CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 12-2013: An 18-Year-Old Woman with Pulmonary Infiltrates and Respiratory Failure

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PRESENTATION OF CASE

Dr. James Sawalla Guseh (Medicine): An 18-year-old woman was admitted to this hospital because of pulmonary infiltrates and respiratory failure.

The patient had been well until 3 weeks before admission, when fever and a cough productive of white, nonbloody sputum developed. During the next week, night sweats, extremely painful pharyngitis, pleuritic chest pain, increasing shortness of breath, nausea, vomiting, and diarrhea occurred. She self-administered doses from an inhaler obtained from a relative, with transient improvement in dyspnea. Thirteen days before admission, she went to the emergency department at another hospital. On examination, the temperature was reportedly 39.4°C. Erythromycin and an albuterol inhaler were prescribed, and she returned home.

Two days later, the patient went to a second hospital because of increasing cough productive of thick white sputum, fever, vomiting, diarrhea, shortness of breath, and anorexia. She reported chest pain that she rated at 10 on a scale of 0 to 10, with 10 indicating the most severe pain. She had removed a tick from her abdomen approximately 1 week earlier. On examination, she was in mild respiratory distress. The blood pressure was 140/74 mm Hg, the pulse 127 beats per minute, the temperature 37.3°C, the respiratory rate 20 breaths per minute, and the oxygen saturation 94% while she was breathing ambient air. Her lips were dry, and coughing and scattered wheezing were heard. There was mild tenderness at the costovertebral angles and in all quadrants of the abdomen, without rebound; the rest of the examination was reportedly normal. Within 3 hours after arrival, the temperature rose to 38.9°C. Blood levels of lipase and amylase and results of tests of renal and liver function were normal; other test results are shown in Table 1. Urinalysis revealed trace protein, leukocytes, and bacteria and was otherwise normal.

Dr. Victorine V. Muse: A chest radiograph obtained at the second hospital showed patchy opacities in the left middle and lower lung zones and in the right lung base, a finding suggestive of pneumonia. The cardiomediastinal silhouette was normal (Fig. 1A).

Dr. Guseh: The patient was admitted to the second hospital, and azithromycin, ceftriaxone, doxycycline, levalbuterol, hydromorphone, and acetaminophen were

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Table 1. Laboratory Data.*

Variable	Reference Range, Age-Adjusted†	On Admission, Second Hospital	5th Day, Second Hospital	10th Day, Second Hospital	On Admission, This Hospital
Hematocrit (%)	36.0–46.0 (women)	38.9	35.6	30.2	30.5
Hemoglobin (g/dl)	12.0–16.0 (women)	13.3	12.2	10.5	10.8
White-cell count (per mm^3)	4500–13,000	17,200	16,700	21,000	21,600
Differential count (%)					
Neutrophils	40–62	82	69	92	61
Band forms	0–10	5 (ref 0–7)	23		4
Lymphocytes	27–40	10	5	7	26
Monocytes	4–11	3	3	1	2
Eosinophils	0–8				1
Myelocytes	0				2
Metamyelocytes	0				4
Platelet count (per mm^3)	150,000–400,000	348,000	491,000	490,000	752,000
Thick and thin Giemsa-stained peripheral-blood smears		No organisms seen			No organisms seen
Erythrocyte sedimentation rate (mm/hr)	0–17				55
Sodium (mmol/liter)	135–145	133	134	134	135
Potassium (mmol/liter)	3.4–4.8	3.7	3.5	5.0	3.7
Chloride (mmol/liter)	100–108	100	98	93	100
Carbon dioxide (mmol/liter)	23.0–31.9	24	27	31	26.2
Glucose (mg/dl)	70–110	146	155	122	77
Lactate dehydrogenase (U/liter)	110–210		346 (ref 0–250)		
Haptoglobin (mg/dl)			359 (ref 30–200)		
Creatine kinase MB isoenzymes (ng/ml)	0.0–6.9				1.0
Troponin T (ng/ml)	<0.03				<0.01
Lactic acid (mmol/liter)			1.3 (ref 0.5–2.2)		
Galactomannan index	<0.5				<0.5
1,3-β-D-glucan (pg/ml)	<60				<31
Anaplasma DNA	Negative				Negative
Ehrlichia DNA	Negative				Negative
Blood gases and oximetry					
Specimen type	Venous		Unspecified	Unspecified	Venous
Fraction of inspired oxygen			0.70	0.55	0.60
pH	7.30–7.40		7.35 (ref 7.35–7.45)	7.45 (ref 7.35–7.45)	7.41
Partial pressure of oxygen (mm Hg)	35–50		49 (ref 70–95)	111 (ref 70–95)	41
Partial pressure of carbon dioxide (mm Hg)	38–50		43 (ref 35–45)	44 (ref 35–45)	43
Base excess (mmol/liter)					2.0
Oxygen saturation (%)			76 (ref 95–98)	97 (ref 95–98)	

