Case Series

Pulmonary Amyloidosis: Diverse Clinical and Histopathological Manifestations - A Series of Five Cases

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Abstract

Pulmonary amyloidosis, a rare condition caused by the abnormal deposition of protein fibrils, most often the AL (light chain) type, within the lung, frequently presents a diagnostic challenge. Its clinical manifestations often resemble more prevalent lung diseases like cancer or infections. A crucial step is to differentiate between disease limited to the respiratory system and widespread systemic involvement, as this guides the appropriate treatment. This report provides a retrospective analysis of five histologically confirmed cases of pulmonary amyloidosis, detailing their presenting clinical features, radiological findings, microscopic tissue characteristics, immunohistochemical analysis, and results from systemic evaluations. Our patient group, comprising three males and two females aged between 38 and 67 years, presented with varied initial symptoms: three had lung masses, one exhibited pleural effusion with concurrent liver disease, and another was being treated for tuberculosis. Microscopic examination revealed discrete amyloid nodules in three cases, diffuse interstitial deposition in one, and a pleural based accumulation in another. Immunohistochemical studies confirmed AL-type amyloid in three cases, AA-type in one, while the specific amyloid type remained undetermined in a fifth case. A confirmed diagnosis of systemic amyloidosis was made in only one patient. In one instance, nodular pulmonary amyloidosis occurred alongside fungal colonization. Pulmonary amyloidosis often poses a diagnostic conundrum in lung pathology. While localized nodular forms generally follow a benign clinical course, diffuse patterns necessitate a thorough systemic evaluation, even when serological indicators are negative. Advanced techniques like mass spectrometry and extensive imaging are becoming more vital for accurate subtyping and informed treatment decisions.

Keywords: Pulmonary amyloidosis; Localized amyloidosis; Systemic amyloidosis; Congo red staining; Immunohistochemistry; Lung Pathology; Case series; Amyloid subtyping

Introduction

Amyloidosis comprises a heterogeneous group of disorders characterized by the extracellular deposition of misfolded protein fibrils that stain positively with Congo red and demonstrate apple green birefringence under polarized light. Amyloid deposits within the lungs are uncommon and can present either as a manifestation of widespread systemic disease or as a lesion confined solely to the respiratory system.[1] Pulmonary amyloidosis exhibits several morphologic patterns, including solitary or multiple parenchymal nodules, diffuse alveolar septal infiltration, tracheobronchial involvement, and pleural based disease, each showing characteristic appearances on imaging and histology.[2, 3]

Localized nodular pulmonary amyloidosis is generally indolent and often detected incidentally on imaging performed for unrelated reasons, whereas diffuse pulmonary amyloidosis is more frequently associated with systemic disease and carries a poorer prognosis.[1, 4] Diagnosis can be challenging, as radiologic appearances often mimic malignant, granulomatous, or infectious processes such as tuberculosis or sarcoidosis.[5, 6] An incorrect diagnosis can postpone appropriate management and may result in interventions that are not clinically warranted.

Tissue biopsy remains the definitive diagnostic approach, with amyloid deposits verified by Congo red staining, and the specific fibril type determined through immunohistochemistry or, when necessary, advanced proteomic techniques such as mass spectrometry.[6, 7] The latter offers higher accuracy in cases with inconclusive immunostaining results. While amyloid deposition itself is usually sterile, secondary infection or colonization may occur, complicating both diagnosis and management.[8]

In this series, we present five cases of histologically confirmed pulmonary amyloidosis with varied clinical, radiological, and histopathological findings, including one case of fungal colonization within an amyloid nodule - a rare and diagnostically challenging presentation.

Case Presentations

We retrospectively analyzed five cases of pulmonary amyloidosis diagnosed in the pathology department of a tertiary-care center between 2005 and 2015. Written informed consent was obtained from all patients for publication of clinical data and images. Clinical records, radiologic findings, histopathological features, and immunohistochemistry (IHC) profiles were reviewed in detail as shown in Table 1 and Figures 1-5. Amyloid deposits were confirmed by Congo red staining, which displayed the characteristic apple-green birefringence under polarized light.

