Fatal Inhalational Anthrax With Unknown Source of Exposure in a 61-Year-Old Woman in New York City

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A 61-year-old woman who was a New York City hospital employee developed fatal inhalational anthrax, but with an unknown source of anthrax exposure. The patient presented with shortness of breath, malaise, and cough that had developed 3 days prior to admission. Within hours of presentation, she developed respiratory failure and septic shock and required mechanical ventilation and vasopressor therapy. Spiral contrast–enhanced computed tomography of the chest demonstrated large bilateral pleural effusions and hemorrhagic mediastinitis. Blood cultures, as well as DNA amplification by polymerase chain reaction of the blood, bronchial washings, and pleural fluid specimens, were positive for *Bacillus anthracis*. The clinical course was complicated by liver failure, renal failure, severe metabolic acidosis, disseminated intravascular coagulopathy, and cardiac tamponade, and the patient died on the fourth hospital day. The cause of death was inhalational anthrax. Despite epidemiologic investigation, including environmental samples from the patient's residence and workplace, no mechanism for anthrax exposure has been identified.

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ANTHRAX IS CAUSED BY THE BACterium *Bacillus anthracis* and recently has been used as an agent of bioterrorism.[1,2] The *B anthracis* spores lead to the disease by entering the body cavity through skin contact, ingestion, or inhalation.[3] Pulmonary anthrax is the most lethal form of the disease.[4] Along with smallpox, tularemia, plague, and botulism, anthrax is now at the forefront in the age of biological warfare.[5-7]

See also pp 863, 869, 898.

As of January 9, 2002, a total of 23 cases of anthrax have been reported to the Centers for Disease Control and Prevention (CDC; Atlanta, Ga): 11 cases were confirmed inhalational anthrax and 12 cases (7 confirmed and 5 suspected) were cutaneous anthrax.[8] An estimated 32 000 people were prescribed prophylactic antibiotic therapy between October 9 and November 9, 2001.[9] Anthrax spores have now been found at government buildings, post offices, and media centers in Florida, Washington, DC, New Jersey, and New York, NY. In this article, we report the first case of inhalational anthrax in New York City, a 61-year-old hospital employee who had none of the exposure risks previously described in this cluster of cases.

CASE REPORT

On October 28, 2001, a 61-year-old Vietnamese woman was brought into the emergency department of Lenox Hill Hospital in New York City complaining of weakness, chest heaviness, dyspnea, malaise, cough, and chills for

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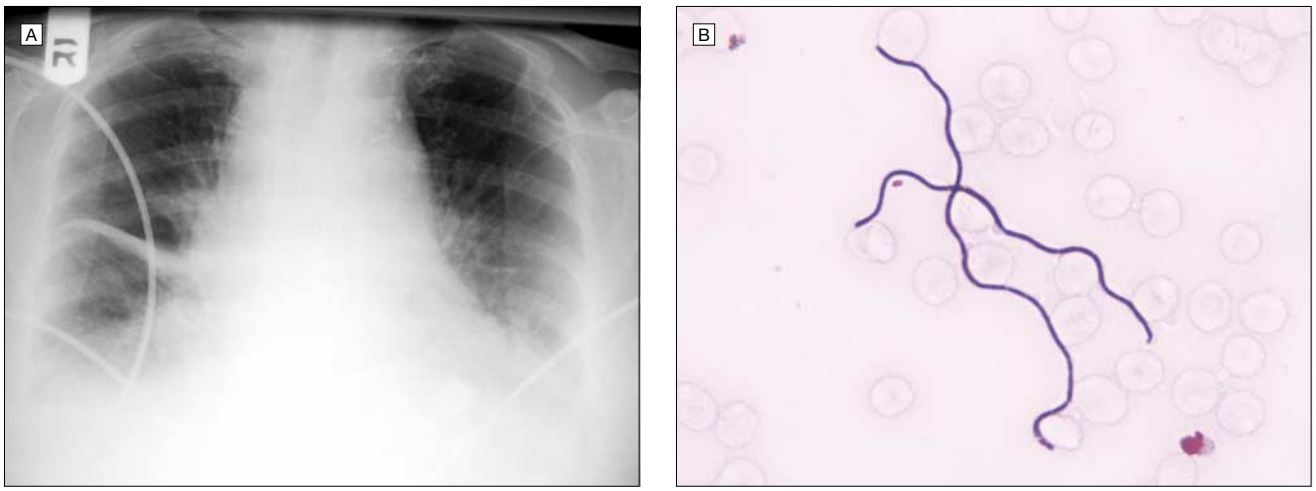
the preceding 3 days. On the day prior to admission, the cough was associated with pink-tinged sputum. The patient previously had been in her usual state of health and had worked until 2 days prior to admission. The patient denied headache, neck pain, fever, sore throat, or skin rash. The patient had a medical history of hypertension controlled with amlodipine and fosinopril. The patient was a nonsmoker and denied alcohol use or recreational drug use. She had immigrated to the United States from Vietnam 20 years earlier but had no recent travel. She worked in the central supply room of a Manhattan hospital in a space shared with a mail receiving and sorting room.

