Mimicking pulmonary multiple metastatic tumors: A case of primary nodular parenchymal pulmonary amyloidosis with review of the literature

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Abstract. Primary pulmonary amyloidosis is a relatively rare condition, characterized by amyloid deposition in the lungs and other associated structures. We report a case of primary nodular parenchymal pulmonary amyloidosis in a 44-year-old male. The patient was referred to our hospital for further evaluation of multiple lobulated nodules in both lungs. As the multiple lung nodules were suspected to be metastatic, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) was conducted, which revealed that the nodules had a mild uptake of ^{18}F-FCG. Amyloidosis was confirmed by conducting a percutaneous CT-guided fine-needle aspiration (FNA) biopsy in the left lung nodule. A literature review of previous studies on primary nodular parenchymal pulmonary amyloidosis from Medline (1970-October 2011) and Embase (1989-October 2011) was also included. Despite its rarity, primary nodular parenchymal pulmonary amyloidosis with a pattern of multiple nodules also forms part of the differential diagnosis of pulmonary metastases with high ^{18}F-FDG uptake on PET/CT.

Introduction

Amyloidosis is a clinical disorder caused by extracellular deposition of insoluble abnormal fibrils in various organs and is derived from the aggregation of misfolded, normally soluble, proteins (1). Primary pulmonary amyloidosis is a relatively rare pattern of amyloidosis that is confined to the lungs and associated structures without any other organ involvement. It occurs in 3 patterns: tracheobronchial, diffuse interstitial and nodular parenchymal (2). Radiographically, the lesions of primary nodular parenchymal pulmonary amyloidosis may be single or multiple, and are able to calcify or cavitate. It is usually considered in the differential diagnosis of pulmonary primary or metastatic neoplasms. In the present study, we report a case of primary nodular parenchymal pulmonary amyloidosis and review the literature for related cases in Medline (1970-October 2011) and Embase (1989-October 2011).

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Patient and methods

Case report. A 44-year-old male was referred to our hospital for further evaluation of multiple lobulated nodules of varying sizes in both lungs that were detected on a chest computed tomography (CT) scan conducted in a health examination 1 week earlier. The patient's medical history included an appendectomy that was conducted 10 years previously. Additionally, the patient was a non-smoker and did not suffer from pulmonary or systemic symptoms. Physical examinations and laboratory findings, including analysis of tumour markers, were all of no significance. As metastases was suspected in the multiple lung nodules, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) /CT was conducted to characterize the nodules and to detect a possible primary malignancy. The ^{18}F-FDG PET/CT revealed that the nodules had a mild uptake of ^{18}F-FDG suggestive of malignancy, with a maximum standardized uptake value (SUVmax) of 1.19 (Fig. 1). Other than these pulmonary nodules, there was no evidence of a high-uptake lesion indicative of a primary malignancy anywhere else in the body. A percutaneous CT-guided fine-needle aspiration (FNA) biopsy was conducted in the left lung nodule. Histologically, the specimens contained amorphous, homogeneous material with a few lymphocytes. Congo red staining was positive (Fig. 2), which confirmed the deposition of amyloid within the specimen. Therefore, we established a diagnosis of primary nodular parenchymal pulmonary amyloidosis and discharged the patient without chemotherapy. The patient enjoys good clinical condition 1 year later.

Methods. We searched for previous cases of primary nodular parenchymal pulmonary amyloidosis in Medline (1970-October 2011) and Embase (1989-October 2011), using

a search strategy combining medical subject headings and the key words 'lung' and 'amyloidosis'.

Results

We identified 19 articles (3-21) describing primary nodular parenchymal pulmonary amyloidosis in Medline and Embase. Data on clinical presentation, radiographic pattern, biopsy and survival of 58 patients (including our case) are summarized in Table I. Ages ranged from 44 to 89 years and, consistent with previous findings, the average age of the patients was in the sixth decade (9,12,16). There were 8 male and 12 female cases, while the gender was not indicated in 38 cases. The patients were usually asymptomatic, and the amyloidosis was discovered accidentally on routine chest radiography. Few of these cases were associated with cough or hemoptysis. Radiologically, the nodular parenchymal pattern appeared as solitary or multinodular infiltrates in any lobe, usually mimicking neoplastic growth. Nodules ranged in diameter from 1 to 4 cm, with 15 cm being the largest nodule reported in the literature (22). Biopsy data were available for 22 patients. Of these 22 patients, nodule resection was conducted in 9, lobectomy was conducted in 8, and percutaneous FNA biopsy was conducted in 5. Patients with a nodular parenchymal pattern were all in good condition during follow-up.

