January 2014 Pulmonary Case of the Month: Too Much, Too Late

Chidinma Chima-Okereke MD

Department of Pulmonary Medicine
Cedars Sinai Medical Center
Los Angeles, CA

Chief Complaint: Difficulty breathing

History of Present Illness

A 49-year-old gentleman with history of hepatitis C cirrhosis complicated by ascites presented to the emergency room of Olive View Medical Center in San Fernando Valley, California complaining of worsening shortness of breath. The patient reports that he occasionally has shortness of breath, usually about 2-3 times a year. However for the past 2 months, he has had worsening dyspnea on exertion and cannot walk further than 5 minutes. He also reports orthopnea and paroxysmal nocturnal dyspnea. He has been having a dry cough for the past 3-4 weeks.

He has a history of chronic ascites that has required multiple taps. He has been taking his prescribed diuretics however instead of taking these medications daily he takes them about every other day due to financial constraints.
However, his abdominal distention and his lower extremity swelling are stable. He reports some nausea with decreased appetite. He also has a new symptom of left-sided chest pain that radiates down his left arm and shoulder that lasts about 20 minutes and has no associated symptoms.

He denies any fevers or chills or weight change. He has no sick contacts.

Past Medical and Surgical History

- Hepatitis C cirrhosis
- Chronic lower extremity edema
- Ascites, status post multiple large volume paracentesis
- History of chronic abdominal pain treated with morphine
- Status post chest tube when he was a 17-year-old due to a gunshot wound

Social History

- History of incarceration, released about 8 months ago
- 6-pack of beer a day – quit 12 years ago.
- Former smoker, quit 10 years ago, 7 pack-years
- IV heroin use 15 years ago
- No cocaine, amphetamines or any inhaled substances

- No recent travel, occupational, pet or bird exposures
- Lives with his fiancé in Lancaster, California

Family History

- Father died of an MI at age 56.
- Mother - SLE, DM, Stroke
- Sister - Colon cancer
- Brother - Hepatitis C cirrhosis

Medications

- Controlled-release morphine sulfate 15 mg p.o. every morning and 30 mg p.o. every evening.
- Furosemide 40 mg p.o. daily.
- Spironolactone 50 mg p.o. daily.
- Lactulose 15 mL p.o. b.i.d. p.r.n.

Review of Systems

Positive for pleuritic chest pain, night sweats, chills, dry cough - unproductive of sputum, lightening and darkening of urine, lower extremity edema, palpitations, decreased appetite, dry mouth, joint stiffness in the morning.

Physical Examination

- Vital signs: T 97.4 BP 115/67, HR 89, RR 20, SpO2 93%/RA
- Lung exam was significant for bilateral crackles midway up the back.
- Abdominal exam was non-tender and not suggestive of ascites
- Lower extremities: 1+ bilateral pitting edema up to the knees.
- Multiple skin tattoos and erythema in his lower extremities
- Muscle strength was 3/5 in the lower extremities, 4/5 in upper extremities bilaterally.
- Otherwise the physical exam was unremarkable.

Laboratory

- Basic Metabolic Panel was within normal limits.
- Complete blood count (CBC): White count 6.3 X $10^3/mm^3$ with 8.3% eosinophils, hemoglobin 12.3 g/dL, platelets 130,000/µL.
- Liver function tests (LFTs): AST 78 IU/L, ALT 42 IU/L, alkaline phosphatase 115, total bilirubin 1.3 mg/dL, INR 1.3, albumin 2.7 g/dL.
- Brain naturetic peptide (BNP) 38 ng/L, troponin is 0.008 ng/ml.

Radiography

A chest x-ray was obtained (Figure 1).

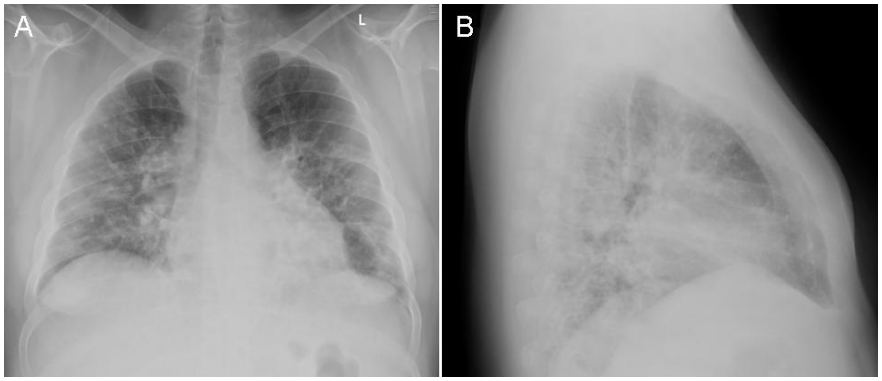

Figure 1. Admission AP (Panel A) and lateral (Panel B) chest x-ray.

