Pleural amyloidosis: timely unmasking of apple-green birefringence in pleural biopsy

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SUMMARY

8%–25% of cases of pleural effusion remain undiagnosed after routine workup. Some of the causes for pleural effusion are less often considered as a differential diagnosis owing to their rarity. While not all require a pleural biopsy, it remains a valuable tool for the definitive diagnosis of uncommon pleural effusions and guides treatment decisions. This case exemplifies the value of timely intervention in uncovering an unconventional form of pleural amyloidosis. An elderly male presenting with right-sided pleural effusion. The patient underwent timely medical thoracoscopy and was subsequently diagnosed with AL amyloidosis. Following therapy, the patient demonstrated marked clinical improvement, with radiographic resolution of the effusion and a favourable haematologic response.

BACKGROUND

AL amyloidosis results from the extracellular deposition of fibril-forming monoclonal immunoglobulin (Ig), which is usually secreted by small number of plasma cell clones. Most patients show evidence of isolated monoclonal gammopathy. The conformational change due to abnormal secondary or tertiary structure of the light chain (LC) is responsible for abnormal protein folding. This folding leads to the assembly of monomers that tend to stack, forming amyloid fibrils.[1] Localised AL is usually associated with distinct pattern of organ involvement. The initial laboratory evaluation to exclude systemic disease could be limited to serum and urine immunofixation in most patients. Recurrence is quite common, but long-term outcomes are variable.[2] The respiratory manifestations of amyloidosis include tracheobronchial involvement and nodular or diffuse parenchymal disease. Amyloid deposits in the pleura are an exceptional and uncommon manifestation of amyloidosis. If seen, it may present in any form, from pleural thickening to effusion; these findings carry a wide range of differentials. Treatment of AL amyloidosis is mainly chemotherapy-based, aiming to control the underlying plasma clone that produces amyloidogenic LC, followed by careful monitoring of haematological response by serial measurement of free LC in serum. Survival in AL amyloidosis depends on the spectrum and the severity of the individual organs involved.[1]

CASE PRESENTATION

A male in his early 60s, a non-smoker and non-drinker, presented with complaints of progressive breathlessness and right-sided chest pain over 2 months. He had no known comorbidities or any prior history of hospitalisation. The patient's vital signs were within the normal range, with SpO2 at 96% on room air and a respiratory rate of 18 per minute. The patient's body habitus was normal. Head-to-toe examination showed raccoon eyes and macroglossia (figure 1). On auscultation, the patient had vesicular breath sounds in all areas with reduced air entry in the right mammary, axillary and infra-scapular regions. On further evaluation, a right pleural effusion was noted on chest radiography (figure 2). Laboratory investigations showed no significant abnormality in complete blood count, renal, thyroid and liver function tests. A diagnostic right pleural tap was performed, yielding a grossly yellow sample. The biochemical fluid examination was suggestive of an exudative effusion, with a total leucocyte count of 550 cells/mm^3 (90% lymphocytes), glucose of 136 mg/dL, total protein of 4 g/dL and LDH of 177 IU/L. The cultures of the pleural fluid were negative. Cytology was negative for malignant cells. CT scan of the thorax showed right moderate to large pleural effusion and minimal left pleural effusion without parenchymal abnormality (figure 3). No definitive diagnosis could be made; hence, the patient was planned for medical thoracoscopy.

Medical thoracoscopy revealed yellow and black plaques and small nodules on the parietal pleura (figure 4). A biopsy was taken, and histopathological examination showed predominantly amyloid deposition, demonstrating apple-green birefringence after Congo red staining, consistent with pleural amyloidosis (figure 5). To determine the aetiology of amyloidosis, further workup was performed, and a bone marrow biopsy showed a normocellular marrow with normal trilineage haematopoiesis. A positron emission computed tomogram (PET/CT) scan was performed to assess systemic involvement, which demonstrated only right moderate and left minimal pleural effusions without significant metabolic activity, and a few mildly metabolically active subcentimetric left supraclavicular lymph nodes.

Beta 2 microglobulin value was 3484 ng/mL (normal value: 800–2340) (figure 6). Immunofixation electrophoresis (IFE) suggested monoclonal gammopathy with IgA and lambda (figure 7). Serum free kappa (LC) was 22.94 mg/L (biological reference interval 3.3–19.4), free lambda (LC) was 232.49 mg/L (biological reference interval 5.71–26.30) and free kappa:lambda ratio was 0.10 (biological reference interval 0.26–1.65).

