

## Case report

# A perplexing airspace: peace of mind now or later

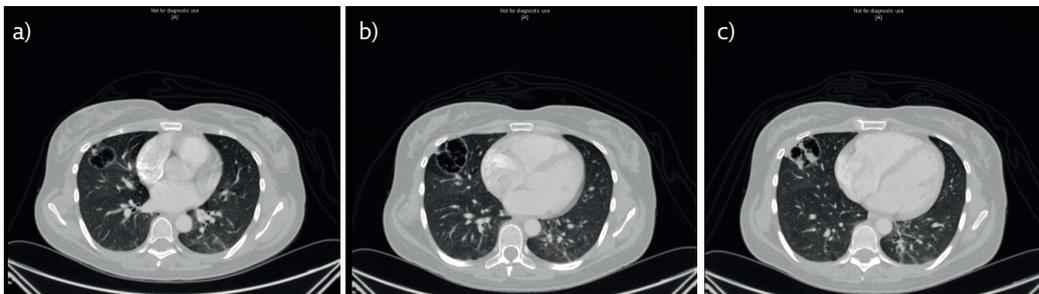
A 36-year-old, nonsmoking woman with a history of asthma presented for a second opinion about a “cavitating” right middle lobe (RML) lesion that was found incidentally 6 months prior, during preoperative evaluation for cholecystectomy. The lesion in question was pleural based, measuring 5.4×4×4.5 cm with thin and thick inner septations along with low-density right hilar and mediastinal adenopathy (figure 1a-c).

### Task 1

Which of the following is present on the CT chest (figure 1)?

- a) Pneumatocele
- b) Cyst
- c) Cavity
- d) Bullae

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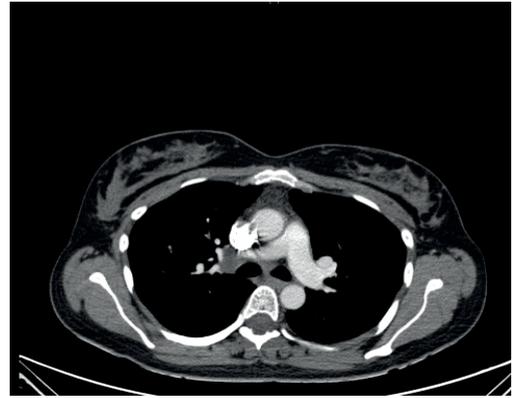
**Figure 1** a-c) CT images demonstrating the mostly thin-walled, pleural-based, cavitary lesion in the periphery of the RML.

**Answer 1**

The image demonstrates a round parenchymal lucency with a well-defined interface with a normal lung better defined as a cyst. Per Fleischner society criteria [1], cysts measure more than 1 cm in diameter, are usually thin-walled (<2 mm), contain air, fluid or solid material, and occur without associated pulmonary emphysema. In contrast, a bulla is accompanied by emphysematous changes in the adjacent lung. A cavity is a thick-walled, gas-filled space, seen as a lucency within pulmonary consolidation, a mass or a nodule. Finally, a pneumatocele is a transient thin-walled, air-filled space in the lung related to an acute inflammatory process, most commonly acute bacterial pneumonia or trauma [2].

Further evaluation with bronchoscopy, transbronchial lung biopsies (TBLB), and transbronchial needle aspiration (TBNA) mediastinal sampling at the time of the original diagnosis was negative for bacteria, mycobacteria, fungi and malignant cells. The patient sought a second opinion due to concerns of underlying malignancy.

At the time of our evaluation, her subjective symptoms were cough, exertional dyspnoea, fatigue and weight loss. She denied haemoptysis, fevers and night sweats. While she could not more precisely specify her symptoms, she reported that there was a significant disruption of her usual and desirable exertional functioning within the preceding 6 months due to all the above. Her physical examination was unremarkable. Complete blood count and differential were normal. Repeat sputum cultures, acid-fast



**Figure 2** CT demonstrating the low density enlarged right hilar lymph node. Similar appearing nodes were also present elsewhere in the mediastinum.

bacilli, fungal and autoimmune serologies were negative. Attempts to measure pulmonary function were futile due to the patient's inability to coordinate respiratory efforts required for the study; however, her oxygen saturation in ambient air was 98%.

An updated repeat CT of the chest, abdomen and pelvis with contrast was obtained (figure 2). When compared to the original study, it showed that the RML abnormality was smaller (4.5×2 cm), the hypodense solid components were with Hounsfield unit (HU) densities near 0, while the low-density lymphadenopathy (HU density 19) was approximately the same size.

