REVIEW ARTICLE

CURRENT CONCEPTS

Fungal Infections Associated with Contaminated Methylprednisolone Injections — Preliminary Report

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We are in the midst of an unprecedented outbreak of fungal infections associated with epidural injection of methylprednisolone that was contaminated with environmental molds. The index case, which prompted clinicians at Vanderbilt to call the Tennessee Department of Health and which brought this event to national attention, is now reported by Pettit et al. in the *Journal*.[1]

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 is intriguing about this case report is that the mold causing meningitis was reported to be *Aspergillus fumigatus*, an organism that has not been detected in any of the subsequent 200-plus cases. The major culprit appears to be *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 in at least 25 patients and has been detected in at least one unopened vial from the implicated lot of methylprednisolone.

Shortly after the Tennessee Department of Health was notified on September 18, the implicated lots were quickly identified, all centers that had received the implicated lots were alerted, and patients who had received injections (either epidural or intraarticular) from these lots were notified of the potential for fungal infection. It is estimated that over 14,000 patients received injections from these implicated lots. The compounding pharmacy producing the drug was closed, and all products (not just the implicated lots) were recalled. The Centers for Disease Control and Prevention provided timely information regarding appropriate diagnostic testing and treatment, and the agency is providing daily updates on its website (www.cdc.gov). As the outbreak has evolved, numerous questions have been raised by physicians, patients who received injections from the implicated lots, and the public. We attempt to answer some of those questions here.

What Do We Know About the Identified 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.[2,3] Human infection is uncommon and is usually restricted to allergic sinusitis, keratitis, and localized soft-tissue infection. In rare cases, invasive infection occurs in immunocompromised patients.

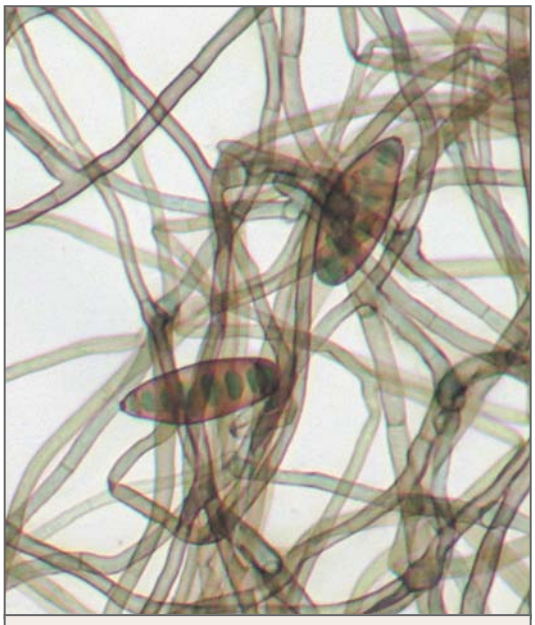

Figure 1. Photomicrograph of *Exserohilum rostratum* Isolate from Cerebrospinal Fluid Grown for 48 Hours on Potato Flakes Agar.

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

The conidia of this organism have distinctive morphologic features (Fig. 1) that allow its identification. The organism grows readily on the usual fungal culture mediums, 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 may be negative, as has been true for other mold infections of the central nervous system (CNS). Molecular identification can be used to establish a diagnosis, and PCR assays on cerebrospinal fluid have been useful in the current outbreak. It is important to note that the performance characteristics of this specific PCR assay have not been well characterized.

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 species were associated with a disturbingly similar outbreak of infections including meningitis that were traced back to a contaminated lot of glucocorticoid injections from a U.S. compounding pharmacy,[4] and *Exophiala jeanselmei* was identified in an outbreak associated with contaminated water.[5,6]

WHAT IS THE 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, although there are no clinical data that strongly support that recommendation. Recent series indicate susceptibility to voriconazole for the majority of isolates, with the MIC ranging from 0.06 to 4 μg per milliliter; the MIC for amphotericin B ranges from 0.03 to 1 μg per milliliter.[2] The MIC is 0.015 to 8 μg per milliliter for posaconazole, 0.015 to 16 μg per milliliter for itraconazole, and 2 to 64 μg per milliliter for fluconazole. Only a limited number of isolates from this outbreak have been tested to date; the MIC for voriconazole has ranged from 0.5 to 2 μg per milliliter.

CLINICAL DIAGNOSTIC ISSUES

HOW HAS THIS 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, as in the case reported in the *Journal*,[1] were common. 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. Headache is a prominent symptom and may be accompanied by neck stiffness, photophobia, and weakness. Whether some patients with mild symptoms may have worsening symptoms and complications in spite of antifungal therapy is unknown, but the hope is that early diagnosis and treatment will avert severe complications, such as strokes.

The incubation period for most patients has been 1 to 4 weeks after injection, but at least one patient presented at 6 weeks. It is not clear

whether some of the less common manifestations, such as epidural abscess and osteoarticular infection, fall within this same time period. There have been reports of a few patients with increasing back pain as the only symptom of an epidural abscess, with or without diskitis or vertebral osteomyelitis. We know little about the progression of osteoarticular infection, since only a few cases of septic arthritis have been reported. Pain and swelling are likely to be the major symptoms. It appears that either the risk of development of infection is less or the symptoms are delayed and more subtle in comparison with a CNS infection. Most important, patients who have received epidural or intraarticular injections and their physicians should remain vigilant for symptoms beyond the typical period that has been reported to date.

