The Upside of Bias: A Case of Chronic Meningitis Due to *Sporothrix Schenckii* in an Immunocompetent Host

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Abstract

Chronic meningitis of unknown etiology is a vexing illness for patients and clinicians. Identification of the correct pathogen can be challenging and time consuming, leading to delays in appropriate treatment. Although *Sporothrix schenckii* is a recognized and treatable cause of chronic meningitis, neurologists and infectious diseases physicians may not regularly evaluate for *Sporothrix* infection. We describe an immunocompetent patient with chronic meningitis who partially responded to empiric fluconazole. Prompted by a recent culture-confirmed case of meningeal sporotrichosis, we tested for *S schenckii* antibodies from the cerebrospinal fluid, which were positive. His clinical and functional status improved, and the *S schenckii* antibody titer decreased with itraconazole therapy. Clinicians should consider *S schenckii* in the differential diagnosis for chronic meningitis, even in immunocompetent patients, particularly when the clinical picture does not respond to standard empiric therapy.

Keywords

Sporothrix schenckii, sporotrichosis, chronic meningitis, fungal, central nervous system infection

Case Report

A 34-year-old-man with no past medical history presented with 3 months of fever, headache, and confusion. The patient was originally from Mexico but had lived in Northern California for over a decade. He had not traveled out of state but had driven through central California on multiple occasions. He worked on construction jobs involving roofing, laying tile, and removing carpet. A family member was recently diagnosed with tuberculosis. He denied alcohol, tobacco, or other substance use.

He presented to a local emergency department where a head computed tomography (CT) scan was normal. Lumbar puncture (LP) revealed 500 white blood cells (WBC)/mm³ (86% lymphocytes), low glucose, and elevated protein (Table 1). Cerebrospinal fluid (CSF) bacterial culture and herpes simplex virus 1 and 2 polymerase chain reaction were negative. He was treated empirically with acyclovir, ampicillin, vancomycin, and ceftriaxone for 7 days.

His headache and fever fluctuated over the next 2 months. He returned to a local hospital where LP demonstrated an elevated opening pressure of 30 cm H₂O with ongoing lymphocyte-predominant pleocytosis, low glucose, and elevated protein. He was treated with various antimicrobial agents including fluconazole before transfer to our hospital.

Upon arrival to our hospital, 3 months after initial presentation, he was confused and disoriented. No skin lesions were present. Lumbar puncture again demonstrated a lymphocyte-predominant pleocytosis with persistently low, although improved, glucose and elevated protein. An extensive evaluation of the CSF and serum for an infectious etiology was negative (Table 2). Magnetic resonance imaging (MRI) of the brain and spine showed meningeal enhancement and subacute infarcts in the basal ganglia (Figure 1). A chest CT scan demonstrated a 6-mm nodule in the left upper lobe. Based on epidemiologic risk factors and the CSF profile, meningitis due to *Mycobacterium tuberculosis* and *Coccidioides* species were high on the differential diagnosis, although evaluation for these diagnoses was negative (Table 2).

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Table 1. Lumbar Puncture Results Over the Course of Illness.

Time Since Initial Presentation	Interval Events	Cerebrospinal Fluid (CSF) Profile				
		WBC Cells/mm ³ , (% Lymphocytes)	Glucose, mg/dL	Protein, mg/dL	Opening Pressure, cm H ₂ O	<i>Sporothrix Schenckii</i> Antibody Titer
0 month	3 months after symptom onset on initial presentation to local hospital	500 (86)	19	170	—	—
2 months	Received 7 days of empiric antibiotic therapy 2 months prior	330	18	168	30	—
3 months	On admission to our hospital	263 (69)	32	184	—	—
5 months	Started antituberculous therapy and fluconazole 2 months prior	2	33	98	—	—
18 months	Discontinued fluconazole 1 month prior	183 (54)	23	241	—	—
22 months	After restarting on fluconazole	128 (77)	16	466	—	1:8
25 months	Initiated itraconazole 2 months prior	16 (89)	34	114	—	1:4
37 months	After 1 year of itraconazole treatment	3 (91)	48	50	—	1:2

Abbreviation: WBC, white blood cells.

He was empirically treated with standard 4-drug therapy (rifampin, isoniazid, pyrazinamide, and ethambutol) for tuberculous meningitis and fluconazole for coccidioidal meningitis with clinical improvement. Two months after initiation of therapy, a repeat LP demonstrated 2 WBC/mm³ low glucose and improved protein. The fluconazole was discontinued, which resulted in recurrent symptoms and worsened CSF profile. He was restarted on fluconazole but lost to follow-up. One year later, he was readmitted to our hospital with headaches after discontinuing fluconazole 1 month prior to admission. An LP 18 months after initial presentation again revealed a lymphocytic pleocytosis, low glucose, and elevated protein.

