

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 40-2009: A 29-Year-Old Man with Fever and Respiratory Failure

Timothy M. Uyeki, M.D., M.P.H., M.P.P., Amita Sharma, M.D.,
and John A. Branda, M.D.

PRESENTATION OF CASE

From the Epidemiology and Prevention Branch, Influenza Division, Centers for Disease Control and Prevention, Atlanta (T.M.U.); and the Departments of Radiology (A.S.) and Pathology (J.A.B.), Massachusetts General Hospital; and the Departments of Radiology (A.S.) and Pathology (J.A.B.), Harvard Medical School — both in Boston.

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Dr. Wilson Tak-Yu Kwong (Medicine): A 29-year-old man was admitted in July 2009 to the critical care unit of this hospital because of fever and respiratory failure.

The patient had been well until 9 days earlier, when a nonproductive cough and myalgias in his legs developed. One week before admission, he had a temperature of 39.4°C, associated with headache. During the next week, sore throat and nasal congestion developed, the cough became productive of clear sputum, and he noted mild chest pain under his ribs during inspiration. Four days before admission, he was seen at the emergency department of another hospital. He did not have neck pain or photophobia. He reported finding a tick on his scalp 1 month earlier. On examination, he appeared in mild distress. The temperature was 38.2°C and the pulse 106 beats per minute; the remainder of the examination was normal. A rapid test of a specimen from a buccal swab was negative for influenza A and B antigens, and no parasites were seen on a peripheral-blood smear; other test results are shown in Table 1. Acetaminophen, ketorolac, and ceftriaxone were administered, and normal saline was infused. Doxycycline was prescribed, and he was discharged.

The patient returned the next afternoon because of persistent fever, cough, myalgias, low back pain, and new scrotal pain. The temperature was 39.0°C, and the other vital signs were normal. There were rhonchi in the left lower lung field, and the remainder of the examination was normal. A test for Lyme disease, sent the day before, was negative. Other test results are shown in Table 1. A chest radiograph showed incomplete segmental consolidation of the apical posterior segment of the right upper lobe and right hilar prominence, features suggestive of pneumonia and lymphadenopathy, respectively. Levofloxacin was prescribed, and he was sent home.

During the next 2 days, nausea and vomiting developed, with blood-tinged emesis. One day before admission to this hospital, the patient returned to the other hospital. The temperature was 38.6°C, the blood pressure 135/70 mm Hg, the pulse 113 beats per minute, the respiratory rate 34 breaths per minute, and the oxygen saturation 88% while he was breathing 4 liters of oxygen by nasal cannula. A chest radiograph revealed progression of the process in the right upper

lobe and patchy air-space disease in the right lower lobe and the middle and lower lobes on the left side. Nucleic acid testing for *Babesia microti* and *Anaplasma phagocytophilum* and testing for serum antibodies to *Borrelia burgdorferi*, sent 3 days earlier, were negative. A rapid screening test for pharyngitis due to group A streptococcus and review of a blood smear for parasites were negative; other results are shown in Table 1. He was admitted to the hospital. Doxycycline, levofloxacin, gentamicin, ibuprofen, acetaminophen, ondansetron, guaifenesin-codeine cough syrup, and ranitidine were administered. Respiratory distress worsened. Testing for antibodies to *Francisella tularensis* was negative. Approximately 14 hours after admission, he was transferred to this hospital by helicopter and admitted to the critical care unit.

The patient reported transient arthralgias in his ankles and knees, which had resolved; he had not had rash, lymphadenopathy, visual symptoms, diarrhea, dysuria, hematuria, or bruising. He had been well before the illness. He lived with his wife in a rural area in southern New England that has a high rate of tickborne illness. Two weeks earlier, he had been exposed to a child with an upper respiratory infection who had been visiting from the southeastern United States; there were no other exposures to ill persons and no recent travel. He worked indoors and outdoors, and except for the tick, he had no recent history of insect bites or exposure to animals. He had swum in the ocean but not in fresh water, and he had cleaned fish 2 weeks earlier. He did not drink alcohol, smoke, or use illicit drugs. On examination, he appeared ill and dyspneic. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 26.6. The temperature was 37.3°C, the blood pressure 119/68 mm Hg, the mean arterial pressure 93 mm Hg, the pulse 108 beats per minute, the respiratory rate 29 breaths per minute, and the oxygen saturation 92 to 95% while he was breathing 50% inspired oxygen. There were rhonchi in both lung bases and occasional wheezes; the remainder of the examination was normal. Tests for tularemia agglutination, Rocky Mountain spotted fever, typhus, heterophile antibodies, and antibodies to the human immunodeficiency virus and *B. burgdorferi* were negative, as was nucleic acid testing for anaplasma and ehrlichia. Multi-

