

Case Records of the Massachusetts General Hospital



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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Case 14-2000

PRESENTATION OF CASE

A 60-year-old man was admitted to the hospital because of pneumonia.

The patient had been well until 10 days earlier, when exertional dyspnea developed, with chills, fever, and night sweats. Two days later, his temperature rose to 40°C. Four days before being admitted to this hospital, he was admitted to another hospital, where a radiograph of the chest showed one area of consolidation in the left lower lobe, another area in the right upper lobe, and a small left pleural effusion. The white-cell count was 12,700 per cubic millimeter, with 60 percent neutrophils and 26 percent band forms. Specimens were obtained for culture. Cefuroxime therapy was begun, and cefuroxime was subsequently replaced by ceftriaxone, gentamicin, and erythromycin. The temperature rose to 40°C daily, and daily headache was reported. A sputum culture yielded gram-negative rods, which were suspected to be a species of haemophilus. By the fifth hospital day, the pleural effusion had enlarged. Microscopical examination of a sputum specimen revealed occasional gram-positive diplococci and a few gram-variable bacilli. The patient was transferred to this hospital.

The patient worked on a farm on the island of Nantucket, Massachusetts, where he was exposed to chickens, turkeys, horses, sheep, and domestic rabbits; he was not aware of any exposure to wild rabbits or deer. Seven years before admission, he had been treated with an antibiotic for Lyme disease. He was allergic to amoxicillin. His father had died of psittacosis and cardiac disease, and his mother had died of sarcoidosis. There was no history of wheeze, productive cough, hemoptysis, pleuritic chest pain, nausea, vomiting, diarrhea, weight loss, recent trav-

TABLE 1. HEMATOLOGIC LABORATORY VALUES ON ADMISSION.

VARIABLE	VALUE
Hematocrit (%)	38.2
Mean corpuscular volume (μm^3)	99
White-cell count (per mm^3)	10,300
Differential count (%)	
Neutrophils	69
Band forms	6
Lymphocytes	19
Reactive lymphocytes	2
Monocytes	4
Platelet count (per mm^3)	323,000
Prothrombin time	Normal
Partial-thromboplastin time	Normal

TABLE 2. BLOOD CHEMICAL VALUES.*

VARIABLE	ON ADMISSION	8TH HOSPITAL DAY
Protein (g/dl)	5.8	
Albumin	2.1	
Globulin	3.7	
Calcium (mg/dl)	7.9	
Sodium (mmol/liter)	141	Normal
Potassium (mmol/liter)	4.1	Normal
Chloride (mmol/liter)	97	Normal
Carbon dioxide (mmol/liter)	29.4	Normal
Magnesium (mmol/liter)	1.2	Normal
Aspartate aminotransferase (U/liter)	94	43
Lactate dehydrogenase (U/liter)	431	286
Alkaline phosphatase (U/liter)	251	162

*To convert the value for calcium to millimoles per liter, multiply by 0.250. To convert the value for magnesium to milliequivalents per liter, divide by 0.5.

el, or exposure to persons with tuberculosis or other acute illnesses, and there were no risk factors for human immunodeficiency virus (HIV) infection.

The temperature was 38.5°C, the pulse was 75, and the respirations were 22. The blood pressure was 100/80 mm Hg.

On examination, the patient was slightly tachypneic. No skin lesions or enlarged lymph nodes were found. Dullness and crackles were present at the base of the left lung, with egobronchophony, and consolidation was detected at the apex of the right lung.

Laboratory tests were performed (Tables 1 and 2).



Figure 1. Radiograph of the Chest Obtained on Admission, Showing a Moderate Left Pleural Effusion and Consolidation Involving Almost the Entire Left Lung and Part of the Right Upper Lobe.

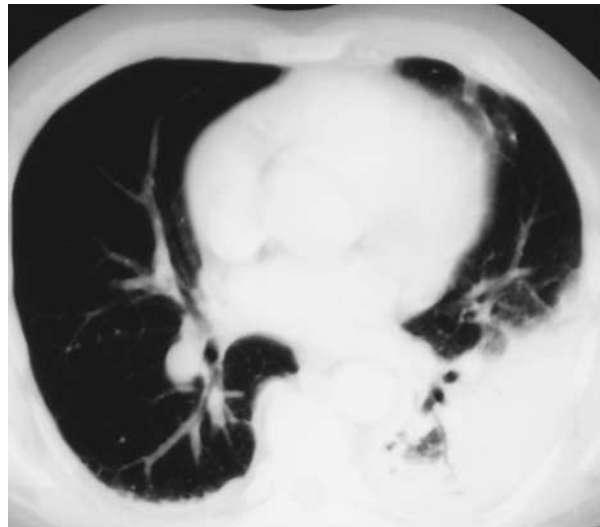


Figure 2. CT Scan of the Chest Showing Consolidation in the Left Lower Lobe.

TABLE 3. FINDINGS ON EXAMINATION OF THE PLEURAL FLUID.

VARIABLE	FINDING
Appearance of fluid	Yellow, moderately turbid
White-cell count (per mm ³)	666
Differential count (%)	
Neutrophils	31
Lymphocytes	56
Monocytes	5
Nonhematic cells	8
pH	8
Glucose (mg/dl)*	116
Protein (g/dl)	3.6
Lactate dehydrogenase (U/liter)	2818
Microscopical findings	No malignant cells and no microorganisms (including acid-fast bacilli and fungi)
Test for HIV antibodies†	Negative
Test for urinary legionella antigen (<i>Legionella pneumophila</i> serogroup 1)	Negative

*To convert the value for glucose to millimoles per liter, multiply by 0.05551.

