We describe the 11th case of bioterrorism-related inhalational anthrax reported in the United States. The presenting clinical features of this 94-year-old woman were subtle and nondistinctive. The diagnosis was recognized because blood cultures were obtained prior to administration of antibiotics, emphasizing the importance of this diagnostic test in evaluating ill patients who have been exposed to *Bacillus anthracis*. The patient’s clinical course was characterized by progression of respiratory insufficiency, pleural effusions and pulmonary edema, and, ultimately, death. Although her *B. anthracis* bacteremia was rapidly sterilized after initiation of antibiotic therapy, viable *B. anthracis* was present in postmortem mediastinal lymph node specimens. The source of exposure to *B. anthracis* in this patient is not known. Exposure to mail that was cross-contaminated as it passed through postal facilities contaminated with *B. anthracis* spores is one hypothesis under investigation.
Aavitamin tablet, and she rarely drank alcohol. Her diet was unremarkable. The patient had lived alone since the death of her husband 22 years earlier. She had previously worked as a legal secretary. She had no recent travel and had no pets. Additional history obtained following admission revealed that she did not remember opening any mail containing powder.

On admission, the patient's vital signs were a temperature of 102.3°F (39.1°C), blood pressure of 106/50 mm Hg with no orthostatic changes, pulse of 119/min, and respiratory rate of 18/min. Oxygen saturation was 93% while breathing room air. She was alert and oriented, there were no signs of meningeal irritation, and the remainder of the physical examination, including skin, was unremarkable.

Laboratory findings included a total white blood cell count of 8.1 × 10^3/µL (78% neutrophils, 15% lymphocytes, and 7% monocytes) and normal hematocrit and platelet counts. Serum urea nitrogen level was 39 mg/dL (13.9 mmol/L), serum creatinine level was 1.3 mg/dL (115 µmol/L), and serum electrolyte levels were within normal ranges, except for a sodium level of 134 mEq/L. Serum chemistry levels were normal except for an aspartate aminotransferase of 45 U/L. Urinalysis showed 3 to 5 white blood cells per high-power field and moderate bacteria. Posterior-anterior and lateral chest radiographs were initially interpreted as having no evidence of pulmonary infiltrates, widened mediastinum, or pleural effusion (FIGURE 1A). However, later comparison with films obtained 3 years previously suggested possible interval enlargement of the left hilum and a possible small left pleural effusion. Computed tomography of the chest was not performed.

Blood and urine cultures were obtained, and the patient was admitted to the hospital with a diagnosis of viral syndrome and dehydration. Initial treatment included intravenous hydration and observation. Antibiotic therapy was not initiated on the day of admission.

On the morning of November 17, the patient developed respiratory distress. Her white blood cell count was 13.3 × 10^3/µL (80% neutrophils, 11% lymphocytes, and 9% monocytes) and her oxygen saturation decreased to 90% while receiving 2 L/min of oxygen via nasal cannula. A chest radiograph showed clear evidence of a left pleural effusion (FIGURE 2A). Intravenous vancomycin and oral ciprofloxacin were continued, ampicillin/sulbactam was discontinued, and intravenous erythromycin (500 mg every 6 hours) was initiated in the early hours of November 19.

On November 19, review of the preliminary microbiologic analysis of the blood isolate raised suspicion for anthrax; therefore, the Connecticut Department of Public Health was notified.
about the positive blood culture results, and assistance in ruling out *B. anthracis* was requested. The patient’s condition deteriorated with worsening hypoxemia and renal function (serum urea nitrogen and serum creatinine levels of 43 mg/dL [15.4 mmol/L] and 2.6 mg/dL [230 µmol/L], respectively). Her white blood cell count was 25.0 × 10^9/µL (83% segmented neutrophils, 8% band forms, and 8% lymphocytes). Chest radiograph showed progression of the left pleural effusion. A left thoracentesis yielded 800 mL of serosanguinous fluid, with 4224 red blood cells, 1463 white blood cells, a pH of 7.12, lactate dehydrogenase level of 611 U/L, glucose level of 259 mg/dL (14.4 mmol/L), and protein level of 3.4 g/dL. No organisms were seen on the Gram stain of the pleural fluid, and bacterial culture of the fluid did not grow, but subsequent testing at the Centers for Disease Control and Prevention showed that the *B. anthracis*–specific polymerase chain reaction (PCR) assay was positive. The patient required endotracheal intubation and mechanical ventilation. In addition to vancomycin, clindamycin, 900 mg intravenously every 6 hours, was begun, erythromycin was discontinued, and the route of ciprofloxacin administration was changed from oral to intravenous. Methylprednisolone, 40 mg intravenously every 8 hours, was initiated.

