ILLUSTRATIVE CASE

Not All Aseptic Meningitis Is Created Equal

Sameer Pathare, MD[a,b,c]

CASE

A 16-year-old Chinese American boy was brought to the emergency department by his parents after 1 day of headache, neck pain, fever, and fatigue. He denied any cough, vomiting, diarrhea, or weight loss, but he did report having an erythematous, papular skin rash along his hairline for the past 6 weeks. A dermatologist evaluated the rash and diagnosed impetigo. A trial of topical bacitracin and oral cephalexin temporarily improved the rash. He is a native of southern California, was previously healthy, was fully immunized, had no previous hospitalizations, and had no pertinent family history. It is of note that he had no ill contacts, had no recent illnesses, and denied travel outside of southern California.

On examination, the patient had a temperature of 38.9°C, a heart rate of 78 beats per minute, a blood pressure reading of 110/46 mm Hg, a respiratory rate of 16 breaths per minute, and an oxygen saturation of 96% on room air. He was not ill-appearing. His lungs were clear to auscultation, and his heart sounds suggested a regular rate and rhythm with no murmurs. His abdomen was soft, nontender, nondistended, and without hepatosplenomegaly. On neurologic examination, he was alert and oriented with no focal findings; specifically, he had no nuchal rigidity or photophobia. His skin examination was notable for crusted excoriated papules along the anterior hairline and a solitary lesion on the right forearm. Laboratory evaluation of peripheral blood revealed a white blood cell (WBC) count of 11.3 k/μL, with a differential of 86.2% neutrophils, 7.2% lymphocytes, 4.8% monocytes, and 1.1% eosinophils; a hemoglobin level of 12 g/dL; a platelet concentration of 285 k/μL; a C-reactive peptide level of 19.9 mg/L; a erythrocyte sedimentation rate of 27 mm/hour, a sodium concentration of 139 mmol/L; a potassium level of 3.8 mmol/L; a chloride level of 105 mmol/L; a bicarbonate level of 27 mmol/L; a blood urea nitrogen concentration of 12 mg/dL; a creatinine level of 0.9 mg/dL; a glucose measurement of 98 mg/dL; an aspartate aminotransferase level of 23 U/L; an alanine aminotransferase concentration of 23 U/L; and a total bilirubin reading of 0.5 mg/dL. Noncontrast computed tomography of the head revealed normal results. A lumbar puncture (LP) was performed in the emergency department in response to the patient's persistent headaches. Cerebrospinal fluid (CSF) analysis revealed a WBC count of 187/μL, with a differential of 24% neutrophils, 40% lymphocytes, 33% monocytes, and 3% eosinophils; a red blood cell count of 13/μL; a protein level of 127 mg/dL; and a glucose reading of 47 mg/dL. A Gram-stain revealed many WBCs

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but no organisms. Enterovirus (EV) and herpes simplex virus (HSV) polymerase chain reaction tests were sent, and, while awaiting culture results, the patient was started on ceftriaxone (2 g every 12 hours) and vancomycin (1 g every 6 hours) in response to the CSF findings of elevated WBCs, elevated protein, and low glucose. He was admitted to the hospital, and, within 24 hours, his headache improved and his fever resolved. His blood and CSF bacterial cultures revealed negative results. His polymerase chain reaction tests were negative for both EV and HSV. He was back to his neurologic baseline, and he was discharged from the hospital on hospital day 2 because of the improvement in his symptoms.

Question: What is the differential diagnosis for a teenager with aseptic meningitis?

Discussion

In this age group, the differential diagnosis for acute aseptic meningitis is extensive. According to Seehusen et al,[1] cell count and differential alone cannot distinguish between bacterial and nonbacterial meningitis. Of patients with bacterial meningitis, 87% will have CSF WBCs >1000/mm^3, whereas having <100 CSF WBCs/mm^3 is more common with viral meningitis.[1] Lymphocytosis is nonspecific and can be seen in viral, fungal, and tuberculous meningitis.

Viral etiologies of meningitis include the nonpolio EVs, which are ubiquitous and present year-round in southern California, with increased incidence in the summer months. West Nile virus has a similar pattern, peaking in the summer when mosquitoes are plentiful. HSV can cause either aseptic meningitis or meningoencephalitis. *Mycobacterium tuberculosis*, although unlikely, is also a possibility but would only be expected in this age group if immunosuppression were present.

