Neurologic Complications of Anthrax

A Review of the Literature

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A review of the literature suggests that the major neurologic symptom complex of infection by Bacillus anthracis is a fulminant and rapidly fatal hemorrhagic meningoencephalitis and that the reported initial mode of entry can be via the cutaneous or inhalation route. For febrile patients with acute neurologic deterioration with associated findings of dark necrotic pustules on the extremities, gram-positive rods in the cerebrospinal fluid, and multifocal areas of unexplained intracerebral hemorrhage on computed tomographic scans, anthrax should be considered within the differential diagnosis. A low cerebrospinal fluid glucose level has been reported, with gram-positive rods often noted on the gram stain of the cerebrospinal fluid in severely affected patients. Reports indicate that death usually occurs within a week.

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Given the recent public health concerns for the 11 confirmed cases of inhalational anthrax and 12 other cases of confirmed or suspected cutaneous anthrax, physicians need to be aware of the potential neurologic symptoms and complications associated with this rare disease. The few recent reports on sporadic cases that exist in the literature, including experimental studies in animals as well as a large exposure study in Russia, confirm that anthrax can manifest as an acute, rapidly progressive hemorrhagic meningoencephalitis. Neurologists must therefore be prepared to be on the front lines for potential confrontations with acute illness from this organism as well as other infectious diseases resulting from possible bioterrorism. The clinical features and treatment approaches for the few anthrax meningitis cases found in the modern medical literature are summarized in this article, along with the molecular and laboratory features of the disease.

GENERAL FEATURES AND EPIDEMIOLOGICAL CHARACTERISTICS

Bacillus anthracis is a large endospore-forming, aerobic, gram-positive nonmotile bacteria that produces a black, eschar-like cutaneous lesion after cutaneous inoculation, giving rising to the name anthrax, which in Greek means “coal.” According to an excellent review by Shafazand et al., anthrax may have caused 2 Egyptian plagues in 1491 BC. Inhalational anthrax occurred in England in the 19th century as woolsorter’s disease, and in Germany it became known as ragpicker’s disease as a result of the infection of mill workers with anthrax spores from contaminated fibers from goats. Prior to the 2001 bioterrorism-related outbreak of 11 inhalational cases and 12 suspected or confirmed cases of cutaneous anthrax, there had been only 18 sporadic cases total in the United States during the 20th century, with the last case in 1976.

The anthrax bacterium measures about 1 to 1.5 µm × 4 to 10 µm with a centrally located spore. It grows well on blood agar for 18 to 24 hours, but when grown at a temperature higher than 45ºC, it becomes avirulent and loses its capsule. As an aerosolized spore, the lethal inhaled dose for 50% of human subjects has been estimated at only 8000 to 10000 spores vs 40000 to 65000 for chimpanzees; the World Health Organization estimates that 50 kg of spores dispersed in ideal conditions above the earth could travel upwind for more than 20 km and kill up to 95000
Fortunately, the organism is highly sensitive to penicillin, amoxicillin, erythromycin, and streptomycin sulfate and is also susceptible to doxycycline, ciprofloxacin, and chloramphenicol. Current treatment recommendations include either ciprofloxacin or doxycycline plus 1 or 2 other agents that work in vitro against the cultured organism. Spore size can affect the likelihood of disease; aerosolized spores greater than 5 µm are trapped within the upper airways, but smaller spores between 2 and 5 µm can reach the alveoli within the lungs.

**MOLECULAR FEATURES**

Once the spores have reached the lung, they can germinate and release edema factor and lethal factor, which induce severe hemorrhagic mediastinitis with similar systemic complications of edema and hemorrhage as the toxins enter into the systemic circulation. These toxins are encoded by 2 plasmid genes: pX01 and pX02. As shown in Figure 1, edema factor acts by converting adenosine triphosphate into cyclic adenosine monophosphate and then into an infected cell, which induces edema and inhibits oxidative bursts within leukocytes that are normally needed to fight infection. Low levels of lethal factor cause the expression of tumor necrosis factor and interleukin 1, which may accumulate within infected cells and cause sudden death when massive amounts of these inflammatory mediators are released along with cell lysis; antibodies against tumor necrosis factor and interleukin 1 protect mice against a lethal dose of anthrax toxin. Higher accumulated levels of lethal factor seem to directly cause macrophages to lyse. A third factor, named for its ability to render protective immunity, is called protective antigen. It binds to target cell surface receptors, allowing lethal factor and edema factor to bind and then enter the cell to cause their deleterious effects.