†HIV denotes human immunodeficiency virus.

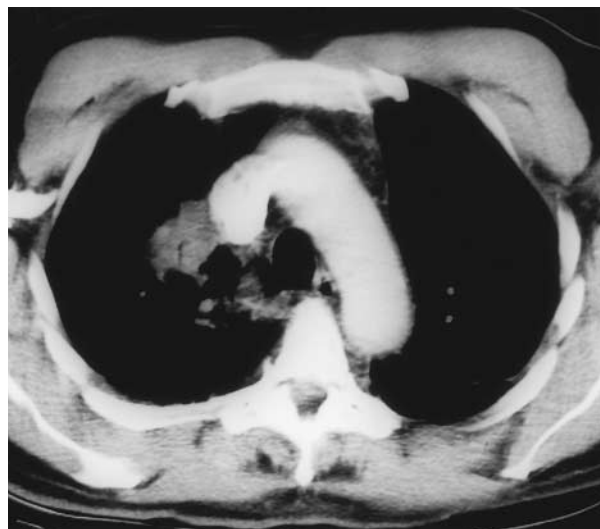


Figure 3. CT Scan of the Chest Showing a Nodular Opacity in the Right Upper Lobe with Air Bronchograms.

The oxygen saturation was 94 percent while the patient was breathing ambient air. A radiograph of the chest (Fig. 1) revealed diffuse air-space disease in the right upper lung zone and in the left lung except for the apex. A left pleural effusion was present. A left-sided thoracentesis was performed (Table 3).

Specimens of blood, sputum, and pleural fluid were obtained for bacterial and viral cultures. Ceftriaxone (2 g daily), erythromycin (1 g every 6 hours), and vancomycin (1 g every 12 hours) were infused intravenously. Nebulized albuterol and supplemental oxygen were provided. The temperature rose to 39°C on the day of admission, to 38.7°C on the second hospital day, and to 38.1°C on each of the next three days. Thereafter, the temperature did not exceed 37.6°C. On the second hospital day, a chest

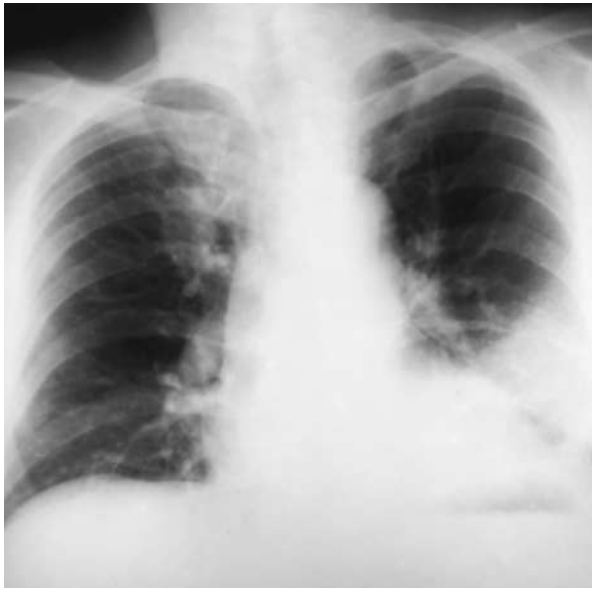


Figure 4. Radiograph of the Chest Obtained Just before the Patient's Discharge from the Hospital. There is improvement in the opacities in the left lower lobe and right upper lobe and a decrease in the left pleural effusion.

tube was inserted to drain the left pleural effusion. On the following day, a computed tomographic (CT) scan of the chest (Fig. 2 and 3), obtained after the intravenous administration of contrast material, showed a mass, 2 cm in diameter, in the right upper lobe, with air bronchograms; ground-glass opacification in the right upper and right lower lobes; air-space consolidation in the left lower lobe; and volume loss in both lower lobes. The administration of vancomycin was discontinued.

On the fourth hospital day, the patient felt better, although he coughed up blood-streaked sputum. All culture specimens remained negative. A tuberculin skin test (purified protein derivative, 5 TU) was negative, and a skin test with candida antigen was positive at 48 hours. The chest tube was removed on the fifth hospital day, 24 hours after the drainage of fluid had stopped. Fiberoptic bronchoscopic examination revealed no purulent material or obstructing lesions. Microscopical examination of bronchoalveolar-lavage fluid showed no neutrophils and no fungi, acid-fast bacilli, or other microorganisms. In addition to routine cultures, cultures for legionella, fungi, and viruses were obtained.

On the eighth hospital day, the patient was afebrile, without cough, dyspnea, or chest pain. Examination showed only a few crackles at the base of the left lung. Laboratory tests were repeated (Table 2). A subsequent sputum culture performed at the referring hospital yielded colonies of *Candida albicans* and normal respiratory tract flora, as well as one col-

ony of gram-negative rods. The culture was sent to another laboratory for identification of the gram-negative colony.

On the 11th hospital day, chest radiographs showed improvement in the air-space opacities and in the pleural effusion (Fig. 4). All culture specimens remained negative. On the 12th day, the administration of ceftriaxone and erythromycin was discontinued. The patient was discharged with instructions to take clarithromycin (500 mg twice a day) for 14 days.

A diagnostic report was received.

DIFFERENTIAL DIAGNOSIS

DR. DANIEL S. SHAPIRO*: May we review the radiologic studies?

DR. BRADLEY SABLOFF: The chest radiograph obtained on admission to this hospital (Fig. 1) shows consolidation in the left lung, except for the apex; an area of increased opacity in the right upper lung zone; and a moderate left pleural effusion. A CT scan of the chest obtained the next day, during drainage of the effusion, shows an area of consolidation in the left lower lobe (Fig. 2). In the right upper lobe, there is a nodular opacity (Fig. 3), 2 cm in diameter, which contains air bronchograms. The radiograph obtained just before discharge (Fig. 4) reveals decreased opacity in the left lower and right upper lung zones and a small, residual, left pleural effusion.

