



## A rare etiology of pulmonary nodules

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### ABSTRACT

**Introduction:** Pulmonary nodules are a frequent finding on chest imaging studies, with differential including multiple benign entities, but malignancy is often also a concern. Computed Tomography (CT) and Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) scans have improved the characterization of pulmonary nodules. However, many nodules remain indeterminate and require periodic monitoring. Here we report two nodular pulmonary amyloidosis cases as a rare etiology of enlarging pulmonary nodules with FDG avidity.

**Case presentation:** Case 1: 75-year-old woman with a history of asthma, emphysema, bronchiectasis, and a 48 pack-year smoking history was found to have subcentimeter groundglass pulmonary nodules in the right lower lobe (RLL). Follow-up imaging demonstrated an increased solid component of a RLL bulla associated with mild FDG uptake on PET scan. A CT-guided biopsy revealed amyloid deposition. Case 2: 77-year-old man with a history of interstitial lung disease, asbestos exposure, prior tobacco use, and atrial fibrillation treated with amiodarone was found to have a 1.6cm RLL nodule. Follow-up imaging identified an interval increase to 2.0cm associated with moderate FDG uptake on PET scan. Transthoracic biopsy identified amyloid deposition.

**Discussion:** Nodular pulmonary amyloidosis is a rare form of amyloidosis which may present as an enlarging pulmonary nodule with FDG avidity, raising concern for malignancy. A CT-guided biopsy is a safe way to establish a diagnosis. Recent studies have demonstrated an association between nodular pulmonary amyloidosis and marginal zone lymphomas, which warrants longitudinal follow-up for evolution to lymphoproliferative disorder.

### 1. Introduction

Pulmonary nodules are a frequent incidental finding on chest imaging studies but may require significant work-up to establish a definitive diagnosis. Differential diagnosis of new or enlarging pulmonary nodules include several benign causes including infectious and inflammatory, but malignancy is often a concern as well. Clinical and radiological factors and quantitative predictive models help determine the risk of malignancy and guide further management [1]. Computed

Tomography (CT) and Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) scans have improved the characterization of pulmonary nodules. The degree of avidity of FDG uptake can help differentiate between benign and malignant solid nodules. However, many nodules remain indeterminate and require longitudinal imaging to document stability or care escalation through invasive diagnostic procedures if growth is demonstrated.

Nodular pulmonary amyloidosis is a rare benign cause of pulmonary nodules. Amyloidosis is a disorder caused by the misfolding of

**Abbreviations:** AL, Amyloid light-chain; CT, Computed Tomography; FDG, Fluorodeoxyglucose; FISH, Fluorescence In-situ hybridization; FLC, Free Light Chain; MALT, Mucosa-Associated Lymphoid Tissue; PET, Positron Emission Tomography; RLL, Right Lower Lobe; SPEP, Serum Protein Electrophoresis; SUV, Standardized Uptake Value; TTE, Trans-Thoracic Echocardiography.

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autologous proteins and their extracellular deposition as fibrils (amyloid), resulting in vital organ dysfunction and eventually death. Amyloidosis can be systemic with multisystem amyloid deposition or isolated to a single organ [2]. Lung involvement is common and may be localized or a component of systemic amyloidosis. Three different patterns of pulmonary involvement are recognized: nodular pulmonary amyloidosis, diffuse alveolar-septal amyloidosis, and tracheobronchial amyloidosis [3]. In this case series, two cases of FDG avid nodular amyloidosis are presented as a rare etiology of enlarging pulmonary nodules.

## 2. Case presentation

**Case 1:** A 75-year-old woman with a history of asthma, emphysema, bronchiectasis, and a 48 pack-year smoking history was found to have sub centimeter ground glass pulmonary nodules with bulla in the right lower lobe (RLL) (Fig. 1A). Follow-up CT chest demonstrated an increased solid component within the RLL bulla (Fig. 1B) with associated mild FDG uptake with a maximum Standardized Uptake Value (SUV) of 0.5 on a subsequent PET scan (Fig. 1C). Biopsy of the lesion demonstrated amyloid deposition and plasma cells with immunostaining showing kappa light chain predominance. While undergoing evaluation for the RLL nodule, the patient developed severe back pain and was found to have vertebral compression fractures, and underwent percutaneous vertebroplasty. Due to concern for underlying multiple myeloma, a bone marrow aspirate and biopsy were performed and did not find evidence of myeloma or amyloid deposition. However, flow cytometry revealed a small (2%) kappa-restricted B-cell population and a <1% kappa-restricted plasma cell population. Cytogenetics and FISH (Fluorescence in-situ hybridization) were unrevealing. In conjunction with the biopsy findings from the RLL lesion, these findings were felt to represent a low-level involvement of the marrow by the patient's likely pulmonary marginal zone lymphoma.