**Task 2**

What is your differential diagnosis?

**Answer 2**

In the clinical context of the patient's reported symptoms, the differential diagnosis included atypical mycobacterial, fungal or parasitic infection, or less likely cavitating or cystic malignancy.

A cystic lesion with lymphadenopathy may be caused by various inflammatory or infectious aetiologies, including *Mycobacterium tuberculosis*, and numerous other atypical mycobacteria, fungi, and parasites [2, 3]. Thick-walled cavitary lesions with endophytic soft tissue lesions and air meniscus sign occur with fungal infections [2]. The patient's records indicated that she received treatment for pneumonia at the time of identifying her lung lesion; thus, an improving or progressively changing pneumatocele was in the differential. Furthermore, the updated imaging demonstrated an improving trajectory in the absence of any treatment. This clinical information was against an active infection or was thought to reflect a self-contained condition. Cystic lesions may appear in the context of connective tissue diseases like granulomatosis with polyangiitis or in rheumatoid arthritis following a necrobiotic nodule [2]. Our young patient was not immunosuppressed nor carried any connective tissue diagnosis or symptoms.

**Answer 3**

Taken together, a symptomatic patient (fatigue, weight loss and cough) with a nonspecific CT chest warrants further investigation. Bronchoscopy with lavage for direct inspection of the bronchial mucosa, followed by EBUS for mediastinal/hilar tissue sampling, was deemed the highest yield diagnostic step for histopathological diagnosis. CT-guided biopsy was thought to have higher risks for the lower yield. PET scanning would not be helpful at this stage, as we had just obtained an updated CT of the chest, abdomen and pelvis with contrast, and the imaging was unlikely to change the need for sampling. Furthermore, the sensitivity of 2-fluoro-2-deoxy-D-glucose (FDG) PET-CT in cyst-related malignancies is unreliable.

**Task 3**

What would be your preferred diagnostic step?

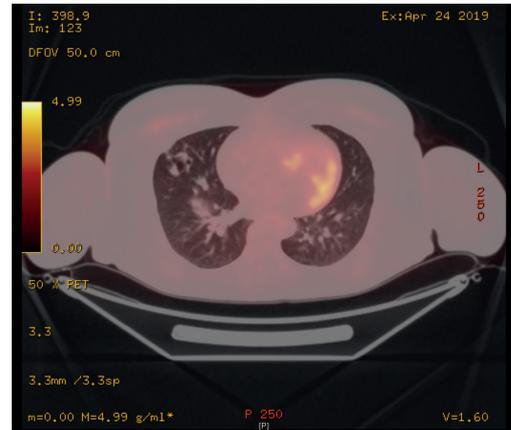
- a) Percutaneous CT-guided lung biopsy
- b) Endobronchial ultrasound (EBUS)-guided biopsy
- c) Positron emission tomography (PET)
- d) Do nothing

EBUS-guided biopsies with a convex probe yielded normal scarce lymphoid tissue. Flow cytometry and infectious studies were nondiagnostic. Following the EBUS, the patient continued endorsing worsened symptoms and nervousness about the lack of an exact diagnosis to explain her symptoms. *Mycobacterium fortuitum* was cultivated in a single bronchoscopic sample; yet, this was considered unlikely to explain the patient's symptoms. At this point, a PET scan showed that the cystic lesion was smaller with a less solid component. However, the mediastinal and hilar adenopathy had enlarged. The cystic lung lesion had no FDG activity (figure 3), while the previously biopsied mediastinal and hilar lymph nodes had mild FDG activity, similar to blood pool activity. A transcutaneous CT-guided biopsy was obtained from the cystic lesion. This was nondiagnostic due to sparse tissue.

#### Task 4

What would now be your next step?