DR. SHAPIRO: A diagnosis of either primary or metastatic cancer must be considered in a 60-year-old patient with a mass-like opacity in a lung and a pleural effusion. However, the presence of high fever, the prominent leftward shift in the peripheral-blood leukocyte count, and the clinical response to antibiotics suggest the presence of an infectious process rather than a malignant tumor. The patient had a negative serologic test for antibodies to HIV and was apparently immunocompetent. The presence of the disease in both lungs and the absence of an identifiable endobronchial obstruction make a postobstructive pneumonia unlikely. There was no history of aspiration, focal neurologic deficit, or altered sensorium — findings that would suggest the presence of an aspiration pneumonia. Therefore, the patient probably had a community-acquired pneumonia. Organisms that may cause community-acquired infectious pneumonia in immunocompetent adults are listed in Table 4.¹

This patient's history is notable for his contact with many different animals. There are reportedly more than 175 zoonotic diseases.² Although zoonotic causes of pneumonia are uncommon in the United States, this patient's exposure to animals suggests that his

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TABLE 4. ORGANISMS THAT CAUSE COMMUNITY-ACQUIRED PNEUMONIA IN IMMUNOCOMPETENT ADULTS.

Common agents
<i>Streptococcus pneumoniae</i>
<i>Mycoplasma pneumoniae</i>
<i>Staphylococcus aureus</i>
<i>Chlamydia pneumoniae</i>
Legionella species
Other aerobic, gram-negative bacilli
Influenza A virus
Occasional agents
<i>Haemophilus influenzae</i>
Mycobacteria
Adenovirus
<i>Moraxella catarrhalis</i>
<i>Neisseria meningitidis</i>
Group A beta-hemolytic streptococci

TABLE 5. CAUSES OF ZOONOTIC PNEUMONIA.

<i>Bacillus anthracis</i> (anthrax)
<i>Bordetella bronchiseptica</i>
Brucella species (brucellosis)
<i>Burkholderia mallei</i> (glanders)
<i>Chlamydia psittaci</i> (psittacosis, ornithosis)
<i>Coxiella burnetii</i> (Q fever)
Hendra virus, formerly known as equine morbillivirus
<i>Francisella tularensis</i> (tularemia)
Influenza A virus, avian and swine strains (influenza)
Leptospira species (leptospirosis)
<i>Mycobacterium bovis</i> and <i>Mycobacterium tuberculosis</i>
<i>Pasteurella multocida</i> (pasteurellosis)
<i>Rhodococcus equi</i>
<i>Rickettsia rickettsii</i> (Rocky Mountain spotted fever)
Sin Nombre virus and other hantaviruses (hantavirus pulmonary syndrome)
<i>Toxoplasma gondii</i> (toxoplasmosis)
Toxocara species (visceral larva migrans)
<i>Yersinia pestis</i> (plague)

pneumonia may have had such a cause. In this case, I shall discuss zoonotic causes of pneumonia, including clinical microbiologic aspects of the pathogens, taking an approach similar to that of a previously published case report of pneumonia in a veterinarian.³ Many of the organisms that can cause zoonotic pneumonia (Table 5) can be used in biologic warfare and bioterrorism.⁴ Clinicians and microbiologists must therefore be alert to the possibility that diseases caused by these organisms may occur outside their established geographic range.

In this case, most of the common causes of uncomplicated community-acquired pneumonia can be ruled out by the slow response of the infection to

antibiotics, but I shall discuss several causes that are included in the differential diagnosis. I shall also discuss some less common types of pneumonia, with a focus on zoonotic infections because of the patient's history of exposure to animals.

This patient's fever, headache, and prominent radiographic findings are consistent with most forms of atypical pneumonia, of which the most common cause is *Mycoplasma pneumoniae*. Numerous mycoplasma species have been recovered from domestic animals.⁵ An unusual species is *Mycoplasma arginini*, which has been isolated from sheep and goats and from the blood and bronchial washings of a patient with non-Hodgkin's lymphoma.⁶ Infection with a zoonotic mycoplasma is a very unlikely diagnosis in this case, however, since the patient was immunocompetent. Zoonotic mycoplasma infections have been described only as case reports in the literature. Also, mycoplasmal pneumonia is characterized by a prominent cough, which this patient did not have, and he had relative bradycardia, which has not been described as a feature of mycoplasmal pneumonia.

The clinical features of this case can be explained by infection with *Chlamydia psittaci*. Although most commonly associated with pet birds, this organism can infect all species of birds. Of the 1025 cases of human psittacosis reported to the Centers for Disease Control from 1975 to 1984 for which a probable source of infection was identified, 159 (16 percent) were attributed to exposure to turkeys.⁷ In humans, pneumonia caused by chlamydia often has a gradual onset, with upper respiratory tract symptoms, and is frequently associated with severe headache as well as relative bradycardia,⁸ both of which were present in this case. The disease is usually not severe.

Legionella pneumophila causes approximately 90 percent of cases of legionellosis; *L. micdadei* is the next most common cause.⁹ *L. pneumophila* serogroup 1 accounts for the majority of cases of legionellosis and is the only serogroup that can be detected with the commercially available test for urinary legionella antigen. Culture of this organism requires special medium, such as buffered-charcoal yeast-extract agar. It is impossible to rule out legionellosis in this patient on the basis of the negative urinary antigen test, but the negative result decreases the probability that *L. pneumophila* serogroup 1 is the causative organism. Legionellosis has been associated with relative bradycardia^{8,10} and would be the most likely cause of this patient's illness, were it not for his history of exposure to animals.

