CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

Sick as a Dog

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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A 42-year-old man presented to an emergency department in rural Colorado with a 2-day history of fever, cough with scant hemoptysis, chest pain, and myalgias. He reported no sick contacts and no oropharyngeal or gastrointestinal symptoms, rashes, or lymphadenopathy. He was feeling well until the symptoms with which he presented began abruptly. He reported a near-drowning incident while river kayaking 1 month earlier, but he recovered without sequelae. The patient's medical history included gastroesophageal reflux and gout. He has smoked less than a pack of cigarettes per day for 20 years. He reported drinking two beers daily and reported no recreational-drug use. Medications included allopurinol and pantoprazole. His family history was notable for diabetes and coronary artery disease in his mother and hypertension in his father. The patient lived in rural Colorado and worked as an environmental engineer inspecting condemned buildings for asbestos removal, including buildings affected by the floods of 2013. He had no recent travel history and no known tuberculosis exposures.

Bacterial pneumonia is the leading consideration, given the constellation of symptoms. Although waterborne pathogens such as aeromonas, pseudomonas, or proteus would be unusual 1 month after a water exposure, scedosporium species are commonly associated with near-drowning incidents and can have a delayed presentation in immunocompetent persons. Working in abandoned buildings raises concern about environmental exposures, although diseases related to such exposures generally do not present acutely. Tuberculosis is also unlikely, given the acuity of presentation and absence of risk factors. Water damage to buildings may increase exposure to pathogenic fungi and legionella species.

The patient appeared ill and diaphoretic. The temperature was 40.2°C (104.4°F), heart rate 107 beats per minute, and blood pressure 119/60 mm Hg. The respiratory rate was 38 breaths per minute, and the oxygen saturation was 94% while the patient was breathing ambient air. He had good dentition. Rales were heard over the right middle and right lower lung fields. The examination was otherwise normal. The serum sodium level was 133 mmol per liter, chloride 97 mmol per liter, and creatinine 1.4 mg per deciliter (124 μmol per liter). The results of liver-function tests were normal except for a total bilirubin level of 1.4 mg per deciliter (24 μmol per liter); bilirubin was not fractionated. The white-cell count was 22,500 per cubic millimeter, with 87% neutrophils and 5% lymphocytes. The hematocrit was 44.8%, and the platelet count was 200,000 per cubic millimeter. Chest radiography revealed an infiltrate in the right lower lobe (Fig. 1A). Treatment with intravenous levofloxacin (750 mg daily)

