CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 39-2015: A 22-Year-Old Man with Hypoxemia and Shock

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N Engl J Med 2015;373:2456-66.
DOI: 10.1056/NEJMcpc1507212

PRESENTATION OF CASE

Dr. Peggy S. Lai: A 22-year-old man was admitted to the intensive care unit of this hospital in the winter because of hypoxemia and shock.

The patient had been well until 5 days before admission, when head congestion, subjective fever, chills, and a nonproductive wet cough developed. He self-administered ibuprofen and acetaminophen, without improvement. One day before admission, he was seen in the emergency department of another hospital. On examination, the temperature was 37.3°C, the blood pressure 119/69 mm Hg, the pulse 97 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. Rales and wheezing were heard in the lungs, and the remainder of the examination was normal.

Dr. Jo-Anne O. Shepard: A posteroanterior chest radiograph was clear (Fig. 1A).

Dr. Lai: A diagnosis of bronchitis was made. Albuterol and ipratropium were administered by nebulizer, and a 4-day course of prednisone was begun. The patient's symptoms reportedly improved, and he was discharged home with instructions to continue the prednisone course, begin therapy with an albuterol inhaler, and follow up with his physician.

Approximately 24 hours later, relatives took the patient back to the emergency department of the other hospital because of cough, shortness of breath, diarrhea, diaphoresis, nausea, and vomiting; he reported no chest pain. On examination, he was in severe respiratory distress. The temperature was 36.8°C, the blood pressure 51/33 mm Hg, the pulse 165 beats per minute, the respiratory rate 55 breaths per minute, and the oxygen saturation 79% while he was breathing ambient air. His skin was ashen and mottled, and he had diffuse rales in both lungs; the abdomen was soft, and there were no cardiac murmurs or edema. Laboratory test results are shown in Table 1. A rapid influenza diagnostic test of a nasal swab was reportedly negative. Blood cultures were obtained. High-flow oxygen through a nonrebreather face mask and normal saline were administered. The oxygen saturation rose to 89% within minutes.

Dr. Shepard: A chest radiograph showed diffuse bilateral consolidations with some nodular opacification that were more prominent in the right lung than in

the left lung; some had nodular contours. The size of the heart was normal, and no pleural fluid or pneumothorax was seen (Fig. 1B).

Dr. Lai: An electrocardiogram revealed a ventricular rate of 161 beats per minute and was otherwise normal. A continuous infusion of norepinephrine was begun. Thirty minutes after the patient's arrival at the other hospital, respiratory distress persisted, with labored breathing, nasal flaring, retractions, and diminished breath sounds throughout. Treatment with bilevel positive airway pressure was initiated, and the oxygen saturation rose to 100%; the respiratory rate was 12 breaths per minute, the blood pressure 102/85 mm Hg, the pulse 159 beats per minute, and the rectal temperature 40.7°C. Oseltamivir, piperacillin–tazobactam, levofloxacin, vancomycin, clindamycin, methylprednisolone, and ketorolac were administered. Three hours 10 minutes after the patient's arrival, the oxygen saturation was 88% while he was receiving treatment with bilevel positive airway pressure. He was sedated, the trachea was intubated, and mechanical ventilation with positive end-expiratory pressure (PEEP) was begun. A triple-lumen central venous catheter was placed in the right internal jugular vein.

The patient was transported by medical helicopter to this hospital, arriving approximately 6 hours after his presentation at the other hospital. Additional history was obtained from family members. The patient had been well and was taking no medications until this illness developed. He had recently started spray painting buildings for work. He had no history of travel. He had visited the home of his adoptive parents the previous week; one relative had felt ill but the condition had since improved.

On examination, the patient was unresponsive and cold to the touch. He had poor capillary refill while he was receiving ventilatory support with high-flow oxygen at a rate of 30 breaths per minute, with a fraction of inspired oxygen of 1.0, a PEEP of 20 cm of water, and a tidal volume of 7 ml per kilogram of predicted body weight. He had intermittent agonal spontaneous breaths over the ventilated breaths, and the oxygen saturation was 82% while he was receiving ventilatory support. The temperature was 36.1°C, and the femoral pulses were 125 beats per minute; when measurements of systemic blood pressure were attempted, no reading could be obtained. The height was 180 cm, the weight 76.2 kg, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 23.5. The lips were blue. The breath sounds were diminished bilaterally, with diffuse rhonchi and