The chest x-ray was interpreted as poor inspiration with elevation of the right diaphragm. The heart is at least upper limits of normal in size. Pulmonary vessels are congested. The azygos vein is mildly dilated. No significant pleural effusion is detected in these two views.

A CT angiogram was obtained to rule out pulmonary embolism (Figure 2).

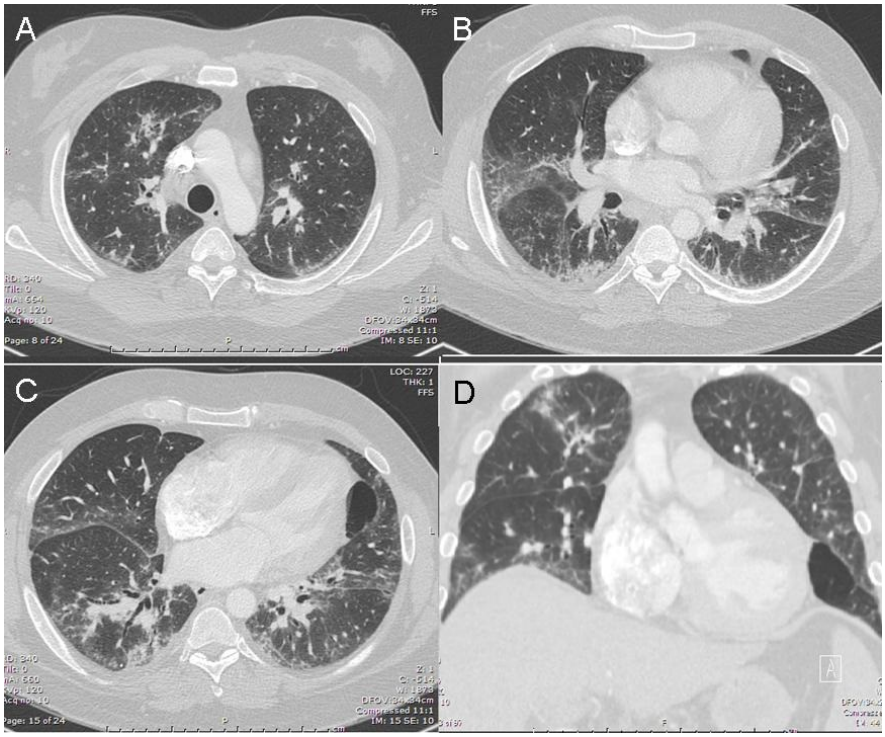

Figure 2. Representative images from the thoracic CT scan lung windows.

Hospital Course

He was admitted to the medicine wards, diuresed with furosemide 40 mg IV, spironolactone 100 mg by mouth and fluid restricted.

At this point which of the following are ***diagnostic tests that should be ordered***?

1. Coccidiomycosis serology
2. HIV
3. Quantiferon TB and sputum AFB
4. Rheumatologic work up including anti-neutrophil cytoplasmic antibody (ANCA), ANA and subtypes, RA and anticentromere antibodies
5. All of the above

Correct!
5. All of the above

He has many abnormalities on his CT scan which are not all accounted for by pleural effusions and pulmonary edema.

The following additional laboratory tests were ordered:

- **Anti-SSA 3.3 U, RA 30 IU/ml**
- Coccidiomycosis: negative
- HIV: negative
- Quantiferon TB/AFB: negative
- Sputum culture, viral PCR: negative
- Hepatitis C viral load: 1681
- **Negative: ANCA, ANA, CCP, Anti-jo, RNP/SM, SS-B, anticentromere**
- CT angiogram demonstrated no pulmonary embolus.

Based on these findings which of the following are ***reasonable differential diagnosis*** possibilities?

1. Atypical infection
2. Hypersensitivity reaction/talc pneumonitis due to prior IV drug use
3. Idiopathic interstitial pneumonia
4. Sjogren's disease or other connective tissue disease associated pulmonary disease
5. All of the above

Correct!
5. All of the above

At this early stage in the work up, his symptoms could be consistent with an atypical infection, hypersensitivity reaction, idiopathic interstitial pneumonia, Sjogren's Disease associated pulmonary disease (especially in the setting of a positive SS-A) or mixed connective tissue disease.

Case Continued

He had slight clinical improvement with diuresis, steroids and was discharged home on hospital day 3 on 2-3 liters by nasal cannula. He was referred for pulmonary and rheumatology follow-up and scheduled for a VATS lung biopsy in 5 days.

