Ann Nucl Med (2012) 26:522–526
DOI 10.1007/s12149-012-0606-3

CASE REPORT

# Lung amyloid nodule detected by $^{99m}$Tc-aprotinin scintigraphy

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Received: 2 March 2012 / Accepted: 24 April 2012 / Published online: 19 May 2012


**Abstract** We present a case in which an amyloid lung nodule was diagnosed preoperatively by amyloid scintigraphy $^{99m}$Tc-aprotinin. A 65-year-old man complained of marked weight loss (9 kg) over a period of 6 months. An abnormal shadow in the middle field of the right lung was detected on chest X-ray, corresponding to a 16-mm nodule in the right middle lobe on thoracic computed tomography (CT). Total protein and immunoglobulin G levels were elevated to 8.3 and 2245 mg/dl, respectively, but other blood tests including several tumor marker levels and *Cryptococcus* antibodies were all within normal range. Fluorodeoxyglucose positron emission tomography showed no uptake by the lung nodule, so lung amyloidosis was considered as differential diagnosis. To avoid risk of bleeding on bronchoscopy, noninvasive amyloid scintigraphy using $^{99m}$Tc-aprotinin was first performed. A nodular, abnormal accumulation was observed in the right middle lung lobe. Diagnostic imaging strongly suggested amyloidosis, so video-assisted thoracic surgery was performed rather than bronchoscopy. Pathological samples showed positive staining with Congo red, and A-$\lambda$ amyloidosis was diagnosed on the basis of immunostaining. Scintigraphy using $^{99m}$Tc-aprotinin offers a useful, noninvasive method for assessing lung amyloidosis.

**Keywords** Amyloidosis · $^{99m}$Tc-aprotinin scintigraphy · Solitary pulmonary nodule · FDG-PET

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## Introduction

Amyloidosis is a disorder in which abnormal fibrous protein called amyloid is deposited in the organs. Pulmonary lesions in amyloidosis manifest as well-defined nodular lesions with round shape on thoracic computed tomography (CT) [1]. The principal differential diagnoses based on imaging are lung cancer, lung metastasis, tuberculoma and cryptococcosis. Definitive diagnosis of amyloidosis can be provided by Congo red staining of pathological sample. Bronchoscopy and biopsy under CT guidance are sometimes performed for the differential diagnosis of nodular lesions, but the diagnostic yield is low, and the procedure carries a high risk of complications such as hemorrhage [2, 3]. As a result, diagnosis of lung amyloidosis has rarely been confirmed prior to surgery. Differentiation of this disorder by diagnostic imaging prior to invasive tests such as bronchoscopy would obviously be preferable. We report herein a case of amyloidosis in which the patient was diagnosed preoperatively on the basis of amyloid scintigraphy with $^{99m}$Tc-aprotinin.

## Case report

A 65-year-old man had been referred to our hospital after 9 kg of weight loss during 6 months. There were no

abnormalities in thoracic and abdominal CT, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), or in upper and lower gastrointestinal endoscopy.

Half a year later, an abnormal shadow was found in the right lung and he was referred to our hospital for further examination. He had a history of hepatitis B and lumbar spinal stenosis, and been a heavy smoker of Brinkman index 2400. All physical examinations and vital signs were normal, except hypesthesia in both legs, particularly in the soles of the feet.

White blood cells (3270/μl) were mildly depressed, while levels of total protein (8.3 g/dl) and immunoglobulin (Ig) G (2245 mg/dl) were elevated. Negative results were obtained for *Cryptococcus* antibodies, and levels of tumor markers were within normal limits. Chest radiography showed a nodule in the right lung (Fig. 1). Thoracic CT revealed a smooth, nodular shadow (diameter 16 mm) in the right middle lung lobe (Fig. 2a). FDG-PET showed no intense uptake by this nodule, indicating a low probability of malignancy (Fig. 2b). Elevated IgG levels and short-term weight loss are common in patients with amyloid disorder, so $^{99m}$Tc-aprotinin scintigraphy was performed before conducting invasive procedures, such as bronchoscopy or VATS (Fig. 3a–c).

