

# Pulmonary sequestration associated with increased serum tumor markers and elevated standard uptake value level in PET/CT

## A case report and literature review

Xiaojun Li, MD<sup>a</sup>, Wenlong He, MD<sup>b</sup>, Jinhua Li, MD<sup>b</sup>, Ruoyun Ouyang, PhD<sup>b</sup>, Ping Chen, PhD<sup>b</sup>, Hong Peng, PhD<sup>b</sup>, Dandan Zong, MD<sup>b,\*</sup>

### Abstract

**Rationale:** Pulmonary sequestration (PS) is a congenital pulmonary malformation wherein a piece of tissue that ultimately develops into lung tissue is not attached to the pulmonary arterial blood supply, sometimes it is difficult to diagnosis with no specific laboratory tests, discover an abnormal blood supply from aorta by imaging tests is a key step in diagnosis.

**Patient concerns:** A 54-year-old male smoker presented with cough, expectoration and blood in the sputum.

**Diagnoses:** Computed tomography (CT) shows lesion in right lung, moderate standard uptake value (SUV) elevation of position-emission tomography/computed tomography (PET/CT) in a part of the lesion, and an increased (1,3)- $\beta$ -D-glucan assay (G test), Galactomannan enzyme immune-assay (GM test) and tumor marker level, biopsy of lung in different times produced inconclusive results, then finally diagnosis of pulmonary sequestration is made by observing an abnormal blood supply from the thoracic aorta and volume change of mass.

**Interventions:** The patient refused lower lobectomy which is the main treatment of PS. He was discharged with oral hemostatic and was advised to undergo regular medical checkups.

**Outcomes:** The patient has been followed for a year under an outpatient regimen. Symptoms of the cough and expectoration were relieved, however, blood in the sputum remains unchanged.

**Lessons:** It suggests the need for criteria for a thorough diagnostic work-up. It put emphasis on the importance of considering PS as part of the diagnosis of a lesion in the lung disease and underscore the blood supply of mass. Bronchoscopy or pulmonary lobectomy and follow up of the patient are important for patients diagnosed with pulmonary sequestration.

**Abbreviations:** CT = computed tomography, ELS = extralobar pulmonary sequestrations, FDG PET/CT = fluorodeoxyglucose position-emission tomography/computed tomography, G test = (1,3)- $\beta$ -D-glucan assay, GM test = Galactomannan enzyme immune-assay, ILS = intralobar sequestrations, PET/CT = position-emission tomography/computed tomography, PS = pulmonary sequestration, SUV = standard uptake value.

**Keywords:** computed tomography, 18F-fluorodeoxyglucose, fungal infection, positron-emission tomography, pulmonary sequestration, tumor marker

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<sup>a</sup> The Second Xiangya Hospital, <sup>b</sup> Department of Respiratory Medicine, the Second Xiangya Hospital; Research Unit of Respiratory Disease; Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan, China.

\* Correspondence: Dandan Zong, Department of Respiratory Medicine, the Second Xiangya Hospital, Research Unit of Respiratory Disease, Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan 410011, China (e-mail: zongdandan0402@csu.edu.cn).

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## 1. Introduction

Pulmonary sequestration (PS) is a relatively rare congenital pulmonary malformation, characterized by an abnormal lung tissue supplied by a systemic artery, lacking the normal connection with the bronchial tree.<sup>[1]</sup> PS is classified into extralobar pulmonary sequestrations (ELS), consisting of lung parenchyma masses with a distinct pleural covering separated from the adjacent normal lung tissue, and intralobar sequestrations (ILS), where the pulmonary masses are contiguous with the adjacent normal lung and shares the visceral pleura with an otherwise normal pulmonary lobe.<sup>[1,2]</sup> ILS is more common than ELS (approximately, 75%–93% of PS cases), and the ratio of ILS to ELS in patients is about 3:1.<sup>[2]</sup> More patients have been diagnosed with PS compared to years past due to technological developments and wider recognition of PS.<sup>[3–6]</sup>

