

Case Report

A 51-year-old man with chronic cough and left hilar prominence

A 51-year-old male in good overall health presented with a dry cough of 5 months' duration. He was working as a long-distance truck driver and was a life-long nonsmoker. He had no associated dyspnoea, wheezing, rhinosinusitis, haemoptysis or syncope, nor constitutional symptoms such as weight loss or fevers. Physical examination and vital signs were normal on presentation. Chest

radiographs with posterior–anterior and lateral views are shown in figure 1.

Cite as: Kourouni I, Aesif SW, Tamarkin SW, *et al.* A 51-year-old man with chronic cough and left hilar prominence. *Breathe* 2021; 17: 210018.

Task 1

Describe the chest radiographs in figure 1.

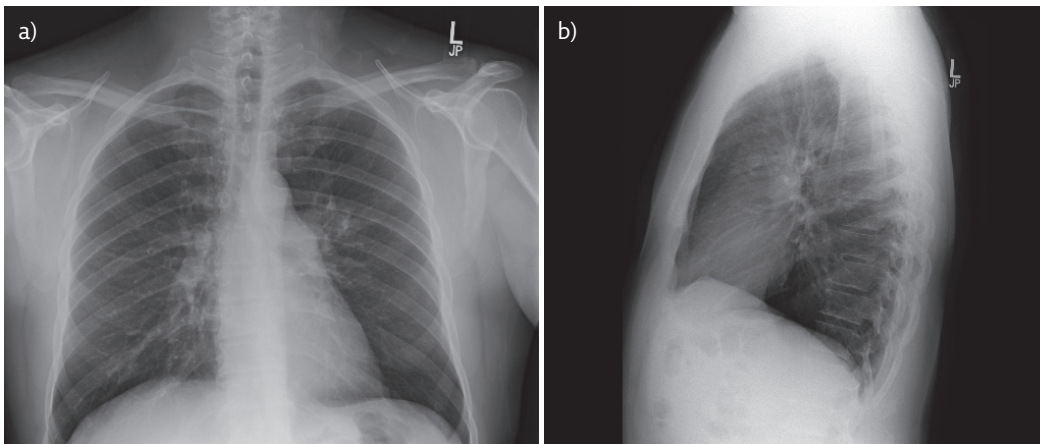


Figure 1 Chest radiographs with a) posterior–anterior and b) lateral views.

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What is the diagnosis of this man with a chronic dry cough and left hilar prominence on chest radiography? <https://bit.ly/3fL7QMx>



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Figure 2 Three-dimensional reconstruction of the coronal views of chest CT scans, correlating with the initial chest radiograph (figure 1a).

Answer 1

The chest radiographs show the prominence of the left hilar structures and raise the suspicion of a left hilar mass lesion and nodule in the left upper lobe anteriorly. There is no apparent parenchymal disease. On a closer look, note the relative paucity of vascular markings in the left lung, which is suggestive of oligoemia (figure 2).

A contrast-enhanced computed tomography (CT) scan revealed a large, heterogeneously hypodense filling defect occupying much of and nearly occluding the pulmonary trunk, both main pulmonary arteries, left upper and left lower lobar pulmonary arteries, and their peripheral branches (figure 3). The involved left upper lobe

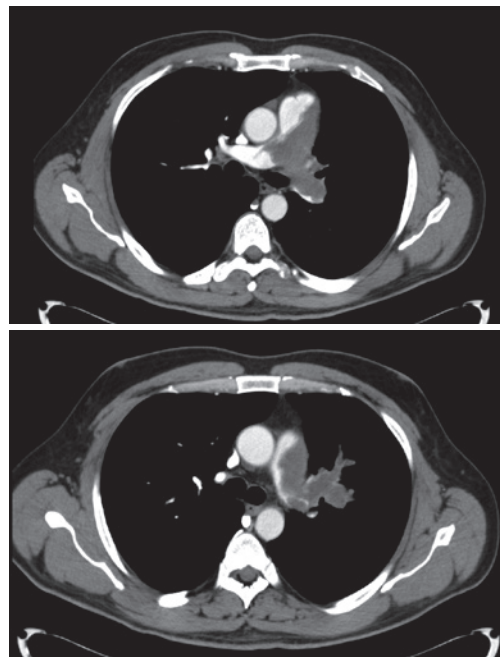


Figure 3 Contrast-enhanced CT scans showing a large tumour thrombus burden nearly completely occluding the main, left main and proximal right main pulmonary arteries. Complete or partial occlusion of left upper and left lower proximal pulmonary arterial branches by thrombus/tumour thrombus.