In this patient, the original LP findings revealed a modest elevation of WBCs with lymphocyte predominance. The presence of eosinophils suggests parasitic or fungal etiologies. Parasites can include amoeba and helminths, such as those causing neurocysticercosis.[1] Fungal possibilities include those present in the soil of the southern California deserts, such as *Coccidioides imitus*, and those not typically found in southern California, such as *Histoplasma capsulatum* and *Blastomyces dermatitidis*.

CASE CONTINUATION

The patient continued to have persistent headaches, neck pain, and intermittent vomiting for 2 weeks at home, which prompted his return for medical attention. There was concern about the possibility of increased intracranial pressure and a subacute central nervous system infection. A magnetic resonance imaging (MRI) scan of the brain with contrast was performed, the results of which were normal, without hydrocephalus or brain abscess. Because of the persistence of severe headaches and the development of photophobia, a repeat LP was performed. The repeat CSF test revealed a WBC count of 892/μL, with a differential of 33% neutrophils, 47% lymphocytes, 5% eosinophils, and 10% monocytes; a protein level of 218 mg/dL; and a glucose reading of <20 mg/dL. An infectious disease consultation was requested in response to the persistently abnormal CSF findings.

Question: What is the differential diagnosis for chronic meningitis with elevated protein and hypoglycorrhachia?

Discussion

The persistence of inflammatory changes coupled with the additional findings of elevated protein and depressed glucose in the CSF narrows the differential diagnosis considerably. Most cases of chronic meningitis can be divided into infectious, autoimmune, and neoplastic etiologies, with the infectious etiology being most common.[2] A brain abscess is a consideration, with the members of the *Streptococcus anginosus* group (*Streptococcus intermedius*, *S anginosus*, and *Streptococcus constellatus*) increasingly recognized as pathogens.[3–5] However, a brain MRI with normal results that do not reveal a contrast-enhancing lesion effectively rules out a brain abscess. In addition, pretreated bacterial meningitis needs to be considered if antibiotics were given before the original LP, which was not the case with this patient. *Brucella* and *Leptospira* are also rare causes of chronic menigitis.[6–8]

Other more likely possibilities include mycobacterial and fungal infections (see Table 1). Tuberculous meningitis is usually confined to children <2 years of age or to immunocompromised patients and often presents with disseminated disease. The presence of eosinophilia (defined as >10 eosinophils/mm3)[1] is unusual and warrants further evaluation for fungal or parasitic etiologies. *Cryptococcus*

TABLE 1 CSF Parameters for Tuberculous and Fungal Meningitis

Organism	CSF WBC Count	Differential	Glucose	Protein	CSF Testing
M tuberculosis	Increased	Mononuclear	Decreased	Increased	AFB smear, PCR and AFB culture
C neoformans	Increased or normal	Mononuclear	Decreased	Increased	India ink, cryptococcal antigen, fungal culture
C immitus	Increased or normal	Early neutrophilic, lymphocytic, or eosinophilic	Decreased	Increased	Complement fixation serum antibody, fungal culture
H capsulatum	Increased	Mononuclear	Decreased	Increased	Histoplasma antigen, fungal culture
B dermatitidis	Increased	Early neutrophilic or lymphocytic	Decreased	Increased	Fungal culture

Adapted from Zunt JR, Baldwin KJ. Chronic and subacute meningitis. *Continuum (Minneap Minn)*. 2012;18(6):1290–1318. AFB, acid-fast bacilli; PCR, polymerase chain reaction.

neoformans is the most common central nervous system fungal infection in immunocompromised patients, particularly in those with HIV. Endemic mycoses such as *Histoplasma*, *Blastomyces*, and *Coccidioides* may all present with modestly elevated WBCs, elevated protein, and low glucose, even in healthy patients. Furthermore, parasites such as cestodes, trematodes, and protozoans can infect the central or peripheral nervous system, but are less common.[9]

CASE RESOLUTION

A purified protein derivative skin test was placed to further evaluate for tuberculous meningitis and revealed negative results at 48 hours. Because chronic skin lesions can also be seen in disseminated fungal disease, a skin punch biopsy was obtained from the solitary lesion on the patient's forearm. *Coccidioides* titers by complement fixation were sent to a reference laboratory, and fluconazole was started empirically. The pathology results from a skin biopsy revealed mild to moderate chronic active inflammation with a necrotizing granuloma. An acid-fast bacilli stain yielded negative results, but the results of a periodic acid-Schiff stain were positive for fungal infection, with 1 intact spherule suggestive of *Coccidioides* (Fig 1).