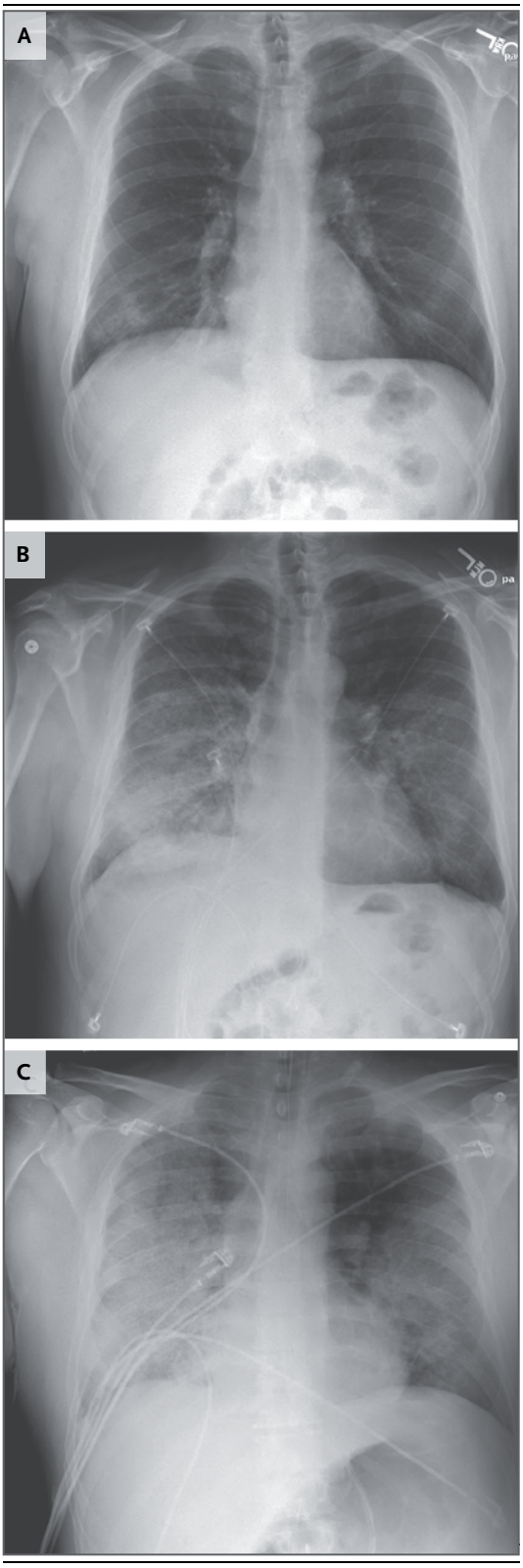

Figure 1. Serial Radiographs of the Chest.
Panel A shows a posteroanterior view with an alveolar infiltrate in the right lower lobe on hospital day 1. Another posteroanterior view, in Panel B, shows progression to diffuse air-space opacities (more in the right lung than in the left) on hospital day 6. In Panel C, continued worsening is apparent in an anteroposterior view on hospital day 8.

was initiated, and the patient was admitted for treatment of presumed community-acquired pneumonia.

The patient's presentation supports a diagnosis of bacterial pneumonia. Common etiologic agents associated with hemoptysis include *Streptococcus pneumoniae*, gram-negative rods (particularly klebsiella), and some atypical organisms. Concurrent mild hyponatremia, liver-function abnormalities, and the overall severity of illness specifically raise the possibility of legionella infection. Levofloxacin is appropriate initial therapy for community-acquired pneumonia and would provide coverage for legionella. Rodentborne diseases, such as leptospirosis, tickborne relapsing fever, and hantavirus infection, are also possible, given his occupational exposures in abandoned buildings, although the patient does not have thrombocytopenia, which would be expected with each of these three diseases.

On day 2 of hospitalization, worsening dyspnea developed, and the patient required up to 10 liters of oxygen supplementation per minute through a face mask. Computed tomography (CT) of the chest with contrast showed bilateral ground-glass opacities, bilateral small effusions, and right hilar and subcarinal lymphadenopathy (Fig. 2). Gram's staining of expectorated sputum showed many gram-negative rods, but sputum cultures grew normal respiratory flora at 48 hours. Cultures of blood samples obtained at admission grew gram-negative rods in a single anaerobic bottle. Owing to the patient's deteriorating clinical status, intravenous vancomycin (1.5 g every 8 hours) and meropenem (2 g every 8 hours) were added to the levofloxacin.

The increase in oxygen requirement, in conjunction with the microbiologic findings, raises concern about progression of a fulminant anaerobic

bacterial pneumonia. Many gram-negative anaerobes, including bacteroides, prevotella, porphyromonas, and fusobacterium species, can cause pulmonary disease, but most tend to have an indolent course. Although infections with fusobacterium can progress more rapidly, they typically begin in the deep neck spaces and occur after pharyngitis. Levofloxacin does not have activity against gram-negative anaerobes, which may explain the progression of disease. Empirical "double" coverage for gram-negative organisms and the addition of anaerobic coverage in a patient with a worsening clinical status is reasonable. The use of vancomycin is not clearly indicated.

On hospital day 6, the organism from blood culture was identified as *Pseudomonas luteola*. Antibiotic-susceptibility testing could not be performed because the organism grew too slowly in standard culture media. Repeat chest radiography showed progression of air-space opacities (Fig. 1B). On hospital day 7, worsening tachypnea developed, with increased oxygen requirement. The white-cell count remained elevated at 19,700 per cubic millimeter. A serum test for antibodies to human immunodeficiency virus types 1 and 2 and a urine test for legionella antigen were negative. Meropenem was replaced with intravenous piperacillin–tazobactam (4.5 g every 6 hours). Repeat blood cultures obtained on hospital day 6 had no growth by day 8. Endotracheal intubation and bronchoscopy were recommended, but the patient declined to undergo either procedure. On hospital day 8, he was transferred to our hospital.

Pseudomonas species use aerobic metabolism, so the identification of *P. luteola* in anaerobic culture only is unexpected and raises the possibility of misidentification. Specifically, *Yersinia pestis* has previously been misidentified as *P. luteola* on automated blood-culture systems and is endemic in the western United States, including Colorado. *P. luteola* is a rare human pathogen that is typically found only in patients who have compromised immune function or implanted hardware, neither of which appears to apply to this patient. Antibiotic susceptibility and outcomes data are lacking for *P. luteola*, but the change from meropenem to piperacillin–tazobactam may have been prompted by concern about carbapenem resistance among other pseudomonas isolates in the referring facility.