Mycobacterium tuberculosis and, less often, *Mycobacterium bovis* can cause community-acquired pneumonia. Usually tuberculosis is acquired by contact with persons who have tuberculosis, but it can also be acquired by the consumption of contaminated milk. In rare cases, mycobacterial pneumonia is acquired as a zoonosis by the respiratory route. The negative tu-

berculin skin test in this patient makes the diagnosis of tuberculosis unlikely, because a negative test is uncommon in the presence of tuberculous pleurisy. Infection with *Leptospira interrogans* can cause pneumonia, but the patient had no known exposure to contaminated water and did not have the conjunctival suffusion and biphasic illness characteristic of infection with this organism. Also, the radiographic finding of a mass-like opacity in the right lung would be an unusual feature of leptospirosis.

Since the patient was exposed to horses and to soil, the equine pathogen *Rhodococcus equi* is a possible cause of his pneumonia. This gram-positive, catalase-positive rod is a facultative intracellular pathogen that has been reported to cause pneumonia most often in patients whose cell-mediated immunity is compromised, especially those with the acquired immunodeficiency syndrome. In this type of pneumonia, pulmonary lesions often cavitate, and pleural effusions have been reported.¹¹ The illness is typically less severe than it was in this patient, however, and he was not known to be immunocompromised.

Rocky Mountain spotted fever, a tick-borne disease found in the area of Massachusetts that includes Nantucket, may be manifested as a community-acquired pneumonia. Headache is often prominent, and a rash develops in approximately 80 percent of cases.¹² However, this patient did not have a rash, nor did he have myalgia, thrombocytopenia, or hyponatremia. In the absence of these findings, I shall rule out that diagnosis.

Coxiella burnetii, the cause of Q fever, can also cause atypical pneumonia. The usual sources of infection are exposure to aerosols containing infected placental products from sheep and other farm animals and exposure to cats giving birth.¹³ Although this patient had been exposed to sheep, the extent of his exposure is unclear. This bacterium is hardy, however, and survives well in the environment. The patient's daily headache is consistent with the diagnosis of Q fever. Finally, although influenza A virus has been transmitted to humans by both poultry¹⁴ and swine,¹⁵ the radiographic findings in this case do not suggest a viral pneumonia.

In the absence of a bioterrorist event, several causes of pneumonia can be dismissed on the basis of their geographic distribution. Pneumonic plague, which can result from contact with small mammals, including cats,¹⁶ occurs in the southwestern United States but not in Massachusetts. Inhalational anthrax is very uncommon in the United States. Glanders, a disease that may be transmitted to humans by horses and other equus species, has not been reported in the United States since 1938.¹⁷ Although patients with blastomycosis may present with pneumonia and radiographic findings suggestive of a mass, this patient's clinical response to antibiotics and the absence of a history of recent travel make this diagnosis unlikely.

Hantavirus pulmonary syndrome, originally reported in the southwestern United States in 1993, may be caused by any of several members of the hantavirus genus. The virus responsible for the initial outbreak, Sin Nombre virus, was identified in the deer mouse, *Peromyscus maniculatus*. Although the syndrome has been reported outside the southwestern United States, its occurrence in Massachusetts has not been confirmed. Also, the course of the illness, characterized by a rapid progression to noncardiogenic pulmonary edema, hypotension, and hemoconcentration, is unlike this patient's clinical course.¹⁸ Another virus, Hendra virus, can be transmitted from infected horses to humans,¹⁹ causing a potentially fatal pneumonia or meningoencephalitis; however, this infection has been limited to Australia, where its reservoir is pteropid bats.

Among the parasitic pneumonias that can be caused by exposure to animals, toxoplasmosis, which is acquired by consumption of undercooked meat and less often by exposure to contaminated cat feces, is unlikely to occur in an immunocompetent person. The absence of eosinophilia and the clinical response to antibiotics in this case also make visceral larva migrans involving the lungs, another parasitic pneumonia, an improbable diagnosis.

The first sputum culture obtained at the referring hospital yielded gram-negative rods that were suspected to be a species of haemophilus. The appropriate role of Gram's staining and culture of sputum in the evaluation of patients with community-acquired pneumonia is controversial,^{20,21} but in this case it would be helpful to have detailed information about the initial Gram's staining of the first sputum culture. Was a gram-negative bacillus the predominant bacterial organism in this culture? Was the organism the same as the one found in the second culture, which was sent to another laboratory for identification? It is very unusual for a diagnostic-microbiology laboratory to pursue identification of the species of a single colony of a gram-negative bacillus in a culture in which normal respiratory tract flora are also present, unless the physician who ordered the culture specifically requests that a particular organism be identified. Communication between the physician and the laboratory is important in such cases.

Since the gram-negative bacillus initially isolated was suspected to be a species of haemophilus, I assume that its growth was supported by chocolate agar, a nonselective medium that contains both X factor and V factor. *Haemophilus influenzae* is not difficult to identify, nor are most of the other haemophilus species. Organisms that can cause pneumonia and that may be confused with these species include *Pasteurella multocida* and bordetella, brucella, and francisella.