On physical examination, the patient had a respiratory rate of 38/min and was in respiratory distress. Blood pressure was 128/60 mm Hg, pulse was 86/min, and temperature was 97°F (36°C). Head examination results were normal without scleral icterus or oral thrush. The neck was supple with no bruits or jugular venous distension, and the trachea was midline. There was no evidence of cervical or axillary adenopathy. Chest examination revealed inspiratory rales and decreased breath sounds bilaterally. Heart examination revealed regular rate and rhythm, with normal S_1 and S_2 and no S_3, S_4, or murmurs. The abdomen was soft, nontender, and nondistended, and no organomegaly was evident. There were no neurological deficits. No skin lesions were detected.

The initial portable view of the chest obtained shortly after presentation demonstrated marked widening of the superior mediastinum, with moderate bilateral pleural effusions, fluid in the minor fissure, and bilateral perihilar infiltrates (FIGURE 1A). An electrocardiogram showed sinus tachycardia at a rate of 101/min without any signs of myocardial ischemia. Arterial blood gas values obtained while the patient was receiving supplemental oxygen (100% nonrebreather face mask) were: pH, 7.41; partial pressure of carbon dioxide, 40 mm Hg; partial pressure of oxygen, 122 mm Hg; and oxygen saturation, 99%. Laboratory values on hospital admission are shown in the TABLE. A bedside echocardiogram showed normal left ventricular function and wall motion, slight aortic regurgitation, a small pericardial effusion, and an aneurysm of the ascending aorta. Blood cultures were drawn and were submitted in aerobic and anaerobic culture bottles (BioMerieux, Raleigh-Durham, NC). The patient was initially treated presumptively for congestive heart failure with 20 mg of intravenous furosemide. Empirical intravenous levofloxacin, 500 mg/d, was administered for community-acquired pneumonia and the possibility of inhalational anthrax.

The patient was admitted to the medical intensive care unit. Her respiratory and hemodynamic status deteriorated rapidly, and she was immediately intubated because of tachypnea, respiratory distress, and oxygen desaturation. Frothy pink secretions were suctioned from the endotracheal tube. Pulmonary artery catheterization revealed right atrial pressure of 4 mm Hg (reference range, 0-6 mm Hg), right ventricular pressure of 17/5 mm Hg (reference range, 20-30/0-5 mm Hg), and pulmonary artery pressure of 20/10 mm Hg (reference range, 20-30/5-15 mm Hg), but pulmonary artery wedge pressures could not be measured. After unsuccessful crystalloid resuscitation, vasopressor therapy (norepinephrine, phenylephrine, and, later, vasopressin) was initiated. The differential diagnosis included dissecting ascending aortic aneurysm with leakage, severe community-acquired pneumonia, vasculitis (Wegener granulomatosis), and inhalational anthrax. Rifampin, 300 mg intravenously every 8 hours, and clindamycin, 800 mg every 8 hours, were

Figure 1. Chest Radiograph on Admission and Gram Stain of Blood Culture Obtained on Admission



A, Chest radiograph shows marked widening of the paratracheal stripe and superior mediastinum. There are moderate bilateral effusions with fluid in the minor fissure and bilateral perihilar infiltrates. B, Gram stain of blood culture shows gram-positive bacilli (original magnification ×1000).

added to the antibiotic regimen, and the levofloxacin dosage was increased to 500 mg every 12 hours.

Repeat chest radiograph revealed progressive widening of the mediastinum, and the tip of the pulmonary artery catheter was positioned in the main pulmonary artery trunk. Spiral computed tomography of the chest demonstrated large bilateral pleural effusions, a small amount of blood layering in the dependent portion of the right pleural space, and a large amount of edema and hemorrhage in the soft tissues surrounding the trachea, bronchi, and hilar regions bilaterally, with complete infiltration of the mediastinal fat planes, bronchial mucosal thickening, encasement and compression of the hilar vessels (FIGURE 2)A. An intact 4.2-cm aneurysm of the ascending aorta was incidentally noted. Delayed images at 20 minutes demonstrated multiple confluent ringlike areas of enhancement with hypodense centers compatible with hemorrhagic lymph node necrosis involving the subcarinal, paratracheal, subaortic, and azygoesophageal recess nodes (Figure 2B). A high-density pericardial effusion, suggesting hemorrhage, was also present.

