

¹⁸F-FDG PET/CT in Patients with Nodular Pulmonary Amyloidosis: Case Report and Literature Review

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Key Words

Amyloidosis · Pulmonary nodules · Lung cancer · ¹⁸F-FDG PET/CT

Abstract

A 62-year-old woman was found to have multiple bilateral pulmonary nodules showing different ¹⁸F-fluorodeoxyglucose (FDG) uptakes on positron-emission tomography/computed tomography (PET/CT). Only the largest nodule in the left lower lobe showed an increased ¹⁸F-FDG uptake on PET/CT. Three nodules were surgically resected from different lobes of the left lung. Two lobes were benign and showed amyloid deposition. The largest nodule in the left lower lobe showed adenocarcinoma and a heavy amyloid deposition. Pulmonary amyloidosis should be added to the differential diagnosis for cases with multiple pulmonary nodules that show different ¹⁸F-FDG uptakes on PET/CT. To the best of our knowledge, this is the second reported case of a lung nodule consisting of adenocarcinoma and amyloid deposition.

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Introduction

Amyloidosis is a rare disorder in which insoluble fibrillar proteins are deposited in extracellular tissue [1]. Pulmonary involvement of amyloids may be localized or systemic, primary or secondary, hereditary or acquired [2]. Nodular pulmonary amyloidosis may manifest as single or multiple nodules, which are able to calcify or cavitate. It is usually misconstrued as primary lung carcinoma or metastatic tumor.

Positron-emission tomography/computed tomography (PET/CT) with ¹⁸F-fluorodeoxyglucose (FDG) is used to evaluate patients with possible cancers [3]. In the case

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of pulmonary nodules, ¹⁸F-FDG PET has been demonstrated to have a high sensitivity and specificity for malignancy [4, 5]. In the present study, we report an unusual case of multiple pulmonary amyloid nodules in a patient with different ¹⁸F-FDG uptakes on PET/CT. We also conducted a review of the literature in PubMed, EmBase and the ISI Web of Science looking for cases with histologically proven pulmonary amyloidosis who had undergone ¹⁸F-FDG PET/CT.

Case Report

A 62-year-old nonsmoking female presented with a 2-month history of cough with white phlegm and occasionally blood-tinged sputum. The patient did not have any other significant medical condition. She denied having any other symptoms, including chest pain, dyspnea, weight loss, fevers, chills, and night sweats. The findings of her physical examination were unremarkable.

The tumor marker NSE was mildly elevated to 17.63 µg/l (normal range 0–16.30). The other tumor markers, including CYFRA19, CEA and SCC, were within normal limits. The complete blood count, serum electrolytes, renal and liver function, and comprehensive metabolic profile findings were normal. Sputum smears and cultures were negative for acid-fast bacilli, fungi or other microorganisms. A pulmonary function test indicated increased airway resistance (2.05 cm H₂O/l/s, 139% of predicted). An arterial blood gas analysis obtained while breathing room air revealed a PO₂ of 92.6 mm Hg, a PCO₂ of 45.5 mm Hg and a pH of 7.407. The electrocardiogram was normal and the echocardiogram revealed normal cardiac function. No echocardiographic signs of restrictive cardiomyopathy or cardiac amyloidosis were found.

High-resolution CT of the chest revealed multiple bilateral pulmonary nodules varying in size up to 3.5 cm, with no evidence of lymphadenopathy (fig. 1). The largest nodule measuring 3.5 × 2.5 cm was noticed in the posterior segment of the left lower lobe (fig. 1b). The mass and a few nodules showed focal, punctate calcifications. Calcification in the nodules was apparent in the mediastinal windows (fig. 1, right). Mediastinal lymphadenopathy was not present. The multiple lung nodules were suspicious of metastatic lesions from a hidden malignancy. To rule out a malignancy of the nodules, the patient underwent an ¹⁸F-FDG PET/CT scan (fig. 2). The PET/CT scan indicated an intense ¹⁸F-FDG activity in the left lower lobe (standard uptake value = 6.1), corresponding to the largest pulmonary nodule on the CT image. The degree of activity was highly suspicious of malignancy. The rest of the nodules in the lung fields did not show any uptake on the PET/CT scan. There were no metastases to other organs or bone lesions anywhere.