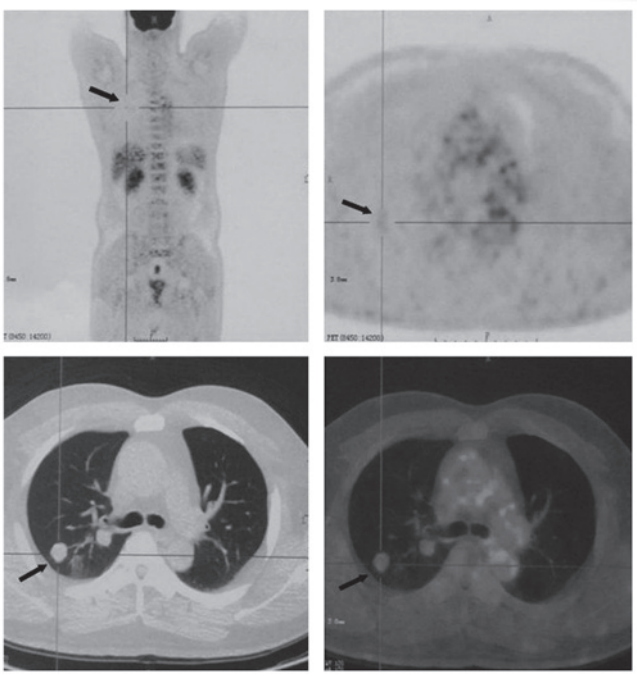

Figure 1. ^{18}F-FDG PET/CT of the present case showing multiple lung nodules with mild ^{18}F-FDG uptake and a SUVmax of 1.19 for a nodule in the right lower lobe (arrow). ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; SUV, standardized uptake value.

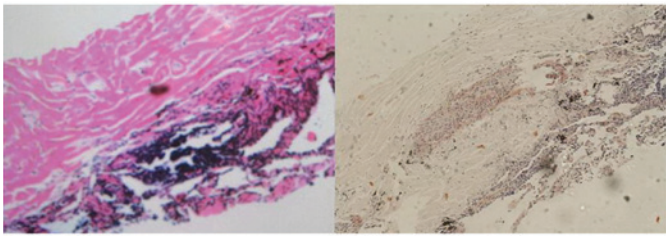

Figure 2. Histology of the present case showing the deposition of amyloid within the nodule. (left, H&E staining; right, Congo red staining; magnification, x100). H&E, hematoxylin and eosin.

Discussion

Amyloidosis is a disease caused by extracellular amyloid deposits (23). Amyloid fibres are formed by the folding of various fibril precursor proteins into an alternative conformation rich in β-sheet structures. This characteristic structure results in specific staining with Congo red dye that yields an apple-green birefringence under polarized light microscopy. The genetic and/or environmental factors in individual susceptibility to amyloid deposition have not been elucidated (22). Primary pulmonary amyloidosis is characterized by amyloid deposition in the lungs and other associated structures. Radiologically, the primary nodular parenchymal pulmonary amyloidosis appear as single or multiple nodules in any lobe, and should be considered in the differential diagnosis of pulmonary primary or metastatic neoplasms. In our study, there is no specific examination for the preoperative diagnosis of primary nodular parenchymal pulmonary amyloidosis without the presence of classic clinical findings, laboratory tests and radiological results. The final diagnosis usually requires histological confirmation.

The optimal technique for biopsy is uncertain. In our study, open lung biopsy was the most commonly used method for obtaining biopsy material, but it was more invasive than CT-guided percutaneous FNA biopsy. It is worth noting that CT-guided percutaneous FNA biopsy has also been used when a less invasive approach is necessary and 5 cases of our study were diagnosed solely on the basis of material obtained by percutaneous FNA biopsy, avoiding unnecessary invasive surgical resection. Once the diagnosis is clear, nodular parenchymal amyloidosis rarely requires treatment, which may involve surgical resection if a large nodule causes a space-occupying effect. Additionally, the majority of patients with a nodular parenchymal pattern were in good condition during follow-up.

