

Death Due to Bioterrorism-Related Inhalational Anthrax

Report of 2 Patients

Luciana Borio, MD

Dennis Frank, MD

Venkat Mani, MD

Carlos Chiriboga, MD

Michael Pollanen, MD, PhD

Mary Ripple, MD

Syed Ali, MD

Constance DiAngelo, MD, MS

Jacqueline Lee, MD

Jonathan Arden, MD

Jack Titus, MD

David Fowler, MD

Tara O'Toole, MD, MPH

Henry Masur, MD

John Bartlett, MD

Thomas Inglesby, MD

ON OCTOBER 9, 2001, A LETTER containing anthrax spores was mailed to a US senator's office in Washington, DC.¹ That letter was processed at the Brentwood postal facility, one of the largest in the Washington, DC, metropolitan area, and eventually opened by the senator's staff 6 days later. As of October 30, 2001, 5 postal workers who worked at or handled bulk mail from that facility had been hospitalized with confirmed inhalational anthrax. Two of them died shortly after admission to area hospi-

See also pp 2549, 2595, and Patient Page.

On October 9, 2001, a letter containing anthrax spores was mailed from New Jersey to Washington, DC. The letter was processed at a major postal facility in Washington, DC, and opened in the Senate's Hart Office Building on October 15. Between October 19 and October 26, there were 5 cases of inhalational anthrax among postal workers who were employed at that major facility or who handled bulk mail originating from that facility. The cases of 2 postal workers who died of inhalational anthrax are reported here. Both patients had nonspecific prodromal illnesses. One patient developed predominantly gastrointestinal symptoms, including nausea, vomiting, and abdominal pain. The other patient had a "flulike" illness associated with myalgias and malaise. Both patients ultimately developed dyspnea, retrosternal chest pressure, and respiratory failure requiring mechanical ventilation. Leukocytosis and hemoconcentration were noted in both cases prior to death. Both patients had evidence of mediastinitis and extensive pulmonary infiltrates late in their course of illness. The durations of illness were 7 days and 5 days from onset of symptoms to death; both patients died within 24 hours of hospitalization. Without a clinician's high index of suspicion, the diagnosis of inhalational anthrax is difficult during nonspecific prodromal illness. Clinicians have an urgent need for prompt communication of vital epidemiologic information that could focus their diagnostic evaluation. Rapid diagnostic assays to distinguish more common infectious processes from agents of bioterrorism also could improve management strategies.

JAMA. 2001;286:2554-2559

www.jama.com

tals. These 2 fatal cases are reported here to educate clinicians about the clinical presentation and course of illness of inhalational anthrax following exposure to anthrax spores.

PATIENT 1

On October 16 (day 1), a 47-year-old male postal worker who worked in the mail sorting area of the Brentwood facility developed nausea, abdominal pain, and "flulike" symptoms. He attributed his

symptoms to "food poisoning" and continued to work despite ongoing symptoms. On October 20 (day 5), while in church, he had a brief, self-limited syncope episode. By the time paramedics arrived, he felt better. He went home, did not eat, and immediately went to bed, un-

Author Affiliations are listed at the end of this article. **Corresponding Author and Reprints:** Luciana Borio, MD, Johns Hopkins Center for Civilian Biodefense Studies, Johns Hopkins University, Candler Bldg, Suite 850, 111 Market Pl, Baltimore, MD 21202 (e-mail: lborio@nih.gov).

like his usual routine. He reported to work that evening and on October 21 (day 6), at 2 AM, he developed worsening nausea, vomiting, abdominal pain, and profuse sweating and drove to an emergency department. On arrival, he also complained of lightheadedness and diaphoresis and denied dyspnea and chest pain. He had no significant medical history. His only chronic medical problem was asthma, and salmeterol was his only medication.