Use of $^{99m}$Tc-aprotinin scintigraphy was approved by the institutional review board in our hospital, and written informed consent was obtained from the patient prior to testing. We have prepared labeling kits following the methods of Smyth [4]. We used pyrophosphate kits to produce $^{99m}$Tc labeling kits of aprotinin. Addition of $^{99m}$Tc at the time of use is enough for labeling. Production is carried out by sterile manipulation in a clean bench. Quality assessments of the kits produced in our hot laboratory have been performed by Fujifilm RI Pharma (Tokyo, Japan) to maintain the objectivity of the evaluation, revealing a mean labeling efficiency of 99.5 %. Planar and tomographic imaging was performed 90 min after injection of 740 MBq of $^{99m}$Tc-aprotinin using a single photon emission computed tomography (SPECT) system (e-com signature; Siemens, Erlangen, Germany). Significant uptake was identified in the right middle lung lobe on $^{99m}$Tc-aprotinin scintigraphy. In addition, significant uptake was observed in the left ventricular myocardium, suggesting cardiac amyloidosis. The locations of lesions differed slightly from CT and SPECT, probably due to respiratory movements and changes in body position. Finally, VATS was performed to confirm the diagnosis. Macroscopically, a reddish-brown nodular lesion (1 cm in diameter) was identified (Fig. 4a). This was surrounded by fibrous capsule, and hematoxylin and eosin (HE) staining showed amorphous eosinophilic material (Fig. 4b). The eosinophilic material appeared orange-red under Congo red staining, and exhibited apple-green birefringence under polarized light after Congo red staining (Fig. 4c), confirming the presence of amyloid. Staining did not disappear with potassium permanganate treatment, ruling out AA amyloidosis, and AL amyloidosis was suggested. On immunohistochemical examination, it showed positive staining for λ chain (Fig. 4d). Upper and lower gastrointestinal endoscopy was performed, and amyloid deposits were pathologically proven by the biopsy specimen. Lip biopsy also showed amyloid deposition.

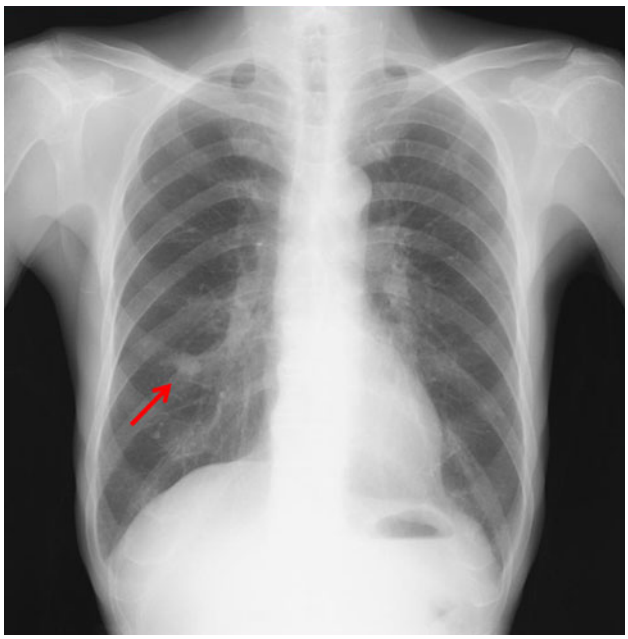

**Fig. 1** Chest radiography showing a nodular shadow, 16 mm in diameter, in an area overlapping the anterior edge of the right 5th rib

Scintigraphy with $^{99m}$Tc-aprotinin and cardiac ultrasonography indicated amyloid deposition in the cardiac wall, and decreasing neurotransmission speed was suspected to have been caused by neural amyloid. Since amyloid deposition was pathologically confirmed in at least three organs, systemic amyloidosis (amyloid protein, AL; precursor protein, λ chain) was finally diagnosed. The patient was referred to hematologists and was treated using bortezomib as a proteasome inhibitor and dexamethasone, achieving improvements in symptoms.

## Discussion

Amyloidosis is a metabolic disorder of unknown etiology in which fibrillar protein, called amyloid, is deposited in organs throughout the body. Amyloidosis of the respiratory system is classifiable into three types, tracheobronchial amyloidosis; nodular pulmonary amyloidosis; and diffuse alveolar septal amyloidosis [5].