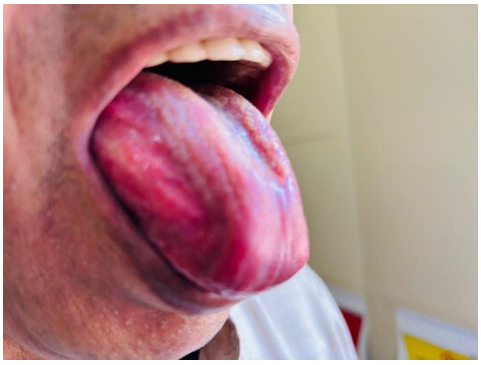

Figure 1 Macroglossia.

Biochemical or immunohistochemical typing of the deposit could not be done. Despite the lack of tissue typing, a diagnosis of immunoglobulin LC (AL) type pleural amyloidosis with IgA lambda, Mayo stage III, was made based on the systemic plasma cell dyscrasia.

TREATMENT AND OUTCOME

Given the diagnosis, the patient was initiated on a combination chemotherapy regimen including bortezomib, dexamethasone and cyclophosphamide, targeting the underlying plasma cell dyscrasia.

Due to logistical constraints and the high cost, daratumumab, a monoclonal antibody often added to such regimens, could not be administered. Nevertheless, the patient tolerated the initial chemotherapy well.

The patient received a total of 7 cycles of chemotherapy. After three cycles, significant improvement was observed, marked by the disappearance of the monoclonal (M) spike on serum electrophoresis. However, the patient developed grade 2 peripheral neuropathy, a known adverse effect of bortezomib. Bortezomib was therefore discontinued, and the patient was maintained on cyclophosphamide and dexamethasone only.

Following the completion of four additional cycles, a repeat chest X-ray showed significant clearing of the pleural effusion, confirming a radiological response to therapy (figure 8). Patient also showed marked improvement in raccoon eyes and macroglossia. The patient continued to do well clinically and remains under close follow-up.

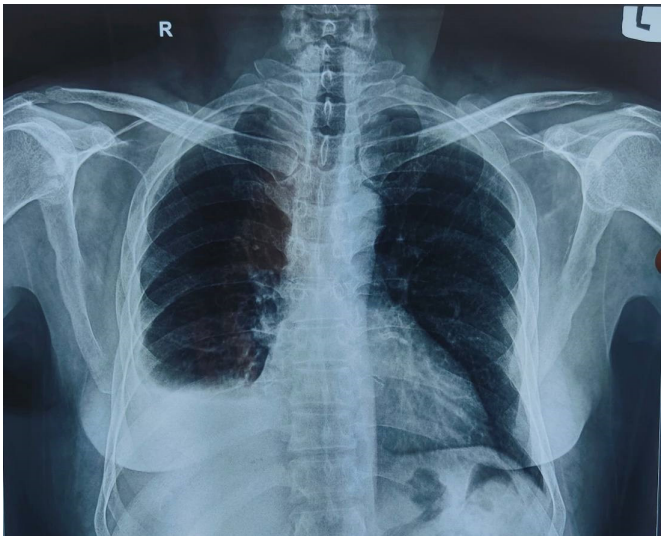

Figure 2 Chest X-ray of the patient showing right-sided pleural effusion.

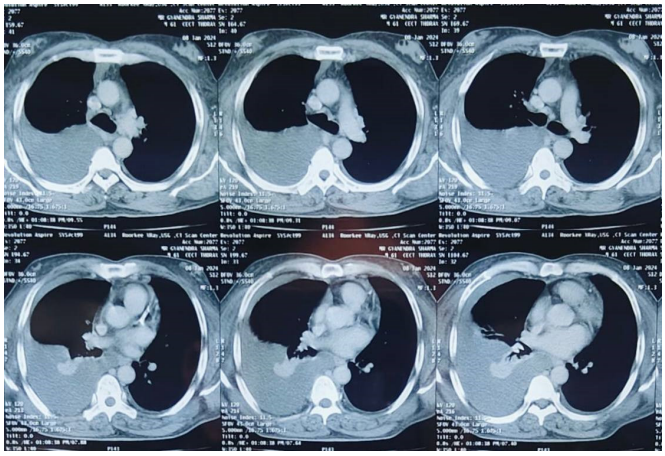

Figure 3 CT scan of the thorax showed right moderate to large pleural effusion and minimal left pleural effusion without parenchymal abnormality.

