

## Case Report

# Pulmonary epithelioid hemangioendothelioma coexisting with pulmonary nodular amyloidosis: case discussion and review of the literature

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**Abstract:** A 38-year-old female was found to have multiple bilateral lung nodules in a routine chest X-ray examination. Thoracoscopy was performed with biopsy of three nodules from the right lower lobe and Congo red staining showed typical amyloid pattern. Initial diagnosis of pulmonary nodular amyloidosis was made. However, one nodule in the right upper lobe enlarged as detected by follow-up CT scan. The patient underwent F-18 fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG-PET)/CT and a significant high FDG uptake in the largest nodule in right upper lobe was observed while the uptake was normal or mildly increased in the other nodules. Meanwhile, right hilar and mediastinal lymph nodes adenopathy was noted. Right upper lobe was resected by thoracotomy. Surprisingly, histopathological findings showed pulmonary epithelioid hemangioendothelioma (PEH) with metastasis of hilar and mediastinal lymph nodes. To our knowledge, this is the first described case of PEH coexisting with pulmonary nodular amyloidosis.

**Keywords:** Pulmonary epithelioid hemangioendothelioma, amyloidosis, <sup>18</sup>F-FDG-PET/CT

### Case reports

A 38-year-old female without any symptoms was found to have multiple bilateral lung nodules in a routine chest X-ray examination (**Figure 1**). She had ten years of smoking history of one pack/day. She had no prior medical history. There was no family history of cancer. On physical examination, she was not clubbed and there were no abnormally enlarged lymph nodes. Physical examination of the lung was normal. The result of pulmonary function test was normal. Bronchoscopy was performed without any abnormal findings. A chest enhanced CT scan was performed on June 11, 2012, showing multiple, approximately 1-25 mm, well-demarcated noncalcified nodules diffusely in both lungs. The largest nodule was observed in the right upper lobe which was 25 mm in diameter (**Figure 2A**). There were no enlarged mediastinal lymph nodes.

Thoracoscopy were performed with biopsy of three nodules from the right lower lobe.

Pathological examination of the nodules showed that Congo red staining was positive with typical amyloid deposition, suggesting the diagnosis of pulmonary amyloidosis (**Figure 3A, 3B**). To investigate the possibility of primary systemic amyloidosis, urine and serum protein electrophoresis including immunofixation were performed without evidence of monoclonal protein. Bone marrow aspirate and biopsy were also performed without evidence of clonal plasma cell, and amyloid staining of bone marrow was negative, suggesting localized pulmonary amyloidosis. Therefore, an initial diagnosis of primary pulmonary nodular amyloidosis was made. The patient was not given any specific treatment.

On October 14, 2012, the patient was hospitalized again, complaining with low-grade fever, cough, and sputum. She also complained chest pain during deep breathing, pain of finger and ankle joint, and night sweats. Physical examination showed mild edema of lower limbs and

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**Figure 1.** Chest x-ray showing multiple bilateral lung nodules, the biggest nodule in right upper lobe was 20 mm in diameter.