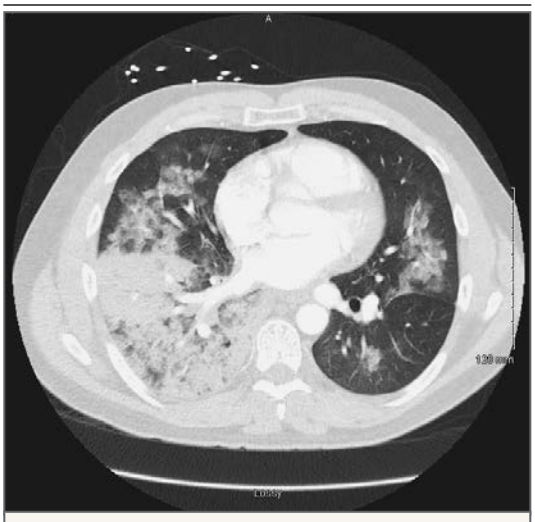

Figure 2. CT of the Chest 1 Day after Presentation.
An axial CT image with intravenous contrast shows bilateral ground-glass opacities with superimposed interlobular septal thickening and intralobular lines.

On arrival at our institution, the patient was persistently febrile and required 10 liters of oxygen per minute through a face mask. He was placed on droplet precautions and intubated shortly after transfer owing to worsening respiratory distress; as a result, no further history could be obtained initially. A postintubation physical examination was notable for bibasilar rales with normal air movement and trace symmetric, subcutaneous edema in the arms and legs. No skin lesions, lymphadenopathy, or hepatosplenomegaly were noted. The serum creatinine level had decreased to 0.7 mg per deciliter (62 μmol per liter), and the total bilirubin level had decreased to 0.7 mg per deciliter (12 μmol per liter); the results of other serum chemical tests and liver-function tests were normal except for an albumin level of 2.2 g per deciliter. The white-cell count was 21,600 per cubic millimeter; no differential count was performed. The hematocrit was 35.0%, and the platelet count was 381,000 per cubic millimeter. Single-view chest radiography revealed worsening bilateral opacities (Fig. 1C). Intravenous vancomycin, piperacillin–tazobactam, and levofloxacin were continued. Streptomycin (15 mg per

kilogram of body weight every 12 hours) and voriconazole (400 mg every 12 hours) were initiated. The patient underwent diagnostic bronchoscopy with bronchoalveolar lavage.

The persistent fever, along with the overall clinical picture, is most suggestive of inadequately treated infection and is less likely to indicate a noninfectious cause, such as a drug reaction, thrombus, or underlying cancer. Piperacillin–tazobactam and levofloxacin constitute reasonable antipseudomonal coverage in the absence of susceptibility data. However, the continued severity of illness is unexpected, given treatment with three broad-spectrum agents that have activity against pseudomonas. Voriconazole is appropriate therapy for scedosporium infection (a risk after the patient's near-drowning incident), but the addition of this drug is probably unnecessary, given that another organism has already been isolated. Similarly, without an isolated gram-positive organism, vancomycin could be discontinued. The history of rodent exposure, combined with the disease severity, the lack of a response to initial treatment, and earlier reports of misidentification of *Y. pestis*, suggest a high likelihood of pneumonic plague, so the addition of streptomycin is appropriate. *Francisella tularensis* is also a gram-negative, rodentborne pathogen with pulmonary involvement that does not respond to routine antibiotics. Tularemia, however, would not explain the purported pseudomonas isolate identified at the referring hospital, and hemoptysis is uncommon with pneumonic tularemia. Droplet precautions are indicated whenever there is suspicion of pneumonic forms of plague or tularemia.

On hospital day 9, further history was obtained from the patient's family. The patient raised horses, llamas, goats, sheep, chickens, and geese, and multiple dogs and cats roamed his property. He and his family routinely drank unpasteurized goat's milk and provided unpasteurized goat's milk to their dogs. One of their dogs had acute ataxia and respiratory distress with hemoptysis several days before the patient's initial presentation and was euthanized within 36 hours. The symptoms were attributed to ingestion of a coumarin rodenticide that had been used against a colony of prairie dogs near the house several months earlier. The patient had transported the dog's remains to a veterinary referral center for necropsy; the animal had no detectable level of rodenticide, and severe bronchopneumonia was diagnosed on gross examination. Meanwhile, the patient continued to have persistent fevers and oxygen requirements as high as 70% on the ventilator. Intravenous doxycycline (100 mg every 12 hours) was initiated.

