July 2012 Pulmonary Case of the Month: Pulmonary Infiltrates - Getting to the Heart of the Problem

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**History of Present Illness**

A 63 year old man was transferred from outside facility with ventricular tachycardia. He has a past history of ventricular tachycardia and had an intracardiac defibrillator (ICD) placed due to a low ejection fraction. The ICD had administered several shocks to the patient prior to admission.

His present medications included:
- Lisinopril 10 mg bid
- Diazepam 10 mg bid
- Amiodarone 400 mg daily
- Dutasteride 0.5 mg daily
- Tamsulosin 0.4 mg daily
- Dexlansoprazole 60 mg daily
- Levothyroxine 100 mcg daily

The patient underwent and electrophysiology (EP) procedure. He was intubated prior to the procedure. He developed sustained ventricular tachycardia when the ICD was turned off. Eleven cardioversions were required with an accumulated 108 seconds of ventricular tachycardia. He became hypotensive and received 6.2 L boluses of fluids and 5, 400 mg boluses of amiodarone and was placed on an amiodarone drip.

He remained intubated receiving mechanical ventilator after the EP procedure. He was extubated after 2 days and was initially on oxygen at 6L/min nasal cannula. Over the next several days he developed increasing oxygen requirements and was treated with BiPAP and increasing oxygen.

**PMH, SH and FH**

As noted above he had a history of recurrent ventricular tachycardia and a dilated cardiomyopathy with an ejection fraction of 30-35%. In addition he had a history of paroxysmal atrial fibrillation, obstructive sleep apnea which resolved with weight loss, hypothyroidism and mild restriction on pulmonary function.
testing, possibly related to amiodarone or to kyphosis. He is a life-long nonsmoker.

**Physical Examination**

His vital signs included a Tmax of 38.8 C, heart rate of 79 beats/min, blood pressure of 113/67 mm Hg, respiratory rate of 38 breaths/min, and oxygen saturation of 94% on a 75% high flow mask. His weight had increased to 102 kg from 96.6 kg on admission.

Cardiovascular exam revealed an irregular rhythm but no murmur. There was jugular venous distention present. There was a trace of pedal edema but deeper pitting edema at the hips.

Pulmonary auscultation revealed bilateral rales with diminished breath sounds at the bases.

**Chest X-ray**

Admission and current chest x-ray are shown in Figure 1.

![Figure 1. Admission chest x-ray (panel A) and current chest x-ray (panel B).](image)

**Laboratory Evaluation**

Arterial blood gases showed a pH of 7.42, a pCO₂ of 39 and a pO₂ of 73 on 70% FiO₂. The white blood cell count (WBC) was elevated at 15.1X10³ cells/mm³.

Which of the following could explain the patient’s increased oxygen requirements?

1. Pulmonary edema
2. Pneumonia
3. Amiodarone lung toxicity
4. A + B
5. A + C
6. All of the above
Correct!

6. All of the above

Pulmonary edema is possible from either a cardiac cause because of his history of heart failure and his positive fluid balance or from a noncardiac cause. Pneumonia is possible with his fever, elevated WBC and clinical situation of recent intubation. Amiodarone lung toxicity given the large amount he has received and can present with an acute syndrome which mimics pulmonary edema or pneumonia.

A CT scan was performed (Figure 2).

![CT scan images](image)

Figure 2. Representative images from the CT scan.
What should be done next?
   1. Right heart catheterization
   2. Bronchoscopy
   3. Antibiotics
   4. Steroids
   5. Diuresis
   6. Lung Biopsy
Correct!
3. Antibiotics
5. Diuresis

Broad spectrum antibiotics for possible hospital acquired pneumonia would seem appropriate as would diuresis for possible cardiogenic pulmonary edema. Neither right heart catheterization nor bronchoscopy are wrong but seem overly aggressive at this time. Steroids would not seem appropriate in the absence of a diagnosis and open lung biopsy seems overly aggressive at this stage.

The patient received piperacillin/tazobactam, levofloxacin and vancomycin were started. His WBC decreased to $10^3$ cells/mm$^3$ and his fever resolved. He received diuresis with furosemide and his weight decreased by 2 kg. However, he failed to clinically improve.

Because of his failure to improve right heart catheterization was performed with the major results below:
- Pulmonary artery pressure: 36/16 (24 mean) cm H$_2$O
- Wedge: 16 cm H$_2$O
- Cardiac output: 5.8 L/min

His CT scan was repeated (Figure 3).