pulmonary artery branches appeared enlarged, with notable dilation of the pulmonary outflow tract (34 mm). The density of the filling defect ranged from 12 to 50 Hounsfield Units (HU). A circumscribed 14×11 mm nodule was present in the right upper lobe (figure 4), along with a few nodules of 2–3 mm elsewhere in the lungs. Because of concern for pulmonary embolism, the patient was hospitalised. Laboratory studies were unremarkable except for a D-dimer level of 487 ng·mL⁻¹ (normally <250 ng·mL⁻¹). Vascular studies were negative for lower extremity thrombosis. Further imaging revealed a 40-mm enhancing hepatic lesion suggestive of metastatic malignancy (figure 5).

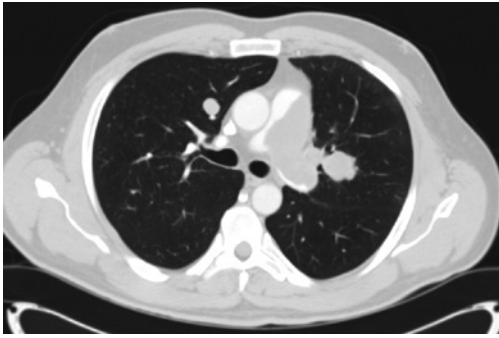


Figure 4 Contrast-enhanced CT scan showing a 14-mm nodule within the right upper lobe medially.

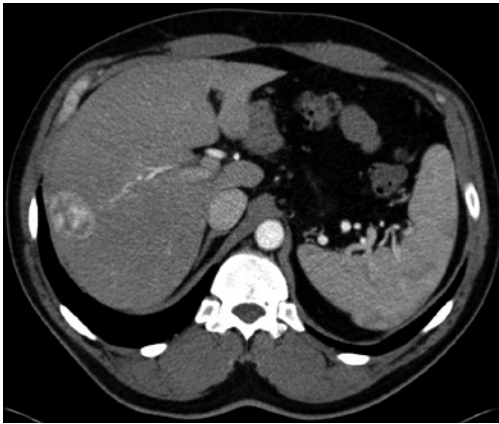


Figure 5 Enhancing mass in the right hepatic lobe, shown by contrast-enhanced CT, is concerning for metastatic disease. This was biopsied and was consistent with hepatic haemangioma.

Task 3

With the current information, what is your next step in management?

- Proceed with therapeutic anticoagulation and re-image in 3 months; biopsy if no resolution
- Proceed with positron emission tomography (PET)
- Percutaneous CT-guided lung biopsy
- Percutaneous CT liver biopsy
- Magnetic resonance imaging (MRI) of the abdomen

Task 2

What is the least likely diagnosis?

- Acute pulmonary embolism
- Tumour embolism from non-lung primary
- Stage IV lung cancer with arterial invasion by a primary lung tumour and liver metastasis
- Intraluminal mass
- Chronic thromboembolism

Answer 2

a. Acute pulmonary embolism.

At the time of evaluation, our patient complained only about a persistent cough that failed to respond to antihistamines and anti-reflux medication for 2 months. He had no signs of respiratory distress nor limitations to exercise. He had no risk factors for deep venous thrombosis nor of thrombophilia and no known previously diagnosed malignancy. The patient could not recollect any time of experiencing chest pain, dizziness or syncopal episode, nor shortness of breath. This clinico-radiological contrast of a healthy-appearing patient against his bulky central angiographic findings rapidly triggered the suspicion that the arterial filling defect could not be of acute nor subacute onset.

Echocardiography showed normal right and left ventricular function without evidence of pulmonary hypertension. Pulmonary function testing demonstrated normal spirometry and diffusing capacity of the lung for carbon monoxide (D_{LCO}).

Task 4

How do you explain the normal D_{LCO} in the setting of a large filling defect in the left pulmonary artery?

Answer 3

d. Percutaneous CT liver biopsy.

The priority of the investigation was to rule out the possibility of a metastatic tumour from other regions of the body. Tumour thrombosis from a hepatic origin and pulmonary arterial invasion from advanced-stage lung primary were high in the original differential. The liver lesion was the only extrathoracic focus. The liver lesion was peripheral, relatively easily accessible, and had the lowest risks of complications for higher diagnostic yield as it could potentially upstage a lung primary. Percutaneous CT-guided lung or bronchoscopic biopsy was initially avoided due to a higher risk of bleeding and procedural complications. Neither PET nor liver MRI of the abdomen would alter the decision to proceed with a potentially diagnostic liver biopsy during the hospitalisation.