ple tests of nasopharyngeal secretions for influenza viruses, parainfluenza virus, respiratory syncytial virus, and adenovirus and tests of the urine for legionella and histoplasma antigens were negative. Testing for antibodies to toxoplasma was suggestive of past infection. No malarial or babesial forms were seen on peripheral-blood smears. Cultures of specimens of blood, urine, and sputum were sterile. Other results are shown in Tables 1 and 2. Urinalysis revealed clear yellow urine with a pH of 5.5, a specific gravity of 1.005, 1+ ketones, 2+ blood, 1+ albumin, and 0 to 2 red cells and 3 to 5 white cells per high-power field. A chest radiograph showed low lung volumes, with air-space disease in the right upper and middle lung and the left lower lung and elevation of the right minor fissure, features consistent with multifocal pneumonia. An electrocardiogram showed sinus tachycardia and was otherwise normal. Oral levofloxacin; intravenous vancomycin, gentamicin, and doxycycline; and oral oseltamivir (150 mg twice daily) were administered.

During the first 6 hours, dyspnea and respiratory distress worsened; the respiratory rate was 24 to 26 breaths per minute, with 85 to 90% oxygen saturation while he was breathing 100% oxygen through a face mask that prevents re-breathing. Nine hours after arrival, computed tomography (CT) of the chest, without the administration of contrast material, showed extensive bilateral multifocal asymmetric consolidation involving all lobes, trace pleural effusion on the right, and multiple enlarged mediastinal or hilar lymph nodes (up to 1.3 cm in diameter). Within 18 hours after arrival, tachypnea increased further; the partial pressure of oxygen was 58 mm Hg while he was breathing high-flow oxygen, and the trachea was intubated. The partial pressure of oxygen rose to 83 mm Hg while the patient was being ventilated with 100% oxygen. A central venous catheter was placed, a feeding tube inserted, and parenteral nutrition begun. The maximum temperature was 39.4°C.

On the second day, hypoxemia (Table 2) and renal failure (Table 1) developed and urine output fell to 20 to 30 ml per hour. Transthoracic echocardiography showed an ejection fraction of 50% and was otherwise normal. Microscopical examination of the urine sediment revealed white-cell casts and granular casts, with tubular cells

