ORIGINAL ARTICLE

Clinical Findings for Fungal Infections Caused by Methylprednisolone Injections

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ABSTRACT

BACKGROUND

Since September 18, 2012, public health officials have been investigating a large outbreak of fungal meningitis and other infections in patients who received epidural, paraspinal, or joint injections with contaminated lots of methylprednisolone acetate. Little is known about infections caused by *Exserohilum rostratum*, the predominant outbreak-associated pathogen. We describe the early clinical course of outbreak-associated infections.

METHODS

We reviewed medical records for outbreak cases reported to the Centers for Disease Control and Prevention before November 19, 2012, from the six states with the most reported cases (Florida, Indiana, Michigan, New Jersey, Tennessee, and Virginia). Polymerase-chain-reaction assays and immunohistochemical testing were performed on clinical isolates and tissue specimens for pathogen identification.

RESULTS

Of 328 patients without peripheral-joint infection who were included in this investigation, 265 (81%) had central nervous system (CNS) infection and 63 (19%) had non-CNS infections only. Laboratory evidence of *E. rostratum* was found in 96 of 268 patients (36%) for whom samples were available. Among patients with CNS infections, strokes were associated with an increased severity of abnormalities in cerebrospinal fluid (P<0.001). Non-CNS infections were more frequent later in the course of the outbreak (median interval from last injection to diagnosis, 39 days for epidural abscess and 21 days for stroke; P<0.001), and such infections developed in patients with and in those without meningitis.

CONCLUSIONS

The initial clinical findings from this outbreak suggest that fungal infections caused by epidural and paraspinal injection of a contaminated glucocorticoid product can result in a broad spectrum of clinical disease, reflecting possible variations in the pathogenic mechanism and in host and exposure risk factors. (Funded by the Centers for Disease Control and Prevention.)

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Since September 18, 2012, state and local health departments, the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration have been investigating the largest documented health care–associated outbreak in the United States. Fungal meningitis and other infections developed after patients received epidural, paraspinal, or joint injections with contaminated methylprednisolone acetate from a single compounding pharmacy.[1-3] The most commonly identified pathogen among patients was the mold *Exserohilum rostratum*, an extremely rare human pathogen. In the absence of known contamination, infectious complications of epidural or paraspinal injections occur infrequently (in <0.1% of patients) and usually result in bacterial meningitis or abscess rather than fungal disease.[4]

As of July 1, 2013, a total of 749 outbreak-associated cases and 61 deaths had been reported. We describe the findings of the initial clinical investigation of outbreak-associated cases of central nervous system (CNS) and parameningeal infections.

METHODS

EPIDEMIOLOGIC INVESTIGATION

Details of the ongoing public health investigation to identify outbreak-associated infections have been described previously.[1] Briefly, patients were considered to have probable cases if they received injections from one of three contaminated lots of methylprednisolone acetate after May 21, 2012, and had any one of the following conditions: meningitis of unknown cause, posterior circulation stroke without a cardioembolic source, spinal or paraspinal infection near the site of injection, or osteomyelitis or arthritis of a peripheral joint. Confirmed cases were defined as probable cases with laboratory evidence (on culture, histopathological analysis, or molecular assay) of a fungal pathogen associated with the clinical syndrome.

CLINICAL INVESTIGATION

Included in this report are data from patients with probable or confirmed infection who were admitted to a hospital or emergency room before November 19, 2012, in the six states with the highest number of cases (Florida, Indiana, Michigan, New Jersey, Tennessee, and Virginia). Patients with peripheral-joint infections were excluded. For each patient, detailed clinical information was abstracted during a single review of emergency room and inpatient medical records. The chart reviews were performed between October 1 and November 19, 2012.

This investigation was part of an emergency public health response; as such, it was not considered to be research that required review by an institutional review board or informed consent from the patients. Clinical data were collected with the use of a standardized case-report form developed for the outbreak.

CLINICAL DISEASE TYPES

Patients were categorized according to the following disease types: meningitis, stroke, arachnoiditis, epidural or intradural abscess, spinal osteomyelitis or diskitis, and paraspinal or facet-joint infection (Fig. S1B in the Supplementary Appendix, available with the full text of this article at NEJM.org). Meningitis was defined on the basis of signs or symptoms of meningitis and pleocytosis (white-cell count, >5 per cubic millimeter) in cerebrospinal fluid, corrected for the presence of red cells. All other case definitions were based on written reports describing the results of computed tomography or magnetic resonance imaging of the brain or spinal cord in the patient's medical record (for details, see the Supplementary Appendix).