ILS manifests at any age, and unless detected during an antenatal ultrasound test rarely causes problems before the age of 2 years.<sup>[1,7]</sup> It is usually diagnosed in adult patients with the symptoms of recurrent infections, hemoptysis, mass effect and secondary symptoms like pleural effusion.<sup>[8]</sup> However, it is easily

**Table 1**  
**Pulmonary sequestration complicated with positive 18F-FDG PET/CT in the literature.**

Author	Year	Sex	Age, y	SUVmax	Symptom	Localization	Side-Lobe	Diagnose
Sen et al <sup>[9]</sup>	2012	F	75	3.2	Back and abdominal pain	Peripheral	Left-lower	Extralobar
Akgul et al <sup>[10]</sup>	2014	F	56.9	3	—	Peripheral	Left-lower	Intralobar
Asanuma et al <sup>[11]</sup>	2016	F	51	11.29	Cough and fever	Peripheral	Right-lower	Intralobar
Evman et al <sup>[12]</sup>	2012	F	56	High	Progressive dyspnea	Peripheral	Left- lower	Extralobar
		M	54	Modest	Asymptomatic	Peripheral	Right-lower	Extralobar

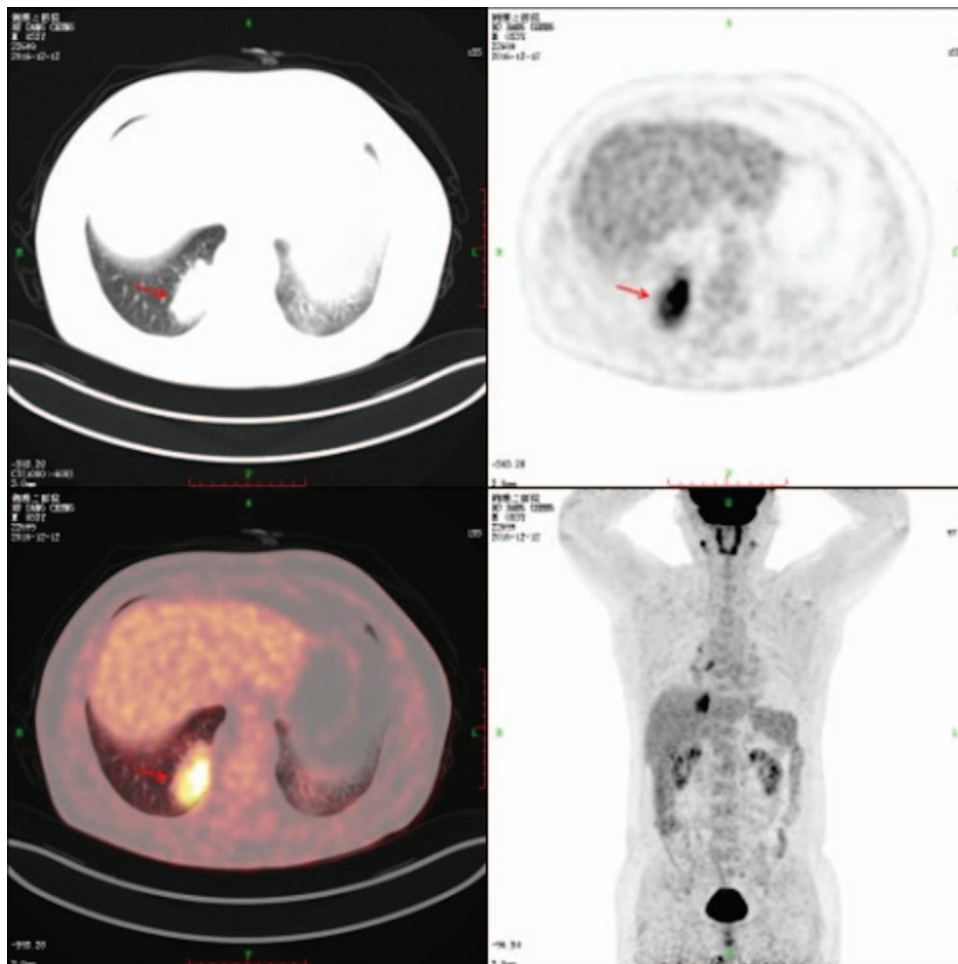
F=female, FDG PET/CT = fluorodeoxyglucose position-emission tomography/computed tomography, M=male, SUV=standard uptake value.