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Other Hospital				This Hospital			
		4 Days before Admission	3 Days before Admission	1 Day before Admission	Day of Admission	On Admission	2nd Day	3rd Day (Morning)	3rd Day (Evening)
Hematocrit (%)	41.0–53.0 (men)	42	45	44	41.5	38.2	38.1	40.7	42.1
Hemoglobin (g/dl)	13.5–17.5 (men)	14.5	15.1	15.3	14.2	13.4	13.7	14.6	15.1
White-cell count (per mm ³)	4,500–11,000	4,400	4,000	3,200	2,200	2,300	4,700	8,800	9,000
Differential count (%)									
Neutrophils	40–70	79	71	86	79	69	54	92	82
Band forms	0–10	0				19	18	4	10
Lymphocytes	22–44	13	21	10	17	11	21	3	4
Atypical lymphocytes	0	0		0	0	0	1	0	0
Monocytes	4–11	6	7	3	4	1	5	1	4
Eosinophils	0–8	1	0	0	0	0	0	0	0
Basophils	0–3	0	1	0	0	0	0	0	0
Metamyelocytes	0	0	0	0	0	0	1	0	0
Platelet count (per mm ³)	150,000–400,000	98,000	90,000	86,000	85,000	103,000 (some large forms)	160,000	234,000	192,000
Erythrocyte sedimentation rate (mm/hr)	0–11 (men)	4				7			
Activated partial-thromboplastin time (sec)	21.0–33.0					39.3		77.1 (manual, lipemic specimen)	>150.0 (lipemic specimen)
Prothrombin time (sec)	10.8–13.4					15.4		14.9 (lipemic specimen)	14.5 (lipemic specimen)
International normalized ratio						1.3		1.3 (lipemic specimen)	1.2 (lipemic specimen)
Sodium (mmol/liter)	135–145	131	135	130	133	136	126	123‡	128
Potassium (mmol/liter)	3.4–4.8	3.9	3.9	3.5	3.7	3.4	3.8	5.1	5.1
Chloride (mmol/liter)	100–108	100	98	95	99	98	92	88	86
Carbon dioxide (mmol/liter)	23.0–31.9	23	25	24	25	24.6	19.7	21.3	22.7
Urea nitrogen (mg/dl)	8–25	13	9	14	9	8	23	40	36
Creatinine (mg/dl)	0.60–1.50	0.86	0.89	0.77	0.83	0.79	2.47	5.38‡	5.56
Estimated glomerular filtration rate (ml/min/1.73 m ²)	≥60	>60	>60			>60	34	14	13
Glucose (mg/dl)	70–110	111	103	131	125	106	102	89	88
Bilirubin (mg/dl)									
Total	0.0–1.0	0.2	0.3	0.5	0.5	0.4	0.7	4.1	
Direct	0.0–0.4			0.1	0.1	0.2	0.3	2.5	

* Ref denotes the reference range at the other hospital. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

‡ The number has been corrected for lipemia.

Table 2. Arterial Blood Gas Measurements.

Variable	Reference Range, Adults*	On Admission, This Hospital	2nd Day	3rd Day, Morning	3rd Day, Evening
Fraction of inspired oxygen		0.50 (by face mask)	1.00	1.00	1.00
pH	7.35–7.45	7.45	7.42	7.19	7.20
Base excess (mmol/liter)		0.4	–0.3	–8.2	–7.4
Partial pressure of oxygen (mm Hg)	80–100	80	61	74	70
Partial pressure of carbon dioxide (mm Hg)	35–42	35	37	54	56

* Reference ranges are for adults while they are breathing ambient air. Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

and nondysmorphic red cells. Continuous venovenous hemofiltration was begun, complicated by catheter-related thrombosis. Heparin was administered.

On the third day, a test for antinuclear antibodies was positive at a dilution of 1:40, in a speckled pattern, and negative at dilutions of 1:80 and 1:160 (reference range, negative at 1:40 and 1:160); a test for antibodies to double-stranded DNA was negative; and levels of lactic acid, complement (C3 and C4), and methemoglobin were normal. Other laboratory data are shown in Tables 1 and 2. Hypotension developed, with a mean systemic arterial pressure between 40 mm Hg and 50 mm Hg; pressors were administered, methylprednisolone was added, and heparin was discontinued. On the evening of the third day, the right pupil became eccentric, irregular, and dilated to 8 mm in diameter, without reactivity to light; the left pupil was round, 5 mm in diameter, and reactive to light to 3 mm, and there was no papilledema on funduscopic examination. The patient was considered too unstable for imaging studies of the brain to be obtained. Hypertonic saline, mannitol, and ceftriaxone were administered.

On the sixth day, a diagnostic-test result was received.

DIFFERENTIAL DIAGNOSIS

Dr. Timothy M. Uyeki: May we review the imaging studies?

Dr. Amita Sharma: A posteroanterior chest radiograph (Fig. 1A) obtained at the other hospital 3 days before admission to this hospital shows

consolidation in the right upper lobe. A repeat chest radiograph 2 days later (Fig. 1B) shows progressive consolidation in the right upper lobe and new consolidation in the left upper lobe and lower lobes. A chest CT obtained without the administration of contrast material on the day of admission to this hospital (Fig. 2) shows bilateral multifocal consolidation affecting all lobes. There is lymphadenopathy within the right paratracheal, prevascular, and subcarinal regions and both hila. The rapidly progressive multifocal consolidation is most consistent with a multifocal pneumonia.