Meningitis, stroke, arachnoiditis, and intradural abscess were considered to be CNS disease types, and all other disease types were considered to be non-CNS disease. Patients with CNS disease types were classified as having CNS disease, regardless of whether they also had non-CNS disease types; patients without evidence of CNS disease types were classified as having non-CNS disease only.

MICROBIOLOGIC AND PATHOLOGICAL INVESTIGATION

Clinical specimens were tested at the CDC Fungus Reference Laboratory with the use of a polymerase-chain-reaction (PCR) assay and broad-range, internal-transcribed-spacer fungal primers.[5,6] Sequencing of amplified fungal DNA and DNA that was extracted from fungal isolates was performed for fungal species identification. Also performed at the CDC were gross evaluation of specimens and autopsy photographs; histopathological, special stain, and immunohistochemical testing of tissue obtained on autopsy or biopsy; and PCR and DNA sequencing of amplified fungal DNA from tissue.[7,8]

Table 1. Characteristics of Patients with Disease Affecting the Central Nervous System (CNS) and Non-CNS Disease.*

Characteristic	All Patients (N=328)	Patients with CNS Disease (N=265)	Patients with Non-CNS Disease (N=63)	P Value†
Median age (IQR) — yr	66 (55–74)	66 (55–75)	64 (52–72)	0.70
Male sex — no. (%)	135 (41)	106 (40)	29 (46)	0.40
Underlying condition — no. (%)				
Chronic renal insufficiency	13 (4)	10 (4)	3 (5)	0.70
Coronary artery disease	38 (12)	33 (12)	5 (8)	0.30
Diabetes mellitus	77 (23)	69 (26)	8 (13)	0.02
Hypertension	84 (26)	74 (28)	10 (16)	0.049
Hyperlipidemia	103 (31)	88 (33)	15 (24)	0.10
Immunosuppressive condition‡	32 (10)	29 (11)	3 (5)	0.10
Chronic liver disease	1 (<1)	1 (<1)	0	NA
Injection type — no./total no. (%)				
Epidural	270/327 (83)	225/264 (85)	45/63 (71)	0.01
Facet-joint	15/327 (5)	10/264 (4)	5/63 (8)	0.20
Sacroiliac-joint	4/327 (1)	2/264 (<1)	2/63 (3)	0.20
Injection location (epidural only) — no./total no. (%)				
Cervical	35/270 (13)	25/225 (11)	10/45 (22)	0.04
Thoracic	5/270 (2)	5/225 (2)	0	NA
Lumbar	222/270 (82)	189/225 (84)	33/45 (73)	0.09
Injection approach, epidural only — no./total no. (%)				
Translaminar	189/242 (78)	168/200 (84)	21/42 (50)	<0.001
Transforaminal	41/242 (17)	21/200 (10)	20/42 (48)	<0.001
Median interval between last injection and diagnosis (IQR) — days§	19 (10–28)	19 (11–27)	24 (7–35)	0.10
Symptoms at presentation — no./total no. (%)				
Headache	248/328 (76)	213/265 (80)	35/63 (56)	<0.001
Fever	92/328 (28)	85/265 (32)	7/63 (11)	<0.001
Back pain				
Any	182/328 (55)	132/265 (50)	50/63 (79)	<0.001
Severe	29/49 (59)	18/29 (62)	11/20 (55)	0.60
Median duration of follow-up (IQR) — days¶	14 (7–27)	15 (6–28)	12 (8–18)	0.10

* Meningitis, stroke, arachnoiditis, and intradural abscess were considered to be CNS diseases, and all other disease types were considered to be non-CNS disease. Patients with CNS disease were classified as having a CNS disease regardless of whether they also had non-CNS disease. Patients without evidence of CNS disease were classified as having non-CNS disease only. IQR denotes interquartile range, and NA not applicable.
† P values have not been adjusted for multiple testing.
‡ An immunosuppressive condition was defined as human immunodeficiency virus infection, the acquired immunodeficiency syndrome, need for long-term immunosuppressive therapy, connective-tissue disorder, cancer (solid or hematopoietic), or need for organ transplantation.
§ Data in this category were available for 228 patients with CNS disease and 38 patients with non-CNS disease.
¶ Follow-up was measured from the day of admission to a hospital or emergency room.