The patient underwent open lung biopsy to investigate the possibility of malignancy. Surgical exploration revealed widespread palpable nodules present on the surface of the left lung. Two small nodules from the apical and anterior segment of the left upper lobe, and the lingular segment of the left lower lobe, were wedged out and sent for frozen section procedure. The histopathologic findings of the two nodules were benign (fig. 3a). Then, the largest mass in the posterior segment of the left lower lobe was wedged out.

Histologically, all the resected nodules contained massive deposition of homogenous eosinophilic amorphous material with focal calcification. The eosinophilic material stained positive with Congo red (fig. 3c) and showed apple-green birefringence under polarizing microscopy, features pathognomonic of amyloidosis (fig. 3d). In addition to the amyloid material, minimally invasive adenocarcinoma (mainly) and a papillary predominant (focally) growth pattern were also found in the largest mass from the left lower lobe which showed

an increased ¹⁸F-FDG uptake on PET/CT (fig. 3b). The postoperative pathological diagnosis was moderately differentiated adenocarcinoma of the lung (p-T_{1b}N_xM₀R₀, stage IA).

Afterwards, the patient was investigated for evidence of myeloma or plasma cell dyscrasias. All subsequent investigations including serum and urine protein electrophoresis and immunofixation, bone marrow biopsy and immunohistochemistry were normal. Until now, the patient has been followed up regularly with serial CT scans for 9 months. Her condition has remained unchanged, without significant clinical, physiological or radiological deterioration or evidence of systemic amyloidosis or recurrence of the adenocarcinoma.

Literature Search

We searched for previous cases of patients with histologically proven pulmonary amyloidosis who had undergone ¹⁸F-FDG PET/CT in the following databases: PubMed, EmBase and the ISI Web of Science. The search was limited, including the period from the year 2000 to October 2014, and to human studies and English-language publications. In the PubMed database, the search words were ‘amyloidosis’, ‘pulmonary’, ‘lung’, ‘PET/CT’, and ‘¹⁸F-FDG’. Corresponding words were used in the EmBase database and the ISI Web of Science.

Results of Different Publications

We identified 19 articles [6–24] describing pulmonary amyloidosis and PET/CT scan in Medline, EmBase and the ISI Web of Science. Data on the clinical presentation, histopathological and imaging findings of 41 patients (including our case) are summarized in table 1 (PET positive) and table 2 (PET negative). There were 16 male and 23 female cases, while the age and gender were not indicated in 2 cases [9, 12]. Ages ranged from 32 to 85 years and, consistent with previous findings [17, 18, 24], the average age of the patients was in the sixth decade (64 years).

Radiologically, the nodular parenchymal pattern appeared as solitary (36%) or multinodular (64%) infiltrates in any lobe. Nodules ranged in diameter from satellite nodularity to 5.5 cm. Thirty-three patients had a positive ¹⁸F-FDG uptake on PET (table 1), whereas the maximum standard uptake value ranged from 1.2 to 15 (with a mean of 4.7, n = 21), and in 71% of cases, it was >2.5. Histopathologically, pulmonary involvement in amyloidosis can be associated with mucosa-associated lymphoid tissue lymphoma, plasma cells, giant cells, and other immunoreactive cells (macrophages, monocytes and lymphocytes).

Discussion

Amyloidosis is a group of disorders characterized by extracellular deposition of proteins in a β-pleated sheet fibrillar form. The most common presentations are nephrotic syndrome, idiopathic peripheral neuropathy, cardiomyopathy, and unexplained hepatomegaly [1]. Pulmonary involvement rarely causes symptoms unless gas exchange in alveolar structures is severely affected by amyloid deposits [2, 18, 24]. Histologically, amyloid deposits are identified on the basis of eosinophilic amorphous deposits which take up Congo red stain and typically exhibit apple-green birefringence when examined under polarized light [1, 7, 22, 24, 25].

Pulmonary nodules are seen in various pulmonary diseases, including tumor, tuberculosis and infection, but amyloidosis is infrequently considered as a candidate in the differential diagnosis of such lesions. The incidence of pulmonary amyloidosis is unclear because many cases are diagnosed incidentally during open lung biopsy or at autopsy. Quiaia et al. [12] reported 76 patients with pulmonary tumor(s) suspected for malignancy between 2004 and 2006, and only 1 case was identified with amyloidosis.

For pulmonary amyloidosis, there are three types of location: parenchymal nodules (nodular parenchymal form), diffuse interstitial deposits (diffuse alveolar septal form) or submucosal deposits in the airways (tracheobronchial form) [2]. Calcification is common [15, 19, 20, 23], and a chest CT scan may show calcified deposits in over one third of patients with pulmonary amyloidosis [26]. In this study, the patient presented with multiple amyloid nodules with partial calcification in both lung fields on CT scan (fig. 1).

