

March 2014 Pulmonary Case of the Month: The Cure May Be Worse Than the Disease

Sudheer Penupolu, MD
Philip J. Lyng, MD
Lewis J. Wesselius, MD

Department of Pulmonary Medicine
Mayo Clinic Arizona
Scottsdale, AZ

History of Present Illness

A 51 year old woman was seen with a chief complaint of gradually increasing shortness of breath. She was at baseline five months prior to presentation but noticed dyspnea on minimal exertion initially at a higher altitude, gradually progressing to dyspnea at rest. She was tried on 2 courses of antibiotics with no significant improvement. In addition to the dyspnea, she has some non productive cough but no fevers.

PMH, SH, FH

She had a renal transplant in 1997 for IgA disease and has a history of type II diabetes and hypertension.

She is a life long nonsmoker and has only occasional alcohol use. She is employed as a utility designer and has no exposure to any dusts, fumes or exotic animals.

Family history is noncontributory.

Medications

- Atenolol
- Lasix
- Prednisone 2 mg q daily
- Rosuvastatin
- Sirolimus 2 mg po q daily

There have been no changes in the doses in the past few years.

Physical Examination

Physical examination reveals no abnormalities and her lung auscultation is clear.

Laboratory

Her complete blood count (CBC), urinalysis, liver function tests, and calcium were all within normal limits.

Radiology

An x-ray of the chest is shown in Figure 1.



Figure 1. Initial PA chest radiograph.

Which of the below is the **best interpretation** of her chest x-ray?

1. Cardiomegaly
2. Left upper lobe consolidation
3. Normal
4. Right upper lobe consolidation
5. All of the above

Correct!
2. Left upper lobe consolidation

There is an area of consolidation in the left upper lobe (Figure 2).

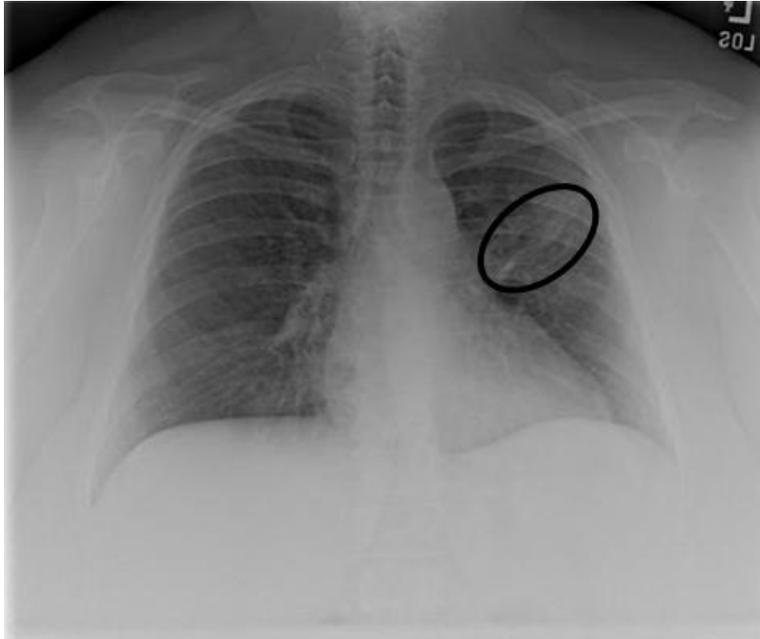


Figure 2. Initial PA chest radiograph with the abnormality circled.

There is also a question of right lower lobe consolidation but that is not one of the choices. There is no cardiomegaly or right upper lobe consolidation.

Which of the following radiologic procedures is ***indicated next?***

1. Needle biopsy of the left upper lobe
2. PET scan
3. Serial chest radiography
4. Thoracic CT angiography
5. Thoracic CT scan

Correct!
5. Thoracic CT scan

In immunocompromised hosts a conservative approach can be risky. The patient may progress quickly. Therefore, following the patient with serial chest x-rays is not appropriate. Needle biopsies are usually done for masses although it could be done in this case. PET scans are usually done to assess the metabolic activity of masses. It is unclear how that would be helpful in this case. CT angiography is usually done for pulmonary embolism, which although possible, is unlikely. Therefore a thoracic CT scan was performed (Figure 3).

