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September 2021 Pulmonary Case of the Month: A 45-Year-Old Woman with Multiple Lung Cysts

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History of Present Illness

A 45-year-old woman presented with increasing dyspnea on exertion and a history of recurrent pneumothoraces. In March 2018 she had laparoscopic ovarian cyst removal and noted some subsequent shortness of breath. In August 2018 she developed a right pneumothorax requiring chest tube placement. In September 2018 she had recurrent right pneumothorax and had video-assisted thoracoscopic surgery (VATS) with a right pleurodesis. The operative note from the outside VATS indicates a RUL bleb was removed and a wedge biopsy was done from posterior segment of the RUL. Pathology from the wedge biopsy reported "minimal emphysematous disease without other diagnostic abnormality". She continued to be short of breath after the operation.

PMH, SH, and FH

- In 1975 she reportedly had pulmonary tuberculosis.
- In 2018 the pneumothoraces, pleurodesis and the right ovarian cyst resection noted above.
- She is a never smoker and has no family history of lung disease or pneumothoraces.

Medications

- Advair 115-21
- Hydroxyzine

Review of Systems

- In addition to her dyspnea she also reported a dry mouth.

Physical Examination

- Vital Signs: BP 143/93, afebrile, SpO2 99% at rest, Body Mass Index (BMI) 25.9
- Chest: breath sounds diminished, no crackles
- CV: regular, no murmur
- Ext: no clubbing or edema

Radiography

Prior outside CT scans are available from January 2019 (Figure 1) and December 2020.

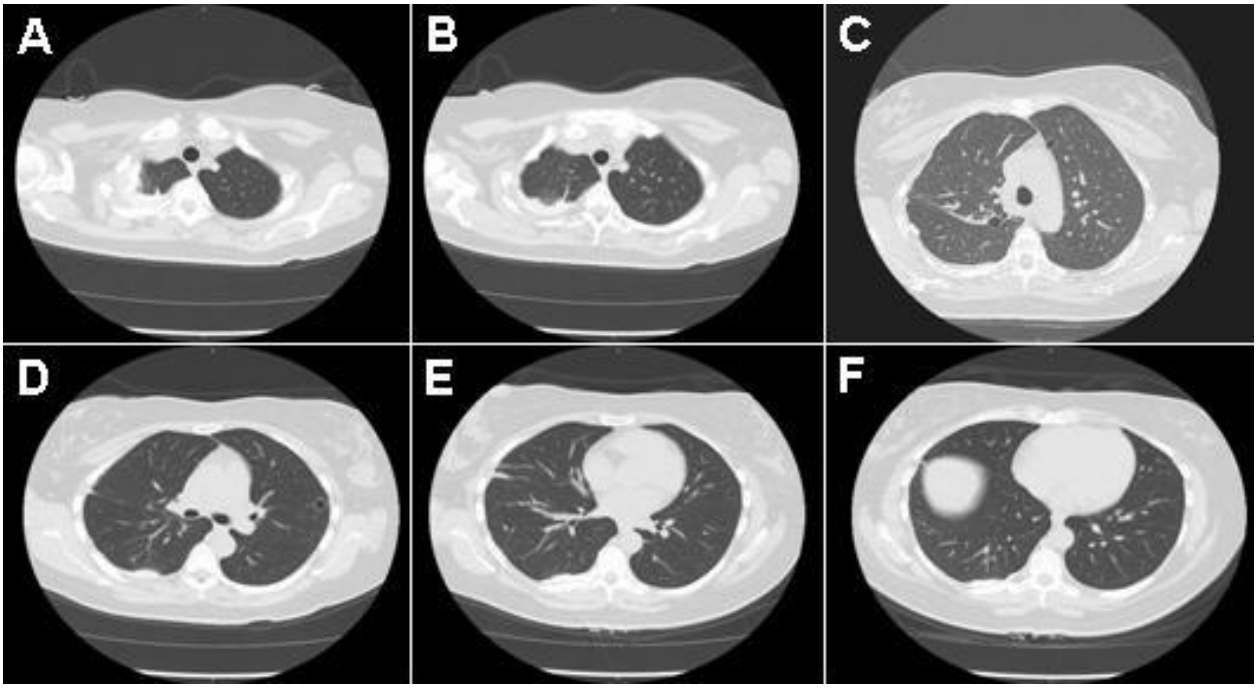


Figure 1. Representative images from January 2019 high resolution thoracic CT scan in lung windows.