Nodular pulmonary amyloidosis is characterized by single or multiple parenchymal nodules or masses. The size of the nodules varies from a few millimeters to several centimeters. It is usually a silent disease and found incidentally on chest radiographs in asymptomatic, older individuals [17–19, 24, 25]. It may show a slow progression of increased size or number of nodules but not always reveals a restrictive pattern of lung function or impairment of gas exchange. The natural history of nodular pulmonary amyloidosis is associated with a relatively benign prognosis [2, 18, 19, 21, 25].

Because of its nodular appearance, nodular pulmonary amyloidosis is usually misconstrued as neoplasm. The differential diagnoses of multiple nodules include a broad spectrum of etiologies: infections, pneumoconiosis, tumor, sarcoidosis, rheumatoid arthritis, and other uncommon illnesses such as amyloidosis or pulmonary alveolar microlithiasis [2, 27].

PET/CT with ^{18}F -FDG is used to identify focal areas of increased cellular metabolism [3–5]. ^{18}F -FDG is an excellent tracer for identifying malignant lesions because of the high glucose metabolism observed in cancer cells. ^{18}F -FDG PET is widely accepted as an important diagnostic tool in identifying potentially malignant lesions. ^{18}F -FDG PET has a high sensitivity and specificity for the characterization of pulmonary nodules [5]. As with all diagnostic modalities, ^{18}F -FDG PET gives false-positive [6–24] and false-negative [28–30] results. A number of metabolically active nonmalignant diseases, such as histoplasmosis, sarcoidosis, tuberculosis and aspergillosis, can result in increased ^{18}F -FDG accumulation [3, 4]. On the other hand, tumors with low glycolytic activity such as carcinoids, localized bronchoalveolar carcinomas and small-sized tumors have revealed false-negative findings on a PET scan [28–30].

Several case reports mention patients with nodular pulmonary amyloidosis who underwent ^{18}F -FDG PET/CT, most of them showing an increased FDG uptake (table 1), but no FDG uptake has also been mentioned (table 2). A recently published study by Glaudemans et al. [22] evaluated the role of ^{18}F -FDG PET/CT in a group of patients with both systemic and localized amyloidosis; ^{18}F -FDG uptake was seen in all patients with localized amyloidosis, but none was seen in all patients with systemic amyloidosis. The giant cells in localized amyloidosis may participate in the transformation of the soluble full-length light chains into insoluble fibrils [31]. The high amounts of serum amyloid P make the amyloid deposits unavailable for inflammatory phagocytic cells in systemic amyloidosis [32]. Two studies reported by Baqir et al. [20, 24] showed that mucosa-associated lymphoid tissue lymphoma was associated with pulmonary amyloid and ^{18}F -FDG uptake, which might be due to plasma cell differentiation [33].

One case report by Miyazaki et al. [34] demonstrated the association of pulmonary amyloidosis with adenocarcinoma, but without manifestation by PET scan. In the current case, our patient had a cough of 2 months' duration with no other symptoms. Being a

nonsmoker as well as the normal physical examination and negative routine workup results suggested a nonmalignant condition. However, due to the multiple bilateral pulmonary nodules found on chest CT and the need to exclude a neoplastic process, a PET/CT scan was initially performed. Intense focal ¹⁸F-FDG uptake of the largest nodule in the left lower lobe on the PET/CT scan indicated the possibility of malignancy. However, other nodules did not show an increased ¹⁸F-FDG uptake on PET/CT imaging and were thought to be benign. Later, an open-lung biopsy was performed. Although histopathologic findings of two nodules without increased ¹⁸F-FDG uptake suggested a benign lesion, a subsequent biopsy of the nodule with increased ¹⁸F-FDG uptake was still clinically required, which was later shown to be composed of adenocarcinoma and amyloid deposition. The nodules with a normal ¹⁸F-FDG uptake on PET/CT showed amyloid deposition. Thus, for multiple pulmonary nodules, the differential diagnosis should include malignant neoplasm, and histological confirmation is mandatory. Our study emphasizes the importance of screening for multiple pulmonary amyloid nodules with PET/CT in the case of suspected malignancy before a biopsy is undertaken.

