Acute pneumonia and systemic lupus erythematosus

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CASE PRESENTATION

MICHELLE V. SUN, MD: On March 29, 2000, a 40-year-old black woman with known systemic lupus erythematosus (SLE) presented to Baylor University Medical Center (BUMC) with fevers to 40°C (104°F), yellow to green diarrhea without blood, dyspnea, fatigue, headache, photophobia, cold sores, and a productive cough of 3 days' duration. She was on chronic prednisone therapy. Five days before admission, she had received her first dose of a course of monthly intravenous cyclophosphamide for type IV lupus nephritis and autoimmune hepatitis. She denied any new rashes, chest pain, or other gastrointestinal or urinary complaints.

Her SLE was originally diagnosed in October 1998. She was then lost to follow-up for over a year. On February 1, 2000, she was admitted to an outside hospital with complaints of fatigue, nausea, and jaundice and was found to have elevated liver function tests with an obstructive pattern. An abdominal ultrasound showed gallbladder thickening, and she subsequently underwent a laparoscopic cholecystectomy.

At the time of her surgery, her liver was found to be fatty and possibly cirrhotic. The biopsy specimen was consistent with autoimmune hepatitis. During that hospitalization, she also developed acute renal insufficiency with a creatinine of 4.1 mg/dL. She was subsequently transferred to BUMC on February 12, 2000, for further care. Her C3 and C4 levels were both low, indicating active disease. She was started on pulse-dose steroids and underwent renal biopsy, with findings consistent with type IV lupus nephritis. Her hepatic and renal functions remained stable, and she was discharged home on February 23, 2000, on prednisone 40 mg twice a day, with a creatinine of 3.8 mg/dL. Intravenous cyclophosphamide was delayed at that time because of poor healing of her surgical wounds and persistent leak of ascitic fluid.

On March 24, 2000, she had been readmitted for elective left subclavian Port-A-Cath placement and intravenous cyclophosphamide therapy (800 mg). She also received intravenous acyclovir for recurrent fever blisters. Her white blood cell count was $11.6 \times 10^3/\mu\text{L}$ (5% lymphocytes and 88% neutrophils); hematocrit, 28%; platelets, $130 \times 10^3/\mu\text{L}$; and creatinine, 1.1 mg/dL. She was discharged home the following day on prednisone and oral acyclovir.

The patient's past medical history was significant only for hypertension and SLE as described above. Her current medications, all taken orally, included lansoprazole, 30 mg daily; furosemide, 40 mg daily; amlodipine, 10 mg daily; prednisone, 40 mg

twice daily; and acyclovir, 400 mg 4 times daily. The patient noted that she had had nausea after taking ciprofloxacin and methocarbamol. She reported no family history of connective tissue disease. She was married with 2 children. She had not smoked for 2 years but did have a 10-pack-year smoking history. She denied any history of alcohol use, intravenous drug use, or transfusions.

On examination, she had fever to 39.1°C (102.4°F), tachycardia (140 beats per minute), and elevated blood pressure (170/90 mm Hg). She was thin, ill-appearing, diaphoretic, dyspneic, and slightly disoriented. Her pupils were equally round and reactive to light, and the extraocular muscles were intact. She had no adenopathy in her neck, jugular venous distention, or meningismus. Precordial examination disclosed no murmurs, rubs, or gallops. She had decreased breath sounds, with dullness to percussion at the bases, with the right much worse than the left. She had normal active bowel sounds. Her abdomen was nontender but was noted to be distended and slightly tympanitic, with a fluid wave. The liver was not enlarged. She had 2+ pitting edema to the mid calf. Her Port-A-Cath site was not tender or red. Her neurologic exam revealed mild confusion but was otherwise nonfocal.