- Watchful waiting
- Re-do bronchoscopy
- Transthoracic biopsy
- Mediastinoscopy with right middle lobectomy

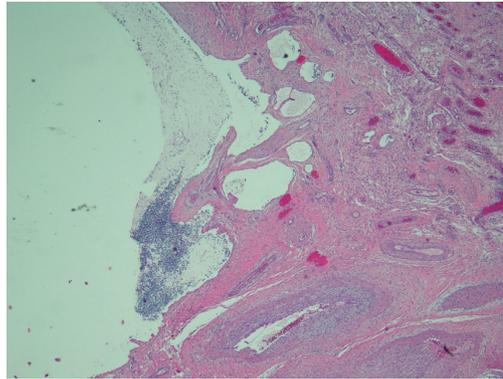


**Figure 3** Lack of FDG activity in the cavity lesion on a fused PET/CT image.

**Answer 4**

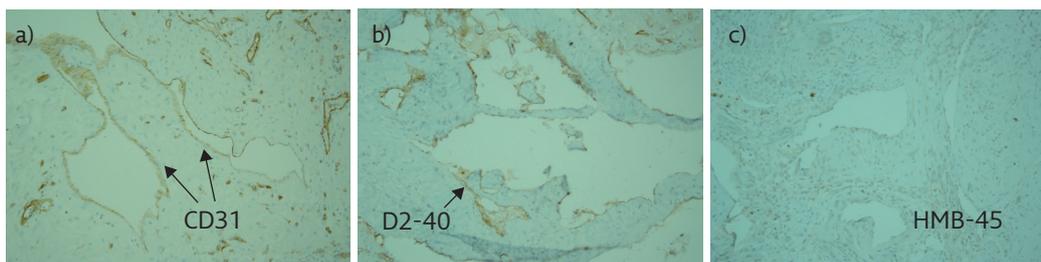
After multidisciplinary discussions, the patient was offered the options of mediastinoscopy with right middle lobectomy or serial CT imaging surveillance to monitor the changes in size and solid components of the cyst.

At this point, consideration of a nonmalignant diagnosis was reviewed with the patient, and monitoring with serial surveillance CT chest imaging was offered. A second option of diagnostic workup with mediastinoscopy and right middle lobectomy was also offered for a conclusive diagnosis that would explain her symptoms. As she wanted to pursue further workup but was reluctant to undergo surgery, another percutaneous CT-guided 18-gauge core biopsy of the RML cystic lesion was carried out. Results showed fragments of fibrous tissue with focal necrosis and findings suggestive of old haemorrhage. Because of the patient's persistent worry of a missed underlying malignancy, a right middle lobectomy was performed.

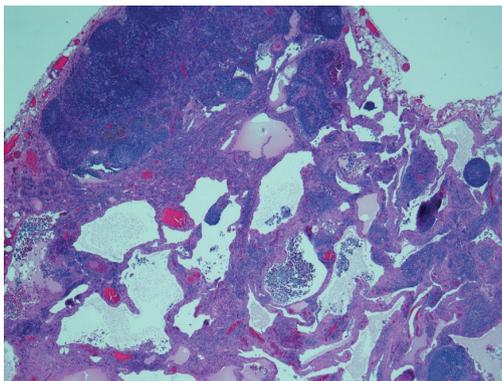


**Figure 4** Pathology slide from pulmonary resection showing multiple, cystically dilated lymphatic spaces surrounded by a reactive myofibroblastic proliferation, abundant haemosiderin and scattered granulomas. Large, abnormal collateral pleural vessels were present, intermixed with the lymphangioma and resulting in a sizable pleural adhesion to the chest wall.

Pathology slides are shown in figures 4, 5 and 6. The pathological specimens were consistent with pulmonary lymphangiomatosis.



**Figure 5** a-c) Immunostaining for CD31 and D2-40 confirmed the lymphatic nature of the cystic spaces, and the surrounding myofibroblastic reaction was negative for HMB-45, excluding lymphangioleiomyomatosis.



**Figure 6** Lymph node resection depicting lymphangioma within the lymph node.

## Discussion

Primary disorders of the pulmonary and thoracic lymphatic system are rare. Lymphangiomas are rare and benign neoplasms thought to arise from abnormal lymphangiogenesis. Their embryopathogenesis remains controversial [4]. These abnormalities most commonly occur in the head, neck, abdomen, and axilla [5, 6]. Pulmonary lymphangiomas, although rare, are perhaps the most common abnormality of the pulmonary lymphatic system. Mediastinal lymphangiomas are reportedly more common than intrapulmonary lesions, with an incidence of 7% and <1%, respectively. Pleural effusions, interlobular septal thickening and ground-glass opacities may also be seen [7]. Lymphangiomatosis of the bone may be extremely debilitating and disfiguring. Visceral involvement carries a bleak prognosis [8]. Other clinical presentations include chyloptysis, haemoptysis, lymphedema, pericardial effusion, protein-wasting enteropathy, chylous ascites and hemi-hyperplasia [4, 7, 9].