A nodular pattern of amyloid deposition surrounding the adenocarcinoma in the lung is occasionally seen [34]. Little is known about the association between amyloidosis and the neoplastic condition. Intratumoral amyloid deposition may contribute to the pathogenesis of the neoplastic condition [35]. Carcinoma-associated antigens might induce the deposition of the amyloidogenic immunoglobulin light chain and nodular lesions [36]. Considering that the lung cancer in our patient was present in only one of the multiple pulmonary amyloidosis nodules, amyloid deposition has probably developed before the neoplastic condition.

In conclusion, our case of pulmonary amyloidosis presenting with multiple nodules showed that PET/CT can be useful in disease management and decision-making before a biopsy is undertaken. Pulmonary amyloidosis needs to be added to the differential diagnosis when multiple pulmonary nodules show different ¹⁸F-FDG uptakes on PET/CT.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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Table 1. ¹⁸F-FDG PET-positive cases with nodular pulmonary amyloidosis described in the literature

First author/year	Age, years / gender	Number of nodules	Maximum dimension, cm	Location of nodules	SUV _{max}	Histological findings around amyloid deposits
Kung [6], 2003	68 / F	single	–	right lung	6.8	–
Ollenberger [7], 2004	85 / M	single	3.0	left upper lobe	2.4	mononuclear inflammatory cells
Pusztaszeri [8], 2005	72 / F	single	5.1	right upper lobe	–	–
Grubstein [9], 2005	59 / F	single	–	left lung	–	–
	59 / M	single	–	left lung	–	–
Currie [10], 2005	73 / F	single	–	right middle lobe	–	–
Yadav [11], 2006	55 / M	multiple	2.5	bilateral	–	–
Quaia [12], 2008	–	single	1.0	–	–	–
Fukatsu [13], 2010	62 / M	multiple	3.0	right lung	6.7	–
Tan [14], 2010	50 / F	multiple	–	bilateral	–	–
Seo [15], 2010	54 / F	multiple	2.5	bilateral	1.8	–
Soussan [16], 2011	70 / M	multiple	–	bilateral	4.6	histiocytic infiltration
Mekinian [17], 2012	85 / M	–	–	–	15	–
	70 / M	–	–	–	5	–
Zhang [18], 2012	44 / M	multiple	–	bilateral	1.2	a few lymphocytes
Khan [19], 2012	68 / M	single	2.0	right upper lobe	–	–
Baqir [20], 2013	53 / F	multiple	–	bilateral	2.2	MALT lymphoma
Xu [21], 2013	62 / M	multiple	–	bilateral	1.9	scattered plasma cells
	75 / M	multiple	3.0	bilateral	4.0	macrophage giant cells, plasma cells
Glaudemans [22], 2013	56 / F	multiple	–	–	–	–
	81 / F	single	–	right lung	–	–
	62 / M	single	–	left lung	–	–
	72 / F	multiple	–	–	–	–
Mukherjee [23], 2014	48 / M	single	5.5	left upper lobe	4.4	–
Baqir [24], 2014	64 / F	multiple	–	–	5.2	MALT lymphoma
	78 / F	multiple	2.4	right upper lobe	6.7	MALT lymphoma
	67 / M	multiple	–	–	2.1	–
	73 / F	multiple	–	–	5.7	MALT lymphoma
	69 / F	single	–	–	7.2	plasmacytoma
	54 / F	multiple	–	–	3.2	–
	75 / F	multiple	–	–	2.6	–
	75 / M	single	–	–	3.1	MALT lymphoma
Present case	62 / F	multiple	3.5	bilateral	6.1	adenocarcinoma

SUV_{max} = Maximum standardized uptake value; F = female; M = male; MALT = mucosa-associated lymphoid tissue; – = not stated.

Table 2. ¹⁸F-FDG PET-negative cases with nodular pulmonary amyloidosis described in the literature

First author/year	Age, years / gender	Number of nodules	Maximum dimension, cm	Location of nodules	Histological findings around amyloid deposits
Grubstein [9], 2005	-	-	-	-	-
Mekinian [17], 2012	49 / F	-	-	-	-
	66 / F	-	-	-	-
Baqir [20], 2013	74 / F	multiple	-	bilateral	MALT lymphoma
	75 / F	multiple	-	bilateral	-
	32 / F	multiple	-	bilateral	-
	58 / F	multiple	-	bilateral	-
	39 / M	multiple	-	bilateral	follicular bronchiolitis

F = Female; M = male; MALT = mucosa-associated lymphoid tissue; - = not stated.