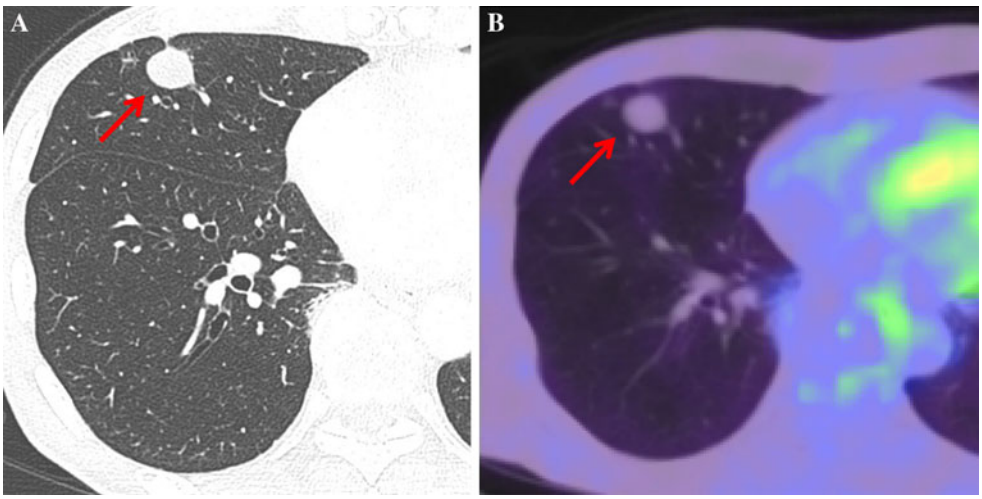


**Fig. 2** Thoracic CT shows a nodular shadow, 16 mm in diameter, in the right middle lobe (**a**). The nodule is circular and smooth, with clearly demarcated borders. No FDG uptake by the nodule is seen on FDG-PET (**b**). The location of lesions differed slightly from CT and SPECT, probably due to respiratory movements and changes in body position

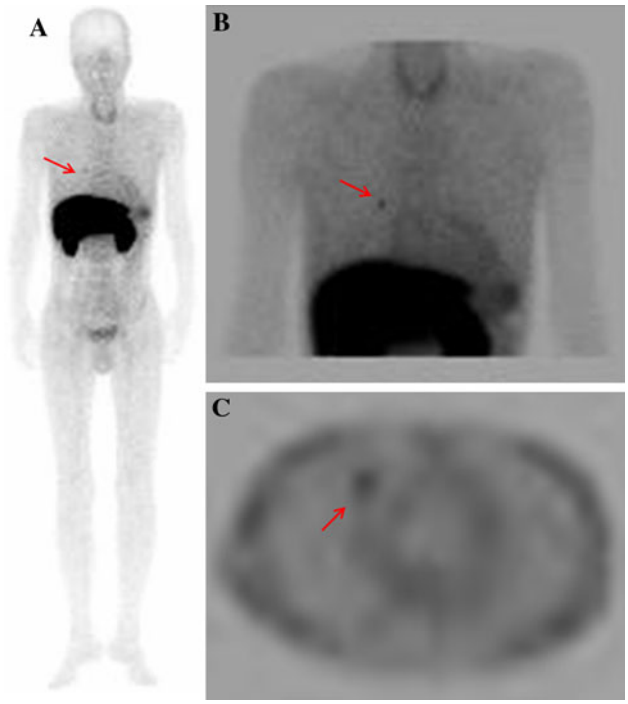


**Fig. 3** Scintigraphy using $^{99m}$Tc aprotinin shows nodular uptake in the middle lobe of the right lung. Significant uptake is also observed in the myocardium (left ventricular myocardium), suggesting cardiac amyloidosis. Anterior and posterior planar images (**a**, **b**) and single photon emission computed tomography (SPECT) image (**c**)

Nodular pulmonary amyloidosis is difficult to differentiate from malignancy or from tuberculosis only by imaging such as CT or FDG-PET, and invasive procedures such as bronchoscopy are required. Although transbronchial lung biopsy (TBLB) has a diagnostic rate of about 37–74 % for nodular lesions, the rate for nodular amyloidosis is much lower, at only 17 % [6]. According to Ulz et al. [2], around 100 ml of hemorrhage was evident in 2 of 11 patients who underwent bronchoscopy. Mortality due to hemorrhage after TBLB has also been reported in a case that was also complicated by air embolism [3]. Aprotinin is a basic polypeptide consisting of 58 amino acids with a molecular weight of 6512, and has been reported to bond to amyloid $\beta$ sheet structures with high affinity due to its 3-D structure and electrostatic properties [7]. In terms of safety, $^{99m}$Tc aprotinin has been used in over 1700 patients in Europe with no side effects, even with twice or more uses [8]. Aprile et al. [8] were the first to evaluate $^{99m}$Tc-aprotinin for the imaging of amyloid deposits. They reviewed the scintigraphic findings for 24 patients with AL amyloidosis, finding myocardial accumulation in 11 patients. Other report has also described the utility of $^{99m}$Tc-aprotinin as an imaging agent for myocardial amyloidosis [9]. $^{99m}$Tc-aprotinin has a sensitivity of 95 % and specificity of 97 % in the heart lesion [8]. However, diagnostic ability has not been reported for lung lesions. The uptake of $^{99m}$Tc-aprotinin in other diseases (such as malignant tumors and tuberculosis) also has not been elucidated, and needs future investigation. According to Schaadt et al. [10], significant accumulations were evident in 22 of 23 AL amyloidosis patients who underwent $^{99m}$Tc aprotinin scintigraphy. Uptake was particularly significant in areas such as the lungs, pleura, and myocardium. Uptake of $^{99m}$Tc-aprotinin in the lungs was observed in 9 of the 23 patients [10]. Biopsy was performed for only two of these patients, but the presence of amyloid was pathologically confirmed in both patients. Visualization with $^{99m}$Tc-aprotinin in the lung is clear due to the absence of physiological accumulation and background, as little

