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Clinicopathology Conference: 41-Year-Old Woman with Chronic Relapsing Meningitis

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A 41-year-old woman was seen at the National Institutes of Health (NIH) Neuroimmunology Clinic in 2017 for recurrent episodes of fever, neck stiffness, and back and leg pain.

In 2002, at age 26 years, she had several episodes of back and neck pain, malaise, and fever, each lasting 1 to 3 days (Fig 1). A chest x-ray and complete blood count were normal. Cerebrospinal fluid (CSF) during one of these episodes showed pleocytosis (60 white blood cells [WBC]/μl; 60% monocytes, 25% lymphocytes, 15% neutrophils), with elevated protein (96 mg/dl) and low glucose (26 mg/dl, Supplementary Table 1). Magnetic resonance imaging (MRI) of the brain showed subtle fluid-attenuated inversion recovery (FLAIR) hyperintensity in the sulcal CSF. MRI of the spine was normal. Extensive investigations including CSF *Mycobacterium tuberculosis* (TB) complex polymerase chain reaction (PCR) and culture, *Coccidioides* antibodies, histoplasma antigen, cryptococcal antigen, and herpes simplex virus and varicella zoster virus PCRs were negative (see Supplementary Table 1). Nonetheless, she was treated empirically with valacyclovir for 2 weeks. She had had a recent exposure to TB and had converted from a negative purified protein derivative (PPD) skin test in 2001 to a positive result at the time of her presentation in 2002. Thus, she was also treated empirically for TB meningitis (TBM) with rifampin, pyrazinamide, and ethambutol for 1 year. Isoniazid (INH) was started but was discontinued after several weeks due to transaminitis and nausea. She did not receive adjunctive steroids.

Her symptoms resolved until 2006 when, immediately following spinal epidural anesthesia during childbirth, she developed a fever with headache, neck stiffness, back pain, and night sweats. She was treated for endometritis but continued to have similar but less severe symptoms for several months. In early 2007, she acutely developed bilateral gluteal pain and left leg dysesthesias. CSF again showed pleocytosis (130 WBC/μl; 83% lymphocytes, 13% monocytes, 2% neutrophils, 2% other) with elevated protein (132 mg/dl) and low glucose (10 mg/dl). CSF TB PCR and culture, cryptococcal antigen, bacterial and fungal cultures, and viral PCRs, as well as CSF cytology and flow cytometry for malignant cells,

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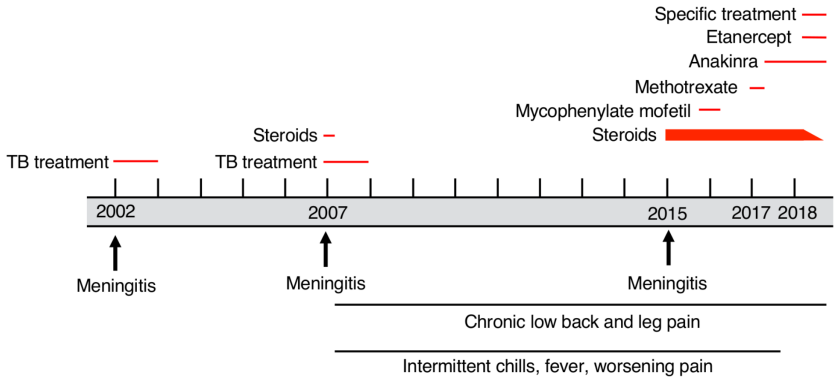

FIGURE 1: Clinical timeline. TB = *Mycobacterium tuberculosis*.

were negative (see Supplementary Table 1). MRI of the lumbar spine now showed abnormal enhancement and nerve-root thickening in the caudal thecal sac, indicating arachnoiditis (see Fig 2A, B); brain, cervical, and thoracic spine MRI was normal. Repeat lumbar spine MRI 2 months later showed more extensive enhancement and clumping of the cauda equina. Computed tomography (CT) scans of the chest, abdomen, and pelvis, and a gallium scan, were unremarkable.

