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## Vascular complications of fungal meningitis attributed to contaminated methylprednisolone injections

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### Abstract

**Importance**—Fungal meningitis due to contaminated methylprednisolone injections can present with vascular sequelae in immunocompetent individuals. This is particularly germane to neurologists as better recognition of the clinical characteristics of patients with fungal meningitis and ischemic stroke will provide more timely and efficient care.

**Observations**—A case series of three patients who presented to Vanderbilt University Medical Center with acute ischemic stroke and later diagnosed with fungal meningitis attributed to contaminated methylprednisolone epidural injections. Of these three cases, 2 were female, 1 male, mean age of 75.3. Medical records and imaging were reviewed. All cases presented with acute ischemic strokes, and had a history of epidural methylprednisolone spinal injections for low back pain. Patients had one or more traditional risk factors for stroke. There were differing vascular patterns of presentation: 2 presented with small vessel (lacunar) pattern infarctions, while the other presented with a large vessel infarct. Of these cases, 2 died and underwent autopsy evaluation,

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which revealed *Exserohilum rostratum* as the presumed cause of death. In 2 cases, fever and meningeal signs were absent on presentation.

**Conclusions**—Patients with fungal meningitis may present with ischemic stroke on initial imaging. Definitive diagnosis should not delay early antifungal treatment.

### Search terms

Cerebrovascular disease/Stroke; Meningitis; Fungal infections

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## Background

Recent identification of contaminated methylprednisolone injections has highlighted the diverse clinical presentation of fungal meningitis. When a contaminated methylprednisolone injection is the cause of fungal meningitis, there is often a prolonged incubation period between the last spinal injection to clinical presentation lasting 1 to 4 weeks, yet even longer incubation times have been reported.<sup>1,2,3</sup> A recent series of the Tennessee cases revealed approximately 1/8 of patients have presented with strokes.<sup>3</sup> These cases show that the organisms were primarily *Exserohilum rostratum* and in one case, *Aspergillus fumigatus*. Increased risk of infection is due to specific contaminated lots, older vials, higher corticosteroid doses, multiple procedures, and a translaminal approach.<sup>3</sup> The objective of this series is to describe a cohort of patients who present with ischemic infarction in differing vascular distributions. These cases emphasize an unusual diagnostic dilemma, where an ischemic infarct is initially attributable to known stroke risk factor such as atrial fibrillation or the presence of antiphospholipid protein antibodies, yet patients were later found to have a fungal infection accounting for the presentation.

## Case Series

### Case one

A 78-year-old-male presented with acute onset left sided weakness and dysarthria. Past medical history included low back pain, hyperlipidemia (HLD), hypertension (HTN), and atrial fibrillation. Upon presentation, he was afebrile and complained of a mild persistent headache. Neurologic examination revealed dysarthria, left lower facial weakness, left upper and lower extremity weakness in an upper motor neuron distribution. No meningeal signs were noted. Initial work up was notable for a mild leukocytosis. Magnetic resonance imaging (MRI) of the brain showed a small vessel (lacunar) ischemic infarct of the right anterior superior pons/lower midbrain (Figure 1). Magnetic resonance angiography (MRA) of the head and neck, and transthoracic echocardiogram (TTE) were unremarkable. On hospital day 3, the patient had an exacerbation of left sided weakness. Repeat MRI showed an extension of the infarct in the right midbrain and a new small lacunar infarct in the right thalamus (See Figure 1, Panel A2). On hospital day 4, the patient became unresponsive with a right dilated pupil. Repeat imaging showed enlargement and evolution prior infarcts, along with a new right superior cerebellar artery occlusion. The patient died on hospital day 6. An autopsy was performed as he was noted to have received an epidural steroid injection approximately two weeks prior to presentation. Autopsy showed small areas of focal cortical

and pontine subarachnoid hemorrhage, as well as fungal cerebral vasculitis with aneurysm formation. *Exserohilum* species were found microscopically.