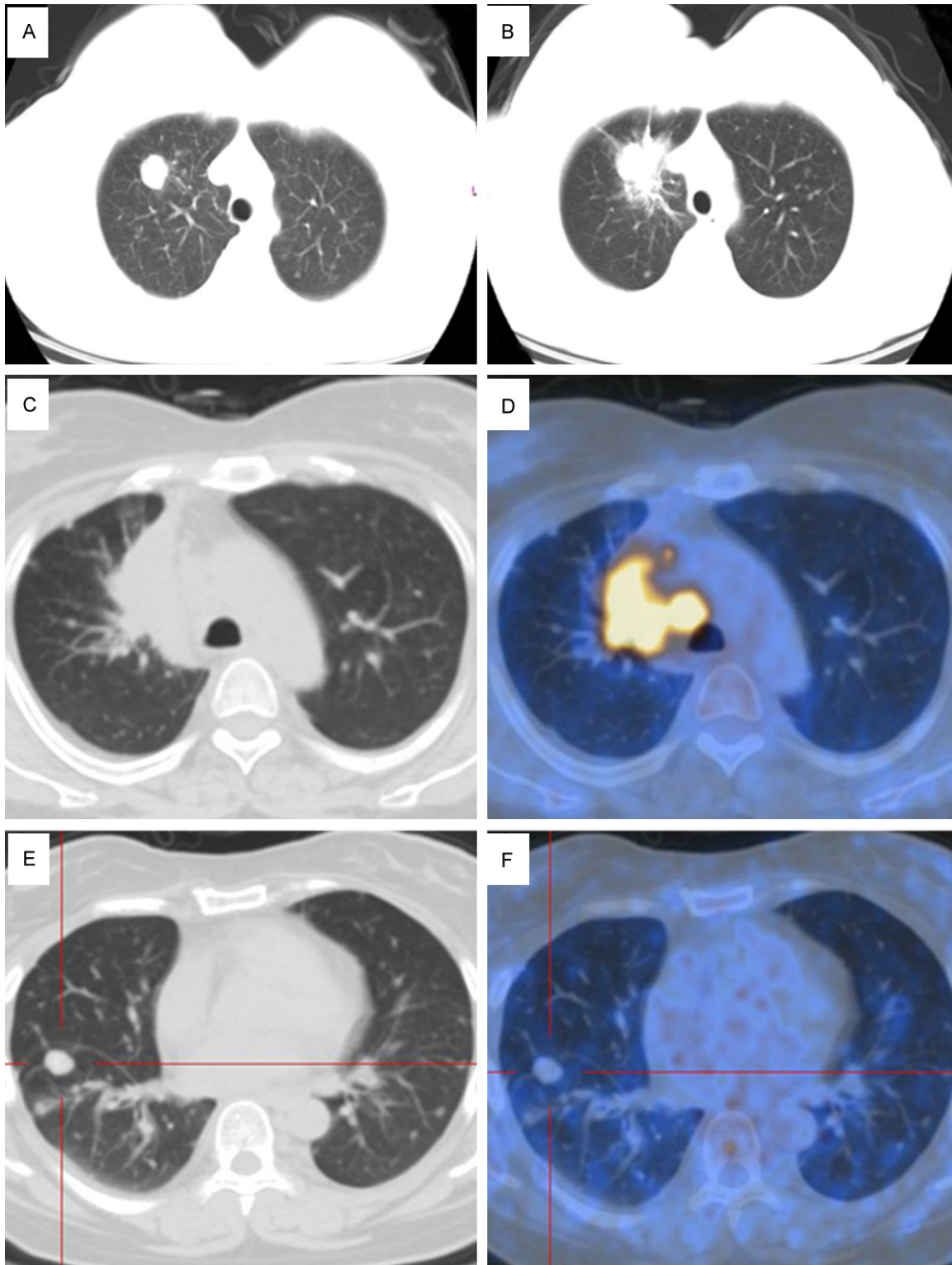
clubbing fingers. A chest CT scan was performed again on October 19, 2012 (**Figure 2B**), showing the largest nodule at the right upper lobe was 35 mm in diameter, with spiculation sign and fibrous stripes connecting with pleura. The serum level of tumor makers including CEA, NSE, CYFRA21-1, SCC, AFP, and CA125 were within normal ranges. Bronchoscopy was performed again showing the right upper lobe bronchus was narrow and the membrane was coarse. Airway brushing of the right upper lobe bronchus was performed and cytology examination showing no cancer cells, also negative for acid fast bacilli. Pathological examination of the biopsy of right upper lobe bronchus showed chronic inflammatory cell infiltrating lamina propria mucosae and red material phagocytosis by macrophages. A chest enhanced CT scan was performed again on November 8, 2012. The largest nodule at the right upper lobe enlarged in size and was suspected to be malignant, while the other nodules have no obvious change. Moreover, the adenopathy of right hilar and mediastinal lymph nodes were noted. Radionuclide bone scan by single photon emission computed tomography (SPECT) was performed with the result suggesting hypertrophic pulmonary osteoarthropathy. ( $^{18}\text{F}$ -FDG-PET)/CT scan was performed on November 21 and the result showed an abnormally high FDG uptake in the largest nodule in the right upper lobe, with a standardized uptake value (SUV) of 9.4 at maximum (**Figure 2C, 2D**), while the SUV was normal or only mildly increased in other nodules (**Figure 2E, 2F**). Increased SUV of 9.5-10.9 of right hilar and mediastinal lymph nodes was observed (**Figure 2D**).