On November 20, the isolate was identified as *B. anthracis* by the Connecticut state laboratory, with confirmation at the Centers for Disease Control and Prevention the following day. Confirmatory testing of the isolate included gamma phage lysis and detection of capsule and cell-wall antigens by direct fluorescent antibody assays. In addition, PCR showed that the isolates contained *B. anthracis*–specific DNA. The isolates were susceptible to ciprofloxacin, tetracycline, penicillin, and a number of other antibiotics. The antibiotic susceptibilities were identical to the isolates obtained from other patients during this bioterrorism-related anthrax outbreak. She developed hypotension requiring treatment with vasopressors and required high levels of supplemental oxygen (80% fraction of inspired oxygen) to maintain adequate oxygenation. Chest radiographs revealed progressive consolidation and a new right pleural effusion (Figure 2B). A chest tube was placed in the left pleural space. Total white blood cell count increased to 43.6 × 10^9/µL (83% segmented neutrophils, 12% lymphocytes, and 5% monocytes) and serum creatinine level increased to 3.7 mg/dL (327 µmol/L). Hematocrit, platelet count, liver enzymes, and coagulation profile remained normal, with the exception of an aspartate aminotransferase level of 61 U/L. The patient’s condition continued to deteriorate, and she died on November 21.

The case was reported to the state medical examiner. An autopsy was performed 8 hours after death. More than 1 L of serosanguinous fluid was present in the right pleural cavity, and the right lung had areas of patchy consolidation. A chest tube was noted within the left pleural space. There was no evidence of a primary cutaneous lesion. Hematocrit, white blood cell count, and liver enzymes remained normal, with the exception of an aspartate aminotransferase level of 61 U/L. The patient’s condition continued to deteriorate, and she died on November 21.

The case was reported to the state medical examiner. An autopsy was performed 8 hours after death. More than 1 L of serosanguinous fluid was present in the right pleural cavity, and the right lung had areas of patchy consolidation. A chest tube was noted within the left pleural space. There was no evidence of a primary cutaneous lesion. The mediastinal lymph nodes were en-
larged and hemorrhagic. The central nervous system was unremarkable, and, except for small, granular, and cystic kidneys, the abdominal organs were grossly normal. Microscopic examination demonstrated extensive necrosis and hemorrhage of mediastinal lymph nodes (Figure 3A), intra-alveolar and interstitial edema with focal hemorrhage and fibrin deposition in the lungs, and splenic necrosis. There was no histopathologic evidence of pneumonia.

Immunohistochemical staining using *B. anthracis* capsule and cell-wall monoclonal antibodies showed abundant bacilli and granular staining in the mediastinal lymph nodes (Figure 3B), cellular fraction of the pleural effusion, visceral and parietal pleura, and pulmonary interstitium. No pathologic or immunopathologic evidence of *B. anthracis* was identified in the abdominal organs or central nervous system using tissue Gram stains or immunohistochemical stains. Postmortem blood, pleural fluid, and spleen, lung, liver, and mediastinal lymph node tissue specimens were inoculated onto bacteriologic media for culture and tested for *B. anthracis*-specific DNA using PCR. Growth of *B. anthracis* was detected only from the mediastinal lymph node; all other postmortem specimens were sterile. The mediastinal lymph node tissue was also the only postmortem specimen from which *B. anthracis* DNA was detected by PCR assay. The cause of death was certified as inhalational anthrax.

Serial serum samples obtained on November 16, 17, 18, and 19 were tested for IgG antibody to the protective antigen component of the anthrax toxins by enzyme-linked immunosorbent assay; all samples were nonreactive.

**COMMENT**

This report describes the 11th patient with bioterrorism-related inhalational anthrax identified in the United States. The *B. anthracis* isolate from the patient’s bloodstream was indistinguishable by molecular typing and by antibiotic susceptibilities from isolates from the other recently identified patients with inhalational and cutaneous anthrax, indicating an epidemiologic relationship with the recent bioterrorism-related outbreak. The source of the exposure for this patient has not been identified. Extensive environmental sampling of the patient’s home and all other locations she was known to have visited in the 60 days prior to onset of symptoms have failed to find *B. anthracis*. Environmental sampling performed at the southern Connecticut postal processing and distribution center that processed her mail identified *B. anthracis* spores in 3 high-speed mail sorters. No direct exposure to mail known to contain *B. anthracis* spores has been identified for this patient, but at least 1 resident of her community is known to have received a *B. anthracis*-contaminated envelope that was likely to have become cross-contaminated as it passed through the postal system. These findings do not provide definitive evidence of the route of exposure for the patient reported here, but they are consistent with the hypothesis that the exposure to *B. anthracis* may have
resulted from receipt of mail that was cross-contaminated with spores.