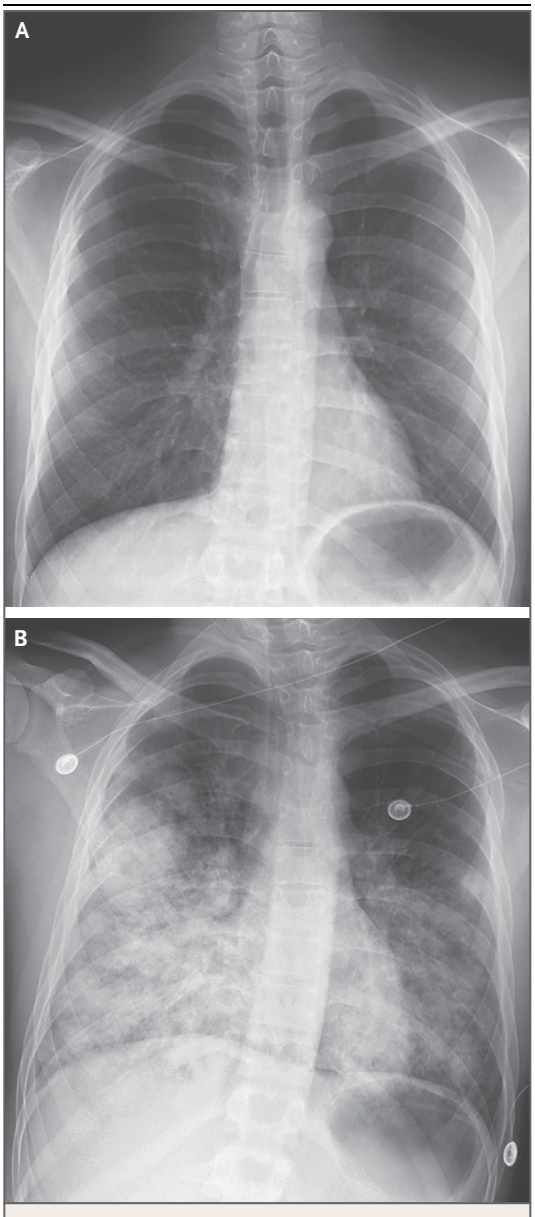

Figure 1. Chest Radiographs Obtained at the Other Hospital.

A posteroanterior chest radiograph that was obtained 1 day before admission (Panel A) is clear. An anteroposterior portable chest radiograph that was obtained on the day of admission (Panel B) shows new bilateral consolidations with nodular opacification that are more prominent in the right lung than in the left lung, a finding consistent with pneumonia.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation, Other Hospital	1.5–2 Hr after Presentation, Other Hospital	On Admission, This Hospital	30 Min after Admission, This Hospital
Hematocrit (%)	41.0–53.0 (men)	55.1 (ref 42.0–52.0)	41.4	49.0	
Hemoglobin (g/dl)	13.5–17.5 (men)	19.4 (ref 14.0–18.0)	14.6	16.6	
White-cell count (per mm^3)	4500–11,000	900	700	1620	
Differential count (%)					
Neutrophils	40–70	4	2	4.0	
Band forms		8 (ref 0–10)	9		
Lymphocytes	22–44	52	72	78.0	
Atypical lymphocytes	0	13	8	6.0	
Monocytes	4–11	14	4	6.0	
Metamyelocytes	0	5 (ref 0–1)	4	2.0	
Myelocytes	0	4 (ref 0)	1	4.0	
Nucleated red-cell count (per 100 white cells)	0			1.60	
Description of peripheral-blood smear		Slight smudge cells, poikilocytosis, anisocytosis	Slight smudge cells, poikilocytosis, anisocytosis, some giant platelets	Burr cells, 1+ tear drops, large platelets	
Platelet count (per mm^3)	150,000–400,000	85,000	46,000	37,000	
Activated partial-thromboplastin time (sec)	22.0–35.0			76.7	
Prothrombin time (sec)	11.0–14.0			31.0	
Prothrombin-time international normalized ratio	0.9–1.1			2.7	
Sodium (mmol/liter)	135–145	136		137	
Potassium (mmol/liter)	3.4–5.0	3.6		5.5 (hemolyzed)	
Chloride (mmol/liter)	100–108	91		105	
Carbon dioxide (mmol/liter)	23–32	20		16	
Plasma anion gap (mmol/liter)	3–17	25		16	
Urea nitrogen (mg/dl)	8–25	34		31	
Creatinine (mg/dl)	0.60–1.50	2.7		2.08	
Estimated glomerular filtration rate (ml/min/1.73 m^2)‡	≥60	30		40	
Glucose (mg/dl)	70–110	227		93	
D-Dimer (ng/ml)		>1050.0 (ref 0–255)			
Protein (g/dl)					
Total	6.0–8.3	7.2		4.6	
Albumin	3.3–5.0	4.1		2.4	
Globulin	1.9–4.1			2.2	
Phosphorus (mg/dl)	2.6–4.5			5.9	
Magnesium (mg/dl)	1.7–2.4	1.8 (ref 1.8–2.5)		1.7	
Calcium (mg/dl)	8.5–10.5	8.9		5.9	
Alkaline phosphatase (U/liter)	45–115	30		21	

Table 1. (Continued.)