In April 2007, she had a laminectomy and biopsy at L5/S1. The dura was thick, and there were adhesions within the thecal sac and scar tissue surrounding the nerve roots. Histology showed lymphohistiocytic inflammation and a poorly formed non-necrotizing granuloma. Mycobacterial cultures were negative. There was concern that premature discontinuation of INH in 2002 may have led to incomplete treatment of TBM, so she was again treated empirically for TB with rifampin, INH, pyrazinamide, ethambutol, and moxifloxacin for 1 year, as well as 3 weeks of prednisone 60 mg daily followed by a 3-week prednisone taper. This time, pyrazinamide was stopped early due to transaminitis and nausea, and ethambutol was stopped after several months when her CSF profile improved. Repeat lumbar punctures (LPs) showed normalization of protein and glucose with mild residual CSF pleocytosis (5–10 WBC/μl). Her symptoms improved significantly, and she resumed her daily activities. However, she continued to have intermittent mild low back pain, sometimes accompanied by chills.

In 2015, at age 39 years, several days after a partial thyroidectomy for an incidentally discovered thyroid nodule, the patient again developed low back and leg pain, chills, headache, fever, and neck stiffness. She was treated with valacyclovir for possible herpes meningitis, as well as prednisone 60 mg daily for 5 weeks for arachnoiditis, with immediate improvement in symptoms. However, her pain recurred when prednisone was tapered gradually over the next several months, and she also developed pain with eye movement, urinary frequency and hesitancy, and subjective sensory changes in the left leg distally from the knee. MRI showed evidence of worsening lumbosacral arachnoiditis with thickening and enhancement of the cauda equina. There was also displacement of the cauda equina posteriorly and laterally by a loculated cystlike structure (see Fig 2A, B). She had another LP; however, only a small amount of fluid was obtained, possibly due to the loculation. The CSF was bloody (1,075 red blood cells [RBC]/μl) with 9 WBC/μl (78% lymphocytes, 22% neutrophils), elevated glucose (179 mg/dl), and low protein (13 mg/dl). Cryptococcal antigen and fungal cultures were negative. She had a whole body fluorodeoxyglucose positron emission tomography (FDG-PET) CT that was normal. The etiology of the arachnoiditis was thought to be postinfectious or autoimmune. She was treated with a 3-day course of intravenous methylprednisolone, followed by oral prednisone, with dramatic improvement; however, pain, neck stiffness, and fever again recurred when steroids were tapered several weeks later.

She was subsequently maintained on prednisone, and any attempt to decrease to <35 mg/day resulted in worsening of her back pain, fatigue, and intermittent low-grade fevers and night sweats. Due to concern for neurosarcoidosis or another autoimmune disorder, she was placed on concomitant mycophenolate mofetil (up to 3,000 mg/day) for several months in 2016, without any improvement. While continuing the prednisone, she was transitioned from mycophenolate mofetil to methotrexate up to 15 mg/wk in early 2017, also with no improvement or ability to taper steroids. She developed bilateral cataracts attributed to chronic corticosteroid use.

At the time of her presentation to the NIH Neuroimmunology Clinic in 2017, she had constant dull, aching pain in her back and buttocks that worsened with prolonged activity or stress. Every 1 to 3 months, she had several days of malaise and fever up to 38.3°C accompanied by more severe back and buttock pain. She complained of a sensation of urinary retention, although postvoid residuals were normal. She denied constipation or bowel incontinence, weakness or numbness, or neurological symptoms