STATISTICAL ANALYSIS

We conducted bivariate analyses using a Wilcoxon rank-sum test, a chi-square test, or Fisher's exact test, as appropriate. We developed an extended Cox proportional-hazards model to evaluate risk factors for death or stroke among patients with meningitis. Treatment was included as a time-dependent variable to evaluate the relative hazard

of a poor outcome during treatment in the hospital. All the results that are presented were derived from the full model without backward elimination. The Cochran–Armitage test was used to evaluate trends in the case fatality rate. A multivariate logistic-regression model was developed to evaluate factors associated with CNS disease among patients in Michigan. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

CLINICAL INVESTIGATION

Clinical data were obtained for 328 of the 478 patients (69%) in whom fungal meningitis or another infection was diagnosed on or before November 19, 2012. Of these patients, a majority were from either Michigan (126 patients [38%]) or Tennessee (80 patients [24%]). The median duration of follow-up from the date of initial hospital admission was 14 days (interquartile range, 7 to 27). Clinical, demographic, and other data are provided in Table 1.

DISEASE TYPES

Of the 328 patients included in this investigation, 265 (81%) had CNS infection and 63 (19%) had non-CNS infections only. Figure 1 shows the detailed distribution of disease types among all patients; 122 of the 328 patients (37%) had more than one disease type. Meningitis was the predominant disease type identified in the study population, followed by epidural abscess and arachnoiditis.

Meningitis

Of the 250 patients with meningitis, 229 (92%) received the diagnosis at the time of initial hospital admission, and 21 patients (8%) received the diagnosis later. Among patients with meningitis at presentation, 187 (82%) had meningitis only, whereas 42 (18%) also had one or more other disorders (stroke in 11 patients, arachnoiditis in 23, and abscess in 11). Of the 187 patients with meningitis only at presentation, 12 (6%) received a diagnosis of stroke a median of 10 days after the meningitis was diagnosed; arachnoiditis was diagnosed in 24 patients (13%) a median of 18 days after the meningitis diagnosis, and epidural abscess was diagnosed in 22 patients (12%) a median of 20 days after the meningitis diagnosis. A total of 137 of the 250 patients with meningitis (55%) never received a diagnosis of another disorder. Clinical characteristics of the patients are provided in Table 2.

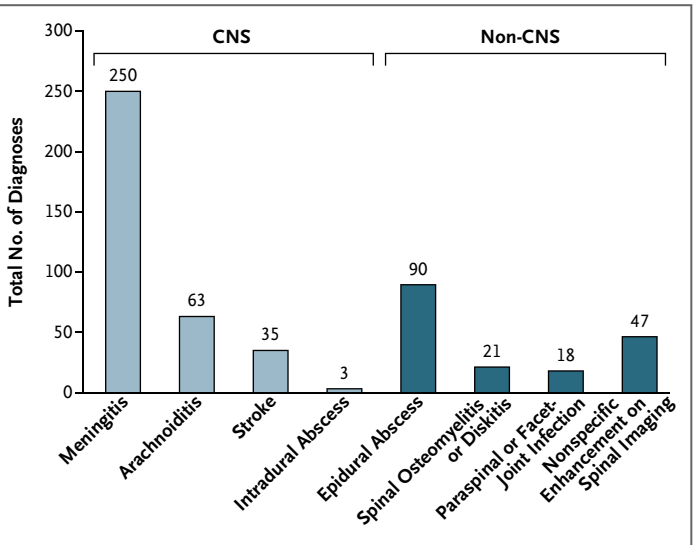

Figure 1. Distribution of Disease Types in the Clinical Cohort.

Shown are data for 328 patients, according to the total number of diagnoses. Patients with multiple diagnoses were included in more than one category.

Stroke

Among the 35 patients who had evidence of stroke, lumbar puncture was performed in 29; all had pleocytosis in cerebrospinal fluid that was consistent with meningitis. A total of 17 of the 35 patients with stroke (49%) received the diagnosis before September 30, 2012. Neurologic-deficit symptoms, documented fever, and meningeal signs were more common in patients with stroke than in those with nonstroke CNS infection ($P=0.07$, $P<0.001$, and $P=0.06$, respectively). In analyses of cerebrospinal fluid, patients with stroke also had a higher white-cell count, a lower glucose level, and a higher protein level than those with nonstroke CNS infections ($P<0.001$ for all comparisons). Among the 30 patients who had stroke with localized findings on imaging, the anatomical location of the stroke involved areas supplied by vertebrobasilar vessels (cerebellum or brain stem) in 23 (77%), basal ganglia in 16 (53%), and cerebral cortex in 1 (3%)[1] (Fig. 2).

