Active systemic anthrax infection or lingering anthrax infection of cerebrospinal compartment?

To the Editor:

The case report by Tyler C. Cymet, DO, et al, "Symptoms associated with anthrax exposure: Suspected 'aborted' anthrax" (*J Am Osteopath Assoc* 2002;102:41-43) suggests "aborted" anthrax as the source of their patient's affliction.

While 1-week durations of active systemic anthrax infection (eg, demonstrated by successful culturing of bacteria from the peripheral blood over the reporting interval) in humans have been reported, one persisting for more than 1 month apparently is unknown in the literature.[1,2] From a mechanistic point of view, it is unclear how a pathogen with a doubling-time of one half hour under favorable circumstances—50 doublings per day—could be maintained in marginal arrest so precisely as to sustain degrees of morbidity over an interval of several weeks without mortality supervening. In the present case report, the inability to demonstrate *Bacillus anthracis* in the patient's serum at any time during the extended course of treatment undeniably militates against any interpretation of anthrax infection, aborted or otherwise. Doubt is heightened further by a normal leukocyte profile during the first acute phase of the disease and by no report of elevated titers of antibodies to any anthrax antigen during the entire clinical course. If this be anthrax, even if somehow "aborted," how can it be that all of the microbiologic markers are entirely missing?

An interpretation seemingly more consistent with the reported case history is lingering anthrax infection of the cerebrospinal compartment (CSC), one apparently cleared—perhaps narrowly so—by the second course of multiantibiotic treatment. The several-day interval between initial exposure and clinical presentation was certainly of sufficient duration for the patient with inhalatory anthrax exposure to have clinical symptoms, development of which may have been critically enabled by the intermittency of ciprofloxacin dosing before hospitalization. Hemorrhagic meningitis is a well-known feature of anthrax bacteremia, so much so that the "cardinal's cap" is a classic indicator of anthrax at autopsy. It is therefore plausible that early penetration of the infection into the CSC may have occurred in the patient. In the CSC, the infecting bacteria would find relatively low concentrations of both the macrophages and regional lymph nodes which they preferentially parasitize. The bacteria would, however, enjoy blood-brain barrier shielding against high serum concentrations of administered antibiotics—shielding crucial to the infection's potential ability to persist (albeit perhaps under rather inhibited conditions) in the cerebrospinal "sanctuary." Concurrently, even a brief interval of bactericidal levels of ciprofloxacin may have cleared the infection from the peripheral circulation by initial clinical presentation.

It is especially notable that none of the antibiotics given to the patient exhibits good diffusive penetration into the CSC, with typical concentrations of less than 10% of those in the peripheral blood seen in the cerebrospinal fluid (CSF). These greatly-reduced levels are comparable to the corresponding minimum inhibitory concentrations (MIC) for *B anthracis* in vitro, and are well below the bactericidal ones. Ciprofloxacin, for instance, has a reported MIC of 0.08 μg/mL and a bactericidal MIC of approximately 0.2 μg/mL for *B anthracis*, but the time-averaged serum concentration of approximately 1.0 μg/mL (ie, an area under the curve of 11.6 μg/mL, for the typical 500 mg twice-daily dosing) combined with the observation that CSF levels are less than 10% of serum levels[3] suggest that robustly bactericidal levels of ciprofloxacin are seldom if ever attained in the CSF and that even bacterial inhibition by this antibiotic may be marginal in the CSF in the time-average, with typical 500 mg twice-daily dosing.

Persistent leakage of anthrax proteins back through a focally-compromised, blood-brain barrier could account for the systemic clinical symptoms, while the relative paucity of target cells and tissues in the CSC and antibiotic levels in the vicinity of the MIC ones in the CSF could result in lingering morbidity without acute threat of mortality and—critically—would explain why little if any humoral immune response and no circulating bacteria were seen, as the CSC is immunologically privileged and the blood-brain barrier is normally impervious to bacteria. In this interpretation, only synergic effects of triple antibiotic therapy prevailed during the second hospitalization, perhaps involving CSF antibiotic levels augmented by a compromised blood-brain barrier. Interestingly, one anecdotally-reported case of inhalation-originated anthrax with basic features similar to those of the present case—that of a US government microbiologist who died in 1952 with no discernible bacteremia—is said to have had clinically-occult CSC involvement seen at autopsy.

Apt treatment in such cases thus would include exceptionally aggressive administration of pertinent antibiotics so as to attain and then sustain robustly bactericidal concentrations in the CSF for a 2- to 3-day interval (eg, ciprofloxacin 750-mg tablets given every 6 hours, preferably supplemented with augmentin 875-mg tablets also given every 6 hours, or the IV equivalents). Antibiotic prophylaxis at normal dosing levels would thereafter protect against late-germinating endospores outside of the CSC.

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2. Dixon TC, Meselson M, Guillemin J, Hanna PC. Anthrax. *N Engl J Med.* 1999;341:815-826.

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Can we afford to lose another osteopathic teaching facility?

To the Editor:

We at Riverside Osteopathic Hospital (ROH) are in desperate need of help in saving our osteopathic teaching facility. Riverside Osteopathic Hospital has been successfully operating in Trenton, Michigan, since 1944. In 1995, ROH affiliated with Henry Ford Health System (HFHS) for the betterment of our teaching program and institute.

Recently, HFHS has struggled financially, as has ROH and most hospitals in the United States. As part of a desperate plan to save HFHS, ROH is to be downgraded to an outpatient facility, and our osteopathic teaching program is to be moved to a community hospital that is neither a teaching facility nor one that has an osteopathic teaching department. Most osteopathic physicians at ROH believe this will severely damage the hospital's teaching programs as well as the osteopathic profession and the future healthcare of our community.

Does anyone out there care? Can anyone help us save Riverside Osteopathic Hospital? Is there hope for the future of our profession?

Please feel free to contact me at my office at 734-676-5353, or 676-5354, or by fax at 734-676-5524. ◆

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