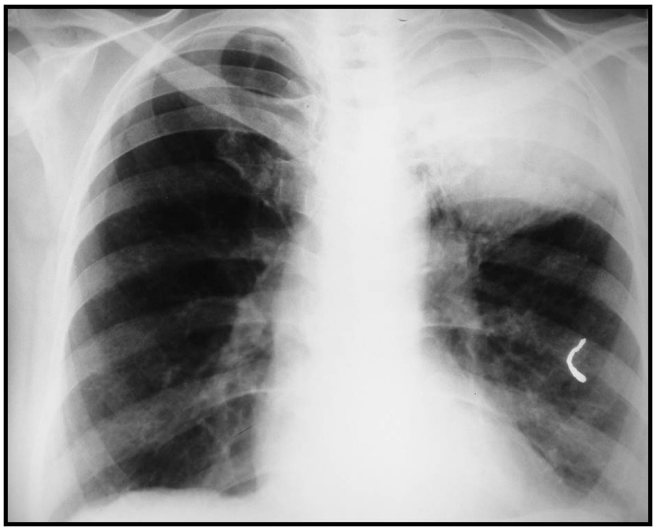

Figure 1: Chest X-ray showing homogenous opacity in left upper zone of lung.

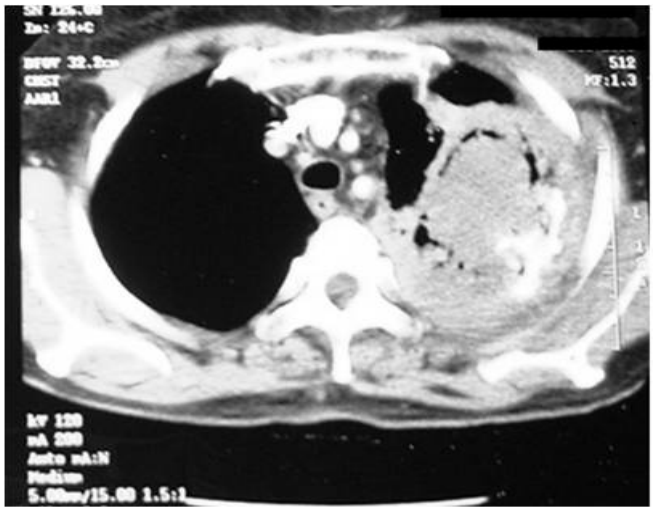

Figure 2: High-resolution computed tomography of the thorax demonstrating a large nodular mass in the left upper lobe measuring approximately 4.5 cm in maximum diameter, consistent with localized pulmonary amyloidosis (case 2).

IHC: Immunohistochemistry; AL: Amyloid light chain; AA: Amyloid A; SAA: Serum amyloid A; FLC: Free light chain;

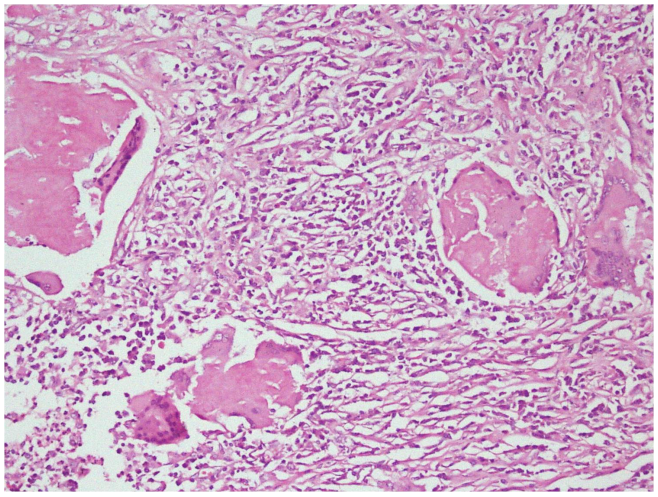

Figure 3: Histopathology showing nodular amyloid deposits with surrounding lymphoplasmacytic infiltrate (case 1). Amorphous eosinophilic material characteristic of amyloid is present. (Hematoxylin and eosin stain, original magnification ×100, scale bar = 100 µm).

