congo red stain was positive in the pleural tissue (Fig. 4). When viewed under polarized light, the affected tissue typically shows apple-green birefringence after staining with Congo red (Fig. 5). The stainability of Congo red stain was not lost by potassium permanganate treatment, the lesion was pathologically confirmed to be amyloidosis, excluding the amyloid protein A (AA) type (Fig. 6). The patient refused bone marrow biopsy. We could not further distinguish whether the disease was primary or secondary, despite there were no significant clinical symptom of multiple myeloma. As a result, immunoglobulin light chain (AL) type amyloidosis of pleura was suggested.

The final diagnosis of this patient was AL pleural amyloidosis and left lower pulmonary embolism.

In aspect of pulmonary embolism, Nadroparin calcium combined Warfarin were performed as anticoagulative therapy. Thirteen days later, chest CT angiography did not see previous pulmonary embolism lesion (Fig. 7). And the patient's heart was functioning normally. In aspect of pleural amyloidosis, the patient was repeatedly advised to undergo bone marrow biopsy and pleurodesis. The patient refused and requested for discharge after serious consideration. The patient's shortness of breath was relieved at the time of discharge, and the pleural effusion was less than before. After discharge, the patient's phone could not be connected during our follow-up.

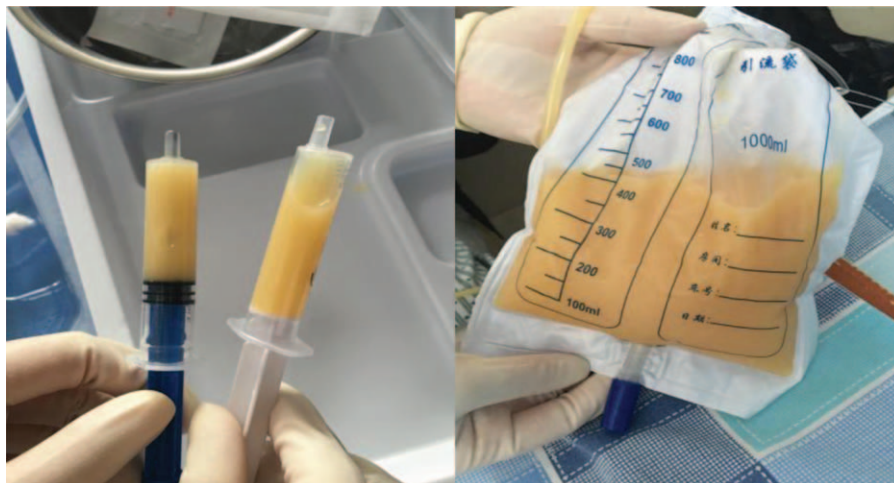


Figure 1. The 1st thoracentesis which is performed on day 1 of admission drained egg-yellow effusion.

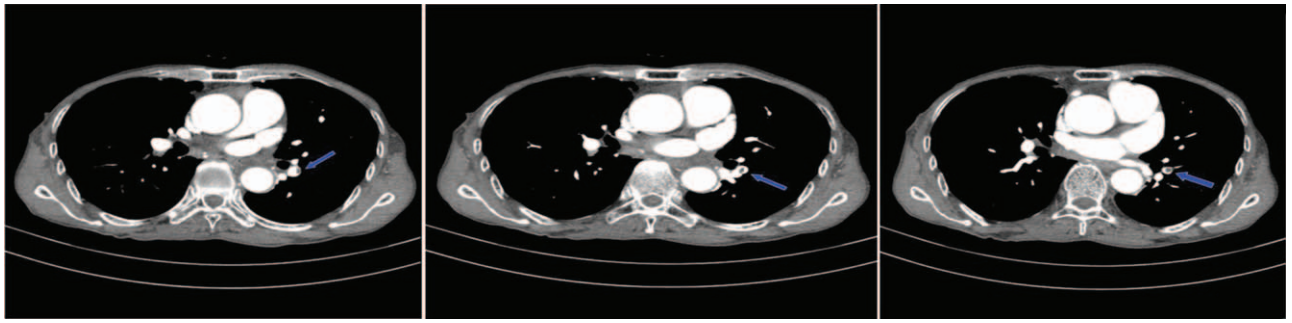


Figure 2. CT angiography scan of the chest showed left lower pulmonary embolism (blue arrow). CT=computed tomography.

