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Acute Cardiopulmonary Failure in a Young Man*

Hisham Hamam, MD; Bruce A. Greenberg, MD, MBA, FCCP; Gunther Hsue, MD; and Stuart A. Roop, MD, FCCP

A previously healthy 24-year-old man presented with a 2-day history of fever, myalgias, nausea, and vomiting. On the morning of hospital admission, cough and progressive dyspnea developed in the patient. He denied other symptoms, including chest pain, abdominal pain, or sore throat. This military recruit had been participating in field training in southern New Mexico for 2 weeks prior to presentation and had previously been living in Maricopa County, AZ. He lived in field barracks but denied sick contacts, and no other members of his unit were ill. He reported no contact with household or farm animals, rabbits, birds, or toxins, and he denied the use of illicit drugs.

Physical Examination

At presentation, he had a pulse rate of 130 beats/min, BP of 130/85 mm Hg, a respiratory rate of 36 breaths/min, and a temperature of 39.3°C. The patient was alert but in moderate respiratory distress. Chest auscultation revealed bilateral rales in the middle and lower lung fields. The cardiac examination findings were normal except for tachycardia. There was no jugular venous distention, peripheral edema, skin rash, or nodules. The conjunctiva were normal.

Laboratory and Radiographic Findings

The hemogram showed a WBC count of 24,400 cells/µL, a hemoglobin concentration of 19 g/dL, and a platelet count of 89,000 cells/µL. The manual differential count of peripheral blood leukocytes showed 66% segmented neutrophils, 22% band forms, 5% normal lymphocytes, and 5% atypical lymphocytes. Coagulation study findings and albumin concentration (3.7 g/dL) were normal; aspartate aminotransferase concentration was 76 IU/L, creatinine concentration was 1.3 mg/dL, and arterial blood gas measurements with the patient breathing room air showed the following: pH, 7.46; PCO₂, 22 mm Hg; PO₂, 47 mm Hg; and oxygen saturation, 77%.

Chest radiographic findings revealed bilateral infiltrates involving all lung fields (Fig 1). A contrast-enhanced CT scan of the chest showed no embolism;
the lung fields demonstrated dense alveolar consolidation bilaterally with relative sparing of the peripheral lung fields (Fig 2).

Hospital Course

Cultures were taken from blood and sputum, and therapy with broad-spectrum antibiotics were started in the emergency department. An empiric dose of methylprednisolone, 125 mg IV, was given. Within 6 h of arrival, the patient required mechanical ventilation for treatment of hypoxic respiratory failure. Copious clear-yellow secretions were suctioned from the endotracheal tube following intubation, with a total accumulation of 1.5 L over 3 h. Hypoxia worsened, with a PaO\textsubscript{2} of 50 mm Hg despite high mean airway pressures and a fraction of inspired oxygen of 100%. The patient’s BP progressively declined, requiring fluid resuscitation and increasing vasopressor support. Bedside echocardiography showed a normal left ventricular ejection fraction and no pericardial effusion. Repeat laboratory studies showed the following: hemoglobin concentration, 21.6 mg/dL; albumin concentration, 1.9 g/dL; and platelet count, 66,000 cells/\mu L. His circulatory and respiratory compromise worsened despite aggressive treatment, and he died within 10 h of initial presentation.

Pathology Findings

Lung specimens taken at autopsy revealed bilateral pleural effusions, ARDS with acute hemorrhagic alveolitis, and fibrin strands with hyaline membranes in the alveolar spaces (Figs 3, 4). There were no viral cytopathologic findings, and there were few leukocytes in the alveolar spaces. The heart was normal.

What is the diagnosis?
What is the test of choice?
What is the treatment?
Diagnosis: Hantavirus pulmonary syndrome
Test of choice: Serology for IgM directed against Hantavirus
Treatment: Supportive care

Discussion

The following two forms of Hantavirus infection have been described in humans: hemorrhagic fever with renal syndrome; and the Hantavirus pulmonary syndrome (HPS). HPS was first recognized in 1993 in the four-corners region of the southwestern United States. The virus is shed in the urine, feces, or saliva of rodents of the family Muridae, and transmission to humans occurs via the inhalation of aerosolized rodent excreta. Person-to-person transmission has not been reported in the United States, but a few cases have been described in Argentina and Chile involving a specific strain, Andes virus. Sin Nombre virus (SNV), a Hantavirus common in the southwestern United States, is associated with a severe form of HPS that has a case fatality rate of 40 to 50%. The reservoir for SNV is the deer mouse (Peromyscus maniculatus), which is one of the most common small mammals in the United States. Most cases of HPS occur during the spring and summer months, though, depending on climate conditions, patients may present in the winter months. Our patient died in February.