Variable	Reference Range, Adults†	On Presentation, Other Hospital	1.5–2 Hr after Presentation, Other Hospital	On Admission, This Hospital	30 Min after Admission, This Hospital
Aspartate aminotransferase (U/liter)	10–40	40		100	
Alanine aminotransferase (U/liter)	10–55	15		16	
Lactate dehydrogenase (U/liter)	110–210				
Troponin T (ng/ml)	<0.03	<0.01 (ref ≤0.03)		<0.01	
Lactate (mmol/liter)	0.5–2.2	7.5 (ref 0.5–2.2)			
N-terminal pro–B-type natriuretic peptide (pg/ml)	0–450 (<50 yr of age)			5088	
Thyrotropin (μIU/ml)		1.64 (ref 0.34–5.60)			
Antibodies to human immunodeficiency virus types 1 and 2 and p24			Nonreactive		
Blood gases					
Source		Venous	Arterial	Venous	Arterial
Fraction of inspired oxygen (%)		Not specified	1.00 (with bilevel positive airway pressure§)	1.00 (with ventilatory support)	1.00
pH	7.30–7.40 (venous); 7.35–7.45 (arterial)	7.15 (ref 7.32–7.43)	7.30 (ref 7.35–7.45)	6.92	7.10
Partial pressure of carbon dioxide (mm Hg)	38–50 (venous); 35–42 (arterial)	56.0 (ref 41–51)	40.0 (ref 35–48)	107	64
Partial pressure of oxygen (mm Hg)	35–50 (venous); 80–100 (arterial)	35.0 (ref 30–40)	63.0 (ref 83–108)	27	48
Bicarbonate (mmol/liter)		16.2 (ref 22–29)	19.8 (ref 22–27)		
Base excess (mmol/liter)			−6.3	−14.6	−11.2
Oxygen saturation (%)			89.0 (ref 92–100)		

* The term 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 phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for lactate to milligrams per deciliter, divide by 0.1110.

† 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.

‡ If the patient is black, multiply the value by 1.21.

§ The expiratory positive airway pressure was 10, and the inspiratory positive airway pressure was 8.

poor air movement. The heart sounds were distant and tachycardic, without murmurs. The skin was cool and poorly perfused; there was no peripheral edema, and the abdomen was soft. Bloody respiratory secretions were suctioned.

Blood levels of total and direct bilirubin, amylase, lactase, and alanine aminotransferase were normal; other test results are shown in Table 1. Urinalysis revealed amber cloudy urine, with a specific gravity of 1.013, 2+ occult blood, 1+ glucose, and 2+ albumin; the urine sediment showed 3 to 5 red cells and 5 to 10 white cells per high-power field, 10 to 20 hyaline casts and 5 to 10 granular casts per low-power field, squamous cells, and mucin. Toxicologic screening of the urine revealed cannabinoids; screening of the blood and urine for other toxins was negative. An electrocardiogram revealed sinus tachycardia.

The rate of infusion of norepinephrine was increased, and dobutamine and vasopressin were added. Sodium bicarbonate, fentanyl, versed, propofol, vecuronium bromide, vancomycin, cefepime, trimethoprim–sulfamethoxazole, levofloxacin, and phytonadione were administered.

Platelets were transfused. An indwelling catheter was placed transcutaneously into the femoral artery. Transthoracic ultrasonography, which was performed at the bedside, revealed diffuse decreased cardiac function, a decreased ejection fraction, and no evidence of right ventricular enlargement or pericardial effusion; hypotension persisted. Four hours after the patient's arrival at this hospital, extracorporeal membrane oxygenation (ECMO) was begun at the bedside.

Dr. Shepard: A portable chest radiograph that was obtained shortly after the patient was admitted to this hospital showed slight, gradual progression in consolidations bilaterally and showed the placement of an endotracheal tube, a central venous catheter, and a nasogastric tube (Fig. 2A). On a radiograph that was obtained 4 hours later, an ECMO catheter was present in the superior vena cava and other findings were unchanged (Fig. 2B).

Dr. Lai: The patient was admitted to the intensive care unit. Diagnostic test results were received.