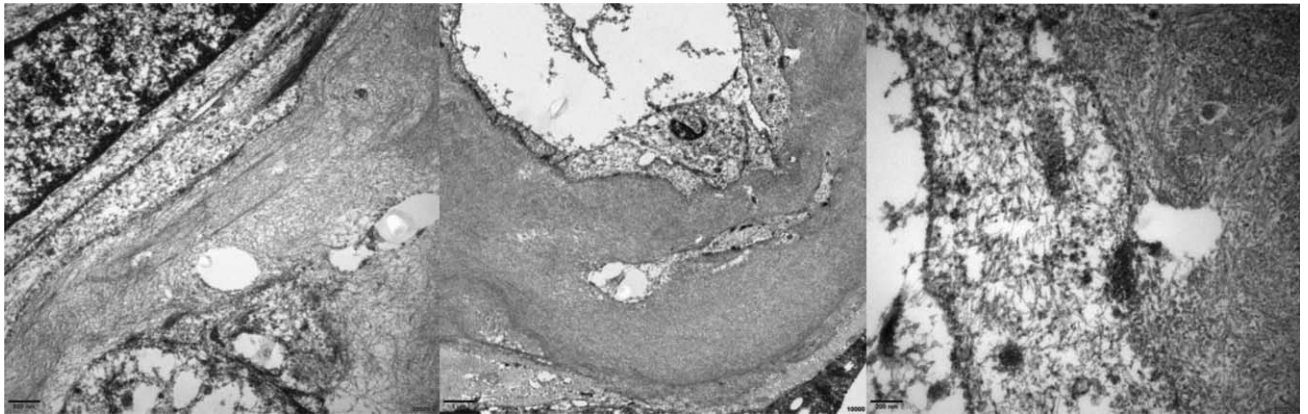


Figure 3. Paraffin electron microscopy of pleural biopsy was consistent with pleural amyloidosis.

5. Discussion

Amyloidosis is a rare condition characterized by extracellular deposition of proteinaceous fibrils in a β -pleated sheet configuration, which produce dysfunction of deposited organs or tissues to a different degree.^[3] This results in a wide range of clinical manifestations depending upon their chemical composition, location and amount. Various classification schema of amyloid-

osis are currently in use and are based on anatomy, pathogenesis, chemical properties of pathogenic proteins. One of the classification methods based on clinical features and amyloid biochemical components can more accurately reveal the cause and guide treatment. More than 30 proteins that can cause human amyloidosis have been discovered.^[4] The most frequent types of amyloidosis are the AL amyloidosis and the serum