DISCUSSION

Pleural involvement in systemic AL amyloidosis is an uncommon but significant clinical manifestation, often leading to diagnostic delays due to its non-specific presentation. It is typically characterised by persistent, non-resolving exudative effusions, as seen in our patient. It may be either due to direct amyloid infiltration of the pleura or secondary to associated cardiac or renal dysfunction. In our case, the presence of pleural-based plaques and histopathological confirmation of amyloid deposition were crucial in establishing the diagnosis, prompting a focused evaluation for an underlying plasma cell dyscrasia.

Diagnosis of pleural amyloidosis

In patients with amyloidosis, pleural involvement presents in a somewhat elusive manner, often making the diagnosis challenging. Pleural effusions usually appear in individuals over the age of 50 and tend to be bilateral and small to moderate in size, although extensive collections have also been described. The fluid is most often clear and serous, but it may occasionally be milky in the setting of chylothorax or blood-tinged, reflecting the varied mechanisms by which amyloid deposits affect the

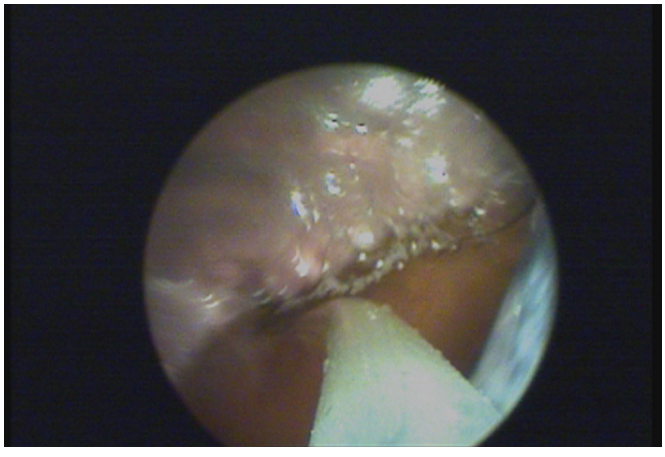

Figure 4 Medical thoracoscopy showing small nodules on parietal pleura.

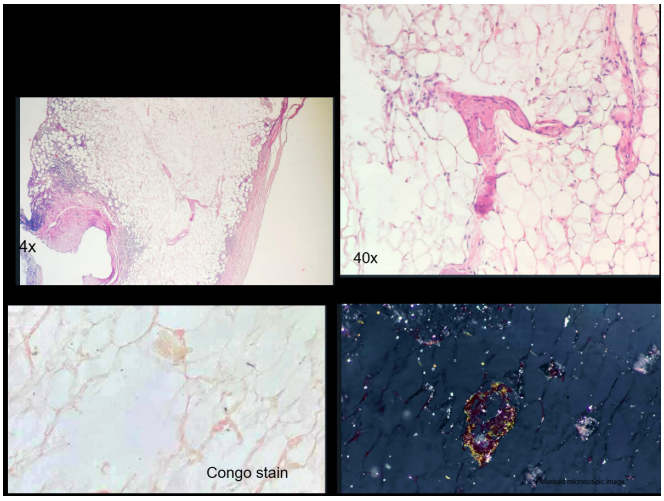

Figure 5 4× low power view of pleura, 40× high power view of amyloid deposit around the blood vessel, Congo stain showing congophilia and apple-green birefringence seen on polarised microscope respectively.

pleura and surrounding structures. Biochemical analysis is not diagnostic, as the effusion may behave as either a transudate—particularly when cardiac involvement leads to raised hydrostatic pressures—or as an exudate, when direct pleural infiltration is present. A consistent feature across many reports is a lymphocyte-predominant fluid, yet this too lacks specificity. Cytology and microbiology generally offer little help, with cultures almost always sterile and cytology unremarkable.