### Case two

A 78-year-old female presented with subacute complaints of vertigo, nausea and headache. Past medical history noted low back pain, HTN, HLD, and coronary artery disease (CAD). Exam was notable for left hand dysmetria and mild ataxia. MRI revealed ischemic infarcts of the left lateral pons, superior cerebellar peduncle, and superior cerebellum suggestive of a large vessel (superior cerebellar artery) etiology (Figure 1). CTA did not reveal any significant posterior circulation stenosis and TTE was unremarkable. Screening labs revealed a new diagnosis of diabetes mellitus type II. Due to history of several prior miscarriages and infarct pattern, a hypercoagulable panel was ordered and positive for lupus anticoagulant and elevated antiphospholipid protein antibodies. The patient was anticoagulated. On hospital day 4, a low grade fever and mild encephalopathy was noted. Repeat brain MRI showed a new ischemic left pontine stroke. On hospital day 6, the patient developed acute urinary retention. Since she had received an epidural injection two weeks prior to admission, a lumbar spine MRI with and without contrast was obtained, and abnormal periarticular enhancement with central canal enhancement at L4-5 was noted but no drainable fluid. Initial blood cultures revealed methicillin sensitive staphylococcus aureus. Later, due to continued altered mental status and a recent report of fungal meningitis<sup>4</sup> a lumbar puncture was performed (Table 1). Intravenous (IV) antibiotics and voriconazole at 6 mg/kg IV twice daily for two doses, followed by 4 mg/kg twice daily were initiated 15 days after initial presentation. Despite therapy, the patient died 50 days after presentation. Autopsy revealed a left superior cerebellar artery mycotic aneurysm with vascular infiltration of the arterial wall by hyphal fungal forms (Figure 2). Based on positive pre-mortem CDC PCR studies, these forms are thought to represent *Exserohilum*.

### Case Three

A 70-year-old female presented with headaches, balance difficulty, nuchal rigidity and fever. Past medical history was notable for HLD and chronic back pain with most recent epidural spinal injection one month prior. Exam revealed mild dysarthria and bilateral dysmetria. MRI brain revealed acute small vessel right thalamic and internal capsule ischemic strokes. MRA of the head and neck showed no significant stenoses. Due to concern for meningitis, a lumbar puncture was performed (see Table 1). Based on initial CSF results intravenous antibiotics, voriconazole in a similar regimen to case 2, and liposomal amphotericin B (stopped after 4 days) were initiated. A MRI thoracic and lumbar spine revealed evidence of lumbosacral arachnoiditis with abnormal enhancement within the posterior epidural space at L4-5 and L5-S1 but again no drainable fluid. On hospital day 7, the patient became encephalopathic and repeat MRI revealed a new acute small vessel left internal capsule. Mental status and CSF cell counts slowly improved with voriconazole monotherapy. The patient was discharged 37 days later.

## Comment

We describe three cases presenting with acute ischemic strokes but upon further workup revealed fungal infections attributable to contaminated lots of methylprednisolone associated with epidural injections reportedly received at identified healthcare facilities<sup>5</sup>. Presenting symptoms in all three patients were, at least in part, related to neurologic sequelae of ischemic stroke. Early MRI findings had evidence of restricted diffusion. Initial imaging did not show evidence of hemorrhage or mycotic aneurysm. Interestingly, all cases were in the 8<sup>th</sup> decade and all had one or more traditional risk factors for stroke. The pattern of infarcts differed, where two cases initially presented with a small vessel infarcts and one with a large vessel pattern. In case 2, progressive vascular occlusion of the superior cerebellar artery was attributed to fungal infiltration at autopsy. Importantly, case 3 received earlier antifungal treatment and we suspect that this halted further vascular progression of her infection.

