A 20-Year-Old Woman With Headache and Transient Numbness

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Case Presentation

A 20-year-old woman with a history of migraine presented with 4 days of progressive ptosis, discoordination, paresthesias in her hands and feet progressing to her forearms and shins, and diplopia after an upper respiratory tract illness the prior week. Laboratory evaluation at this time was notable for a positive immunoglobulin (Ig)G Lyme antibody (negative IgM), antinuclear antibody (ANA) 1:80 in a speckled pattern, and a positive GD1b antibody. Lumbar puncture (LP) showed white blood cells 30/ μ L (87% lymphs), red blood cells 3/ μ L, protein 68 mg/dL, glucose 49 mg/dL, and a negative Gram stain and bacterial culture. Brain magnetic resonance imaging (MRI) was normal. She was diagnosed with Miller-Fisher variant Guillian-Barré Syndrome and treated with a 5-day course of intravenous Ig, after which her symptoms markedly improved. She was evaluated in the clinic 3 times over the course of the next 4 months, and was found to have a normal neurologic examination except for absent reflexes at each clinic visit, and was otherwise asymptomatic. She was then lost to follow-up.

Two-and-a-half years later, she again sought medical attention after a transient sensory disturbance which she described as numbness that began in the roof of her mouth with progression over the course of 10 minutes to involve her entire face and left arm. The numbness lasted 1 hour and then fully resolved. She had experienced a minor headache 2 hours prior that was alleviated by caffeine. Neurologic examination at this time was normal, but a brain MRI showed abnormal leptomeningeal enhancement (Figure 1), and a subsequent LP showed a lymphocytic pleocytosis with a markedly elevated protein and low glucose (Table 1). She underwent an extensive evaluation but no cause for the leptomeningeal enhancement on MRI or the abnormal cerebrospinal fluid (CSF) profile was identified.

Two months later, she began to develop progressively worsening vertigo, headache, nausea, and diplopia. The MRI showed new enhancing lesions in the brain and enhancement of the leptomeninges along the entire length of the spinal cord (Figure 1). Evaluation of the spinal fluid at this time again

showed CSF pleocytosis and hypoglycorrhachia with an opening pressure of 14 cm water (Table 1), but a cause for these abnormal radiologic and CSF findings could not be identified. Neurosurgical evaluation deemed a biopsy of the affected area would subject the patient to an unacceptably high risk of serious permanent neurologic deficit, and therefore biopsy was deferred. She was placed on empiric treatment for tuberculous meningitis with rifampin, isoniazid, pyridoxine, ethambutol, and a steroid taper. Her symptoms improved rapidly and she was asymptomatic over the course of the next 2 months, with an interval LP demonstrating improvement in the CSF profile (Table 1), and brain MRI showing near resolution of her leptomeningeal enhancement. Unfortunately, after completing her steroid taper she developed nausea, vomiting, and a headache that was worse when lying in the recumbent position. The MRI showed worsening hydrocephalus with return of contrast enhancement of the basilar leptomeninges, as well as the presence of fluid in the maxillary sinus with mucosal thickening. A right inferior nasal turbinate biopsy was unrevealing. Lumbar puncture again showed a CSF lymphocytic pleocytosis with elevated protein and low glucose (Table 1). She was restarted on dexamethasone. One month later, she had a generalized tonic-clonic seizure that was witnessed by her boyfriend. The MRI showed worsening hydrocephalus, and a LP revealed an elevated opening pressure of 40 cm water. A ventriculoperitoneal (VP) shunt was placed at this time to

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Figure 1. Brain magnetic resonance imaging. A, Axial T1 sequence with gadolinium contrast 30 months after initial presentation showing leptomeningeal enhancement along the ventral surface of both the cerebral peduncles (arrow). B, Axial T1 sequence with gadolinium contrast 2 months later showing new enhancing lesions in the left cerebral peduncle (arrow) and worsening communicating hydrocephalus. C, Axial T1 sequence with gadolinium contrast 37 months after initial presentation, demonstrating marked increase in contrast enhancement of the basilar meninges compared to (A). D, Axial diffusion-weighted imaging at 37 months showing an ischemic infarct in the left thalamus. Imaging artifact in the right temporal region is caused by the patient's ventriculoperitoneal shunt.

relieve the hydrocephalus. Leptomeninges was biopsied during shunt placement but the biopsy was benign. Placement of the shunt improved her hydrocephalus, but she continued to experience headache, nausea, and vomiting. Two weeks later, she developed altered mental status and was unable to walk without assistance, and was again admitted to the hospital.

Past medical history was significant for migraine. She had received the BCG vaccine when young in Ukraine before immigrating to the United States with her parents before the age of 10, and had a positive purified protein derivative (PPD) test. She had last traveled back to Ukraine in 2006, with no known tuberculosis (TB) contacts. She had traveled extensively within the United States, and had also briefly visited Mexico and Colombia a number of years earlier. There were no known

dietary exposures, and she did not have pets. Before becoming ill, she had worked at a health food grocery store and was attending college. Her brother had type I diabetes, but there was otherwise no significant medical history in the family.