Laboratory values at the time of admission are reported in the *Table*. On her peripheral blood smear, 2+ anisocytosis was noted, as were many Döhle bodies and 3+ toxic granules. An arterial blood gas on room air revealed a pH of 7.45; PCO₂, 30 mm Hg; PO₂, 55 mm Hg; saturation, 88%; base excess, -3; and bicarbonate, 21 mmol/L. On urinalysis, she had 3+ protein, 3+ blood, positive nitrites, trace leukocyte esterase, 3 to 5 white blood cells, 3 to 5 red blood cells, light bacteria, and 3 to 5 granular casts. Electrocardiogram revealed sinus tachycardia (rate, 140) and low voltage. Chest radiograph showed a new infiltrate in the right middle and right lower lobes. She had pleural effusions bilaterally, with the right much larger than the left.

Broad-spectrum antibiotics—including vancomycin, gentamicin, piperacillin/tazobactam, and acyclovir—were started after initial cultures were obtained. Sputum Gram's stain revealed few white blood cells and no organisms. She was given stress-dose steroids, as well as filgrastim. Ascitic fluid was not consistent with

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Table. Initial laboratory values

Sodium	136 mEq/L	Fibrinogen	591 mg/dL
Potassium	3.1 mEq/L	Fibrin split products	>20 µg/mL
Chloride	105 mEq/L	D-Dimer	0.8–1.6 µg/mL
Bicarbonate	22 mEq/L	Lactate dehydrogenase	4864 U/L
Blood urea nitrogen	27 mg/dL	White blood cell count	$1.2 \times 10^3/\mu\text{L}$
Creatinine	1.4 mg/dL	Differential	49% bands
Glucose	105 mg/dL		19% metamyelocytes
Total protein	4.5 g/dL		18% segments
Albumin	1.9 g/dL		8% lymphocytes
Total bilirubin	3.7 mg/dL	Hemoglobin	6.3 g/dL
Direct bilirubin	1.7 mg/dL	Hematocrit	19.1%
Alkaline phosphatase	159 U/L	Platelets	$28 \times 10^3/\mu\text{L}$
Aspartate aminotransferase	31 U/L	Erythrocyte sedimentation rate	130 mm/h
Alanine aminotransferase	37 U/L	Creatine phosphokinase	128 mg/dL
Prothrombin time	13.7 seconds		
Partial thromboplastin time	36.4 seconds		

bacterial peritonitis. Within hours, she became more dyspneic and hypoxemic with declining mental status and was intubated and placed on a mechanical ventilator.

On the following day, a bedside thoracentesis was performed, yielding 40 mL of yellow, slightly cloudy fluid, with a red blood cell count of $2.0 \times 10^3/\mu\text{L}$ and a white blood cell count of 340/ μL (15% leukocytes, 71% neutrophils, and 13% monocytes). pH was 7.49; glucose, 58 mg/dL; total protein, 2.46 g/dL; and lactate dehydrogenase, 12,545 U/L. Gram's stain of her pleural fluid showed no bacteria. Repeat sono-guided thoracentesis later that day drained 400 mL of bloody fluid (440,000 red blood cells). Bacterial and fungal cultures were started on both the sputum and the pleural fluid. At this point, the patient was hypotensive, required pressor support, and was anuric. Fluconazole was added to her antimicrobial regimen.

On hospital day 3, the patient was unresponsive, hypotensive (despite vasopressors), and hypoxemic. Continuous veno-venous hemodiafiltration was attempted but was not tolerated. As her stool was positive for white blood cells, a flexible sigmoidoscopy was done, revealing a mild colitis but no pseudomembranes. Metronidazole was added to her antimicrobial therapy.

On hospital day 4, her pupils became fixed and dilated. Care was withdrawn per family wishes. She died later that morning.