**Table 1** *Clinical characteristics of lymphangiomas and differential diagnosis*

<b>Age at presentation</b>	Childhood (90% <2 years-old)
<b>Aetiology</b>	Congenital Acquired when in the context of chronic lymphatic obstruction due to chronic infection, radiation therapy or trauma
<b>Sex predilection</b>	None in early diagnosis, female when diagnosed in adults
<b>Thoracic manifestations</b>	Intrapulmonary mass Mediastinal mass (equal distribution among compartments) Chylous pleural or chylous pericardial effusion
<b>Extrathoracic manifestations</b>	Head, neck, axilla, abdomen, bones
<b>Classification</b>	Capillary or simple, cavernous, cystic
<b>Natural history</b>	No spontaneous resolution Secondary infections may occur
<b>Differential diagnosis [9]</b>	Lymphangiectasis (primary or secondary) Lymphangiomatosis Lymphatic dysplasia syndromes ( <i>e.g.</i> lymphedema, yellow nail syndrome) Lymphangiosarcoma Acquired lymphatic injuries ( <i>e.g.</i> traumatic) Other lymphatic abnormalities ( <i>e.g.</i> lymphangioliomyomatosis, lymphangioliomas, haemangioliymphangiomas)

These lesions are often congenital malformations and are most frequently diagnosed in children by the age of 1 year [7]. Conversely, congenital or acquired lymphangiomas may get diagnosed as late as the eighth decade of life at sites of chronic lymphatic obstruction due to chronic infection, radiation therapy or trauma [9, 10]. Female gender predilection has been reported in adults [11]. Table 1 summarises the clinical characteristics and differential diagnosis of lymphangiomas.

Historically, the literature has been challenging to interpret due to inconsistent terminology and the presence of predominantly case reports. In 1990 a classification of lymphatic abnormalities was proposed by HILLIARD *et al.* [12]. This was modified by FAUL *et al.* [9] in 2000, with four proposed categories: lymphangioma, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. Our case is characterised by a solitary pulmonary lymphangioma with additional small lymphangiomas present in two hilar lymph nodes.

## Radiology discussion

Mediastinal lymphangiomas are usually smoothly marginated and have homogeneous low attenuation, but can have higher attenuation due to proteinaceous content, haemorrhage or infection [5]. The most common locations are the anterior [4] superior and right paratracheal mediastinum [5]. Intrapulmonary lymphangiomas are less well-circumscribed and may be indistinguishable from atypical morphological forms of necrotic cavitating or cystic pulmonary metastases.

### Task 5

Cystic malignancies are associated with:

- Lung adenocarcinoma
- Head and neck cancers metastatic to the lung
- Soft tissue sarcomas metastatic to the lung
- Renal cell cancer metastatic to the lung
- All of the above

**Answer 5**

Cyst-related malignancies of lung origin are most commonly adenocarcinomas, followed by squamous cell carcinomas and uncommonly small cell carcinomas [13, 14]. Their estimated incidence ranges from 0.5–4%. They may appear in any lobe; they are more commonly peripherally located while they may progress into solid nodules or masses [13]. Metastatic cystic lung lesions have been reported secondary to cancers of head and neck origin [15], adenocarcinomas of the gastrointestinal tract [15], transitional cell carcinoma, breast and sarcomas such as Ewing's sarcoma, Wilms' tumour, osteogenic sarcoma and angiosarcoma [7].

Spiculated or irregularly shaped lymphangiomas may occur. Calcification or contrast enhancement in imaging is atypical and suggests a different diagnosis [5]. The pathological subtypes of lymphangioma (capillary or simple, cystic and cavernous) cannot be distinguished by CT or magnetic resonance imaging [5].

In our case, imaging features were nonspecific. In the original film (figure 1a–c), the cyst had a smooth inner wall, was located in the subpleural space, contained septations and had a solid component. The surrounding parenchyma appeared healthy. There were no accompanying nodular lesions in the lung parenchyma nor ground-glass opacities. The mass was again smaller with a less solid component on a subsequent PET scan, but the mediastinal and hilar adenopathy had enlarged. The cystic lung mass had no FDG activity (figure 5), and the mediastinal and hilar lymph nodes had mild FDG activity, similar to blood pool activity. This differs from another reported case of a pulmonary lymphangioma that was hypermetabolic [16]. Our patient's presentation was atypical, involving both intrapulmonary pathologies and mediastinal and hilar structures without evidence of pleural or pericardial effusion, interlobular septal thickening, or peribronchovascular interstitial prominence. Furthermore, it is reported that FDG PET-CT may also be misleading as not all cyst-related malignancies show FDG uptake.

