REVIEW ARTICLE

CURRENT CONCEPTS

Fungal Infections Associated with Contaminated Methylprednisolone Injections

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AN UNPRECEDENTED OUTBREAK OF FUNGAL INFECTIONS HAS BEEN ASSOCIated with injection of methylprednisolone that was contaminated with environmental molds. The index case, which prompted clinicians at Vanderbilt University to call the Tennessee Department of Health and which brought this event to national attention, was reported by Pettit et al. on October 19, 2012, at NEJM.org and in the November 29, 2012, issue of the *Journal*.[1] We now summarize our understanding of this outbreak as of June 7, 2013.

At the outset of the outbreak, the persistence and progression of neutrophilic meningitis of unknown cause was the trigger for obtaining the history of a recent epidural injection of methylprednisolone. Then events fell into place. After the alarm was sounded about this association, other physicians throughout the country realized that they too had struggled to find a cause for similar cases in recent weeks. What was intriguing about this case report was that the mold causing meningitis was reported to be *Aspergillus fumigatus*, an organism that has not been detected in any of the subsequent 700-plus cases. It has since been determined that the major culprit is *Exserohilum rostratum*, a plant pathogen that rarely causes human disease. This mold has been cultured or identified by means of a polymerase-chain-reaction (PCR) assay from cerebrospinal fluid or tissues in 152 patients and has been detected in unopened vials from two of the three implicated lots of methylprednisolone.

Shortly after the Tennessee Department of Health was notified on September 18, 2012, the implicated lots were quickly identified, all centers that had received the implicated lots were alerted, and patients who had received injections from these lots were notified of the potential for fungal infection. More than 13,400 patients could have been exposed to contaminated methylprednisolone from one of the three implicated lots. The compounding pharmacy producing the drug, New England Compounding Center (NECC), was closed, and all products (not just the implicated lots) were recalled. The Centers for Disease Control and Prevention (CDC) provided timely information regarding appropriate diagnostic testing and treatment on its website (www.cdc.gov). Further epidemiologic studies by the Tennessee Department of Health and the CDC showed that one lot (number 06292012@26) was associated with an increased number of cases, especially when the vials that were used had been manufactured more than 50 days earlier.[2,3]

IDENTIFICATION OF THE MOLD

E. rostratum is a dematiaceous, or black, mold containing melanin in its cell wall. It is widely found in the environment, on plant debris, in soil, and in water.[4,5] Human infection is uncommon and is usually restricted to allergic sinusitis, keratitis, and

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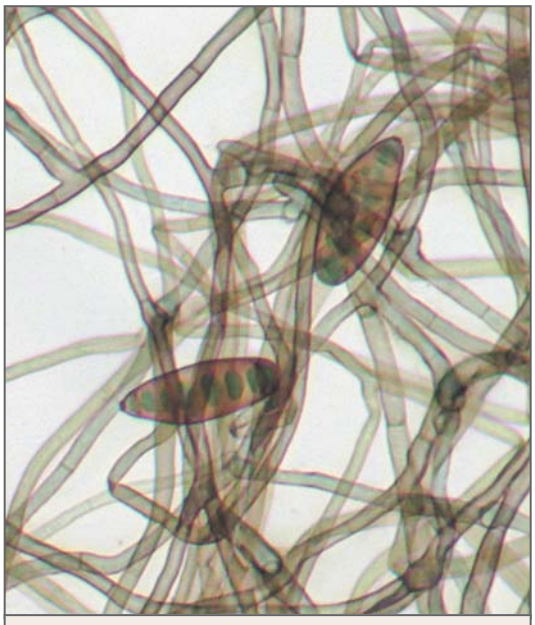

Figure 1. Photomicrograph of *Exserohilum rostratum* Isolate from Cerebrospinal Fluid Grown for 48 Hours on Potato Flakes Agar.

Courtesy of Annette W. Fothergill, Fungus Testing Laboratory, University of Texas Health Science Center at San Antonio.

localized soft-tissue infection. In rare cases, invasive infection occurs in immunocompromised patients.

The conidia of this organism have distinctive morphologic features (Fig. 1) that allow its identification. The organism grows readily on usual fungal culture medium, but sporulation to identify the conidia typically requires the use of a plant-based medium, such as potato dextrose agar. Even though the mold grows readily in the laboratory, cultures from cerebrospinal fluid and tissues may be negative, as has been true for other mold infections of the central nervous system (CNS). Molecular identification was used to establish a diagnosis, and PCR assays on cerebrospinal fluid were useful in the outbreak. It is important to note that the performance characteristics of this specific PCR assay had not been characterized previously because this organism had rarely caused disease.