Further work-up confirmed a kappa LC gammopathy (low-level IgG kappa monoclonal protein with a kappa lambda ratio of 3.58) by serum-free light chain assay. Serum and urine immunofixation proved unremarkable, and there was no evidence of systemic amyloidosis. Abdominal fat aspirate did not detect amyloid deposits. Heart (BNP, Troponin I, ECG, TTE), kidneys (serum creatinine, creatinine clearance, proteinuria) and liver (transaminases, alkaline phosphatase, bilirubin) examinations did not identify signs of functional disruption by amyloid infiltration. A final diagnosis of nodular pulmonary amyloidosis was established representing a localized clonal plasma cell process without an underlying lymphoproliferative disorder. The patient is being followed for disease progression and evolution to a lymphoproliferative disorder. Follow-up chest CT after biopsy showed slight enlargement of the solid component of the nodule which was subsequently followed for two years without significant change in size.

**Case 2:** A 77-year-old man with a history of interstitial lung disease, asbestos exposure, pleural plaques, prior tobacco use, atrial fibrillation treated with amiodarone, and 7 pack-year smoking history was being followed for a 1.6cm RLL nodule which was favored to be benign given focus of calcification (Fig. 2A–B). Follow-up CT identified an interval increase in the size of the RLL mass to 2 cm with an associated increase in the prominence of calcified prevertebral adenopathy (Fig. 2C). A PET-CT scan demonstrated moderate FDG uptake (max SUV of 4.1) in the RLL lesion and interval increase in the FDG uptake (max SUV of 5.9) in prevertebral calcified lymph nodes (Fig. 2D). A transthoracic biopsy of the RLL lung nodule demonstrated amyloid deposition, and liquid chromatography-mass spectrometry detected a peptide profile consistent with AL (kappa) – type amyloid deposition. SPEP (Serum Protein Electrophoresis) with immunofixation revealed a monoclonal band IgM kappa, and serum-free light chain assay revealed a kappa lambda ratio of 1.88. No intervention was indicated. Follow up imaging demonstrated continued enlargement of the RLL nodule measuring up to 2.4 cm which then subsequently remained unchanged for 2 years. The patient is being

followed with regular chest CT scans, regular SPEP with immunofixation, and serum-free light chain assay to assess for disease progression.

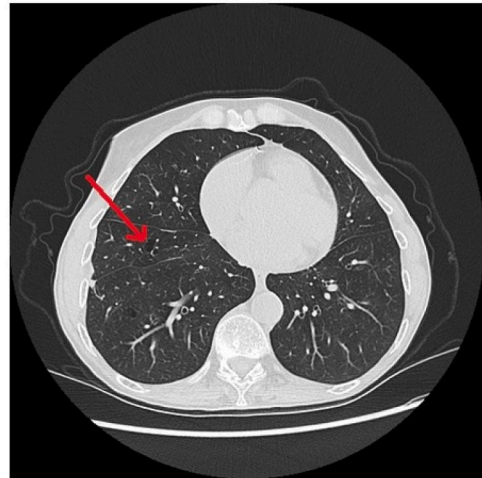
## 3. Discussion

Pulmonary nodules are a common finding on chest imaging. FDG PET-CT scan is an essential tool to assess pulmonary nodules of adequate size to help differentiate between benign and malignant solid nodules and reduce inappropriate, invasive interventions with the latter having higher standardized uptake values (SUVs) [4]. However, FDG has scant uptake in tumors with low metabolic activity such as slowly growing malignancies and carcinoid, while certain infectious and inflammatory processes including pneumonia, tuberculosis, amyloidosis, sarcoidosis, and rheumatoid nodules may demonstrate significant FDG uptake [5,6]. Therefore, it is also important to realize that FDG-PET may not accurately identify malignant lesions in populations with endemic infectious lung diseases. A meta-analysis by Deppen et al. found that FDG-PET combined with CT was less specific in diagnosing malignancy in populations with endemic infectious lung disease than nonendemic regions [7]. Many pulmonary nodules remain indeterminate after the initial workup and require longitudinal imaging to demonstrate stability or invasive diagnostic modalities for definitive diagnosis.

