A 71-Year-Old Woman With an Unusual Cause for Pleural Effusions

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Case Presentation

A 71-year-old Filipino woman and homemaker with progressive shortness of breath for 6 months was admitted to the hospital. She had returned from the Philippines, where bilateral pleural effusions of unknown etiology and paroxysmal atrial fibrillation had been found. Her treatment abroad included antibiotics and empirical antituberculous therapy. The pleural effusions had rapidly reaccumulated postthoracentesis by report. Results from imaging and thoracentesis performed in the Philippines were not available to us. Nevertheless, \(\beta\)-blockade successfully controlled the ventricular response rate associated with her atrial fibrillation. Her medical history was notable for osteopenia. Social and family histories were unremarkable; she did not smoke, drink alcohol, or use illicit drugs. A review of systems revealed two-pillow orthopnea, exertional dyspnea, and nausea without emesis.

On physical examination, the patient was afebrile with a BP of 93/50 mm Hg and an irregular heart rate of 62 bpm. Her jugular venous pressure was 10 cm above the sternal angle when measured at 45\(^\circ\) recumbency. Heart sounds were normal with an accentuated pulmonary component of the second heart sound. Pulmonary examination revealed bilateral basal dullness to percussion posteriorly, decreased breath sounds, and midzone crackles. Abdominal examination demonstrated shifting dullness suggestive of ascites. She had bilateral 3+ pitting lower-extremity edema.

Her CBC count, chemistry, liver function panel, and thyrotropin values were unremarkable except for a low albumin level (2.3 g/dL). HIV serology was negative. Serum protein electrophoresis revealed an elevated IgM level of 1,745.5 mg/dL (reference, 48.0-271.0 mg/dL) with \(\kappa\) and \(\lambda\) light chains (\(\kappa:\lambda = 0.07\)). Urinalysis was normal.
The patient's chest radiograph (Fig 1) showed bilateral pleural effusions. CT scan of the chest (Fig 2) revealed large, bilateral pleural effusions and a pericardial effusion. No mediastinal adenopathy, airway abnormalities, pleural nodularity or enhancement, or pulmonary emboli were seen. CT scan of the abdomen showed abnormal gastric thickening and ascites (Fig 2). A transthoracic echocardiogram revealed a moderate pericardial effusion without tamponade. Her left ventricular ejection fraction was 65% with a normal chamber size. Her right ventricular systolic pressure was 40 mm Hg, estimated.

**Figure 1** Posteroanterior chest radiograph showing hypoinflation, cardiomegaly, indistinct vascular markings, and large bilateral pleural effusions.
pleural thickening or nodularity. A, Mediastinal view. B, Lung window. C, The stomach wall appears thickened (double-headed arrow) despite incomplete distension by oral contrast media. D, Abdominal CT scans showing ascites (arrows). The well-defined hepatic cystic lesion (C) is likely an incidental cyst or hemangioma.

Left thoracentesis revealed an exudative effusion with a fluid lactate dehydrogenase level of 329 U/L, fluid protein level of 3.5 g/dL, serum protein level of 6.1 g/dL, and a pH of 7.66. The cell count showed a WBC count of 11,000/µL (15% neutrophils, 48% lymphocytes, 26% macrophages, 10% histiocytes). Pleural fluid bacterial cultures and acid-fast bacilli stains were negative, and cytology did not reveal malignant cells. The fluid adenosine deaminase level was normal (5.2 U/L). Pleural biopsy specimen acid-fast bacilli stains were negative. Bronchoscopic examination was unremarkable. BAL cultures remained negative. An esophagogastroduodenoscopy-guided biopsy of the gastric mucosa and a video-assisted thoracoscopic pleural biopsy were performed.