Past. multocida, an oxidase-positive, gram-negative coccobacillus, has been isolated from numerous animal hosts. It causes pneumonia in calves, sheep, pigs,

rabbits, and poultry.¹⁵ In humans, the organism is commonly isolated from wounds caused by animal bites, especially those of cats, and has been reported to cause osteomyelitis, bacteremia, and meningitis.²² It also causes pneumonia, particularly in patients with preexisting pulmonary disease. This patient was exposed to animals that might have been infected with *Past. multocida*. Although the organism does not grow on MacConkey agar and can be confused with *H. influenzae* on Gram's staining, it grows well on sheep's-blood agar and is easily identified with commercially available kits. It is unlikely that it would be sent to a reference laboratory for identification.

Bordetella bronchiseptica, one of the causes of kennel cough in dogs, also causes atrophic rhinitis in pigs and snuffles in rabbits.⁵ It has been isolated from patients with pneumonia, some of whom were exposed to animals.^{23,24} In one well-documented case,²⁴ a woman who had pneumonia followed by persistent infection with *B. bronchiseptica* was found to have a strain that was identical on pulsed-field gel electrophoresis to a strain isolated from her pet rabbit. The veterinary literature offers specific recommendations for preventing *B. bronchiseptica* infection in immunocompromised persons who have pets.²⁵ This organism tends to grow readily on MacConkey agar. Its motility distinguishes it from haemophilus species.²⁶

The frequency of brucellosis in the United States has declined in recent years. Pulmonary brucellosis is unusual; in a study of 160 abattoir-associated cases, there were no abnormal findings on chest radiographs.²⁷ Therefore, it would be surprising for a patient with brucellosis to present with predominantly pulmonary manifestations. *Brucella* species are slowly growing, gram-negative bacilli, but unlike haemophilus species, they require X factor and V factor for growth and isolation. In the absence of a positive culture, the diagnosis of brucellosis is often established on the basis of serologic findings. It is worth noting that infection with *Brucella canis*, the least common cause of brucellosis, does not result in seroconversion to the standard antigen used in the diagnosis of this disease.

Francisella tularensis, the cause of tularemia, is a fastidious, gram-negative coccobacillus. Its isolation is difficult and hazardous, and the laboratory should be informed when the organism is considered a possible pathogen so that appropriate methods of growth are used and the risk of accidental exposure is minimized. *F. tularensis* usually grows slowly on routine laboratory mediums, and primary isolation is best accomplished with an enriched medium containing cysteine, such as cysteine–glucose blood agar. Thayer–Martin medium may be useful in isolating the organism from a mixed bacterial population.²⁶ In one study, seven strains of *F. tularensis* that did not require cysteine on primary isolation and that were initially identified as haemophilus species or “un-

identified gram-negative bacilli” were subsequently identified as *F. tularensis*.²⁸ Isolates of *F. tularensis* from two patients were reported to grow well on sheep's-blood agar, chocolate agar, modified Thayer–Martin agar, and trypticase soy agar.²⁹ These two isolates were not agglutinated by commercially available *F. tularensis* antiserum. The absence of such agglutination compounded the difficulty of identifying these atypical isolates, as did the use of commercially available identification kits, which incorrectly identified the organism in one isolate and identified no organisms in the other isolate.²⁹ Interestingly, serum samples drawn from both patients during their convalescence were negative for the *F. tularensis* antigens used in commercially available tube-agglutination assays. In one reported case of tularemic pneumonia, a sputum culture with a light growth of gram-negative rods tentatively identified as a haemophilus species was not investigated further until the attending physician insisted that it be sent to the state laboratory, where it was identified as *F. tularensis*.³⁰ *F. tularensis* has been grown on buffered-charcoal yeast-extract agar, the same medium that is used to isolate legionella species.³¹

Tularemia can be acquired from direct or indirect contact with numerous mammals,³² the bites of ticks or deer flies,³³ the consumption of contaminated water, or the inhalation of the infecting organism. On Nantucket, which has many ticks, tularemia is endemic. Lagomorphs such as rabbits, hares, and jackrabbits are reservoirs of the organism and can transmit the disease to humans. It is unlikely that this patient's contact with domestic rabbits conferred the degree of risk associated with skinning or eating a wild rabbit, but the domesticity of the rabbits to which he was exposed should be confirmed. According to the veterinary literature, no cases of tularemia have been reported to result from exposure to *Oryctolagus cuniculus*,³⁴ the European rabbit, which is the species that has been domesticated.

The absence of a known tick bite, ulcer, or lymphadenopathy does not rule out the diagnosis of tularemia, since in cases of typhoidal tularemia, pulmonary involvement can occur in the absence of these features. In Finland, farmers have acquired tularemia from airborne transmission of the organism during the cutting of fresh hay.³⁵ The patient under discussion worked outdoors and may have inhaled the organism while mowing grass that contained droppings from small animals. Since the radiographic appearance of pulmonary tularemia can resemble that of cancer, tuberculosis, or mycotic infection,³⁶ and since severe headache and relative bradycardia can also be features of tularemia,³⁷ the findings in the current case are consistent with this diagnosis. Although streptomycin remains the drug of choice for the treatment of tularemia, erythromycin has also been successful.³¹

In this case I cannot distinguish among legionel-

losis, Q fever, psittacosis, and tularemia with certainty, but because of the exposure history, psittacosis and tularemia are the two leading diagnoses. Several features of this case — the patient's exposure to several kinds of animals in an area where tularemia is endemic, the presence of pneumonia with a pleural effusion and a mass-like opacity, and the growth of a gram-negative bacillus thought to be a haemophilus species — lead me to favor the diagnosis of tularemia.

DR. DAWN L. DEMEO: Our differential diagnosis included multiple zoonoses, tuberculosis, and cancer. We initially implemented isolation precautions and negative air-flow pressure, according to hospital policy. An additional finding on physical examination was an eschar on his left ear, which the patient said had been there for about a month.