He returns to the Emergency Department 4 days later complaining of worsening shortness of breath - gasping for breath. He now has an increased oxygen requirement to 5L after exertion and his activity is limited to walking 2 steps. He reports 3 pillow orthopnea and PND sleeping for 1hr, awaking with night sweats, and chills - all unchanged. His dyspnea is very positional and he reports platypnea. He reports an episode of sudden loss of consciousness after ambulating sustaining superficial injury to bridge of nose 2 days before presentation.

Vitals: T: 98.6 BP: 147/83 P: 66 RR: 17 SpO2: 91% 5LNC at rest
Exam essentially unchanged but less peripheral edema

What should be ***done next*** in his diagnostic work up?

1. Echocardiogram
2. Fiberoptic bronchoscopy
3. Repeat chest X-ray
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

At this point, he has very significant hypoxia and a repeat chest x-ray to determine if he has developed pneumonia or reaccumulated pulmonary effusions or edema in the period following hospital discharge. An echocardiogram is also appropriate to determine if he has any cardiogenic causes of dyspnea especially in light of his sudden LOC.

A two-dimensional transthoracic echocardiogram with color flow and Doppler was performed which demonstrated borderline concentric left ventricular hypertrophy. The Ejection Fraction estimate is >70%. The left ventricle is hyperdynamic. No regional wall motion abnormalities were noted. Injection of contrast documented no interatrial shunt. The estimated PA pressure is 52 mmHg.

The repeat chest x-ray was obtained (Figure 3).

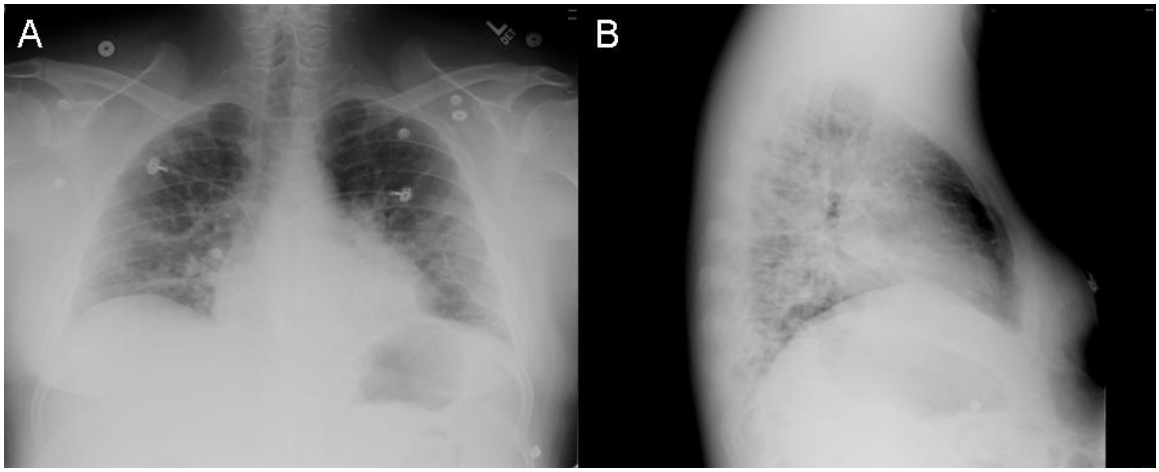

Figure 3. Repeat chest PA (Panel A) and lateral (Panel B).

Which of the following ***best describe(s) the chest x-ray (Figure 3)***?

1. Diffuse increase in his interstitial pattern
2. Normal lungs
3. The heart is not enlarged
4. Large bilateral pleural effusions
5. 1 and 3

Correct!
5. 1 and 3

The chest x-ray on the previous page demonstrates small lung volumes, a diffuse interstitial pattern suggestive of chronic fibrotic lung disease, a normal sized heart and no pleural effusions (Figure 3).

What ***other studies will you consider*** for working up the cause of his worsening hypoxia?

1. High resolution CT scan
2. Macroaggregated albumin nuclear study
3. Right heart catheterization
4. 1 and 3
5. 1, 2 and 3

Correct!
5. 1, 2 and 3

A high resolution CT scan (HRCT) is important to further access the fibrotic changes noted on chest x-ray. It can be very specific in identifying certain radiological patterns of disease such as usual interstitial pneumonia (UIP) which is highly suggestive of idiopathic pulmonary fibrosis (IPF).

A right heart catheterization is also reasonable to obtain in evaluating a patient with severe pulmonary hypertension seen on echocardiogram.