Arachnoiditis

Among the 63 patients with arachnoiditis, lumbar puncture was performed in 58 (92%); 52 of these 58 patients (90%) had pleocytosis in cere-

Table 2. Characteristics of the Patients, According to Disease Type.*

Variable	Meningitis Only (N=137)	Stroke (N=35)	Arachnoiditis (N=63)	Epidural Abscess (N=90)
Clinical presentation — no. (%)				
Headache	119 (87)	26 (74)	49 (78)	61 (68)
Subjective fever	42 (31)	16 (46)	23 (37)	17 (19)
Neck pain	47 (34)	11 (31)	22 (35)	27 (30)
Back pain	61 (45)	10 (29)	41 (65)	65 (72)
Meningeal symptom†	64 (47)	14 (40)	26 (41)	30 (33)
Neurologic-deficit symptom‡	40 (29)	17 (49)	26 (41)	26 (29)
Temperature >38.3°C, or 101°F	8 (6)	8 (23)	4 (6)	1 (1)
Altered mental status	6 (4)	8 (23)	2 (3)	1 (1)
Meningeal sign§	9 (7)	6 (17)	5 (8)	4 (4)
Neurologic-deficit sign¶	9 (7)	8 (23)	8 (13)	8 (9)
Cerebrospinal fluid on initial lumbar puncture‖				
Median white-cell count (IQR) — cells/mm^3**	47 (10–798)	1485 (665–2949)	539 (165–1910)	11 (1–183)
Median glucose (IQR) — mg/dl	54 (45–63)	33 (26–48)	43 (33–57)	57 (41–65)
Median protein (IQR) — mg/dl	69 (44–109)	166 (122–259)	113 (60–196)	70 (51–139)
Treatment				
Median interval from symptom onset to initial antifungal treatment (IQR) — days	8 (3–22)	8 (5–17)	10 (3–20)	17 (8–31)
Treatment received — no. (%)				
Voriconazole	118 (86)	26 (74)	62 (98)	89 (99)
Amphotericin B	62 (45)	23 (66)	45 (72)	62 (69)
Voriconazole and amphotericin B††	60 (44)	21 (60)	40 (64)	58 (64)
Death — no. (%)	1 (1)	22 (63)	2 (3)	4 (4)

* Listed are data for 311 of the 328 patients included in the study. Patients could be listed under more than one category of disease, so totals across the columns may be larger than the number of patients. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† A meningeal symptom was defined as stiff neck and light sensitivity.
‡ A neurologic-deficit symptom was defined as slurred speech, decreased vision or visual disturbance, limb weakness, numbness, urinary retention, fecal incontinence, or ataxia.
§ A meningeal sign was defined as nuchal rigidity and either Kernig's sign or Brudzinski's sign on examination.
¶ A neurologic-deficit sign was defined as hemiplegia or paraplegia, hemiparesis or paraparesis, dysarthria, sensory loss, or reflex abnormality.
‖ Data regarding the analysis of cerebrospinal fluid were reported for 68 of 90 patients with epidural abscess who underwent lumbar puncture.
** The white-cell count was corrected for the presence of red cells.
†† Patients who received both voriconazole and amphotericin B did not necessarily receive the two drugs at the same time.

brospinal fluid that was consistent with meningitis on lumbar puncture; 5 of the 63 patients with arachnoiditis (8%) had evidence of stroke. Most of the patients with arachnoiditis had headache (78%) and back pain (65%). Physical signs of meningeal inflammation and neurologic deficit were infrequent, with incidences of 8% and 13%, respectively. The median white-cell count in cerebrospinal fluid was increased by a factor of 10 among patients with arachnoiditis, as compared with those with meningitis alone (539 vs. 47 cells per cubic millimeter, P<0.001).

Epidural Abscess

Of the 90 patients with an epidural abscess, 28 (31%) had an epidural abscess only, 39 (43%) also had meningitis, and 23 (26%) also had another infection in addition to meningitis. Among all the patients with an epidural abscess, the condition was diagnosed at the initial presentation in 57 patients (63%) and at a later time in 33 (37%). The interval from the last injection of methylprednisolone acetate to the diagnosis of abscess did not differ significantly between patients with meningitis and those without meningitis (me-

