

Clinical Presentation of Inhalational Anthrax Following Bioterrorism Exposure

Report of 2 Surviving Patients

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THE USE OF ANTHRAX AS A weapon of biological terrorism has moved from theory to reality in recent weeks. This report describes the clinical presentation, diagnostic workup, and initial therapy of 2 patients with inhalational anthrax. The clinical course is in some ways different from what has been described as the classic pattern for inhalational anthrax. A high degree of clinical suspicion, coupled with abnormal findings on chest radiographs and non-contrast-enhanced computed tomography (CT) imaging of the chest led to a presumptive diagnosis of inhalational

See also pp 2554, 2595, and Patient Page.

The use of anthrax as a weapon of biological terrorism has moved from theory to reality in recent weeks. Following processing of a letter containing anthrax spores that had been mailed to a US senator, 5 cases of inhalational anthrax have occurred among postal workers employed at a major postal facility in Washington, DC. This report details the clinical presentation, diagnostic workup, and initial therapy of 2 of these patients. The clinical course is in some ways different from what has been described as the classic pattern for inhalational anthrax. One patient developed low-grade fever, chills, cough, and malaise 3 days prior to admission, and then progressive dyspnea and cough productive of blood-tinged sputum on the day of admission. The other patient developed progressively worsening headache of 3 days' duration, along with nausea, chills, and night sweats, but no respiratory symptoms, on the day of admission. Both patients had abnormal findings on chest radiographs. Non-contrast-enhanced computed tomography of the chest showing mediastinal adenopathy led to a presumptive diagnosis of inhalational anthrax in both cases. The diagnoses were confirmed by blood cultures and polymerase chain reaction testing. Treatment with antibiotics, including intravenous ciprofloxacin, rifampin, and clindamycin, and supportive therapy appears to have slowed the progression of inhalational anthrax and has resulted to date in survival.

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anthrax in both cases, later confirmed by blood cultures and polymerase chain reaction (PCR) testing. Timely intervention with antibiotic therapy, including ciprofloxacin, rifampin and clindamycin, and supportive therapy appears to have slowed the progression of inhalational anthrax and has resulted to date in improved clinical outcome.

Until recently, inhalational anthrax was a rare disease, with the last case in the United States reported in 1978. The potential use of anthrax as a bioterrorism agent has been described for more than 75 years, and nearly 20 countries

are known to have investigated its use as a biological weapon.^{1,2} Current understanding of the clinical course and presentation of inhalational anthrax has

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been largely shaped by 3 sources: the unintentional anthrax exposure in Sverdlovsk in the former Soviet Union in 1979³; scattered outbreaks of the disease, usually among wool sorters or laboratory workers^{4,5}; and experimental animal models.^{6,7}

We recently diagnosed and treated documented inhalational anthrax in 2 patients, whose clinical symptoms, diagnostic workup and clinical course suggest that some redefinition of the natural history of inhalational anthrax in its initial presentation is warranted, at least in the setting of a bioterrorism event.

BACKGROUND

On October 15, 2001, a staff member of a US senator's office opened a tightly sealed envelope and noticed a "small burst of dust."⁸ The following day, the letter was shown to contain *Bacillus anthracis* by PCR testing. While criminal and epidemiologic research indicated a discrete area of exposure at the US Capitol, postal workers outside this area were not known to be at risk.

PATIENT 1

On October 19, 2001, a 56-year-old male postal worker from the Brentwood fa-

cility in Washington, DC, presented to the emergency department. He had been well until 3 days prior to admission, when he developed low-grade fever, chills, cough, dyspnea on exertion, and generalized malaise. The cough was initially productive of clear sputum until the night of admission, when it became blood tinged. The dyspnea was progressive and accompanied on the day of admission by a feeling of midsternal, non-radiating, pleuritic chest tightness.