HPS has been seen in patients aged 10 to 75 years, with both sexes equally represented. The disease typically progresses from a nonspecific febrile prodrome to a fulminant cardiopulmonary phase, followed by a recovery phase in survivors. Following an incubation period of about 2 to 3 weeks (range, 14 to 32 days), the prodrome phase is characterized by fever, chills, myalgias, and headache. Nausea, vomiting, and malaise can also be seen, but some classic features of upper respiratory tract infection such as rhinorrhea and pharyngitis are absent. Early laboratory findings may be normal, but thrombocytopenia and increased serum lactate dehydrogenase levels can be seen. The prodrome phase usually lasts 2 to 5 days.

A cough (initially nonproductive) typically signals the transition to the cardiopulmonary phase, in which a fulminant capillary leak syndrome leads to rapidly progressive pulmonary edema and shock. As seen in our patient, this transition can occur rapidly, in as little as 4 h, and has led to recommendations for the transfer of these patients to tertiary care centers at the earliest signs of HPS. Bronchorrhea with copious proteinaceous edema fluid, with or without diffuse alveolar hemorrhage, can be seen. Labora-

tory findings during this phase include marked leukocytosis with a leftward shift, worsening thrombocy-

topenia, elevated serum lactate dehydrogenase and aspartate aminotransferase, hemoconcentration, and low serum albumin due to capillary leak. Additional findings on the peripheral blood smear that are highly suggestive of HPS include a relative lack of toxic granulation of the neutrophils, and immuno-

blasts accounting for ≥10% of the total lymphocyte population. An elevated serum lactate level, which is associated with poor outcome, can be seen in severe cases; in one early series, all patients with a peak serum lactate concentration of >4 mmol/L died.

The definitive diagnosis of HPS relies on the demonstration of Hantavirus antibodies in blood or tissue samples. Once symptomatic, patients uniformly have anti-Hantavirus IgM. Few centers have onsite testing, so a presumptive diagnosis based on exposure history and clinical presentation is usually necessary to guide therapy. There is no effective antiviral therapy for HPS, with a controlled trial of IV ribavirin in North America showing no benefit. ICU support with mechanical ventilation, the early use of pressors, and the avoidance of volume over-

load are recommended. Extracorporeal membrane oxygenation has been used for treatment in centers where it can be initiated expeditiously; it seems to be associated with improved outcomes in patients with severe hypoxemia and depressed cardiac function.

Prevention is the most effective intervention, and is based on good personal hygiene, rodent control in areas of human habitation, and use of a mask and protective clothing when working around areas with

| Table 1—Differential Diagnosis of Fever and Rapidly Progressive Cardiopulmonary Disease |
|-----------------------------------------------|
| **Infectious diseases** | Severe community-acquired pneumonia |
| | Q fever (Coxiella burnetti) |
| | Viral pneumonia (eg, influenza, cytomegalovirus, and severe acute respiratory syndrome) |
| | Hantavirus |
| | Dengue fever/yellow fever |
| | Plague (Yersinia pestis) |
| | Tularemia (Franciella tularensis) |
| | Leptospirosis (Leptospira interrogans) |
| **Noninfectious diseases** | Acute eosinophilic pneumonia |
| | Rapid-onset interstitial lung disease (eg, acute interstitial pneumonia, cryptogenic organizing pneumonia, and acute hypersensitivity pneumonitis) |
| | ARDS due to other causes (eg, drug overdose, drug reaction, or inhalation injury) |
| | Vasculitides (eg, Wegener granulomatosis, Goodpasture disease, or catastrophic antiphospholipid antibody syndrome) |
known rodent excretions. Dormant buildings should be aired out prior to entry, with appropriate cleaning of heavily infested areas.

The differential diagnosis for acute cardiopulmonary failure in a previously healthy patient is listed in Table 1. Our patient presented at the onset of the cardiopulmonary phase of HPS, and demonstrated the classic fulminant progression to ARDS and shock. Serum IgM directed against SNV (HN107 strain) drawn at hospital admission was markedly elevated, with a positive titer seen out to a 1:12,800 dilution (by enzyme-linked immunosorbent assay; optical density values of >0.2 were considered to be positive). The findings of IgG and all other cultures and serologies were negative.

**Clinical Pearls**

1. HPS should be considered in the differential diagnosis for patients presenting with acute onset of fever, dyspnea, cough, hypoxemia, diffuse pulmonary infiltrates, and potential exposure to rodents in Hantavirus endemic areas.

2. Thrombocytopenia may be an early finding during the prodromal phase of HPS.

3. Aggressive supportive care is needed, and early transfer to a tertiary care facility, preferably with extracorporeal membrane oxygenation capabilities, should be considered.

4. The definitive diagnosis of Hantavirus is serologic, but clinical and hematologic findings should provide a presumptive diagnosis.

5. Prevention of human exposure to aerosolized rodent urine and feces is the major mechanism of disease control.

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**Suggested Readings**

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