Dr. Uyeki: I am aware of the diagnosis in this case. An acute febrile respiratory illness developed during midsummer in this previously healthy young man. It progressed to multifocal pneumonia, the acute respiratory distress syndrome (ARDS), shock, and renal failure, despite treatment with antibiotics. The history and clinical features are suggestive of an acute infectious process, and the differential diagnosis includes a variety of community-acquired infections that could progress to respiratory failure and ARDS.

TICKBORNE ILLNESSES

The finding of a tick in the patient's scalp 3 weeks before the onset of his illness mandates consideration of tickborne infections. In New England, Lyme disease, anaplasmosis, babesiosis, tularemia, and Rocky Mountain spotted fever are prevalent. There were transient arthralgias, but there was no characteristic erythema migrans rash. Furthermore, Lyme disease does not typically cause rapidly progressive multifocal pneumonia, although an atypical case of ARDS has been re-

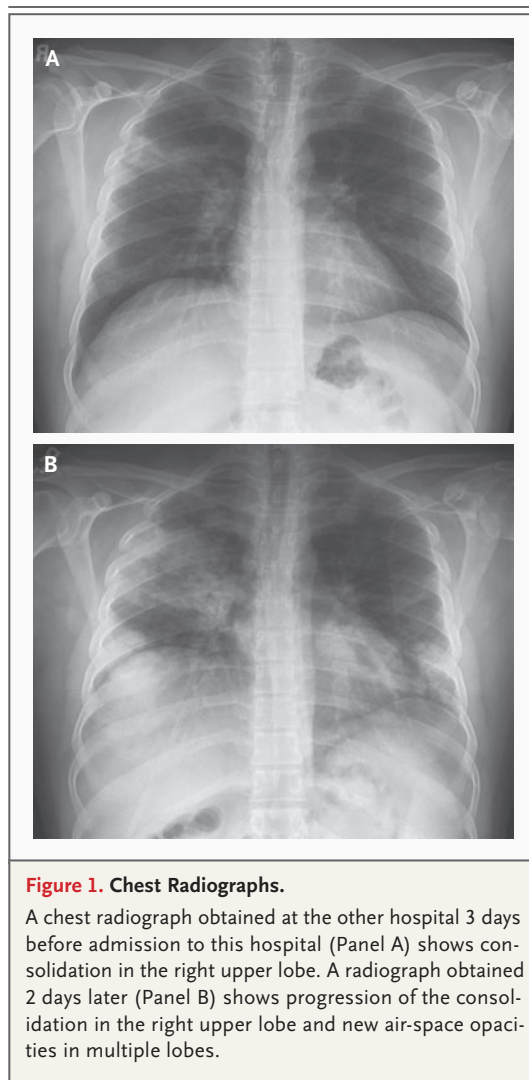


Figure 1. Chest Radiographs.

A chest radiograph obtained at the other hospital 3 days before admission to this hospital (Panel A) shows consolidation in the right upper lobe. A radiograph obtained 2 days later (Panel B) shows progression of the consolidation in the right upper lobe and new air-space opacities in multiple lobes.

ported.¹ Testing for Lyme disease was negative, although this may also be inconclusive early in the infection. The patient was treated with doxycycline. Anaplasmosis (caused by *A. phagocytophilum*) could result in a lower respiratory tract disease, such as ARDS.² However, the incubation period is generally shorter than 21 days, fulminant disease is unlikely to occur in a previously well young man, and clinical improvement should have occurred with doxycycline and levofloxacin treatment.

The history of tick exposure and a 3-week incubation period is consistent with babesiosis. Although pulmonary complications of babesiosis have been reported,^{3,4} severe disease is more likely to occur in elderly and asplenic persons.⁵ The absence of hemolytic anemia, jaundice, or

splenomegaly and the negative findings on the blood smear and nucleic acid testing make babesiosis unlikely. Although Rocky Mountain spotted fever (caused by *Rickettsia rickettsii*) can cause pneumonia, the patient had no rash, the incubation period was longer than is typical, and laboratory testing was negative.

