

## Two cases of monoclonal nodular pulmonary amyloidosis and review of the literature

Kendal M. Endicott,<sup>1</sup> Conor F. Hynes,<sup>1</sup>  
Cindy M. Hsieh,<sup>2</sup> Edina Paal,<sup>2,3</sup>  
Gregory Trachiotis<sup>1,4</sup>

<sup>1</sup>Division of Cardiothoracic Surgery, Veterans Affairs Medical Center, Washington, DC; <sup>2</sup>Department of Pathology, The George Washington University, Washington, DC; <sup>3</sup>Pathology and Laboratory Medicine Service, Veterans Affairs Medical Center, Washington, DC; <sup>4</sup>Division of Cardiothoracic Surgery, The George Washington University, Washington, DC, USA

### Abstract

Nodular pulmonary amyloidosis (NPA) is an uncommon pathology of insoluble protein depositing in pulmonary parenchyma. This localized pulmonary form of amyloidosis is most often found to contain combinations of kappa and lambda immunoglobulin light chain and immunoglobulin heavy chain proteins with a polyclonal lymphoplasmacytic infiltrate. Herein we present two cases of NPA of the rarely reported monoclonal (light-chain restricted) form with review of the literature and discussion of the clinical, radiographic, and histologic features of NPA.

### Introduction

Amyloidosis is a disease that results from tissue deposition of abnormally folded protein. To date, more than 30 different types of amyloid have been described, which all share the morphologic characteristics of fibrillar beta-pleated sheet configuration.<sup>1</sup> The most common type of amyloid is derived from immunoglobulin light chain (AL) and usually presents as a systemic disease, commonly involving the kidneys, liver and spleen.<sup>2</sup> Localized amyloid deposition can be organ specific where amyloid precursor is normally produced by the organ, or amyloid (most frequently AL amyloid) may deposit in a non-specific localized form, confined to a specific organ system.<sup>3</sup> Amyloidosis involving the lung can be divided broadly into cases associated with systemic amyloidosis or those restricted to localized pulmonary anatomy.

Localized pulmonary forms are most often found to contain of kappa or lambda AL.

Histologically, three main subtypes have been described including tracheobronchial, diffuse alveolar septal amyloidosis, and nodular pulmonary (NPA).<sup>4</sup> Of these types, NPA and tracheobronchial are typically confined to the lung with NPA being the most common form accounting for about half of reported cases. NPA is typically of the AL type and can be associated with a polyclonal lymphoplasmacytic infiltrate, though rare monoclonal types with multiple lesions have been reported.<sup>5-10</sup>

Herein we report two clinical cases of monoclonal nodular pulmonary amyloidosis including one with a previously unreported presentation of a single, dominant lesion in addition to a review of the literature.

### Case Report

#### Case #1

A 55 year-old male with a chronic non-productive cough and 20 pack-year smoking history was referred to the surgical service with CT finding of a 1.4 cm spiculated nodule in the right middle lobe of his lung adjacent to the visceral pleura. PET scan showed moderate avidity with SUV of 4.2. CT-guided percutaneous lung biopsy revealed non-diagnostic aspirate of rare atypical cells. Physical exam revealed no neurologic dysfunction. Liver function tests and creatinine clearance were normal. Cardiac MRI demonstrated an interventricular septum (IVS) of 8 mm, ejection fraction (EF) of 75%, and normal left ventricular (LV) mass for age and gender (56.2 g/m<sup>2</sup>). There was also no evidence of late gadolinium enhancement to suggest cardiac amyloid.

Thorascopic wedge biopsy and mediastinal lymph node dissection were obtained which identified a 2.2 cm lesion consistent with a localized pulmonary amyloidoma. The wedge resection demonstrated a firm, homogenous dry grey-white mass puckering the pleura (2.2x1.5x1.0 cm). Histologically, the lesion was a circumscribed nodule with acellular, amorphous eosinophilic material filling the alveolar spaces and foci of osteoid metaplasia. Multinucleated giant cells and a mature appearing lymphoplasmacytic infiltrate were present, most notably at the edge of the lesion. On Congo-Red stain, the material had a salmon-colored appearance which showed apple-green birefringence under polarized light. Immunohistochemical stains revealed lambda light chain restriction of the plasma cells (Figure 1). The final diagnosis was pulmonary amyloidoma with osteoid metaplasia. Mediastinal lymph nodes showed no significant histopathologic abnormality.