Obtaining a macro-aggregated albumin nuclear scan is warranted to evaluate for hepato-pulmonary syndrome in this patient with decompensated cirrhosis and symptoms consistent with platypnea.

Results

The repeat chest CT scan demonstrates regions of inter and intralobular septal thickening, peribronchial thickening with mild ground-glass and centrilobular reticulations. There is increased atelectasis in the lung bases. An area of air trapping is identified in the lingula. No significant pleural effusion is present. No significant areas of honey combing or bronchiectasis.

A right heart catheterization demonstrated normal hemodynamics with the following findings:

- HR- 106
- RA (mean): 7/6/6
- RV (S/D): 30/6/14
- PA (S/D): 24/20/21
- PAW (mean): 6
- Cardiac output (Fick) - 8.64 L/min
- Cardiac index- 3.97 lit/min/m2
- Pulmonary arteriolar resistance- 138.9 dynes sec/cm5
- Oxygen saturations in cardiac chambers in %-
  RA- 76.1
  RV- 76.9
  PA- 76.9

The macroaggregated albumin nuclear study obtained to better characterize the possible presence of hepatopulmonary syndrome demonstrated no evidence of right to left shunt.

His supplemental oxygen requirement continued to increase and on hospital day 8, he was transferred to the ICU in respiratory distress saturating 80% on 6L face mask.

What is the ***best choice*** as the next diagnostic step in accurately diagnosing his ILD?

1. Bronchoscopy with bronchoalveolar lavage (BAL)
2. Bronchoscopy with transbronchial biopsy (TBLB)
3. CT guided biopsy
4. Endobronchial ultrasound (EBUS)
5. Video-assisted thorascopic surgery (VATS) biopsy

Correct!
5. Video-assisted thorascopic surgery (VATS) biopsy

Studies have shown that video assisted thorascopic surgery has the highest yields in diagnosing undefined interstitial lung diseases (1,2). However in a cirrhotic with a MELD score of 13, Yeh et al. (3) demonstrated that the 30 day post-operative mortality is 25% and Park et al. (4) showed a 28.6% mortality rate if surgical biopsy was performed during the acute exacerbation. Therefore the risk of this elective procedure may far outweigh the value of the biopsy.

Transbronchial lung biopsy (TBLB) is frequently diagnostic in certain forms of ILD for example granulomatous lung disease, but in most cases, the tissue retrieved is often inadequate or nondiagnostic (6), and the risk of complications are higher with TBLB than with BAL (7,8).

The American Thoracic Society practice guidelines (9) state that there is insufficient data to confirm that BAL cell analysis is beneficial in the diagnosis of certain types of ILD and, therefore it is impossible to fully weigh the potential benefits against the risks, costs, and burdens of the procedure. The decision to perform BAL should be made on a case by case basis.

Hospital Course Continued

VATS was cancelled in favor of conservative management due to his high peri-operative risk. He was pulsed with high dose steroids with no improvement and broad spectrum antibiotics were also empirically initiated.

For the next 10 days, the patient was often transferred back and forth between ICU and step down unit due to hypoxia. Finally, as he was not improving and was too ill for surgical biopsy, bronchoscopy with BAL and transbronchial biopsy was obtained demonstrating normal airways and only non-specific fibrosis.

Azathioprine 50mg/day was initiated as a last resort. He received Azathioprine for two weeks with no improvement in hypoxia. He was transitioned to 100% on non-rebreather mask in the ICU still worsening dyspnea and positional desaturation.

He was not a candidate for lung transplantation due to his severe cirrhosis and was ruled out for liver transplantation due to his untreated active Hepatitis C.

Would a surgical lung biopsy have ***changed his treatment course***?

1. Yes
2. No

Correct!
2. No

While establishing a correct diagnosis in patients with ILD is of paramount importance, one recent study (10) demonstrated that in the majority of patients with undefined ILD, surgical lung biopsy does not lead to a therapeutic change. An accurate diagnosis of a specific type of interstitial lung disease (ILD) requires a multidisciplinary approach working closely with a pathologist, radiologist and pulmonologist that involves obtaining a complete patient history, careful physical examination, laboratory testing and thoracic imaging (11).

Case Conclusion

Goals of care discussions occurred at several points during his ICU stay and on hospital day 40, following his failed trial of azathioprine and corticosteroids, palliative care was consulted and he was transitioned to hospice.

Based on his clinical course and imaging, what is the ***likely diagnosis***?