DIFFERENTIAL DIAGNOSIS

PETER J. KAPLAN, MD: The patient is a 40-year-old immunocompromised woman with advanced SLE and acute pleuropulmonary infection. She presented with a 3-day history of high fever with dyspnea, mucus-producing cough, and diarrhea. Examination revealed tachycardia, fever, hypotension, and apparent delirium. She had pancytopenia, disseminated intravascular coagulation (DIC), and hyponatremia. I include hyponatremia even though the case report says her serum sodium is 136 mEq/L. (The normal value in the emergency department at that time was 147 mEq/L.) She also had cholestatic elevations in her liver function tests. The electrocardiogram showed low voltage, which suggested a possibility of pericardial effusion. Her chest radio-

graph revealed lobar infiltrates with bilateral effusions, greater on the right. Paracentesis revealed essentially "benign" ascites. She rapidly progressed to septic shock with respiratory failure, renal failure, and cardiovascular collapse despite broad-spectrum antibiotics. She was also given acyclovir, stress-dose steroids, and filgrastim. Thoracentesis was performed, revealing an exudate. The pleural fluid white blood cell count was relatively low, but neutrophils were predominant. Gram's stain identified no organisms. Repeated thoracentesis revealed hemorrhagic fluid. During her hospital course, fluconazole and metronidazole were added. The patient suffered a central nervous system injury, and support was withdrawn.

I suspect the patient had an *acute bacterial pneumonia* with or without empyema, but we also have to consider *acute fungal pneumonia*, as she was at risk for opportunistic infections. Another consideration is line sepsis, with *septic pulmonary embolism*. The line, however, was inserted only 5 days

before her admission, and it is unlikely that it had become so severely infected in those 5 days to result in such profound deterioration. Infective *endocarditis* is also a possibility because of her recent surgery and line insertion, which could have been complicated by bacterial seeding of the heart valves, particularly on the right side.

I should mention some potential noninfectious causes of her deterioration. *Venous thromboembolism* is a common complication in patients with SLE, who are at high risk for deep venous clots. This patient does not have a history of anticardiolipin antibodies, lupus anticoagulant, or deep venous thrombosis, but I suspect she had had a certain degree of inactivity because of her chronic illness and recent hospitalizations. Venous thromboembolism can present with all kinds of abnormalities on chest radiograph, and these patients can rapidly deteriorate, become hypotensive, and die.

Lupus pneumonitis is generally categorized as either acute or chronic. This patient had no evidence of chronic pneumonitis, but an acute pneumonitis is possible. The progression in acute pneumonitis is rapid, but it is generally a bilateral interstitial process that would not be expected to proceed to the point of septic shock. Lastly, a *cyclophosphamide-induced lung injury* is possible, because she had just started on a course of cyclophosphamide 5 days before this admission. However, cyclophosphamide-induced lung injuries generally occur after higher doses of this medicine, 10-fold higher than what this patient received.

I think the patient had a complicated pneumonia. The question comes down to etiology in order to effect proper treatment. This depends on multiple factors: the host, the environment, and the organism. We tend to categorize pneumonia as either community acquired (in healthy hosts or abnormal hosts) or nosocomial (1). This patient presented from home, so it is possible that she had a community-acquired pneumonia. However, she also had had recent hospitalizations, which were sufficient in duration to colonize her with pathogens endemic to a hospital setting. Also, she was subjected to instrumentation with endotracheal intubation for the insertion of the Port-A-Cath. This

greatly increased her risk for nosocomial infection of the airways as well as aspiration pneumonias. Other environmental concerns would include *endemic or zoonotic exposures*. There is really no reason to suspect zoonotic exposures in this case on the basis of the history provided.

Pneumonias may be considered typical or atypical. Typical bacterial pneumonia may be lobar or segmental, but we do not tend to see diffuse radiographic abnormalities. Typical pneumonia is usually considered in patients presenting within a couple of days of onset of symptoms, and symptoms typically include dyspnea, cough productive of purulent sputum, and prostration. In contrast, atypical pneumonia often has a more indolent course, with nonproductive cough and a variety of extrapulmonary findings prominent in the presentation. Radiographs typically reveal bilateral interstitial or alveolar infiltrates in atypical pneumonia. Cavitation might suggest necrotizing organisms or anaerobes after aspiration. The chest radiograph may assist in formulating the differential diagnosis, but it can mislead.