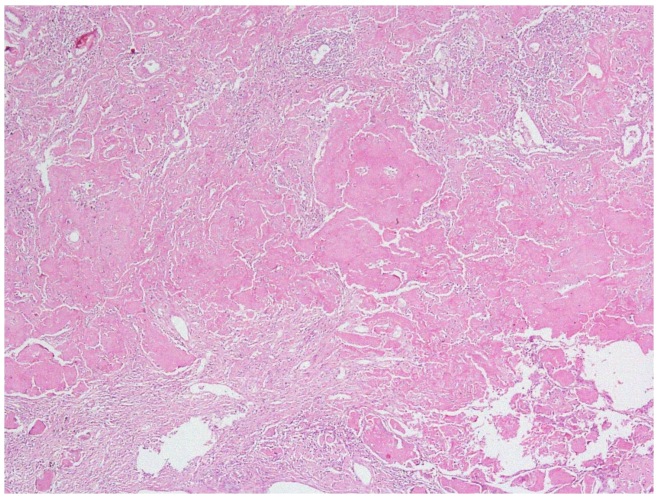

Figure 4: Histopathology demonstrating nodular amyloid deposition with co-existing fungal colonization (case 2). Note the presence of septate hyphae within the amyloid deposit. (Hematoxylin and eosin stain, original magnification ×200, scale bar = 50 µm).

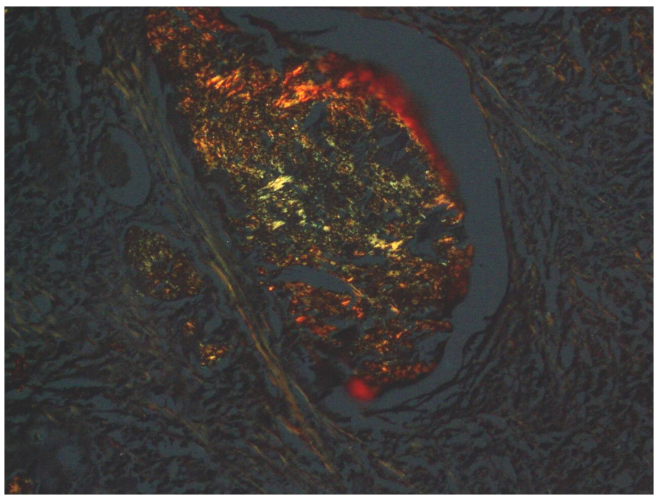

Figure 5: Congo red staining demonstrating characteristic apple-green birefringence under polarized light microscopy, confirming the presence of amyloid deposits. (Congo red stain under polarized light, original magnification ×200, scale bar = 50 µm).

$\kappa : \lambda$: kappa:lambda ratio (normal range: 0.26–1.65)

Immunohistochemistry (IHC) and systemic amyloidosis definition.

Subtyping of amyloid was performed on formalin-fixed paraffin-embedded sections using the following primary antibodies: polyclonal rabbit anti-human *kappa* light chains (Dako/Agilent, catalog A0191; dilution 1:100), polyclonal rabbit anti-human *lambda* light chains (Dako/Agilent, catalog A0193; dilution (1:100)), and monoclonal mouse anti-*Serum Amyloid A* (SAA)

Table 1: Clinical, radiological, and histopathological characteristics of five cases of pulmonary amyloidosis.