Neurologic Examination

Examination on admission to the hospital showed an ill-appearing young woman with a supple neck, who was somnolent but able to open her eyes to voice and able to follow simple commands, with intact repetition and a digit forward span of 7. On cranial nerve examination, she was hypophonic and dysarthric with a nasal quality to her voice and had difficulty producing guttural sounds. She also had a weak gag. She

Table 1. Cerebrospinal Fluid Profiles.

Months After Initial Presentation	0 (Initial)	30	32	34	35	36
WBC with differential count, n/mm ³	30 (87% L, 1% N, 11% M)	105 (84% L, 2% N, 14% M)	52 (92% L, 3% N, 5% M)	11 (83% L, 9% N, 7% M)	86 (88% L, 9% N, 3% M)	144 (35% L, 30% N, 35% M)
RBC, n/mm ³	3	161	3	9	4	25
Protein, mg/dL	68	210	186	71	206	206
Glucose, mg/dL	49	<20	<20	40	<20	<20

Abbreviations: WBC, white blood cell; RBC, red blood cell; L, lymphocytes; N, neutrophils; M, monocytes.

had a mild right-sided hemiparesis with pronator drift in the right arm, slowed finger taps in the right hand, and 3 of 5 Medical Research Council scale strength in the right wrist extensors, finger extensors, and interosseous muscles. She was unable to walk without assistance. Reflexes were 3+ in the right bicep and patella, with an extensor plantar response in the right but were absent elsewhere.

Investigations

Computed tomography (CT) of the chest, abdomen, and pelvis with whole-body positron emission tomography (PET) showed only a few small (≤ 5 mm) nonspecific pulmonary nodules that were not easily amenable to biopsy and were not hypermetabolic by PET. Transvaginal ultrasound and mammogram were normal. Cytology and flow cytometry performed on the CSF were negative for malignancy. Serum protein electrophoresis and urine protein electrophoresis were normal, and the cancer antigen 125 cancer marker was negative. Multiple CSF mycobacterial cultures and CSF fungal cultures were negative. Polymerase chain reaction (PCR) on CSF for mycobacteria was negative. The CSF Venereal Disease Research Laboratory (VDRL) test and CSF cryptococcal antigen were negative. Rapid plasma reagin (RPR) testing of serum for syphilis was negative. Antibodies against human immunodeficiency virus (HIV), brucella, *Bartonella quintana*, and *Bartonella henselae*, *Coxiella burnetii* (Q fever), *Coccidioides*, cryptococcus, blastomyces, West Nile virus, mycoplasma, Epstein-Barr virus, and enterovirus were not detected in the serum. Serum Lyme IgG was positive by enzyme immunoassay, but both IgG and IgM antibodies were negative by Western blot. Testing for *Histoplasma* antibodies in the serum by immunodiffusion was initially positive, but repeat testing by enzyme-linked immunosorbent assay (ELISA) and complement fixation (CF) was negative, and CSF CF and antigen testing for histoplasma was also negative. The PCRs for herpes simplex, varicella zoster, and human herpes virus 6 viral DNA were negative. A test for β -D-glucan was negative. The TB interferon- γ release assay (QuantiFERON-TB, Cellestis, Valencia, CA) was indeterminate. The CSF angiotensin-converting enzyme (ACE) was elevated at 6.0 U/L (ref 0.0-2.5 U/L), but serum ACE was normal. Microsomal antibody, rheumatoid factor, and anti-Sjogren's syndrome A (anti-SSA) and

Sjogren's syndrome B (SSB) antibodies were negative or normal. Antinuclear antibody was elevated at 1:80 in a speckled pattern.

The CSF analysis over this time period is shown in Table 1. The MRI of the brain obtained on admission showed progression of the leptomeningeal enhancement now involving all the cranial nerves, with magnetic resonance angiography (MRA) demonstrating new vessel irregularity in the anterior and posterior circulation. The diffusion sequence showed multiple small-vessel infarcts involving the thalamus, brainstem, and right medial temporal lobe (Figure 1). A diagnostic test was performed.

Discussion

Two-and-a-half years after an apparent episode of Miller-Fisher variant Guillain Barré Syndrome, a 20-year-old woman developed a neurological illness associated with a CSF lymphocytic pleocytosis, severe hypoglycorrhachia, and leptomeningeal enhancement on MRI. These abnormalities continued to worsen over several months, with extension of the leptomeningeal enhancement and development of intraparenchymal enhancing lesions. She initially appeared to respond to steroids and multidrug anti-TB therapy, but her signs and symptoms worsened when steroids were tapered and she ultimately developed hydrocephalus requiring VP shunting. Her core clinical features included somnolence, involvement of bulbar musculature evidenced by a nasal hypophonic dysarthria and a diminished gag reflex, and a right hemiparesis with associated upper motor neuron signs including hyperreflexia and an extensor plantar response. In addition to evidence of meningoencephalitis, the patient had MRA findings consistent with small-vessel infarcts involving the thalamus, brainstem, and right temporal lobe.