The patient's CSF cultures grew fungus at day 5, which was eventually identified as *Coccidioides immitus/posadasii*. His serum *Coccidioides* serology test by complement fixation revealed positive results at a 1:128 ratio, whereas his quantitative serum immunoglobulins were at normal levels and his HIV enzyme-linked immunosorbent assay was nonreactive.

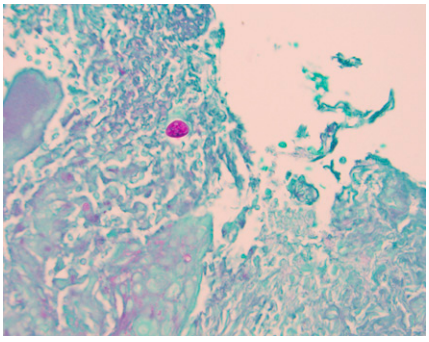

FIGURE 1 Intact spherule on skin biopsy.

He required serial LPs to help manage his headache symptoms, each time with transient improvement. His opening pressure was measured on subsequent LPs and was >40 cm water (normal: <20 cm water[10]).Acetazolamide therapy was initiated to help manage his increased intracranial pressure. Because of the need for continued LPs to manage his intracranial pressure and headache, a ventriculoperitoneal shunt was placed. Further history revealed that he most likely had exposure to *Coccidioides* in the California high desert at an outdoor shopping mall ~1 to 2 months before onset of his symptoms. After a 3-week hospitalization, he has been doing well as an outpatient for well over 1 year on oral fluconazole therapy.

CONCLUSIONS

C immitus and *C posadasii* are endemic fungi found in the southwestern United States, northern Mexico, and some areas of South America, causing the disease commonly known as "Valley Fever." The fungi are found in warm, sandy soil, in climates with hot, arid summers and mild rainfall. The dimorphic fungi grow as hyphae in the soil. Spores (arthroconidia) are stable and can remain viable for many years. Infection is through inhalation of the aerosolized spores. When inhaled into the lungs after soil disruption by wind, construction, or cultivation, the fungus initiates growth by forming a spherule. The spherule expands and undergoes nuclear division, producing endospores. When spherules rupture the endospores are released, each is capable of developing into new spherules, which can disseminate hematogenously to any organ.[11]

Most coccidioidal infections are asymptomatic or cause a self-limited disease with mild respiratory infection; therefore, a delay in diagnosis is common. However, dissemination can occur more commonly in Filipinos, African Americans, pregnant women, and immunocompromised patients (especially those with HIV or on immunosuppressive therapy).[12,13] Disseminated diseases include pneumonia, soft tissue infection, osteomyelitis, and meningitis.

Pediatric patients hospitalized with coccidioidomycosis often have severe and sometimes life-threatening disease. In a case series of 33 hospitalized pediatric patients in central California, 6% had meningitis.[14] When discussing disseminated disease, the percentage of meningitis rises to 30% to 50%, and hydrocephalus subsequently develops in 20% to 50% of patients with coccidioidal meningitis. For patients with increased intracranial pressure at the time of diagnosis, the Infectious Disease Society of America recommends medical therapy, imaging (including brain MRI scans with and without contrast), and repeated LPs as initial management. They also recommend obtaining a neurosurgical consultation for ventriculoperitoneal shunt placement in cases in which increased intracranial pressure does not resolve.[15] In a study by McCarty et al,[14] 3% of patients with coccidioidal meningitis required shunt placement.[12] Coccidioidal meningitis treatment involves 4 weeks of induction with high-dose fluconazole, whereas refractory coccidioidal meningitis treatment regimens also include intrathecal amphotericin B. All initial treatment regimens are followed by daily azole maintenance treatment for life.[9,15]