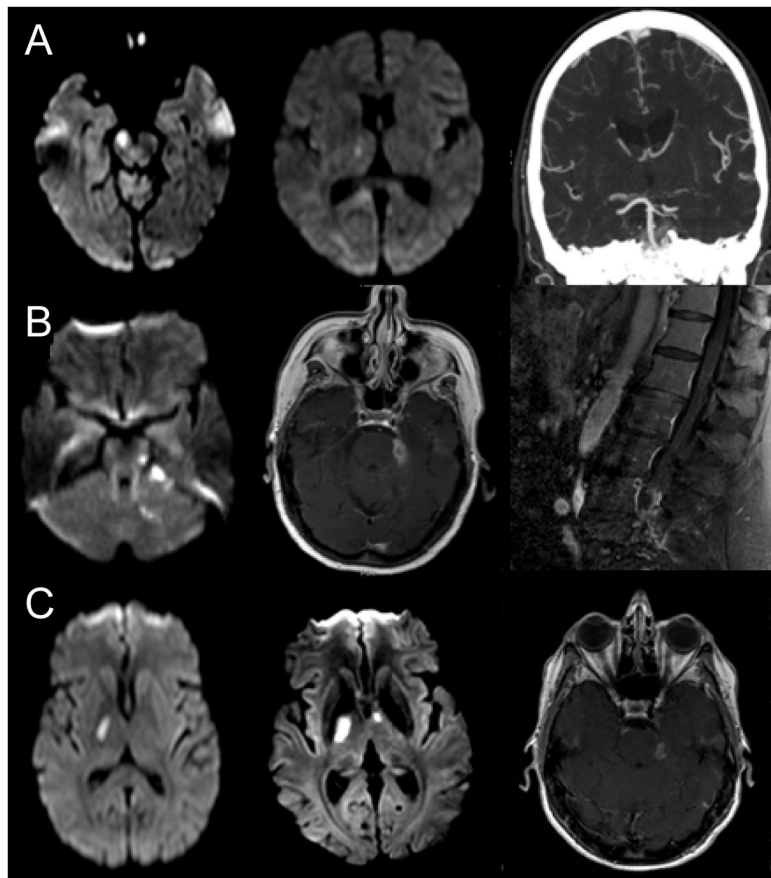
Regarding the territory of strokes, all presented with posterior circulation infarcts (supplied by the basilar, superior cerebellar and posterior cerebral artery branches/perforators). It is now apparent that a high index of suspicion should be raised for possible fungal meningitis in patients who present with posterior circulation ischemic strokes after recent epidural spinal injection<sup>3</sup>. However, it remains unknown why there appears to be a predilection for the posterior circulation in epidural injection associated fungal meningitis. We hypothesize that the proximity of the epidural space may account for fungal infiltration to the posterior vasculature. Definitive diagnosis could not be made during hospitalization, and was made upon autopsy or by polymerase chain reaction (PCR) test for *Exserohilum*. Due clinical suspicion, the patient without a known causative agent was treated early with both antibiotics and antifungals. This patient survived hospitalization.

Though much larger in scale, this is not the first fungal meningitis outbreak due to epidural spinal injection of contaminated corticosteroids.<sup>6,7,8</sup> These cases highlight a diagnostic dilemma of neurologists. Patients with fungal meningitis who present with ischemic strokes may be afebrile, lack signs of meningeal irritation, and have traditional stroke risk factors. In cases where small vessel infarctions expand locally or develop new infarctions in the same vascular territory, an atypical pathogenesis should be considered. We highlight that the angioinvasive nature of some fungal species<sup>4</sup>, including *Exserohilum*, can lead to progressive vascular occlusion. An awareness of the presentation and vascular sequelae of fungal meningitis in immunocompetent patients should lead to earlier treatment and improved outcomes prior to a definitive diagnosis.