* Ref denotes the reference range at the other hospital. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

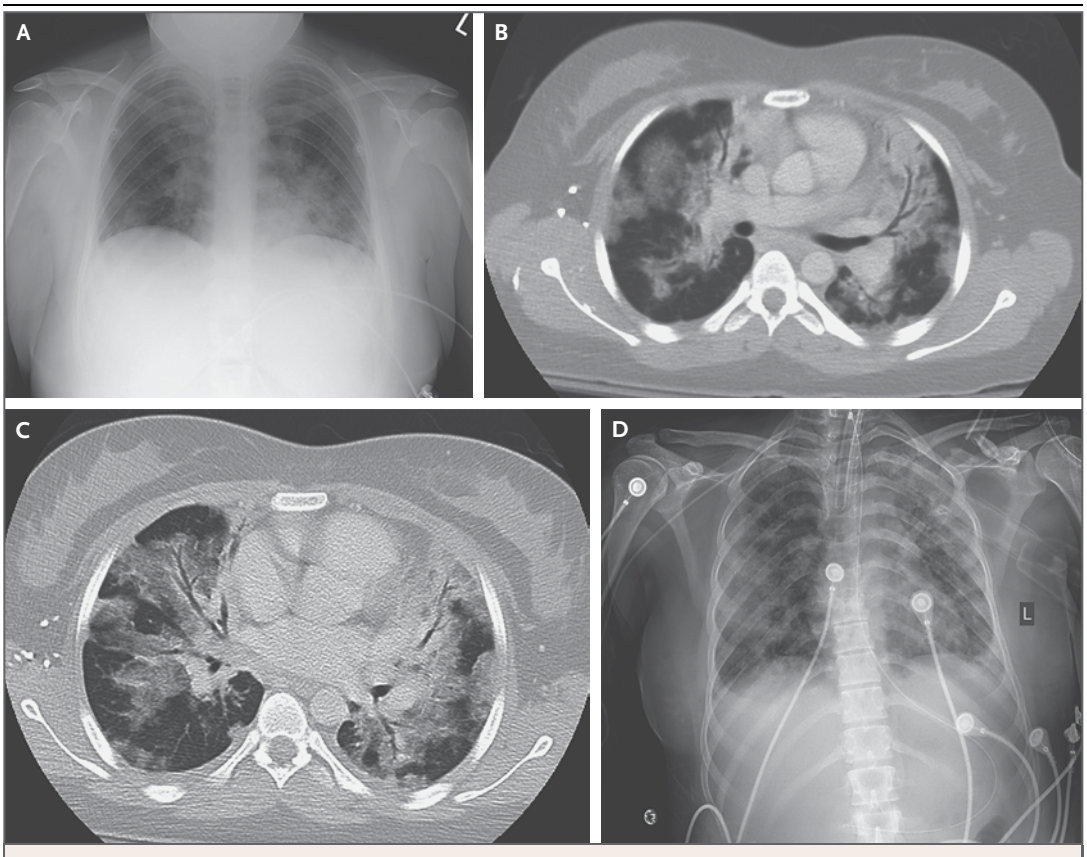

Figure 1. Chest Imaging.