In summary, aseptic meningitis is a benign self-limited disease, particularly when it is of viral etiology. Patients who are not improving as expected require a broader evaluation and approach, particularly during the winter season, when viral etiologies are less common. A complete evaluation should include routine CSF studies, such as WBC count with differential, tests for protein and glucose levels, cultures, and tests of opening pressure. As this case reveals, the presence of elevated WBCs, elevated protein, low glucose, and eosinophils in the CSF of a patient who resides or has traveled to the southwestern United States should lead to the consideration of *Coccidioides* infection as the diagnosis. An infectious disease consultation should be obtained when the CSF parameters are not consistent with those expected for a self-limited disease. Opening pressure on CSF is not routinely performed in pediatrics; however, it may be

valuable in the evaluation and management of coccidioidal meningitis. When disseminated *Coccidioides* is suspected, diagnostic testing of *Coccidioides* serum antibodies, fungal culture, CSF *Coccidioides* titers by complement fixation, opening pressure, and biopsy of any skin lesions should be performed.

LEARNING POINTS

- A chronic skin rash may be a subtle finding of systemic disease.
- Elevated protein, low glucose, and eosinophilia in the spinal fluid may indicate fungal or parasitic disease and warrant further evaluation, including an infectious disease consultation.
- CSF opening pressures are helpful in the management of fungal meningitis.
- Fungal meningitis may lead to prolonged increased intracranial pressure, often requiring the placement of a ventriculoperitoneal shunt.
- Coccidioidal meningitis requires azole treatment for life.

REFERENCES

1. Seehusen DA, Reeves MM, Fomin DA. Cerebrospinal fluid analysis. *Am Fam Physician*. 2003;68(6):1103–1108
2. Baldwin KJ, Zunt JR. Evaluation and treatment of chronic meningitis. *Neurohospitalist*. 2014;4(4):185–195
3. Maliyil J, Caire W, Nair R, Bridges D. Splenic abscess and multiple brain abscesses caused by Streptococcus intermedius in a young healthy man. *Proc Bayl Univ Med Cent*. 2011;24(3):195–199
4. Carpenter J, Stapleton S, Holliman R. Retrospective analysis of 49 cases of brain abscess and review of the literature. *Eur J Clin Microbiol Infect Dis*. 2007;26(1):1–11
5. Deutschmann MW, Livingstone D, Cho JJ, Vanderkooi OG, Brookes JT. The significance of Streptococcus anginosus group in intracranial complications of pediatric rhinosinusitis. *JAMA Otolaryngol Head Neck Surg*. 2013;139(2):157–160
6. Bodur H, Erbay A, Akinci E, Colpan A, Cevik MA, Balaban N. Neurobrucellosis in an endemic area of brucellosis. *Scand J Infect Dis*. 2003;35(2):94–97
7. Mantur BG, Akki AS, Mangalgi SS, Patil SV, Gobbur RH, Peerapur BV. Childhood brucellosis–a microbiological, epidemiological and clinical study. *J Trop Pediatr*. 2004;50(3):153–157
8. Wilhelm CS, Marra CM. Chronic meningitis. *Semin Neurol*. 1992;12(3):234–247
9. Walker MD, Zunt JR. Neuroparasitic infections: cestodes, trematodes, and protozoans. *Semin Neurol*. 2005;25(3):262–277
10. Rangel-Castilla L, Gopinath S, Robertson CS. Management of intracranial hypertension [published correction appears in *Neurol Clin*. 2008;26(3):xvii]. *Neurol Clin*. 2008;26(2):521–541, x
11. Nguyen C, Barker BM, Hoover S, et al. Recent advances in our understanding of the environmental, epidemiological, immunological, and clinical dimensions of coccidioidomycosis. *Clin Microbiol Rev*. 2013;26(3):505–525
12. Mathisen G, Shelub A, Truong J, Wigen C. Coccidioidal meningitis: clinical presentation and management in the fluconazole era. *Medicine (Baltimore)*. 2010;89(5):251–284
13. Ruddy BE, Mayer AP, Ko MG, et al. Coccidioidomycosis in African Americans. *Mayo Clin Proc*. 2011;86(1):63–69
14. McCarty JM, Demetral LC, Dabrowski L, Kahal AK, Bowser AM, Hahn JE. Pediatric coccidioidomycosis in central California: a retrospective case series. *Clin Infect Dis*. 2013;56(11):1579–1585
15. Galgiani JN, Ampel NM, Blair JE, et al. Executive summary: 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63(6):717–722

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