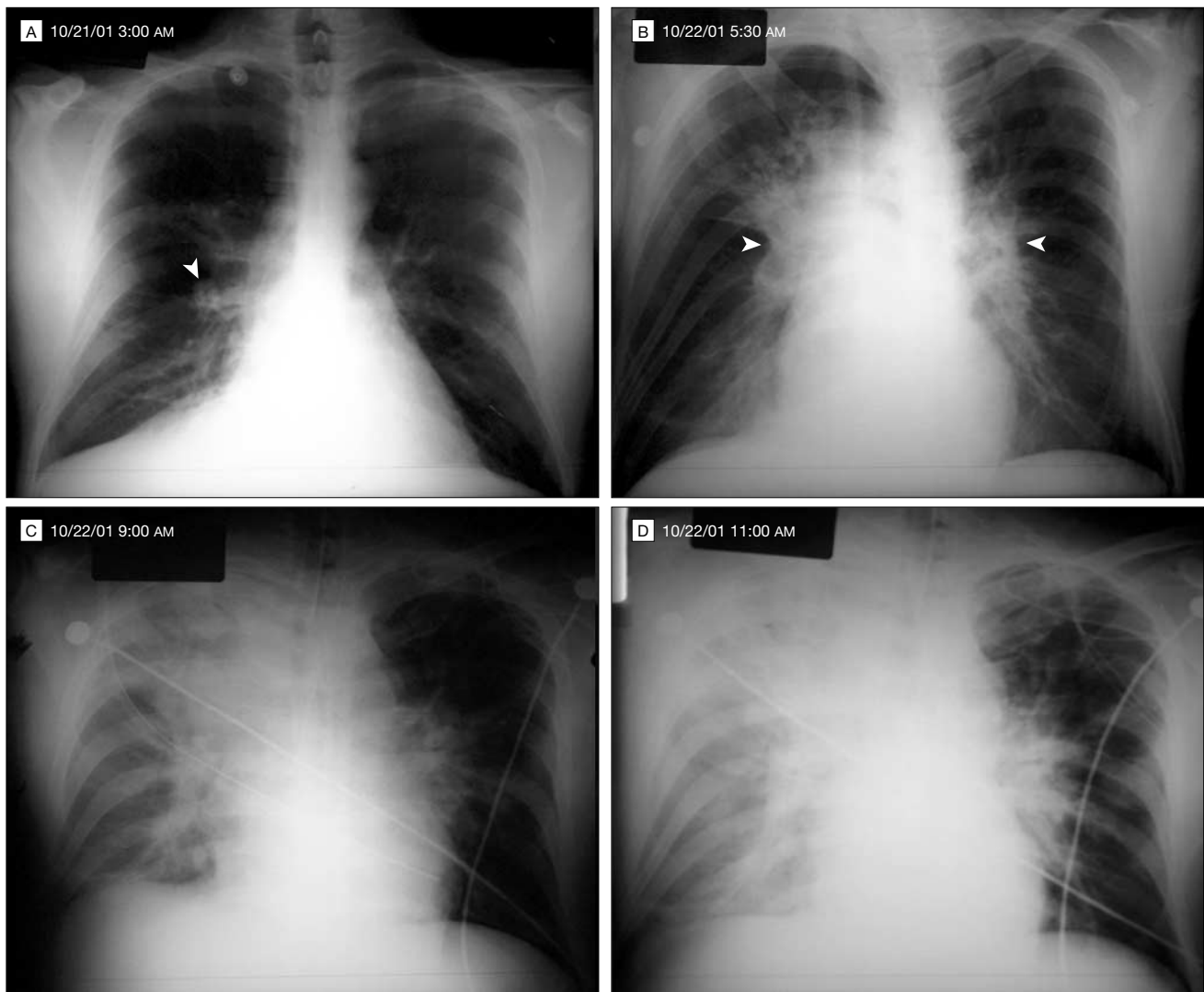
The patient's temperature was 36.1°C, blood pressure was 82/59 mm

Hg, pulse was 95/min, respirations were 18/min, and oxygen saturation was 99% in room air. Physical examination was unremarkable. Laboratory data revealed mild leukocytosis and hemoconcentration. Chest radiograph (FIGURE 1) showed a subtle and ill-defined area of increased density in the right subhilar region; follow-up with computed tomography (CT) was suggested. After treatment with intravenous fluids, promethazine, and famotidine, his symptoms resolved. At 4 AM, vital signs were as follows: tempera-

ture, 36.6°C; blood pressure, 109/68 mm Hg; pulse, 86/min; and respirations, 20/min. He was discharged to home at approximately 5 AM with a presumptive diagnosis of gastroenteritis and instructions to see his primary care physician the following day.