This patient falls into the general diagnostic category of "chronic meningitis." This syndrome is arbitrarily defined by the presence of clinical and laboratory evidence of persistent meningeal inflammation lasting for at least a month.¹ The 1-month duration provides a convenient marker to differentiate "chronic" cases from the substantially more common cases of acute meningitis, which differ significantly in etiology. For example, in immunocompetent adult hosts the majority of cases of acute viral meningitis are due to enteroviruses, herpes simplex virus, or other herpes viruses; and most cases

of acute community-acquired bacterial meningitis are due to *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes*. None of these agents are important causes of chronic meningitis.

Chronic meningitis should also be distinguished from “recurrent” meningitis in which patients have discrete episodes of meningitis separated by intervals in which they are asymptomatic and laboratory tests are normal. In cases of recurrent bacterial meningitis, the CSF cultures typically identify the etiologic agent, and the diagnostic difficulty is to identify the host’s susceptibility factor leading to repeated infections (eg, an immunological deficit or an abnormal communication between the CSF space and the outside world). The syndrome of benign recurrent lymphocytic meningitis, previously often referred to as “Mollaret meningitis,” is most commonly due to recurrent herpes simplex meningitis, with diagnosis established by amplifying herpes simplex virus DNA from CSF by PCR.^{2,3}

This patient clearly had a “chronic meningitis,” and even if the original neurological illness 2.5 years ago is set aside, she had CSF pleocytosis and leptomeningeal enhancement persisting for at least 6 months. No CSF specimen during this interval was normal, nor did her signs and symptoms resolve, excluding recurrent meningitis. Unfortunately, the differential diagnosis of chronic meningitis is broad, including both infectious and inflammatory etiologies (Table 2). Even with concerted and repeated diagnostic efforts, a specific etiologic diagnosis may not be established in up to one-third of the cases.^{4,5} Nonetheless, features in the history, examination, and diagnostic tests may help focus or narrow the search for an etiologic agent.

The patient’s history helps establish the likelihood that meningitis is chronic rather than recurrent, and helps identify (along with the physical and laboratory studies) whether the disease process is likely confined to the CNS or part of a larger systemic process. For example, patients with chronic meningitis associated with vasculitis, sarcoidosis, or carcinoma may have specific symptoms indicative of organ dysfunction outside the CNS. A history of prior infections or certain types of risky behaviors may be clues to immunocompromised states such as HIV infection. Travel to, or residence in, specific geographic areas may provide clues to specific pathogens. Exposure and possible infection due to fungi including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis* show specific geographic predilections within the United States, as does infection with *Borrelia burgdorferi*. Exposure or close contact to an infected individual may be a clue to TB, and dietary exposure to unpasteurized dairy products increases risk of Brucellosis. Unfortunately, we have few clues pointing to specific pathogen exposure in this patient. She had traveled “extensively” within the United States and so could have been exposed to any of the fungal agents noted earlier, and conversely none of these agents can be easily excluded due to lack of likely exposure. She was of Ukrainian heritage and had relatively recent travel there.

Table 2. Causes of Chronic Meningitis in Immunocompetent Hosts.

Bacteria and mycobacteria	
<i>Mycobacterium tuberculosis</i>	(Tuberculosis; common)
<i>Treponema pallidum</i>	(syphilis)
<i>Borrelia burgdorferi</i>	(Lyme)
<i>Brucella abortus</i>	(Brucellosis; rare)
Fungal infections	
<i>Blastomyces dermatitidis</i>	(Blastomycosis; rare)
<i>Cryptococcus neoformans</i> or <i>C. gatii</i>	(common)
<i>Coccidioides immitis</i>	(Coccidioidomycosis)
<i>Histoplasma capsulatum</i>	(Histoplasmosis)
<i>Sporothrix schenckii</i>	(Sporotrichosis; rare)
Note. Infection due to candida, aspergillus, zygomycetes, and pseudallescheria are rarely seen in immunocompetent hosts without predisposing risk factors.	
Parasitic infections	
Cysticercosis	
Note. Infection due to <i>Angiostrongylus cantonensis</i> is not indigenous in the United States.	
Noninfectious diseases	
Neoplastic meningitis (eg, CNS gliomatosis, meningeal carcinomatosis, lymphomatous meningitis)	
Sarcoidosis	
Vasculitis (eg, primary CNS vasculitis/granulomatous angiitis or CNS-systemic vasculitides)	
Behçet disease, Vogt-Koyanagi-Harada syndrome	
Viral infections	
HIV	
Note. Viral infections other than HIV do not generally cause chronic meningitis in immunocompetent hosts.	

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus.

Tuberculosis, including infection with multidrug resistant strains, has emerged as a significant problem in many regions of the old Soviet Union, and remains an issue in many areas of Central and South America, which the patient had also visited. However, no specific contact with an infected individual was known. Her occupational history did not suggest any particular risks. For example, odd cases of chronic meningitis associated with the dimorphous fungus *Sporothrix schenckii* have been associated with exposure to this agent through gardening or landscaping activities. As noted earlier, most patients with brucella infections have a history of exposure to cattle or unpasteurized dairy products.