A chest radiograph obtained on admission to the second hospital (Panel A) shows patchy opacities in the left middle and lower lung zones and in the right lung base, a finding suggestive of pneumonia. Lung windows from a CT study of the chest obtained 4 days later (Panels B and C) show multifocal segmental and subsegmental consolidations and ground-glass opacities, with air bronchograms. A portable chest radiograph obtained on admission to this hospital (Panel D) shows persistent but improved bilateral multifocal pneumonia.

administered. Testing for serum antibodies to *Borrelia burgdorferi*, *Anaplasma phagocytophilum*, and the human immunodeficiency virus (HIV), as well as for legionella urinary antigen, was negative; doxycycline was stopped. During the first 4 days, respiratory distress worsened and fevers persisted.

Dr. Muse: Computed tomography (CT) of the chest showed peribronchial thickening, patchy alveolar consolidation with geographic ground-glass opacities and air bronchograms, and adjacent small bilateral pleural effusions (Fig. 1B and 1C). A small pericardial effusion, a right paratracheal lymph node that was 1.5 cm in diameter, and precarinal lymph nodes were the only notable findings in the mediastinum. The visualized portions of the upper abdomen were normal.

Dr. Guseh: Ceftriaxone was stopped; vancomycin, cefepime, trimethoprim–sulfamethoxazole, and methylprednisolone were begun, and azithromycin was continued. On the fifth day, dyspnea increased, and the trachea was intubated in an emergency procedure. Test results are shown in Table 1. Bronchoscopy revealed clear airways, without endobronchial lesions. Bronchoalveolar aspirate from the right upper lobe was hypocellular, with a few polymorphonuclear leukocytes, a few epithelial cells, and no organisms. Testing for *Pneumocystis jirovecii* and mycobacteria was negative; specimen quantity was limited, and viral studies could not be performed. Cultures of the bronchial washing grew normal respiratory flora; fungal and mycobacterial cultures were negative. A sputum specimen showed no eosino-

phils. Cultures of the blood were sterile. Insulin, furosemide, albuterol, and lorazepam were given. On the sixth day, all antibiotics except azithromycin were stopped. Three days later, the patient was extubated. Increasing dyspnea and tachypnea developed, and the trachea was reintubated later that day.

The following day, a CT scan of the chest showed persistent patchy, dense consolidation and air bronchograms, greater in the upper lobe of the left lung than in the lower lobe. Transthoracic echocardiography revealed a left ventricular ejection fraction of 65%, a mildly enlarged right ventricle, an estimated right ventricular systolic pressure of 35 mm Hg, and a pericardial effusion without evidence of tamponade. Test results are shown in Table 1. Vancomycin and a combination of piperacillin and tazobactam were administered, and azithromycin was stopped.

On the 11th hospital day, the patient was transferred to this hospital and admitted to the medical intensive care unit while receiving mechanical ventilation. Medications on transfer included vancomycin, piperacillin–tazobactam, methylprednisolone, insulin, propofol, omeprazole, albuterol and ipratropium by nebulizer inhalation, nicotine, nystatin suspension, dalteparin, and miconazole powder.

The patient had had tonsillitis and hand surgery in the past. She had no known allergies. She lived with her family and a cat and worked outdoors. Her bedroom reportedly was damp and moldy. She had not traveled recently, had a new boyfriend, and had no ill contacts. She smoked cigarettes and marijuana. Relatives had asthma, hypertension, coronary artery disease, chronic obstructive pulmonary disease, and lung cancer.

On examination, the patient was sedated, intubated, and ventilated. She had a crusted lesion on her lip. The blood pressure was 112/64 mm Hg, the pulse 65 beats per minute, the temperature 37.0°C, the mean arterial pressure 78 mm Hg, and the oxygen saturation 95% while she was breathing 60% oxygen, with a positive end-expiratory pressure of 10 cm of water. Expiratory breath sounds were louder in the right lung than in the left lung; other lung sounds were obscured by ventilation. The first cardiac sound was normal, and there was prominent physiologic splitting of the second cardiac sound, with accentuation of the sound of pulmonic-valve closure. Pulsus paradoxus measured 4 mm Hg. The neurologic examination was limited by sedation; the remainder of the examination was normal. Blood levels of calcium, magnesium, phosphorus, and angiotensin-converting enzyme were normal, as were the results of renal-function tests; other test results are shown in Table 1.

Dr. Muse: A portable chest radiograph obtained on admission to this hospital shows persistent but improved bilateral multifocal pneumonia (Fig. 1D).

