Cerebrospinal Fluid (1,3)-β-D-Glucan Detection as an Aid for Diagnosis of Iatrogenic Fungal Meningitis

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This case series highlights our experience with use of the Fungitell assay for quantifying (1,3)-β-D-glucan in cerebrospinal fluid during the current U.S. outbreak of fungal meningitis related to contaminated methylprednisolone acetate. This test may prove a useful adjunct in diagnosis and management of exposed patients.

(1,3)-β-D-glucan (BG) is found in cell walls of multiple fungi. Its detection in serum assists in diagnosis of invasive fungal infections (1). Recently, diagnostic challenge has arisen in the fungal meningitis outbreak associated with exposure to contaminated epidural steroid injections (2). Diagnosis in this setting has been established by culture of cerebrospinal fluid (CSF) and/or detection using a pan-fungal PCR assay performed by the Centers for Disease Control (CDC). However, these tests have not always been positive in suspected cases (3). One early study has demonstrated the proof of concept of using CSF BG detection in diagnosis of fungal central nervous system infection in an experimental heterogenous Candida meningoencephalitis model (4). Here we report our experience with CSF BG measurement in 5 individuals from Johns Hopkins Hospital and Indiana University Hospital who were exposed to potentially contaminated drugs. Cases were diagnosed and managed according to CDC guidelines. BG was tested at Beacon Diagnostics Laboratory (East Falmouth, MA) using the Fungitell assay. Information was obtained by chart review with approval from the Johns Hopkins Institutional Review Board.

The first case was a 55-year-old woman who developed headaches, blurred vision, and injection site pain 1 week after lumbar epidural injection with potentially contaminated methylprednisolone and was admitted 35 days after symptom onset when the outbreak was recognized. CSF showed 30 white blood cells (WBCs)/mm³ and normal glucose and protein; no opening pressure was recorded. Intravenous voriconazole was initiated, but symptoms continued despite troughs of 2 to 3 µg/ml. Repeat lumbar puncture (LP) showed opening pressure of 42 cm H₂O, 974 WBC/mm³ (56% neutrophils, 16% lymphocytes, 21% monocytes), 1,000 red blood cells (RBCs)/mm³, normal glucose, and 93 mg/dl protein, with a negative culture. CSF PCR performed by the CDC was negative. With serial LPs for persistent headache and elevated opening pressures and voriconazole increase to maintain troughs of 3 to 5 µg/ml, her symptoms resolved. CSF fungal cultures from postinjection days 57, 69, and 73 were negative. CSF BG samples sent on postinjection days 57, 69, and 73 were negative. CSF BG was below the detection limit (<31 pg/ml). His headaches resolved and did not return after voriconazole cessation.

The second case was a 37-year-old man who underwent lumbar epidural injection with potentially contaminated methylprednisolone acetate from an implicated methylprednisolone lot. Lumbosacral MRI was unremarkable. On postexposure day 38, CSF showed 54% neutrophilic pleocytosis with 32 WBC/µl, elevated protein at 90 mg/dl, and normal glucose; she was admitted and voriconazole initiated. Fungal culture and PCR performed at CDC were negative. Repeat MRI showed cauda equina enhancement and injection site edema. She was discharged after 2 weeks but self-discontinued voriconazole due to nausea and diarrhea; her symptoms returned 2 weeks later. BG was detectable in CSF from day 72 at 96 pg/ml (Table 1). Voriconazole was reintiated and symptoms resolved with troughs of 6 µg/ml.

The fourth case was a 45-year-old woman with a history of epidural injection from an implicated methylprednisolone lot who developed rhinorrhea, cough, and sore throat more than 6 weeks after her injection, progressing over several days to include headache and mild neck stiffness. Her symptoms were thought to be due to a respiratory virus. Fungal culture was negative, and fungal PCR was not performed given the lack of pleocytosis (Table 1). CSF BG was below the detection limit.

The fifth case was a 65-year-old man who received lumbar epidural steroid injections on 7 May 2012, 16 July 2012, and 4

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September 2012 with methylprednisolone from contaminated lots. He was apprised in mid-October and requested evaluation prior to a previously scheduled surgery. His neurologic examination was normal, and he was asymptomatic. Serum and CSF galactomannan tests (Platelia; Bio-Rad Laboratories) were negative (index, <0.5). The BG was positive in serum at 183 pg/ml and detectable in CSF at 39 pg/ml (Table 1). Intravenous voriconazole therapy was initiated. A lumbar MRI showed a discitis at L1-L2 and 3-mm abnormal enhancement in the ventral epidural space that was new since 5 October 2012. After 2 months of voriconazole, the fluid collection resolved and serum BG decreased to 88 pg/ml.

Confirmed cases of fungal meningitis in the current outbreak have primarily involved *Exserohilum rostratum* (3, 5–8). However, most cases have remained clinically “probable” due to lack of laboratory confirmation. Culture has relatively low sensitivity, confirming only one-third of reported cases (3). The performance of the PCR is not yet known. Cases 1, 3, and 5 had symptoms, CSF pleocytosis, and/or abnormal imaging suggestive of infection but negative fungal cultures and PCR; all three had detectable CSF BG, suggesting fungal involvement. In cases 2 and 4, CSF BG was negative, and alternative diagnoses were considered likely based on clinical presentation, CSF studies, and/or radiographic findings. It is noticeable that CSF BG was detectable in case 5 in the absence of pleocytosis. As fluctuations in CSF WBC count have been noted during this outbreak (unpublished data), it is possible that the Fungitell assay may be very sensitive in detecting fungal elements in the CSF without pleocytosis. In the absence of culture and PCR results, BG detection in CSF raises the possibility of its use as an adjunct to aid in the diagnosis especially while this current epidemic continues to pose diagnostic challenges. Additionally, serum BD may be useful in detection of parasitological infections that have not penetrated the CSF.

Detection of CSF BG has not been cleared by the FDA as an aid to diagnosis of fungal meningitis, and the appropriate quantitative cutoff for positivity in CSF is unknown (9, 10). It is possible that CSF BG concentration may be lower than that of serum for this assay, as illustrated in case 5 (none of the other cases had serum BG tested during hospitalization), but more data would be necessary to confirm. One study suggested that BG is undetectable in normal

### REFERENCES


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