Patients with chronic meningitis need a complete physical examination. Unfortunately, this patient had no abnormalities noted on physical examination to suggest an etiology for her meningitis. Skin examination is particularly important. For example, patients with Lyme disease may have a history or residual signs of erythema migrans; secondary syphilis may be associated with a maculopapular rash; and specific skin lesions may be clues to the diagnosis of sarcoidosis, TB, or certain fungal infections. Enlarged lymph nodes, if present, may provide a site for a diagnostic biopsy. Obviously, finding a mass may be the clue to a breast or other carcinoma. Unfortunately, no specific findings to aid in the diagnosis of her meningitis were found on her general physical examination.

Certain tests should be performed in all patients with chronic meningitis as part of the early workup. A CSF cryptococcal polysaccharide antigen test is extremely sensitive for diagnosis of this infection (see below). The presence of a negative serum fluorescent treponemal antibody (FTA) largely excludes syphilis from the diagnosis. The HIV status of all patients should be determined as the detection of this infection can significantly alter the differential diagnosis. Fungal cultures should also always be sent. The diagnosis of fungal and mycobacterial infections as a cause of chronic meningitis is established by a positive CSF culture. It is important to remember that due to variations in organism burden and difficulty with culturing both mycobacteria and fungi, the mantra is (1) culture often (multiple CSF specimens), (2) culture a lot (large volumes of CSF, eg, 10-30 mL), (3) culture different CSF sites (eg, ventricular or cisternal CSF, not just lumbar), and (4) keep cultures for at least 6 weeks. It is extremely valuable to consult with the microbiology laboratory and infectious disease specialists prior to culture, as specific techniques and culture media may enhance the diagnostic yield, and keeping cultures for a minimum of 4 to 6 weeks may allow the cultivation of slow-growing organisms potentially present in only low colony number in the inoculum.

Diagnosis can be enhanced by a variety of antigen and antibody tests on CSF and serum and, in some cases, urine. These tests vary greatly in sensitivity and specificity, and are generally initially selected based on clues such as likely geographic exposures. In a patient such as this one, in addition to testing for syphilis and *Cryptococcus*, obvious initial serological testing would cover the more common causal infections in immunocompetent hosts, including:

1. *H capsulatum*: CSF and serum antibody and antigen testing, urine antigen testing;
2. *C immitis*: CSF and serum antibody testing;
3. *B dermatitidis*: CSF and serum antibody testing;
4. *Borrelia burgdorferi*: Serum ELISA and confirmatory Western blot if positive, CSF antibody testing and *B burgdorferi* PCR;
5. Brucella: serum antibody testing.

Neuroimaging was performed in this patient. The finding of leptomeningeal enhancement is nonspecific, although the fact that it was perhaps more noticeable in the basilar meninges and involved spinal as well as cranial meninges is typical of an infectious process. Significant involvement of basilar meninges with obstruction to CSF outflow at the foramina of Lushka and Magendie often results in communicating hydrocephalus, as was noted here. Another frequent concomitant is involvement of the third, fourth, and sixth cranial nerves innervating extraocular muscles and resulting in diplopia, although diplopia was not noted in this patient. The study presented (Figure 1) shows the presence of intraparenchymal lesions (eg, left cerebellar peduncle) and a left thalamic lesion, possibly infarctive. The presence of intraparenchymal lesions

in a patient with chronic meningitis of an infective etiology may be due to either infective masses (eg, tuberculoma, gumma, cryptococcoma or similar masses caused by other fungi) or to the presence of inflammatory vasculopathy (eg, meningovascular syphilis or arthritis associated with other infectious agents). In this case, syphilis is made less likely by the presence of a negative CSF VDRL and a negative serum RPR. Unfortunately, an FTA absorption test was not performed. A negative CSF FTA test essentially excludes the presence of neurosyphilis, although a miniscule amount of blood contamination can render the test positive; so a positive test result is not specific for neurosyphilis.

