A Case of Naturally Acquired Inhalation Anthrax: Clinical Care and Analyses of Anti–Protective Antigen Immunoglobulin G and Lethal Factor

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This report describes the first case of naturally acquired inhalation anthrax in the United States since 1976. The patient’s clinical course included adjunctive treatment with human anthrax immunoglobulin. Clinical correlation of serologic assays for the lethal factor component of lethal toxin and anti–protective antigen immunoglobulin G are also presented.

The last known case of naturally acquired inhalation anthrax in the United States occurred in 1976 [1]. Naturally occurring anthrax is transmitted to humans through contact with contaminated animal products or through direct contact with infected animals. Clinical anthrax in humans occurs primarily in 3 forms: cutaneous, inhalational, and gastrointestinal [1]. The virulence associated with Bacillus anthracis infection is believed to be secondary to anthrax toxins, lethal toxin, and edema toxin [1].

Anthrax associated with the handling of animal hides outside of an industrial processing plant is rare, and is most often of the cutaneous form [2]. Epidemiologic investigation indicated that our patient’s exposure to B. anthracis spores most likely occurred during his processing of untreated animal hides in a poorly ventilated, confined space [3]. This report describes the patient’s clinical course, including his receipt of adjuvant therapy with human anthrax immunoglobulin (AIG), and clinical correlation of serologic assays for the lethal factor (LF) component of lethal toxin and for anti–protective antigen (PA) IgG.

Case report. A 44-year-old man presented to a local hospital in Pennsylvania on 16 February 2006 with dyspnea, nonproductive cough, chest pain, and profuse diaphoresis. The patient reported that symptoms started 2–3 days prior to admission to the hospital. His most recent travel included a trip to Cote d’Ivoire in December. His past medical history included a reported necrotizing fasciitis of the left thigh and surgeries for a recurrent, nonmalignant tumor of the right mandible. At the time of hospital admission, the patient was taking no medications. The patient is a professional musician and dancer for an African dance troupe.

On admission, the patient’s vital signs included a temperature of 37.6°C (99.7°F), blood pressure of 111/77 mm Hg, a pulse of 92 beats per min, and a respiratory rate of 24 breaths per min. Oxygen saturation while breathing room air was 98%. The patient was alert and oriented, but appeared ill and exhibited mild respiratory distress. Physical examination revealed decreased breath sounds in the left lung fields and normal breath sounds in the right lung fields, except for end-expiratory wheezing at the base posteriorly. Other physical examination findings included a large, well-healed skin graft on the left anterior thigh and scarring from the donor site on the right thigh. There were no other cutaneous lesions reported. The remainder of the findings of physical and neurologic examinations were unremarkable.

Laboratory findings included a total WBC count of $8.28 \times 10^3$ cells/µL (63% neutrophils, 24% lymphocytes, and 11% monocytes) with a normal hematocrit and platelet count. Serum electrolyte levels were within normal limits. The patient’s glucose level was elevated at 162 mg/dL. His serum creatinine level was 1.2 mg/dL. Serum chemistry levels included a lactate dehydrogenase level of 200 U/L, an aspartate aminotransferase level of 42 U/L, an alanine aminotransferase level of 28 U/L, and albumin level of 3.3 g/dL. Posterior-anterior and lateral chest radiographs revealed cardiomegaly, a left upper-lobe opacity, and a small right lower-lobe opacity. Bilateral pleural...
effusions were noted with evidence of loculation on the left. Blood, serum-plasma, and pleural fluid samples were also obtained for evaluation of LF and anti-PA IgG content. Blood samples were obtained for culturing, and the patient was admitted to the intensive care unit. Ceftriaxone and azithromycin therapy was initiated for presumed community-acquired pneumonia. A chest CT with contrast performed on 17 February revealed a large amount of mediastinal fluid accumulation extending from the great vessels to the heart. Echocardiography showed minimal pericardial fluid, with the majority of the collection located outside the pericardium. Mediastinal lymphadenopathy was not present. Atelectasis of the left upper lobe was believed to be secondary to compressive forces on the left lobe bronchus from the accumulation of mediastinal fluid. There was a loculated left pleural effusion and a simple right pleural effusion, which were contiguous with the mediastinal process. Late in the day on 16 February, blood cultures were performed and were determined to be positive in <12 h in 4 of 4 bottles via the BactAlert System (BioMérieux) growing gram-positive rods. Initial isolates were received by the Pennsylvania Public Health State Laboratory, part of the Laboratory Response Network, on 21 February. The isolates were identified as *B. anthracis* using the Laboratory Response Network real-time PCR assay within 5 h and were confirmed to be *B. anthracis* by susceptibility to γ-phage lysis on 22 February [4, 5].