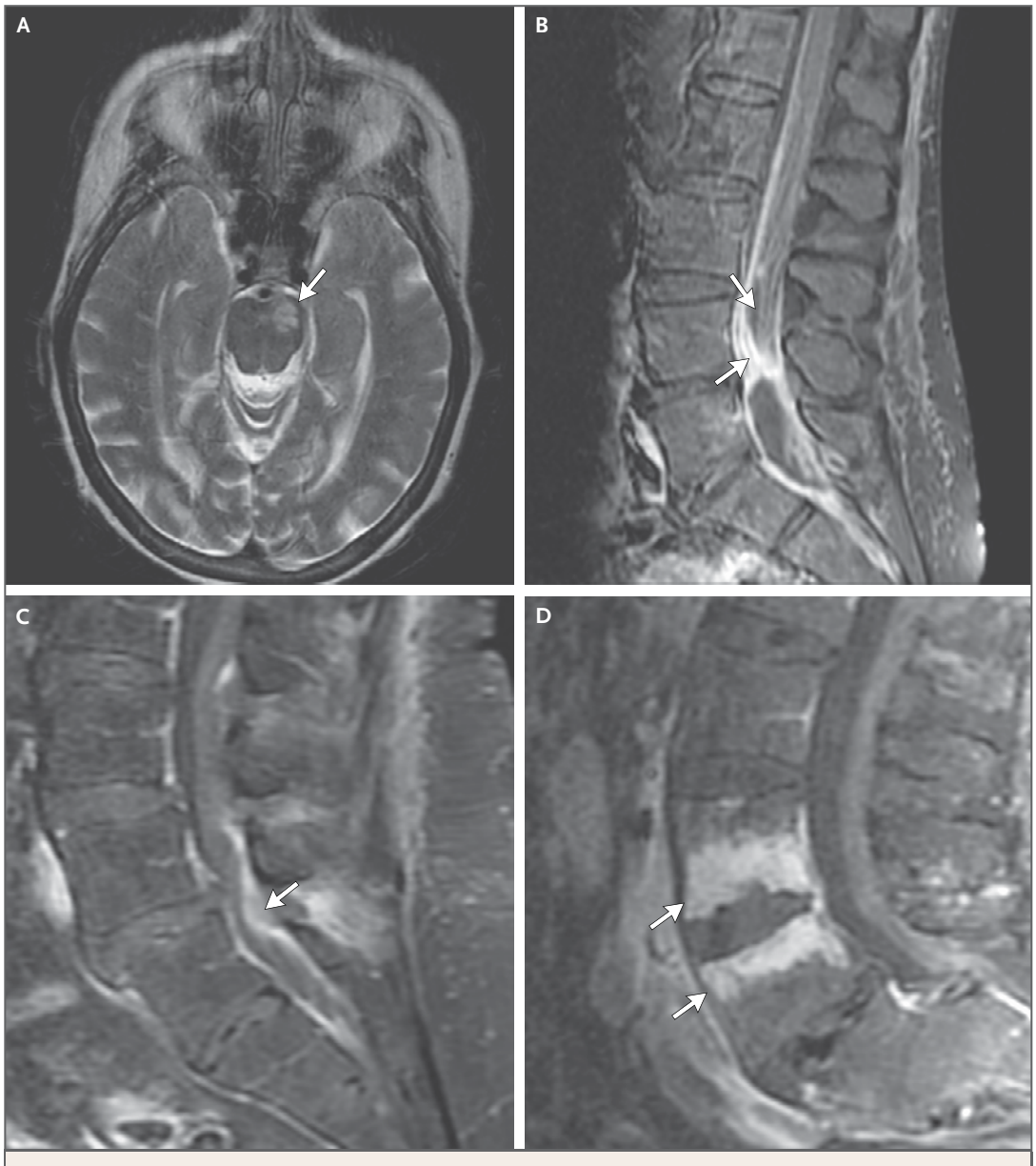

Figure 2. Typical Neuroradiologic Findings.

Panel A shows an axial T_2-weighted image of the brain from a patient with meningitis and posterior circulation stroke (arrow). Panel B shows a sagittal T_1-weighted, fat-saturated image of the lumbar spine, obtained after the administration of contrast material, showing clumped intradural enhancement (arrows) that is consistent with arachnoiditis. Polymerase-chain-reaction assays of spinal fluid obtained from patients in Panels A and B were positive for *Exserohilum rostratum*. Panel C shows a rim-enhancing fluid collection in the dorsal epidural space that is consistent with an epidural abscess (arrow). Tissue obtained during surgery showed fungal hyphae, and culture yielded exserohilum species. Panel D shows linear end-plate enhancement (arrows) that is consistent with diskitis or osteomyelitis.

dian interval, 44 days and 43 days, respectively; P=0.30).

DEATHS

There were 26 deaths among the 328 patients who were included in this analysis. Among those who died, 22 (85%) had stroke, 1 (4%) had arachnoiditis without stroke, 1 (4%) had meningitis only, and 2 (8%) had meningitis with epidural abscess. Most deaths (58%) occurred before October 15, 2012. The median survival time among those who died was 9 days (interquartile range,

7 to 19) after hospital admission. Of the 328 patients, 9 (3%) died before receiving antifungal therapy; all these patients died before October 8, 2012.