The thoracic CT scan in ***Figure 1 shows*** which of the following.

1. Pleural thickening and scarring
2. A subpleural pulmonary nodule in the RUL
3. Multiple lung cysts
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

There are multiple lung cysts and pleural thickening and scarring surrounding the right lung (Figure 2).

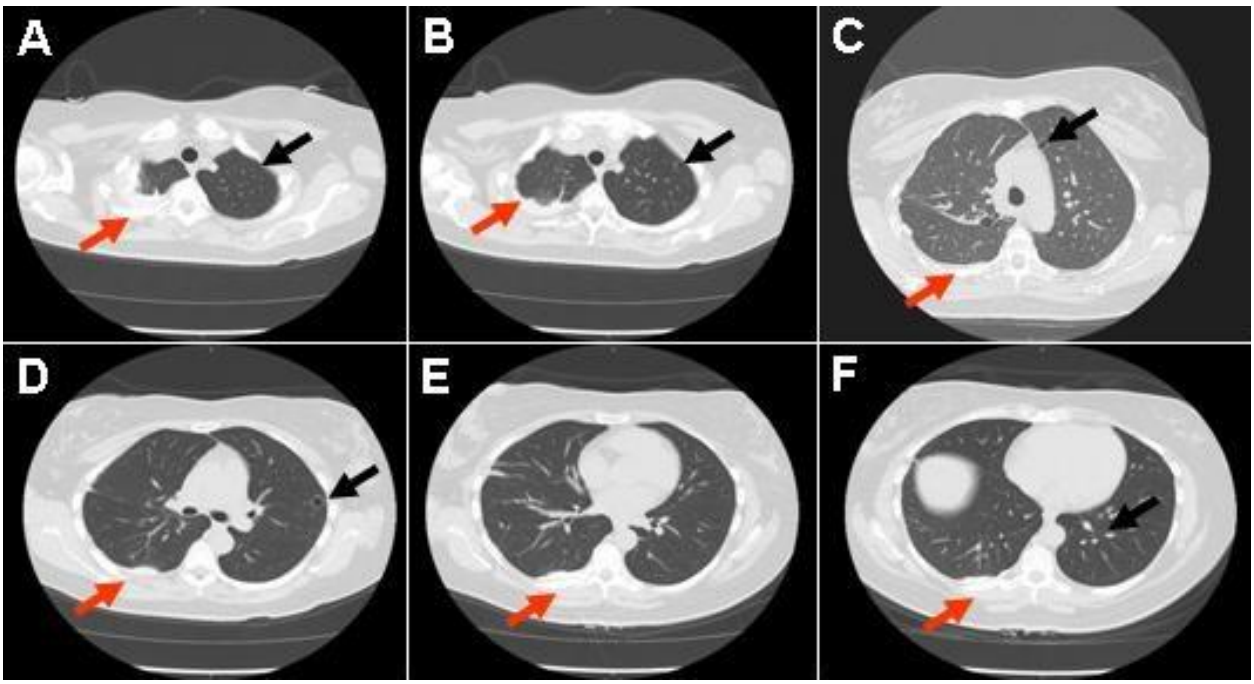


Figure 2. Identical to Figure 1 except black arrows added to identify cysts and red arrows added to indicate pleural thickening and scarring.

Based on the thoracic CT scan, the patient has multiple cystic lung disease. A cyst is defined as a round air-filled space in the lungs surrounded by an epithelial or thin fibrous wall typically 2 mm or less in diameter (1-3).

Which of the following ***should be done*** at this time?