F. tularensis is the most likely tickborne pathogen to have caused severe acute pulmonary disease in this patient. Although the time from discovery of the tick to the onset of illness is too long, the patient may have had other undetected tick bites. Since he worked outdoors in an area in which *F. tularensis* is endemic, he could have been exposed to aerosolized bacteria; his symptoms, disease progression, and radiographic findings are consistent with pneumonic tularemia.^{6,7} Treatment with doxycycline and gentamicin, which was initiated after lower respiratory tract disease was already present, might not have prevented progression of pulmonary disease. Negative testing of serum obtained during the acute phase of illness does not rule out the diagnosis of *F. tularensis*; serum obtained during the convalescent phase is also needed for serologic diagnosis.

ZOOONOTIC INFECTIONS

The lack of known contact with animals in an immunocompetent host appears to rule out zoonotic infections, such as *Coxiella burnetii*, that can cause severe pulmonary disease. The patient had swum in the ocean but not in fresh water, which could have been contaminated by animal urine, and he did not have pulmonary hemorrhage; therefore, leptospirosis seems unlikely. Without exposure to birds, *Chlamydia psittaci* infection is unlikely.

COMMUNITY-ACQUIRED PNEUMONIA

Infections with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *S. pyogenes*, or *Staphylococcus aureus* can cause severe pulmonary disease, especially in patients with antecedent influenza. These pathogens should have responded to the broad-spectrum antimicrobial therapy; therefore, these pathogens are unlikely to have been the sole cause of the patient's illness. Atypical bacterial pathogens such as *Legionella pneumophila* may cause multifocal pneumonia but usually do not cause such upper respiratory tract symptoms as this patient had. The negative test of the urine for legionella

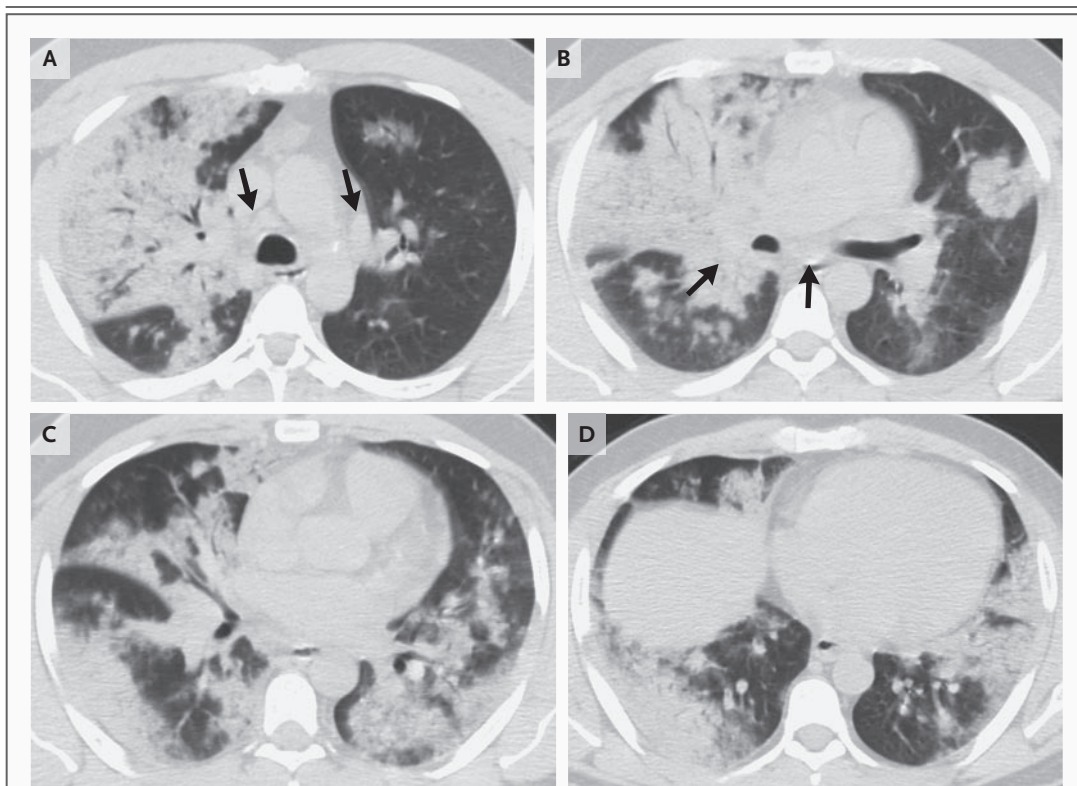


Figure 2. CT Scans Obtained on Admission to This Hospital.