Among patients with meningitis, risk factors for death or stroke that remained significant in a multivariate, extended Cox proportional-hazards model included older age, the presence of fever, altered mental status, and a high white-cell count in cerebrospinal fluid (Table S2 in the Supplementary Appendix). The white-cell count in cerebrospinal fluid at presentation was positively associated with the case fatality rate among patients with meningitis (P<0.001) (Table S3 in the Supplementary Appendix).

ADVERSE EVENTS ASSOCIATED WITH ANTIFUNGAL THERAPY

Among 178 patients treated with amphotericin B, 171 (96%) received liposomal amphotericin B formulation; the median daily dose was 5 mg per kilogram of body weight per day. Acute kidney injury (serum creatinine level, >2 times the patient's baseline level) developed in 46 patients (26%) receiving amphotericin B therapy, with 3 patients requiring dialysis. The median time to acute kidney injury was 5 days (interquartile range, 4 to 8).

Among 297 patients receiving voriconazole, the median daily dose was 6 mg per kilogram every 12 hours. Of these patients, 55 (19%) had an aspartate aminotransferase or alanine aminotransferase level of more than 120 U per liter; visual disturbances developed in 77 patients (26%), and hallucinations in 49 (16%).

MICROBIOLOGIC FINDINGS

Samples were obtained from 268 of the 328 patients (82%) for testing at the CDC. A total of 96 of these 268 patients (36%) had laboratory evidence of *E. rostratum*: 66 on PCR assay alone, 15 on culture alone, and 15 on both PCR and culture. Seven other fungal species were detected on culture alone: *Alternaria alternata* in 1 patient, *Aspergillus fumigatus* in 1 patient, *Asp. terreus* in 3 patients, *Asp. tubingensis* in 1 patient, cladosporium species in 3 patients,[1] *Paecilomyces niveus* in 1 patient, and *Stachybotrys chartarum* in 1 patient. Cladosporium species were identified in cerebrospinal fluid in a fourth patient on PCR assay.

Susceptibility testing was performed on 53 *E. rostratum* isolates obtained from patients during the outbreak. The median and range of minimum inhibitory concentration values were as follows: voriconazole, 1 μg per milliliter (range, 1 to 4); amphotericin B, 0.25 μg per milliliter (range, 0.03 to 2.00); posaconazole, 0.50 μg per milliliter (range, 0.25 to 1.00); itraconazole, 0.50 μg per milliliter (range, 0.25 to 4.00); and fluconazole, 64 μg per milliliter (range, 16 to 128).

PATHOLOGICAL FINDINGS

Pathologists at the CDC examined tissue specimens from 26 patients (8%) included in this analysis. Tissue specimen types included brain, spinal cord, meninges, paraspinal soft tissue, bone, and visceral organs. In the CNS and paraspinal soft-tissue specimens, the degree of inflammatory reaction to the fungal hyphae varied from minimal to extensive, and the spectrum of response ranged from neutrophilic inflammation with necrosis to granulomatous inflammation with abundant giant cells (Fig. 3). Fungal hyphae were observed within meningeal infiltrates and frequently within the walls of basilar and middle cerebral arteries, with associated vasculitis, thrombosis, and parenchymal infarction. Thromboembolic CNS spread was seen in only 1 patient, and there was no evidence of dissemination to visceral organs, including lung, liver, spleen, kidney, or heart.[8]

CNS VERSUS NON-CNS DISEASE

A total of 265 patients (81%) had evidence of CNS disease, and 63 (19%) did not have evidence of CNS disease (Table 1). More patients with CNS disease than with non-CNS disease received the injection in states other than Michigan (P<0.001), received a cumulative dose of methylprednisolone acetate of 80 mg or higher (P=0.04), received a translaminar epidural injection (P<0.001), and had an underlying medical condition (specifically, diabetes [P=0.02] or hypertension [P=0.05]). Patients with non-CNS disease were more likely to have received the 06292012@26 lot of methylprednisolone acetate (P=0.001), a nonepidural injection (P=0.01), and a transforaminal epidural injection (P<0.001). The interval between the injection and diagnosis was shortest for patients with stroke (median, 21 days) and longest for those with an epidural abscess (median, 39 days; P<0.001).