Because the largest nodule in right upper lobe was suspected to be malignant, thoracotomy was performed to resect right upper lobe and systematic mediastinal lymphadenectomy was also performed. The nodule was 50 mm×60 mm×50 mm, adhered to pleura. Surprisingly, histopathological examination of the resected nodule and lymph nodes revealed PEH with metastasis of lymph node. In supporting of this diagnosis, immunohistopathologic staining showed that the tumor cells were endothelial cells and immunoreactive for CD31, CD34 and vimentin (**Figure 4**); negative for epithelial membrane antigen (EMA), thyroid transcription factor (TTF-1), cytokeratin (CK) 20, CK7, and muscular differentiation marker (Myogenin and MyoD1). Other makers including PCK, Villin, CDX-2, CgA, Syn, CD56, calretinin, WT-1, D2-40, CK5/6, CD117, DOG1, SMA, DES, Bcl-2, HMB45, Melan-A, GFAP, Calponin, HMW-34 $\beta$ E12, CD20, CD79 $\alpha$ , PAX-5 were also negative, and Ki-67LI <20%. Therefore, the final diagnosis was PEH coexisting with pulmonary nodular amyloidosis.

### Discussion

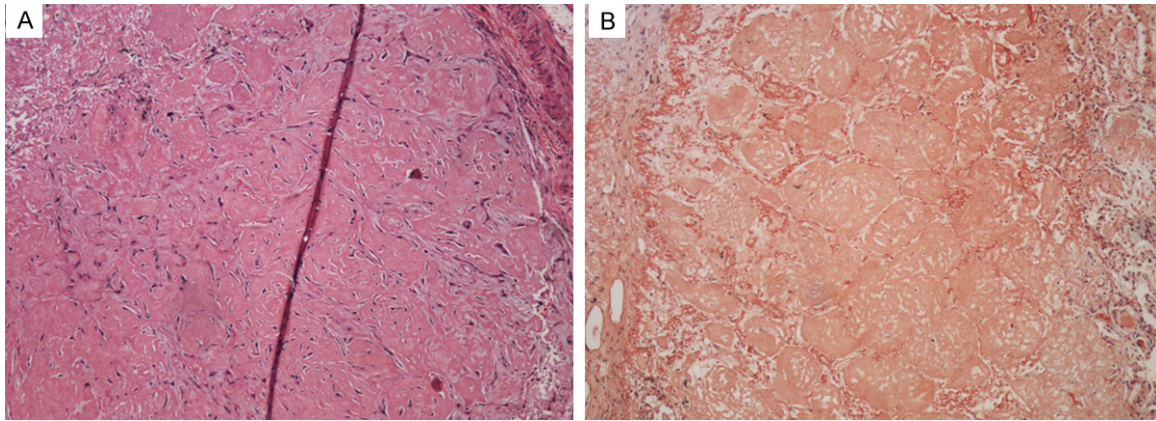
The epithelioid hemangioendothelioma is a rare vascular tumor of low-grade malignancy, which was first described by Dail and Liebow in 1975 as an intravascular bronchioloalveolar tumor [1]. Epithelioid hemangioendothelioma has been reported in liver, thyroid, skin, bone, pleura, lung and other organs. So far, about 120 cases of pulmonary epithelioid hemangioendothelioma (PEH) have been reported [2]. Amyloidosis results from insoluble protein-based amyloid fibrils depositing in the extracellular matrix [3]. Pulmonary amyloidosis occurs in three patterns: tracheobronchial, nodular parenchymal, and diffuse interstitial [4]. Amyloidosis is uncommon with an incidence of 8 patients per million per year [5]. Primary amyloidosis is usually associated with the plasma cell disorders such as multiple myeloma, and secondary amyloidosis is associated with chronic inflammatory disease and tumor [6].

To our knowledge, the present case report is the first report describing PEH coexisting with pulmonary nodular amyloidosis. Both PEH and pulmonary nodular amyloidosis are very rare diseases. In this case, pulmonary nodular amyloidosis may be secondary to PEH. Secondary