This patient had multiple CSF examinations over a 6-month period (Table 1, 30-36 months) all of which showed a lymphocytic pleocytosis, typically with 83% to 88% lymphocytes (her last LP had a mononuclear pleocytosis with 35% lymphocytes and 35% monocytes). The presence of a lymphocytic pleocytosis is the most frequent finding in chronic meningitis and does little to narrow the diagnosis. Occasional patients with chronic meningitis have a predominance or significant number of neutrophils or eosinophils, and when this occurs it may suggest certain etiologic agents (see below). The magnitude of the nucleated cell pleocytosis and the degree of CSF glucose depression (hypoglycorrhachia) may provide some general clues to the diagnosis. This patient's CSF cell counts varied between a low of 11 cells/mm³ and a peak of 144 cells/mm³. In general, patients with chronic meningitis associated with neurosarcoidosis, central nervous system (CNS) vasculitis, carcinomatous meningitis, and infections due to HIV or *Borrelia burgdorferi* (Lyme) have less than 50 cells/mm³, and only rarely have greater than 100 cells/mm³ in their CSF. Conversely, patients with chronic meningitis due to fungal infections, TB (*Mycobacterium tuberculosis*), syphilitic meningitis (*Treponema pallidum*), or chemical meningitis typically have CSF cell counts greater than 50 cells/mm³.⁶ Similarly, patients with noninfectious causes of chronic meningitis often have normal or only mildly depressed CSF glucose values, with a notable exception being patients with carcinomatous meningitis whose CSF glucose concentration may be profoundly depressed. Conversely, patients with fungal or tuberculous meningitis often have low CSF glucose concentration, and in the absence of treatment it is common to see that the CSF glucose concentration progressively decreases over time. Taken together, this patient's combination of a significant lymphocytic pleocytosis and a profound hypoglycorrhachia suggests that fungal and tuberculous meningitis should be the leading diagnostic considerations. It is important to note that this patient had no evidence on imaging, cytology, or serologic testing to suggest a malignancy. She had no serological evidence to suggest the presence of a connective tissue or collagen vascular disease except for the nonspecific finding of a positive ANA (1:80 speckled). Similarly, neither her MRI abnormalities nor her chest imaging suggested the presence of sarcoidosis, or neurosarcoidosis more specifically. Her

serum ACE was normal, although her CSF ACE was elevated. The sensitivity and specificity of CSF ACE testing is uncertain. In patients with neurosarcoidosis, elevated values are generally found in about 50%, compared to approximately 10% of the patients with systemic disease alone. Higher elevations may have greater specificity for the diagnosis of neurosarcoidosis, and in 1 series a CSF value greater than 8 nmol/mL per minute had a sensitivity of 53% and a specificity of 94% for the diagnosis of neurosarcoidosis.⁷ This patient's CSF ACE was elevated, and although the upper boundary of normal was noted to be 2.5 U/L, many laboratories (including Mayo) have an upper normal limit of 4 U/L. She had no systemic findings to suggest sarcoidosis. An isolated CSF ACE elevation can be seen in a patient with sarcoid isolated to the CNS. This patient's CSF and MRI findings are not typical of isolated CNS sarcoid, and I suspect that the "intermediate" value of her CSF ACE is a nonspecific reflection of another infectious or inflammatory process.

In patients in whom the diagnosis remains uncertain after numerous CSF cultures and examinations (see below), the next step is often a meningeal biopsy. In one series of 25 cases of chronic meningitis of unknown etiology, the meningeal biopsy was abnormal in approximately two-third of the cases, although a specific diagnosis was made in only 20%.⁸ In another series of 37 cases, a definitive diagnosis was made in almost 40% of the cases, but the yield was higher depending on a number of factors, including the presence of meningeal enhancement at the site of meningeal sampling. If a sample of enhanced meninges was taken the diagnostic yield approached 80%, whereas a sample of unenhanced meninges had a yield of less than 10%.⁹ In my experience and in the reported literature, meningeal biopsy is most useful in providing a diagnosis of granulomatous disease (eg, TB, sarcoid, "granulomatous angiitis"), vasculitis, or neoplastic disease, and the yield is lower for nongranulomatous infections. This patient had her leptomeninges biopsied during placement of her VP shunt, which was reportedly benign. However, as noted, it is unclear whether this sample would have been from an area of enhanced meninges, and in the series noted above, sampling of frontal meninges (as would likely have been the case here) had a considerably lower diagnostic yield than sampling basilar or posterior meninges through a suboccipital approach.⁹

At this point there is little to go on besides the suspicion that the patient had an infective process (based on the degree of pleocytosis, the MRI findings, and the profound hypoglycorrachia). It is useful at this point to consider some of the more common diagnostic possibilities. Testing for *M tuberculosis* should be performed in all patients even in the absence of an exposure history. In many series of chronic meningitis, TB is the most common identified cause, accounting in some cases for up to 40% of the cases.⁴ Patients typically present with headache, fever, meningeal signs, altered consciousness, and less commonly with focal neurological findings that can include hemiparesis, aphasia, or cranial nerve palsies.