misdiagnosed as other bronchopulmonary diseases, such as bronchiectasis disease, pneumonia, lung abscess, and lung cancer. Importantly, the abnormal blood supply from one or more anomalous systemic arteries to the pathological tissue is helpful for the clinical diagnosis (Table 1).<sup>[9–12]</sup>

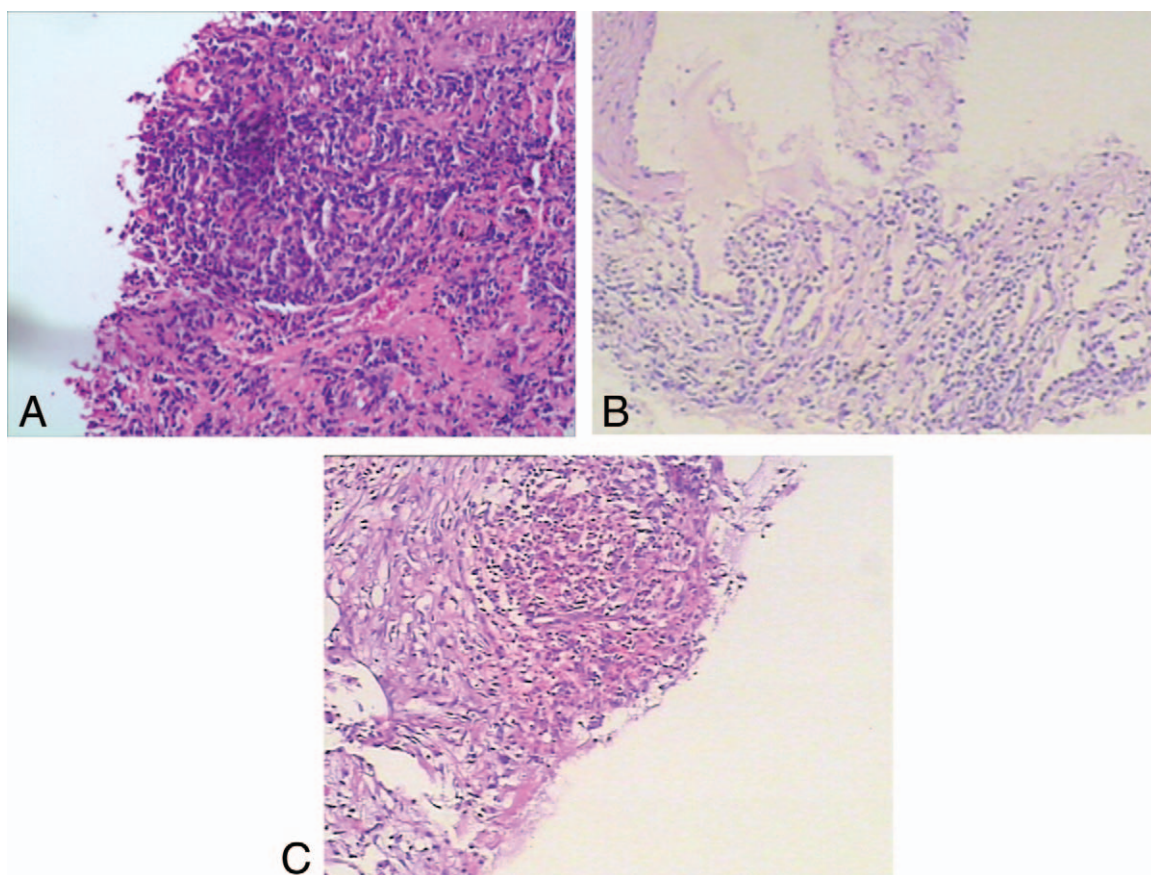
In our case, a 54-year-old male with a history of smoking, presented with cough, expectoration, and blood in the sputum. Computed tomography (CT) imaging revealed a lesion in the right lung. Moderate elevation in the standard uptake value (SUV) of position-emission tomography/CT (PET/CT) was observed in a part of the lesion. It's rare for non-neoplastic disease in lung present with moderate elevation of SUV except tuberculosis. The final diagnosis of PS was made by observing the abnormal blood supply from the thoracic aorta and the change in the mass volume.