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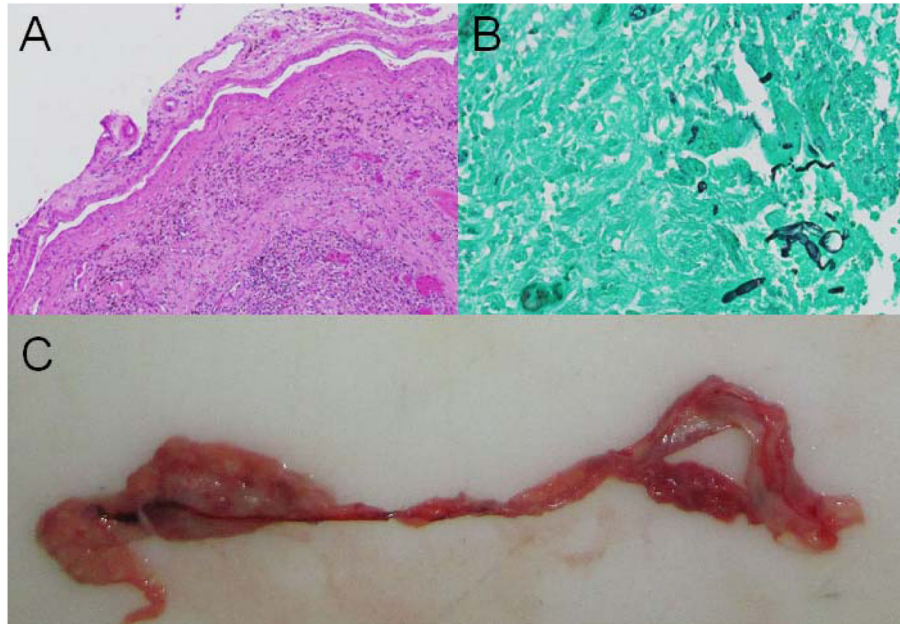
**Figure 1. Imaging Findings**

A. Case 1 (1) Hospital day 1, diffusion weighted imaging (DWI) with acute upper pontine/lower midbrain ischemic stroke suggestive of small vessel etiology (2) Hospital day 3, repeat MRI with direct extension of stroke into right thalamus suggestive of a large vessel etiology (3) Hospital day 4, CTA with occlusion of right superior cerebellar artery

B. Case 2 (1) Hospital day 1, DWI with acute left pontine and cerebellar ischemic strokes suggestive of large vessel etiology (2) Hospital day 15, T1 sequence with contrast revealing an abscess adjacent to the left cerebellopontine angle (3) Hospital day 15, lumbar MRI T1 sequence with contrast showing extradural enhancement and clumping of nerve roots suggesting arachnoiditis

C. Case 3 (1) Hospital day 1, DWI with right small vessel internal capsule stroke (2) Hospital day 7, DWI with right internal capsule and left internal capsule genu stroke (3) Hospital day 7, T1 sequence with contrast also revealing a left sided cerebellopontine abscess





**Figure 2. Pathology Findings**

- A. Hematoxylin and eosin stain of mycotic aneurysm of the left superior cerebellar artery
- B. Higher power view of Gomori's methenamine silver stain of hyphal elements within the mycotic aneurysm of the superior cerebellar artery
- C. Gross photograph: mycotic aneurysm of the left superior cerebellar artery

**Table 1**

## Case Presentation, Lab and Imaging Summary

	Case 1	Case 2	Case 3
Ages	78	78	70
Gender	Male	Female	Female
Presenting symptoms and signs	Headache, left sided weakness, dysarthria	Headache, vertigo, nausea, dysmetria, ataxia	Headache, nuchal rigidity, fever, dysarthria, dysmetria
Last epidural injection prior to admission	2 weeks	2 weeks	One month
CSF results:	N/A		
Nucleated cells (per $\mu$ L)		2,974	1485
Polymorphonuclear cells (%)		93	53
Lymphocytes (%)		4	36
Red cells (per $\mu$ L)		468	6
Protein (mg/dL)		245	290
Glucose mg/dL)		28	12
Gram stain		No bacteria	No bacteria
Bacterial culture		No growth	No growth
CDC <sup>a</sup> Exserohilum PCR		Positive	Negative
AFB culture		No growth	No growth
Aspergillus antigen index		Negative	Negative
Methenamine silver stain		N/A	Negative
Initial Imaging results	Pontine/midbrain small vessel ischemic stroke	Pontine, cerebellar ischemic strokes suggesting large vessel etiology	Thalamic/internal capsule small vessel ischemic stroke
Pathologic/Autopsy results	<i>Exserohilum rostratum</i>	Fungus with hyphal features	N/A

<sup>a</sup>Centers for Disease Control