A few months prior, a 25-year-old-man with diabetes mellitus was admitted with headache and unsteady gait. He tended rose bushes and had 2 healthy cats at home. Brain MRI demonstrated marked ventricular dilatation with extensive meningeal enhancement. Lumbar puncture revealed 167 WBC/mm³ (70% lymphocytes), glucose 43 mg/dL, protein 388 mg/dL, and 4 oligoclonal bands unique to the CSF. The CSF acid-fast bacilli culture yielded growth identified by molecular testing as *S. schenckii*. *Sporothrix* antibody titer by latex agglutination (LA) was 1:16 in the CSF and 1:8 in the serum (Mayo Medical Laboratories, Rochester, Minnesota). Influenced by the availability heuristic,¹ this recent case of culture-positive *Sporothrix* meningitis prompted us to evaluate the CSF of our patient for antibodies to *S. schenckii*. LA for antibodies to *S. schenckii* in the CSF returned positive at a titer of 1:8 (Mayo Medical Laboratories).

The patient declined treatment with liposomal amphotericin B and was started on itraconazole. Two months later, repeat LP revealed improved CSF profile. *Sporothrix* antibody titer from the CSF was 1:4, and serum antibodies were negative. After 1 year of itraconazole therapy, LP demonstrated 3 WBC/mm³ (91% lymphocytes) with normal glucose and

protein. *Sporothrix* antibodies from the CSF declined 4-fold from baseline to 1:2, and he has returned to work.

Discussion

Sporotrichosis is caused by thermally dimorphic fungi belonging to the genus *Sporothrix*, which are found in soil and plant material throughout the world. Molecular methods have reclassified *S. schenckii* into several different pathogenic species comprising the *S. schenckii* complex.² While the incidence of sporotrichosis may be on the rise in certain tropical and subtropical regions where the infection is endemic,³ data are limited regarding its incidence in the United States and other countries in which *Sporothrix* infection is less common and not a reportable disease.⁴

Infections usually result from traumatic inoculation of the skin with soil or vegetation contaminated by the fungus. Zoonotic transmission of *Sporothrix* through animal scratches or bites is well described,⁵ and veterinarians are a known risk group for zoonotic transmission from infected animals, especially cats.⁶

Most *Sporothrix* infections in immunocompetent individuals are limited to cutaneous and subcutaneous manifestations. Erythematous papulonodular lesions arise from sites of skin trauma and spread proximally along lymphatic vessels. Extracutaneous involvement occurs via hematogenous or contiguous spread of local disease. Musculoskeletal disease, including osteomyelitis and septic arthritis, is the most frequent extracutaneous site of infection.⁷ Pulmonary involvement arises after direct inhalation of the fungus or hematogenous spread from another source and can present with cavitary or noncavitary lesions.⁸

Meningeal sporotrichosis is rare and can present with associated complications of meningitis, such as infarcts and hydrocephalus.⁹ The CSF profile typically demonstrates a moderate lymphocyte-predominant pleocytosis with low glucose, elevated protein, immunoglobulin G index, and oligoclonal bands.^{9,10}

Table 2. Testing Performed on Cerebrospinal Fluid (CSF) and Serum as Part of the Chronic Meningitis Evaluation (All Negative or Within Normal Limits Unless Otherwise Indicated).^a

Specimen	Test
CSF	<p>Histoplasma capsulatum Ab by immunodiffusion and complement fixation</p> <p>Histoplasma capsulatum Ag</p> <p>VDRL for syphilis</p> <p>Varicella zoster virus PCR</p> <p>Coccidioides species Ab by immunodiffusion and complement fixation</p> <p>Cryptococcal Ag</p> <p>Mycobacterium tuberculosis PCR</p> <p>Universal PCR using bacterial 16S rDNA and fungal 28S rDNA primers</p> <p>β-D-glucan (tested after long-term therapy with fluconazole)</p> <p>Bacterial, fungal, and AFB culture (on multiple and large volume samples)</p> <p>Immunoglobulin G index 2.3</p> <p>Oligoclonal bands: >5 unique well defined γ restriction bands in CSF</p> <p>Sporothrix schenckii Ab by card latex agglutination</p> <p>1:8 (January 2014)</p> <p>1:4 (April 2014)</p> <p>1:2 (April 2015)</p>
Serum	<p>ANA, dsDNA, rheumatoid factor, anti-Sm Ab, anti-RNP Ab, anti-SSA Ab, and anti-SSB Ab</p> <p>HIV Ab</p> <p>RPR for syphilis</p> <p><i>Borrelia burgdorferi</i> Ab</p> <p><i>Blastomyces dermatitidis</i> Ab</p> <p><i>Histoplasma capsulatum</i> Ab by immunodiffusion and complement fixation</p> <p><i>Histoplasma capsulatum</i> Ag</p> <p><i>Coccidioides</i> species Ab by immunodiffusion and complement fixation</p> <p>Cryptococcal Ag</p> <p>West Nile virus immunoglobulin G and immunoglobulin M Ab</p> <p>Quantiferon Gold test for tuberculosis</p> <p>C-reactive protein 13.6 mg/L</p> <p>Erythrocyte sedimentation rate 24 mm/h</p> <p>Angiotensin-converting enzyme (ACE)</p> <p><i>Balamuthia mandrillaris</i> Ab</p> <p><i>Acanthamoeba</i> Ab</p> <p>Multiple blood cultures</p>
Other	Urine <i>Histoplasma</i> Ag, tuberculin skin test (purified protein derivative)

Abbreviations: CSF, cerebrospinal fluid; Ab, antibody; Ag, antigen; PCR, polymerase chain reaction; AFB, acid fast bacilli; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory; anti-Sm, anti-Smith; anti-RNP, anti-ribonucleoprotein; anti-SSA, anti-Sjogren's syndrome antigen A; anti-SSB, anti-Sjogren's syndrome antigen B.