The prairie-dog colony near the patient's home heightens concern about plague, because prairie dogs are a common reservoir for *Y. pestis*. Other zoonotic infections, including brucellosis, Q fever, cryptococcosis, and psittacosis, should be considered; all these infections can present with acute pneumonia. Cryptococcal pneumonia is subclinical in most immunocompetent hosts and tends to present subacutely with weight loss and night sweats, making it an unlikely diagnosis in this case. Consumption of raw goat's milk is a major risk factor for brucellosis and Q fever, but respiratory failure requiring intubation is highly unusual in patients with brucella, coxiella, or chlamydophila infection.

Blood cultures showed no growth. The Colorado Department of Public Health and Environment (CDPHE) was contacted for further testing of the pseudomonas isolate from the referring hospital. On hospital day 10, polymerase-chain-reaction testing by the CDPHE State Laboratory confirmed that the isolate initially identified as *P. luteola* was consistent with *Y. pestis*. Other infectious workup, including bacterial and fungal cultures and specific assays for coccidioides, cryptococcus, histoplasma, leptospira, hantavirus, *Coxiella burnetii*, brucella, Epstein–Barr virus, and cytomegalovirus, was negative. Piperacillin–tazobactam, vancomycin, voriconazole, and doxycycline were stopped. Streptomycin and levofloxacin were continued.

By hospital day 14, the patient had nearly constant fevers oscillating between 38.0°C (100.4°F) and 38.8°C (101.8°F). His oxygen requirement remained high at 70%, with a positive end-expiratory pressure of 10 cm of water. Repeat CT of the chest with contrast revealed no abscess but showed progression of previous areas of ground-glass opacity into areas of dense consolidation as well as worsening bilateral effusions. Owing to suspicion of drug fever, streptomycin was stopped and gentamicin (7 mg per kilogram every 24 hours) was begun. Levofloxacin and gentamicin were continued through hospital day 17. The maximum

temperature trended down after the antibiotic change, and fever resolved by hospital day 18. The oxygen requirement decreased to 50% by day 18. The patient's course was complicated by an aspiration event, but he was extubated on hospital day 19 and discharged home on hospital day 24 while he was breathing supplemental oxygen at a rate of 4 to 6 liters per minute through a nasal cannula. By 5 months after hospital discharge, he no longer required supplemental oxygen, and he had dyspnea only with intense activity.

A public health investigation resulted in confirmation of plague in our patient's dog and identified three additional cases in humans.[1] Although the dog was the likely source of transmission to our patient and two of the three other persons, the fourth person had exposure to both the dog and our patient, so human-to-human transmission may have occurred.[1]

COMMENTARY

Y. pestis is a gram-negative, facultatively anaerobic bacillus or coccobacillus and the causative organism for a spectrum of diseases referred to as plague.[2] It is non–lactose-fermenting and can grow on MacConkey or blood agar, although its small colonies may be overlooked in the presence of other Enterobacteriaceae — which might explain why it was not found on respiratory culture in this case.[3] The organism has been misidentified previously by automated bacterial-identification systems as *P. luteola*, *Acinetobacter lwoffii*, or *Y. pseudotuberculosis*.[4] *Y. pestis* is listed as a category A (high-priority) bioterrorism agent by the Centers for Disease Control and Prevention, and biosafety level 3 precautions must be observed for cultured specimens.[5] Hospital laboratories and the public health department should be notified whenever plague is considered.[5] Delayed diagnosis in the current case resulted in 114 exposures to an infected patient or laboratory specimen, including 68 persons exposed in the health care setting.[1] Postexposure prophylaxis was recommended to 88 persons, and no additional cases were identified beyond the three noted.[1] Acute and convalescent serologic testing can confirm the diagnosis when culture results are negative.

Y. pestis is found in temperate-to-tropical regions worldwide, with enzootic foci in the western United States.[2] Rodents, including prairie dogs, are the primary reservoir, although cases of plague transmission have been linked to domestic cats and dogs.[6,7] Disease in humans is most commonly transmitted by flea bite, which results in bubonic plague (80 to 90% of cases) or septicemic plague without bubo formation.[2,6] Pneumonic plague is most often the result of hematogenous spread from a systemic infection (secondary) but can, although rarely, occur by direct inhalation of aerosolized bacteria (primary).[8,9] The incubation period for primary pneumonic plague has been variably reported from as short as several hours to as long as 6 days.[2,10] Close proximity (≤2 m) to an infected host with a high burden of disease is generally required for transmission.[8] Accordingly, primary pneumonic plague, which we believe this patient had, was diagnosed in only 13 persons in the United States between 1925 and 2006.[11] Although rates of human-to-human transmission are very low,[8,9] droplet precautions should be instituted if *Y. pestis* infection is suspected and should be continued until appropriate antimicrobial therapy has been administered for at least 48 hours.[5,8] In our case, droplet precautions were initiated shortly after the patient's transfer to our institution and remained in place until resolution of the fever.