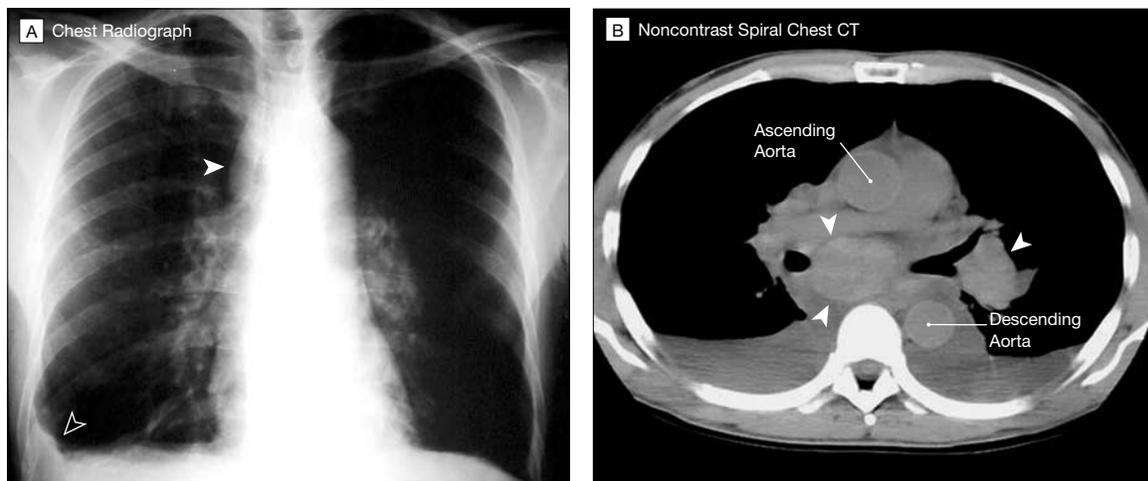
On review of systems, the patient noted myalgias, arthralgias, anorexia, and a sore throat. There was no congestion or other nasal symptoms. The patient had a childhood history of asthma but had been asymptomatic since adolescence. He denied any history of smoking tobacco. His primary duties at work involved distribution of express mail letters from the Brentwood and Baltimore–Washington–International Airport postal centers to government agencies, including the Senate office building.

The patient's initial vital signs were temperature of 37.5°C, pulse of 110/min, respirations of 18/min, blood pressure of 157/75 mm Hg, and oxygen saturation of 98% in room air. The physical examination revealed a thin but other-

wise healthy patient in no apparent distress. The only abnormality on physical examination was a decrease in breath sounds in the left lower lung base, without dullness, percussion, or egophony. The white blood cell count was 7500/ μ L (segmented neutrophils, 76; bands, 8; lymphocytes, 7; monocytes, 7). Serum chemistry results were normal, with the exception of creatine kinase, which was 207 U/L, with a creatine kinase–MB fraction of 1 U/L. Arterial blood gas analysis showed pH of 7.45, PaCO₂ of 27 mm Hg, PaO₂ of 80.3 mm Hg, and oxygen saturation of 97% on room air.

A posterior-anterior and lateral chest radiograph depicted a minimally widened mediastinum (most notable in the right paratracheal region), bilateral hilar masses, a moderate right pleural effusion, a suggestion of a left subpulmonic effusion, and a slight right lower lobe air-space opacity (FIGURE 1A). A contrast spiral CT of the chest showed profuse and slightly hyperattenuating paratracheal, anterior-posterior window, subcarinal, hilar, and azygoesophageal recess adenopathy (Figure 1B). The largest lymph node was in the subcarinal region and measured 4.2 cm in maximal transverse diameter (upper limit of normal, 1.0–1.5 cm). In ad-

Figure 1. Imaging Characteristics of Patient 1



A, Chest radiograph depicts a minimally widened mediastinum (white arrowhead), bilateral hilar adenopathy, moderate right pleural effusion (black arrowhead), and a subtle left lower lobe air-space opacity. B, Large hyperdense lymph nodes (arrowheads) are depicted in the subcarinal space and left hilum on this noncontrast spiral computed tomography (CT) image. The density of the lymph nodes is equal to that of blood in the adjacent ascending and descending aorta. Bilateral pleural effusions and edema of the mediastinal fat are also present.

dition, there was evidence of diffuse infiltrating mediastinal edema, bilateral moderate-sized pleural effusions, bibasilar air-space disease, and thickened peribronchial tissue.

Blood cultures obtained at the time of admission showed prominent gram-positive rods on Gram stain at 11 hours, consistent with *B anthracis* (FIGURE 2). The patient was given parenteral ciprofloxacin, 400 mg every 8 hours; rifampin, 300 mg every 12 hours; and clindamycin, 900 mg every 8 hours. He was admitted to the hospital for further therapy, where he was in serious but stable condition on the 20th hospital day. *Bacillus anthracis* was confirmed as the etiologic organism at the Virginia State Health Laboratory and the Centers for Disease Control and Prevention (CDC) by PCR on October 21.