Pleural (Fig 3) and gastric biopsy specimens showed abundant eosinophilic, amorphous extracellular matrix deposition that stained positive with the Congo red stain (Fig 4). Apple-green birefringence was seen when examined under plane-polarized light (Fig 4). The bone marrow core biopsy specimen showed multiple paratrabecular and nonparatrabecular lymphoid aggregates along with an interstitial increase in small, mature-appearing lymphocytes. Immunohistochemical stains performed on the bone marrow core biopsy specimen showed a predominance of B cells (CD20, CD79a) within the lymphoid aggregates, positive for Bcl-2 and negative for a Bcl-1, Bcl-6, and CD10. CD3 and CD5 highlighted background-scattered small T cells, and CD138 and κ/λ immunostains highlighted scattered polytypic plasma cells. The Congo red stain showed a focal positive bright-orange amorphous material in a perivascular location, which displayed green birefringence by polarization.

Figure 3 Pleural biopsy specimens showing perivascular and interstitial amyloid deposits with characteristic waxy pink appearance on routine staining (hematoxylin-eosin, original magnification ×200). A, Perivascular amyloid deposits. B, Interstitial amyloid deposits. a = amyloid deposits; L = lymphoid cells.

Figure 4 A Congo red stain for amyloid is positive in the observed deposits. A, In regular light, staining is intensely eosinophilic, here, present around a small artery. B, Under plane-polarized light, apple green birefringence is demonstrated, confirming the presence of amyloid (Congo red histochemical stain, original magnification ×400).

What is the diagnosis?
**Diagnosis:** Primary amyloid light chain amyloidosis (pleural and gastric involvement) associated with a low-grade, B-cell, lymphoproliferative disorder

Although the patient’s newly diagnosed atrial fibrillation is suggestive of cardiac involvement with amyloidosis, this condition was not confirmed by myocardial biopsy specimen or cardiac MRI.

**Discussion**

**Clinical Discussion**

Amyloidosis is a family of protein-misfolding disorders caused by the overexpression of proteins that deposit in tissues as insoluble β-pleated fibrils. Amyloid light chain (AL) amyloidosis, also referred to as primary amyloidosis, is caused by a clonal plasma cell dyscrasia and is characterized by widespread deposition of amyloid fibrils derived from monoclonal immunoglobulin light chains, leading to multisystem organ failure and death. Other causes of a monoclonal gammopathy such as multiple myeloma, Waldenström macroglobulinemia, or a limited clonal expansion such as monoclonal gammopathy of undetermined significance or cryoglobulinemia are part of the differential diagnosis. Rarely, AL amyloidosis can be associated with a B-cell lymphoproliferative disorder, as was the case with this patient.

Unlike those originating from plasma cell dyscrasias, AL amyloidosis associated with lymphoproliferative disorders may be caused by monoclonal immunoglobulin light chains produced by neoplastic B cells. Few cases of this finding are described. Sanchorawala et al reviewed 812 patients with AL amyloidosis. Only 16 (2%) of these patients had an underlying B-cell lymphoproliferative disorder, with a median age of 68 years compared with 61 years among patients with AL amyloidosis secondary to plasma cell dyscrasias. Furthermore, 75% vs 3% had an IgM gammapathy, as was the case in the present 71-year-old patient. Advanced multisystem disease (two or more organ systems involved) was found in 81% of patients compared with 60% of patients with plasma cell dyscrasias.

Although amyloidosis is known to involve various organs (most commonly the kidneys), the respiratory system is less involved and usually is associated with systemic AL amyloidosis. Amyloid deposition in the lungs may be restricted to the respiratory tract (alveolar/tracheobronchial deposition or localized nodular amyloid) or may be widespread, involving many organs. An even rarer finding of amyloidosis is that associated with pleural effusion, as was diagnosed in the present patient. Although the exact mechanism for the development of pleural effusion secondary to amyloidosis is unclear, it is believed to be due to the local synthesis of amyloid substance that either impairs fluid resorption or increases fluid production.