In tissues, *E. rostratum*, like many other dematiaceous fungi, appears as irregular, beaded hyphae, as compared with the broad, rarely septate, ribbonlike hyphae seen in the order Mucorales and with the narrow, septate, acutely branching hyaline hyphae of aspergillus species. Special stains for cell-wall melanin (e.g., Masson–Fontana stain) are useful to confirm the presence of a dark-walled mold.

Several outbreaks in the past decade have been associated with contamination with black molds. *Exophiala dermatitidis* was associated with a disturbingly similar outbreak of infections including meningitis that was traced back to a contaminated lot of glucocorticoid injections from a U.S. compounding pharmacy,[6,7] and *Exophiala jeanselmei* was identified in an outbreak associated with contaminated water.[8]

SUSCEPTIBILITY TO ANTIFUNGAL AGENTS

Generally, exserohilum species are susceptible to available antifungal agents, but for some strains, the minimal inhibitory concentration (MIC) for the usually recommended agents, including voriconazole, is increased. Thus, susceptibility testing is advised. Analyses have shown that most isolates from this outbreak are susceptible to voriconazole (MIC, 1 to 4 μg per milliliter; mode, 1 to 2 μg per milliliter), amphotericin B (MIC, 0.03 to 2 μg per milliliter; mode, 0.4 μg per milliliter), itraconazole (MIC, 0.25 to 4 μg per milliliter; mode, 0.5 μg per milliliter), and posaconazole (MIC, 0.25 to 1 μg per milliliter; mode, 0.5 μg per milliliter).[9] This organism is resistant to fluconazole.

CLINICAL DIAGNOSTIC ISSUES

HOW THE OUTBREAK EVOLVED

Early in the outbreak, patients had symptoms of meningitis for weeks before the diagnosis was made. Neutrophilia in cerebrospinal fluid was extreme in many cases, and complications, including basilar-artery stroke, were common.[1-3,10,11] The incubation period for patients who presented with meningitis was 1 to 4 weeks after injection. After notifying patients at risk and performing lumbar punctures as soon as even mild headache occurred, clinicians began to see patients who had milder clinical disease.

As the outbreak evolved, it became increasingly rare for a patient to present with meningitis. The manifestations of infection changed to those related to localized infection at the injection site. Early in the outbreak, a few patients

had increasing back pain as the prominent symptom and were found to have an epidural abscess or diskitis or vertebral osteomyelitis at the site of injection. It is now clear that in some centers, epidural abscess or phlegmon, arachnoiditis, and diskitis or vertebral osteomyelitis became the major disease manifestations. Michigan had a disproportionate number of these cases, and the pain clinic in which most of these injections were administered had received lot number 06292012@26 from the NECC. Fewer patients had infection of peripheral joints or bursae from the implicated lots, but 33 infections in these sites have been documented to date, with most of the patients presenting with increasing pain several months after injection.

SPINAL TAP, JOINT ASPIRATION, OR IMAGING STUDIES

Exposed patients were alerted to tell their physician about any new-onset headache, neck stiffness, photophobia, fever, or strokelike symptoms. Because the symptoms of CNS fungal infection are often more subtle than those usually seen with bacterial meningitis, there was a very low threshold for performing lumbar puncture if any symptom suggesting possible CNS infection occurred. Even with headache as the only symptom, values for cerebrospinal fluid have been abnormal in some patients. The criterion for initiating therapy was suggested to be a white-cell count above that which is considered normal (i.e., >5 cells per cubic millimeter). White-cell counts in patients in this outbreak of fungal meningitis have ranged from 13 cells to 15,000 cells per cubic millimeter, almost always with a neutrophil predominance. Glucose and protein levels were not suggested as criteria for initiating therapy. Most important, it was suggested that empirical antifungal treatment be given as soon as pleocytosis is detected in the cerebrospinal fluid, without waiting for results of diagnostic studies.