WHEN SHOULD SPINAL TAP, JOINT ASPIRATION, OR IMAGING STUDIES BE PERFORMED?

Patients should be 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 should be a very low threshold for performing lumbar puncture if any symptom suggesting possible CNS infection occurs. Even with headache as the only symptom, values for cerebrospinal fluid have been abnormal in some patients. The criterion for initiating therapy should 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. There are not yet clear data correlating the clinical manifestations with the white-cell count in cerebrospinal fluid. Glucose and protein levels are not suggested as criteria for initiating therapy. Most important, empirical antifungal treatment should be given as soon as pleocytosis is detected in the cerebrospinal fluid, without waiting for results of diagnostic studies.

Increasing back pain or pain that differs in quality from the chronic back pain for which a patient received an epidural injection may be the only symptom of an epidural abscess, diskitis, or vertebral osteomyelitis. Magnetic resonance imaging of the spine should be performed in such patients, since early symptoms of these complications can be subtle, and localized infection may occur without meningitis. Any collection of epidural fluid should be aspirated, if possible, for culture and PCR studies.

Patients who received an intraarticular injection should be alert for new pain, especially if it differs in quality from their original pain, or if they have erythema or swelling of a joint. In such cases, aspiration of synovial fluid should be performed immediately for diagnostic studies. There is increased variability in what is considered a normal number of white cells in synovial fluid, and no firm guidance has been given for the number of cells required to initiate therapy. Clinical judgment must be used, with the symptoms and signs of joint disease before the injection taken into account. If there is any question of whether infection could be present, arthroscopy to obtain synovial fluid and possibly synovial biopsy for culture and PCR studies should be performed as soon as possible.

Patients who have no symptoms should not undergo lumbar puncture or joint aspiration. However, they should be told to call immediately if symptoms occur.

HOW SHOULD THE INFECTION BE TREATED?

Recommendations for the treatment of this rare infection are based on small case series, individual case reports, and personal experience. A large number of patients in this outbreak are older adults, many of whom have substantial coexisting illnesses that make therapeutic decisions challenging. Treatment recommendations will certainly evolve as clinicians gain more experience with managing these infections. 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.

In the current outbreak, 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 amphoteri-

cin 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 is experience in the use of voriconazole for various mold infections. Both intravenous and oral formulations are available, and oral administration produces serum levels equivalent to those achieved by intravenous administration. Levels of the drug in cerebrospinal fluid are approximately 50% of serum levels,[7] 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 is erratic.

CURRENT RECOMMENDATIONS

DRUGS AND DOSES

For patients with mild or moderate CNS disease, 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 7.5 mg per kilogram daily) is recommended.

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. The role of adjunctive surgery should not be underestimated in patients with osteoarticular mold infections.[8]

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, leading to toxic levels. 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 meningitis, 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. 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 accumulation of cyclodextrin in renal failure does not exacerbate underlying renal dysfunction, and if needed, voriconazole can be given intravenously.[9]

OTHER ISSUES RELATED TO TREATMENT

DURATION OF THERAPY

The duration of therapy is not known, but at this time, it is recommended that patients receive at least 3 months of antifungal therapy, and probably more for vertebral osteomyelitis. Therapy should continue until all clinical signs and symptoms have resolved and abnormal laboratory values have normalized.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring is an important aspect of antifungal therapy and is especially important in this outbreak, since there is little experience in treating this condition.[10] 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 extremely important. A voriconazole 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 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

Should patients who have symptoms but are found to have fewer than 5 white cells per cubic millimeter in cerebrospinal fluid be treated? Without objective evidence of infection in the cerebrospinal fluid, treatment is not recommended. However, patients who have symptoms should be monitored closely, and if there is even subtle progression of symptoms, a repeat lumbar puncture should be performed immediately. If the number of white cells has increased, then empirical antifungal treatment should be initiated immediately.

PROPHYLAXIS

What should we tell patients who would like to be treated with an antifungal agent to prevent infection? The agents used for treatment are amphotericin B and voriconazole. It is unlikely that anyone would consider using amphotericin B for prophylaxis. Voriconazole is less toxic, but adverse effects have been encountered frequently in patients treated for CNS infection in this outbreak, and drug–drug interactions are many, as noted above. Another concern is that the prophylactic use of antifungal agents may delay the onset or change the course of the disease so that it appears months later and the organism may have become resistant to the agent used.

SUMMARY

This outbreak of fungal meningitis caused by contaminated methylprednisolone used for epidural injections is evolving rapidly and now involves more than 200 patients. The primary pathogen appears to be *E. rostratum*, but it is possible that other pathogens could emerge, and it remains a mystery as to why the index case is the sole case in which *A. fumigatus* was detected. It is encouraging to note that clinically apparent disease has developed in only a small percentage of exposed patients. Management recommendations will almost assuredly change as more information becomes available regarding the pathogenesis of these infections.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org

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