Patients with AL amyloidosis and pleural effusions were retrospectively reviewed by Berk and colleagues to investigate the pathophysiology of these pleural effusions. The authors found that hypoalbuminemia and the nephritic syndrome were not associated with a greater incidence of pleural effusions in these patients. A prior prospective study in which patients with pleural effusions of unknown etiology were stratified according to levels of albumin also found that hypoalbuminemia alone was not the cause of the effusion. Hence, in patients with unexplained pleural effusions and hypoalbuminemia, prospective follow-up of the patients’ clinical course identified potential causes other than hypoalbuminemia.

Furthermore, Berk et al found that aggressive diuretic therapy was unsuccessful at resolving persistent AL amyloidosis effusions, which is likely due to an impaired ability of the lymphatic system to reabsorb excess fluid. Multiple case reports have described a plethora of amyloid nodules measuring up to 5 mm in diameter on patients’ parietal pleura. The mechanical occlusion of the parietal stomata is thought to be the cause for the persistence of pleural effusions in AL amyloidosis. Amyloid infiltration rather than left atrial hypertension may actually promote fluid secretion as well as inhibit resorption and may help to account for the persistence of effusions despite large-volume chest tube drainage even after normalization of cardiac filling pressures.

Pleural effusions secondary to amyloidosis can be exudative or transudative. A retrospective review of 35 patients with AL amyloidosis with large, refractory pleural effusions revealed that 37% of cases were exudates. More than one-half (55%) of the exudates were determined by elevated fluid protein levels. Pleural fluid cell counts were nonspecific. Chylothorax occurred in two patients. Additionally, characteristics of amyloid-related pleural effusion reported in the literature were reviewed. Of 23 reported cases, 15 offered information supporting a diagnosis of AL amyloidosis. Congestive heart failure accompanied the pleural effusions in 12 (80%) of 15 cases. Interestingly, five of these 12 patients had exudates. In our patient who had a lymphocytic exudate, other causes such as TB, lymphoma, rheumatoid arthritis, chylothorax, and sarcoidosis were considered and deemed unlikely. Although this patient’s pleural fluid pH level of 7.66 is above that expected for exudates (range, 7.30-7.45), it was unlikely due to infections from urease-producing organisms such as Proteus mirabilis because the pleural fluid and biopsy specimen cultures were negative.

In patients too ill to undergo treatment, those with AL amyloidosis and pleural effusions have a lower survival rate than those without. Survival times in patients with persistent pleural effusion have been reported to be as short as up to 2 months.
In comparison, patients with AL cardiac disease alone demonstrate a survival time of up to 6 months. 

**Pathologic Discussion**

The diagnosis of amyloidosis is based on clinical suspicion and tissue biopsy specimen, requiring a demonstration of binding of the Congo red stain to tissue deposits and birefringence when viewed with polarized light microscopy. Either closed percutaneous pleural biopsy or thoracoscopic biopsy, as was performed in our patient, are acceptable and safe measures of obtaining pleural tissue.

**Conclusion**

This patient represents a rare case of AL amyloidosis associated with a B-cell lymphoproliferative disorder as well as pleural effusions. Upon literature review, it is unique for this disease combination to present as pleural effusions. Our case highlights the importance of maintaining a high index of suspicion for amyloidosis in patients with unexplained pleural disease, especially effusions. This suspicion is enhanced in patients with monoclonal gammopathy and lymphoproliferative disorders.

This patient subsequently underwent bilateral talc pleurodesis because of recurrent pleural effusions. She was started on prednisone and melphalan for primary amyloidosis and rituximab for B-cell lymphoma. We speculate that the patient also had cardiac involvement from AL amyloidosis. Cardiac involvement with amyloidosis in patients with an IgM gammopathy has a negative impact on survival. The patient declined further investigation of likely pulmonary hypertension and possible cardiomyopathy. Unfortunately, she demonstrated a poor response to chemotherapy and died of complications of the disease 9 months after diagnosis.

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**REFERENCES:**

5. Graham DR, Ahmad D: Clinical aspects of pulmonary amyloidosis. *Chest* 92. (3): 576b-577.1987; Citation