Lung windows from axial CT of the chest performed without contrast material show bilateral multifocal consolidation (Panels A through D) and paratracheal, prevascular, hilar, and subcarinal lymphadenopathy (arrows).

antigen argues against legionella. *Mycoplasma pneumoniae* and *C. pneumoniae* do not usually cause such fulminant pulmonary disease, and all these infections should have responded to doxycycline and levofloxacin.

VIRAL INFECTION OF THE RESPIRATORY TRACT

The occurrence of this patient's illness during midsummer argues against most viral infections of the respiratory tract, which are more prevalent during the fall, winter, and spring. However, infection with adenovirus or influenza virus must be considered.

Adenovirus type 14 is the most likely cause of severe viral pneumonia in a young adult. Although severe disease is associated with older age and chronic underlying conditions, severe and fatal disease in previously healthy young adults has been reported.⁸⁻¹⁰ Radiographic findings may include lobar infiltrates, although these are more characteristic of bacterial pneumonia.¹⁰ The fact

that this patient had multiple negative respiratory virus panels (which typically include testing for adenovirus) makes this diagnosis unlikely.

Infection with seasonal influenza A or B viruses can cause severe pulmonary disease, but this is rare in previously healthy young adults unless a secondary invasive bacterial pneumonia develops.¹¹ The occurrence of illness in midsummer makes seasonal influenza unlikely unless the patient or a close contact had an exposure to an out-of-season outbreak, through travel to areas where influenza viruses were circulating, including an outbreak on a cruise ship.¹² There was no known exposure to pigs, so direct infection with a swine influenza virus in this patient is unlikely.¹³ Although the clinical and laboratory findings and recent exposure to a child with an upper respiratory infection could be suggestive of a rare, sporadic case of limited human-to-human transmission of highly pathogenic avian influenza A (H5N1) virus,^{14,15} the lack of recent travel

to a country where the virus is endemic and the lack of exposure to sick or dead poultry argue against H5N1 influenza.

During the spring of 2009, a novel influenza A (H1N1) virus of swine origin emerged to cause infections in humans in North America.¹⁶ It is believed that this virus emerged among humans in Mexico and spread initially among travelers to the United States and Canada and subsequently worldwide, to cause the first influenza pandemic since 1968. This virus is antigenically and genetically distinct from circulating seasonal human influenza A (H1N1) virus strains and from swine influenza viruses circulating among pigs in North America and being sporadically transmitted to people who have close contact with pigs.^{13,17} As of November 15, 2009, more than 6770 deaths of persons with confirmed 2009 H1N1 influenza had been reported to the World Health Organization from 206 countries and overseas territories or communities.¹⁸ Attack rates have been particularly high among children and young adults. The vast majority of cases have been self-limited, uncomplicated, febrile or afebrile upper respiratory disease with myalgia and occasional gastrointestinal manifestations. However, severe and fatal disease has occurred, primarily among pregnant women and persons with coexisting conditions but also among previously healthy children and young adults in the United States.^{16,19-24} The epidemiology of 2009 H1N1 influenza indicates a shift to a younger age distribution as compared with seasonal influenza, in which the highest hospitalization and mortality rates are in elderly persons.^{25,26} The 2009 H1N1 virus circulated throughout the United States in the spring and summer, and activity increased again in the fall.