Involvement of "basilar" cranial nerves such as those innervating extraocular movements (III, VI) is particularly common. Her CSF pleocytosis and differential count were certainly consistent with TB, and it is important to note that about 25% of the patients can have a predominance of neutrophils rather than lymphocytes in the CSF. About half of patients will have a CSF cell count between 10 and 50 cells/mm³, an increased protein between 100 and 200 mg/dL, and a depressed glucose between 20 and 45 mg/dL. The CT shows abnormalities in at least 50% of the cases, and MRI shows abnormalities in a significantly higher percentage. The most common abnormalities include hydrocephalus and meningeal enhancement that is often basilar. Patients may have evidence of infarction or, in rare cases, mass lesions (tuberculoma). Definitive diagnosis is based on positive CSF culture, which occurs in approximately 80% of the cases. Culture of mycobacteria on solid media (Lowenstein-Jensen) can detect as few as 10 organisms/mL, but growth of visible colonies can take up to 2 months. Other useful tests on CSF include amplification of mycobacterial DNA by PCR, which has a sensitivity of approximately 60% to 90%.¹⁰ This test is extremely specific and can provide same day results, but is less sensitive than culture. In this patient, multiple CSF mycobacterial cultures and PCR for mycobacterial DNA were all negative. Other CSF markers of TB can include an elevated adenosine deaminase (sensitivity approximately 66%). A Ziehl-Neelsen or Kinyoun stain for acid-fast bacilli (AFB) should be performed in all CSF specimens because a staining test is inexpensive and can provide immediate results. Staining typically requires the presence of greater than 10 000 organisms/mL, and as a result staining of CSF for AFB is very insensitive (positive in only one-third of cases). The sensitivity of the staining test is extremely dependent on the volume and number of CSF specimens examined, the diligence and duration with which the CSF is examined, and the expertise of the examiner. A tuberculin skin test (TST; eg, Mantoux or PPD) is positive in about 75% of the immunocompetent cases of tuberculous meningitis; however, up to 25% of the individuals immunized with BCG after the age of 5 will have a positive TST. Newer tests such as QuantiFERON-TB assays are replacing TSTs. The QuantiFERON assay measures interferon- γ released by a patient's lymphocytes after exposure to a mixture of 3 mycobacterial antigens. The stimulating antigens are not present in BCG, and as a result the test is typically negative in BCG-immunized individuals. However, her "indeterminant" result is not diagnostically useful. Other laboratory abnormalities that may suggest the presence of tuberculous meningitis can include hyponatremia (due to syndrome of inappropriate antidiuretic hormone secretion [SIADH]) and an elevated erythrocyte sedimentation rate, although neither is specific. Chest x-rays show abnormalities in about two-thirds of the adult cases including miliary disease, interstitial or lobar infiltrates, or hilar adenopathy. These changes are obviously not specific to TB, and similar abnormalities can occur with fungal infections or sarcoidosis, or in the presence of cancer.

Regardless, her chest CT was notable only for “nonspecific” pulmonary nodules. So taken together, although her presentation, CSF results, and imaging studies were consistent with TB, the negative CSF cultures and PCR make this diagnosis less likely. She appropriately received an empiric trial of antimycobacterial therapy and did not seem to respond clinically (although she may have responded to the coadministered steroids). However, her positive TST is worrisome and her failure to respond to antimycobacterial chemotherapy might have been due to the presence of multiple drug-resistant organisms that have been isolated with increasing frequency in parts of the world, including the Ukraine.¹¹

The second major diagnostic possibility is fungal meningitis. Cryptococcal infection is the most important diagnostic consideration in this group, and like TB, should always be considered. Patients with HIV infection and prior steroid use are at particularly high risk of cryptococcal infection, but neither of these circumstances was present here. The presentation is not easily distinguished from that described above for TB, with headache, fever, and altered mental status commonly present. Interestingly, especially in immunocompetent individuals, an indolent course lasting weeks to months before diagnosis can occur. As with TB, it is common for patients to have signs of basilar cranial nerve involvement, or signs and symptoms related to hydrocephalus and increased intracranial pressure. Recently, organisms belonging to the species *Cryptococcus gattii* have been increasingly recognized as an important cause of infection in immunocompetent individuals, in addition to the more widely recognized *C. neoformans* species. However, the basic clinical and diagnostic features of both species are generally similar. Fortunately, there are a number of highly sensitive and specific diagnostic tools for the identification of cryptococcal infection. Over 90% of the patients with cryptococcal meningitis will have a positive CSF cryptococcal polysaccharide antigen test (ELISA or latex agglutination), and greater than 90% will have positive CSF cryptococcal cultures. Staining CSF with India ink is rapid and inexpensive, and will reveal encapsulated organisms in about 50% of the cases. Similar to AFB stains, this test has a significant “art” component, and both false positives and negatives are common (eg, false positives from identifying lymphocytes as *Cryptococci*). Hydrocephalus is extremely common on neuroimaging studies, and mass lesions (Cryptococcoma) may be seen. The CSF again shows a lymphocytic predominance with cell counts generally greater than 100 cells/mm³ and an elevated protein. The degree of protein elevation and hypoglycorrhachia is generally less profound than that seen in TB. Elevations of adenosine deaminase are less frequent than in cases of TB (approximately 15%), and hyponatremia due to SIADH is infrequent. The negative CSF cryptococcal antigen and negative serum antibodies in this patient make this diagnosis unlikely.