Case	Age/Sex	Clinical Presentation	Imaging Findings	Histopathological Features	Amyloid Type (IHC)	Serum FLC Ratio ($\kappa : \lambda$)	Systemic Workup Results	Follow-up Duration	Clinical Outcome	Final Diagnosis
1	42/M	Chronic cough, unexplained weight loss	Solitary nodule in right lower lobe	Nodular amyloid deposition with plasma cell infiltrates	AL-lambda	0.58 (normal)	All systemic evaluations negative	24 months	Stable, no progression	Localized pulmonary AL amyloidosis
2	67/M	On treatment for pulmonary tuberculosis	Mass in right upper lobe	Nodular amyloid with coexisting fungal colonization	AL-kappa	1.12 (normal)	Abdominal fat pad biopsy negative	18 months	Improved after antifungal therapy	Localized pulmonary AL amyloidosis with *Aspergillus* co-infection
3	59/F	Progressive dyspnea, pleural effusion	Diffuse pleural thickening	Diffuse alveolar-septal amyloid deposits	AL-lambda	4.23 (elevated)	Monoclonal protein detected, positive bone marrow biopsy	12 months	Deceased due to progressive disease	Systemic AL amyloidosis
4	38/M	Incidental lung mass	Lesion in left lower lobe	Nodular amyloid, positive for SAA	AA	0.95 (normal)	All systemic evaluations negative	36 months	Stable, no progression	Localized AA amyloidosis
5	53/F	History of cirrhosis, recurrent pleural effusion	Pleural-based nodule	Amyloid in pleura	Indeterminate (AL & SAA negative)	1.05 (normal)	Duodenal and abdominal fat pad biopsies negative	15 months	Stable	Localized pleural amyloidosis

(clone mc1, Dako/Agilent; dilution (1:50)). Heat-induced epitope retrieval was performed in the Tris-EDTA buffer (pH 8.0) at 98°C for 20 minutes. Sections were incubated with primary antibodies for 30 minutes at room temperature, followed by a polymer-based detection system (EnVision+ System-HRP, Dako/Agilent). Positive and negative controls were included. Immunoreactivity was considered positive when $\geq$50% of amyloid deposits showed moderate to strong staining intensity.

Systemic amyloidosis was defined as biopsy-proven amyloid deposition in at least one extra-pulmonary site (bone marrow, duodenum, or abdominal fat pad), or the detection of a monoclonal protein on serum/urine immunofixation electrophoresis with supportive clinical features and an abnormal‘$\kappa : \lambda$‘ free light chain ratio (‘$\kappa : \lambda$‘ ratio $>$1.65 indicating *kappa* excess; $<$0.26indicating *lambda* excess). Evaluation included serum and urine protein electrophoresis with immunofixation, serum free light chain assay, bone marrow biopsy, skeletal survey, and, where indicated, abdominal fat pad or duodenal biopsies.

The cohort comprised three men and two women, aged 38–67 years, with varied initial presentations. Three patients were found to have lung masses on imaging, one was undergoing treatment for pulmonary tuberculosis, and one had chronic liver disease with associated pleural effusion. In only two cases was pulmonary amyloidosis suspected before histological confirmation; the other three were initially worked up for malignancy.

Histologically, three cases showed discrete nodular amyloid deposits, while two demonstrated diffuse interstitial or pleural infiltration. Four cases were ultimately classified as localized pulmonary amyloidosis, and one as systemic. Two cases showed marked plasma cell infiltration. One case was remarkable for giant cell reaction and a neutrophil-rich abscess containing fungal hyphae morphologically consistent with *Aspergillus* species. Fungal identification was based on characteristic morphologic features including acute-angle branching septate hyphae measuring 3–5 µm in diameter on hematoxylin and eosin staining and Grocott's methenamine silver staining. Fungal culture was not performed in this case. The patient received a 12-week course of oral voriconazole (200 mg twice daily) with clinical improvement and radiological resolution of the cavitary component on follow-up imaging.