DIFFERENTIAL DIAGNOSIS

Dr. Erica S. Shenoy: This young, previously healthy, presumably immunocompetent man presented with a several-day history of fever, chills, and cough, as well as hypoxemic respiratory failure and evidence of rapidly progressive multifocal consolidations on imaging studies. His condition rapidly declined, ultimately requiring mechanical ventilation and ECMO. The most impressive features of the case are the remarkable tempo and severity of illness, both of which suggest an infectious cause and help to narrow the differential diagnosis. These features also raise the question of whether there might have been more than one infectious process or an underlying immune defect that conferred a predisposition to either an opportunistic infection or a more severe form of a common illness. In the patient's history, there is mention of recent exposure to spray paint; however, a toxic exposure (e.g., toluene) and a hypersensitivity reaction are unlikely causes because of the severity of the illness and the timing of the exposure relative to the timing of the presentation.

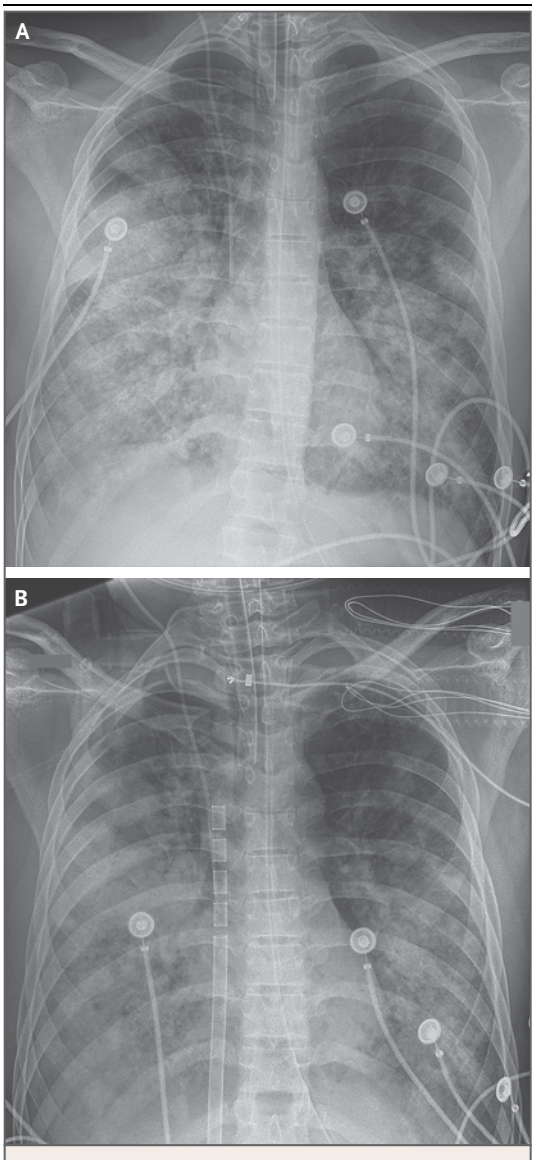

Figure 2. Chest Radiographs Obtained at This Hospital.
A portable chest radiograph that was obtained on admission (Panel A) shows slight, gradual progression in bilateral pneumonia; an endotracheal tube is present in the trachea, a central venous catheter is present in the superior vena cava, and a nasogastric tube is present in the stomach. A portable chest radiograph that was obtained 4 hours later (Panel B) shows the presence of a catheter for extracorporeal membrane oxygenation coursing through the inferior vena cava and terminating in the superior vena cava; the other findings were unchanged.

BACTERIAL INFECTIONS

Over a period of approximately 36 hours, the results of chest radiography evolved, from showing clear lungs to multifocal consolidations. This time course could be consistent with either a primary or a secondary bacterial pneumonia.

The most common pathogens responsible for a

community-acquired pneumonia that could cause such a rapid clinical decline are *Streptococcus pneumoniae* and *Staphylococcus aureus*. Both should be considered in this patient; *S. aureus* is an important diagnostic consideration because of its proclivity to cause necrotizing pneumonia. Although the patient had no history of skin or soft-tissue infections, approximately 30% of the general population is colonized with methicillin-susceptible *S. aureus*, and approximately 3% is colonized with methicillin-resistant *S. aureus*. Other causes of bacterial pneumonia that should be considered in this patient include agents that cause atypical pneumonia, such as *Legionella pneumophila*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*. Given the patient's age and the absence of an underlying lung disease, *Haemophilus influenzae* would be an unusual cause, because chronic obstructive lung diseases, cystic fibrosis, and very young and very old age are known risk factors for *H. influenzae* infection.