For this reason, a pleural biopsy becomes central in confirming the diagnosis. Pleural amyloid deposits are identified in more than 80% of cases when tissue is obtained, with thoracoscopic biopsies providing the highest diagnostic yield compared with blind closed techniques. The diagnostic performance is particularly strong in unilateral and exudative effusions, settings in which clinical suspicion should be heightened. Therefore, pleural effusion in amyloidosis does not carry unique pleural fluid characteristics but acts as an important clinical clue. When encountered in an older patient with otherwise unexplained recurrent or persistent effusion, it should prompt consideration of pleural amyloidosis and guide the clinician toward tissue sampling for definitive diagnosis. This highlights the importance of moving beyond fluid analysis alone and recognising biopsy as the cornerstone of diagnosis in such cases.[3]

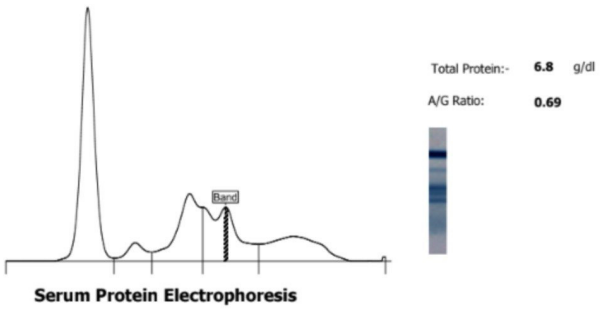

Figure 6 Serum protein electrophoresis (SPE) showing a monoclonal (M)-band.

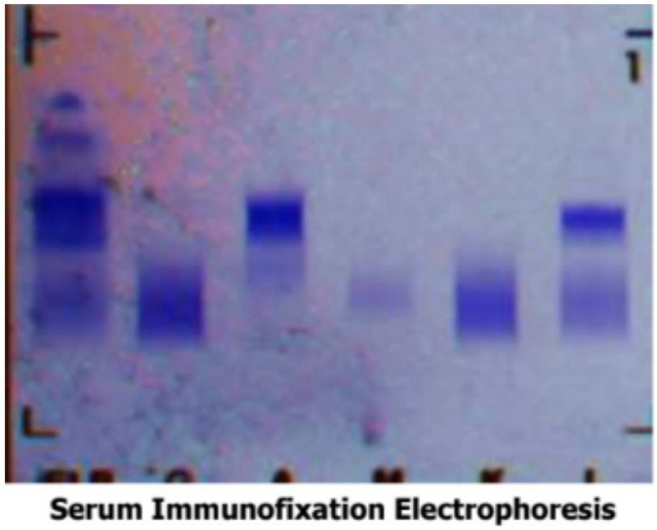

Figure 7 Serum immunofixation electrophoresis suggested monoclonal gammopathy with IgA and lambda.

Rationale for chemotherapy selection

The cornerstone of AL amyloidosis management is the rapid reduction of free light chain production by targeting the underlying plasma cell clone. Among available options, the bortezomib-based CyBorD regimen (cyclophosphamide, bortezomib and dexamethasone) has become the first-line therapy for most patients with AL amyloidosis due to its rapid haematologic response, favourable organ response rates and manageable toxicity profile. Bortezomib, a proteasome inhibitor, induces apoptosis in plasma cells by disrupting protein homeostasis and has demonstrated efficacy even in patients with significant organ dysfunction.[4]

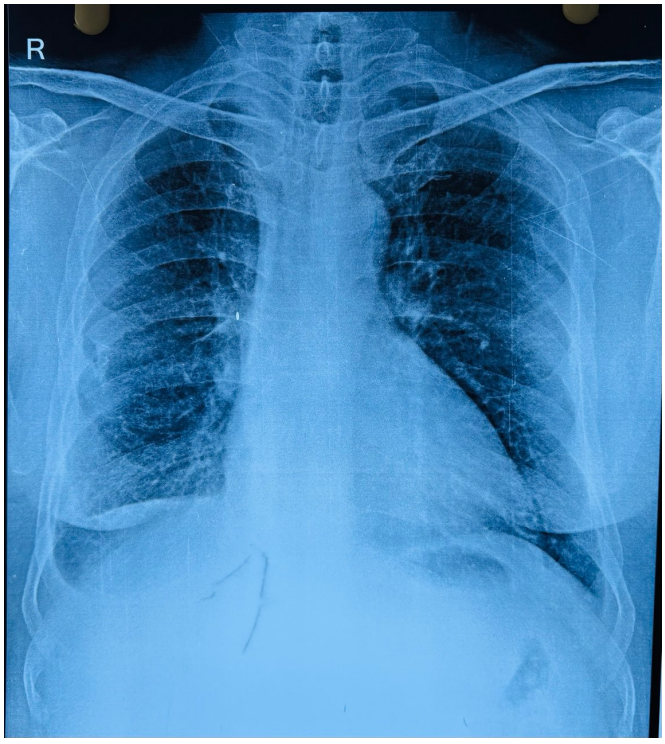

Figure 8 Post-treatment chest X-ray of the patient showing complete resolution.