It is important, of course, to make the proper etiologic diagnosis so that proper treatment can be implemented. The etiology of pneumonia is identified in only about half of the cases in which it is attempted, and the patient may not be cured even if we identify the source and institute appropriate therapy. Our chief methods of making a diagnosis rely on studies of the sputum and pleural fluid, blood cultures, and invasive testing such as bronchoscopy. Sputum specimens are subjected to Gram's stain and cultures. Blood cultures are positive 10% to 20% of the time (2). Culture of pleural fluid in the presence of empyema may yield bacterial growth 20% to 40% of the time if obtained prior to antibiotic initiation. Assays are being developed or already exist for certain organisms for which specific antigens or antibodies may be measured in the serum or for which protein targets may be identified in sputum specimens. Polymerase chain reaction testing is also being developed to identify certain organisms.

This patient was quite compromised. Besides having SLE, which affects all components of immunity, she had been on high-dose corticosteroids for an extended period. She also had chronic renal and liver disease, both of which predispose to certain types of pneumonia, particularly gram-negative pneumonia. She was recently intubated for her Port-A-Cath, which implies a direct compromise of the airway. She was just started on cyclophosphamide chemotherapy. Her neutrophil count was probably declining, and this may have been the final insult that enabled the pneumonia to begin.

What are the *viral possibilities*? It is not likely that this patient died of a viral pneumonia. If we consider the more common causes of viral pneumonia, influenza and varicella are chief among those. However, this patient became ill late in the influenza season, making this less likely. Influenza pneumonia tends to be bilateral, with interstitial rather than lobar infiltrates. She may have had an underlying viral illness that predisposed her to a bacterial superinfection, as influenza is known to do, but she was well when she underwent placement of her Port-A-Cath. I doubt that she had influenza. No cutaneous lesions were described to support a diagnosis of *varicella pneumonia* (3). We have no known travel history to the Four Corners states, although that is not necessary to contract Sin Nombre viral pneumonia. Cases of hantavirus pneumonia have been described in Texas, but ex-

posure to deer mouse droppings is required (4). *Cytomegalovirus pneumonia* is a possibility in this patient, because she was immunosuppressed. Cytomegalovirus pneumonia tends to be indolent and not life threatening. It is also not typical to have consolidation of 1 or 2 lobes in a cytomegalovirus disease.

Mycobacterial disease warrants consideration in anyone presenting with pneumonia or infiltrates on chest x-ray, because of the prevalence of tuberculosis. Primary pulmonary tuberculosis is often unilateral and may involve the lower lobe rather than the upper lobe; it also may be associated with effusion. It is almost never a fulminant type of disease. In immunosuppressed patients it is more aggressive, but it does not proceed to septic shock unless a secondary bacterial infection is present.

Fungal organisms also must be considered. *Blastomycosis* and *coccidioidomycosis* are endemic to certain areas. Blastomycosis does cause pulmonary infiltrates. It is more endemic in the southeastern USA and is associated with cutaneous lesions, which do not fit this case. Coccidioidomycosis is endemic to the western desert states. In fact, the development of coccidioidomycosis does not require recent exposure but may result from activation of an exposure long ago. Reactivation of latent disease occurs most commonly in immunosuppressed individuals like this patient. *Cryptococcus*, which is a ubiquitous organism, would be expected to be present in a more indolent fashion with bilateral nodular type infiltrates.

Mucormycosis is uncommon. It is particularly seen in patients with diabetic ketoacidosis, prolonged neutropenia, iron overload states, and severe malnutrition. Although this patient developed neutropenia, this was recent and probably secondary to her cyclophosphamide therapy. Mucormycosis would be more likely if the neutropenia had been present for an extended period. Mucormycosis generally causes infections in the upper airways, classically the sinuses, causing a necrotic invasive infection of the maxillary sinuses (5).