Dr. Guseh: Cefepime, vancomycin, nicotine, dalteparin, insulin, nystatin suspension, fentanyl, and propofol were administered, and the last two were gradually increased to enhance synchrony with the mechanical ventilator. Four hours after admission, the blood pressure decreased to 86/44 mm Hg, and the patient became diaphoretic; the administration of phenylephrine was begun, with improvement.

Bronchoscopic examination revealed irritated mucosa in the airways of the right lung, with inflammation. Examination of bronchoalveolar-lavage aspirate from the right middle lobe and its lateral segment revealed colorless fluid with slight turbidity, 321 nucleated cells (51% neutrophils, 18% lymphocytes, 16% monocytes, and 15% macrophage-lining cells), and a few clumps of cells.

Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Daniel P. Hunt: This patient is a young, presumably healthy woman who had a respiratory illness that progressed over a period of 10 days to respiratory failure. The illness appears to be consistent with bilateral pneumonia. However, the apparent progression of the illness despite the use of antibiotics raises the possibility of a diffuse, noninfectious pulmonary process. When developing my differential diagnosis, I will summarize the patient's illness in a list of problems, account for each problem, and try to arrive at the final diagnosis (Table 2).

COMMON CAUSES OF PNEUMONIA

In a young patient without coexisting illnesses, there are many potential infectious causes of pneumonia.[1] The patient's history gives us several

clues that help in reducing the list of possible pathogens. This patient underwent bronchoscopy and bronchoalveolar lavage. Negative bacterial cultures argue against common, easy-to-culture bacterial pathogens. Furthermore, the patient did not have a response to multiple, broad-spectrum antibacterial therapy including erythromycin, azithromycin, ceftriaxone, doxycycline, vancomycin, cefepime, trimethoprim–sulfamethoxazole, and piperacillin–tazobactam. I would expect that infection with an atypical, community-acquired pathogen such as legionella or mycoplasma would improve with macrolide therapy and doxycycline. The negative test for legionella urinary antigen also makes this diagnosis unlikely.

This patient was not known to be immunocompromised, and a negative HIV test lowers the likelihood that she was infected with an opportunistic pathogen. *P. jirovecii*, a common cause of pneumonia in patients with the acquired immunodeficiency syndrome, is highly unlikely in this case because of the negative HIV test and the absence of *P. jirovecii* in the bronchoalveolar-lavage fluid. However, pneumocystis could be a possibility if this patient had a transient depression in the CD4+ T-cell count, which is sometimes seen in patients with acute HIV infection.[2]

Table 2. List of Problems.

Severe bilateral pneumonia
Community acquired
Extensive abnormalities on chest imaging
Bronchoscopic findings of clear airways, as well as bronchoalveolar-lavage fluid with few polymorphonuclear leukocytes and no organisms
No improvement despite the administration of multiple broad-spectrum antimicrobial agents
Symptoms associated with pneumonia
Severe pharyngitis
Pleuritic chest pain
Nausea
Vomiting
Diarrhea
Anorexia
Leukocytosis
Thrombocytosis
Elevated erythrocyte sedimentation rate
Mildly elevated lactate dehydrogenase level
Pericardial effusion on echocardiography
Crusted lesion on lip

ENVIRONMENTAL FACTORS

By combining host characteristics with environmental influences and exposures, we can produce a list of possible pathogens. In this case, the host is a healthy young female smoker. Her exposures include a tick bite, a moldy bedroom, a cat, outdoor work, marijuana, and a new boyfriend. The moldy bedroom raises the possibility of a fungal infection, but this seems unlikely. Cats have been associated with leptospiral pneumonia, toxoplasmic pneumonia, infection with *Pasteurella multocida* ("cat cuddler's cough"), and pneumonic plague. None of these seem likely, given the negative initial bronchoscopic evaluation and cultures. Marijuana has been associated with eosinophilic pneumonia,[3] necrotizing pulmonary granuloma,[4] and fungal pneumonia,[5] but this patient did not have eosinophils in the bronchoalveolar-lavage fluid, no fungi were identified, and the illness seems inconsistent with necrotizing granuloma. Perhaps the new boyfriend is a clue, so I will keep him in mind as I consider other possibilities.