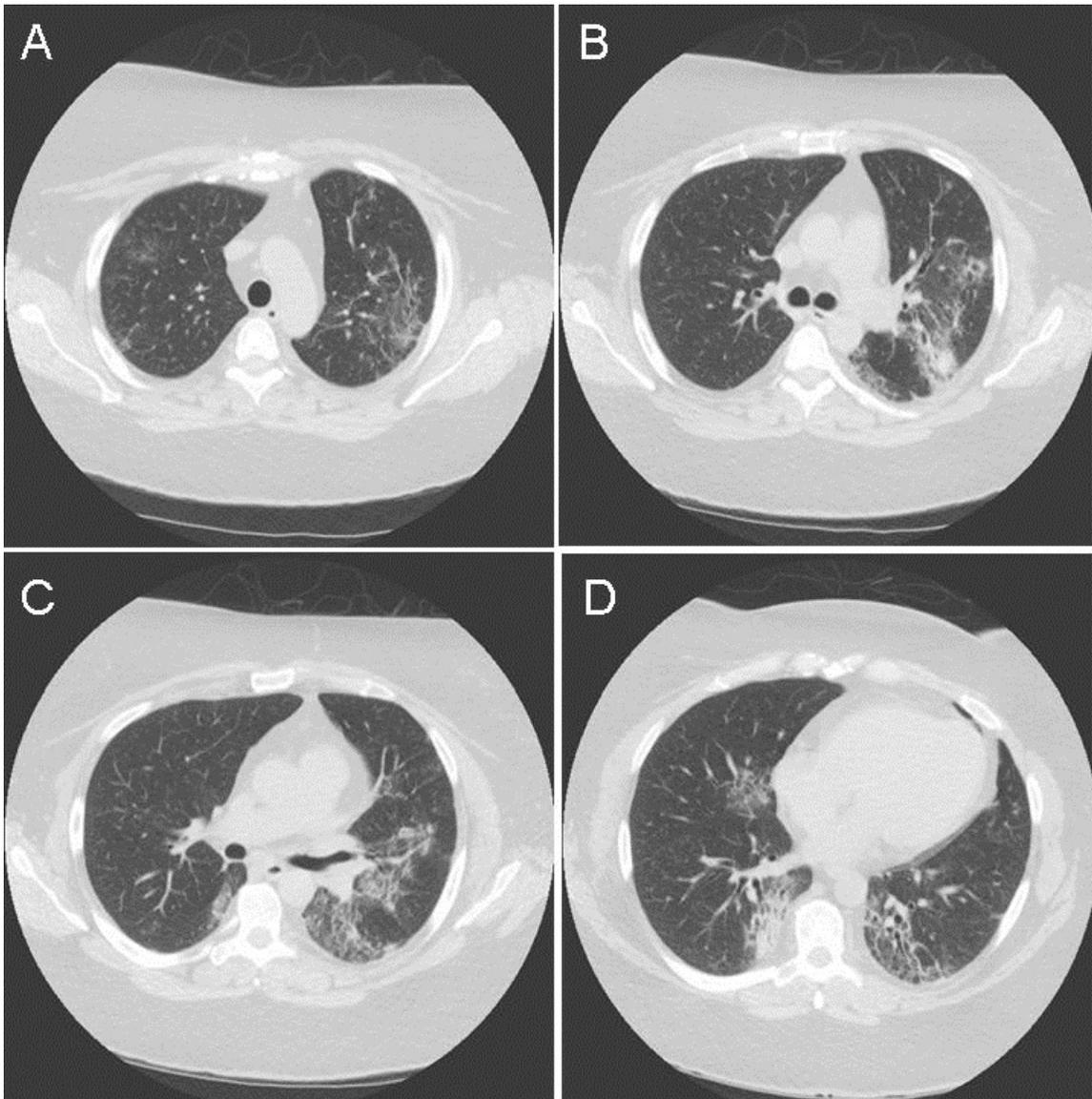


Figure 3. Representative lung windows from the thoracic CT scan.