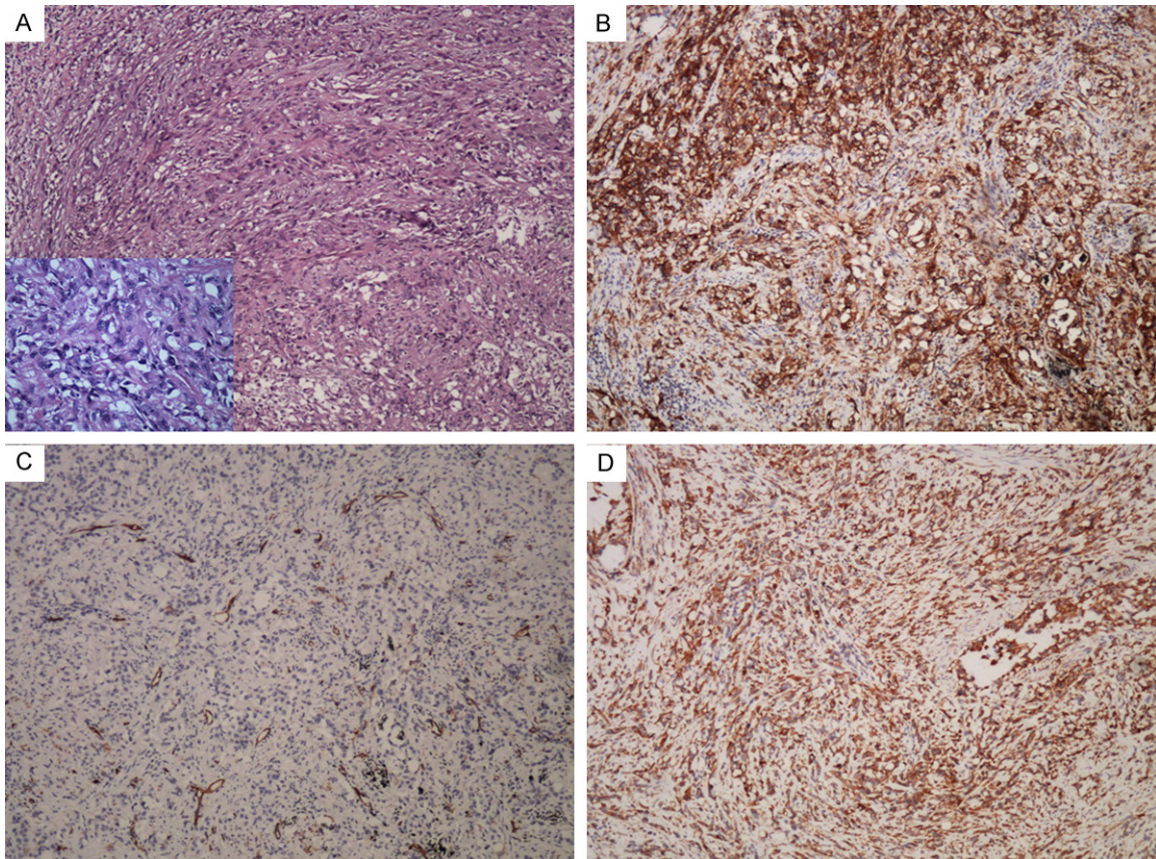


**Figure 2.** A: CT on presentation showing multiple nodules in bilateral upper lobes, the biggest nodule in right upper lobe was 20 mm in diameter. B: Follow-up CT scan showed the biggest nodule increased in size with 35 mm in diameter. C, D: ( $^{18}\text{F}$ -FDG-PET)/CT scan showed the biggest nodule in the right upper lobe and mediastinal lymph nodes adenopathy with a significantly high FDG uptake at the maximum of SUV 9.4. E, F: ( $^{18}\text{F}$ -FDG-PET)/CT scan of nodules in bilateral lower lobes did not exhibit increased  $^{18}\text{F}$ -FDG uptake.

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**Figure 3.** A: Hematoxylin and eosin (H&E) staining of biopsy specimen of the nodule from right lower lobe showed eosinophilic amorphous material deposits ( $\times 10$ ). B: Congo red staining of biopsy specimen of the nodule from right lower lobe was positive, confirming the diagnosis of amyloid ( $\times 10$ ).



**Figure 4.** (A) H&E staining of the biggest nodule of right upper lobe showed increased number of cells forming nests ( $\times 10$ , the inset  $\times 40$ ). (B-D) Immunohistochemical staining of the biggest nodule of right upper lobe showed tumor cells were positive (in brown color) for CD31 (B) CD34 (C) and vimentin (D) ( $\times 10$ ). The histopathological diagnosis was epithelioid hemangioendothelioma.

amyloidosis is usually associated with chronic inflammatory disease such as tuberculosis, chronic renal disease, chronic inflammation,

inflammatory bowel disease, leprosy, and rheumatoid arthritis. Amyloidosis was also reported to be secondary to tumor [6, 7].