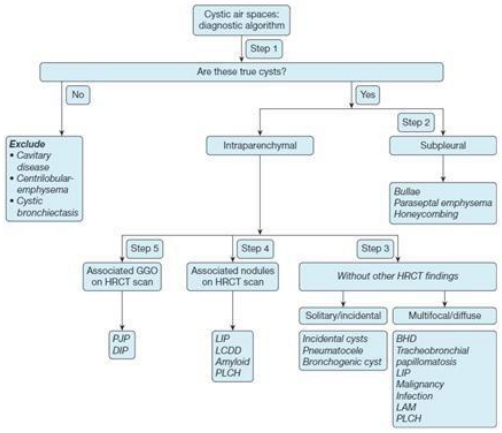
1. Pulmonary function testing (PFTs)
2. Repeat the high resolution thoracic CT scan
3. Serology for connective tissue disorders
4. 1 and 3
5. All of the above

Correct!

5. All of the above

All should be ordered in a patient with multiple cystic lung disease (1-3). As with all diseases, the first step in establishing the correct diagnosis multiple cystic lung disease is a detailed history and physical examination. The development of acute, rapidly progressive cystic change is suggestive of an infectious, inflammatory, or traumatic origin, whereas chronic processes are more likely secondary to congenital, vascular, connective tissue or possibly neoplastic disorders. A history of tobacco exposure or the presence of sicca symptoms can provide insights into smoking and connective tissue disease etiologies, respectively. A detailed family history, especially history of pneumothoraces, skin lesions, and renal tumors in children, siblings, parents, and more distant blood relatives, is useful information for establishing the diagnosis of lymphangioleiomyomatosis (LAM) and folliculin gene-associated syndrome (Birt-Hogg-Dubé, BHD). As part of the detailed pulmonary examination, particular attention must be given to signs of a connective tissue disease or skin findings suggestive of BHD or tuberous sclerosis complex, which may be associated with LAM.

Critical review of a high resolution CT scan by an expert radiologist is essential for accurate diagnosis. The cyst characteristics and associated radiographic findings can suggest the underlying disease. Radiological information can be further supplemented by serum biomarkers such as vascular endothelial growth factor-D, SS-A, SS-B, and α 1-antitrypsin. Genetic studies on peripheral blood can be helpful in BHD. Lung biopsy with histopathologic evaluation in conjunction with special studies may be required to establish a definitive diagnosis, given the extensive overlap of clinical and radiographic features in some cases. Raoof et al. (4) have proposed a diagnostic algorithm for the diffuse or multiple cystic lung diseases as shown in Figure 3.



BHD = Birt Hogg Dube syndrome; DIP = desquamative interstitial pneumonia; HRCT = high-resolution CT scan; LAM = lymphangioleiomyomatosis; LCDD = light-chain deposition disease; LIP = lymphoid interstitial pneumonia; PJP = pneumocystis jirovecii pneumonia; PLCH = pulmonary Langerhans cell histiocytosis.

Figure 3. Detailed algorithmic approach to cystic lung disease as proposed by Raoof et al. (4).

The high resolution thoracic CT scan was repeated in December 2020 (Figure 4).

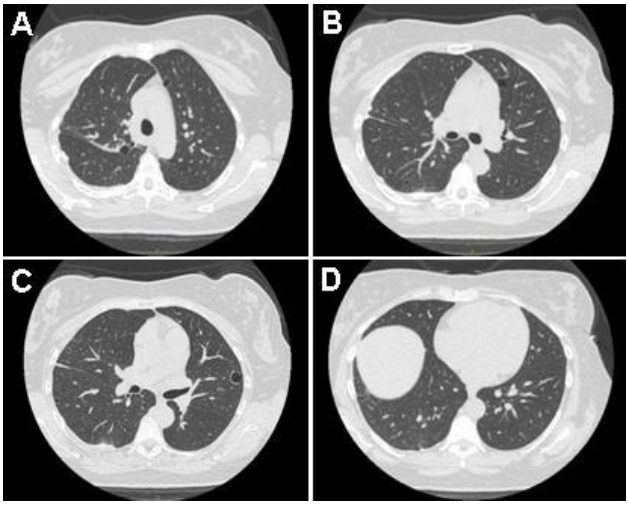


Figure 4. Repeat high resolution thoracic CT scan done in lung windows done in December 2020.