Pneumocystis has become a common illness among immunocompromised and immunosuppressed patients, who are often treated with empiric prophylaxes because of its prevalence. This disease is typically bilateral, although chest x-ray may be unremarkable. Effusions are extremely uncommon. The disease can progress to respiratory failure but generally not to septic shock.

Candida is a fungal organism that could lead to septic shock. It would be unusual to see candidiasis present as pneumonia, but the patient was started on fluconazole, so it might have been a consideration of the treating physicians. Increased mucosal candidal colonization has been seen in patients who are treated with chronic immunosuppressive medications and have been on antibiotics. If this were candidemia, it would more likely have occurred as an infection from the indwelling line, either the one that was placed surgically 5 days before her presentation or from a previous intravenous line site. *Candida* is diagnosed readily with standard blood cultures (3), and we do not have any description of positive blood cultures in the first 24 to 48 hours of her presentation.

Histoplasmosis, particularly progressive disseminated histoplasmosis, has reemerged with AIDS and increased use of immunosuppressive drugs (6). This disease usually presents with bilateral nodular infiltrates and sometimes with adenopathy. It can be a primary infection or be reactivated with the onset of immuno-

compromise. Typically, patients with histoplasmosis have hepatosplenomegaly and mucosal ulcers in the gastrointestinal tract, which are commonly bleeding because of DIC. The organisms can sometimes be seen within the neutrophils on a peripheral blood smear. These can be identified on lysis centrifugation blood cultures but do take a week or two to grow.

Invasive *aspergillosis* is worth mentioning. *Aspergillus* is a ubiquitous airborne organism, which we classically see after prolonged neutropenic episodes (3). Typically, bone marrow transplant units or other types of transplant units are most concerned about this organism. It presents as an unrelenting pneumonia with vascular invasion and metastasis to the skin and other organs. Analysis of the sputum may reveal hyphae, but bronchoscopy is often required to obtain washings or biopsies for characteristic histopathology. Some new diagnostic techniques are under development, including serum antigen tests, that will make diagnosis easier (7). *Aspergillosis* is unlikely in this patient because she had been neutropenic for only a few days.

I want to shift to what I think is the most likely cause for her illness: *bacterial pneumonia*. With bacterial pneumonia, we have uncommon, conventional, and atypical organisms. A few uncommon organisms that cause fulminant pneumonia include *anthrax* and *plague*. These are zoonotic organisms that are now in the biological arsenals of certain military groups. There is no history to suggest such exposure. *Tularemia* is another zoonotic infection. We have no history of her having handled rabbits, birds, or mice.

Nocardiosis is quite an opportunist and can cause a progressive and fatal pneumonia. It tends to be a little more indolent and is associated with metastasis to the brain.

Pneumococcus is the most common of the bacterial pneumonias. We see it in immunocompetent and immunocompromised patients. Those with immunologic or splenic abnormalities are at higher risk for bacteremia and sepsis (2). This infection follows colonization of the oropharynx with *Streptococcus pneumoniae* and typically presents with consolidation, sometimes with pleural effusion. Patients may progress to septicemia, shock, and DIC, which is compatible with this patient's presentation. Diagnosis is conclusive in approximately 50% of cases, and septic patients' blood cultures are more likely to be positive. The chances of recovering bacteria from the sputum or pleural fluid are increased in patients who are very toxic. *Pneumococcus* deserves consideration primarily because of its prevalence.

Staphylococcus infections are considered either sensitive to methicillin (MSSA) or resistant to methicillin (MRSA). Typically, *Staphylococcus* infections are hematogenous (3). In hospitalized patients, these pathogens are seen in indwelling lines, surgical or nonsurgical wounds, and a variety of other sources. Bronchopulmonary acquisition typically occurs after nasal colonization, which occurs in 20% to 40% of normal individuals (8). *Staphylococcal* pneumonia has been associated with viral lower respiratory infections, although either may occur without the other. *Staphylococcal* pneumonia is a suppurative pneumonia, frequently progressing to necrosis and pleural involvement with empyema. Some patients with staphylococcal disease present with toxic shock syndrome, although that should be associated with a diffuse rash, which was not seen in this patient. *Staphylococcus aureus* is quite readily cultured and identified from sputum, blood, and other bodily fluids when present in acute infections.