Although bubonic plague presents with acute lymphadenitis near the bite of an infected flea, forming the characteristic bubo, primary pneumonic plague typically presents with sudden onset of cough with bloody sputum, dyspnea, and pleuritic chest pain. High fever, malaise, myalgias, and nausea may accompany both forms of disease and also tend to start abruptly.[8] Radiography of primary pneumonic plague most commonly shows patchy, bilateral infiltrates, although a lobar appearance has been described.[10] The incidence of primary pneumonic plague is low, but mortality is as high as 100% without treatment and 50% with treatment.[2]

Clinical trials are lacking to guide antimicrobial therapy for human plague. Streptomycin is considered the drug of choice,[3,10,12] but owing to the limited availability of streptomycin and its ototoxicity, gentamicin is often effectively substituted, either alone or in combination with tetracyclines.[13] Data on the use of fluoroquinolones in humans are limited,[13,14] but the availability and safety of these drugs make them alternatives for treatment and preferred agents for postexposure prophylaxis of plague.[2,3] Our patient's survival may have been attributable in part

to the initial choice of levofloxacin for presumed community-acquired pneumonia. Although susceptibility studies of *Y. pestis* are scarce, resistance to streptomycin, tetracyclines, carbapenems, chloramphenicol, and ampicillin has been reported.[15] The appropriate duration of therapy is unclear. Ten days has been suggested on the basis of animal models,[10] but some experts recommend treating until 3 days after defervescence.[14]

Although plague is uncommon, all forms of the disease are associated with substantial morbidity and mortality. Clinicians must have a high index of suspicion in the context of severe pneumonia with rapid onset, particularly in immunocompetent hosts who have spent time in endemic areas. Awareness of common clinical manifestations can facilitate early detection and treatment of this highly lethal but treatable disease.

No 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.

REFERENCES

1. Runfola JK, House J, Miller L, et al. Outbreak of pneumonic plague with dog-to-human and possible human-to-human transmission — Colorado, June-July 2014. MMWR Morb Mortal Wkly Rep (in press).
2. Prentice MB, Rahalison L. Plague. Lancet 2007;369:1196-207.
3. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. JAMA 2000;283:2281-90.
4. Tourdjman M, Ibraheem M, Brett M, et al. Misidentification of Yersinia pestis by automated systems, resulting in delayed diagnoses of human plague infections — Oregon and New Mexico, 2010-2011. Clin Infect Dis 2012;55(7):e58-e60.
5. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guidelines for isolation precautions: preventing transmission of infectious agents in healthcare settings. Atlanta: Centers for Disease Control and Prevention, 2007.
6. Gage KL, Dennis DT, Orloski KA, et al. Cases of cat-associated human plague in the Western US, 1977-1998. Clin Infect Dis 2000;30:893-900.
7. Gould LH, Pape J, Ettestad P, Griffith KS, Mead PS. Dog-associated risk factors for human plague. Zoonoses Public Health 2008;55:448-54.
8. Campbell GL, Hughes JM. Plague in India: a new warning from an old nemesis. Ann Intern Med 1995;122:151-3.
9. Ratsitorahina M, Chanteau S, Rahalison L, Ratsifasoamanana L, Boisier P. Epidemiological and diagnostic aspects of the outbreak of pneumonic plague in Madagascar. Lancet 2000;355:111-3.
10. Pollitzer R. Plague studies. VIII. Clinical aspects. Bull World Health Organ 1953;9:59-129.
11. Butler T. Plague into the 21st century. Clin Infect Dis 2009;49:736-42.
12. Butler T. A clinical study of bubonic plague: observations of the 1970 Vietnam epidemic with emphasis on coagulation studies, skin histology and electrocardiograms. Am J Med 1972;53:268-76.
13. Boulanger LL, Ettestad P, Fogarty JD, Dennis DT, Romig D, Mertz G. Gentamicin and tetracyclines for the treatment of human plague: review of 75 cases in New Mexico, 1985-1999. Clin Infect Dis 2004;38:663-9.
14. Dennis DT, Gage KL, Gratz N, Poland JD, Tikhomirov E. Plague manual: epidemiology, distribution, surveillance and control. Geneva: World Health Organization, 1999.
15. Wong JD, Barash JR, Sandfort RF, Janda JM. Susceptibilities of Yersinia pestis strains to 12 antimicrobial agents. Antimicrob Agents Chemother 2000;44:1995-6.