1. Cryptogenic organizing pneumonia (COP)
2. Desquamative interstitial pneumonia (DIP)
3. Hypersensitivity pneumonitis (HP)
4. Idiopathic interstitial fibrosis (IPF)
5. Nonspecific interstitial pneumonitis (NSIP)

Correct!
5. Nonspecific interstitial pneumonitis (NSIP)

This case is most suggestive of NSIP. Like IPF, NSIP usually presents with chronic dyspnea and cough. Patients typically present between age 40 and 50. HRCT scan reveals ground-glass abnormality, most commonly bilateral and subpleural in distribution with lower lobe volume loss. Patchy areas of airspace consolidation and reticular abnormalities may be present. Honeycombing and traction bronchiectasis as seen in IPF is rare. However there is a continuum of findings in NSIP, with some cases radiographically indistinguishable from IPF (12).

The surgical lung biopsy in NSIP is characterized by varying degrees of inflammation and fibrosis, with some biopsies showing a predominance of inflammatory changes ("cellular" pattern) and others a predominance of fibrotic reaction ("fibrotic" pattern). UIP has more of a temporal heterogeneous pattern.

Hypersensitivity pneumonitis is unlikely as not only did he not respond to corticosteroids, he was removed from his home environment and any likely inciting factors during his prolonged hospital admission without any improvement in his symptoms.

Cryptogenic organizing pneumonia (COP) is also unlikely as this usually presents in an acute to subacute form with HRCT demonstrating a predominance of bilateral, patchy consolidation, most commonly with a subpleural or peribronchial distribution. Unlike this case, it often has an excellent clinical response to corticosteroids with improved survival compared with IPF.

While desquamative interstitial pneumonia (DIP) will present in smokers in their 30s and 40s, it usually demonstrates more diffuse ground-glass abnormality on HRCT with a histopathological feature of pigment-laden macrophages. Many cases of DIP resolve with smoking cessation and corticosteroids and the prognosis is generally good.

References

1. Raghu G, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: A prospective study. Chest. 1999;116(5):1168-74. [CrossRef] [PubMed]
2. Luo Q, Han Q, Chen X, Xie J, Wu L, Chen R. The diagnosis efficacy and safety of video-assisted thoracoscopy surgery (VATS) in undefined interstitial lung diseases: a retrospective study. J Thorac Dis 2013;5(3):283-8. [PubMed]
3. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM, Plevak DJ, Talwalkar JA, Kim WR, Kamath PS. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology. 2007;132:1261–9. [CrossRef] [PubMed]

4. Park JH, Kim DK, Kim DS, Koh Y, Lee SD, Kim WS, Kim WD, Park SI. Mortality and risk factors for surgical lung biopsy in patients with idiopathic interstitial pneumonia. Eur J Cardiothorac Surg. 2007;31(6):1115-9. [CrossRef] [PubMed]
5. Ramakrishna G, Sprung J, Ravi BS, Chandrasekaran K, McGoon MD. Impact of pulmonary hypertension on the outcomes of noncardiac surgery: predictors of perioperative morbidity and mortality. J Am Coll Cardiol. 2005;45(10):1691-9. [CrossRef] [PubMed]
6. Berbescu EA, Katzenstein AL, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. Chest 2006;129:1126-31. [CrossRef] [PubMed]
7. Ahmad M, Livingston DR, Golish JA, Mehta AC, Wiedemann HP. The safety of outpatient transbronchial biopsy. Chest 1986;90:403-5. [CrossRef] [PubMed]
8. Simpson FG, Arnold AG, Purvis A, Belfield PW, Muers MF, Cooke NJ. Postal survey of bronchoscopic practice by physicians in the UK. Thorax 1986;41:311-7. [CrossRef] [PubMed]
9. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, Drent M, Haslam PL, Kim DS, Nagai S, Rottoli P, Saltini C, Selman M, Strange C, Wood B; American Thoracic Society Committee on BAL in Interstitial Lung Disease. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Resp Crit Care Med 2012;185(9):1004-14. [CrossRef] [PubMed]
10. Blackhall V, Asif M, Renieri A, Civitelli S, Kirk A, Jilaihawi A, Granato F. The role of surgical lung biopsy in the management of interstitial lung disease: experience from a single institution in the UK. Interact Cardiovasc Thorac Surg. 2013;17(2): 253-7. Published online 2013 May 14. [CrossRef] [PubMed]
11. Flaherty KR, King TE Jr, Raghu G, Lynch JP 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170:904–910. [CrossRef] [PubMed]
12. Collard HR, King, Jr. TE. Chapter 10. Idiopathic Interstitial Pneumonia. In: Hanley ME, Welsh CH, eds. CURRENT Diagnosis & Treatment in Pulmonary Medicine. New York: McGraw-Hill; 2003. http://www.accessmedicine.com.mlprox.csmc.edu/content.aspx?aID=575919 Accessed November 16, 2013.