TICKBORNE ILLNESSES

How about the tick? Tickborne illnesses associated with pulmonary complications include *B. burgdorferi*, *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, *Babesia microti*, and *Francisella tularensis*.[6] Testing and clinical findings seem to effectively rule out all tickborne pathogens in this case except *F. tularensis.* Could this patient have pneumonic tularemia? Pneumonic tularemia is unusual, with approximately 100 to 200 cases noted per year.[7] It occurs almost exclusively in the northern hemisphere, and outbreaks have been reported on Martha's Vineyard, Massachusetts.[8] We do not know from the case history whether this patient recently visited Martha's Vineyard. The usual incubation period for tularemia is 3 to 5 days, with a range of 1 to 21 days. The illness begins abruptly with fever, chills, headache, malaise, anorexia, and fatigue, but the presentation may also include cough, myalgias, chest discomfort, vomiting, sore throat, abdominal pain, and diarrhea. This patient had many of these symptoms.

Are the radiographic findings consistent with pneumonic tularemia? Multilobar or diffuse infiltrates occur in 30 to 74% of reported cases, whereas effusions are present in 21 to 30% of

cases, and hilar lymphadenopathy in up to 45% of cases.[7] It seems that the findings in this patient are consistent with this disease, although we might expect more lymphadenopathy with pneumonic tularemia than is seen on this patient's CT scan. This patient received many antibiotics; however, only doxycycline would be expected to have activity against tularemia, and this agent was discontinued after fewer than 3 days of use. It would not be surprising for tularemia to rapidly relapse in a patient who had short-term treatment with a bacteriostatic agent.

Does pneumonic tularemia account for the other problems on our list? A review of a 30-year experience with 88 cases of tularemia indicates that in pneumonic tularemia, sputum examination is not helpful, white-cell counts on admission range from 5000 to 22,000, elevation of the serum lactate dehydrogenase level is common, pharyngitis may be mistaken for infectious mononucleosis, and pericarditis may occur.[9] Tularemia has been described as "an enigmatic community-acquired pneumonia that does not respond to routine therapies."[1] I believe an argument for pneumonic tularemia could be made in this case. The illness is certainly enigmatic, and it did not respond to routine therapies. I would be interested in performing serologic tests for *F. tularensis*. I would also be tempted to add gentamicin or streptomycin to the patient's antibiotic coverage, depending on her clinical status. However, three things give me pause. First, the history suggests that the patient was ill before the tick bite. Second, we have not ruled out viral causes of pneumonia in a young, healthy patient. And third, the new boyfriend still lurks.

THE BOYFRIEND

What pathogens might a new boyfriend harbor? Epstein–Barr virus, herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), chlamydia, gonorrhea, syphilis, and HIV lead the list. Early in her illness, this patient had severe pharyngitis. Organisms identified among college students with acute pharyngitis include group A streptococcus, Epstein–Barr virus, influenza virus, HSV, and mycoplasma.[10] If we consider viruses that cause pharyngitis and pneumonia, Epstein–Barr virus seems unlikely, since it only rarely causes pneumonia in immunocompetent patients.[11,12] HSV-1 is also an unusual cause of pneumonia in immunocompetent patients,[13-15] but it is not unusual to find this organism in patients who have received prolonged mechanical ventilation.[16] It may be difficult to determine whether the organism is the primary cause of severe pneumonia in this case. If HSV is the culprit, can we account for the last items on our list of problems? In a case of HSV infection of the lower respiratory tract, a pericardial effusion is described in an otherwise healthy 20-year-old woman who had prolonged and severe HSV pneumonia.[17] We do have a small amount of evidence to link the pericardial effusion to HSV. Also, the crusted lesion on the lip may in fact be a healing "fever blister" and the biggest clue in this case.

In summary, although I am unable to rule out pneumonic tularemia with certainty, I believe this young, otherwise healthy patient has HSV pneumonia that she may have acquired from a new boyfriend.