Throughout the day of October 21 (day 6), the patient's gastrointestinal symptoms progressed and he developed dyspnea and diaphoresis. On October 22 (day 7) at 4:45 AM, his wife found him slumped in the bathroom. He was taken to a hospital by ambulance. On

Figure 1. Chest Radiographs for Patient 1



A, Initially, only subtle bilateral hilar prominence (arrowhead) and right perihilar infiltrate was noted, but subsequent images (B-D) revealed a progressively widened mediastinum (B, arrowheads) and marked perihilar infiltrates, peribronchial cuffing, and air bronchograms.

arrival, he reported nausea, vomiting, and lightheadedness and denied dyspnea or chest pain but was ill-appearing and in respiratory distress. Temperature was 35.5°C, blood pressure was 76/46 mm Hg, pulse was 152/min, respirations were 28/min, and oxygen saturation was 96% in room air. Physical examination revealed regular tachycardia, decreased breath sounds at the lung bases, diffuse wheezes and rhonchi, mild abdominal tenderness, and mottled and cool skin.

A working diagnosis of inhalational anthrax was made because of reports in the media that 2 postal workers had been hospitalized in the Washington, DC,

metropolitan area with inhalational anthrax.² Laboratory data (TABLE) showed leukocytosis, hemoconcentration, azotemia, and an elevated amylase level. Chest radiographs (Figure 1) revealed progressive pulmonary infiltrates and, compared with the radiograph of October 21, new pleural effusions and a widened mediastinum. A Gram stain of the admission peripheral blood buffy coat revealed numerous large, gram-positive bacilli (FIGURE 2). At that time, a Gram stain was requested on blood that had been incubated for 1 hour in BD Bactec (BD, Sparks, Md) culture media. The long chains of gram-positive bacilli

(FIGURE 3A) and the “jointed bamboo-rod” appearance (Figure 3B) were considered typical of *Bacillus anthracis*. Anthrax was confirmed by the Centers for Disease Control and Prevention (CDC) in the following days³ (the CDC confirms *B anthracis* in culture when 2 tests are positive: polymerase chain reaction and gamma phage lysis).

Despite prompt initiation of therapy with one 500-mg dose of parenteral levofloxacin; penicillin G, 3 million U every 4 hours; one 2-g dose of ceftriaxone; and one 600-mg dose of rifampin, the patient developed progressive hypoxic respiratory failure and marked hypotension. Mechanical ventilation and vasopressor therapy was instituted. Gram stain of an endotracheal aspirate showed few white blood cells and rare large gram-positive bacilli. A cotton swab from the nose was obtained for culture at admission, plated on sheep blood agar, and read at 24 hours, and was negative for *B anthracis*. The patient developed abdominal distention; a CT scan with intravenous contrast revealed moderate ascites and small-bowel intramural pneumatosis (FIGURE 4A). A chest CT image revealed parenchymal infiltrates, pleural effusions, and a widened mediastinum (Figure 4B). On October 22 (day 7), 5 hours after admission, the patient developed ventricular tachycardia followed by refractory bradycardia and asystole and died despite attempts at cardiac resuscitation.

At autopsy, there were multifocal hemorrhagic foci in the mediastinum with extension along hilar and parenchymal bronchi and blood vessels. There was hilar lymphadenopathy (2.5 cm) and hemorrhagic necrotizing hilar lymphadenitis; microscopic examination showed effacement of the nodal architecture, acute hemorrhagic necrosis, abundant karyorrhectic debris, and infiltration of polymorphonuclear leukocytes. Brown and Brenn stain of the hilar soft tissue and lymph nodes showed abundant gram-positive bacilli. There was no gross or microscopic evidence of pneumonia but there were large serous pleural effusions bilaterally (right, 250 cc; left, 500 cc).