**2. Case report**

A 54-year-old male was first presented to our hospital's outpatient department with a 7 months' history of a cough, expectoration, and blood in the sputum (approximately 0.5 mL of blood each time). The patient was a former cigarette smoker, with a history of smoking 2 packs/day for 20 years and had quit smoking for more than 10 years. The patient's physical examination was normal; however, thoracic CT scan revealed a lesion (5 × 2 cm) on the lower lobe of the right lung, with coarse margin. Next, fluorodeoxyglucose PET/CT (FDG PET/CT) was performed after the patient had fasted for 6 hours before receiving an intravenous injection of FDG. An abnormal FDG uptake into the right lower lung mass (maximum standardized uptake values, SUVmax of 13.3), and lymph nodes of the mediastinal and



**Figure 1.** PET-CT showing a lesion (arrow) on the right lower lobe with increased FDG uptake, SUVmax=13.3.



**Figure 2.** A–C, Histological features of the pulmonary tissue showing an infiltration of lymphocytes and neutrophil infiltration of the local tissue, revealing inflammation. (Hematoxylin and Eosin,  $\times 150$ ).

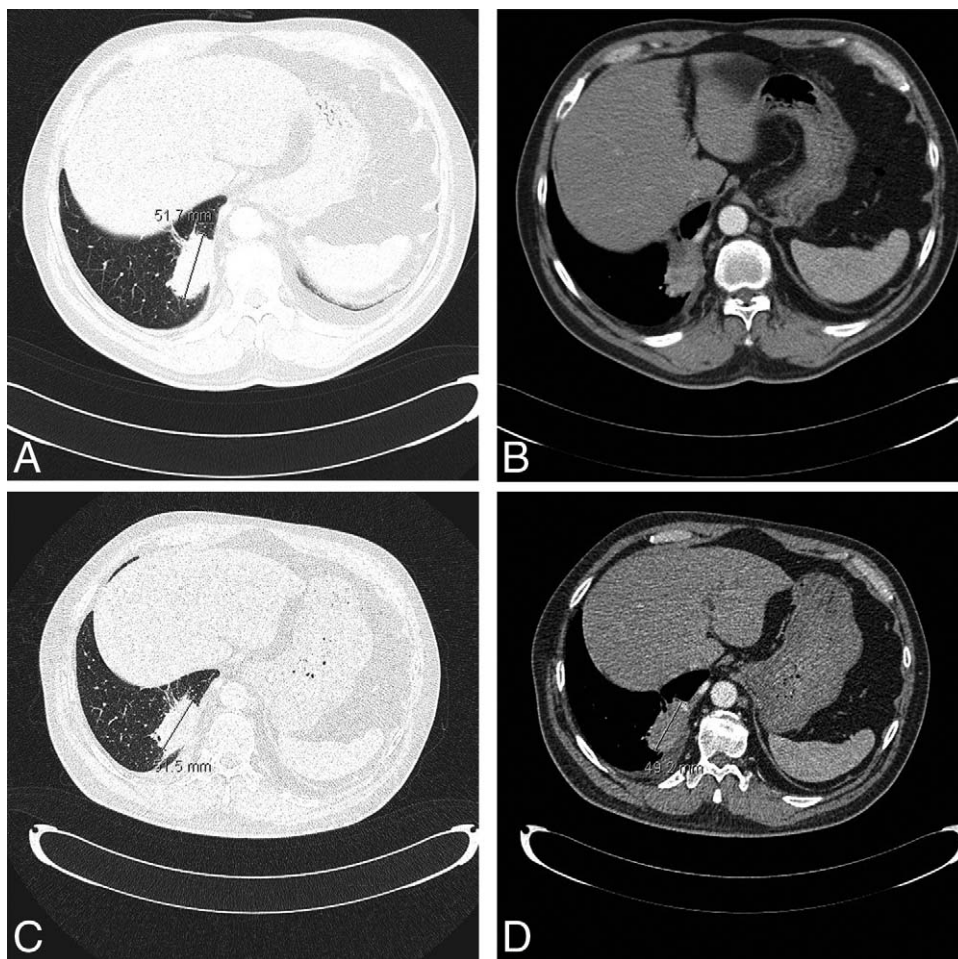
bilateral pulmonary hilar (SUVmax of 5.7) were observed (Fig. 1). Lung cancer was strongly suspected, and a CT-guided percutaneous transthoracic needle biopsy of the mass was performed under CT guidance. However, the histopathological examination revealed no malignant cells (Fig. 2 A). Further, the patient refused another biopsy and decided to receive palliative care with traditional Chinese medicine for 1 month.