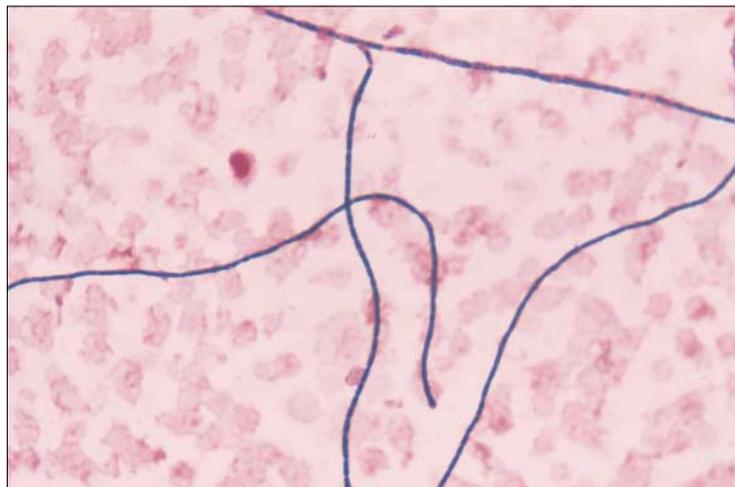
PATIENT 2

On October 20, 2001, a 56-year-old man who worked at the Brentwood post office in the mail sorting center presented to the emergency department with a progressively worsening headache of 3 days' duration, described as gradual in onset, global, and constant. He also complained of nausea, chills, and night sweats, but denied fevers, vomiting, photophobia, visual complaints, nuchal rigidity, slurred speech, or weakness. He had no respiratory complaints other than a mild sore throat, and the remainder of his review of systems was negative.

The patient's vital signs were temperature 37.6°C, pulse of 127/min, respirations of 20/min, blood pressure of 133/87 mm Hg, and oxygen saturation of 94% in room air. Physical examination revealed a well-developed man in no acute distress whose neurologic examination result was completely normal. The remainder of physical examination was notable only for diffuse rhonchi and decreased breath sounds in both lung bases.

His white blood cell count was 9700/ μ L with a normal differential, and the remainder of his laboratory studies yielded normal results. A noncontrast head CT image was normal. He un-

Figure 2. Gram Stain of Blood Culture at 11 Hours of Growth Showing Prominent Gram-Positive Rods, Later Confirmed as *Bacillus anthracis*



Original magnification $\times 40$.

derwent a lumbar puncture, which showed 20 red blood cells per high-power field, 4 white blood cells per high-power field, cerebrospinal fluid glucose level of 92 mg/dL (5.1 mmol/L), and no organisms on Gram stain. Culture and Gram stain of the cerebrospinal fluid were negative. Serum electrolytes were normal.

Anterior-posterior chest radiograph showed a widened mediastinum and low lung volumes, along with bilateral hilar masses, a right pleural effusion, and bilateral perihilar air-space disease (FIGURE 3A). A noncontrast spiral chest CT showed profuse and slightly hyperattenuating paratracheal, AP window, subcarinal, hilar, and azygosophageal recess adenopathy, although to a lesser extent than in patient 1 (Figure 3B). Diffuse mediastinal edema, bilateral pleural effusions, bibasilar air-space disease, and thickened peribronchial tissue were noted.

Because of the markedly abnormal chest radiograph and CT scans, a presumptive diagnosis of inhalational anthrax was made and the patient was given parenteral ciprofloxacin, 400 mg every 8 hours; rifampin, 300 mg every 12 hours; and clindamycin, 900 mg every 8 hours. *Bacillus anthracis* grew from the blood at 15 hours and was con-

firmed by PCR by the Virginia Department of Health and the CDC. The patient remained stable on the 21st hospital day.

COMMENT

Current literature on inhalational anthrax has stressed the rarity of this disease but has also emphasized several important features.⁹⁻¹⁴ First, it has been emphasized that early diagnosis of inhalational anthrax is exceedingly difficult, particularly if there is not a clearly defined exposure known to the clinicians treating a patient. It has been suggested that syndromic surveillance could be an important component in raising clinical suspicion of the disease, since it has been presumed that identification of an increase in flulike syndromes leading to clinical deterioration and death would be a harbinger in identifying the disease.¹⁰⁻¹³

Second, the illness has been characterized as having a 2-stage clinical course, with early nonspecific respiratory symptoms followed in 24 to 72 hours by the abrupt onset of fever, dyspnea, profound respiratory distress, and shock, with death occurring in 80% to 90% of patients.¹¹⁻¹⁵ Third, radiographic findings of a widened or abnormal mediastinum in previously healthy patients with

flulike symptoms have been considered pathognomonic of inhalational anthrax.^{9,11-15} However, these radiographic signs have been described as a relatively late finding associated with a poor prognosis.^{9,11,12} A recent consensus statement indicated that "treatment at this stage would be unlikely to alter the outcome of the illness."⁹