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

Dr. Jeffrey A. Gelfand (Infectious Diseases): I was initially concerned about streptococcal pneumonia and legionella, which were ruled out on the basis of negative culture results, a negative test for legionella urinary antigen, and a lack of clinical response to extensive antimicrobial therapy targeting these pathogens. This young woman was a gardener and had a history of tick and cat exposure, so I also considered pneumonic tularemia, infection with *P. multocida*, and leptospirosis. Given the history of marijuana use, aspergillus pneumonia was also a consideration. Regardless of these possibilities, the patient appeared to have a viral pneumonia. When I asked her about her new boyfriend, she mentioned that she had been told not to date him because "he had something he could pass." The crusted lesion on the lip and the history of a boyfriend who might have herpes made HSV pneumonia a likely diagnosis.

When I examined the patient, I noted something else: she had weakness in her legs without a sensory defect. I became concerned about the development of the Guillain–Barré syndrome, which could fit with pneumonia caused by an influenza virus but, in my mind, could also fit with an HSV infection. Varicella–zoster virus was also considered, because if the varicella were atypical, the presentation could include both pneumonia and the Guillain–Barré syndrome.

DR. DANIEL P. HUNT'S DIAGNOSIS

Herpes simplex virus pneumonia.

CLINICAL DIAGNOSIS

Herpes simplex virus pneumonia complicated by Guillain–Barré syndrome.

PATHOLOGICAL DISCUSSSION

Dr. Martha B. Pitman: The diagnostic procedure was a bronchoalveolar lavage performed on the first day at this hospital. Cytologic examination of the bronchoalveolar-lavage fluid showed numerous cells with enlarged nuclei. The cells either had single nuclei or were multinucleated. In the multinucleated cells, the nuclei were molded together, and the chromatin pattern was very washed out and clumped around the peripheral nuclear membrane. Such ground-glass nuclear changes are called Cowdry type B viral inclusion bodies. In this case, classic Tzanck cells were apparent (Fig. 2A). There were numerous infected cells in this bronchoalveolar-lavage specimen that were associated with a background of inflammatory cells. The inflammatory cells included neutrophils, lymphocytes, histiocytes, and monocytes. The morphologic appearance of these cells and the associated inflammatory response are diagnostic of an HSV infection.

After discussing this case with Dr. Gelfand, we made a cell-block preparation from the residual bronchoalveolar-lavage fluid for additional testing. Cells in the preparation showed the classic cytopathological effect of HSV (Fig. 2B). Immunohistochemical staining for HSV-1 and for HSV-2 was positive (Fig. 2C). There is known cross-reactivity between these stains. Immunohistochemical staining for varicella was negative.

Serum antibody against HSV-1 was positive, antibody against HSV-2 was negative, and antibody against varicella was negative. These findings confirmed the diagnosis of pneumonia with HSV-1.