![CT Scan Images]

Figure 3. Representative images from the repeat CT scan. What should be done next?
1. Bronchoscopy
2. Empirically switch antibiotics
3. Add amphotericin B
4. Steroids
5. Lung Biopsy
In our view bronchoscopy is the next logical choice. Switching antibiotics or adding amphotericin would not seem appropriate with the patient becoming afebrile and a decreasing WBC. Steroids for amiodarone toxicity is not wrong but this is a diagnosis of exclusion and other causes have not been totally excluded. Lung biopsy is not wrong but does seem overly aggressive since not all less invasive procedures have been performed.

Bronchoscopy showed purulence noted at the left lower lobe orifice. Bronchoalveolar lavage was performed of the right middle lobe (due to the CT findings) and washings were performed of the left lower lobe.

All the cultures were negative. Cytology revealed no malignancy, fungi or viral inclusions.

Because the diagnosis was still unclear a video-assisted thorascopic (VATS) biopsy was performed (Figure 4).

Figure 4. VATS showing organizing acute lung injury; prominent foci of organizing pneumonia; and prominent foamy alveolar macrophages. Special stains for organisms were negative.
Which of the following explain the patient’s clinical picture?
1. Cardiogenic pulmonary edema
2. Pneumonia
3. Amiodarone lung toxicity
4. Noncardiac pulmonary edema (ARDS)
5. More than one of the above
Amiodarone lung toxicity is a clinical diagnosis made with a compatible clinical situation, absence of other likely diagnosis and compatible pathology. This case would fulfill all criteria.

The incidence of amiodarone toxicity is estimated at 1-15%. Risk factors include:
- Age (3x for every 10 years >60 years)
- Male gender (HR 1.37)
- Underlying lung disease
- Thoracic surgery
- Pulmonary angiography
- Dose...

The highest risk is in men over the age of 60 years on who have received amiodarone for 6-12 months. Dose associations can be either accumulative or daily dosing. With higher daily doses (>400mg) there is a 5-15% incidence but with lower doses used today (<400 mg) the incidence is about 2%.

Several types of lung injury have been reported including:
- Chronic Diffuse Interstitial Pneumonitis (similar to NSIP or IPF)
- Organizing Pneumonia
- Acute rapidly-progressive diffuse pneumonitis
- ARDS
- Nodules
- Pleural thickening

Clinically 50-75% of patients have progressive dyspnea and nonproductive cough. There may be fever, pleurisy, or weight loss. Physical exam shows hypoxia and bilateral rales. Usually there is no clubbing.

Laboratory findings are nonspecific. KL-6, a mucinous high-molecular weight glycoprotein, expressed on type II pneumonocytes, is often elevated in the serum of patients with amiodarone toxicity, but is nonspecific, being elevated in most active interstitial pneumonias. Amiodarone levels are not useful in diagnosing amiodarone lung toxicity.

Pulmonary function testing usually shows a restrictive pattern with a low FVC, TLC and DLCO. A stable DLCO suggests amiodarone toxicity is unlikely while a decrease of 15% or more is suggestive, but not diagnostic.

Chest x-ray and CT scans may have alveolar, interstitial or mixed opacities. In the case of organizing pneumonia the opacities may be migratory. Pleural effusions are rare.
On bronchoalveolar lavage the inflammatory cell types are highly variable with lymphocytes, neutrophils and eosinophils all reported. Foamy macrophages are present in 50% of patients on amiodarone and are not specific for pulmonary toxicity. However, if absent, amiodarone toxicity is unlikely.

Diagnosis may be made with typical history, clinical findings and imaging and the exclusion of other clinical syndromes cardiogenic pulmonary edema, infection, pulmonary embolus and noncardiogenic pulmonary edema (ARDS). Lung biopsy may be necessary when the diagnosis is unclear.

Which of the following are not recommended therapies for amiodarone lung toxicity?

1. Stopping amiodarone administration
2. Supportive care
3. Corticosteroids
4. Lung transplantation
4. Lung transplantation

Removal of the offending agent is usually recommended although amiodarone has a very long elimination half-life and this alone is often ineffective. Of course, supportive care is recommended but the mainstay of therapy is corticosteroids. These are usually initiated at 0.5-1 mg/kg and tapered gradually as tolerated over 2-6 months. Symptoms can recur during taper and returning to the last effective dose and then slowly tapering is recommended.

Therapy for our patient was initiated with high-dose corticosteroids which resulted in improved oxygenation. However, he developed subcutaneous emphysema with a persistent airleak, volume overload requiring hemofiltration, elevated liver function tests, thrombocytopenia, and functional deficits requiring rehabilitation.

He slowly improved on tapering doses of prednisone and had no recurrence of symptoms. His SpO₂ is 95% on room air and is walking 1000 feet and doing 30 deep knee bends without dyspnea. He has no recurrence of his ventricular tachycardia.

References