It is always important to consider uncommon pathogens that may cause a clinical presentation similar to that seen in this case, because they are rare and likely to go undiagnosed. Infection with *Bacillus anthracis*, the agent that causes anthrax, usually begins with a nonspecific prodromal illness similar to that seen in this patient and then leads to an abrupt decline, respiratory shock, and death. However, this patient had no known exposure to this pathogen and did not have a widened mediastinum, a feature that is characteristic of anthrax. Furthermore, persons with inhalational anthrax usually have high-grade bacteremia, so the diagnosis is fairly easily to make after routine blood cultures are obtained. Patients infected with *Yersinia pestis*, the agent that causes bubonic plague, often present with fever, cough, and respiratory failure, and an outbreak was recently identified in Colorado.[1] However, this patient had no known travel to an area in the United States in which cases of human plague have been identified (i.e., northern New Mexico, northern Arizona, southern Colorado, California, southern Oregon, and far western Nevada); therefore, this diagnosis is unlikely. Finally, infection with *Francisella tularensis*, the agent that causes tularemia, also starts with a brief prodromal illness similar to that seen in this patient and may result in critical illness, including fulminant respiratory failure. Two outbreaks of tularemia have occurred in Massachusetts,[2,3] suggesting that there is a persistent local reservoir in this state. However, this patient presented in the winter, and thus exposure to *F. tularensis* was unlikely.

FUNGAL INFECTIONS

Fungal infections should be considered, although they are less likely than bacterial infections in this case. Most life-threatening fungal infections are associated with an underlying risk factor in the host or a relevant exposure. Neutropenia after the recent administration of chemotherapy, pharmacologic immunosuppression after organ or bone marrow transplantation, and the acquired immunodeficiency syndrome are all commonly associated with the development of invasive fungal infection. Because this patient was young and had reportedly been previously healthy, most fungal infections can be ruled out on the basis of history alone.

This patient did have a positive toxicologic screening for cannabinoids, a finding suggestive of recent marijuana use. Although inhalation of marijuana is unlikely to be the cause of this patient's illness, it has been implicated in pulmonary aspergillus infection. Infection with *Pneumocystis jirovecii* can be ruled out in this patient because he had a negative test for human immunodeficiency virus 1 and the rapid tempo of his illness would be very unusual with pneumocystis pneumonia. Finally, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis* may all cause pneumonia, but this patient had no reported travel to an area in which these agents are endemic. *Cryptococcus neoformans* can cause pneumonia, but most healthy persons would have a subclinical infection and only rarely present with this magnitude of disease.

VIRAL INFECTIONS

Could this patient have severe influenza? He presented at the height of the influenza season with an influenza-like illness, characterized by several days of fever, chills, cough, and gastrointestinal symptoms followed by the onset of respiratory failure and shock. Although influenza can be considered to be a self-limited winter nuisance, it is important to remember that it is responsible for approximately 200,000 hospitalizations and 23,000 deaths each year in the United States. There is wide season-to-season variation in the

number of deaths caused by influenza, and the rate of death when influenza A (H3N2) virus is the predominant circulating strain is 2.7 times as high as the rate when other strains predominate.[4] This patient presented during the winter of the 2014–2015 influenza season, when influenza A (H3N2) virus was the predominant strain in circulation and overall; the season was considered to be moderately severe, most likely because of a mismatch in the vaccine formulation.

The classic risk factors for severe influenza include age younger than 5 years or older than 50 years, pregnancy, and chronic conditions, including pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, and metabolic diseases, immunosuppression, and morbid obesity.[5-7] The evidence to support some of these associations is limited,[8] and to my knowledge, this patient had none of these classic risk factors that would help to explain the severity of his illness.

The patient's negative rapid influenza diagnostic test should not deter us from considering an empirical diagnosis of influenza and initiating treatment. Although such tests are widely used, they have variable sensitivity and specificity that depends in part on the type of specimen obtained (throat swab; nasopharyngeal wash or aspirate; or nasal wash, aspirate, or swab), the patient's age, and the timing of sample collection relative to the onset of symptoms. The technique for specimen collection is also critical to ensure that an adequate specimen is obtained. The sensitivity of the rapid influenza diagnostic test correlates directly with the amount of virus present in the clinical specimen, and therefore the collection technique and the timing of sample collection are very important. This patient reportedly had had symptoms for 5 days before the test was performed. The rapid influenza diagnostic test has peak sensitivity on the third day of symptoms; the timing of the test may explain the negative result in this case. In hospitalized patients, a sputum specimen from the lower respiratory tract may be obtained if examination of a specimen from the upper respiratory tract is negative and the clinical suspicion of influenza remains high.[9-11] Furthermore, the negative rapid influenza diagnostic test in this patient should not deter the immediate institution of appropriate isolation measures for infection control in order to protect other patients, staff, and visitors and to limit nosocomial outbreaks[12] while a definitive diagnosis is sought.

