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Silent Struggles: Tackling Recurrent Pleural Effusions in Primary Pulmonary Amyloidosis

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Abstract: ***Background**: Recurrent pleural effusions occurring in association with immunoglobulin light chain (AL) amyloidosis, particularly without amyloid cardiomyopathy, are rare and typically indicate a poor prognosis. The mean survival time for these patients is approximately 1.6 months. Effective treatment strategies are not well established. **Methods**: We report a case involving a 60-year-old female presenting with recurrent pleural effusions. Comprehensive diagnostic evaluations, including imaging, pleural fluid analysis, and biopsy, were performed to determine the underlying cause. Following diagnosis, the patient was treated with a combination therapy consisting of Cyclophosphamide, Bortezomib, and Dexamethasone. **Results**: The patient was diagnosed with pulmonary amyloidosis associated with plasma cell myeloma. Upon initiation of the Cyclophosphamide-Bortezomib-Dexamethasone regimen, the patient exhibited significant clinical improvement. During the four-month follow-up period, she experienced no further hospitalizations or recurrences of pleural effusion. **Conclusion**: Recurrent pleural effusions in the context of AL amyloidosis without cardiomyopathy present a significant treatment challenge. This case demonstrates that a regimen of Cyclophosphamide, Bortezomib, and Dexamethasone can be effective, as evidenced by the patient's positive response and lack of effusion recurrence over four months. Further studies are needed to establish optimal treatment protocols.*

Keywords: Primary Pulmonary Amyloidosis, Recurrent Pleural Effusions, Immunoglobulin Light Chain Amyloidosis, Plasma Cell Myeloma, Cyclophosphamide, Bortezomib, Dexamethasone.

1. Introduction

Amyloidosis is a rare disorder characterized by the misfolding and deposition of proteins in various organs and tissues. Primary amyloidosis often occurs in association with plasma cell dyscrasia, whereas secondary amyloidosis is linked to chronic inflammatory diseases. The most common type of primary amyloidosis is immunoglobulin light chain (AL) amyloidosis. This disorder can present with a wide range of clinical manifestations, affecting organs such as the kidneys, heart, gastrointestinal tract, nervous system, muscles, blood, and skin. Pulmonary involvement is uncommon, with only 1-2% of patients with systemic amyloidosis developing persistent pleural effusions. Clinically, the presence of pleural effusions in these patients is significant due to its association with a poor prognosis, with a mean survival time of 1.6 months if untreated. Early diagnosis is crucial but challenging, requiring a high index of suspicion and often invasive biopsy procedures to confirm.

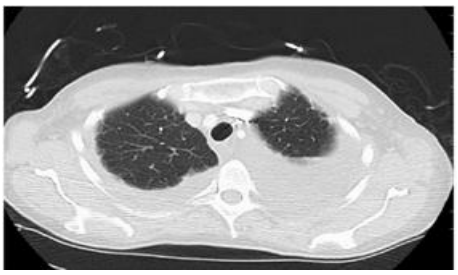
Here, we present the case of a 59-year-old woman with persistent pleural effusions who was diagnosed with primary pulmonary amyloidosis associated with plasma cell myeloma.

2. Case Report

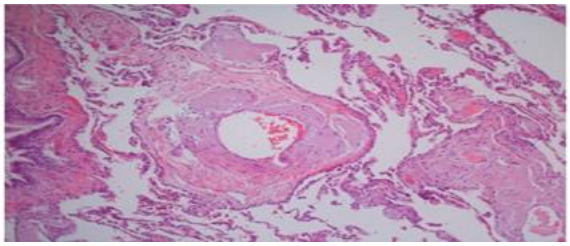
A 59-year-old woman with a history of recurrent bilateral pleural effusions was admitted with worsening dyspnea and a nonproductive cough lasting one week. She had an outpatient thoracentesis the day before admission, draining 1500 mL of pleural fluid from the right side.

The patient had experienced recurrent pleural effusions for three months prior to this admission, with two thoracentesis procedures for the right side and six for the left side, none yielding a conclusive diagnosis. The thoracentesis results indicated transudative effusions, and cultures were negative.

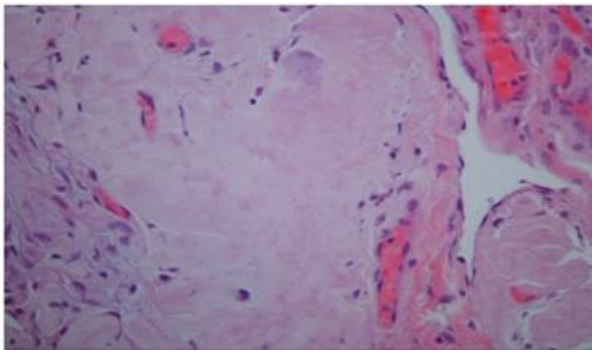
On physical examination, the patient was mildly dyspneic without retractions or accessory muscle use. Breath sounds were decreased at both lung bases. Vital signs were: temperature 98.5°F, heart rate 94/min, respiratory rate 18/min, blood pressure 95/58 mm Hg, and oxygen saturation 98% on room air. Laboratory tests showed: WBC 7.3 thou/µL, Hb 13.2 g/dL, Hct 39.1 g/dL, Plt 259 thou/µL, sodium 139 mmol/L, potassium 3.5 mmol/L, chloride 91 mmol/L, bicarbonate 33 mmol/L, BUN 14 mg/dL, creatinine 0.6 mg/dL, and glucose 111 mg/dL. Serum immunofixation electrophoresis revealed a small lambda monoclonal protein without Bence-Jones proteinuria. A chest X-ray indicated a moderate to large left-sided pleural effusion and right lower lobe consolidation.