**CLINICAL FEATURES**

Infection via the cutaneous route is believed to comprise about 90% of cases; of these, 80% are thought to be self-limiting. Only 5% are thought to be from the pulmonary route, and the other 5% arise from gastrointestinal tract infection. Prior to the 1979 Russian outbreak of inhalational anthrax with the subsequent development of fatal meningitis, it was believed that cutaneous skin infection was the most common mode of organism entry when meningitis ensued.
Although few cases are found in the current post–computed tomography (CT) era medical literature, postmortem analysis of anthrax meningitis cases from the 19th century and early 20th century have confirmed hemorrhagic changes within the brain. One of the earliest cases of hemorrhagic meningitis from anthrax in the United States was described in 1920 by House and is shown in Figure 2. Postmortem analysis of the brain from a 15-year-old boy who died in a coma 65 hours after the onset of a febrile illness unexpectedly revealed the growth of anthrax from cultured cerebrospinal fluid (CSF); free blood was found beneath the dura mater, and “numerous red pinpoint spots” were found on the surface of the convolutions. Axial sectioning, as shown in Figure 2, revealed widespread cortical and subcortical hemorrhages of “rather uniform size... [with] very few hemorrhages of the white matter.” Although no clear risk factors were identified for this 15-year-old boy, House reported other autopsy-proven cases of anthrax-related hemorrhagic meningitis; namely, in 2 adults who both worked in a factory in Chicago, Ill, handling “curled hair” from South America.

The recent report of a heroin-injecting drug user developing fatal anthrax meningoencephalitis with hemorrhagic qualities on autopsy raised new questions about the mode of entry for the organism. The authors postulated that this patient in Oslo, Norway, was infected from contaminated heroin that may have come from either Afghanistan, Pakistan, or Iran, where anthrax is common and Europe’s heroin supply originates, but stated that other intentional or unintentional sources could not be ruled out. Polymerase chain reaction testing was positive for all 3 markers: the protective antigen precursor, lethal factor, and the encapsulation protein. Despite high-dose penicillin, chloramphenicol, and dexamethasone, this particular patient died within 3 days after coming to the hospital in a coma and cardiovascular shock, 8 days after the onset of a soft tissue infection of the right buttock. As shown in the Table, CSF examination on the day of admission revealed a low glucose level and a high white blood cell count; many large gram-positive rods without endospores were visible on the gram stain of the CSF.

Other recent reports from Korea documented 2 cases with presumed entry via the skin after the patients ingested contaminated beef; another 3 patients, from a group of 30 or more potentially exposed farmers, had limited cutaneous infections that were cured. One patient developed forearms lesions within 4 days of exposure and became febrile with evidence of hemorrhagic meningoencephalitis 6 days after the skin eruption. Subarachnoid, intracerebral, and intraventricular hemorrhage as well as leptomeningeal enhancement were seen on CT and magnetic resonance imaging scans. Despite penicillin therapy, he died within 6 days of hospital admission. The second case developed more rapidly, with dark vesicles on the hand occurring within 3 days of exposure followed by hospital admission 5 days later and death 2 days afterward; CT revealed the same findings of hemorrhagic meningoencephalitis.

A similar case from Spain was recently reported in which a 49-year-old sheep farmer was admitted to the hospital with a necrotic chin lesion and a 3-day history of obtundation. A CSF examination revealed chains of gram-positive bacilli, and cultures revealed B. anthracis. Despite 24 million units of penicillin G daily, he died a week later with the autopsy confirming hemorrhagic meningoencephalitis. The blood vessel walls were thickened with areas of necrosis.