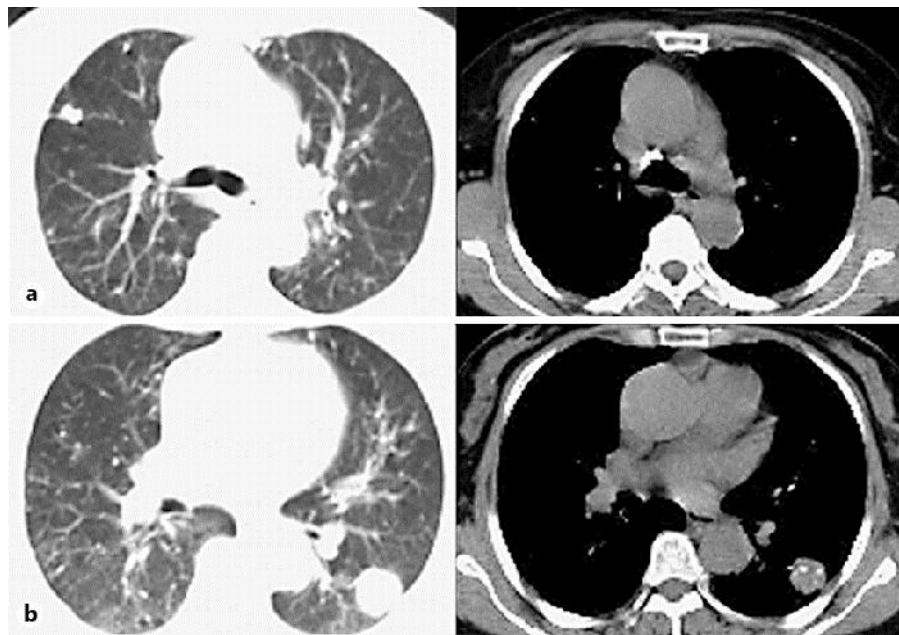


Fig. 1. a, b CT scans (lung window, left) showing variably sized multiple nodules of up to 3.5 cm in both lung fields. Focal punctate calcifications in the nodules are apparent in the mediastinal windows (right). The largest nodule is noticed in the posterior segment of the left lower lobe (b).

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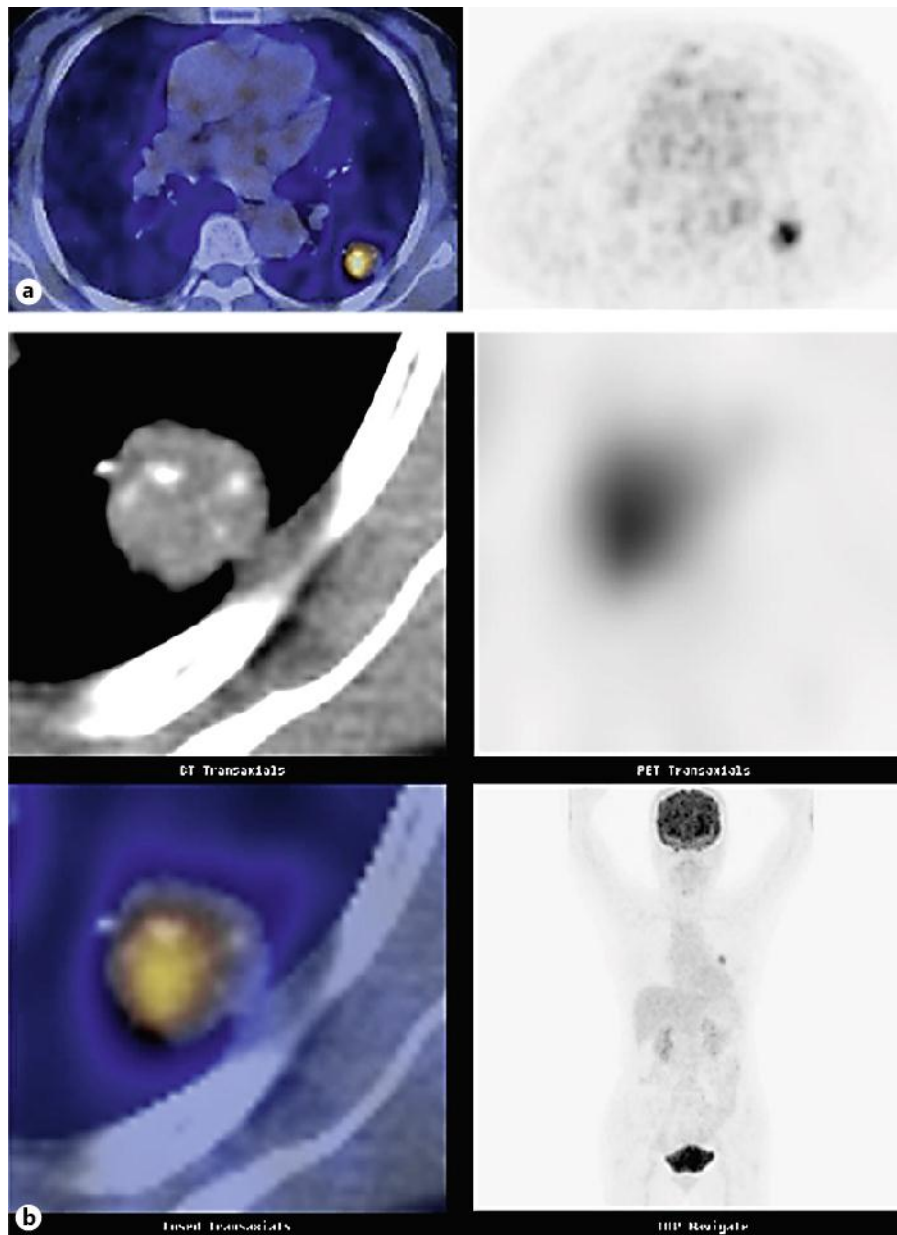