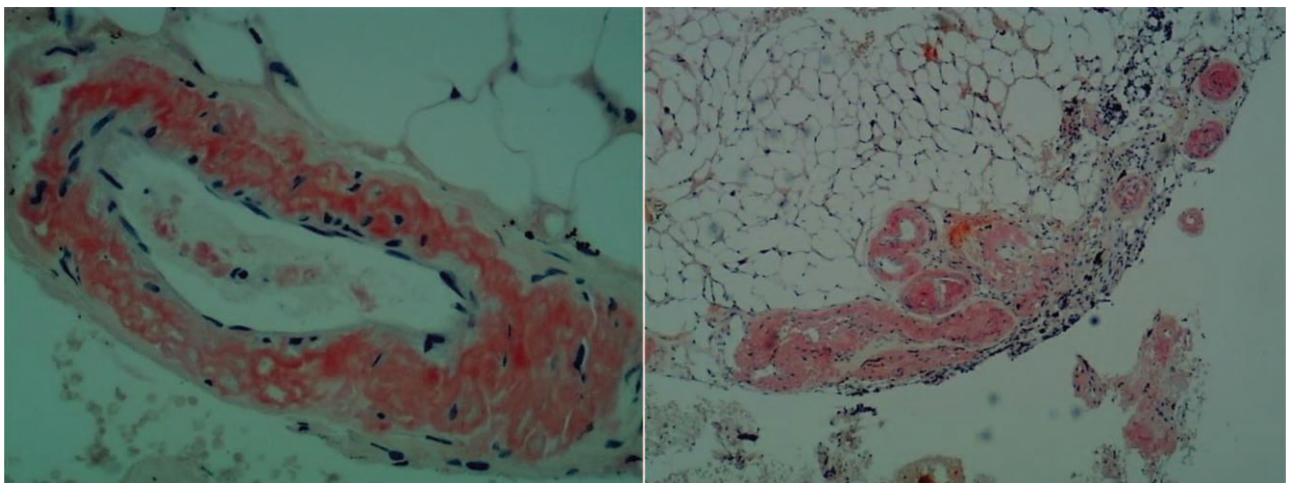


Figure 4. The lesion mainly comprised amyloid deposition showing Congo red stain was positive in the pleural tissue.

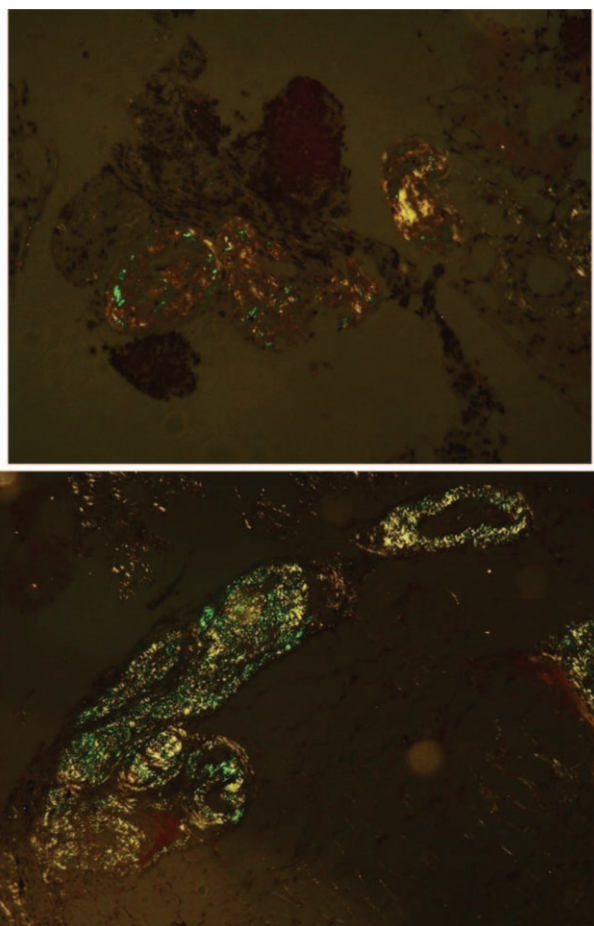


Figure 5. Parietal pleura at polarized light, there was an apple green refringence, confirmed the deposition of amyloid substance.