Of the 63 patients with non-CNS disease, 57 (90%) received the injection in Michigan. To evaluate risk factors for CNS disease in comparison with non-CNS disease, we developed a

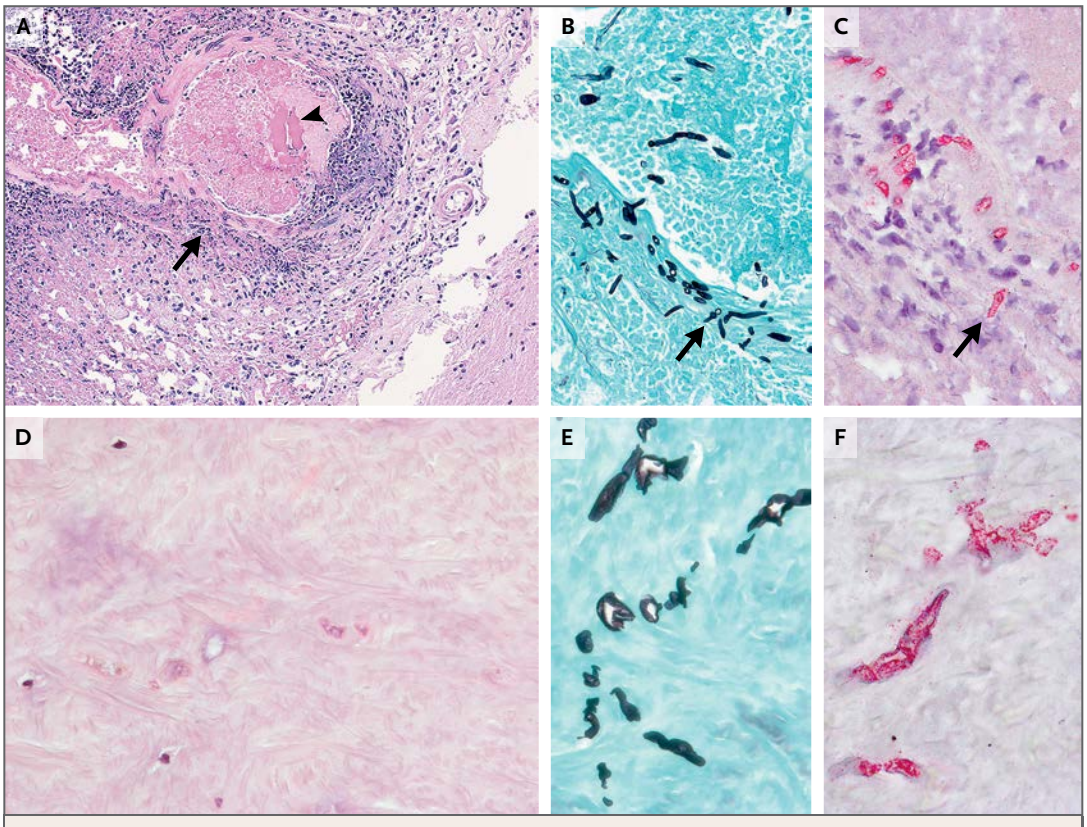

Figure 3. Pathological Features of Exserohilum Infection.

Panel A shows a branch of a basilar artery (arrow) in a patient with meningitis, with visible vasculitis and thrombosis (arrowhead) (hematoxylin and eosin). Panels B and C show serial sections of the same artery at higher magnification, with abundant fungal hyphae clearly visible within the vessel wall (arrows). Panel D shows a sample of paraspinal ligament characterized by minimal inflammation (hematoxylin and eosin). Panels E and F show serial sections of the same ligament with abundant fungal hyphae. (Grocott's methenamine silver staining was performed in Panels B and E and immunohistochemical staining in Panels C and F.)

multivariate logistic-regression model that was restricted to patients in Michigan. Factors that were independently associated with CNS disease were the presence of hypertension (odds ratio, 4.28; 95% confidence interval [CI], 1.47 to 12.48) and receipt of a translaminar epidural injection (odds ratio, 3.83; 95% CI, 1.60 to 9.20). Factors that were included in the model but were not independently associated with CNS disease included the total injected dose of methylprednisolone acetate, the location of the injection (i.e., cervical, thoracic, or lumbar), the drug lot or vial age, and the number of injections.

DISCUSSION

The initial clinical findings from this outbreak suggest that exposure to fungi through epidural and paraspinal injection of a contaminated glucocorticoid product can result in a broad spectrum of clinical disease. The illnesses were characterized by meningitis, stroke, arachnoiditis, and epidural or paraspinal infections localized to the injection site and ranged in severity from very mild to life-threatening.