These features of the disease are derived not only from previous cases of inhalational anthrax but also because of what is known of the pathophysiology of the disease. Inhalational anthrax occurs following deposition of a sufficient number of spores into the alveolar space. These 1- to 5- μm spores are then ingested by macrophages, which are transported by the lymphatic system to the mediastinal lymph nodes. Germination of the spore into the *B anthracis* organism typically occurs within 1 to 3 days, but may occur as long as 60 days following transport to the lymph nodes.^{3,14} Once the bacteria replicate, anthrax toxin is released, comprising 3 proteins: protective antigen, lethal factor, and edema factor. Lethal factor and protective antigen bind to form lethal toxin, which is the predominant virulence factor of the disease. Once production of lethal toxin has occurred, apoptosis and hemor-

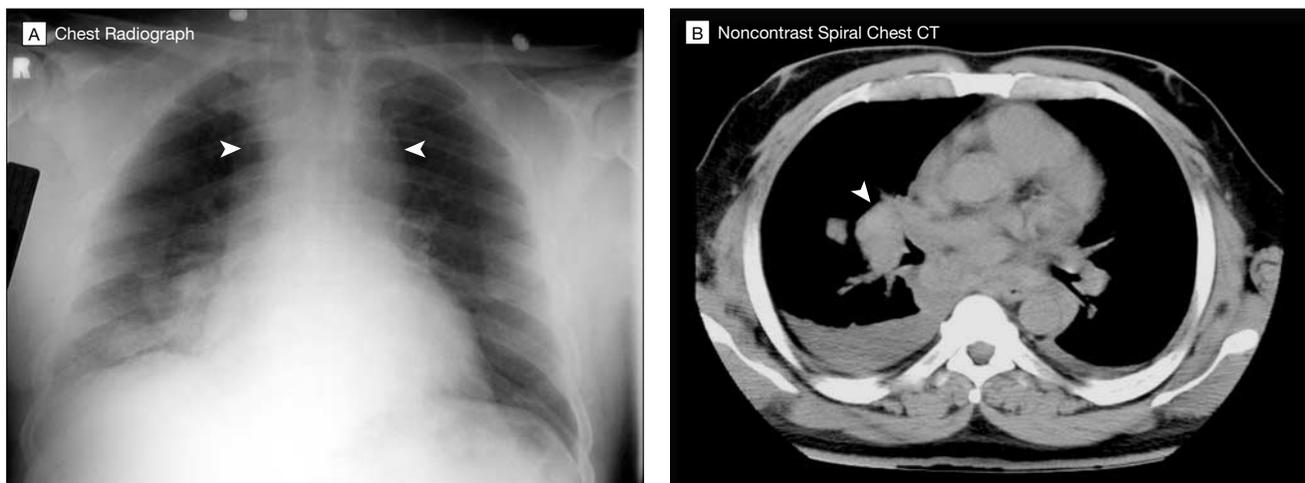
rhagic necrosis of the mediastinal lymph nodes occur rapidly, producing a clinical cascade of hemorrhagic mediastinitis and edema. When hemorrhagic necrosis extends to the pleura, bloody pleural effusions occur. Hematogenous spread of the bacteria and the toxin results in systemic disease, with profound shock, dyspnea, respiratory distress, and, in the majority of cases, death.¹¹⁻¹⁵

The 2 cases we report add to what is known about the natural history of inhalational anthrax and the initial presentation of the disease. Neither of the cases were known at the time of clinical presentation to have been exposed to anthrax or to be at high risk of the disease. In both cases, the treating physicians had a high clinical index of suspicion regarding the disease, based partly on the known *B anthracis* exposures in the Senate office building although the association of the disease with postal workers was not clearly known at the time the first patient presented to the emergency department. Both patients had an increased pulse rate, elevated out of proportion to either symptoms or fever, and an abnormal chest radiograph with bilateral pleural effusions and mediastinal

lymphadenopathy. The second patient presented with a different clinical picture, with severe headache, low-grade fever, night sweats, and nausea. The chest radiograph showed a right pleural effusion and a widened mediastinum; these findings were considered highly suggestive of inhalational anthrax and led to obtaining the chest CT image, which further confirmed the clinical suspicion of the disease.