Table. Laboratory Findings*

	Patient 1			Patient 2	
	10/21/01 2:35 AM	10/22/01 8:31 AM	10/22/01 11:47 AM	10/21/01 6:40 AM	10/22/01 2:00 PM
White blood cells, / μ L	13 300	31 200	47 000	18 800	...
Neutrophils, %	78.3	78	...	79.8	...
Hematocrit, %	51.4	62	42.4	55.3	...
Platelets, / μ L	207 000	250 000	223 000	141 000	...
Sodium, mEq/L	139	148	150	130	137
Potassium, mEq/L	4.7	4.8	4.1	5.3	4.8
Chloride, mEq/L	106	109	122	99	108
Bicarbonate, mEq/L	22	18	12	14	12
Serum urea nitrogen, mg/dL	20	52	44	22	42
Creatinine, mg/dL	1.2	2.8	1.9	1.6	2.4
Glucose, mg/dL	124	...	163	425	531
Calcium, mg/dL	7.9	8.5	4.4	8.5	7.8
Magnesium, mg/dL	2.1	...	1.3	...	2.5
Arterial blood gases					
Fraction of inspired oxygen	...	1.0	...	2L, NC	100%, mask
pH	...	7.13	...	7.42	7.40
Pco ₂ , mm Hg	...	36	...	25	24
Po ₂ , mm Hg	...	150	...	66	71
Oxygen saturation, %	93	100
Creatine phosphokinase, U/L	115	...	51	107	...
Creatine kinase, U/L	1.3	...
Troponin I, ng/mL	0	...	0.2	<0.3	0.6
Prothrombin time, s	12.3	...	22.1	...	13.2
Partial thromboplastin time, s	27.1	...	96	...	27.9
Total protein, g/dL	...	4.5	...	6.8	...
Albumin, g/dL	3.6	2.9	...	3.1	...
Alkaline phosphatase, U/L	119	197	...	116	...
Total bilirubin, mg/dL	0.4	0.2	...	0.9	...
Aspartate aminotransferase, U/L	39	47	...	76	...
Alanine aminotransferase, U/L	44	33	...	77	...
Amylase, U/L	...	318

*To convert creatinine from mg/dL to μ mol/L, multiply by 88.4. To convert glucose from mg/dL to mmol/L, multiply by 0.05551. To convert calcium from mg/dL to mmol/L, multiply by 0.25. To convert magnesium from mg/dL to mmol/L, multiply by 0.4114. To convert bilirubin from mg/dL to μ mol/L, multiply by 17.1. Ellipses indicate test not done; NC, nasal cannula.

There was a large amount of ascites (2500 cc). The small bowel was edematous and multifocal mesenteric soft tissue hemorrhage was present. A portion of the ileum showed hemorrhage and necrotizing infection without visible mucosal ulceration. Microscopic examination of the involved section of the ileum showed serosal and submucosal acute and chronic inflammation extending into the lamina propria. Brown and Brenn stain of the ileum showed abundant gram-positive bacilli. The mesenteric lymph nodes, terminal ileum, and large bowel were grossly unremarkable. Brain and cerebrospinal fluid were not examined. The cause of death was certified as inhalational anthrax. The manner of death was certified as homicide.

PATIENT 2

On October 17 (day 1), a 55-year-old male postal worker who worked as a distribution clerk in the mail sorting area of the Brentwood facility and who had hypertension, diabetes mellitus, and remote history of sarcoidosis sought outpatient medical attention for myalgias, weakness, and fever of 1 day's duration. He was diagnosed as having a viral syndrome and sent home. His symptoms persisted. On October 21 (day 5) at 6 AM,

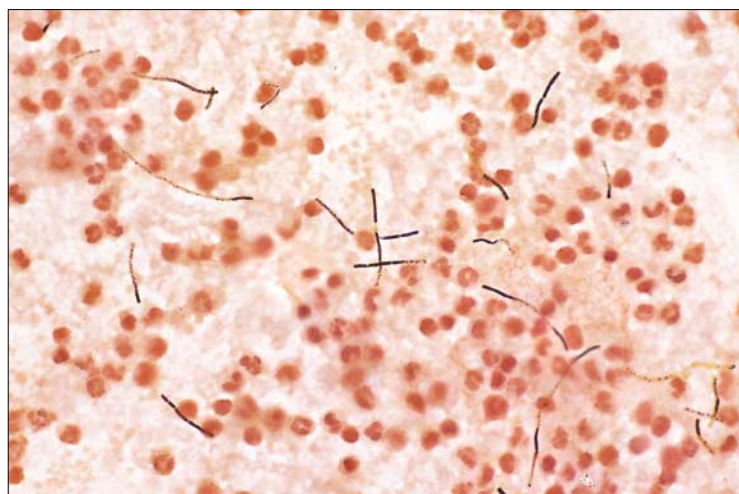
he presented to an emergency department (of a different hospital than that of patient 1) complaining of severe dyspnea, myalgias, weakness, retrosternal chest pressure, high fever, chills, nausea, vomiting, and a cough productive of scant greenish sputum.