A staging PET/CT and MRI of the brain and abdomen with and without gadolinium were obtained following the patient's liver biopsy. Taken together, the liver biopsy results with the MRI of the abdomen were diagnostic for hepatic haemangioma. At this point of the workup, the extrathoracic focus of malignancy was excluded.

Answer 4

Decreased D_{LCO} is a common finding in patients with significant acute thromboembolism [1]; however, in chronic thrombo-occlusive disease, a normal D_{LCO} does not exclude the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) and does not reflect the degree of vascular obstruction. More specifically, D_{LCO} may be reduced due to concurrent restrictive parenchymal scarring in 20% of CTEPH patients. Normalisation of D_{LCO} in the course of the disease is probably secondary to the development of extensive bronchial arterial collateral flow exceeding 10% of cardiac output in these patients [2]. Our patient was a never-smoker and had an excellent physique without any history of prior cardiovascular comorbidities. He had no clinical or echocardiographic signs of right ventricular overload. In this context, we speculate that due to the lumen's gradual occlusion by the intraluminal tumour, the development of collateral bronchial arterial flow explains the normal D_{LCO} .

Upon multidisciplinary discussions, the liver lesion was biopsied. Therapeutic anticoagulation was not pursued due to low clinical suspicion of an acute thromboembolic event. The liver pathology was consistent with a haemangioma.

Task 5

Based on this information, what is the best way to obtain tissue?

- a) Percutaneous CT-guided lung biopsy
- b) Surgical biopsy
- c) Endobronchial ultrasound-guided biopsy
- d) Intravascular biopsy

Answer 5

a. Percutaneous CT-guided lung biopsy.
Peripherally accessible lung parenchymal lesions are best suited for percutaneous CT-guided biopsy. The safest biopsy plan was reviewed in conjunction with cardiothoracic surgery and interventional radiology. Due to the size of the mass, and the affected pulmonary artery's apparent complete effacement, the risk of bleeding by percutaneous CT-guided biopsy was considered low and, therefore, the least invasive and overall safest approach for our patient.

Subsequently, the patient underwent an ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT (figure 6), which revealed intense FDG uptake within the lateral aspect of the pulmonary trunk, the left main pulmonary artery (maximum standardised uptake value (SUV_{max}) 7.2), and in the proximal aspects of the left upper lobe segmental pulmonary arteries (SUV_{max} 5.2). Both areas corresponded to the foci of relatively increased attenuation within the pulmonary artery filling defects on the chest CT and confirmed the original impression of a mural or intraluminal tumour. The right upper lobe pulmonary nodule and liver mass were not FDG avid.

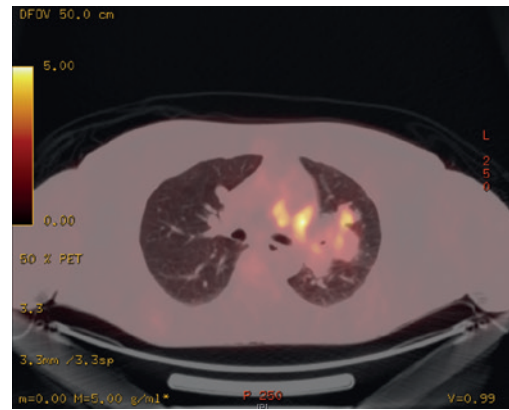


Figure 6 FDG-PET/CT image, showing intense FDG uptake within the lateral aspect of the pulmonary trunk, the left main pulmonary artery (SUV_{max} 7.2) and in the proximal aspects of the left upper lobe segmental pulmonary arteries.

Task 6

Based on the pathology and radiographic information, what is the patient's tumour stage?

Task 7

Which of the following are tumour thrombi associated with? More than one may be correct.

- a) Cholangiocarcinoma
- b) Urothelial carcinoma
- c) Glioblastoma
- d) Hepatocellular carcinoma
- e) Melanoma

Answer 6

A pulmonary artery sarcoma (PAS) staging system has been proposed based on tumour location: stage I tumours are limited to the central pulmonary artery, stage II tumours involve one lung plus the main pulmonary artery, stage III tumours constitute bilateral lung involvement and stage IV tumours present with an extrathoracic spread. Our patient's tumour stage was III.