Which of the **following should be done next?**

1. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy
2. Video-assisted thoracoscopy (VATS)
3. Pulmonary function testing
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

Pulmonary function testing and bronchoscopy are both indicated. VATS is also reasonable although most pulmonary physicians would probably do bronchoscopy first since it is less invasive and has a reasonable chance of yielding a diagnosis (1).

The pulmonary function tests are abnormal (Figure 4).

	PREDICTED		CONTROL		POST-DILATOR*	
	Pred	LLN	Actual	% Pred	Actual	% Chng
-- LUNG VOLUMES --						
TLC (Pleth) (L)	4.93	3.94	*3.35	*67		
SVC (L)	3.41	2.85	*2.59	*75		
RV (Pleth) (L)	1.68	1.34	*0.76	*45		
RV/TLC (Pleth) (%)	36	29	*23	*63		
-- SPIROMETRY --						
FVC (L)	3.41	2.85	*2.73	*80	*2.66	-2
FEV1 (L)	2.69	2.25	2.49	92	2.51	+0
FEV1/FVC (%)	80	67	91	114	*94	+3
FEF 25-75% (L/sec)	2.65	1.46	*4.19	*158	*4.25	+1
FEF Max (L/sec)	6.55	4.91	7.61	116	8.13	+6
MVV (L/min)	101	84	99	98		
-- DIFFUSION --						
DLCObunc (ml/min/mmHg)	22.22	17.78	*13.43	*60		
DLCObcor (ml/min/mmHg)	22.22	17.78				
VA (L)	4.93	4.12	*3.49	*70		
- AIRWAYS RESISTANCE -						
Raw (cmH2O/L/s)	1.86	1.55	*0.76	*40		
Gaw (L/s/cmH2O)	1.03	0.86	*1.33	*128		
sRaw (cmH2O*s)	< 4.76	3.97	1.65			
sGaw (1/cmH2O*s)	0.20	0.17	*0.61	*303		
-- OXIMETRY --						
		<u>Rest</u>	<u>Exercise</u>			
SaO2 (%)		95	85			

Figure 4. Pulmonary function testing.

Bronchoscopy with bronchoalveolar lavage revealed no endobronchial masses, an increase in lymphocytes and stains and cultures were negative. Transbronchial lung biopsies were performed (Figure 5).

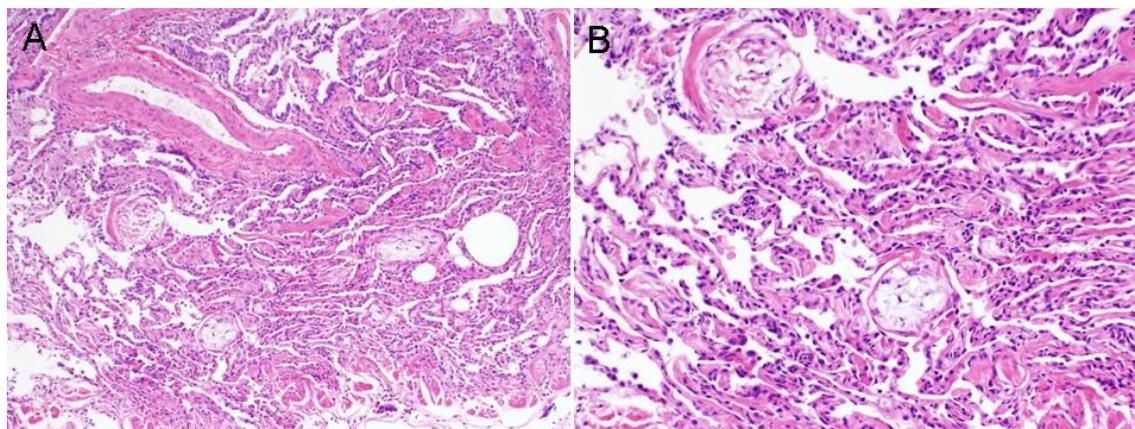


Figure 5. Panel A: Low power H & E stained transbronchial lung biopsy. Panel B. Higher power view.

The biopsy was interpreted as showing organizing pneumonia.

Which of the following is the **best diagnosis**?