On IHC, three cases were identified as AL-type amyloid and one as AA-type, while one case could not be subtyped. Only the AA-type case met the criteria for systemic amyloidosis. The coexistence of fungal elements within amyloid deposits, along with inflammatory cell infiltrates, suggests that amyloid-laden lung tissue may create a microenvironment conducive to opportunistic infections.

Abdominal fat pad and duodenal biopsies were largely unhelpful for diagnosis in this series. Systemic workup, including protein electrophoresis, free light chain assay, bone marrow examination, and skeletal survey, yielded normal results in all but the single systemic case. Duodenal biopsy was positive only in that patient, and fat pad aspirates were negative in all five.

Discussion

Pulmonary amyloidosis represents a spectrum of disorders that may present as isolated nodular lesions or as diffuse pulmonary and pleural infiltration. In our series, the majority were localized nodular cases, in agreement with recent studies showing that this form accounts for most pulmonary presentations and is often AL-type.[2, 9] The single case of diffuse interstitial deposition corresponded to systemic AL amyloidosis, reflecting the recognized association between diffuse alveolar-septal involvement and multisystem disease. [10]

Demonstration of amyloid on Congo red-stained sections is critical for confirmation, and subsequent subtyping can be achieved through targeted immunohistochemical analysis. However, IHC results can sometimes be inconclusive; in such situations, modern proteomic approaches such as laser microdissection with mass spectrometry can precisely determine amyloid fibril composition and are increasingly recommended for routine practice.[7]

An important and unusual finding in our series was the coexistence of fungal hyphae within an amyloid nodule. This phenomenon, although rare, has been described in the literature, with *Aspergillus* and *Candida* being the most common organisms.[11] Amyloid-laden lung tissue may have altered local immunity and distorted architecture, predisposing it to colonization by opportunistic fungi.[11, 12] In these situations, the presence of infection can confound radiologic interpretation and delay diagnosis. Therefore, in patients with pulmonary amyloidosis showing imaging features suspicious for infection, targeted microbiological assessment and fungal cultures should be considered as part of the workup to guide management.

Radiologically, nodular amyloidosis may closely mimic malignancy or granulomatous disease, leading to potential overtreatment or inappropriate therapies. In regions with a high prevalence of tuberculosis, this resemblance is particularly problematic, as exemplified by one of our cases where empirical anti-tuberculous therapy was started before histologic confirmation. This reinforces the principle that any atypical lung mass or consolidation should undergo biopsy before initiating disease-specific treatment.[4, 9]

Study Limitations

This study has several limitations. First, the retrospective design and small sample size limit the generalizability of our findings. Second, fungal identification in Case 2 was based solely on morphologic features without culture or molecular confirmation, which may affect diagnostic certainty. Third, mass spectrometry for amyloid subtyping was not available at our institution during the study period, which may have improved classification accuracy, particularly in the indeterminate case. Fourth, long-term follow-up data were incomplete for some patients, precluding comprehensive survival analysis. Finally, the lack of standardized follow-up protocols across cases limited our ability to assess disease progression and treatment outcomes systematically.

Conclusion

This case series illustrates the broad clinical and histopathological spectrum of pulmonary amyloidosis, from isolated indolent nodules to diffuse systemic disease. Accurate diagnosis hinges on histopathology, with ancillary subtyping techniques providing critical guidance for therapy. The co-occurrence of opportunistic fungal colonization in one case emphasizes the importance of incorporating microbiologic evaluation into the diagnostic pathway, especially in patients with radiological suspicion for infection. Distinguishing between localized and systemic amyloidosis remains central to prognosis and treatment planning: localized disease may be managed conservatively or surgically, while systemic AL amyloidosis necessitates systemic chemotherapeutic regimens, including proteasome inhibitors and monoclonal antibodies. Continued reporting of well-characterized cases will expand current knowledge and may improve diagnostic and therapeutic approaches for this rare but challenging condition.

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