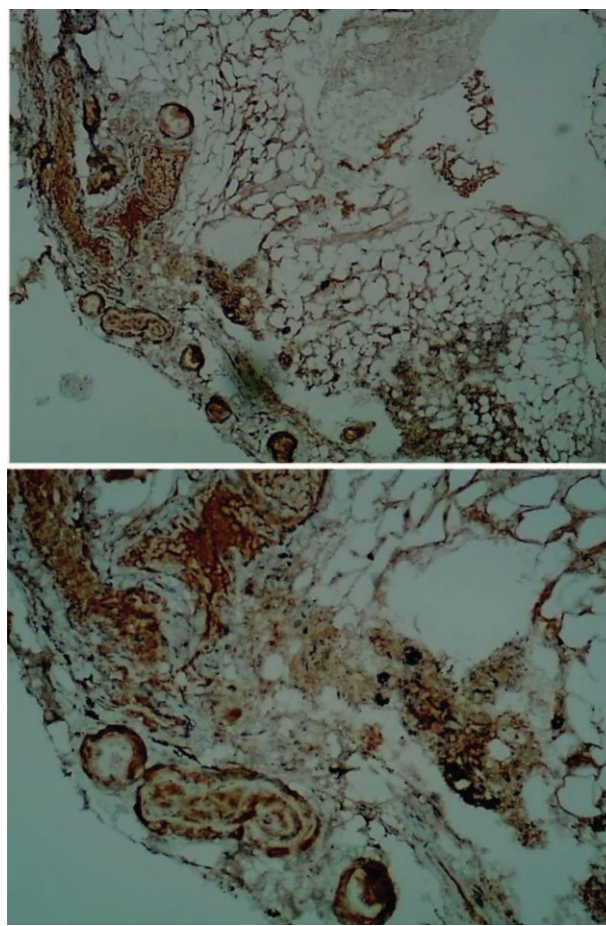


Figure 6. The stainability of Congo red stain was not lost by potassium permanganate treatment, and the lesion of parietal pleural tissue was pathologically confirmed to be amyloidosis excluding the amyloid protein A (AA) type.

amyloid A. Primary systemic amyloidosis (AL) mainly affects the heart, kidneys, gastrointestinal tract, peripheral, and autonomic nerves, skin, joints, and blood vessels of virtually all organs. But pleural amyloidosis with recurrent pleural effusion are rarely reported and it is usually associated with AL amyloidosis, which accounts for up to 80% of pulmonary amyloidosis.^[5,6] Clinical and radiologic manifestations of pleural amyloidosis are non-specific. Clinicians pay less attention to the pleural effusion caused by pleural amyloidosis, leading to missed diagnosis and misdiagnosis. The diagnosis of the disease relies on respiratory tissue biopsy and specific Congo red tissue staining positive. The affected tissue typically shows apple-green birefringence after staining with Congo red under polarized light which is the gold standard for diagnosing amyloidosis.^[7] Typical aspects of thoracoscope consist of hyperaemia of the pleural surface, inflammation with nodular lesions or brown nodules of the parietal pleura.^[8] Persistent pleural effusions occur in 1 to 2% of patients with systemic amyloidosis and are usually associated with poor prognosis and often refractory to treatment. Pleurodesis has been effective in some cases.^[9]

An epidemiological survey in the United Kingdom showed that the incidence of systemic amyloidosis was over 0.8/10 million, most common with the AL type. It usually occurs in patients ages 60 to 69 years old.^[10] Amyloidosis can affect systemic organs, and its clinical manifestations are extensive and complex, often

without specificity. Less than a quarter of the amyloidosis manifests as a single organ involvement.^[11]

In this case, multiple organ systems such as breathing, heart are affected. The main manifestations are pleural effusion and diastolic dysfunction. However, we did not perform endocardial myocardial biopsy on this patient. We were not sure if there were involvement in the myocardium. Cardiac amyloidosis is mainly characterized by restrictive cardiomyopathy and progressive diastolic dysfunction, followed by bilateral ventricular systolic dysfunction and arrhythmia.^[12] In the event of heart failure on the cardiac amyloidosis patients, the average survival time for untreated patients was 6 months.^[13] Recent data show that the life expectancy of with AL amyloidosis patients has increased from 6 months to 16 to 20 months.^[14]

The mechanism of amyloidosis causing pleural effusion is not very clear. If the nature of the pleural effusion is transudate, we should take the systemic factors such as congestive heart failure due to cardiac involvement, nephrotic syndrome due to renal involvement, and hypoproteinemia due to liver involvement into consideration. It can also be caused by amyloid material blocking the lymphatic flow and the deposition of amyloid material in the pulmonary blood vessels leading to increased pulmonary venous pressure. If the nature of the pleural effusion is exudate, considering that it is because the deposition of amyloid material in the pleura caused pleural diffuse inflammation. In this case, the