Fig. 2. a, b PET scans showing intense ^{18}F -FDG activity (maximum standard uptake value = 6.1) corresponding to a nodule in the left lower lobe on CT scan. The rest of the lesions in the lung fields do not show any uptake on PET scan. There are no metastases to other organs or bone lesions anywhere (b).

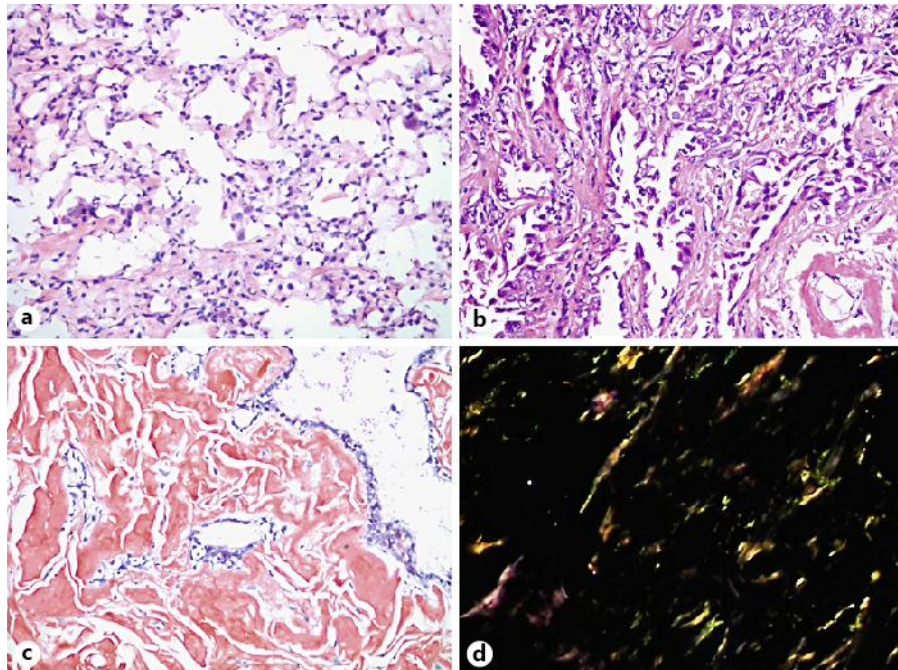


Fig. 3. Histopathological findings of resected pulmonary nodules are shown. **a** The frozen section procedure showed benign nodules. **b** The largest nodule in the left lower lobe consists of minimally invasive adenocarcinoma (mainly) and a papillary predominant growth pattern (focally) as well as massive interstitial deposition of homogenous eosinophilic amorphous material. **c** Congo red staining of the lung lesion. The amorphous eosinophilic material is colored pink or red with the use of the Congo red stain. **d** The eosinophilic material showed apple-green birefringence under polarizing microscopy when stained with Congo red, consistent with amyloidosis.