Review of the newer CT suggests slight enlargement in size of one of the cysts (the one in LUL), otherwise, no change compared to January 2019.

The rheumatology panel was unremarkable (Table 1).

Table 1. Rheumatology panel done in December 2020.

- Sedimentation Rate: 25
- C-Reactive Protein (CRP): 3.4
- Antinuclear Ab,: 0.3
- SS-A/Ro Ab, IgG,: <0.2
- SS-B/La Ab, IgG,: <0.2
- Rheumatoid Factor,: <15

The pulmonary function testing (PFTs) are shown in Figure 5.

	PREDICTED		CONTROL		POST-DILATOR**	
	Pred	LLN	Actual	%Pred	Actual	%Chng
-- SPIROMETRY --						
FVC (L)	3.19	2.66	*1.72	*53	*1.73	+0
FEV1 (L)	2.58	2.15	*1.42	*55	*1.52	+7
FEV1/FVC (%)	81.25	67.84	82.56	101	88.32	+6
FEF 25-75% (L/sec)	2.74	1.51	*1.44	*52	2.12	+46
FEF Max (L/sec)	6.33	4.75	5.38	84	5.45	+1
MVV (L/min)	102	85	*68	*66		
MEP (cmH2O)	150	125	*48	*31		
MIP (cmH2O)	-82	-69	*-68	*82		
-- LUNG VOLUMES --						
TLC (Pleth) (L)	4.46	3.57	*3.14	*70		
SVC (L)	3.19	2.66	*1.69	*52		
RV (Pleth) (L)	1.35	1.08	1.45	107		
RV/TLC (Pleth) (%)	33.07	26.46	*46.29	*139		

Figure 5. Pulmonary function testing done in December 2020.

The PFTs were interpreted as showing moderately severe restrictive lung disease and a subsequent fluoroscopic sniff study demonstrated paralysis of the right hemidiaphragm as a contributing cause.

No specific diagnosis had been established and the patient was upset at the lack of progress towards an answer.

What should be ***done next*** in her evaluation?

1. Repeat the open lung biopsy
2. Bronchoscopy with transbronchial biopsy
3. Review the existing lung biopsy.
4. Reassure the patient and reevaluate the thoracic CT scan, PFTs, etc. in 3 months
5. Repeat the video-assisted thorascopic surgery (VATS) and rebiopsy the right lung

Correct!

3. Review the existing biopsy

The patient was anxious to make a diagnosis and unwilling to wait 3 months for repeat studies. The best course seemed to be to obtain outside lung biopsy specimen for review. Repeat open lung biopsy, VATS, and transbronchial biopsy seem unlikely to establish a diagnosis if a previous open lung biopsy with good specimens did not.

New findings noted on pathology review done at our institution indicating lung cysts with walls containing spindle-like malignant cells with evidence of hypervascularity (Figure 6).