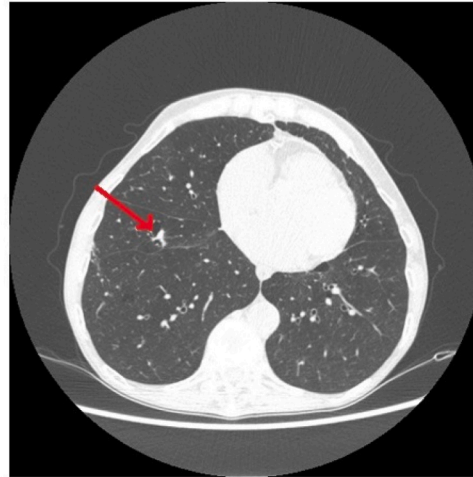
Amyloidosis is primarily a systemic disease caused by the deposition of misfolded autologous proteins in various organs and tissues, leading to progressive organ damage and eventual death [2]. Localized amyloidosis is an extremely rare form that affects a single organ. The overall estimated incidence of systemic amyloidosis is about 14/1,000,000 cases per year. The localized form is even rarer [8]. Diagnosis requires a high index of suspicion and is usually established by biopsy as part of work-up for organ dysfunction that is atypical or to rule out malignancy. Once the diagnosis of amyloidosis is confirmed after verification of amyloid deposition by classic Congo red staining, systemic amyloidosis must be excluded, and precursor protein identified as it would require additional therapy and confer a less favorable prognosis. The presence of an underlying chronic infectious or inflammatory disease, end-stage kidney disease, or a family history of amyloidosis may suggest a specific etiology and helps inform further work-up. Amyloid light-chain (AL) amyloidosis should be suspected in the absence of these conditions, and such patients should undergo further evaluation with protein electrophoresis and immunofixation of both serum and urine, and serum-free Ig light chain (FLC) assay to determine if paraproteins and a plasma cell dyscrasia are present.

Lung involvement is common and may be localized but is usually present in systemic amyloidosis. Three different forms and CT patterns of pulmonary involvement are recognized: diffuse alveolar-septal amyloidosis, tracheobronchial amyloidosis, and nodular pulmonary amyloidosis [3]. Diffuse alveolar-septal amyloidosis is characterized by amyloid deposition in the alveolar septa and vessel walls culminating in impairment of gas exchange. It is usually a manifestation of systemic amyloidosis, although rare cases of localized disease have been described [9–11]. Patients present with progressive interstitial lung disease. Vascular deposits can occasionally give rise to pulmonary hypertension [12]. Management involves treating the underlying systemic amyloidosis.

Tracheobronchial amyloidosis is usually localized and involves amyloid deposition in the trachea and large bronchi, which may lead to airway stenosis when severe. Most patients are asymptomatic. Other common presentations include cough, stridor, wheezing, hoarseness, hemoptysis, and dyspnea [13]. Complications include distal atelectasis, recurrent pneumonia, or lobar collapse depending upon the degree and location of airway disease. CT chest reveals tracheal and bronchial wall thickening with possible calcifications, and tracheobronchial endoscopy usually reveals multifocal submucosal plaques causing diffuse narrowing of the airways [14]. Treatment is largely symptomatic, although systemic chemotherapy has been tried in patients with a progressive disease with limited success [14]. Local measures to treat airway



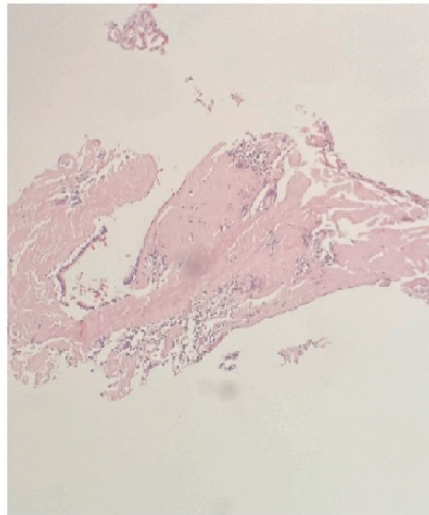
**a.** Pulmonary nodule with bulla in right lower lobe without solid component