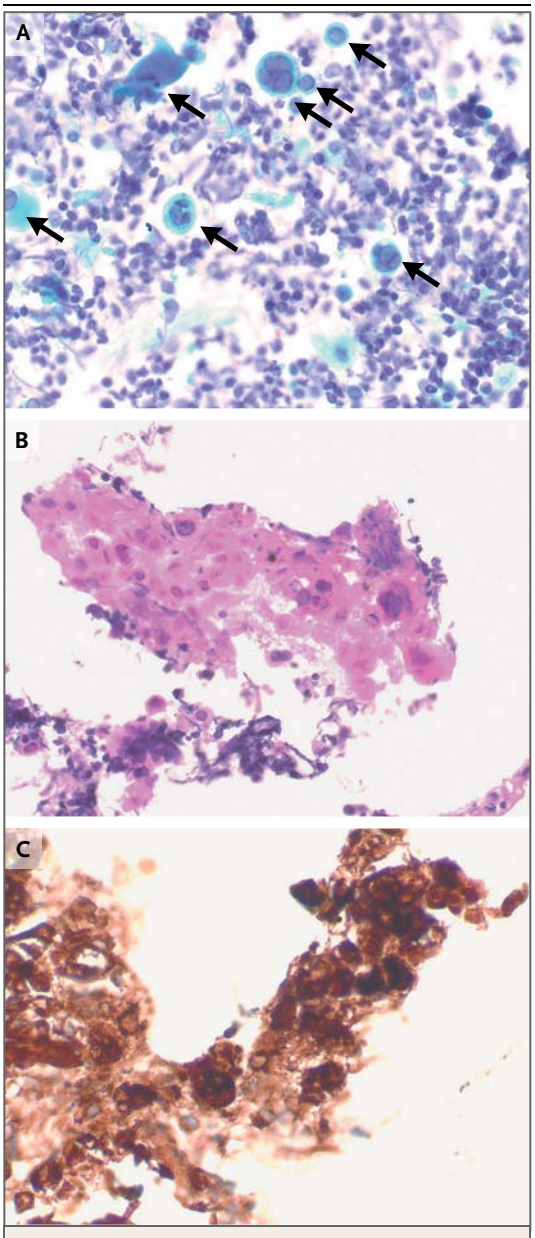

Figure 2. Cytopathological Findings.
A specimen from the bronchoalveolar-lavage fluid shows numerous Tzanck cells (Panel A, arrows; Papanicolaou stain) with cytopathological changes that are typical of herpes simplex virus (HSV) infection. Cells from a cell block prepared from the bronchoalveolar-lavage fluid show the typical cytopathological effect of HSV (Panel B, hematoxylin and eosin); both HSV-1 and HSV-2 antigens are detected with immunohistochemical staining (Panel C, immunoperoxidase).

FOLLOW-UP

Dr. Guseh: After the diagnosis was made, we instituted high-dose acyclovir therapy. Within 48 hours after therapy was begun, the patient's condition substantially improved and she was extubated and transferred to the general medical service. She received a 2-week course of acyclovir. Once she was able to ambulate, we noticed that a foot drop

had developed, more pronounced on the left side than on the right side. The neurology service was consulted, and magnetic resonance imaging, electromyography, and lumbar puncture were performed. The cerebrospinal fluid had a total protein level of 224 mg per deciliter (normal, 5 to 55) and a few white cells, findings consistent with the albuminocytologic dissociation (i.e., high levels of protein in the cerebrospinal fluid and normal cell counts) that can be associated with the Guillain–Barré syndrome. Acute inflammatory demyelinating polyneuropathy (a variant of the Guillain–Barré syndrome) was diagnosed, and the patient was immediately started on a 5-day course of intravenous immune globulin. The results of the electromyographic study later confirmed bilateral peroneal neuropathy.

The foot drop and foot weakness persisted but started to improve, and on hospital day 12, the patient was discharged to a rehabilitation facility. While she was at the rehabilitation hospital, her course was complicated by a rise in the serum creatinine level, from 0.6 mg per deciliter (53 μmol per liter) to 4.1 mg per deciliter (362 μmol per liter), which was thought to be caused by acyclovir-related crystal nephropathy. After 4 days at the rehabilitation hospital, her renal function returned to baseline; 8 days later, she was discharged home. At a follow-up visit, her condition was noted to be much improved. She still had some residual weakness in her left leg, but she had not fallen and was able to go shopping at a mall. She was still somewhat limited by shortness of breath, notably when she was climbing one or two flights of stairs.

Dr. Rosenberg: Sometimes HSV is reactivated in ill patients. How do you know whether this patient had primary HSV infection rather than reactivation?

Dr. Gelfand: It is possible that HSV was reactivated in the patient's airways and that a diffuse tracheobronchitis developed. At the very least, treatment was necessary to improve her pulmonary condition. However, I suspect that she had primary HSV infection, because the cytologic appearance of the alveolar cells convinced me that this was a primary pneumonia and not tracheobronchitis. I think the proof was in her substantial improvement within 48 hours after the initiation of acyclovir therapy.

Dr. Pitman: In addition, the bronchoalveolar-lavage specimen was not from a brushing of the trachea or the airways; it was lavage fluid from the alveoli. Also, the quality and the quantity of the infected cells are consistent with an acute infection.

ANATOMICAL DIAGNOSIS

Herpes simplex virus type 1 pneumonia.

This case was discussed at the medical case conference.

Dr. Muse reports providing expert testimony on behalf of patients in cases involving the interpretation of images of patients with asbestosis. Dr. Pitman reports payment to her institution for a patent on a system and method for identifying tissue with the use of low-coherence interferometry; she also reports receiving payment for providing expert testimony for legal firms on behalf of physicians or patients in malpractice cases involving the cytologic diagnosis of diseases of the gastrointestinal tract. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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