Bilateral chest tubes were inserted and each drained more than 1 L of serosanguinous fluid. Pleural fluid analysis produced the following values: glucose, 147 mg/dL (8.2 mmol/L); total protein, 4.2 g/dL; lactic dehydrogenase, 1264 U/L; white blood cell count, 3.0×10^3/μL; and red blood cell count, 0.073×10^6/μL. At the time of admission to the intensive care unit, the patient had an Acute Physiology and Chronic Health Evaluation III score of 143, with predicted intensive care unit and hospital mortality of 80% and 89%, respectively.

On the second hospital day, fiberoptic bronchoscopy revealed severe hemorrhagic tracheobronchitis with oozing of bloody fluid from the mucosal surfaces and easy sloughing of the mucosa. The patient developed worsening hepatic function with increasing aminotransferases, nonoliguric renal failure with creatinine level increasing to 1.9 mg/dL (168 μmol/L), lactic acidosis (lactate, 75 mg/dL), leukocytosis (23.9×10^3/μL), and disseminated intravascular coagulopathy (Table). A continuous infusion of furosemide was initiated and multiple blood products were transfused. Blood cultures obtained on admission became positive for large gram-positive bacilli after 20 hours of incubation (Figure 1B). Smears of the broth were Gram stained and revealed gram-positive rods in extremely long chains. Examination of a wet preparation of the blood culture broth demonstrated that the organism was nonmotile. Blood, pleural fluid, and bronchial wash specimens were sent for DNA amplification by polymerase chain reaction (PCR). A repeat echocardiogram confirmed a slight increase in the amount of pericardial fluid.

On the third hospital day, phenylephrine was tapered off and the norepinephrine dose was decreased by 50%. The patient's respiratory status deteriorated, with worsening oxygenation and ventilation. The blood culture isolate was confirmed as *B anthracis* by gamma phage lysis and direct fluorescent antibody testing against capsular and cell wall antigens at the New York City Department of Health and the CDC. Blood, pleural fluid, and bron-

Table. Laboratory Data*

Variables	Value			
	Day 1	Day 2	Day 3	Day 4
Hematologic				
White blood cell count, $\times 10^3$/μL	11.4	23.9	25.4	15.8
Differential cell count, %				
Polymorphonuclear cells	83.6	80.6	81.9	88.6
Lymphocytes	9.7	13.1	13.7	7.1
Monocytes	6.7	6.1	4.0	4.2
Hemoglobin, g/dL	15.5	16.2	9.7	10.4
Hematocrit, %	46.3	47.1	28.3	29.3
Platelet count, $\times 10^3$/μL	135	59	37	68
Serum chemistry				
Glucose, mg/dL	179	129	278	163
Sodium, mEq/L	134	134	150	148
Potassium, mEq/L	3.5	5.1	3.6	3.7
Chloride, mEq/L	96	100	100	104
Bicarbonate, mEq/L	26	22	30	27
Serum urea nitrogen, mg/dL	18	39	56	68
Creatinine, mg/dL	0.8	1.9	4.0	4.4
Calcium, mg/dL	7.6	6.1	4.6	6.5
Albumin, g/dL	3.3	2.0	1.5	2.5
Alkaline phosphatase, U/L	96	96	56	92
Lactate dehydrogenase, U/L	1370	4788	6109	. . .
Lactate, mg/dL	. . .	75	. . .	. . .
Aspartate aminotransferase, U/L	240	471	10 044	10 888
Alanine aminotransferase, U/L	263	660	6100	4494
Total bilirubin, mg/dL	. . .	0.1	1.3	2.2
Creatine kinase, U/L	74	198	. . .	. . .
Troponin	Negative			
Coagulation				
Prothrombin time, s	10.3	11.5	23.5	. . .
International normalized ratio	0.8	1.0	4.2	. . .
Partial thromboplastin time, s	23.8	29.3	60.0	. . .
Dimerized plasmin fragment D, mg/L	. . .	. . .	>4000	>4000