On initial physical examination, the patient was alert, well-appearing, and in no acute respiratory distress. Temperature was 38.9°C, blood pressure

was 119/73 mm Hg, pulse was 150/min, respirations were 20/min, and oxygen saturation was 94% in room air. The remainder of the examination was notable for rales and decreased breath sounds at the right lung base and an irregular tachycardia. Electrocardiogram showed atrial fibrillation.

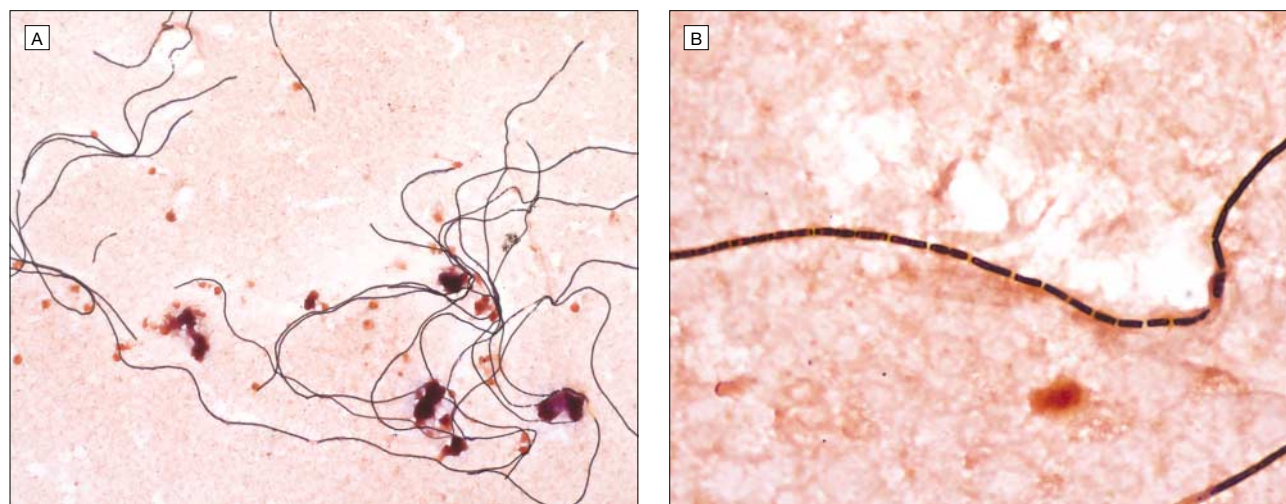
Laboratory data (see Table) revealed marked leukocytosis, profound hemoconcentration, metabolic acidosis, hy-

Figure 2. Gram Stain of Peripheral Blood Buffy Coat for Patient 1



Gram-positive bacilli in short chains (original magnification $\times 40$).

Figure 3. Gram Stain of Blood in Culture Media for Patient 1



A, Gram-positive bacilli in long chains (original magnification $\times 20$). B, Enlargement showing typical "jointed bamboo rod" appearance of *Bacillus anthracis* (original magnification $\times 100$).

perglycemia, azotemia, and hypoxemia. The admission chest radiograph is shown in FIGURE 5A.