Could this patient have an unusual variant of influenza? Avian influenza A viruses typically occur in birds but can infect humans and are associated with high mortality. Sporadic infections in humans have been associated with exposure to infected birds; the case fatality rate associated with avian influenza A (H5N1) virus is approximately 60%,[13] and the recently published estimate of the case fatality rate associated with influenza A (H7N9) virus is 27%.[14] Beginning in December 2014, a variant of the highly pathogenic Asian avian influenza A (H5N1) virus was detected in poultry in multiple states across the United States; however, there have been no confirmed associated human infections.[15] This patient had no known exposure to either wild birds or domesticated poultry in this country and had not traveled to Asia.

Human parainfluenza viruses, respiratory syncytial virus, and the herpesviruses (including cytomegalovirus, herpes simplex virus, and varicella–zoster virus) are all potential causes of respiratory illness, although they are unlikely in this patient because of the absence of a known underlying risk factor. Parainfluenza virus typically causes disease in young children and patients with underlying immunocompromise. Furthermore, most infections with parainfluenza occur outside the traditional influenza season, thus making this an unlikely cause in this case. Similarly, respiratory syncytial virus typically causes acute respiratory illness in children and immunocompromised adults and rarely causes critical illness in young, otherwise healthy adults. Cytomegalovirus, herpes simplex virus, and varicella–zoster virus most commonly occur in immunocompromised persons, although they have been reported in patients with no obvious immune defect.[16-18]

In any patient, and especially in one with fever and respiratory symptoms, it is essential to obtain a history of travel and exposures at the earliest possible entry point to ensure the safety of staff and other patients. This patient did not have epidemiologic risk factors for infection with Middle East respiratory syndrome coronavirus, and thus this possibility may be ruled out but is still worth considering, given the potential need

for implementation of appropriate isolation precautions and expedited diagnostic evaluation.

Because this patient had been previously healthy, had no known underlying host or epidemiologic risk factors, and presented during a moderately severe influenza season, I think that severe influenza A infection is the most likely diagnosis. I suspect that the results of the rapid influenza diagnostic test were misleading in this case and that the test was negative because of either an inadequately collected specimen or a delay in the time of specimen collection after symptom onset. It is also entirely possible that the severity of this patient's illness is due in part to a secondary bacterial superinfection with *S. aureus* or another community-acquired pathogen. Studies of lung tissue from the 1918–1919 influenza pandemic have identified severe bacterial pneumonia as the predominant pathologic process but have also identified *S. aureus*, *S. pneumoniae*, and *S. pyogenes* in almost 50% of all samples.[19] In order to establish the diagnosis of influenza, I would recommend obtaining a sputum specimen from the lower respiratory tract for nucleic-acid testing for influenza and performing a bacterial Gram's stain and culture to assess for the possibility of a secondary bacterial infection.[20]

Dr. Eric S. Rosenberg (Pathology): Dr. Lai, what was your initial impression when you evaluated this patient?

Dr. Lai: In this young, previously healthy patient who presented in the winter with a precipitous onset of multiorgan failure after several days of upper respiratory symptoms, the suspected diagnosis was influenza. We were skeptical about the negative rapid influenza diagnostic test and decided to obtain a specimen for nucleic-acid testing for influenza.

CLINICAL DIAGNOSIS

Acute respiratory distress syndrome due to suspected influenza, septic shock, and septic cardiomyopathy.

DR. ERICA S. SHENOY'S DIAGNOSIS

Influenza with superimposed bacterial pneumonia, possibly due to *Staphylococcus aureus* or *Streptococcus pneumoniae.*

HOSPITAL COURSE AND MANAGEMENT

Dr. Lai: Shortly after the patient was admitted to this hospital, a polymerase-chain-reaction (PCR) assay of an upper respiratory specimen was positive for influenza A virus. Nucleic-acid testing, which was performed at the Centers for Disease Control and Prevention (CDC), ultimately identified influenza A (H3N2) virus in this patient.

The patient was treated with vancomycin, cefepime, levofloxacin, and oseltamivir. On hospital day 2, the patient's right foot was noted to be mottled and cold. An angiogram ruled out an arterial embolus, but vasospasm was identified at the level of the ankle; an infusion of prostaglandin was initiated, and a perfusion cannula was placed in the superficial femoral artery. Pneumothorax developed on the right side, and a chest tube was placed.