The patient was again referred to our department, after 8 months, with complaints of an unalleviated cough and hemoptysis. A few rhonchi in both the lungs were heard during the physical examination. Initial routine laboratory tests were normal except for increases in CYFRA 21-1 (a fragment of Cytokeratin 19; 2.40 ng/mL, normal range = 0–1.8 ng/mL). Thoracic CT scan revealed a peripheral pulmonary mass, the same size as 7 months ago, with new patchy consolidation in the right lung, possibly an infection (Fig. 3A and B). A CT-guided percutaneous transthoracic needle biopsy was performed again, and the histopathology revealed chronic mucopurulent inflammation of the bronchial mucosa and lung tissue, with infiltration of lymphocytes and neutrophil cells (Fig. 2B and C). The diagnosis of lung carcinoma could not be confirmed on the basis of the histopathology report.

To get a confirmed diagnosis, the patient was admitted to our department for the third time, 1 month later. Laboratory examination revealed significant increases in the serum level of the tumor makers: carbohydrate antigen-125 (CA125)=73.77 KU/L (normal levels are <35 KU/L), CA242=40.23 KU/L (normal levels are <20 KU/L), and carbohydrate antigen-19-9

(CA19-9)=171.70 KU/L (normal levels are <35 KU/L). Galactomannan enzyme immune-assay (GM test) and (1,3)- $\beta$ -D-glucan assay (G test) were positive both the times. Additionally, the inflammatory markers and tests for connective tissue disease, such as anti-deoxyribonucleic acid antibodies, anti-neutrophil cytoplasmic antibodies, myeloperoxidase, protease 3, glomerular basement membrane, rheumatoid factor, and complement 3 were all within the normal range. A repeat contrast-enhanced CT was performed and demonstrated that the mass had not significantly changed. Without the typical manifestation of a fungal infection and the classic imaging features in the patient, we could not diagnose the condition as a fungal infection or lung cancer. Interestingly, a suspicious funicular vessel arose from the aorta and coursed to the lesion. The patchy lesion on the right lung, previously observed, was accompanied by a new patchy consolidation in the left lung (Fig. 3C and D). After 9 months of hospital consultations, the final diagnosis of intralobar PS was made. Since the symptoms were mild without any impact on the quality of life, the patient refused lower lobectomy, which is the main treatment of PS. The patient was discharged with oral hemostatic and was advised to undergo regular medical checkups and should seek medical attention if any discomfort.

The patient has been followed for a year under an outpatient regimen. Symptoms of the cough and expectoration were relieved; however, blood in the sputum remains unchanged. We recommend the patient reviewing the CT but he has refused to undergo any further blood tests and CT scan.