Gram-negative aerobes are those that we generally carry with us enterically. Persons who are immunocompromised and persons who have been treated with acid-blocking agents or antacids for long periods have a higher incidence of colonization of the stomach and the oropharynx with these organisms. This patient was at risk for colonization with these organisms and thus subsequent infection. It is quite possible that she had previous airway colonization with these organisms and that her intubation for line placement provided the portal of entry to the lung for these organisms. Shock is mediated by an endotoxin and may accompany a pneumonia. The worst of the gram-negative rods would be *Pseudomonas* (9). *Pseudomonas* is an opportunistic organism, and we see its colonization in about 50% of hospitalized patients from whom sputum cultures are obtained. When *Pseudomonas* colonization progresses to pneumonia, it is frequently necrotizing and proceeds to bacteremia with endotoxin-mediated shock. This is more likely to occur in immunocompromised patients. This organism is fairly easily cultured with standard laboratory techniques.

All of these bacterial organisms are possible causes of the patient's illness. The antimicrobial drugs she was receiving should have covered all of these organisms. However, because she was an immunocompromised, neutropenic patient, treatment with appropriate antibiotics may not have been sufficient for recovery.

When we think of atypical pneumonia, we usually think of mycoplasma, *Chlamydia*, and *Legionella*. The atypical presentation tends to be more indolent, with a nonproductive cough and extrapulmonary findings (2). However, *Legionella* may present in an acute, fulminant form. When treating this type of infection, high intracellular concentrations of antibiotics are necessary; a set of antibiotics different from those prescribed for typical pneumonias is usually used. Treatment duration is usually longer, and cell-mediated immunity is required for clearance. *Legionella* can be community acquired or nosocomial. Immunosuppressed patients, alcoholics, smokers with a history of >50 pack-years, or patients with renal failure, chronic obstructive pulmonary disease, or diabetes have been shown to be at higher risk for this infection. As in this patient, patients often present with complaints of diarrhea, headache, and altered mental status. Hyponatremia is also described in *Legionella*, as are abnormalities of the liver function tests (10).

The diagnosis of *Legionella* pneumonia is more difficult than that of typical pneumonias because Gram's stain of the sputum shows organisms infrequently. *Legionella* does stain gram negatively but is frequently difficult to appreciate because it doesn't hold stain well and is a small rod. Culture of *Legionella* requires a medium that is usually obtained by special request of the laboratory when *Legionella* is suspected. It takes longer to grow the organism than most other bacteria. There are other diagnostic tests: direct fluorescent antibody (DFA) stains of sputum are somewhat less specific than culture, and urinary antigen assay is rapid but picks up only sera group 1. Fortunately, sera group 1 causes 80% of *Legionella* pneumonia, so the urinary antigen test is a useful addition to cultures when this organism is suspected (11).

In summary, I think this patient was an immunocompromised woman with acute bacterial pneumonia, probably with pleural empyema and septic shock. I favor *Legionella* over *Pseudomonas*

because of the other extrapulmonary findings on presentation and the fact that none of the antibiotics used in this patient covered *Legionella* specifically.

DISCUSSION

MICHELLE V. SUN, MD: The diagnosis of Legionnaires' disease was made from a culture of the patient's pleural fluid. Her pleural fluid culture was negative initially. About 2 weeks after she died, however, routine cultures from the BUMC laboratory revealed a fastidious gram-negative rod, which prompted the laboratory to send the culture to the Texas Department of Health. Approximately 5 weeks after her death, *L. pneumophila* serotype 1 was isolated from her pleural fluid culture.