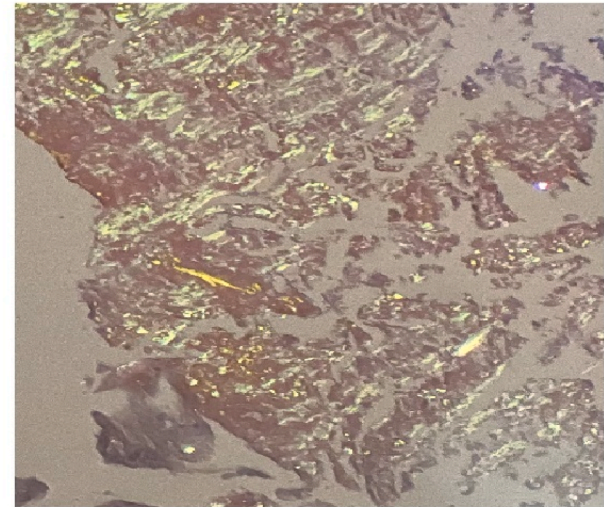
**B:** Increased solid component within the right lower lobe bulla



**C:** PET with mild increased FDG uptake of solid component

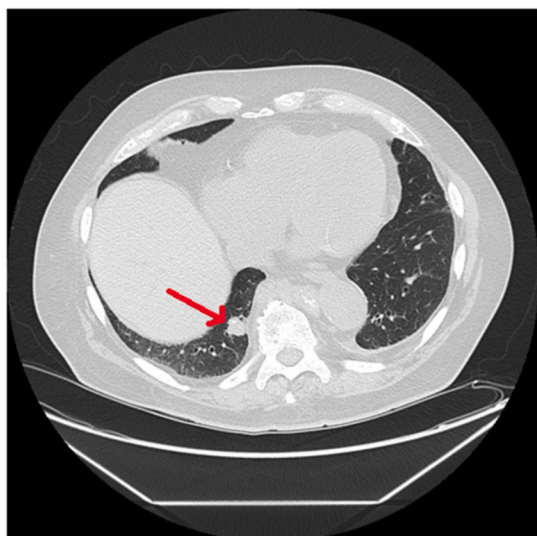


**D:** Histo-pathology

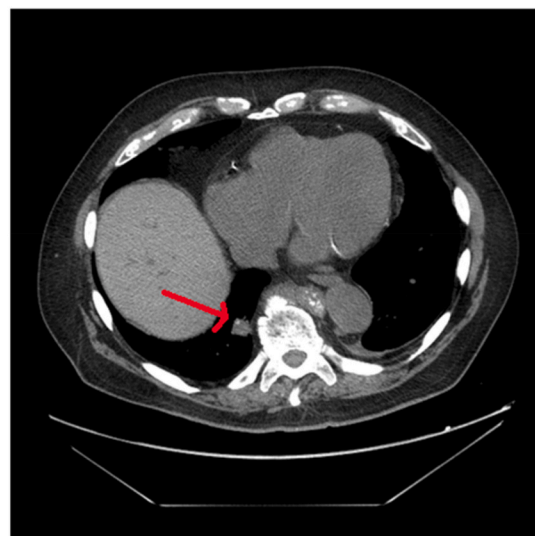


**E:** Congo-red staining

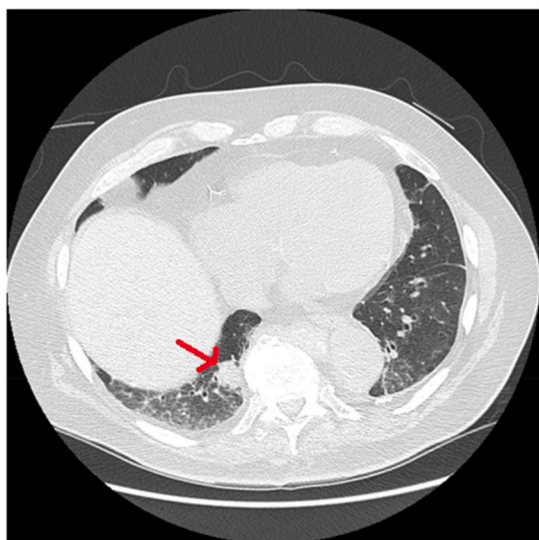
**Fig. 1.** 1A: Pulmonary nodule with bulla in right lower lobe without solid component  
1B: Increased solid component within the right lower lobe bulla  
1C: PET with mild increased FDG (max SUV of 0.5) uptake of solid component  
1D: Histopathological tissue examination  
1E: Congo-Red staining. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