1. Autoimmune-induced lung disease
2. Chronic aspiration
3. Drug-induced lung disease
4. Hypersensitivity pneumonitis
5. Idiopathic organizing pneumonia

Correct!

3. Drug-induced lung disease

All the diagnoses are possible. The biopsy findings are nonspecific. Autoimmune-induced lung disease was excluded by a negative autoimmune work up. Chronic aspiration remains a possibility although there are no clinical symptoms and no food particles are seen on the biopsy. Hypersensitivity pneumonitis is also possible as is idiopathic organizing pneumonia. The pattern with drug-induced lung disease is quite variable and can resemble hypersensitivity pneumonitis (2).

Assuming the diagnosis of drug-induced lung disease is correct, which of her **medications should be stopped first?**

1. Atenolol
2. Lasix
3. Prednisone
4. Rosuvastatin
5. Sirolimus

Correct!
5. Sirolimus

Many drugs produce a diffuse clinical spectrum of drug-induced lung disease (DILD) (3). Aside from the cytotoxic agents which can injure the lung through their cytotoxic effects, antibiotics and anti-inflammatory drugs are frequent culprits in producing DILD. Sirolimus is a macrolide antibiotic with potent anti-inflammatory activity. Although its anti-inflammatory activity might be expected to improve DILD, sirolimus can also cause DILD (4). The most commonly presenting symptoms are dyspnea on exertion and dry cough followed by fatigue and fever. Chest radiographs and high-resolution computed tomography scans commonly reveal bilateral patchy or diffuse alveolar-interstitial infiltrates. Bronchoalveolar fluid analysis and lung biopsy in selected case reports revealed several distinct histologic features, including lymphocytic alveolitis, lymphocytic interstitial pneumonitis, bronchoalveolar obliterans organizing pneumonia, focal fibrosis, pulmonary alveolar hemorrhage, or a combination thereof.

As with most DILD, improvement following discontinuation of the drug confirms the diagnosis. However, the patient also has a renal transplant and needs immunosuppression to prevent rejection. In this case the sirolimus was stopped and replaced with tacrolimus and her dose of prednisone increased to 50 mg daily. She had a marked improvement in both her symptoms and her thoracic CT scan (Figure 6).

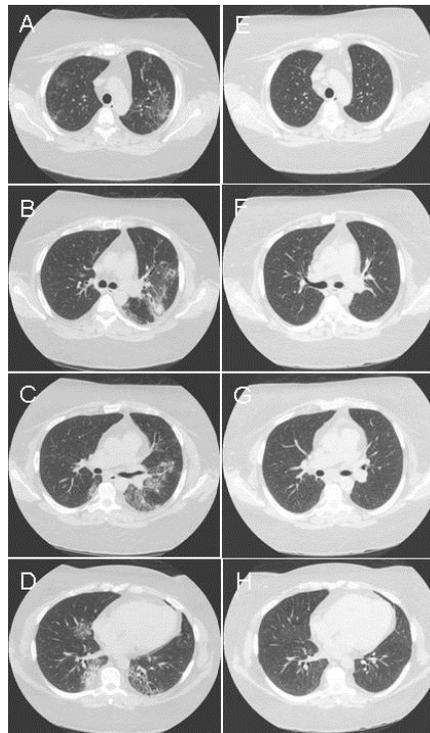


Figure 6. Panels A-D: Initial CT scan. Panels E-H: Corresponding views after sirolimus discontinued.

The patient is currently taking her prior dose of corticosteroids and has restarted working.

References

1. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med.* 1984;101(1):1-7. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Flieder DB, Travis WD. Pathologic characteristics of drug-induced lung disease. *Clin Chest Med.* 2004;25(1):37-45. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Limper AH, Rosenow EC 3rd. Drug-induced interstitial lung disease. *Curr Opin Pulm Med.* 1996;2(5):396-404. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Pham PT, Pham PC, Danovitch GM, Ross DJ, Gritsch HA, Kendrick EA, Singer J, Shah T, Wilkinson AH. Sirolimus-associated pulmonary toxicity. *Transplantation.* 2004;77(8):1215-20. [\[CrossRef\]](#) [\[PubMed\]](#)