^{18}F-FDG PET/CT is most widely used for cancer detection by revealing which tissues have a high metabolic rate and take up greater amounts of glucose in comparison to the surrounding tissues. To a certain extent, the high metabolic rate usually correlates with more aggressive tumors and a greater number of viable tumor cells (24). The use of ^{18}F-FDG PET/CT for the diagnostic workup of pulmonary nodules to reduce inappropriate invasive diagnostic investigation and subsequent complications is emerging. Duhaylongsod *et al* (25) reported that the SUV of ^{18}F-FDG uptake in malignant nodules (SUV≥2.5) was greater than benign pulmonary nodules; the sensitivity, specificity and accuracy were 97, 82 and 92%, respectively. However, ^{18}F-FDG is known to have little uptake in malignancies with low metabolic activity, including bronchoalveolar cancer, carcinoid tumor and mucinous adenocarcinoma. Furthermore, certain noncancerous conditions may also demonstrate high metabolic rates (26).

Table I. Cases of primary nodular parenchymal pulmonary amyloidosis.

Author/Year, (Ref.)	Age (years)/ gender	Clinical presentation	Radiographic pattern	Biopsy (pathology)	Survival
Chaudhuri and Parker, 1970 (3)	66/M	Asymptomatic	Smooth, round shadow in the lateral basal segment of the right lower lung lobe (CXR)	Right lower lobectomy (a round nodule 2.5 cm in diameter, in the lateral basal segment of the right lower lobe)	Patient was well postoperatively
Moldow, *et al*, 1972 (4)	58/F	Six-month history of cough	Infiltrative lesions involving both upper lung lobes (CXR)	Thoracotomy, a wedge resection of an accessible nodule in the left lower lobe (the left upper lobe was studded with numerous form to hard 1-3 cm nodules)	Chest roentgenogram remained unchanged 1 year later
Dyke, *et al*, 1974 (5)	51/M	Chronic cough	Well-circumscribed opacity in the periphery of the left upper lung lobe (CXR)	Thoracotomy, an subpleural nodule (1.5 cm in diameter) of the anterior segment of the left upper lobe was excised	Patient was well until the age of 60 years
Brauner, *et al*, (6) 1974	70/F	Chronic cough	2.5 cm soft tissue lesion in the upper lobe of the left lung (CXR)	A wedge resection of the lesion in the left lung	ND
Bonfils-Roberts, *et al*, 1975 (7)	55/F	Asymptomatic	Lobulated left parahilar mass (4 cm in diamter) (CXR)	Thoracotomy, a left lower lobectomy	Postoperative recovery was satisfactory
Makinen, *et al*, 1977 (8)	67/F	Asymptomatic	Tumour-like infiltration in the lower lobe of the right lung (CXR)	Thoracotomy, the mass was excised (approximately 3 cm in diameter)	ND
Rubinow, *et al*, 1978 (9)	63/M	Asymptomatic	Mass lesion in the left upper lung lobe (CXR)	Left upper lobectomy	Lost in follow-up and died in an automobile accident 3 years later
Desai, *et al*, 1979 (10)	i) 69/M;	i) Chronic cough	i) 2 nodular opacities in the lower half of left lung	i) Transcutaneous biopsy with a needle under fluoroscopic guidance	i) ND
	ii) 48/F	ii) Aymptomatic	ii) Bilateral pulmonary nodules (CXR)	ii) Open biopsy of the lung (a nodule was resected)	ii) ND
Schoen, *et al*, 1980 (11)	64/M	A chronic cough productive of white sputum	A chest roentgenogram showed a peripheral 4x2-cm noncalcified pleural-based mass with irregular borders in the left lateral mid-lung field (CXR)	Wedge resection of 2 nodules in the left upper lobe (4.0x3.5x1.0 cm and 1.8x0.8x0.6 cm)	ND
Hui, *et al*, 1986 (12)	Mean, 64 (28 cases)	Asymptomatic	Nodular lesions were circumscribed, showed no evidence of calcification, and ranged in size from 1 to 4 cm (CXR)	ND	ND
Kamei, *et al*, 1989 (13)	77/M	Asymptomatic	Multiple nodular shadows in both lungs (2 vessel-like shadows connected to 1 nodular lesion in the right lower lobe) (CXR)	Right lower lobectomy	Patient was well with no special treatment following surgery

Table I. Continued.