EBUS was performed to diagnose mediastinal, hilar and peribronchial lymphadenopathy with a 21-gauge needle. On EBUS imaging, the lymph

nodes had ill-defined margins, heterogeneous consistency, and absence of central blood vessels (figure 7a–c). The tissue was exceedingly soft, and in real-time, it created the impression of necrosis. Numerous passes were performed, yet the aspirated material was deemed inadequate in rapid onsite evaluation (ROSE) or as having scarce lymphoid tissue. The cytology was ultimately inconclusive for any malignant or specific benign disease (that is, negative for malignant cells or granuloma). Following the EBUS, a multidisciplinary approach was taken involving pulmonary medicine, infectious diseases, radiology, clinical pathology and thoracic surgery. Because of the ambiguity of nonspecificity and the patient's preferences, we proceeded with tissue diagnosis. She underwent right middle lobectomy, yielding the diagnosis.

## Pathologic discussion

The gross pathological features of the RML lesion were those of a 2.0 cm subpleural, ill-defined mass, which was soft, mottled, red–yellow, and poorly circumscribed. A portion of the parietal pleura and chest wall attached to the lesion area had been removed en bloc with the lobectomy specimen. There were dense adhesions and vascular supply within the visceral pleura overlying the mass. The hilar lymph nodes grossly did not show any abnormalities.

Histologically, the pulmonary lesion was composed of multiple, variably sized, irregularly shaped spaces lined by a delicate, flattened, and attenuated layer of cells, which stained positively for CD-31 and D2-40. The spaces were separated by a haphazard proliferation of fibroblasts with granulation tissue and fibrosis, focal areas of infarct-type necrosis, scattered giant cell histiocytes, a few small granulomas, and abundant haemosiderin deposits with areas of more recent haemorrhage as well. The spindle fibroblastic cells were negative for HMB-45, which excluded lymphangioliomyomatosis. This lesion had been biopsied multiple times before the lobectomy was performed. In addition to the secondary changes of fibrosis and organising haemorrhage described, numerous large abnormal collateral vessels originating from the pleura were identified within the mass's peripheral portions. Movat stain was used to characterise the large collateral vessels.



**Figure 7** a–c) Convex probe EBUS images of subcarinal station showing ill-defined margins, heterogeneous consistency and absence of central blood vessels. Note the absence of Doppler flow signal.

Examination of the two of the five right hilar lymph nodes revealed small intranodal lymphangiomas characterised by thin-walled, delicate, anastomosing vascular channels. The cells lining the vascular spaces also stained positively for D2-40, confirming the lymphatic nature of the endothelium.

## Conclusion

This case emphasises that pulmonary lymphangiomas can be asymptomatic for many years and may present as suspicious mass lesions in adults, either found incidentally or after becoming large enough to cause symptoms. The histopathological diagnosis may be difficult, especially on core biopsy material, as the lymphatic channels may become fragmented and the architecture distorted. Decision-making regarding surgical resection depends on the radiographic certainty that the lesion is of benign nature, the

symptoms associated with compressive phenomena around the malformation such as airway obstruction, dysphagia, frequent infections, the experience of the treating team, and the patient preference. Overall, the prognosis is excellent if completely resected. If resection is incomplete, recurrence can occur. Malignant potential is unknown.

In this case, multiple initial biopsy attempts resulted in marked secondary changes related to haemorrhage and subsequent organisation identified within the resection specimen. Upon retrospective review of the EBUS specimens, which included the application of D2-40 staining, the lymphatic channels were identified within the initial biopsy material. Ultimately, a resection specimen provided the diagnostic histopathological findings. It is noteworthy that after the diagnosis was obtained at 1-year follow-up, the patient received care for asthma control and had no further functional or nonspecific complaints. The anxiety associated with uncertainty of diagnosis also resolved.

## Affiliations

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## Authors contributions

I. Kourouni concept and design, had full access to all of the data, and takes responsibility for drafting the manuscript and editing the images. S.W. Tamarkin takes responsibility for the radiology section. C.M. Abramovich and J.F. Tomashefski Jr take responsibility for the pathology section. E.D. Sivak edited the manuscript. Critical revisions of the manuscript for important intellectual content: all authors

## Conflict of interest

None declared.

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