Serum protein electrophoresis showed hypoalbuminemia but was otherwise unre-

Correspondence: Gregory Trachiotis, Division of Cardiothoracic Surgery, Veterans Affairs Medical Center, Washington, DC, USA.  
Tel: +1.202.745.6075.  
E-mail: gregory.trachiotis@va.gov

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markable. Urine protein electrophoresis was normal. Repeat serum protein electrophoresis was essentially normal with no evidence of monoclonal gammopathy. Serum free lambda light chains were within normal limits. Free kappa light chains were slightly elevated but the kappa to lambda ratio was within the reference range. AA amyloid was negative by immunostain. Abdominal fat pad aspirate was performed to rule out systemic amyloidosis with negative result. Of note, only Kappa and Lambda antibodies are available in our laboratory. These immunostains were done to demonstrate clonality of the surrounding plasmacytic infiltrates. Because of the high background, use of these antibodies is limited to characterize the nature of the amyloid.

#### Case #2

A 76 year-old male presented with severe aortic valve stenosis with symptoms of dyspnea on mild exertion and ostial LAD stenosis confirmed by cardiac catheterization. At this time, he was known to have bilateral pulmonary nodules in all lung lobes. By CT imaging, these were suspicious for nodular pulmonary amyloi-

dosis given their shape, pattern of calcification, and stability in size. Echocardiogram found preserved LVEF of 55% and no visualized myocardial deposits. The IVS measured at 0.98 cm with no evidence of diastolic function. Pulmonary function testing was normal, and the patient had no history of smoking.

Repeat CT scan of the chest without contrast revealed multiple bilateral lung nodules in all lung lobes with irregular calcifications with associated septal thickening suggestive of amyloid infiltration. Bilateral hilar and mediastinal lymphadenopathy were slightly increased in size from previous CT a year prior, however, lung nodules were unchanged. PET scan showed these lesions to have standardized uptake values ranging from 2.3-5.8 SUV. In addition, there was radiotracer uptake in bilateral paratracheal, hilar, prevascular, and subcarinal lymph nodes ranging from 3.6-4.5 SUV.

Transbronchial biopsies of bilateral hilar lymph nodes as well as right upper and middle lobe masses were non-diagnostic, thus left upper lobe wedge resection was performed at the time of aortic valve replacement and coronary artery bypass grafting. Histology was consistent with amyloidosis. The lung parenchyma contained yellow brittle nodules with gross central calcification. Light microscopy identified a deposit of eosinophilic homogenous material with giant cell foreign body reaction on hematoxylin and eosin stain. Congo Red staining under polarized light revealed apple-

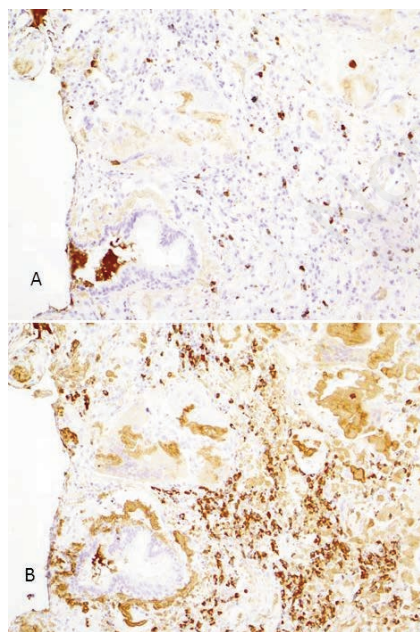
green birefringence confirming the presence of amyloid. Immunohistochemistry showed CD138+ plasma cell infiltration with kappa/lambda light chain antibodies binding at a kappa restricted ratio of 100:1, indicating a monoclonal population. On serum protein electrophoresis, the patient was found to have a faint monoclonal band. Serum and urine free light chains were minimal and within a normal ratio. Bone marrow biopsy demonstrated an atypical plasma cell infiltrate (8% plasma cells), however it did not meet criteria for plasma cell dyscrasia. Bone marrow biopsy also showed no evidence of amyloid. These findings granted the diagnosis of monoclonal gammopathy of undetermined significance.

## Discussion

Amyloidosis can be particularly difficult to diagnose because workup involves imaging, blood, and urine studies – none of which alone are diagnostic. Proper assessment of the amyloid involves typing the protein deposits by immunohistochemical (IHC) staining, immunogold electron microscopy, or mass spectrometry.<sup>11</sup> Typing of the amyloid is ideal but is available only in highly specialized institutions. Congo red stain confirms the presence of amyloid. Staining for lambda and kappa light chains to assess clonality should be done, but clonality is not necessarily associated with systemic disease. Serum and urine protein analysis is necessary to exclude an underlying or concurrent amyloid producing plasma cell dyscrasia or lymphoma. Plasma cell dyscrasia work up includes serum protein electrophoresis, serum free light chain assays, serum and urine immunofixation electrophoreses, and