The visit by a child with an upper respiratory infection 5 days before the onset of illness in the patient represents a plausible exposure to 2009 H1N1 virus. All the signs and symptoms, including vomiting, progressive respiratory disease leading to respiratory failure, refractory hypoxemia and ARDS, vasopressor-dependent shock, renal failure, leukopenia, lymphopenia, thrombocytopenia, and elevated levels of creatine kinase and hepatic aminotransferases, are consistent with critical illness due to 2009 H1N1 virus infection.^{23,27-30} Clotting associated with the patient's central venous catheter is suggestive of a hypercoagulable state, which has been reported in cases of ARDS and infection with the 2009

H1N1 virus.²⁷ Also, an asymmetric dilated pupil developed in this patient. This is suggestive of elevated intracranial pressure, which can occur with influenza-associated encephalopathy and encephalitis^{31,32} and can be a complication of 2009 H1N1 influenza. The radiographic findings do not completely rule out invasive bacterial infection, which has been reported in some fatal cases of 2009 H1N1 influenza.³³ Many critically ill patients have radiographic findings of viral pneumonitis, with bilateral interstitial and alveolar infiltrates, but multifocal and patchy abnormalities as seen in this patient have also been reported in cases of 2009 H1N1 virus infection.^{27,29,30}

The negative testing for influenza antigen on specimens from the upper respiratory tract does not rule out 2009 H1N1 virus infection in this patient, because rapid diagnostic tests and immunofluorescence testing for influenza have low sensitivity and a tendency toward false negative results, as compared with molecular-based testing methods.³⁴⁻³⁷ Furthermore, the initial testing was performed on a buccal swab. Although more data are needed, the optimal specimens from the upper respiratory tract appear to be nasopharyngeal, although nasal and oropharyngeal specimens may also yield viral detection by nucleic acid testing. In patients with respiratory failure in whom the diagnosis of 2009 H1N1 virus infection has not been confirmed by the testing of upper respiratory tract specimens, endotracheal aspirate or bronchoalveolar-lavage specimens should be tested, since viral infections of the lower respiratory tract have been shown in animal models and other studies.³⁸⁻⁴¹ Although the duration of viral shedding in hospitalized patients is not well defined, viral RNA may be detected for a longer time by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) than viable virus is detected by viral isolation. Definitive confirmation of 2009 H1N1 virus infection in this patient would have required a real-time RT-PCR assay of respiratory specimens.

Dr. Eric S. Rosenberg (Pathology): Dr. Nelson, would you tell us what your thoughts were when you initially evaluated this patient?

Dr. Sandra B. Nelson (Infectious Diseases): When this patient was transferred to us, he had an escalating respiratory illness with unusual features that included leukopenia, thrombocytopenia, hepatitis, and elevated creatine kinase and

lactate dehydrogenase levels. Although we considered common causes of community-acquired pneumonia, there were three confounding features. First, the illness occurred in midsummer; second, he was exposed to a sick child who was visiting from the southeastern United States; and third, he resided in rural New England and had known exposure to a tick. We were thus concerned about tickborne illnesses, particularly tularemia. We also considered Rocky Mountain spotted fever, complicated by ARDS, and leptospirosis with multiorgan system injury, hepatitis, and pulmonary disease. However, the recent contact with a child with a respiratory illness and our awareness that a novel influenza A (H1N1) virus was in circulation led us to be most concerned about 2009 H1N1 virus infection. We elected to treat him with oseltamivir while we awaited the results of nucleic acid testing for 2009 H1N1 virus infection.

CLINICAL DIAGNOSIS

2009 pandemic influenza A (H1N1) virus infection.

DR. TIMOTHY M. UYEKI'S DIAGNOSIS

2009 pandemic influenza A (H1N1) virus infection.

PATHOLOGICAL DISCUSSION

Dr. John A. Branda: Real-time RT-PCR, performed at the State Laboratory Institute of the Massachusetts Department of Public Health on a nasopharyngeal swab that had been collected on the patient's second day at this hospital, was positive for 2009 H1N1 virus,⁴² thus establishing the diagnosis.

Rapid testing for detection of influenza antigen and direct fluorescent antibody testing for influenza A had failed to detect the virus. The commercially available rapid antigen tests have shown low-to-moderate sensitivity for detection of the 2009 H1N1 viral strain,^{35,36,43-46} similar to their performance in detecting seasonal influenza A virus subtypes.⁴⁷⁻⁵² Less is known about the accuracy of direct fluorescent antibody tests for the detection of 2009 H1N1 virus, with reported sensitivity ranging from 47 to 93%.^{36,53} At this hospital during the spring of 2009, 88% of cases

of 2009 H1N1 influenza (confirmed with the use of RT-PCR as the standard assay) were detected by direct fluorescent antibody testing in our clinical laboratory.