Author (Ref.), year publi	Age (years)/ gender	Clinical presentation	Radiographic pattern	Biopsy (pathology)	Survival
Davis, *et al*, 1991 (14)	56/M	Pleuritic pain; hemoptysis	Left hilar mass and bilateral dense nodules in the pulmonary parenchyma (CT)	Thoracotomy; the mass was resected and wedge resections were performed on 2 nodules from the left upper lobe (those >1.5 cm in diameter)	Uneventful recovery
Mollers, *et al*, 1992 (15)	88/F	A single episode of hemoptysis	3 partially calcified nodules in both lower lung (CXR)	Transthoracic coaxial fine needle biopsy	Good condition and asymptomatic 20 months later
Utz, *et al*, 1996 (16)	Mean, 67 (7 cases)	NA	Single nodule (5 patients); multiple nodules (2 patients) (ND)	Biopsy (described unclearly)	ND
Khoor, *et al*, 2004 (17)	i) 62/F	i) Episode of severe exacerbation of asthma	i) Multiple, bilateral pulmonary nodules;	i) Thoracotomy (right middle-lobe biopsy) and a video-assisted thoracoscopic wedge biopsy 9 months later (>5.0 cm)	i) Pulmonary nodules were stable 1 year later
	ii) 65/F	ii) Asymptomatic	ii) Solitary pulmonary nodule in the right upper lobe	ii) Right upper lobectomy (2.4 cm)	ii) ND
	iii) 69/F	iii) Asymptomatic	iii) Solitary pulmonary nodule in the left upper lobe (radiological method was not mentioned)	iii) Left upper lobectomy (>4.0 cm)	iii) ND
Biewend, *et al*, 2006 (18)	i) 75	NA	NA	NA	i) No disease
	ii) 73	NA	NA	NA	ii) Stable disease
	iii) 65	NA	NA	NA	iii) ND
Adžić, *et al*, 2008 (19)	52/F	Hemoptysis for 1 year	Nodular, multiple, bilateral soft tissue densities (HRCT)	Open lung biopsy (the nodules measured >3 cm)	Good clinical condition 3 years later
Yang, *et al*, 2009 (20)	58/F	Asymptomatic	Multiple lung nodules (CT)	CT-guided percutaneous FNA biopsy of 1 nodule	ND
Seo, *et al*, 2010 (21)	54/F	Asymptomatic	Multiple nodules (>2.5 cm) in both lungs (CT); mild FDG uptake in the pulmonary nodules (SUVmax 1.8) (PET/CT)	Open lung wedge resection of the right pulmonary nodules	ND
Present case	44/M	Asymptomatic	Multiple lobulated nodules of varying sizes in both lungs (CT); mild FDG uptake in the pulmonary nodules (SUVmax 1.19) (PET/CT)	Percutaneous CT-guided core biopsy was obtained from the left lung nodule	Patient enjoys good clinical condition 1 year later

M, male; F, female; CXR, chest radiography; CT, computed tomography; NA, not available; ND, not described; FDG, fluorodeoxyglucose; FNA, fine-needle aspiration; SUV, standardized uptake value; PET, positron emission tomography.

Increased ^{18}F-FDG activity has been demonstrated in cases of tuberculosis, sarcoidosis, fungal disease, interstitial lung disease, osteoarthritis, vascular thromboses, osteoporosis and rheumatoid nodules (27-29). The reason that noncancerous conditions uptake ^{18}F-FDG may be due to lesions with a high concentration of inflammatory cells, including neutrophils and activated macrophages, which increase glucose uptake (30,31). Our case and the case reported by Seo *et al* (21) exhibited multiple lung nodules of pulmonary amyloidosis with moderate ^{18}F-FDG uptake, and an SUVmax of 1.19 and 1.8, respectively. Our results suggest that positive results of ^{18}F-FDG PET/CT on pulmonary nodules should be interpreted with caution in differentiating pulmonary nodular amyloidosis from malignant lesions.

In conclusion, primary nodular parenchymal pulmonary amyloidosis is a relatively rare condition without classic clinical findings, laboratory tests and radiological results. Despite its rarity, primary nodular parenchymal pulmonary amyloidosis with a pattern of multiple nodules should be cautioned with the differential diagnosis of pulmonary metastases with high ^{18}F-FDG uptake on PET/CT.

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