DR. SHAPIRO: An eschar suggests that the source of the infection was an arthropod.

CLINICAL DIAGNOSIS

? Community-acquired pneumonia, ? zoonotic.

DR. DANIEL S. SHAPIRO'S DIAGNOSIS

Tularemia.

PATHOLOGICAL DISCUSSION

DR. EUGENE J. MARK: The sputum culture contained 150 colonies of normal flora, 50 colonies of *Cand. albicans*, and 1 colony of gram-negative rods, which proved to be *F. tularensis*. The physicians at the other hospital had considered the possibility of tularemia, and their clinical suspicion had prompted the special investigation of the single colony on the culture plate.

Nowadays, fatal cases of tularemia are rare, and receipt of tissue from patients with tularemic pneumonia is even more unusual. A few months ago, I examined slides of specimens from a young man who had just returned to Colorado from field duty in Wyoming with the U.S. Army Reserve. He had become febrile, and pulmonary nodules were found on his chest film. Examination of an open-lung–biopsy specimen showed necrotizing bronchiolitis and bronchopneumonia. The bronchioles were filled with pus, and their walls were replaced by histiocytes (Fig. 5). Abscesses containing nuclear dust lay within sheets of histiocytes (Fig. 6). The septal veins were thrombosed, and fibrin clots were present in air spaces (Fig. 7). Descriptions of the pathology of tularemia in the early literature include changes similar to those seen in this case from Colorado.³⁸⁻⁴² Lobar pneumonia, caseous necrosis, and empyema and abscesses with histiocytes in the walls of organs other than the lung have been reported. Organisms are difficult to see within the necrotic material on Giemsa and Gram's stains but can be identified by immunofluorescence.⁴²

The clinicopathologic forms of tularemia include

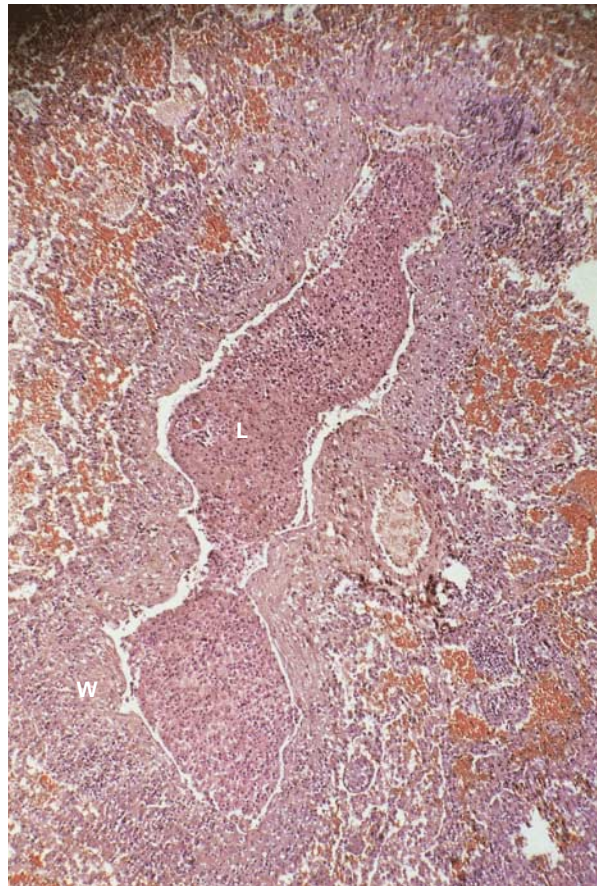


Figure 5. Necrotizing Bronchiolitis in Another Patient with Tularemia (Hematoxylin and Eosin, $\times 50$).

The lumen (L) is filled with purulent exudate. W denotes wall.

ulceroglandular, pharyngeal, typhoidal, bubonic, and pulmonary tularemia, depending on the organ system predominantly involved.^{37,39,41,42} Cutaneous and ocular forms develop mainly after transmission by direct contact of the organism with the skin or eye, respectively. Originally considered to be a species of *pasteurella*, the organism was subsequently reclassified and named to honor Edward Francis, who wrote the seminal article on the disease in 1925.⁴³

DR. CHARLES PERAKIS: What percentage of community-acquired pneumonias are zoonotic?

DR. SHAPIRO: The percentage is very small, except in areas where exposure to causative organisms is common.

DR. MARK: There was a high concentration of lactate dehydrogenase in this patient's pleural fluid. Did he have tularemic empyema?

DR. SHAPIRO: Since the fluid was not grossly purulent and contained less than 1000 white cells per cubic millimeter and neither the glucose level nor pH was low, I would not diagnose an empyema. An-

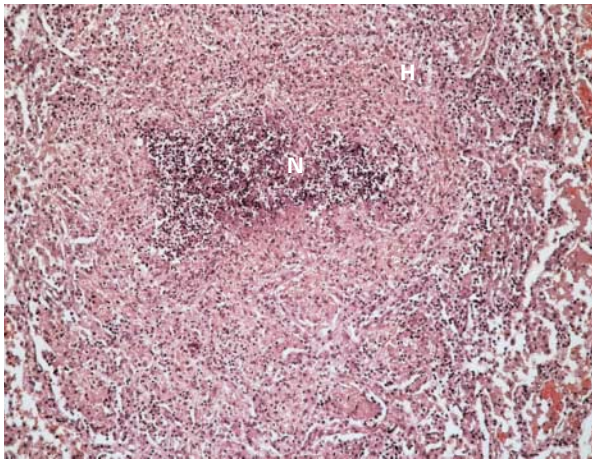


Figure 6. Small Abscess in the Lung in Another Patient with Tularemia (Hematoxylin and Eosin, $\times 100$). A coagulum of neutrophils and nuclear dust (N) is surrounded by histiocytes (H).