Two other similar cases from Mexico that displayed autopsy-confirmed, anthrax-related hemorrhagic meningoencephalitis both developed through a presumed cutaneous route. One case involved a 14-year-old boy who worked in a slaughterhouse for 2 months; he had a 4-day course of fever and headache and died within 12 hours of hospital admission despite the intravenous infusion of 20 million units of aqueous penicillin. Initially, the CSF was cloudy yellow with no red blood cells; it turned bloody 5 hours later, with high white blood cell counts and low glucose levels when examined at both time points (Table). Numerous gram-positive rods were found on the gram stains of both CSF samples. Autopsy revealed leptomeningeal edema with hemorrhagic and inflammatory infiltration of the subarachnoid space. A second patient who had a 2.5-cm round purple lesion with a depressed necrotic center on his forearm died 18 hours after admission for a 2-day history of fever and confusion preceded by 6 days of fatigue and generalized weakness with loss of appetite. The autopsy also revealed leptomeningeal congestion and subarachnoid hemorrhage. Microscopic examination of the brain revealed recent thrombosis of blood vessels that contained numerous gram-positive bacilli.

Figure 2. One of the earliest cases of hemorrhagic meningoencephalitis from anthrax, herein reprinted with permission from a 1920 article by House, who noted numerous focal bleeds in the gray matter but “very few hemorrhages of the white matter.”
et al. report the case of a 63-year-old man who developed a fever, emesis, disorientation, and confusion within 3 days. Autopsy confirmed the common features of hemorrhagic changes in acute meningitis. As noted in the Table, the most consistent feature of anthrax meningitis is a low CSF glucose level with marked infiltration of leukocytes into the CSF, which may stain for gram-positive rods in chains. The additional presence of grossly visible blood or elevated red blood cell counts with hemorrhagic changes on a CT scan may lead to a diagnosis of hemorrhagic anthrax meningitis. Because hemorrhagic changes in acute meningitis are relatively unusual, these laboratory findings should alert the physician to the presence of anthrax. A recent major advance in molecular diagnosis involves the use of rapid polymerase chain reaction techniques such as the LightCycler (Roche Applied Science, Indianapolis, Ind), which can combine amplification and probing of DNA into a half-hour analysis through the use of rapid heating and cooling elements; a final molecular confirmation for the presence of anthrax DNA can be reached within 1 hour. The assay is specific for 144 different anthrax strains from different geographic areas and did not crossreact with other related bacilli, with the exception of 1 related type among 175 tested.

Without the aid of molecular diagnostic abilities, caution is advised; meningitis caused by B. anthracis may be confused with the related bacteria Bacillus cereus, which is commonly found in soil. A case of this type of mistaken identity for the pathogen was reported in Hong Kong in a 13-year-old boy who had a fever. Within 5 hours he became confused, and a CT scan revealed mild cerebral edema. As indicated in the Table, the CSF was bloody with many white blood cells; like other cases, this patient had a low CSF glucose level. The gram stain and culture led to the initial incorrect impression that B. cereus had contaminated the sample. The automated microbial identification system (VITEK Bacillus Card; bioMérieux, Durham, NC) misclassified the bacteria as B. cereus because testing for susceptibility to bacteriophage was not available, and the final diagnosis was delayed until immunofluorescent stains at the local Department of Public Health laboratory confirmed the organism as anthrax. Despite ampicillin and cefotaxime sodium, the patient became comatose and died within 3 days. Autopsy confirmed the common features found in other cases of subarachnoid hemorrhage: a grossly swollen brain with multiple necrotic areas, vasculature distortion, and meningeal infiltration by macrophages and polymorphs.

Meningitis caused by the related bacteria B. cereus has been reported in patients with shunts and lumbar spi-
nal fluid drainage and has also recently been linked to a rash of 30 deaths, during a 6-week period in Scotland and Ireland in the spring of 2001, among heroin users. Although anthrax was suspected, *B cereus* cellulitis was finally diagnosed in those cases studied in detail. At approximately the same time, a 49-year-old Norwegian heroin-injecting drug user died from contaminated heroin, as discussed previously; polymerase chain reaction confirmed the presence of anthrax-associated protective antigen precursor, lethal factor, and encapsulation protein. The authors noted Afghanistan, Pakistan, and Iran as potential sources for both anthrax spores and heroin in addition to the possibility of intentional contamination. The simultaneous occurrence of the *B cereus* outbreak in the United Kingdom raises new questions about possible bioterrorism and intentional contamination of heroin destined for Europe during the spring of 2001.