Legionnaires' disease was first recognized in the midst of a pneumonia outbreak during the 1976 American Legion Convention in Philadelphia (12). The causative agent is now known as *Legionella pneumophila*, and it is a thin, aerobic, gram-negative rod. To date, 41 species of *Legionella* have been identified, 17 of which are known to be human pathogens. *L. pneumophila* is the most pathogenic, and serotype 1 is thought to be responsible for about 80% of all *Legionella* infections (13).

Legionella are facultative, intracellular organisms. In the environment, they live in amoebae; in humans, they reside in macrophages. Cell-mediated immune responses, especially alveolar macrophages, are critical for host defense. The humoral response seems to play a secondary role. People with preexisting antibodies are still susceptible to the disease. The role of neutrophils remains unclear; it does not appear that people who are neutropenic are particularly susceptible to *Legionella* infection (14).

Water is this organism's natural reservoir. Modes of transmission include aerosolization, aspiration of contaminated water, and direct infection of surgical wounds. Person-to-person transmission has never been shown (15).

Variations in the incidence of this disease depend on which studies are examined. Important factors to consider include the degree of contamination, the immune status of those exposed, the intensity of the exposure, and the availability of diagnostic testing. *Legionella* accounts for about 6% of community-acquired pneumonias (15); however, only about 3% of sporadic cases are actually diagnosed (14). This difference is due in large part to empiric pneumonia coverage without any actual microbiologic confirmation. *L. pneumophila* tends to be a more frequent cause of severe community-acquired pneumonia (defined as requiring admission to an intensive care unit). *Legionella* pneumonia follows *S. pneumoniae* as the second most common pathogen in pneumonias requiring admission to the intensive care unit; it has been estimated that approximately 20% to 30% of severe community-acquired pneumonias are caused by *Legionella* (16, 17).

The most important risk factor for acquiring *Legionella* infection is an immunocompromised state, specifically a defective cell-mediated immunity as seen in patients with HIV, patients who have received bone marrow transplants, and patients on chronic glucocorticoid therapy. Other risk factors include underlying debilitating illnesses, smoking, alcohol abuse, and advanced age (15).

Two distinct clinical syndromes fall under the umbrella of legionellosis: Pontiac fever and Legionnaires' disease. Pontiac fever is a nonpneumonic, self-limiting, acute febrile illness. It has

an incubation period of 1 of 2 days and can be due to infection by *L. pneumophila* or other *Legionella* species. Patients have a complete recovery, often without antibiotic treatment. It is thought that strains of the bacteria with reduced virulence may play a role in this milder form of disease (15).

Legionnaires' disease has an incubation period of 2 to 10 days. Patients typically present with an acute onset of nonspecific symptoms. They often have a high fever $>40^{\circ}\text{C}$ ($>104^{\circ}\text{F}$), constitutional symptoms, and respiratory symptoms (usually shortness of breath and a mildly productive cough with occasional hemoptysis). Patients may complain of chest pain, which may be pleuritic or nonpleuritic. Between 20% and 40% of patients will have a watery, nonbloody diarrhea. Often, patients have hyponatremia, usually <130 mEq/L. Typically, Gram's stain reveals numerous neutrophils but no organisms (12).

The chest x-ray findings in Legionnaires' disease are not diagnostic. The pulmonary infiltrates that occur can also be seen with many other types of bacterial pneumonia. One third of patients will have pleural effusions. Patients, especially the immunosuppressed, may have bilateral nodular opacities that may expand and cavitate (12).

Extrapulmonary legionellosis occurs very rarely. The most commonly affected site is the heart (pericarditis, myocarditis, or prosthetic valve endocarditis). *Legionella* has also been implicated in some cases of sinusitis, cellulitis, pancreatitis, peritonitis, and pyelonephritis—usually from blood-borne dissemination from the lung (12).