Figure 7. Through timely anticoagulant therapy, chest CT angiography scan which was performed 13 days after the diagnosis of pulmonary embolism did not see previous pulmonary embolism lesion. CT=computed tomography.

patient experienced 4 thoracentesis. Egg-yellow effusion drained from the 1st thoracentesis showed protein is in the exudate range, whereas LDH is not. The results from the subsequent 2 thoracentesis procedures were suggestive of exudative effusions. Pleural effusion caused by amyloidosis can be unilateral or bilateral and can be exudate or transudate. A retrospective study found that about 37% were exudates.^[9] There reported a case of amyloidosis patients with protein-discordant chylothorax pleural effusion.^[15] Amyloidosis combined with egg-yellow effusion was never reported before. Rarely, transudative chylothoraces can occur in conditions with both chyle leakage and a coexisting process that causes a transudative effusion, such as congestive heart failure, constrictive pericarditis, cirrhosis with hepatic hydrothorax, nephrotic syndrome, superior vena cava syndrome, and amyloidosis. The mechanism may be related to the increase of left subclavian vein pressure.^[15] When we encounter intractable pleural effusion, undetermined effusion, or even chylothorax or egg-yellow effusion in our clinical work, we need to consider the possibility of amyloidosis and perform a thoracoscopic examination based on clinical judgment.

Pulmonary embolism as a fatal disease requires prompt and correct diagnosis and treatment. Pulmonary arterial embolism is the most common cause of pulmonary infarcts. However, non-embolic causes are uncommon. Thromboembolic disease are rare in amyloid patients. There are only a few cases reported in all over the world. In 2010, Jonathan H reported a case of pulmonary amyloidosis presenting with hemoptysis as a result of pulmonary infarcts related to vascular deposition.^[16] In 2017, Avula SR reported a patient with AL cardiac amyloidosis acquire pulmonary embolism during hospitalization. The patient missed opportunity for anticoagulation and progressed rapidly to IV heart failure and was deemed unsuitable for stem cell or heart transplantation.^[17] The mechanism of amyloidosis-induced pulmonary embolism may be related to the increased decomposition of protein and increased amyloid formation. Due to diastolic heart failure and impaired conduction system of the heart, blood flow becomes slow causing amyloid deposition in blood vessels and inducing thrombosis. However, in this case, the source of the embolism remained uncertain whether it originates from the deep veins of the lower extremities or the atrium, or elsewhere. However, we can not rule out the correlation between pleural amyloidosis and pulmonary embolism, so it should still be paid attention to clinical patients. We should closely observe the symptoms and vital signs of these patients and consider the possibility of pulmonary embolism. Therefore, this case suggests that we should consider the increased risk of embolism without typical clinical manifestation in

amyloidosis patients with myocardial damage. Although amyloidosis-related infarction of the lungs may be less common as a result of the lung's dual blood supply, we also should pay close attention to the patient's clinical symptoms to avoid the occurrence of vascular embolic disease. This case highlights the predilection for thromboembolism in AL amyloidosis. We must diagnose and treat these patients timely in order to improve the prognosis.

6. Conclusion

In summary, we present a rare manifestation of AL pleural amyloidosis with recurrent pleural effusion and pulmonary embolism. This case deserves the attention of our clinicians. Firstly, for unexplained exudative or transudative recurrent pleural effusions, especially when combined with systemic multiple organ system dysfunction, we clinicians should take other rare diseases such as amyloidosis into consideration and perform thoracoscopy based on clinical judgement timely. It should be always kept in mind, as pleural effusion is a common manifestation of pulmonary involvement but could also be the presenting manifestation of amyloidosis. Secondly, we must be alert to the occurrence of embolic disease for patients with amyloid disease. Last but not least, we should also think of the possibility of amyloidosis in patients with pulmonary embolism and recurrent pleural effusion. The prognosis of the disease is poor, clinicians must improve their understanding of the disease so as not to delay the diagnosis and treatment of the disease.

Author contributions

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Supervision: Qigang Zeng.
Validation: Qigang Zeng.
Writing – original draft: Chaoling Liu.
Writing – review & editing: Chaoling Liu.

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