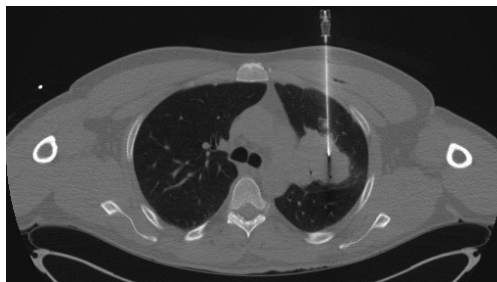


Figure 7 Percutaneous CT-guided transthoracic biopsy. There was an increase in size of the mass within the 5-week interval before it was possible to perform the biopsy.

Answer 7

d. Hepatocellular carcinoma.

Tumour thrombi occur most frequently in renal cell carcinoma, Wilms' tumour, adrenal cortical carcinoma and hepatocellular carcinoma [3]. Many other tumours can develop tumour thrombi but do so less frequently. These include intravenous leiomyomatosis, islet cell tumours of the pancreas, thyroid cancer, testicular cancer and, uncommonly, lung cancer [3]. Some studies have indicated that the risk of tumour embolisation is increased by chemotherapy, radiation and surgical extirpation of the primary tumour, probably because these therapies promote fragmentation of the tumour mass and theoretically enhance tumour embolisation via venous or lymphatic drainage [4].

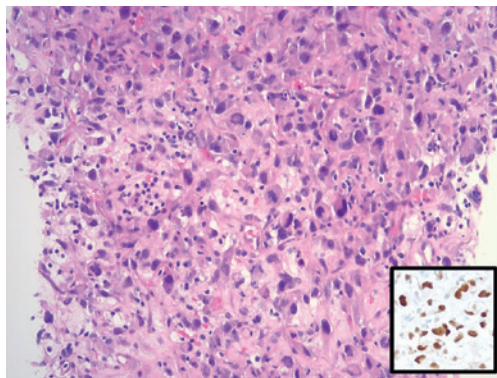


Figure 8 Main image is a representative haematoxylin- and eosin-stained section of the patient's CT-guided biopsy. Inset image demonstrates amplified nuclear MDM2 expression (brown) by immunohistochemistry. Original magnification is 200× for both images.

Following consultations with the thoracic surgery and interventional radiology departments, the patient underwent percutaneous CT-guided transthoracic biopsy (figure 7). The pathological diagnosis was consistent with pulmonary artery intimal sarcoma (PAIS) (figure 8).

Clinical discussion

PAS is a rare malignancy originating from the pulmonary artery tree. PAS belongs in a heterogeneous group of tumours with different histology, most commonly leiomyosarcoma, angiosarcoma and spindle cell sarcoma [5, 6]. Sampling procedures are usually risky, and if the tumour is unresectable, the prognosis is dismal. Nearly a century after it was first described, the present knowledge of this disease is mostly based on large autopsy and retrospective series. The reported incidence of 0.001% [7] is likely an underestimate, considering that these tumours are identified in 1–4% of the pulmonary endarterectomy specimens from patients undergoing intervention for CTEPH [7, 8].

PAS typically occurs in middle age, with no obvious sex predilection [5]. The clinical presentation ranges from the complete absence of symptoms to nonspecific symptoms like dyspnoea, cough, haemoptysis, syncope, weight loss and hypotension [5, 7]. B-natriuretic peptide levels may be elevated in acute, chronic pulmonary embolism or PAS [9, 10], while D-dimer may be elevated either in the setting of the longstanding inflammatory response induced by PAS or by an overlaying thrombus encasing the tumour. Concurrent lower extremity thrombosis has also been reported [10]. It has been reported that echocardiographic evidence of pulmonary hypertension indicates bilateral pulmonary artery disease even in the case of a unilateral CT pattern [9].

Diagnosis can take months from the onset of symptoms [7], affecting the treatment options and overall prognosis. After diagnosis, the reported median survival is 1.5 months in untreated patients (range 1.5–5.5 months) [8, 9], but may be extended to 17–26 months with systemic chemotherapy [6, 9]. In contrast, surgical resection improves PAIS survival to a reported median survival of 26.8–36.5 months [9]. Most patients die due to disease recurrence and/or pulmonary circulation occlusion [8]. Mussot *et al.* [8] reported 1-, 3- and 5-year survival rates of 63%, 29% and 22%, respectively.