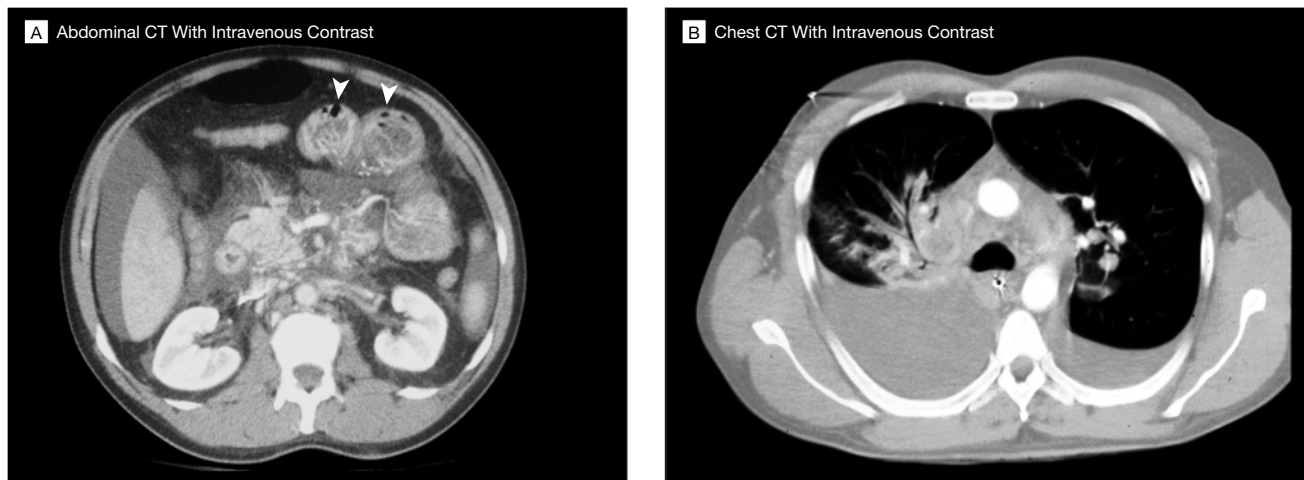
Because the health care staff were aware through media reports that 2 postal workers had been hospitalized in the local metropolitan area with inhalational anthrax, the patient was admitted with a diagnosis of suspected in-

halational anthrax. He was given prompt treatment with one 500-mg dose of parenteral levofloxacin. Within 13 hours of admission, he developed marked hypotension requiring institution of vasopressors and progressive hypoxemic respiratory failure requiring endotracheal intubation. Shortly thereafter, he developed bradycardia and

asystole and died despite attempts at cardiac resuscitation. The case was reported to the medical examiner.

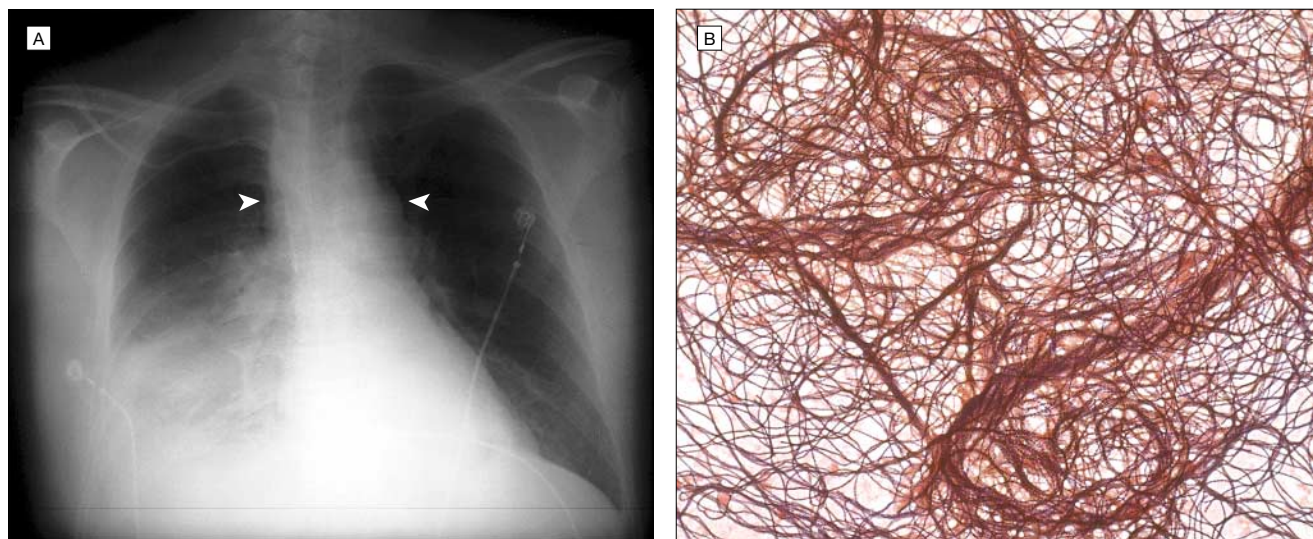
A Gram stain of blood incubated in BD Bactec culture media (Figure 5B) was recognized to have gram-positive rods the next morning, 24 hours after the patient's admission. The CDC subsequently confirmed the organism to be *B anthracis*.³