*Ellipses indicate value not available. To convert glucose from mg/dL to mmol/L, multiply by 0.05551. To convert urea nitrogen from mg/dL to mmol/L, multiply by 0.357. To convert creatinine from mg/dL to μmol/L, multiply by 88.4. To convert calcium from mg/dL to mmol/L, multiply by 0.25. To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

chial washings were also positive by PCR for *B anthracis* at the same laboratories. Levofloxacin was discontinued and ciprofloxacin, 400 mg every 12 hours, was initiated. Repeat echocardiogram confirmed an increase in the size of the pericardial effusion and mild-to-moderate right atrial and ventricular collapse during early diastole. Cardiac index was 2.6 L/(min/m^2) (reference range, 2.4-4.0 L/[min/m^2]), systemic vascular resistance was 1131 (dynes·s·m^2)/cm^5 (reference range, 900-1400 [dynes·s·m^2]/cm^5), and a pulmonary capillary wedge pressure was 13 mm Hg (reference range, 6-12 mm Hg), with no evidence of equalization of pressures. A follow-up echocardiogram 5 hours later documented further increase in the pericardial fluid with evidence of collapse of the right atrium and ventricle.

The patient's respiratory status deteriorated further, and blood gas analysis revealed a pH of 7.49, a partial pressure of carbon dioxide of 37 mm Hg, a partial pressure of oxygen of 59 mm Hg, and an oxygen saturation of 92% with pressure-control ventilation, with pressure control of 20 cm H_2O, 100% oxygen, and positive end-expiratory pressure of 5 cm H_2O. Because of her deteriorating hemodynamic status and inability to maintain adequate oxygenation, a bedside echocardiographically guided pericardiocentesis was attempted unsuccessfully by the interventional cardiology service. The patient decompensated further, with worsening oxygenation and refractory hypotension with vasopressors, and she became bradycardic and pulseless. Cardiopulmonary resuscitation was unsuccessful and the patient died on the fourth hospital day. Repeat blood cultures from the second and fourth hospital days were negative for any pathogens.

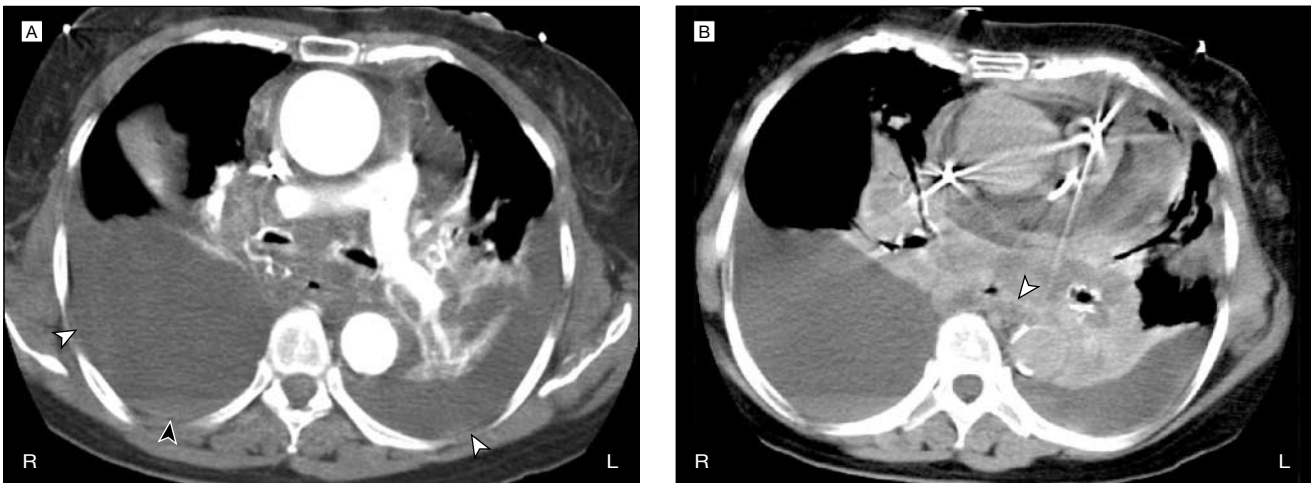
An autopsy performed at the office of the chief medical examiner of the city of New York confirmed marked hemorrhagic mediastinitis. The hilar and peribronchial lymph nodes were enlarged, necrotic, and replaced by hematoma. Touch prep revealed few scattered gram-positive bacilli. There was a large hemorrhagic pericardial effusion and extensive pulmonary edema. There was no meningitis, bronchopneumonia, splenomegaly, or mesenteric lymphadenopathy. There were no hemorrhagic lesions of the liver or kidney. The cause of death was inhalational anthrax and the manner of death was homicide (oral communication, James Gill, MD, New York City Medical Examiner Office, January 14, 2002).

COMMENT

For the patient presented herein, there were no obvious links to any of the settings previously associated with either naturally occurring or bioterrorism-associated anthrax. Inhalational anthrax was considered in this patient from the time of admission because of the widespread publicity surrounding previous cutaneous anthrax cases in New York City and the alerts issued to the medical community by the New York City Department of Health. Despite early institution of antibiotics, the disease progressed rapidly, resulting in multiple organ failure and large pericardial effusion precipitating hemodynamic instability.