Gram's stain will rarely suggest the diagnosis of legionellosis. Some small, pleomorphic, very faintly staining gram-negative rods may be seen, but often no organisms are visible. The culture becomes the definitive method of diagnosis. Sputum samples have a 40% to 50% sensitivity and 100% specificity. If a specimen from the lower respiratory tract, such as bronchoalveolar lavage fluid, can be obtained, the sensitivity is higher, around 80%. Blood has a low sensitivity, around 20%. The laboratory must specifically culture for *Legionella* on a buffered charcoal and yeast extract medium. Thus cultured, *Legionella* can be grown in 3 to 5 days (15).

DFA staining allows quick diagnosis, as results take only 2 to 4 hours. DFA can detect species other than *L. pneumophila*, but its sensitivity tends to be lower than that of culture: bronchoalveolar lavage fluid has the highest sensitivity, sputum the lowest, and tracheal aspirates in between. DFA staining tends to be less sensitive because the test is very operator dependent and requires large numbers of organisms to be readily visualized. As with culture, samples from the lower respiratory tract will be more sensitive. DFA staining can be negative early on in the course of the disease, and it becomes negative after 4 to 6 days of appropriate antibiotic treatment (15).

As mentioned by Dr. Kaplan, the urinary antigen test is very inexpensive, rapid, and noninvasive. It has good sensitivity (around 75%) and specificity (100%) and can be positive as early as 3 days after symptom onset. This test detects only antigens of *L. pneumophila* serotype 1, but this type is responsible for about 80% of all *Legionella* infections. This test can remain positive for weeks despite antibiotic therapy (15).

Serologic diagnosis is based on a 4-fold increase in antibody titer (immunoglobulin M and/or immunoglobulin G) or a single

titer of 1:256 or greater. Serologic testing has a sensitivity of 75% and a specificity of 95%. One drawback of this form of testing is that it takes 4 to 8 weeks to see a 4-fold rise in titers, even longer in the elderly. Moreover, 20% to 30% of patients will never seroconvert. Serologies are useful in epidemiologic studies, but they are less useful clinically, when convalescent titers are needed (15).

Polymerase chain reaction testing is one of the newer methods for diagnosis, and it has been used to detect *Legionella* in the urine, serum, sputum, and bronchoalveolar fluid. It has good sensitivity (50% to 80%, depending on quality of sample) and specificity (99%). This test is rapid, operator independent, and can detect *Legionella* species other than *L. pneumophila* (15).

Legionnaires' disease is associated with a more severe clinical course than the other atypical infections with which it is classified. The disease will progress if it is not treated early (18). In one study, the mortality rate in severe *Legionella* pneumonia was 14% (19). Historically, erythromycin has been the drug of choice for *Legionella* infection. This therapy has some disadvantages, including gastrointestinal intolerance, ototoxicity with high doses, and the necessity for large-volume loading to administer high doses. Quinolones have been shown to have better intracellular and lung-tissue penetration in vitro than the newer macrolides, which are more active than erythromycin. Rifampin in conjunction with a macrolide or quinolone is recommended for those who are severely ill. There have been some documented treatment successes with tetracyclines and anecdotal reports of success with imipenem, sulfamethoxazole/trimethoprim, and clindamycin. Empiric anti-*Legionella* therapy in those with severe community-acquired pneumonia is recommended, and parenteral therapy should be given until an objective clinical response is achieved. Total duration for treatment is usually 10 to 14 days or up to 3 weeks for those who are immunosuppressed (12).

Legionnaires' disease was insightfully characterized by Bartlett as a disease that is "overtreated and underdiagnosed" (20). Before the 1976 epidemic in Philadelphia, beta-lactams were the drugs of choice for virtually anyone with an "enigmatic" pneumonia, which was loosely defined as a clinical pneumonia syndrome with a sputum culture negative for conventional bacteria. Now, macrolides have emerged as the preferred treatment for patients with "enigmatic" pneumonia. It is hoped that, with advances in detection and increasing awareness of this organism as a cause of severe community-acquired pneumonias, this trend of underdiagnosis can be ended (20).

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