In immunocompetent individuals it is appropriate to consider a variety of other fungi in addition to *Cryptococcus*, including *coccidioides*, *blastomyces*, and *histoplasma*. Other

fungi including *candida*, *aspergillus*, and *zygomycetes* generally produce CNS and systemic infection in patients with specific forms of immunodeficiency such as HIV infection, neutropenia, prior steroid use, intravenous drug abuse, or diabetes.¹² *Coccidioides*, *histoplasma*, and *blastomyces* can all produce meningoencephalitis. Infarction from vasculitis may occur with *coccidioides* and *histoplasma* infection, but less commonly with *blastomyces* infection. Infarcts are also extremely common with infection due to *aspergillus* and *zygomycetes* and can occur with *candida*, but as noted these organisms are unusual causes of CNS infection in immunocompetent hosts. Unfortunately, none of these agents is as easy to diagnose as cryptococcal infection. Detection of β -D-glucan, a component of the cell wall of many fungi (not including *cryptococci* and *zygomycetes*), in serum can be a clue to the presence of invasive fungal disease. This test is reasonably specific when 2 positive results are obtained, but it is insensitive (probably <50%), and so a negative result as obtained in this patient is not particularly useful.¹³ Ultimately, diagnosis often depends on culture or CSF serology (detection of antigens or antibody). In this regard, it is absolutely critical to obtain repeated cultures of large volumes (eg, 10-30 mL) of CSF. In patients with basilar meningitis, and even in other situations, it is often useful to obtain a CSF specimen for culture from nonlumbar CSF, such as cisternal or ventricular fluid, as the organism count may be considerably higher in cisternal or ventricular CSF compared to lumbar CSF. The CSF cultures should be supplemented with a variety of CSF serological tests for fungal antigens or antibodies. Most fungal infections produce a lymphocytic pleocytosis, although *coccidioides* may result in a significant CSF eosinophilia, and this is a potential clue to diagnosis. Certain fungi also cause a chronic neutrophilic pleocytosis, and the persisting presence of these cells in the CSF of a patient with chronic meningitis raises the possibility of infection due to *aspergillus*, *zygomycetes*, and *pseudallescheria*. None of these CSF profile abnormalities were present in this patient. Antibodies against *coccidioides* and *blastomyces* were not present in her serum. Importantly, she had at least 1 positive serum test for *histoplasma* antibodies (by immunodiffusion) although related tests for antibodies by other methods (ELISA and CF) were negative on both serum and CSF. Another important lesson in considering fungal infection is to be cautious about disregarding any positive tests, as often the organism burden is extremely low and variable across specimens (even 1 colony grown from CSF may be critical).

C. immitis is endemic in the southwestern United States including Arizona and the Central Valley of California, and can cause chronic basilar meningitis with infarction due to vasculitis. Hydrocephalus can also occur, as can spinal arachnoiditis—all features seen in this patient. A positive CSF culture establishes the diagnosis, but culture is insensitive, and the diagnosis is more frequently made by detecting CF antibodies in the CSF (sensitivity approximately 70%). As noted, CSF eosinophilia occurs in up to 70% of the cases and may be a clue to the diagnosis. Eosinophils may be hard to

distinguish from neutrophils in some cytological stains, and a Wright-Giemsa stain should be requested in suspected cases. Although the only test for *C immitis* performed in this patient was a negative serum antibody result, the absence of CSF eosinophilia also makes this diagnosis less likely.

Blastomyces is an unusual cause of chronic meningitis. It can also produce basilar meningitis with hydrocephalus. Vasculitis and associated infarction is rare. Some patients have a predominance of CSF neutrophils, which were not found here. Culture is relatively insensitive, but specific if positive. Diagnosis is typically serologic. Antibody studies can be performed on CSF and serum, and in this case were negative on serum. The rarity of this diagnosis and the presence of a vasculitic component make this an unlikely choice in this case.

Histoplasma is an endemic fungal infection in many parts of the United States including the Mississippi, Missouri, and Ohio River valleys as well as in Central and South America. Although meningitis occurs in 10% to 25% of the patients with disseminated infection, a syndrome of isolated histoplasma meningitis in immunocompetent individuals has been increasingly recognized.^{14,15} The presentation is typically one of chronic meningitis, although focal lesions (Histoplasmoses), stroke syndromes due to vasculitis, cardiac fungal emboli, and spinal involvement can all occur. Most patients have headache, meningeal signs, and altered mental status. The infection is often indolent, and in some cases disease can progress for months or even years in the absence of specific therapy. Fever is often absent, and in one series fever was present in only about 25% of the cases.¹⁴ Focal neurological signs and cranial nerve palsies occur in about one-fourth to one-third of the cases, and hydrocephalus is particularly common. The CSF shows a lymphocytic pleocytosis typically on the order of 50 cells/mm³, an elevated protein, and a mild to moderately depressed glucose. Unfortunately, culture of CSF yields the organism in only 25% of the cases, and often requires long duration with culture of large CSF volumes. Diagnosis has been enhanced by the development of antigen and antibody tests.¹⁶⁻¹⁸ Antigen tests detect histoplasma polysaccharide antigen typically by ELISA and can be used on serum, urine, and CSF. Antibody tests include ELISAs, CF antibody detection, and immunodiffusion/agar precipitation methods. The relative sensitivity and specificity of these tests varies in different disease settings, and both antigen and antibody tests should be performed. It has been suggested that immunodiffusion assays to detect antibody may be more sensitive than ELISAs or detection of CF antibody, but this has not been rigorously examined. The CSF and serum antibodies are detected in approximately 80% of the cases. Antigen can be found in CSF or in urine in about two-thirds of the cases, and in serum in a smaller number. In one series of cases of isolated histoplasma meningitis in immunocompetent individuals, the immunodiffusion test for antibodies was particularly sensitive, and was positive in CSF in 7 of the 8 examined cases; in serum, the test was positive in 7 of the 7 tested cases, even though positive CSF cultures were present in only 3 of the 11 tested

patients.¹⁴ It is not clear how the sensitivity of this test for antibodies compares to ELISA or CF. Serum antibody tests can be positive when CSF is negative.