Most patients who presented early during the outbreak had CNS disease. Fungal infections that cause CNS disease typically occur among immunocompromised persons and are more commonly caused by cryptococcus or coccidioides species than by aspergillus or candida.[9] The majority of infections in this outbreak were associated with the dematiaceous fungus *E. rostratum*. Of the approximately 30 cases of exserohilum infection reported in the literature before this outbreak, the most common presentations were skin, cor-

neal, and sinus infections.[10,11] Because exserohilum rarely causes human infection, relatively little is known about its pathophysiology, clinical manifestations, or management, particularly in the case of CNS infection. In a small minority of patients who were involved in the outbreak, other fungal species were isolated from clinical specimens. The clinical significance of these isolates is unknown; it is possible that one or more represent a contaminant.

How the pathogen in this outbreak entered the CNS is unclear. Although it is possible that CNS infections resulted from direct inoculation of contaminated material into the subarachnoid space by inadvertent puncture of the dura during the glucocorticoid injection, such complications appear to be rare[12] and probably account for few of the infections associated with this outbreak. It is more likely that exserohilum entered the subarachnoid space by direct contiguous spread from the site of injection. The lack of a local inflammatory response in some patients may have been important in allowing the organisms to spread across tissue planes. Whether the absence of inflammation in these cases is a unique feature of exserohilum infection or was due to the local effect of concomitant injection with antiinflammatory glucocorticoids is unclear.

Of particular note is the disproportionate number of non-CNS infections in our study population that were reported in Michigan. Case reports submitted to the CDC after our data-abstraction period suggest that there was a high degree of state-level variation in the proportion of patients with non-CNS disease.[13] This observation is currently unexplained. Possible explanations include state-specific variation in the use of imaging to screen for disease localized to the injection site,[14] variation in injection approach, or other unidentified factors potentially associated with non-CNS disease. Further epidemiologic investigation is warranted.

In many of the cases that were reported early during the outbreak, the patients presented with severe infections, often with severe meningeal inflammation, as evidenced by a high white-cell count in the cerebrospinal fluid, which was complicated by stroke. The risk of stroke or death was greater among patients with a higher initial white-cell count in the cerebrospinal fluid than among those with a lower initial white-cell count. Posterior circulation strokes, which usually make up less than 20% of all stroke types,[15] accounted for the majority of strokes in this outbreak. Histopathological studies showed evidence of direct fungal invasion of vessel walls in the vertebrobasilar circulation, resulting in vasculitis and thrombosis. Strokes involving the basal ganglia that were observed in this outbreak were similar in pattern (both in frequency and in anatomical location) to strokes in tuberculous meningitis, which occur in 13 to 57% of cases and typically involve deep-brain structures.[16] Flow patterns for cerebrospinal fluid that concentrate inflammatory exudates at the base of the brain, in close proximity to vessels supplying these anatomical areas, probably play a role in the development of stroke.[16] There was no clinical evidence of systemic hematogenous spread in these patients, and visceral organs had no evidence of fungal infection on autopsy.

Localized infections at the site of the injection were common, and patients with localized infections tended to present late in the course of the outbreak and with an increased interval between the last injection and diagnosis. Such infections occurred both in patients receiving antifungal treatment for previously diagnosed meningitis and in patients without meningitis who had not undergone treatment. One hypothesis for the delayed presentation is that the local glucocorticoid injection may have masked early signs and symptoms of inflammation and delayed clinical presentation. Alternatively, given the indolent nature of some fungal infections, the incubation period for a clinically evident focal exserohilum infection at the injection site may be prolonged. Treatment-related factors seem less likely, given that the interval between the last injection and a diagnosis of abscess was similar in patients without meningitis (who had not received treatment before diagnosis) and in those already receiving antifungal therapy for meningitis at the time the abscess was diagnosed.

There were several limitations of this analysis. First, data were obtained from patients in only six states, and these patients might not be representative of the entire outbreak population. Second, data were abstracted early in the course of the outbreak, so a full characterization of continually evolving clinical outcomes was not possible. Third, radiologic classification was based on a review of findings from imaging reports, not on direct examination of images, and data

availability varied according to state. Finally, our analyses were not adjusted for multiple testing; the multivariate analyses should be regarded as exploratory and the results may change as more data become available.

Ongoing analyses of epidemiologic and clinical data from this fungal outbreak may further our knowledge about the pathophysiology of exserohilum infection and contribute to a better understanding of treatment and diagnostic options for iatrogenic CNS and paraspinal fungal infection.

The views expressed in this article are those of the authors and do not necessarily represent the official position of the CDC.

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APPENDIX

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