On hospital day 3, blood cultures from the other hospital were positive for methicillin-susceptible *S. aureus*. On hospital day 4, renal-replacement therapy was initiated. On hospital day 7, the patient was transitioned from veno-arterial to venovenous ECMO; a repeat echocardiogram showed a normal ejection fraction. On hospital day 8, pneumothorax developed on the left side despite therapy with volume-controlled ventilation (with a set tidal volume of 2 ml per kilogram of predicted body weight and a measured peak inspiratory pressure of 31 cm of water). On hospital day 14, worsening leukocytosis developed, followed by severe metabolic acidosis and shock. A bedside exploratory laparotomy revealed no bowel ischemia, and an emergency amputation was performed below the right knee. The patient's condition continued to deteriorate. On hospital day 16, after a discussion with the patient's family about his poor prognosis, life support was withdrawn. He passed away peacefully. An autopsy was performed.

PATHOLOGICAL DISCUSSION

Dr. Richard L. Kradin: At autopsy, each lung weighed approximately 2000 g. The cut surface (Fig. 3A) showed areas of necrosis and hemorrhage. Microscopic examination revealed heterogeneous changes, with areas of organizing pneumonia, hemorrhagic necrosis, and abscess formation.

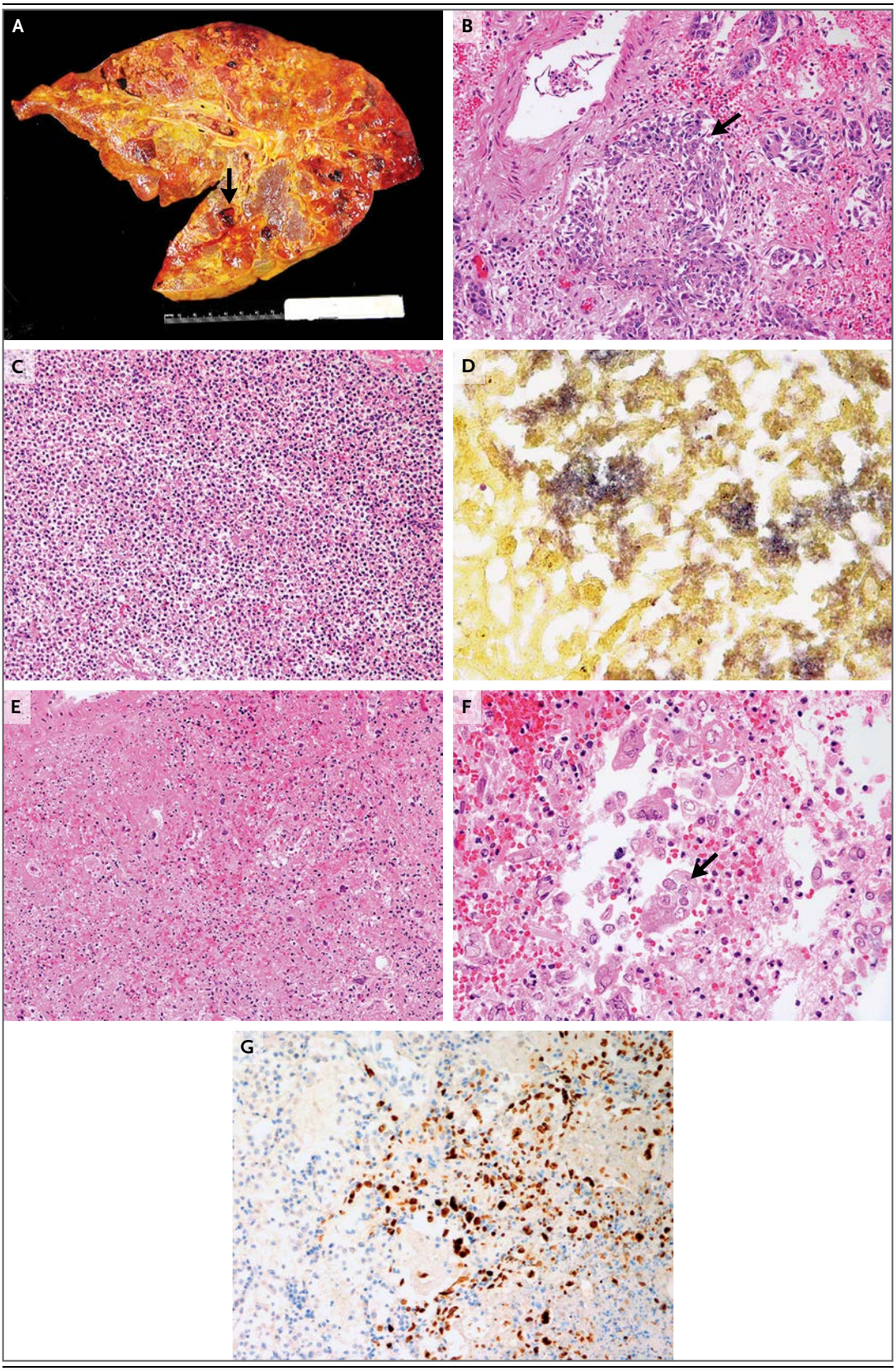

Figure 3 (facing page). Autopsy Specimens.
Autopsy specimens of the lungs were heavy and consolidated, with evidence of cavitation (Panel A, arrow). Hematoxylin and eosin staining showed organizing pneumonia with prominent squamous metaplasia (Panel B, arrow), as well as abscess formation with neutrophilic infiltration (Panel C). Gram's staining of lung tissue revealed gram-positive cocci in clusters, a finding consistent with staphylococcal species (Panel D). Hematoxylin and eosin staining showed multiple foci of both lungs with evidence of hemorrhagic and necrotizing pneumonia (Panel E), as well as many cells with intranuclear amphophilic inclusions and multikaryon formation (Panel F, arrow). Immunohistochemical staining was positive for herpes simplex virus (Panel G).

The small airways showed exuberant squamous metaplasia, a finding that is nonspecific but often accompanies influenza infection (Fig. 3B).[21] However, other areas of the lung showed abscess formation (Fig. 3C) with colonies of gram-positive cocci in clusters, a finding consistent with staphylococcal infection (Fig. 3D). There were also unexpected distinct areas of hemorrhagic infarction, with moderate numbers of neutrophils (Fig. 3E) and cells showing prominent intranuclear amphophilic inclusions, some with multikaryon formation (Fig. 3F). Small pulmonary arteries showed necrotizing angiitis. These features are characteristic of herpetic infection, and immunostaining for herpes simplex virus was strongly positive (Fig. 3G).