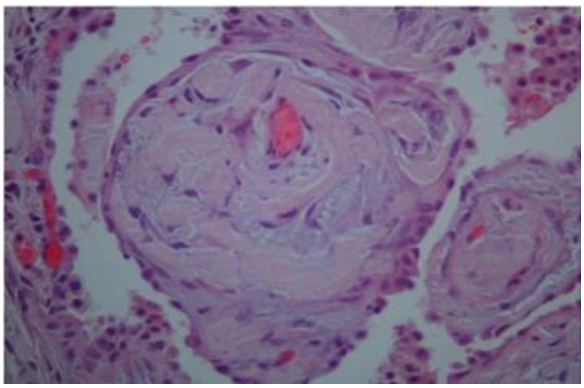
CT scan of the chest showed bilateral pleural effusions, more pronounced on the left.



Thickened intrapulmonary vessel with adjacent interstitial eosinophilic amorphous material confirmed to be amyloid on Congo Red.



Intrapulmonary interstitial deposits of eosinophilic amorphous material that showed apple-green birefringence under polarized light on Congo Red stains



Pulmonary endothelial lined small vascular structure surrounded by amyloid deposits and marginated by a rim of reactive Type II pneumocytes

During hospitalization, thoracentesis revealed: WBC 468 mm³, RBC 36 mm³, lymphocytes 98%, monocytes 1%, glucose 112 mg/dL, total bilirubin 2.1 gm/dL, LDH 72 U/L, amylase 14 U/L, cholesterol 43 mg/dL, triglycerides 16 mg/dL, adenosine deaminase 2.1 U/L, and negative cultures. Cytology showed benign findings with numerous lymphocytes. The patient underwent a biopsy of the left upper lobe of the lung and chemical pleurodesis for the left-sided effusion. Lung biopsy confirmed diffuse pulmonary amyloidosis with positive Congo Red staining. Pleural biopsy was negative for pathology.

Hematology/oncology evaluation included an echocardiogram showing left ventricular hypertrophy, normal rheumatoid factor, and thyroid-stimulating hormone levels. Follow-up tests, including bone marrow biopsy, favored plasma cell myeloma over primary amyloidosis, showing 6% plasma cells on aspirate smears and 15-20% on CD138 immunohistochemical staining. Flow cytometry revealed 1.4% monoclonal plasma cells, indicative of a plasma cell dyscrasia.

The patient was started on Cyclophosphamide, Bortezomib, and Dexamethasone therapy and discharged in stable condition. At the four-month follow-up, she had no recurrent pleural effusions.

3. Discussion

Amyloidosis involves the formation of abnormal protein fibrils and their deposition in various body organs. Amyloid fibrils, composed of low molecular weight protein subunits, exhibit a beta-pleated sheet configuration that binds Congo Red stain, displaying apple-green birefringence under polarized light. AL amyloidosis is caused by immunoglobulin light chain fibril formation and deposition and often occurs with plasma cell dyscrasia. AA amyloidosis, associated with chronic inflammatory diseases, involves fibril formation by amyloid A protein. Familial forms, referred to as AF amyloidosis, are hereditary and show consistent clinical patterns within families. The incidence of AL amyloidosis is reported to be 6-10 cases per million person-years, with a mean diagnosis age of 64 years and a higher prevalence in males (65-70%).

AL amyloidosis presents systemically with varied clinical manifestations depending on the affected organ system, including renal, cardiac, gastrointestinal, neurological, musculoskeletal, hematological, and dermatological involvement. Pulmonary involvement is rare, with persistent pleural effusions occurring in only 1-3% of systemic amyloidosis cases. This case contributes to the literature on primary pulmonary AL amyloidosis, particularly in female patients, who represent a minority of those affected.

The diagnostic criteria for AL amyloidosis, as established by the Mayo Clinic and the International Myeloma Working Group, require: (1) amyloid deposition with distinct organ involvement, (2) amyloid confirmation by Congo Red staining, (3) evidence of immunoglobulin light-chain amyloid, and (4) evidence of a monoclonal plasma cell proliferative disorder. Our patient met all criteria, providing a unique presentation compared to previously reported cases.

In a retrospective analysis of AL amyloidosis patients with isolated respiratory system involvement, high mortality was noted with a mean disease course of 46.5 months. Various presentations included tracheal and bronchial stenosis, atelectasis, pulmonary nodules, lung consolidation, and lymph node enlargement.

Pleural effusions in AL amyloidosis without cardiac involvement have a median survival of 1.6 months if untreated. Chemotherapy and stem cell transplantation improve survival, but optimal treatment for persistent pleural effusions remains undetermined. Case reports indicate both transudative and exudative pleural effusions, suggesting varied pathogenesis, including ventricular dysfunction, nephrotic syndrome, impaired fluid resorption, and increased pleural capillary permeability due to amyloid deposition.

Treatment for AL amyloidosis typically involves chemotherapy and autologous stem cell transplantation. Melphalan and prednisone prolong survival but do not reverse organ dysfunction. High-dose intravenous melphalan and autologous stem cell transplantation have shown hematologic cure and organ function improvement. Persistent pleural effusions require symptomatic relief through drainage and possibly chemical pleurodesis. Chemotherapeutic regimens like vincristine, adriamycin, and dexamethasone (VAD) have shown efficacy in preventing recurrence.

In this case, the patient responded well to Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) therapy, with no

recurrence of pleural effusions at five months, aligning with similar positive outcomes in other reported cases.

4. Conclusion

Pleural effusions in systemic amyloidosis are rare and associated with poor prognosis. Prompt diagnosis and treatment can improve pulmonary function, oxygenation, and survival. This case highlights the effectiveness of CyBorD therapy in treating pleural effusions in AL amyloidosis, contributing to the understanding and management of this challenging condition.

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