The clinical presentation of inhalational anthrax in this patient was typical. Several days of a nonspecific prodrome of malaise, generalized weakness, chills, and occasional chest pain preceded complete respiratory failure, septic shock, a large pleural effusion,

Figure 2. Spiral Computed Tomography of the Chest and 20-Minute Delayed Image



A, Computed tomographic image demonstrates large bilateral pleural effusions (white arrowheads) with a small amount of hemorrhagic debris (black arrowhead) in the dependent portion of the right pleural space. There is a large amount of edema and high-density soft tissue surrounding the trachea, bronchi, and hilar regions bilaterally, with obliteration of the mediastinal fat planes. There is marked bronchial mucosal edema and compression of the hilar vessels. B, This image demonstrates multiple confluent ringlike areas of enhancement with hypodense centers, consistent with subcarinal and mediastinal hemorrhagic lymphadenopathy (white arrowhead). There is additional involvement of the paratracheal, subaortic, and azygoesophageal recess nodes. A high-density hemorrhagic pericardial effusion is also present.

and multiple organ dysfunction. Hemorrhagic mediastinitis and hemorrhagic pericardial effusion may have contributed to respiratory failure. Death occurred 7 days after the onset of symptoms, similar to that reported by Dixon et al.[4]

The anthrax bacillus is a gram-positive, aerobic, spore-forming microorganism. Aerosolized anthrax spores can be trapped in the upper airways, although spores of 2 to 3 µm can pass through the bronchi to the alveoli. The spores are engulfed by macrophages, which carry them to the peribronchial and mediastinal lymph nodes, where they germinate and replicate into vegetative bacilli. This leads to hemorrhagic lymphadenitis and the enlarged mediastinum that is observed on radiographic images.[4,7] Mediastinal hemorrhage with high-density adenopathy in an acutely ill patient with no history of trauma should raise concern for inhalational anthrax infection.

Inhalational anthrax is not considered a true pneumonia, and death results from septicemia, toxemia, or pulmonary complications and usually occurs within 36 hours.[4] As of November 7, 2001, 5 of the 11 patients with inhalational anthrax associated with bioterrorism in the United States have died. The 6 survivors were treated in the prodromal phase of the disease; none of the patients who required intubation or who became hemodynamically unstable have survived.[10] Early suspicion and initiation of antibiotic therapy while awaiting culture results may improve the prognosis.[1]

The initial diagnosis of anthrax is usually made by positive cultures of blood, cerebrospinal fluid, or skin lesion (vesicular fluid or eschar).[3] Rapid identification of the growing organism can be made by direct fluorescent antibody testing and gamma phage lysis. DNA amplification from body fluids by PCR may help in early diagnosis of the disease. Antibody testing by enzyme-linked immunosorbent assay may yield positive results in convalescent serum specimens.[4] Currently, such tests are available only in local and state public health laboratories or at the CDC.

To date, 7 cases of cutaneous anthrax and 1 case of inhalational anthrax have been reported in New York City. All of the cutaneous cases occurred among employees or persons directly associated with the media; 2 were NBC employees, 1 was a CBS employee, 3 were from the *New York Post*, and 1 was the infant of an ABC employee. Environmental samples from these media companies' buildings were positive for anthrax spores.

The patient presented in this case report differed from other reported cases of inhalational anthrax in that no clear risk for exposure has yet been determined. Extensive environmental samples from the patient's residence and workplace were negative for *B anthracis* by PCR and conventional bacterial cultures. Nasal cultures taken from personal contacts and coworkers in the same workplace environment were also negative for *B anthracis*. Environmental samples from surfaces and an air filtration system from the subway route that the patient rode daily were also negative for anthrax (New York City Department of Health and CDC).[8,11-13]

It has been postulated that infection from a cross-contaminated envelope may have been the source of anthrax transmission in this patient.[8] However, it is unclear why she is the only patient in New York City to date who has developed inhalational anthrax. Nonetheless, even patients without obvious sources of possible anthrax exposure may be at risk for bioterrorism-associated diseases. Heightened public health and health care facility surveillance efforts, increased awareness by the public, and health care professional education are needed to ensure that the unusual clinical presentations of such rare infections do not go unrecognized.

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Following discussion with the hospital administrator and human resources department at the patient's place of employment and investigations by the social work department, there is no known living family member, next of kin, or legally authorized representative of this patient to obtain consent for publication.

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