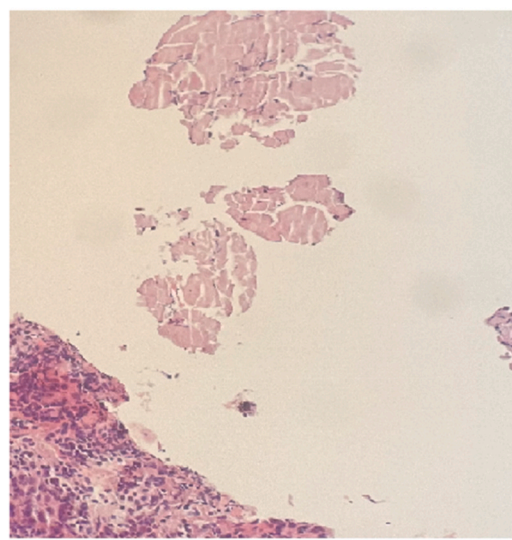
**A: Pulmonary nodule in right lower lobe, 1.6 cm x 1.8 cm**



**B: 1.6 cm nodule with calcification thus likely benign (note calcified pleural plaque adjacent to aorta due to hx of asbestos exposure)**



**C: Increase in size of pulmonary nodule, now 2 cm x 1.8 cm**



**D: Histo-pathology tissue examination**

**Fig. 2.** 2A: Pulmonary nodule in right lower lobe, 1.6 cm × 1.8 cm  
 2B: 1.6 cm nodule with calcification thus likely benign  
 (Note the calcified pleural plaque adjacent to aorta due to hx of asbestos exposure)  
 2C: Increase in size of pulmonary nodule, now 2 cm × 1.8 cm  
 2D: Histopathological tissue examination.

compromise include laser resection, bronchoscopic dilation and stenting, cryosurgery, and external beam radiation [15,16].

Nodular pulmonary amyloidosis is usually localized and presents as single or multiple pulmonary nodules found incidentally on chest imaging. These are more often found in lower lobes and in subpleural or peripheral regions [17]. In this case series, both patients presented with an interval increase in the size of previously stable pulmonary nodules. Lung nodules of pulmonary amyloidosis have also demonstrated FDG avidity as described here and some other rare, reported cases [18]. Therefore, it becomes difficult to differentiate between nodular pulmonary amyloidosis and pulmonary malignancy based on imaging alone. The diagnosis of nodular pulmonary amyloidosis ultimately requires histological confirmation. A CT-guided fine core needle biopsy is a safe and appropriate way to establish a diagnosis and may avoid

unnecessary surgical resection of pulmonary nodules with worrisome features of potential malignancy.

Recent studies have suggested that most cases of nodular pulmonary amyloidosis are the result of an underlying lymphoproliferative disorder in the spectrum of extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [19,20]. This was identified in the first case presented. A study from Mayo Clinic reported six cases in which this association could be made without the coexistent systemic amyloidosis [21]. Nodular pulmonary amyloidosis is seldom symptomatic and is usually managed with continued surveillance. Symptoms due to mass location and impact on nearby structures can be treated satisfactorily with conservative excision. Long term prognosis is excellent.

#### 4. Conclusion

Nodular pulmonary amyloidosis is a rare benign cause of pulmonary nodule and may present as an enlarging pulmonary nodule with FDG avidity. Diagnosis requires tissue biopsy and demonstration of amyloid deposition by classic Congo-red staining. Once the diagnosis of amyloidosis is established, systemic involvement must be ruled out and precursor protein identified as each would require additional therapy and confer a less favorable prognosis. Light-chain (AL) amyloidosis should be included in the differential and further evaluation with protein electrophoresis and immunofixation of both serum and urine and serum-free Ig light chain (FLC) assay is recommended if amyloid is identified. Recent studies have suggested an association between nodular pulmonary amyloidosis and an underlying lymphoproliferative disorder in the spectrum of extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). If a marginal zone lymphoma is identified, like in the first case presented, longitudinal follow-up for evolution to multiple myeloma or lymphoproliferative malignancy is recommended.

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#### Declaration of competing interest

Authors do not have any conflicts of interest or any disclosures.

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