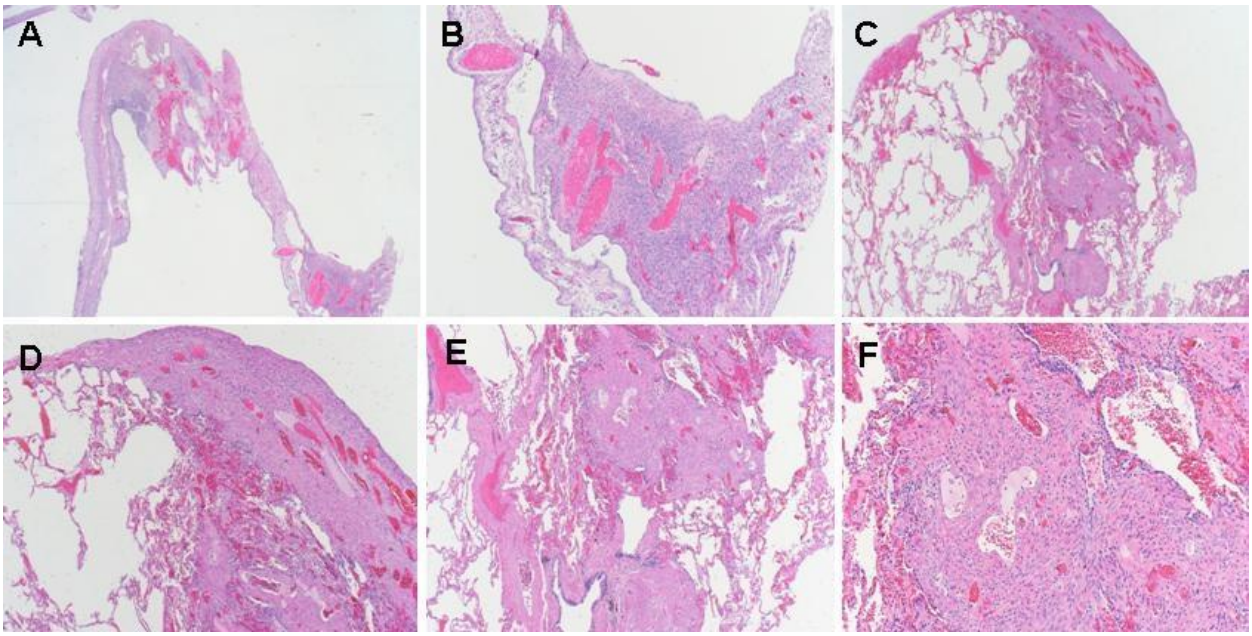


Figure 6. Histopathology with hematoxylin and eosin (H & E) staining. Low power view (A); intermediate power view (B,C); and high power view (D-F).

Which of the following malignancies has been ***associated with lung cysts***?

1. Head and neck squamous cell carcinoma
2. Seminoma
3. Various sarcomas (Ewing's sarcoma, osteogenic sarcoma, angiosarcoma, sarcoma of unknown type).
4. 1 and 3
5. All of the above

Correct!

5. All of the above

There are a number of carcinomas and sarcomas associated with metastatic cystic lung disease (Table 2).

Table 2. Carcinomas/sarcomas associated with cystic lung metastases.

- Head and neck squamous cell carcinoma
- Seminoma
- Ewing's sarcoma
- Wilm's tumor
- Osteogenic sarcoma
- Angiosarcoma
- Transitional cell carcinoma
- Sarcoma of unknown type

Special staining for S100 and HMB 45 was negative but staining for estrogen receptor (ER), smooth muscle actin (SMA), desmin, and CD10 was positive (Figure 7).

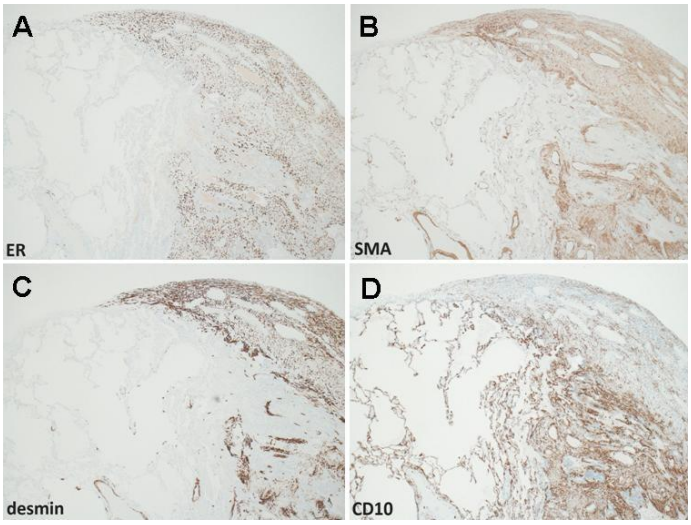


Figure 7. Special stains showing positivity for estrogen receptor (ER), smooth muscle actin (SMA), desmin, and CD10.

The pathologists opined that the tumor was most likely due to metastatic spindle cell carcinoma from the uterus based on the histopathology and the special stains (5).

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