November 2013 Critical Care Case of the Month: A Series of Unfortunate Infections

***Kenneth K. Sakata, MD
Karen L. Sapienza, MD
Lewis J. Wesselius, MD***

Department of Pulmonary Medicine
Mayo Clinic Arizona
Scottsdale, AZ

History of Present Illness

A 22 year old man was admitted with fever for 2 weeks. He had a history of acute lymphocytic leukemia (ALL) and had received a stem cell transplant in (SCT) in May 2013.

PMH, SH, FH

Other than the ALL and STC transplant there was no significant PMH, SH, or FH. The STC was uneventful.

Physical Examination

T 38.6°C with a pulse of 110 beats/min. Otherwise the physical examination was unremarkable.

CT scan

A CT scan of the thorax was performed in a search for the source of the fever (Figure 1).

Figure 1. Admission thoracic CT scan showing an abnormality. The remainder of the CT scan was unremarkable.

Which of the following **best describes** the CT abnormality?

1. Chest wall abnormality in the left chest
2. Focal area of consolidation in the left lung
3. Focal area of consolidation in the right lung
4. Mass in the left lung
5. Mass in the right lung

Correct!

2. Focal area of consolidation in the left lung

By convention the CT scan is presented as if viewing the patient from the feet towards the head. Therefore, the abnormality is in the left lung (Figure 2).

Figure 2. Same as figure 1 with the abnormality circled in red.

The abnormality is rounded and has fuzzy margins. This could be solitary mass but in a bone marrow transplant patient with fevers the overwhelming likelihood is this is a focal area of consolidation.

Which of the following is the **next best step** for diagnosis?

1. Bronchoscopy with bronchoalveolar lavage (BAL)
2. Bronchoscopy with transbronchial biopsy (TBBx)
3. Needle biopsy of the mass
4. Observation with serial CT scans
5. Video-assisted thorascopic biopsy (VATS)

Correct!

1. Bronchoscopy with bronchoalveolar lavage

Bronchoscopy with bronchoalveolar lavage (BAL) is the procedure of choice in patients who have received a bone marrow transplant (1). It can be safely performed in most patients. Transbronchial biopsy (TBBx) can be performed but bone marrow transplant patients are often thrombocytopenic and TBBx usually adds little above BAL except for cytomegalovirus (CMV) pneumonia. Video-assisted thorascopic (VATS) biopsy can be performed but usually BAL is performed first and VATS performed later if the diagnosis is pursued. Following patients with serial CT scans should only be done with great caution. Immunocompromised patients can become critically ill rapidly and delay may increase the risk for diagnostic procedures. Needle biopsy can also be done but again patients are often thrombocytopenic and needle biopsy in disorders which compromise the pulmonary circulation can result in disastrous intrathoracic hemorrhage.

The BAL cultures showed *E. coli*, Legionella, rhinovirus, and adenovirus.

What should be **done next?**

1. Blood cultures
2. Ampicillin for *E. coli* and Legionella
3. Cidofovir for adenovirus
4. 1 and 3
5. All of the above

Correct!
4. 1 and 3

Blood cultures are a standard of care for febrile immunocompromised patients. They can provide additional evidence to separate a contaminant or colonizing organism from an invasive organism, especially when the BAL cultures show multiple organisms. Another source of information can be quantitative cultures.

The patient had a positive blood culture *E. coli* and *Enterococcus faecium*. Unfortunately, the *E. coli* in both the BAL and blood was an extended-spectrum beta-lactamase (+ESBL) organism and ampicillin would likely be ineffective. Usually, a macrolide (azithromycin, erythromycin, clarithromycin, etc.) is the drug of choice for *Legionella* although other drugs such as the tetracyclines and flouroquinolones can be used.

The patient also had a positive blood culture for adenovirus. Quantitative PCR of the blood showed >2,000,000 copies/ml. Cidofovir is an injectable antiviral medication. It suppresses viral replication by selective inhibition of viral DNA polymerase. Cidofovir is the most commonly prescribed drug for adenovirus infection although no controlled trials have been performed (2).

At about this time, the patient was noted to have increasing alanine aminotransferase (ALT) and aspartate aminotransferase (AST), both rising to >5000 units/L. Hepatology was consulted and a liver biopsy was performed (Figure 3).

Figure 3. H & E stains of liver biopsy.

What is the **likely cause** of the abnormal liver enzymes?

1. Adenoviral hepatitis
2. CMV hepatitis
3. Drug-induced hepatitis
4. Graft versus host disease
5. Reactivation of hepatitis B

Correct!
1. Adenoviral hepatitis

There are a number of viral inclusions on the liver biopsy (Figure 4).

Figure 4. Liver biopsy showing multiple viral inclusions (arrows).

Viral inclusions are nuclear or cytoplasmic aggregates of stainable viral capsid proteins. They are a nonspecific finding and can be seen in a number of viral diseases. These in the liver are very similar to those observed in the lung.

In this patient's case the presence of viral inclusions is consistent with hepatitis complicating his known adenoviral infection.

In a series of 89 definite cases of adenoviral hepatitis, 43 (48%) were in liver transplant recipients and 19 (21%) in BMT recipients. Ninety percent of the cases presented within 6 months of transplant. Only 27% survived with only 2 of the 19 BMT recipients surviving.

Which of the following are **therapeutic options**?

1. Adenovirus specific cytotoxic T cells
2. Cidofovir
3. Liver transplant
4. Reduction in immunosuppression
5. All of the above

Correct!
5. All of the above

There is no proven effective treatment for adenoviral hepatitis (4). Ribavirin and cidofovir have been utilized in anecdotal cases but require further study. Similarly, anecdotal reports of liver transplantation and reduction in immunosuppression have resulted in improvement.

Our patient was already receiving cidofovir and was not judged to be a candidate for liver transplantation or a reduction in immunosuppression. He was endotracheally intubated on hospital day 3 with progressive liver, renal, and respiratory failure, and unfortunately, died on hospital day 5

References

1. Yen KT, Lee AS, Krowka MJ, Burger CD. Pulmonary complications in bone marrow transplantation: a practical approach to diagnosis and treatment. Clin Chest Med. 2004;25(1):189-201. [\[CrossRef\]](#)
2. Matthes-Martin S, Feuchtinger T, Shaw PJ, Engelhard D, Hirsch HH, Cordonnier C, Ljungman P. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECIL-4 (2011). Transpl Infect Dis. 2012;14(6):555-63. [\[CrossRef\]](#) [\[PubMed\]](#)
3. McDonald GB, Shulman HM, Wolford JL, Spencer GD. Liver disease after human marrow transplantation. Semin Liver Dis. 1987;7(3):210-29. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Ronan BA, Agrwal N, Carey EJ, De Petris G, Kusne S, Seville MT, Blair JE, Vikram HR. Fulminant hepatitis due to human adenovirus. Fulminant hepatitis due to human adenovirus. Infection. 2013 Aug 24. [Epub ahead of print]. [\[CrossRef\]](#) [\[PubMed\]](#)