Cyclophosphamide adds cytotoxic synergy, and dexamethasone exerts anti-inflammatory and antimyeloma activity, completing the triple regimen. In our patient, this regimen was initiated with the goal of achieving a rapid and deep haematologic response, which is a known predictor of improved survival and organ recovery in AL amyloidosis.

The ANDROMEDA trial further established the superiority of adding daratumumab to the CyBorD backbone, demonstrating significantly higher complete haematologic response rates and greater organ response.[5] However, in resource-constrained settings, the high cost and availability of daratumumab remain barriers, as was the case for our patient. Despite the absence of daratumumab, the patient showed remarkable improvement with CyBorD alone, consistent with earlier studies such as that by Kastritis E. *et al*, which reported an overall haematologic response rate of exceeding 80% with CyBorD and complete response rates approaching 40%.[6]

Response and Toxicity Monitoring

Our patient demonstrated an excellent initial haematologic response, with the disappearance of the M-protein spike after three cycles. This early response is considered a surrogate marker for a favourable prognosis and reduced progression risk. After seven cycles, peripheral neuropathy—an expected dose-dependent adverse effect of bortezomib—necessitated discontinuation of the agent. This highlights the importance of vigilant neurotoxicity monitoring during therapy.

Treatment was continued with cyclophosphamide and dexamethasone, a reasonable approach for partial responders or those intolerant to bortezomib, particularly in settings without access to second-line agents such as lenalidomide or monoclonal antibodies. Notably, the patient maintained haematologic remission and showed radiological improvement in pleural effusion, suggesting that even reduced-intensity regimens may be sufficient to maintain disease control in selected cases.[6 7]

Role of organ response in prognosis

While haematologic remission is the primary therapeutic goal, organ response—particularly resolution or stabilisation of pleural effusion and improvement in functional status—is critical for long-term outcomes. In our case, chest X-ray at the end of seven cycles showed significant clearing of the effusion, thereby suggesting pleural response. This also correlates with studies showing that patients achieving both haematologic and organ responses have superior overall survival and quality of life.

A study by Jaccard *et al*[7] in patients with cardiac amyloidosis treated with CyBorD demonstrated not only haematologic responses but also meaningful improvements in organ function in over half of the patients. Although pleural amyloidosis-specific outcomes are less frequently reported due to its rarity, extrapolation of systemic response benefits is reasonable.[8]

Limitations and future directions

Our case reflects real-world limitations in the treatment of AL amyloidosis in low-resource settings. While daratumumab, autologous stem cell transplant (ASCT) and newer agents like venetoclax (for t(11;14) positive disease) are promising, their accessibility remains restricted. ASCT was not considered in this case due to the patient's age and initial functional status. With improved access to biologics and the development of risk-adapted approaches, outcomes in amyloidosis are expected to improve further.

Additionally, this case underscores the need for early recognition and comprehensive workup of unexplained pleural effusions, especially in the elderly. Thoracoscopic biopsy played a pivotal role here, enabling timely diagnosis and initiation of disease-modifying therapy.[9]

CONCLUSION

This case highlights the importance of early intervention. It demonstrates the efficacy of a CyBorD-based approach in managing IgA lambda pleural amyloidosis and not IgA multiple myeloma, even without access to advanced agents such as daratumumab. Early diagnosis, appropriate risk stratification and careful toxicity monitoring are essential for optimising patient outcomes. As therapeutic options evolve, personalised treatment planning, informed by resource availability and patient comorbidities, remains central to care.

Patient's perspective

Before coming to the Doctor, I was very breathless. I could not perform my daily activities. I got very good treatment, and now I am symptom-free.

Learning points

- Pleural effusion in elderly patients should always be investigated and must not be thought of as tubercular effusions even in high-endemic countries.
- The role of a histopathologist is very crucial in helping to diagnose any case.
- The role of the multidisciplinary team helps diagnose any case.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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