Radiological discussion

Tumours of the pulmonary arteries, most commonly PAS, are often mistaken for the more common acute pulmonary embolism or chronic pulmonary thromboemboli or as tumour thrombi from intravascular tumour extension from lung or other primaries [11]. Most cases are diagnosed after the failure of treatment of a presumed thrombus. Multiple case series have demonstrated typical findings of PAS, which provide diagnostic clues. These include a low-attenuation filling defect of the lumen of the pulmonary outflow tract or of the right or left pulmonary arteries, an involvement of the vessel wall by the mass, lobular proximal mass margin, and aneurysmal dilation of the more distal involved vessels [12]. Our patient had all of these findings, and tumour thrombus was suspected on the initial CT scan interpretation. The aneurysmal peripheral pulmonary artery dilation and probable eclipsing [13] of the vessel wall were initially radiographically described as a suprahilar mass.

A study by Liu *et al.* [12] found that expansive growth of the proximal aspect of the mass was typical for PAS and was not found in cases of chronic central pulmonary emboli. They also reported that PAS demonstrated a “cloudy, inhomogeneous delayed contrast enhancement pattern with gradually increasing intensity” on MRI. MRI was not performed on our patient. Most CT scans performed for suspected pulmonary emboli or masses did not include unenhanced imaging, preventing evaluation of mass enhancement, whereas MRI studies typically have both unenhanced and multiple post-contrast images [12]. CT enhancement (>25 HU) has been shown to differentiate between bland and tumour thrombus in various vessels [9]. A tailored study that includes pre- and post-contrast images may provide diagnostic information in cases of suspected PAS.

PET/CT has been demonstrated to differentiate PAS from emboli based on the degree of FDG uptake. In one study, an SUV_{max} cut-off of 3.63 was used to differentiate tumours from bland thrombus, with a sensitivity of 71.4% and specificity of 90% [14]. Overall, the sensitivity of PET scanning for soft tissue and bone sarcomas is greater for high- and intermediate-grade sarcomas. In our patient, PET/CT demonstrated heterogeneous hypermetabolism in the mass, with the areas of most intense uptake corresponding to subtle areas of relatively increased attenuation in the mass on the CT scan. This increased our diagnostic confidence prior to the decision to obtain a biopsy.

The mode of biopsy depends on institutional expertise, infrastructural support, and factors such as tumour location and distal extension. A PAS staging system has been proposed based on tumour location and extension, where stage I tumours are limited to the main pulmonary artery, stage II tumours involve one lung plus the main pulmonary artery, stage III tumours constitute bilateral lung

involvement, and stage IV tumours present with an extrathoracic spread [6].

Open biopsy and surgical resection are favoured when the disease is amenable to complete resection, if the patient is a good surgical candidate. Pulmonary endarterectomy *via* cardiopulmonary bypass and deep hypothermic circulatory arrest is favoured in patients without metastatic lesions; however, pneumonectomy may be warranted in individualised surgical strategies [15]. One-quarter of patients present with synchronous distant diseases to the lungs by embolising tumour material [9]. Palliative pulmonary endarterectomy may be considered in bilateral PAIS invasion or in patients with pulmonary hypertension [16], aiming to restore the blood flow to the affected areas within the lung and relieve pulmonary hypertension.

Endovascular pulmonary artery catheter aspiration and forceps biopsy have been utilised successfully for patients not eligible for resection but with low intermediate yield due to *in situ* thrombus and necrosis overlaying the sarcomatous mass [15]. The use of endobronchial ultrasound with biopsy has been reported [17]; however, it remains controversial, given risks of massive bleeding secondary to pulmonary hypertension and hypertrophied systemic bronchial arterial system. Peripherally accessible lung parenchymal lesions are ideal for percutaneous CT-guided biopsy. Due to the size of the mass, as well as apparent complete effacement of the pulmonary artery, the risk of bleeding by percutaneous CT-guided biopsy was considered diminished and therefore was the safest approach for our patient (figure 7).

Pathology discussion

Intimal sarcomas of the pulmonary arteries arise from the intimal layer of the elastic pulmonary arteries. The term PAS is often used interchangeably with PAIS; however, PAIS also includes the much rarer mural sarcomas. Location varies from the level of the pulmonary valve to the lobar branches. Most cases of PAIS arise within the pulmonary trunk [8, 18]. Bilateral involvement is common and, when resected, the entire tumour is usually endoluminal. Invasion of the adjacent pulmonary parenchyma or pulmonary metastases can occur. Haemorrhage and necrosis are common in high-grade tumours [10], which may make systemic empirical anticoagulation risky. The histological patterns are heterogeneous, although the most commonly encountered histological type is that of undifferentiated pleomorphic sarcoma. Rarely do tumours demonstrate heterologous elements, such as malignant osteoid or cartilage [19]. The preferred designation in such cases is the histological subtype followed by the presumed site of origin (*e.g.* extraskeletal osteosarcoma of intimal origin). Immunohistochemical stains may demonstrate variable smooth muscle actin or desmin expression.