Increasing back pain, pain that differed in quality from the chronic back pain for which a patient received an epidural injection, or development of the cauda equina syndrome alerted physicians to the possibility of an epidural abscess or phlegmon, arachnoiditis, or diskitis or vertebral osteomyelitis at the site of injection. Magnetic resonance imaging (MRI) of the spine was suggested in such patients. Early symptoms of these complications were often subtle, and localized infection occurred most often without meningitis. It was suggested that any fluid or tissue obtained by means of aspiration or at the time of surgery should be sent for culture and PCR studies for exserohilum. Some centers embarked on a program to perform MRI in all patients who received an injection from the highly contaminated lot. Reports followed that some of these patients who had only subtle symptoms of back pain were found to have an epidural abscess or phlegmon requiring surgical intervention.

It was suggested that patients who received an intraarticular injection should be alert for new pain, especially if it differed in quality from their original pain, or if they had erythema or swelling of a joint. In such cases, it was suggested that aspiration of synovial fluid should be performed immediately for diagnostic studies. Given the variability in what is considered to be a normal number of white cells in synovial fluid, no firm guidance has been given for the number of cells required to initiate therapy. It was suggested that clinical judgment, along with the symptoms and signs of joint disease before the injection, should be used to make therapeutic decisions. If there was any question of whether infection was present, arthroscopy to obtain synovial fluid and possibly synovial biopsy for culture and PCR studies should be performed as soon as possible.

TREATMENT AS THE EPIDEMIC EVOLVED

Recommendations for the treatment of this rare infection were based on small case series, individual case reports, and personal experience. A large number of patients in this outbreak were older adults, many of whom had substantial coexisting illnesses that made therapeutic decisions challenging. Treatment recommendations evolved during the outbreak as clinicians gained more experience with managing these infections. It was suggested that given the paucity of data pertaining to treatment and the complexity of management, decisions about the treatment of patients with proven or suspected infection should be made with the input of an infectious diseases specialist.

Initial recommendations for therapy were to use high doses of both liposomal amphotericin B and voriconazole because the causative organism was not known and the index patient had been shown to have infection with *A. fumigatus*. As

events moved forward, it quickly became evident that the primary pathogen was a black mold, and clinical experience had shown that an azole was the usual drug of choice for infection with such organisms. In addition, a large number of patients had serious toxic effects from the high doses of amphotericin B that were recommended. Thus, the therapeutic regimen was modified in favor of monotherapy with voriconazole, except for the sickest patients or those who had substantial side effects while receiving this agent, for whom amphotericin B could play a role.

Voriconazole was selected over posaconazole and itraconazole for several reasons. First and foremost, there was experience in the use of voriconazole for various mold infections. Both intravenous and oral formulations were available, and oral administration produced serum levels equivalent to those achieved by intravenous administration. Levels of the drug in cerebrospinal fluid are approximately 50% of serum levels,[12] and levels both in cerebrospinal fluid and in serum are above the MIC for many dematiaceous molds. By comparison, neither posaconazole nor itraconazole achieves substantial levels in cerebrospinal fluid, and their oral absorption can be erratic.

CURRENT RECOMMENDATIONS

DRUGS AND DOSES

For patients with mild or moderate CNS disease, including meningitis and localized infections involving the spine, the current recommendation is to administer voriconazole at a dose of 6 mg per kilogram of body weight twice daily. For patients with severe or refractory CNS disease, therapy with a combination of voriconazole (6 mg per kilogram twice daily) and intravenous liposomal amphotericin B (at a dose of 5 to 6 mg per kilogram daily) is recommended. The dose of voriconazole should be modified to achieve serum levels of 2 to 5 μg per milliliter. In many patients, this will lead to a dose reduction from that given initially, but some patients will require even higher doses to achieve those concentrations, which suggests that some patients have more rapid metabolism.[13] Surgery plays an important role in patients who have epidural abscess or phlegmon.

For patients with osteoarticular infection, a loading dose of voriconazole at 6 mg per kilogram for two doses, followed by 4 mg per kilogram twice daily, is recommended. The penetration of voriconazole into the joint space is excellent. The combination of voriconazole and liposomal amphotericin B (at a dose of 5 mg per kilogram daily) should be offered to patients with severe disease. Surgery plays an important role in patients who have osteoarticular infection.

ADVERSE EFFECTS

Voriconazole is associated with a host of drug–drug interactions. As an example, drugs that induce cytochrome P-450 (e.g., rifampin, long-acting barbiturates, and carbamazepine) substantially decrease voriconazole levels. The coadministration of voriconazole with rifabutin or phenytoin not only leads to lower voriconazole levels but also may cause toxic serum levels of rifabutin and phenytoin. Voriconazole interferes with the metabolism of several other drugs, including cyclosporine, tacrolimus, sirolimus, and warfarin, potentially leading to toxic levels of these drugs. The coadministration of voriconazole and other agents, such as statins, benzodiazepines, calcium-channel blockers, sulfa drugs, and proton-pump inhibitors, should be done with care, with attention paid to decreasing the doses of these agents.