Host factors, including advanced age, underlying lung disease, and medication use, may have played a role in this patient’s susceptibility to inhalational anthrax. Advanced age is associated with changes in the immune system that may increase susceptibility to a variety of infections.10 The absence of deaths reported among persons younger than 24 years in the Sverdlovsk outbreak in Russia and the paucity of childhood cases in Russian home industry–based inhalational anthrax during the early part of last century have been interpreted as evidence that increased age may be an important risk factor for this disease,11,12 although it is possible that younger age groups were less likely to be exposed in these settings.

Underlying chronic illness, such as emphysema, is associated with an increased risk of respiratory infection in elderly persons.9 Previously, Brachman et al13,14 hypothesized that underlying pulmonary disease may also predispose to inhalational anthrax. Two of the 18 US cases of inhalational anthrax reported prior to the recent bioterrorism-related outbreak had underlying lung disease; one had beryllium exposure and chronic pulmonary fibrosis and the other had underlying pulmonary sarcoidosis.13,14 The only known exposure for the patient with sarcoidosis was that he walked by the open door of a tannery known to be contaminated with B anthracis. No cases of inhalational anthrax were reported among those who worked in the tannery, raising the hypothesis that his underlying pulmonary disease made him susceptible to infection by exposure to a small number of spores.

The incubation period for this patient’s illness could not be determined, but her onset of symptoms was 56 days after letters containing B anthracis were mailed to New York City media outlets, 35 days after letters containing B anthracis were mailed to US senators, and 3 weeks after onset of illness in the 10th patient with bioterrorism-related inhalational anthrax. These findings suggest that the incubation period of the patient described herein could have been longer than that observed among earlier patients. In nonhuman primates, the incubation period ranges from 2 to 98 days among animals not vaccinated or treated with antibiotics, and evidence suggests that the duration of the incubation period is inversely related to the number of B anthracis–bearing particles to which the animals are exposed (ie, smaller doses result in longer incubation periods).15-17

The hypothesis that the dose of spores is inversely related to incubation period in humans is supported by the Sverdlovsk experience; individuals who died of inhalational anthrax who both lived and worked outside the area of highest calculated dose had a prolonged median incubation period of 21 days. In contrast, those who both lived and worked within the high-dose area had a median incubation period of only 10 days.18 In addition, the incubation period for a laboratory worker who acquired inhalational anthrax after exposure to a massive number of aerosolized B anthracis spores was approximately 1 day (G. Briggs Phillips, PhD, oral communication, January 18, 2002). The onset of illness in this patient is consistent with the hypothesis that infection may have resulted from exposure to small numbers of B anthracis spores.

The presenting signs, symptoms, and laboratory findings for this patient were similar to those of previously reported patients with bioterrorism-related inhalational anthrax.2 The nonspecific nature of these findings makes an accurate presumptive diagnosis difficult. The diagnosis became apparent only after growth of B anthracis was detected in blood cultures. The clinical features of her initial illness were relatively mild despite evidence of high-level B anthracis bacteremia at presentation; growth in blood cultures was detected after 14 hours of incubation. Rapid growth of B anthracis in blood or cerebrospinal fluid cultures was also observed in previously reported patients with bioterrorism-related anthrax who had not received prior antibiotics.2 Of interest, blood cultures obtained from this patient 3 hours following the initiation of antibiotic therapy revealed no growth. Antibiotic therapy appears to rapidly sterilize the bloodstream and greatly diminishes the sensitivity of blood cultures as a diagnostic test for inhalational anthrax,2 emphasizing the importance of obtaining blood cultures prior to initiation of antibiotic therapy for patients suspected to have anthrax.