Figure 4. Abdominal and Chest Computed Tomography (CT) Images for Patient 1



A, Abdominal CT scan with intravenous contrast showing moderate amount of ascites, small-bowel wall edema, and intramural pneumatosis (arrowheads), consistent with a necrotizing enteritis. Other CT windows showed air within the hepatic branches of the portal venous system. B, Chest CT scan with intravenous contrast showing large bilateral perihilar infiltrates, perihilar lymphadenopathy, and widened mediastinum. Other CT windows showed high-attenuation mediastinal lymphadenopathy and blood in the mediastinum, consistent with hemorrhagic lymphadenopathy and hemorrhagic mediastinitis.

Figure 5. Chest Radiograph and Gram Stain of Blood in Culture Media for Patient 2



A, Chest radiograph shows widened mediastinum (arrowheads) with mediastinal and hilar lymphadenopathy, air-space disease of the right middle and lower lobes, and bilateral pleural effusions. B, Gram stain of blood in culture media shows very long chains of gram-positive bacilli (original magnification $\times 20$).

At autopsy, there was marked acute hemorrhagic mediastinitis, hemorrhagic necrotizing lymphadenitis of the hilar and mediastinal lymph nodes (3-5 cm in diameter), and bilateral serosanguinous pleural effusion (right, 1300 cm³; left, 700 cm³). Bilateral acute subpleural hemorrhage was present at the hilum of both lungs with extension along the adventitia of the intraparenchymal branches of the pulmonary arteries. Microscopic examination of the lymph nodes revealed effacement of the nodal architecture, acute hemorrhagic necrosis, infiltration by polymorphonuclear leukocytes, and numerous bacilli. There was no evidence of pneumonia or meningitis. The cause of death was certified as inhalational anthrax. The manner of death was certified as homicide.

COMMENT

Inhalational anthrax presents with nonspecific symptoms that cannot be distinguished from many more common diseases based on early clinical manifestations or routine laboratory tests. Both patients in this report sought medical care for apparently mild, nonspecific illnesses and were sent home. Only after the news media reported cases of inhalational anthrax involving 2 postal workers from the local mail facility did these patients' physicians consider the possibility that they could have inhalational anthrax. At that point, the patients had been ill for 7 days (patient 1) and 5 days (patient 2). The courses of their illness are similar to that reported in an outbreak of anthrax that occurred in Sverdlovsk in 1979.⁴ Despite aggressive medical therapy, both patients developed rapidly progressive disease and died.

These patients received antimicrobial therapy at the discretion of their physicians, before the CDC released formal guidelines on October 26, 2001.³ These guidelines recommend combination therapy for inhalational anthrax and complicated cutaneous anthrax. Ciprofloxacin or doxycycline are recommended in conjunction with another active antimicrobial drug, such as rifampin or clindamycin. Even though all isolates tested were susceptible to peni-

cillin, β -lactamases were identified in these isolates, and penicillin monotherapy for treatment of systemic infection is not recommended. Susceptibility testing also revealed intermediate sensitivity to ceftriaxone and presence of a cephalosporinase. Cephalosporins, therefore, are not indicated for the treatment of *B anthracis* infection.