bone marrow biopsy with flow cytometry. In addition, of particular concern is the assessment for systemic disease resulting in major end organ damage (*i.e.* cardiac, liver, kidney, or nervous system dysfunction.) Assessment of cardiac function by echocardiography, scintigraphy, or magnetic resonance has become standard as cardiac involvement is the major determinant of long-term outcomes. While amyloidosis is seen with some frequency in clinical practice, NPA is less common. Particularly of the polyclonal type, approximately one hundred cases have been reported in the literature of NPA (Table 1).<sup>3,5-17</sup> NPA is typically of the AL variant, specifically lambda light chain despite the usual association of AL amyloid with systemic amyloidosis.<sup>2-4,15</sup> The amyloid is speculated to arise from a reaction to chronic inflammatory conditions of the lung, including connective tissue disorders, tuberculosis, or HIV infection. In keeping with this presumptive origin, pulmonary amyloidoma is thus usually associated with a polyclonal lymphoplasmacytic infiltrate at its periphery.<sup>15</sup> Nine cases, including our two recent cases, have been reported of otherwise histologically typical pulmonary amyloidomas being associated with a monoclonal lymphoplasmacytic infiltrate.<sup>18-23</sup> Of these cases, age ranges from 55 to 73 with male predominance (7 of 9 cases). All cases demonstrated multifocal lesions with the exception of our new case presentation (Case 1). The relevant information from these cases is listed in Table 2. Given the rarity of this pathologic type, its significance is not well understood.

Nodular pulmonary amyloidoma with associated monoclonal plasmacytic infiltrate, a localized amyloid, is thus a rare entity. It is radiographically and morphologically identical to nodular pulmonary amyloidoma without light



**Figure 1.** Immunohistochemistry for kappa (A) and lambda (B) light chains reveals lambda light chain restriction of the plasma cells (original magnifications x200).

**Table 1.** Reported cases of pulmonary amyloidoma with associated polyclonal lymphoplasmacytic reaction.

Reference	Average age (range)	Sex (M:F)	Size (cm)	Number of cases
Hui	64	NR	1-4	28
Thompson	NR	NR	1-15	55
da Costa	49 (28-59)	3:3	2-7	6
Pitz	48	1:0	NR	1
Utz	67 (43-78)	NR	NR	7
Smith	79 (74-87)	2:1	.5-2	3
Cordier	NR	2:0	1-3.5	2
Dacic	55 (25-65)	3:3	NR	6
Kawashima	75	0:1	NR	1
Podbielski	65	0:1	2	1
Desai	59 (48-69)	1:1	NR	1
Pusztaszeri	72	0:1	5	1
Asad	72	0:1	NR	1

NR, not reported.

**Table 2. Reported cases of pulmonary amyloidoma with associated monoclonal light chain lymphoplasmacytic reaction.**

Reference	Age	Sex	Size (cm)	Number of lesions	Light chain
Original case	55	M	2.2	Single	Lambda
Original case	76	M	1.5-9.3	Multiple	Kappa
Miyamoto	72	M	0.9-3.5	Multiple	Kappa
Ross	60	F	0.7-2	Multiple	NR
Ross	73	F	NR	Multiple	NR
Ihing	67	M	2.5	Multiple	Lambda
Ihing	66	M	3	Multiple	Lambda
Davis	56	M	1.5	Multiple	Kappa
Murata	63	M	NR	Multiple	Kappa

NR, not reported.

chain restriction, and may mimic many other lesions on imaging and histology. A tissue sample consisting of amorphous eosinophilic material must be stained with Congo Red to confirm the presence of amyloid. After making the diagnosis of amyloidoma, the lesion should be stained for kappa and lambda light chains to determine clonality. Light chain restriction may represent a low-grade lymphoproliferative disorder, however associated significant systemic disease has not been reported to date. Further workup including serum and urine protein electrophoresis is necessary to avoid missing a diagnosis such as primary pulmonary lymphoma or pulmonary light chain disease which would require further treatment and is associated with worse prognosis.

The principle diagnostic concern with regards to NPA in particular is exclusion of underlying malignancy and systemic disease. Much of this diagnostic goal is derived from imaging properties of the NPA lesions. Classical NPA can be identified by characteristics including sharp lobulated contours, central or irregular calcification, single or multiple lesions of variable shapes and sizes with slow growth over years.<sup>18</sup> As with our case report, nodules can be FDG-avid on PET scan, further increasing the suspicion for malignancy. The nodules may also display central calcification further eliciting a potentially malignant picture. Both B cell lymphoma and mucosa-associated lymphoid tissue (MALT) must be ruled out as both associations have been described in rare cases.<sup>19-22</sup> Diagnostic uncertainty and symptoms secondary to mass effect often prompt biopsy and surgical resection of these lesions. Transbronchial or endobronchial biopsy can sometimes facilitate analysis, however thoracoscopic wedge resection or open lung biopsy are often needed for diagnosis certainty.

## Conclusions

Nodular pulmonary amyloidoma with associated monoclonal plasmacytic infiltrate is a rare

entity. Proper radiographic, histologic, and IHC workup can identify these lesions with particular attention to exclusion of systemic disease and associated malignancy to identify those patients who will benefit from directed treatment strategies.

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