^a Bold-faced type indicates an abnormal result.

Extracutaneous and disseminated sporotrichosis, including meningeal disease, are more common in individuals with immune compromise due to AIDS, alcohol use, cirrhosis,

Figure 1. Magnetic resonance imaging (MRI) of the brain with contrast. Leptomeningeal enhancement was most pronounced in the basilar cisterns (A) and the bilateral fifth and sixth cranial nerves (B) as shown in these gadolinium-enhanced postcontrast T1 images. Foci of reduced diffusion were seen in the left caudothalamic groove, left globus pallidus, and left thalamus (C) as shown in the T2-weighted trace sequence. Moderate communicating hydrocephalus was also present (D) as shown in this T1 sequence.

solid organ transplantation, use of immunosuppressive medications, or malignancy.⁴ Our patient had a negative HIV test, no history of heavy alcohol use, and no known immunosuppression. In 1 study of 1697 patients with sporotrichosis, Galhardo et al found that 2 of the 17 HIV-infected individuals in the cohort developed meningeal disease compared to none of the HIV-uninfected individuals.⁹ When they reviewed 21 cases of meningeal sporotrichosis in the literature, underlying immunosuppression was present in 15 patients. In only half of these cases (and in no individuals who were immunocompetent) was skin or joint involvement observed prior to or in conjunction with meningeal disease, suggesting that isolated meningitis without preceding skin involvement, as was the case with our patient, may not be an atypical presentation.

In addition to lack of awareness of *S schenckii* as a cause of chronic meningitis, diagnosis may be delayed in cases of isolated central nervous system (CNS) disease due to difficulty recovering the organism from the CSF. Culture is considered the gold standard for diagnosis; however, growth can take up to 1 month, and the fungus is challenging to isolate if fungal burden is low.^{3,4} In 1 study of 7 cases of meningeal sporotrichosis, the interval from symptom onset to positive culture ranged from 3 to 11 months.¹⁰

Antibody assays have not been validated for use in standard clinical practice but may assist in establishing a diagnosis. Antibody detection by enzyme immunoassay (EIA) and LA have varying degrees of utility. In 1 study, detection of serum antibodies to *Sporothrix* antigen by EIA was 100% sensitive in culture-proven cutaneous sporotrichosis; however, low cross-reactivity occurred with other infections.¹¹ In another study of culture and mycological examination-confirmed *Sporothrix* cases compared with various controls, serum EIA was 89% sensitive and 82% specific overall and 100% sensitive for extracutaneous disease.¹² Sensitivity and specificity of LA testing have been demonstrated to be as high as 94% and 100%, respectively, when compared to culture-confirmed cases of sporotrichosis and other infections.¹³

Systematic evaluation of serological methods to detect antibodies in specimens other than serum from patients with sporotrichosis has not been performed. In a case series of culture-confirmed meningeal sporotrichosis by Scott et al, antibodies were detected in the CSF and serum from all 7 cases using LA and EIA.¹⁰ No cross-reactivity occurred in individuals with meningeal infections due to other pathogens. In another study, *Sporothrix* antibodies were detected by EIA in the serum of 26 patients with extracutaneous disease including 4 with CNS involvement.¹⁴ Mayo Medical Laboratories uses an LA assay similar to that developed by Scott et al; for this assay, titers $\geq 1:8$ in the serum and any detectable antibody in the CSF is considered positive.

Itraconazole is the treatment of choice for many forms of sporotrichosis and can be used relatively safely for long courses. A lipid formulation of amphotericin B is first line for the initial treatment of meningeal sporotrichosis followed by oral itraconazole for at least 12 months, although our patient has been successfully treated with oral azole therapy alone. Our patient had a partial response to empiric fluconazole but ultimately stopped responding. Fluconazole is only moderately active against *S. schenckii* and should not be used as first-line therapy.¹⁵

Conclusion

A positive serological test does not constitute a definitive diagnosis of sporotrichosis, but the clinical syndrome and response to itraconazole therapy with subsequent decline in *Sporothrix* antibodies observed in our patient were highly suggestive of meningeal sporotrichosis. We may have avoided the 2-year delay in diagnosis for our patient if CSF and serum from patients with chronic meningitis were systematically tested for *Sporothrix* antibodies. Clinicians should consider serological testing for *Sporothrix* antibodies from the CSF and serum in patients with chronic meningitis, especially if routine studies have not determined the diagnosis or response to empiric therapy is incomplete.

Authors' Note

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Declaration of Conflicting Interests

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