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**Table 1.** PET findings of pulmonary epithelioid hemangioendothelioma in literature

Study	Year of publication	No. of patients	Age	Gender	PET	SUVmax	Metastatic spread	Pulmonary nodules	Smoking history
Cazzuffi et al. [16]	2011	1	67	Male	Negative	/	liver and spleen	Multiple bilateral	No
Mizuno et al. [12]	2011	2	30	Female	Negative	/	None	Multiple bilateral	Not mentioned
			67	Female	Negative	/	None	Multiple bilateral	Not mentioned
Okamura et al. [18]	2010	1	19	Female	Positive	4.7	None	Multiple bilateral	No
Watanabe et al. [9]	2008	1	60	Male	Positive	4.61	None	Multiple bilateral	Not mentioned
Ergün et al. [8]	2006	1	40	Female	Positive	Not available	None	Multiple bilateral	Not mentioned
Fagen et al. [19]	2004	1	66	Male	Positive	Not available	None	Right upper lobe mass	Yes
Present study		1	38	Female	Positive	9.4	None	Multiple bilateral	Yes

Patients with PEH are usually asymptomatic or have minor symptoms such as chest pain, cough, and/ or dyspnea. In this case, the multiple bilateral lung nodules were noted on routine health examination while the patient did not have any symptoms. PEH is four times more common in women than men, ranging in age from 12 to 60 years. However, 50% of patients with PEH are less than 40 years old [1, 8]. The typical characteristic of PEH on chest X-ray or CT is the presence of a solitary nodule, or more often, multiple nodules in both lungs up to 20 mm in diameter, with well- or ill-defined margins [1, 8], thus making them difficult to be distinguished from metastatic cancer, or benign non-neoplastic conditions including amyloidosis.

(<sup>18</sup>F-FDG-PET)/CT is considered to be an important tool for PEH diagnosis as the metabolic activity of the nodule can be evaluated [9]. We search for literatures published in English in PubMed, Ovid, and the SCI databases. Six studies including seven cases described the (<sup>18</sup>F-FDG-PET)/CT findings in PEH were retrieved. Among the seven cases of PEH, four cases showed increased FDG uptake (**Table 1**). Malignant tumor cells usually demonstrate increased FDG uptake, and SUV  $\geq 2.5$  is considered to be a criterion for malignancy with the sensitivity, specificity and accuracy is 97%, 82% and 92%, respectively [10]. Kitapci reported a case of epithelioid hemangioendothelioma has different FDG uptake on early and delayed images, and they emphasize the importance of detecting this rare tumor by dual-time-point (<sup>18</sup>F-FDG-PET)/CT images [11]. As shown in **Figure 1**, a significantly increased FDG uptake is detected in the biggest nodule in the right upper lobe, right hilar and mediastinal lymph nodes, while only mild or normal uptakes in other nodules. Even though (<sup>18</sup>F-FDG-PET)/

CT is believed to be a useful tool to evaluate metabolic activity and to search for metastasis of epithelioid hemangioendothelioma, false positive result can occur in cases of tuberculosis, aspergillosis, histoplasmosis and inflammatory disorders [12]. Moreover, Cazzuffi reported three cases of PEH were falsely negative for (<sup>18</sup>F-FDG-PET)/CT, suggesting that a negative (<sup>18</sup>F-FDG-PET)/CT can not completely exclude PEH [13].

The diagnosis of PEH is depending on immunopathological examination of the biopsy specimen. The tumor cells of PEH are round with abundant eosinophilic cytoplasm and intracytoplasmic vacuolization having a signet ring-like appearance. Positive immunohistochemical staining for endothelial markers (CD31, factor VIII and CD34) is pivotal for the diagnosis of PEH [14]. In our case, these endothelial markers were all positive, while the markers for mesothelial cell, epithelial cell, and muscular differentiation were negative.

There is no standard therapy for the PEH. Tumour resection is the most common treatment. Cytotoxic chemotherapy and radiation therapy are also used to treat PEH with limited effect. A report of chemotherapy with an anti-VEGF agent (sorafenib) in hepatic epithelioid hemangioendothelioma recently appeared [15]. Otanik reported a long-term survival case of liver epithelioid hemangioendothelioma with lung metastasis which regressed after giving recombinant interleukin-2 for 22 years. Partial spontaneous regression can be found in some of asymptomatic PEH patients [16]. Distant metastasis and symptomatic patients with multiple bilateral pulmonary nodules or pleural effusion seems to be an important factor in predicting a poor prognosis [17]. In the present case, the patient underwent chemotherapy

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with Gem and Docetaxol after surgery. A long term follow up of this case is needed to observe the progression of the disease.

In summary, we describe a very rare case of PEH coexisting with pulmonary nodular amyloidosis presented with multiple bilateral lung nodules. The diagnosis was made on immunopathological examination of lung biopsy. (<sup>18</sup>F-FDG-PET)/CT scan was useful to differentiate the nodule which was PEH from the other nodules which were pulmonary nodular amyloidosis.

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## Disclosure of conflict of interest

None.

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