The patient was transferred to a regional hospital for further management on 17 February, where piperacillin-tazobactam, moxifloxacin, and clindamycin therapies were initiated for a complicated intrathoracic infection. Inhalation anthrax was believed to be a significant possibility at the time of transfer on the basis of the finding of gram-positive rods in the initial blood cultures. Blood samples obtained <12 h after the initiation of antibiotics were sterile. On 19 February, a right thoracentesis yielded 1700 mL of serosanguineous fluid with a WBC count of 110 cells/μL (25% neutrophils, 24% lymphocytes, and 51% monocytes). No organisms were observed on Gram staining, and bacterial culture of the fluid was sterile. On 20 February, a left thoracotomy with pneumolysis and pleural biopsies was performed, with the placement of 2 chest tubes. Subsequent testing of biopsied pleural tissue and pleural fluid samples at the Centers for Disease Control and Prevention (Atlanta, GA) demonstrated immunohistochemical evidence of *B. anthracis* antigens [6]. LF protein and anti-PA IgG were detected in serum, plasma, and pleural fluid samples using a quantitative mass-spectroscopy technique for LF enzymatic activity and quantitative anti-PA IgG ELISA, respectively. LF was detectable in plasma samples (294.30 ng/mL) and serum samples (203.0 ng/mL) on 17 February and 18 February 2006, respectively, and in the single pleural fluid sample available from 19 February (543.20 ng/mL). The single early pleural fluid sample that was obtained on 19 February contained the highest level of detectable LF (543.2 ng/mL) and no detectable anti-PA IgG. Serum-plasma LF levels decreased steadily from 294.30 to 16.0 ng/mL over the period 17 February–23 February and decreased further to 0.85 ng/mL at 1 h after completion of anthrax immune globulin (AIG) administration on 23 February. A transient increase in detectable serum LF to 1.99 ng/mL over the next 24 h was followed by a continued decrease in serum LF levels, which reached the lowest level of 0.01 ng/mL and approached the lower limit of detection of the assay (0.005 ng/mL) on 28 February. Levels of detectable LF in serum-plasma and pleural fluid decreased in concert. Anti-PA IgG was quantifiable in the patient’s plasma on 22 February (9.0 μg/mL) and reached a >4-fold elevation (17.9 μg/mL) above the lower limit of quantification of the assay (3.0 μg/mL) by 23 February, thus confirming seroconversion. Serum and pleural fluid anti-PA IgG levels were elevated following AIG administration and continued to increase in concert in a step-wise manner from 23 February, onwards, until they reached a maximum value (311.4 μg/mL) on 28 February. The continued increase in antibody concentrations over this period is attributed to a combination of residual AIG and increasing patient antibody levels. As observed for LF, the levels of detectable anti-PA IgG in serum-plasma and pleural fluid samples decreased in concert. Testing at the Centers for Disease Control and Prevention also demonstrated that pleural fluid samples were positive by PCR for DNA of *B. anthracis* and contained levels of LF that were as high as 543.2 ng/mL [7] (figure 1). The patient’s antibiotic regime was modified to moxifloxacin, clindamycin, and ampicillin. Because of the patient’s progressive respiratory distress.
and multiorgan dysfunction (as evidenced by progression of pulmonary infiltrates and elevated liver function tests and serum creatinine), the Centers for Disease Control and Prevention recommended that the patient be treated with liquid 5% AIG (Cangene Corporation) under Emergency Investigational New Drug use protocol [8]. On 23 February, the patient was administered liquid 5% AIG [8]. Reaccumulation of the right pleural effusion required insertion of a right-side chest tube, which yielded 2000 mL of serosanguineous fluid. Chest CT on 24 February revealed bilateral pulmonary opacities with prominent ground glass appearance consistent with acute respiratory distress syndrome. Bronchoscopy was performed for further diagnostic evaluation of the patient’s worsening respiratory status; results were consistent with acute respiratory distress syndrome. Following bronchoscopy, the patient continued to receive mechanical ventilation. From 25 February through 1 March, the patient experienced intermittent fevers but remained normotensive, with improving WBC count. Chest radiographs throughout this period revealed less-prominent infiltrates. On 6 March, the patient was transferred out of the intensive care unit. The patient’s hospitalization was also complicated by a left hemothorax that required surgical repair of a bleeding intercostal artery. The patient was discharged from the hospital on 22 March. Three weeks after discharge, re-evaluation of the patient indicated near-normal pulmonary function studies and it was determined that he no longer required supplemental oxygen. A chest radiograph revealed minimal residual bilateral pulmonary opacities in the right upper lobe.

Discussion. The highest detectable levels of LF in serum (294.3 ng/mL) and pleural fluid (543.2 ng/mL) in this patient were at initial presentation; these emphasize the importance of rapid clinical diagnosis to maximize successful therapy [7] (figure 1). Detectable LF serum-plasma levels decreased over several days, and decreased even further to 0.85 ng/mL 1 h after completion of AIG administration on 23 February (assay limit of detection, 0.0125 ng/mL). The serum-plasma and pleural fluid levels of LF decreased concomitantly with the increase in anti-PA IgG. Anti-PA IgG is considered to be essential to the neutralization of toxin activity [9]. Increasing anti-PA IgG levels were detectable by ELISA in this patient’s serum samples by 22 February. Clinical improvement in this patient appeared to be associated with increasing levels of anti-PA IgG. Correlation between the magnitude of anti-PA IgG levels, the presence of lethal toxin, quantification of LF, and protective immunity will require further evaluation, and may help to guide the duration of an antimicrobial regimen following symptomatic inhalation anthrax.

Aggressive critical care support, including a multiantimicrobial regimen and pleural fluid drainage, were central to this patient’s survival. Historically, administration of anthrax animal antiserum was associated with improved survival in cases of human anthrax [10]. Animal studies suggest that optimal therapy for B. anthracis infection may include the use of antibiotics and early administration of antiserum [11]. Our patient tolerated the administration of AIG without evidence of acute adverse reactions; however, the patient experienced a further deterioration in respiratory function on 24–25 February. There was concern that the administration of AIG might have contributed to this deterioration. Review of the entire clinical context, however, indicated clinical and radiological evidence of worsening respiratory status prior to administration of AIG. Although this is, to our knowledge, the first patient to receive AIG, the continuous decline observed in detectable LF in serum-plasma and pleural fluid subsequent to antibiotic therapy suggests that AIG may provide clinical benefit when administered prior to evidence of clinical symptoms consistent with the proposed intermediate-progressive stage of inhalation anthrax [10, 12]. In summary, adjunct AIG therapy may have been beneficial, but its clinical impact at this time is difficult to delineate. Additional studies using appropriate animal models are required to determine the efficacy and optimal timing of administration of immune therapies in inhalation anthrax.

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