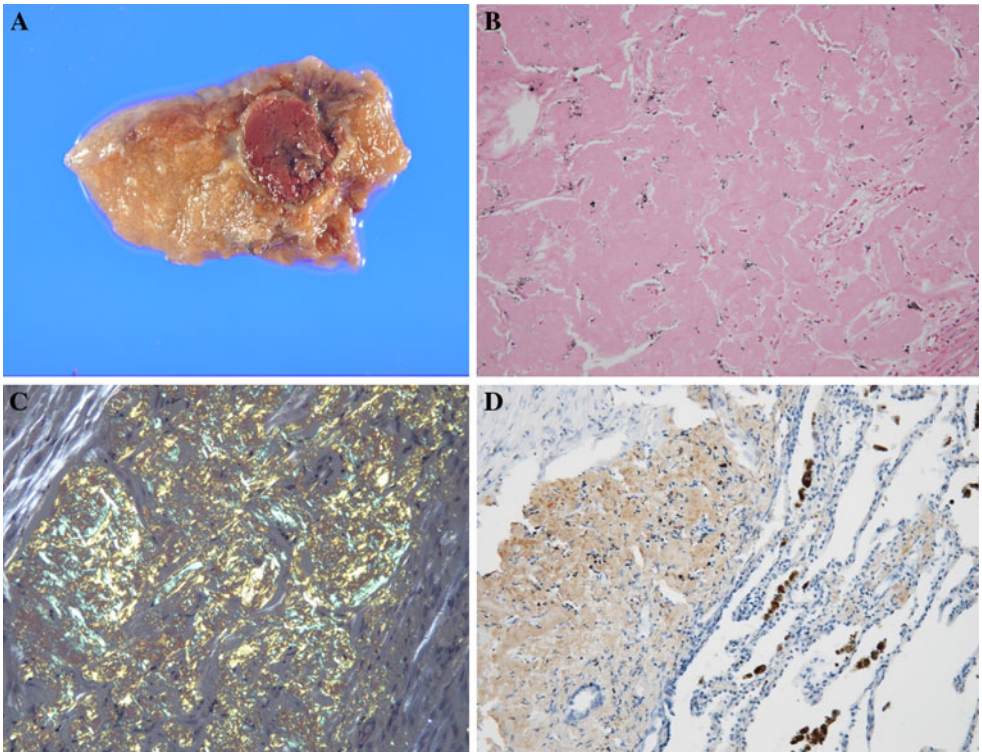


**Fig. 4** Pathologically, a 1-cm diameter, *reddish-brown*, nodular lesion is seen (**a**). This lesion is surrounded by a fibrous capsule, and H&E staining shows amorphous eosinophilic deposits (**b**). Eosinophilic material exhibits apple-green birefringence under polarizing microscopy (**c**). Immunochemistry, staining is positive for the $\lambda$ chain (**d**)

uptake of $^{99m}$Tc-aprotinin occurs in the lung region. However, $^{99m}$Tc-aprotinin shows limitations for detecting amyloid deposits in the abdominal area in terms of physiological uptake in the liver, spleen and kidneys [11, 12].

In the present case, $^{99m}$Tc-aprotinin scintigraphy was useful for detecting lung amyloidosis. As $^{99m}$Tc-aprotinin scintigraphy can be carried out noninvasively, risks arising from bronchoscopy or lung biopsy can be avoided and stress on patients can be reduced. Moreover, whole-body $^{99m}$Tc-aprotinin imaging may indicate other sites of amyloid deposition that can be more easily and safely biopsied, even though limitations are seen in terms of physiological uptake. $^{99m}$Tc-aprotinin scintigraphy is not commercially available in Japan, and further investigation of cases is necessary in the future.

## Conclusion

Scintigraphy with $^{99m}$Tc-aprotinin was useful for noninvasive, preoperative diagnosis of pulmonary amyloidosis.

**Acknowledgments** We wish to thank Dr. Yoshinobu Hoshii of Yamaguchi University School of Medicine for his valuable advice regarding the pathologic diagnosis. This work was supported by a Grant of National Center for Global Health and Medicine No. 22-118 (to Ryogo Minamimoto).

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