Lung tissue was sent to the CDC for consultation. A PCR assay confirmed the presence of influenza A (H3N2) virus in the lungs, although there was no longer any immunohistochemical evidence of active infection. Both PCR and immunocytochemical staining were positive for herpes simplex virus type 2. There was also immunohistochemical evidence of *S. aureus* infection. Superinfection with staphylococcus is common and devastating in patients with influenza, and recent evidence indicates that up to 88% of cases of staphylococcus infection are due to methicillin-resistant strains.[22]

Pneumonia associated with herpes simplex virus type 2 is rare and, to my knowledge, has not been reported as a complication of influenza infection. Herpes simplex virus type 1 produces airway infection in patients who receive mechanical ventilation, but herpetic pneumonia is a fulminant infection that is generally limited to immunosuppressed patients. In this case, severe viral infection and bacterial pneumonia may have depressed the cellular immunity and compromised the normal anatomical boundaries, thus conferring a predisposition to herpetic infection. The distribution of pulmonary infection suggests hematogenous spread of infection in the lung. However, no other organs showed evidence of herpetic infection, although bland splenic infarctions were present that were most likely attributable to hypotension and microvascular compromise.

Dr. Thomas R. Spitzer (Medicine): Had this patient received the influenza vaccine?

Dr. Rosenberg: At the time of transfer, the patient was unable to provide any history. There was no indication from the other hospital of whether he had been vaccinated.

Dr. Shenoy: The circulating influenza A (H3N2) strain was unfortunately mismatched to the influenza A (H3N2) strain contained in the 2014–2015 vaccine because of antigenic drift. Therefore, the effectiveness of the vaccine was reduced.[23]

Dr. Jatin M. Vyas (Medicine): Do you think the patient's death was ultimately due to pneumonia associated with herpes simplex virus?

Dr. Kradin: I think the influenza was probably no longer a very active component of the infection, although it no doubt set the stage for the ensuing events. The patient had bacteremia with methicillin-susceptible *S. aureus*, which is a common complication of severe influenza infection. With that said, the herpes simplex virus was clearly an active component of the infection. I suspect that the terminal events were probably primarily related to infection with herpes simplex virus type 2, although the patient also had septic shock, presumably due to *S. aureus*–associated pneumonia and bacteremia.

ANATOMICAL DIAGNOSIS

Influenza A (H3N2) virus, complicated by staphylococcal pneumonia, bacteremia, and pneumonia associated with herpes simplex virus type 2.

FINAL DIAGNOSIS

Influenza A virus.

This case was presented at the Medical Case Conference.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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