In this patient, multiple direct fluorescent antibody tests were performed, beginning 9 days after the onset of symptoms. The quantity of influenza virus found in respiratory specimens from adults is highest during the first 3 days of illness, and collection within 3 to 5 days after onset is considered optimal, although children and immunocompromised hosts may shed virus at detectable levels for longer periods.⁴³

DISCUSSION OF MANAGEMENT

Dr. Uyeke: In addition to supportive and critical care management, antiviral treatment of a hospitalized patient who has suspected or confirmed 2009 H1N1 virus infection, such as this one, is focused on starting therapy with a neuraminidase inhibitor (oseltamivir or zanamivir) as soon as possible. Treatment with a neuraminidase inhibitor was associated with survival in one study of critically ill patients.²² The 2009 H1N1 virus is resistant to amantadine and rimantadine.^{16,17} Early empirical antiviral treatment with neuraminidase inhibitors for outpatients who have uncomplicated illness and who are at high risk for complications of influenza (infants, pregnant women, and persons with underlying chronic diseases) is also recommended.⁵⁴ Clinicians treating hospitalized patients who have severe or progressive pulmonary disease should consider increasing the dose of oseltamivir and the duration of treatment,⁵⁵ since such patients may have prolonged viral replication in the lower respiratory tract. Infection-control guidance for patients with 2009 H1N1 influenza in health care settings is available.⁵⁶

Hospitalized patients with intractable emesis, diarrhea, and malabsorption and critically ill patients might benefit from treatment with an intravenous neuraminidase inhibitor such as peramivir⁵⁷ or zanamivir.⁵⁸ Zanamivir is indicated for treatment of oseltamivir-resistant 2009 H1N1 virus, which was not suspected in this patient, although rare instances have been reported.^{59,60} Initial antibiotic therapy should target bacterial pathogens implicated in invasive coinfection with the 2009 H1N1 virus, including methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus*,

pneumococcus, and group A streptococcus,³³ and should be adjusted as clinically indicated. Although the pathogenesis of respiratory failure in patients with 2009 H1N1 virus infection is not defined, it might be similar to that of avian influenza A (H5N1) virus infection, in which high viral replication in the lower respiratory tract is believed to trigger cytokine dysregulation.⁶¹ Furthermore, treatment strategies for patients with H5N1 virus infection may be applicable to patients with severe complications of 2009 H1N1 virus,^{14,62} such as this patient. Combination antiviral treatment, immunomodulators, and immunotherapy with plasma from a patient who has recovered or from a recipient of 2009 H1N1 influenza vaccine deserve investigation. The role of high-dose corticosteroids (generally not recommended)⁶³ and the use of extracorporeal membrane oxygenation⁶⁴ for critically ill patients such as this one need to be defined. Clinicians should be aware that nonadjuvanted and adjuvanted 2009 H1N1 influenza vaccine has been shown to be immunogenic and safe,^{65,66} and vaccination is targeted at priority groups, including all health care workers.⁶⁷

Dr. Rosenberg: Dr. Waldo, would you tell us what happened to this patient?

Dr. Stephen W. Waldo (Medicine): Unfortunately, worsening hypotension, hypoxemia, and acidosis

developed. Antimicrobial therapy was broadened to include metronidazole and micafungin. Hypotension and acidosis persisted despite maximum doses of pressors, and the patient died on the ninth hospital day. Permission for an autopsy was denied.

A Physician: In patients with 2009 H1N1 virus infection who are critically ill, and in fatal cases, what proportion of patients had been previously healthy?

Dr. Uyeki: The majority of patients in intensive care units (ICUs) who have 2009 H1N1 influenza have been nonelderly persons with coexisting conditions, including obesity, and pregnant women.^{22-24,30,64,68} However, in case series of patients with 2009 H1N1 influenza in the United States,^{20,24} 27 to 36% of hospitalized patients and 33 to 38% of patients admitted to ICUs⁶⁸ have been previously healthy, nonobese children and young adults, such as this patient.

ANATOMICAL DIAGNOSIS

2009 influenza A (H1N1) virus infection.

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