These 2 cases emphasize that in the event of serious outbreaks of infectious diseases, such as those that occurred following the handling of anthrax-containing letters at the Brentwood postal facility, rapid communication of epidemiologic data to front-line medical care providers (especially emergency physicians and primary care clinicians) is essential so they may initiate appropriate diagnostic procedures and therapies. Efforts should be made to enhance communications systems between public health agencies and clinicians.⁵

A presumptive diagnosis of *B anthracis* can be made readily by most microbiology laboratories. The organism grows readily, can be safely evaluated in a biosafety level 2 facility, has characteristic Gram stain morphology, and should be suspected anytime a nonmotile, nonhemolytic gram-positive rod is identified in the setting of a compatible clinical syndrome. Communicating presumptive diagnostic information throughout the public health and clinical community must be a priority. Nasal swab cultures cannot reliably rule out exposure to *B anthracis*, as stated by the CDC³ and exemplified by patient 1, who, despite severe clinical disease, had a negative nasal swab culture. Whether the culture would have been positive if a Dacron swab had been used, if a more rigorous culturing technique was used, or if a deeper site had been sampled is unknown.

These 2 case reports also emphasize the importance of having microbiology laboratory capacity to more conclusively identify anthrax and other diseases that may be caused by bioterrorism in the clinical settings where these diseases will present. Rapid diagnostic tests to distinguish early anthrax infection from other diseases of similar clinical appearance should be a high prior-

ity on a national research agenda to respond to the threat of bioterrorism. There are distressingly few health care facilities that can provide comprehensive diagnostic services and expert consultative support.

The clinical presentations of these 2 patients provide key information about the clinical presentations and clinical courses of these homicides. Clinicians throughout the country in the full range of health science disciplines must rapidly increase their knowledge about agents of bioterrorism and work collaboratively with governmental, academic, and private organizations to ensure that their communities have the resources and expertise necessary to manage these assaults expeditiously and efficiently.

Author Affiliations: Johns Hopkins Center for Civilian Biodefense Studies of Johns Hopkins Schools of Medicine and Public Health (Drs Borio, O'Toole, Bartlett, and Inglesby) and Office of the Chief Medical Examiner for the State of Maryland (Drs Ripple, Titus, and Fowler), Baltimore; Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Md (Drs Borio and Masur); Greater Southeast Community Hospital (Drs Frank and Ali) and Office of the Chief Medical Examiner for the District of Columbia (Drs Pollanen, DiAngelo, Lee, and Arden), Washington, DC; and Southern Maryland Hospital Center, Clinton (Drs Mani and Chiriboga).

Acknowledgment: We thank the following for their invaluable assistance in preparing the manuscript: David Reagan, MD, Greater Southeast Community Hospital, Washington, DC; Mridula Singh, MD, Bryan DeFranco, MD, and Karen Rexroth, Southern Maryland Hospital Center, Clinton, Md; Dan Lucey, MD, Washington Hospital Center, Washington, DC; Constance DiAngelo, MD, MS, Jacqueline Lee, MD, Jonathan Arden, MD, and their technical staff, Office of the Chief Medical Examiner for the District of Columbia, Washington, DC; and Anthony Suffredini, MD, Brad Wood, MD, and Jennifer Candotti, National Institutes of Health, Bethesda, Md.

We are grateful to the families of these 2 patients for providing permission to publish this important information for the medical community.

REFERENCES

1. Revkin AC. The odyssey of an anthrax-tainted envelope and a trail of death. *New York Times*. October 31, 2001:B8.
2. CNN. Anthrax: new case of inhalation. October 22, 2001. Available at: <http://www.cnn.com/2001/US/10/21/anx.anthrax.facts/index.html>. Accessed November 6, 2001.
3. Centers for Disease Control and Prevention. Investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy. *MMWR Morb Mortal Wkly Rep*. 2001;50:909-919.
4. Grinberg LM, Abramova FA, Yampolskaya OV, Walker DH, Smith JH. Quantitative pathology of inhalational anthrax, I: quantitative microscopic findings. *Mod Pathol*. 2001;14:482-495.
5. Inglesby TV, Henderson DA, Bartlett JG, et al, for the Working Group on Civilian Biodefense. Anthrax as a biological weapon: medical and public health management. *JAMA*. 1999;281:1735-1745.