As noted earlier, a variety of infectious agents other than mycobacteria and fungi can cause chronic meningitis. Viruses other than HIV are rarely implicated in chronic meningitis in immunocompetent hosts. This patient was HIV negative and had negative CSF PCRs for varicella zoster, herpes simplex, and human herpes virus 6 as well as negative serologies for West Nile, EBV, and mycoplasma. She had no known exposure to suggest Brucella, Coxiella, or Bartonella, and her serologies to these organisms were negative. She had a positive screening of ELISA for *Borrelia burgdorferi* (Lyme) but this was not confirmed by Western blotting, and there was no other evidence to suggest Lyme infection.

Given the totality of the picture and the test results obtained, I think it is likely that this patient had an infectious cause for her meningitis rather than a noninfectious inflammatory process such as vasculitis, sarcoidosis, or malignancy. As noted, the leading candidates for infectious causes would be tuberculous or fungal infection. I think TB was unlikely given the negative CSF PCR, negative cultures, failure to respond to anti-TB therapy, and the potential protection against this infection afforded by her BCG vaccination; however, I cannot absolutely exclude this diagnosis. I think this was likely fungal meningitis. Although statistically cryptococcus would be the most likely cause of chronic fungal meningitis, the negative result with the extremely sensitive antigen test makes this diagnosis unlikely. In considering the remaining fungal candidates seen in immunocompetent hosts, I am intrigued by the positive serum immunodiffusion test for histoplasma antibodies, as this was the only fungal test reported as positive. Her clinical course was consistent with isolated histoplasma meningitis in an immunocompetent individual, and the diagnosis could have been established by a positive CSF culture or strongly suspected if repeat antibody or antigen testing on CSF for histoplasma were positive. A less likely diagnosis is that her mycobacterial cultures eventually returned positive and that her failure to respond to empiric therapy reflected a multiple drug-resistant isolate.

Pathologic Findings

Over the course of a year, multiple CSF specimens were sent to the clinical microbiology laboratory for fungal and mycobacterial culture, with negative results. On the most recent hospital admission, a CSF sample was cultured for both fungi and mycobacteria using standard liquid and solid media. After 15 days of incubation, growth was detected in the commercial mycobacterial broth medium. A smear of the broth medium was stained with the Kinyoun stain for AFB. The Kinyoun-stained smear was negative for AFB, but did show yeast-like cells. The broth medium was subcultured onto 2 sabaroud dextrose agar plates and incubated at 30°C and 37°C for detection of fungal growth. After 2 days incubation,

Figure 2. Cerebrospinal fluid (CSF) culture result. A, On the left is shown a sabaroud dextrose agar culture plate grown at 30°C with *Histoplasma capsulatum* in the mold phase. On the right is a mycobacterial broth culture bottle grown at 37°C showing *H capsulatum* in the yeast phase. B, Microscopic inspection of *H capsulatum* in the mold phase by lactophenol blue staining, showing a tuberculate macroconidia and 2 teardrop-shaped microconidia.

pinpoint colonies of a filamentous fungi were observed on the plate incubated at 30°C. A smear of these colonies stained with lactophenol blue showed small, spherical microconidia on short stalks and larger, mace-like tuberculate macroconidia (Figure 2). This pattern of sporulation, with the characteristic mold-like micro- and macroconidia structures at 30°C, and growth as a yeast at 37°C in broth media, is characteristic of *H capsulatum*. A positive DNA hybridization probe for *H capsulatum* confirmed this identification.

Neuropathologic diagnosis: *H capsulatum* meningitis with associated vasculopathy.

Comments

Our patient had no known prior exposures to *H capsulatum*. As noted in the discussion, *H capsulatum* can be extremely

difficult to isolate in culture of CSF. In this case, it was only after the patient's infection had progressed to involve the CNS vasculature that we were able to isolate the organism in culture medium formulated for mycobacterial growth. An interesting feature of this case is the initial clinical presentation, which was suggestive of a neuroinflammatory syndrome such as Miller-Fisher variant Guillian-Barré. We hypothesize that this was likely the point of initial CNS infection with *H capsulatum*. The indolent time course in this case is not unusual for CNS histoplasmosis infections. Cases have been reported where active CNS infection has persisted for up to 22 years.¹⁹

Our patient was treated with liposomal amphotericin B for 6 weeks with gradual improvement, and was eventually switched to an oral triazole antifungal agent. The CNS histoplasmosis should be considered in cases of chronic meningitis with a lymphocytic pleocytosis.

Authors' Note

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