There is appropriate concern about the toxicity of voriconazole, particularly at the doses recommended to treat CNS infection, which often leads to serum levels of more than 5 μg per milliliter. Visual hallucinations have been especially problematic in patients treated in this outbreak and appear to be related to high serum levels. Decreasing the dose of the drug will obviate this effect. Other adverse effects include visual disturbances (e.g., photopsia), confusion, nausea, hepatic-enzyme elevation, rash, and photosensitivity. Long-term tolerance of the high doses required to achieve the recommended drug levels has been poor in many patients who have persistent reports of fatigue, difficulty with concentration, and hair loss. These adverse effects have resolved with the discontinuation of the drug, but the frequency of their occurrence and long-term effect is unknown. The administration of parenteral voriconazole in patients with impaired renal function may lead to the accumulation of the cyclodextrin component of the intravenous solution. There is growing evidence to suggest that if needed, voriconazole can be given intravenously in such patients.[14]

OTHER ISSUES RELATED TO TREATMENT

DURATION OF THERAPY

The duration of therapy is not known. Initially, it was thought that at least 3 months of treatment would be necessary. As the outbreak has evolved, it appears that this duration may be appropriate for some patients who primarily had meningitis and at 3 months have no symptoms and normal results on lumbar puncture. However, for patients who have localized spinal abscess or phlegmon, arachnoiditis, or vertebral diskitis or osteomyelitis, therapy should be continued for 6 months or longer until all clinical signs and symptoms have resolved.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring is especially important in this outbreak.[15] The severity of the infection, the possibility of relatively decreased antifungal susceptibility, and the concentration-dependent toxicity of voriconazole make the measurement of serum antifungal drug levels important. A voriconazole serum trough level of 2 to 5 μg per milliliter is recommended. Unpublished data from the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio show that in 47% of more than 15,000 samples, voriconazole serum levels were 1 to 5 μg per milliliter, but 14% of samples had undetectable levels, and 15% had levels of more than 5 μg per milliliter. Of 167 measurements of cerebrospinal fluid, the median voriconazole level was 2.77 μg per milliliter, but there was substantial variability.

TREATMENT OF PATIENTS WITH NORMAL CEREBROSPINAL FLUID AND SPINE MRI

Without objective evidence of infection in the cerebrospinal fluid (i.e., <5 white cells per cubic millimeter), treatment was not recommended. However, it was suggested that patients who had symptoms should be monitored closely, and that if there was even subtle progression of symptoms, a repeat lumbar puncture be performed immediately. If the number of white cells had increased, then it was suggested that antifungal treatment be initiated immediately.

Similarly, it was suggested that patients who had persistent back pain or peripheral-joint pain but who had a normal MRI study should not be treated. Instead, it was proposed that they should be watched carefully and undergo repeated imaging if there was persistence or any increase in symptoms. Some patients had initially had normal imaging but subsequently were shown to have development of epidural abscess or phlegmon on follow-up MRI that was performed because of persistent symptoms.

PROPHYLAXIS

The agents used for treatment are amphotericin B and voriconazole. During the outbreak it was unlikely that anyone would consider using amphotericin B for prophylaxis. Voriconazole was known to be less toxic but has numerous adverse effects in patients who have serum levels within the recommended range for treatment in this outbreak. Drug–drug interactions with this agent are numerous. Another concern was that the prophylactic use of antifungal agents could delay the onset or change the course of the disease so that it would appear months later or, probably less likely, that the organism may have become resistant to the agent used.

SUMMARY

This outbreak of fungal meningitis caused by injection of contaminated methylprednisolone is in late evolution; there are now known to be more than 700 patients who have been affected. The primary pathogen is *E. rostratum*. It is encouraging to note that clinically apparent disease has developed in only a small percentage of exposed patients. However, among patients who have been infected, some have died, others have major complications, and some remain in chronic care or rehabilitation centers. Even some patients who are doing well in respect to symptoms caused by the infection continue to have major issues with side effects from the antifungal agents. Management recommendations will probably continue to change as more information becomes available regarding the natural history and pathogenesis of these infections.

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