**THERAPY**

Various strategies are being considered to help reduce the inflammatory response and attenuate the infection. Studies in mice using a recombinant carboxy-terminal domain of the protective antigen found that domain 4 of the antigen molecule was the predominant epitope that could prevent infection. Mutations in the gene controlling the expression of a kinesin-like motor protein called Kif1C have recently been found to govern differences in susceptibility that mouse macrophages have to anthrax lethal toxin. This study by Watters et al indicated that intact function of the Kif1C protein is needed to resist the late effects of lethal toxin within the macrophage. A study by Shin et al found that the combined use of dehydroepiandrosterone and melatonin significantly inhibited tumor necrosis factor α release by macrophages after lethal toxin exposure. It remains unknown whether rheumatologic medications such as etanercept and infliximab (Figure 1), which are known to interfere with tumor necrosis factor, have a potential role in helping fight anthrax infection.

Although anthrax vaccines have been given to large numbers of military personnel without causing the commonly encountered major adverse effects, case reports are now emerging that describe occasional adverse effects. Optic neuritis was reported in a 39-year-old patient 1 month after booster vaccination, with good recovery after steroid treatment; a 23-year-old man had similar signs and symptoms within 2 weeks of the booster as well as retinal and nerve autoantibodies. A delayed hypersensitivity reaction was found in a 26-year-old man following 2 doses of anthrax vaccine.

The Centers for Disease Control and Prevention (CDC) has issued a review on antibiotics of choice for anthrax, noting that ciprofloxacin is recommended on the basis of animal studies but that doxycycline should not be used for meningitis because of its poor central nervous system penetration. Further arguments against doxycycline for meningitis include in vitro resistance by *B anthracis* Sterne; resistance to macrolides and quinolones has also been noted. The CDC stated that the bioterrorism-related strain of anthrax was sensitive to quinolones, rifampin, tetracycline, vancomycin, imipenem, meropenem, chloramphenicol, clindamycin, and aminoglycosides; resistant to third-generation cephalosporins, such as ceftriaxone sodium; and resistant to trimethoprim-sulfamethoxazole. The organization raised concerns for the induction of a penicillinase from the anthrax genome; they also cited the presence of a potential cephalosporinase and acknowledged that the issue is complicated. However, for inhalational anthrax, a multidrug regimen was advised to include either ciprofloxacin or doxycycline plus 1 or more traditional agents to which the organism is typically sensitive. They advocate that cutaneous anthrax could also be treated by ciprofloxacin or doxycycline.

**CONCLUSIONS**

In summary, the major neurologic symptom of infection with *B anthracis* is a fulminant and rapidly fatal hemorrhagic meningoencephalitis. For febrile patients who have acute neurologic deterioration with associated findings of dark necrotic pustules on the extremities, gram-positive rods in the CSF, and multifocal areas of unexplained intracerebral hemorrhage on a CT scan, anthrax should be considered within the differential diagnosis. The inhalational form of anthrax may be particularly potent in causing neurologic complications; it was associated with hemorrhagic meningoencephalitis in half the cases autopsied in the Russian 1979 outbreak. Cutaneous forms of the disease may result in a much lower incidence of meningitis; these may not be reported in the literature because the disease process can be halted if recognized early enough and treated with appropriate antibiotics. Reports indicate that death usually occurs within a week for those with neurologic involvement. Although rare cases exist in the literature (for example, 2 patients with anthrax meningitis survived, with the use of antiserum in 1 patient and antiserum and the combined use of parenteral and intrathecal penicillin in the other), further analysis in an excellent recent article by Lanska cast some doubt on these reports. Neurologists clearly need to be aware of the disease and its complications; a recent review of the first 10 cases of bioterrorism anthrax noted only 1 firmly diagnosed case of meningitis even though 5 of the 10 patients initially experienced headache and 4 of the 10 had confusion as a symptom. Considering the long delay in testing samples from a 1993 release of anthrax spores by the Aum Shinrikyo cult over Kameido, Japan, further research is needed to develop more rapid polymerase chain reaction methods to quickly test for the disease. Physicians must become more aware of the manifestations of the illness, and antibiotic treatment must be started immediately in patients suspected of having central nervous system involvement.

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