Both patients were treated with ciprofloxacin, rifampin, and clindamycin and did not develop the classic findings of high-grade fever, dyspnea, profound respiratory distress, and shock. Ciprofloxacin was chosen because of its presumed effect on patients with inhalational anthrax, as evidenced by the fact that it is recommended as first-line therapy for treatment of inhalational anthrax.⁸ Rifampin was used to provide additional gram-positive coverage and because of its primarily intracellular mechanism of action.¹⁶ Clindamycin was added because of its ability to prevent expression of toxin in patients with streptococcal disease.¹⁷ This activity was believed to be of theoretical advantage in anthrax, in which toxin production is a major cause of morbidity and mortality.

Figure 3. Imaging Characteristics of Patient 2



A, Portable chest radiograph depicts a widened mediastinum (arrowheads), bilateral hilar fullness, a right pleural effusion, and bilateral perihilar air-space disease. B, Noncontrast spiral computed tomography (CT) depicts an enlarged and hyperdense right hilar lymph node (arrowhead), bilateral pleural effusions, and edema of the mediastinal fat.

These reports suggest that early diagnosis and treatment may improve the prognosis of inhalational anthrax. Both patients had substantial mediastinal pathologic findings at the time of their clinical presentation, yet aggressive therapy resulted in a good clinical outcome at this stage of their illness. Other possibilities are that these patients were exposed to a lower, sublethal dose of spores or that the strain of *B anthracis* was of a lower virulence than previously reported. However, the presence of substantial mediastinal lymphadenopathy and pleural effusions indicate a substantial degree of disease at the time of initial presentation. This suggests that early diagnosis and intervention interrupted what has primarily been described as a 2-stage cycle of the disease, in which mediastinal necrosis and hemorrhage progress to widespread toxin release and death, with reported mortality rates of 80% to 90%.⁹⁻¹⁴

Reports of the radiographic findings of inhalational anthrax are limited to descriptions of chest radiographs in a small number of cases.^{12,18,19} As the cases presented here illustrate, prior publications have reported widened mediastinum, adenopathy, pleural effusions, and parenchymal infiltrates. While these findings may make a dramatic presentation, there is nothing specific about this constellation of radiographic findings that would, by itself, lead to a diagnosis of inhalational anthrax. Nonetheless, the

presence of pleural effusions in the presence of a clinical history of potential exposure should raise suspicion of inhalational anthrax.

We found chest CT studies to be substantially useful. There are no published reports of the CT findings of inhalational anthrax, and there are no cases of inhalational anthrax with correlative CT imaging accessioned at the Armed Forces Institute of Pathology in Washington, DC (Jeffrey R. Galvin, MD, Armed Forces Institute of Pathology, Washington DC, written communication, October 23, 2001). Both of the cases reported herein had an unusual combination of findings that may prove to be helpful in diagnosing inhalational anthrax, namely, the presence of hyperdense enlarged mediastinal adenopathy and diffuse mediastinal edema. Although pathological correlation was not obtained in these cases, the hyperdensity in the lymph nodes is likely due to the presence of localized hemorrhage, which is known to be present based on prior reports.^{20,21} To optimally depict the presence of hyperdense adenopathy, non-contrast CT images may be more useful than contrast-enhanced images. Each patient presented with abnormal findings on chest radiographs, but CT of the chest showed much more dramatic evidence of mediastinal lymph node enlargement, suggesting that the chest radiograph substantially understates the degree of disease compared with chest CT.

At our institution, symptomatic patients with known or suspected exposure to anthrax spores receive a chest radiograph. If pleural effusion, mediastinal lymphadenopathy, or mediastinal widening is found, a non-contrast-enhanced CT study of the chest is obtained. For patients with normal chest radiographs but who have a substantial clinical suspicion of inhalational anthrax, chest CT also is obtained because this study may reveal important clinical information in such cases.

Our experience with 2 patients with inhalational anthrax resulting from a bioterrorism event suggests that a high degree of clinical suspicion, diagnostic workup including chest CT, and early intervention with appropriate antibiotics may reduce the previously reported mortality of 80% to 90% in inhalational anthrax.^{9,11-15} Although it is unfortunate that inhalational anthrax has reemerged as a distinct clinical entity rather than a theoretical bioterrorism agent, it is extremely important that clinicians be aware of this clinical presentation and be prepared to evaluate and appropriately treat such patients. Unfortunately, only further experience with this devastating disease can clarify its precise natural history and optimal treatment.

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