The patient’s admission chest radiograph was interpreted as normal. However, in retrospect, subtle changes were present in comparison with earlier films. In 2 of the previous cases of bioterrorism-related inhalational anthrax, the presenting chest radiograph was initially interpreted as normal, but in both cases, subsequent review indicated the presence of abnormalities in the hila, mediastinum, parenchyma, or pleural spaces.5 The combined recent experience with bioterrorism-related inhalational anthrax suggests that while abnormalities are usually present on the initial chest radiograph, the changes may be difficult to detect. Chest computed tomographic images may be helpful in characterizing abnormalities of the lungs and mediastinum and revealing mediastinal lymphadenopathy.2

The patient’s hospital course was characterized by fever followed by the onset of respiratory distress with the development of bilateral pleural effusions, progressive respiratory insufficiency, and, ultimately, hypotension and death. Multidrug antibiotic therapy initiated prior to onset of the fulminant phase of the illness was not successful in this patient in contrast with 6 other recent cases of bioterrorism-related anthrax.2 Although the bacteremia was rapidly cleared, histopathology and postmortem culture of mediastinal lymph node tissue indicated the presence of viable B anthracis, suggesting suboptimal bactericidal activity or tissue penetration with the regimen used in this patient. Further study is needed to determine which antimicrobial regimens are most effective in treating this dis-
ease. Use of rifampin in combination with other agents may offer some benefit; 4 of the 6 survivors of bioterrorism-related inhalational anthrax were treated with combinations that included both a fluoroquinolone and rifampin. Persistence and reaccumulation of pleural effusions, interstitial edema, and respiratory distress have been difficult problems in other patients with inhalational anthrax.

The postmortem findings of hemorrhagic lymphadenopathy and necrosis in this patient were consistent with previously described cases of bioterrorism-related inhalational anthrax, with the exception that the pathologic, immunopathologic, and microbiological evidence of B. anthracis was predominately confined to the thorax. In other fatal cases of bioterrorism-related inhalational anthrax, immunohistochemical staining showed B. anthracis bacilli in multiple organs. The presence of abundant B. anthracis in the pleural surface and pleural fluid in this and previous cases highlights the important role of the pleural space in the pathogenesis of anthrax and the value of pleural fluid in the diagnosis of inhalational anthrax. In patients suspected of having inhalational anthrax but in whom the diagnosis is unconfirmed, pleural fluid studies should be obtained and evaluated by bacterial culture, B. anthracis–specific PCR, and immunohistologic staining of the pleural fluid cell block.

In summary, we describe the 11th case of bioterrorism-related inhalational anthrax reported in the United States. The source of exposure to B. anthracis in this patient is not known. Exposure to mail that was cross-contaminated as it passed through postal facilities contaminated with B. anthracis spores is one hypothesis under investigation. The presenting clinical features of this patient were subtle and nondistinctive. The diagnosis was recognized because blood cultures were obtained prior to the administration of antibiotics, emphasizing the importance of this diagnostic test in evaluating ill patients who have been exposed to B. anthracis. New approaches to early diagnosis and more effective treatment of the pulmonary complications of inhalational anthrax are clearly warranted.

Members of the Anthrax Bioterrorism Investigation Team: Greg Armstrong, Kenneth Bell, Mike Bowen, Joe Breeze, Dave Brownell, Joe Burkhart, Greg Burr, Matt Carter, Nicole Coffin, Richard Collins, Larry Cseh, Scott Deitchman, Timothy Dignam, Rick Ekenberg, Marc Fischer, Julie Gerbending, Mike Grout, Jennifer Hamborsky, Alex Hoffmaster, James Hughes, Max Kiefer, Bradley King, Jacob Kool, Leslye LaClaire, Neil Lustig, Jennifer McClellan, Paul Mead, Bruce Newton, Stephanie Noviello, Olibo- Cyanvides, John Painter, Christopher Paddock, Umesh Parashar, Bradley Perkins, Joseph Perz, Conrad Quinn, Renee Ridzon, Ron Sanders, Charles Schable, Karen Spago, Adrian Stoica, David Sylvian, Kathi Tatti, Eyasu Teshale, Rob Weyant, Alicia Williams, Jennifer Williams, Scott Wright, Heather Wurtzel, and Ronald Zabrocki. Acknowledgment: We thank the patient’s family for providing permission to publish information about this case for the medical community. We also acknowledge the valuable contribution of the following to this work: Jeanine Bartlett, Tara Ferebee-Harris, Patricia Greer, James Gruden, Gale Jaccabacci, Jeffrey Montague, Tim Morken, Chalanda Smith, Kay Vadyaren, and the microbiology laboratory and medical housestaff of Griffin Hospital.

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