**Figure 3.** Thoracic CT showing a lesion on right lower lobe with an aberrant artery from the aorta.

This study was approved by the ethics committee of The Second Xiangya Hospital, Central South University, Changsha, China. Additionally, written informed consent was obtained from the patient.

### 3. Discussion

ILS can manifest as recurrent infections, respiratory distress, cough, blood in the sputum, or as an asymptomatic mass.<sup>[11]</sup> The current patient presented with a cough, expectoration, and blood in the sputum. CT scan showed a lesion in the right lung, and moderate SUV elevation in the PET/CT was observed in a part of the lesion. Additionally, we also observed positive results in the G and GM test and elevated tumor marker levels. The lung biopsy, performed on different occasions, produced inconclusive results. The final diagnosis was made by observing an abnormal blood supply from the thoracic aorta and the change in the mass volume.

<sup>18</sup>F-FDG PET is a widely used noninvasive diagnostic modality that is based on the different rates of <sup>18</sup>F-FDG uptake and serves as a nonspecific tumor marker.<sup>[13]</sup> Standardized uptake value (SUV) > 2.5, with <sup>18</sup>F-FDG PET/CT, is often used as the criterion for differentiating lung malignancies from benign cases.<sup>[14]</sup> Many studies demonstrated that <sup>18</sup>F-FDG PET imaging has false negative and false positive diagnoses of lung cancer, and the latter could be as high as 20% to 25%,<sup>[15]</sup> and <sup>18</sup>F-FDG's

uptake significantly overlaps between tumor and non-tumor tissues. Some benign granulomatous diseases that mimic lung malignancy have increased <sup>18</sup>F-FDG uptake due to activated mononuclear cells, leukocytes, and lymphocytes in the granulomatous lesions. The common causes of false positives in <sup>18</sup>F-FDG PET/CT findings in the lungs are infectious diseases, granulomatous diseases, ischemia, or necrosis. However, research studies rarely report the false positive <sup>18</sup>F-FDG PET observed in pulmonary sequestration and only a few false positive cases using <sup>18</sup>F-FDG PET/CT have been reported.<sup>[9–12]</sup> Median SUV in these patients was  $5.83 \pm 4.729$  which suggested malignancy, and SUVmax in this case is as high as 11.29. Interestingly, 2 of them were extra pulmonary sequestration, and the others were cases of intrapulmonary sequestration combined with pneumonia. The positive <sup>18</sup>F-FDG PET scans were ascribed to the chronic inflammation.

Most of the false-positive findings are related to the inflammatory lesions and is considered to be the main reason for high <sup>18</sup>F-FDG uptake in pulmonary sequestration. In our case, based on the negative biopsy result, we assume that the greater SUV elevation in a part of the lesion is due to chronic inflammation. However, multiple cases with CT scan-confirmed lung masses that had a highly suspicious feeding artery arising from the aorta, and increased SUV in PET/CT exam, were diagnosed as pulmonary sequestration with cancer by histopathological examination.<sup>[16–23]</sup> However, in our case, the negative

biopsy, suspicious vessel coursing into the lesion, no increase in the mass size in 9 months, no clinical manifestations of cachexia made us consider that it was an indolent disease and a final diagnosis of pulmonary sequestration was reached.

One clinical symptom of pulmonary sequestration is a recurrent pulmonary infection probably caused by bacteria, fungi, and mycobacteria.<sup>[1,6]</sup> Increased G and GM test levels in our case indicated a superimposed fungal infection. The microorganisms that cause the pulmonary infection that occurs with PS have not been systemically studied before. Some of the infections in PS, especially those due to *Aspergillus*,<sup>[2,25]</sup> are essentially discovered by a culture of the sputum or after surgery. In 2014, Sun et al<sup>[6]</sup> reported 7 cases and reviewed 22 cases in the literature and found that only patients with *Pseudomonas aeruginosa* were treated with antibiotics post-operatively for 3 to 7 days and the other patients with *Aspergillus* infection were not treated with any antifungal medicine. All the patients with a concurrent infection recovered well without any obvious complications. There was no evidence for pathogeny and imaging was not typical in our case; thus, it remains a matter of debate whether it was a fungal infection. Therefore, we did not prescribe any antifungal treatment and no fungal infections were found at the 1-year follow-up. However, the relatively high co-morbidity of aspergillosis in PS patients across many studies<sup>[24,25]</sup> indicates that this relationship needs to be studied further.