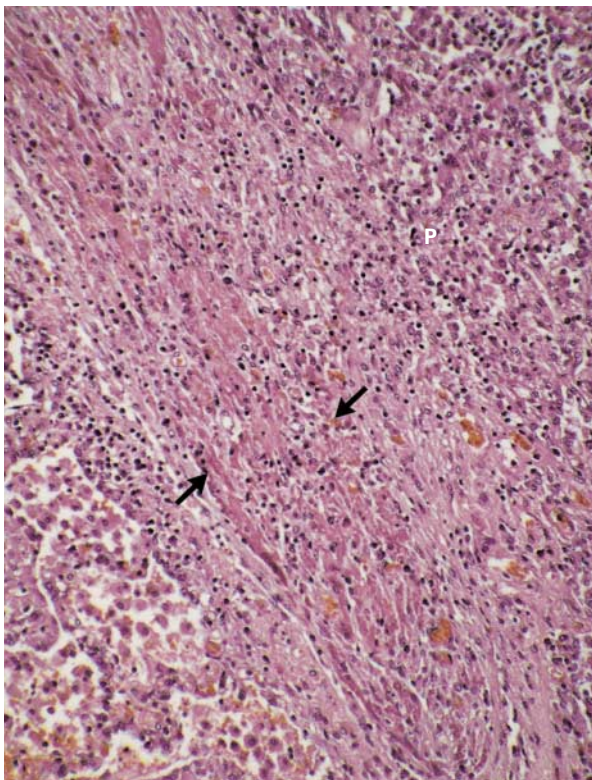


Figure 7. Organizing Thrombus (Arrows) in a Pulmonary Vein in Another Patient with Tularemia (Hematoxylin and Eosin, $\times 125$). The septum that contains the vein is surrounded by fibrinous pneumonia (P).

other finding that would be expected in cases of empyema is a low pH in pleural fluid. In this case, the pH was 8, which is 0.4 unit above the highest level in a study of 178 cases of pleural effusion reported by Light et al.⁴⁴ This level is very unusual, although there have been a few case reports of a very high pH in pleural-fluid specimens due to the presence of proteus species.^{45,46} Proteus is an uncommon cause of community-acquired pneumonia, however, and was not recovered from this patient's sputum.

Remarkably, the pleural-fluid pH, which is the basis for making clinical decisions in cases of cancerous and parapneumonic effusions, is not always measured with a blood gas analyzer,⁴⁷ even though it is this device that has been used to demonstrate the diagnostic utility of the analyte.⁴⁴ The use of pH paper yields values that are higher than those obtained with a blood gas analyzer and are therefore inaccurate.^{47,48} The use of a pH meter has also been shown to be inaccurate, unless the specimen is analyzed immediately after it is placed in the cuvette and the temperature is properly controlled.⁴⁸ In this case, the pH of 8 was probably an artifact.

DR. DEMEO: The patient received five doses of gentamicin and several doses of rifampin initially because of the possibility of tuberculosis. He was discharged with instructions to take clarithromycin. He did not completely recover, and because of the risk of relapse, a complete course of gentamicin was administered. A few weeks later, he felt normal and returned to his farming.

ANATOMICAL DIAGNOSIS

Tularemic pneumonia.

REFERENCES

1. Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995;333:1618-24.
2. Weinberg AN. Zoonoses. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 4th ed. Vol. 2. New York: Churchill Livingstone, 1995:2790-5.
3. Case Records of the Massachusetts General Hospital (Case 27-1985). *N Engl J Med* 1985;313:36-42.
4. Sidell FR, Takafuji ET, Franz DR. *Medical aspects of chemical and biological warfare: textbook of military medicine. Part 1. Warfare, weaponry and the casualty*. Vol. 3. Washington, D.C.: Army Medical Department, 1997.
5. Quinn PJ, Carter ME, Markey BK, Carter GR. *Clinical veterinary microbiology*. New York: Wolfe Publishing, 1994.
6. Yechouron A, Lefebvre J, Robson HG, Rose DL, Tully JG. Fatal septicemia due to *Mycoplasma arginini*: a new human zoonosis. *Clin Infect Dis* 1992;15:434-8.
7. Psittacosis surveillance, 1975-1984. Atlanta: Centers for Disease Control, 1987.
8. Ostergaard L, Huniche B, Andersen PL. Relative bradycardia in infectious diseases. *J Infect* 1996;33:185-91.
9. Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997;337:682-7.
10. Swartz MN. Clinical aspects of Legionnaires' disease. *Ann Intern Med* 1979;90:492-5.
11. Prescott JE. *Rhodococcus equi*: an animal and human pathogen. *Clin Microbiol Rev* 1991;4:20-34.
12. Thorner AR, Walker DH, Petri WA Jr. Rocky Mountain spotted fever. *Clin Infect Dis* 1998;27:1353-60.
13. Langley JM, Marris TJ, Covert A, Waag DM, Williams JC. Poker players' pneumonia: an urban outbreak of Q fever following exposure to a par-turient cat. *N Engl J Med* 1988;319:354-6.