Most cases of PAIS are negative for endothelial markers [20]. Most undifferentiated intimal sarcomas demonstrate amplification of the *MDM2* locus [20].

Histological sections of this patient's CT-guided biopsy demonstrated hypercellular fragments of tissue composed of markedly atypical cells with a pleomorphic morphology, brisk mitotic activity, and abundant tumour necrosis (not shown). Immunohistochemical stains were performed using antibodies raised against pancytokeratins, desmin, smooth muscle actin, myogenin, ERG, INI-1, SOX10 and MDM2. The malignant cells demonstrated retained INI-1 expression (not shown) and amplified MDM2 expression (figure 8). The malignant cells were negative for all other markers tested (not shown). This morphology and immunohistochemical profile support a diagnosis of undifferentiated intimal sarcoma in the appropriate clinical and radiographic settings.

Case conclusion

The patient underwent a confirmatory biopsy for tissue diagnosis and received upfront cytotoxic chemotherapy with five cycles of doxorubicin ($75 \text{ mg} \cdot \text{m}^{-2}$) and ifosfamide ($10 \text{ g} \cdot \text{m}^{-2}$), as well as definitive radiation (total 66 Gy in 33 fractions) with a radiographic response of his tumour (figure 9). At 12 months follow-up, the patient remains in excellent performance status and is under re-evaluation for pulmonary endarterectomy.

Summary

PAS are rare tumours with different histological subtypes, have limited therapeutic options, and

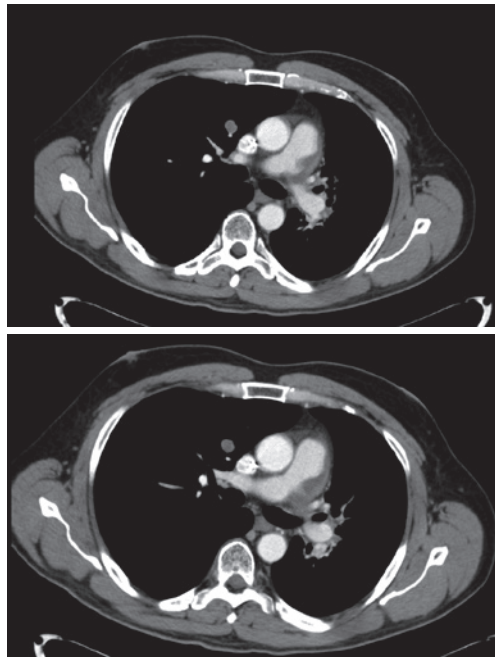


Figure 9 Contrast-enhanced CT scans showing evident decrease in intravascular and extravascular tumour burden after chemo/radiotherapy.

overall dismal prognosis if not operable. PAS can be a radiographic mimicker of acute pulmonary embolism and CTEPH, as well as tumour thrombus. Inappropriate thrombolytic and/or anticoagulant therapy can delay diagnosis by 3–12 months. “Atypical” radiographic features of PAS lead to earlier diagnosis and possibly better outcomes. Pre-procedural diagnostics decrease diagnostic uncertainty and define the safest means of biopsy.

Affiliations

Ismini Kourouni¹, Scott W. Aesif², Stephen W. Tamarkin³, Michael Bolen⁴, Edward Sivak¹, Ziad Shaman¹, Ila Tamaskar⁵, Vaia Florou⁶

¹Division of Pulmonary, Critical Care and Sleep Medicine, Metro Health Medical Center, Case Western Reserve University, Cleveland, OH, USA. ²Division of Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH, USA. ³Dept of Radiology, Metro Health Medical Center, Case Western Reserve University, Cleveland, OH, USA. ⁴Division of Imaging Institute, Cleveland Clinic, Cleveland, OH, USA. ⁵Division of Oncology, Metro Health Medical Center, Case Western Reserve University, Cleveland, OH, USA. ⁶Dept of Medicine, Division of Oncology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA.

Author contributions

I. Kourouni produced the concept and design, had full access to all of the data and takes responsibility for drafting the manuscript and editing the images. S.W. Aesif takes responsibility for the pathology section. S.W. Tamarkin and M. Bolen take responsibility for the radiology section. Critical revisions of the manuscript for important intellectual content: all authors.

Conflict of interest

None declared.

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