The relationship between PS and elevated tumor serum markers has been reported by several investigators since it was first identified by Shiota in 1988.<sup>[26]</sup> In 2015, Dong et al<sup>[27]</sup> reported several cases and reviewed 15 clinical cases demonstrating increased CA19-9 in PS, and interestingly no malignancies were detected in these reported cases after various examinations. PS patients with fungal infections also discovered abnormal shadows were associated with increased tumor serum markers CA19-9, carcinoembryonic antigen, and CA 125.<sup>[28,29]</sup> In the majority of the reported cases, CA19-9 levels decreased to within the normal range, after pulmonary resection, and immunohistochemical staining for CA19-9 in resected tissue demonstrated local CA19-9 in the bronchial and alveolar epithelia of the sequestered lung. Thus, it is possible that the elevated serum tumor marker levels were induced by the PS in our case. The pathogenesis of increased tumor markers in PS is still unclear, and Satoshi<sup>[30]</sup> suggested that the elevated serum CA19-9 levels were caused by PS. The CA19-9 produced in the epithelia of the sequestration tissue may get concentrated in the mucus of the cysts and is then transferred into the blood through the injured mucosa of the cyst walls. This hypothesis is consistent with the observed association between PS and elevated levels of serum CA19-9 and decreases in the levels of CA19-9 after lesion resection. The mechanisms for the elevation of serum CA19-9 in PS need to be further studied to avoid potential diagnostic pitfalls.

The prevailing recommendation of treatment in symptomatic patients of PS is surgical resection, while in asymptomatic patients, surgery should be considered to prevent recurrent infection. Additionally, some studies indicate that video-assisted thoracoscopic surgery might be preferable to thoracotomy for PS.<sup>[31]</sup> The prognosis of PS is usually related to the co-existent pathology. Surgical mortality should be low provided the surgeon carefully evaluates the chest and is able to control the aberrant vascular blood supply. Long-term morbidity from PS includes pneumonia, gastroesophageal reflux, and asthma that requires treatment.<sup>[1]</sup> In our case, the blood in the sputum and abnormal

laboratory index indicated bronchoscopy or pulmonary lobectomy for a definitive diagnosis. However, considering the wishes of the patient, a conservative treatment plan with medicines was chosen. Therefore, it is crucial we follow-up with the patient and set appropriate parameters for diagnosis and treatment since he declined surgery.

In conclusion, observations from our patient underscore the importance of considering PS as a possible diagnosis for any lesion in the lung with increased uptake of 18F-FDG in the lesion. Additionally, PS might be associated with concurrent fungal infection. Bronchoscopy or pulmonary lobectomy, and follow-up with the patient are important in the diagnosis of PS. Surgical resection should be recommended for patients with obvious symptoms of PS.

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## Author contributions

**Conceptualization:** Jinhua Li, Ruoyun Ouyang, Ping Chen, Hong Peng.

**Data curation:** Xiaojun Li, Jinhua Li, Dandan Zong.

**Formal analysis:** Wenlong He, Ping Chen.

**Investigation:** Hong Peng.

**Methodology:** Wenlong He, Ping Chen.

**Project administration:** Hong Peng.

**Resources:** Xiaojun Li.

**Supervision:** Ruoyun Ouyang, Ping Chen, Dandan Zong.

**Validation:** Jinhua Li, Ruoyun Ouyang, Dandan Zong.

**Writing – original draft:** Xiaojun Li.

**Writing – review & editing:** Wenlong He, Ping Chen, Dandan Zong.

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