14. Isolation of avian influenza A(H5N1) viruses from humans — Hong Kong, May–December 1997. *MMWR Morb Mortal Wkly Rep* 1997;46:1204-7.
15. McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. *Arch Intern Med* 1990;150:213-5.
16. Doll JM, Zeitz PS, Ertstad P, Bucholtz AL, Davis T, Gage K. Cat-transmitted fatal pneumonic plague in a person who traveled from Colorado to Arizona. *Am J Trop Med Hyg* 1994;51:109-14.
17. Sanford JP. *Pseudomonas* species (including melioidosis and glanders). In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. 4th ed. Vol. 2. New York: Churchill Livingstone, 1995:2003-9.
18. Moolenaar RL, Breiman RF, Peters CJ. Hantavirus pulmonary syndrome. *Semin Respir Infect* 1997;12:31-9.
19. Murray K, Rogers R, Selvey L, et al. A novel morbillivirus pneumonia of horses and its transmission to humans. *Emerg Infect Dis* 1995;1:31-3.
20. Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998;26:811-38.
21. Niederman MS, Bass JB Jr, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis* 1993;148:1418-26.
22. Weber DJ, Wolfson JS, Swartz MN, Hooper DC. *Pasteurella multocida* infections: report of 34 cases and review of the literature. *Medicine (Baltimore)* 1984;63:133-54.
23. Woolfrey BF, Moody JA. Human infections associated with *Bordetella bronchiseptica*. *Clin Microbiol Rev* 1991;4:243-55.
24. Gueirard P, Weber C, Le Coustumier A, Guiso N. Human *Bordetella bronchiseptica* infection related to contact with infected animals: persistence of bacteria in host. *J Clin Microbiol* 1995;33:2002-6.
25. Greene CE. Immunocompromised people and pets. In: Greene CE, ed. *Infectious diseases of the dog and cat*. Philadelphia: W.B. Saunders, 1998:710-17.
26. Weyant RS, Moss CW, Weaver RE, et al. Identification of unusual pathogenic gram-negative aerobic and facultatively anaerobic bacteria. 2nd ed. Baltimore: Williams & Wilkins, 1996:xxv, 727.
27. Buchanan TM, Faber LC, Feldman RA. Brucellosis in the United States, 1960-1972: an abattoir-associated disease. I. Clinical features and therapy. *Medicine (Baltimore)* 1974;53:403-13.
28. Bernard K, Tessier S, Winstanley J, Chang D, Borczyk A. Early recognition of atypical *Francisella tularensis* strains lacking a cysteine requirement. *J Clin Microbiol* 1994;32:551-3.
29. Clarridge JE III, Raich TJ, Sjosted A, et al. Characterization of two unusual clinically significant *Francisella* strains. *J Clin Microbiol* 1996;34:1995-2000.
30. Fredricks DN, Remington JS. Tularemia presenting as community-acquired pneumonia: implications in the era of managed care. *Arch Intern Med* 1996;156:2137-40.
31. Westerman EL, McDonald J. Tularemia pneumonia mimicking legionnaires' disease: isolation of organism on CYE agar and successful treatment with erythromycin. *South Med J* 1983;76:1169-70.
32. Olsen PE. Tularemia. In: Hubbert WT, McCulloch WF, Schnurrenberger PR, eds. *Diseases transmitted from animals to man*. 6th ed. Springfield, Ill.: Charles C Thomas, 1975:191-223.
33. Evans ME, Gregory DW, Schaffner W, McGee ZA. Tularemia: a 30-year experience with 88 cases. *Medicine (Baltimore)* 1985;64:251-69.
34. DeLong D, Manning PJ. Bacterial diseases. In: Manning PJ, Ringley DH, Newcomer CE, eds. *The biology of the laboratory rabbit*. 2nd ed. San Diego, Calif.: Academic Press, 1994:129-70.
35. Syrjala H, Kujala P, Myllyla V, Salminen A. Airborne transmission of tularemia in farmers. *Scand J Infect Dis* 1985;17:371-5.
36. Miller RP, Bates JH. Pleuropulmonary tularemia: a review of 29 patients. *Am Rev Respir Dis* 1969;99:31-41.
37. Case Records of the Massachusetts General Hospital (Case 27-1985). *N Engl J Med* 1985;313:36-42.
38. Foulger M, Glazer AM, Foshay L. Tularemia: report of a case with postmortem observations and a note on the staining of *Bacterium tularensis* in tissue section. *JAMA* 1932;98:951-4.
39. Bernstein A. Tularemia: report of three fatal cases with autopsies. *Arch Intern Med* 1935;56:1117-35.
40. Kavanaugh CN. Tularemia: a consideration of one hundred and twenty-three cases, with observations at autopsy in one. *Arch Intern Med* 1935;55:61-85.
41. Stuart BM, Pullen RL. Tularemic pneumonia: review of American literature and report of 15 additional cases. *Am J Med Sci* 1945;210:223-36.
42. White JD, McGavran MH. Identification of *Pasteurella tularensis* by immunofluorescence. *JAMA* 1965;194:294-6.
43. Francis E. Tularemia. *JAMA* 1925;84:1243-50.
44. Light RW, MacGregor MI, Ball WC Jr, Luchsinger PC. Diagnostic significance of pleural fluid pH and pCO₂. *Chest* 1973;64:591-6.
45. Pine JR, Hollman JL. Elevated pleural fluid pH in *Proteus mirabilis* empyema. *Chest* 1983;84:109-11.
46. Isenstein D, Honig E. *Proteus vulgaris* empyema and increased pleural fluid pH. *Chest* 1990;97:511.
47. Lesho EP, Roth BJ. Is pH paper an acceptable, low-cost alternative to the blood gas analyzer for determining pleural fluid pH? *Chest* 1997;112:1291-2.
48. Cheng DS, Rodriguez RM, Rogers J, Wagster M, Starnes DL, Light RW. Comparison of pleural fluid pH values obtained using blood gas machine, pH meter, and pH indicator strip. *Chest* 1998;114:1368-72.

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35-MILLIMETER SLIDES FOR THE CASE RECORDS

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