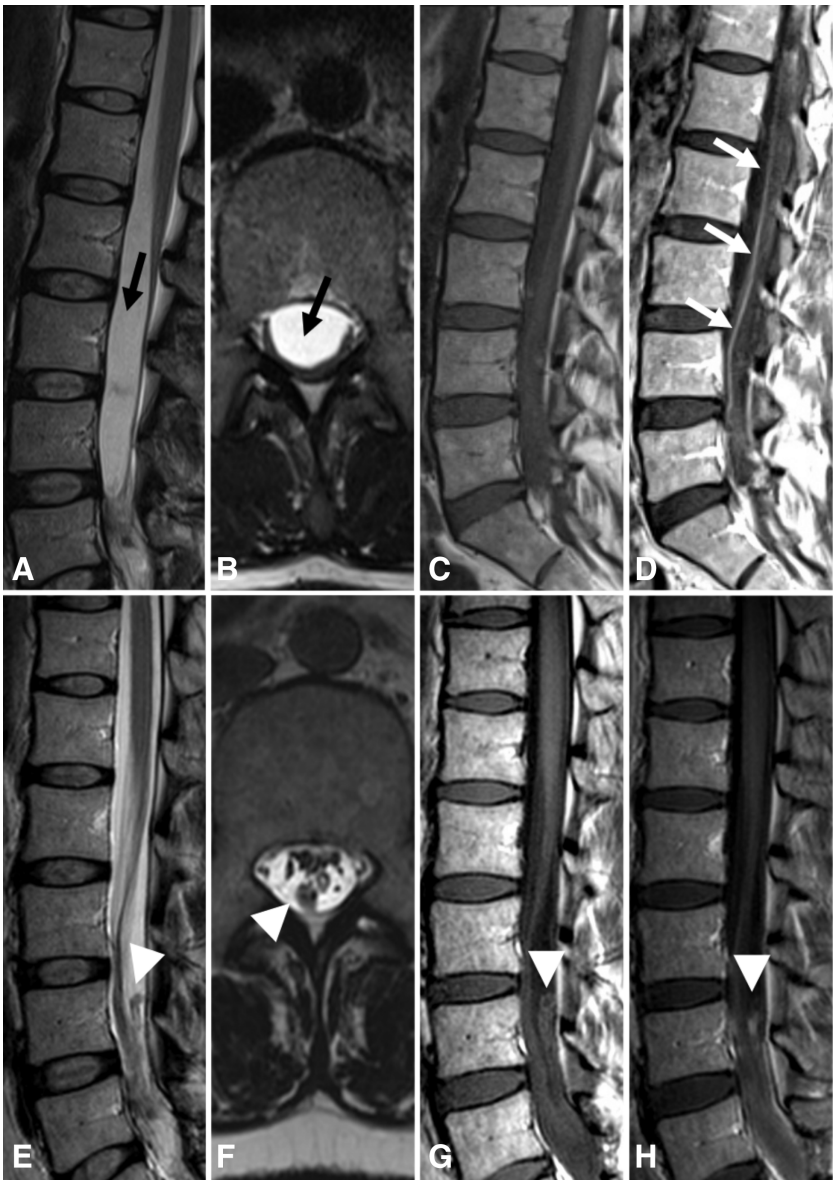

FIGURE 2: Lumbar spine magnetic resonance imaging (MRI) findings. (A, B) MRI of the lumbar spine in 2015 showed a cystlike structure in the lumbosacral sac *(black arrows)* seen on sagittal (A) and axial (B) T2-weighted images. (C, D) Repeat MRI in early 2017 showed clumping of the nerve roots of the cauda equina and enhancement of the nerve roots on postcontrast T1-weighted images (D, *white arrows*) compared to precontrast images (C). (E–H) In late 2017, soon after a symptom flare, lumbar spine MRI showed an extramedullary, intradural nodule *(white arrowheads)* on T2-weighted (E, F) and T1-weighted (G) images, which demonstrated contrast enhancement (H).

in her arms. Treatment of pain with pregabalin was minimally effective and caused drowsiness. Her pain responded to nonsteroidal anti-inflammatory drugs.

She was born in Mumbai, India, immigrated to Arizona at age 22 years, and later moved to New York and then Maryland. She returned to India once, in 2009, and had no other foreign travel. Her medical history was significant for thrombocytopenia during early childhood, hepatitis B virus infection at age 12 years that subsequently resolved, left facial palsy in her teens associated with a herpetic rash in her left ear canal, and fever, headache, and malaise in 1998 at age 22 years, for which she was treated for malaria despite a negative blood smear. She had a sister with breast cancer and several distant family members with cancer, including leukemia, neuroblastoma, lung cancer, and a hepatoma. She had no family history of autoimmune or neurological disease, and no family members with frequent or severe infections.

Her general physical and neurological evaluations were normal with the exception of mild atrophy in both legs without fasciculations and with preserved strength. Lumbar spine MRI again showed arachnoiditis with some extension superiorly compared to 2015 (see Fig 2C, D). Brain MRI showed a few small foci of leptomeningeal

enhancement on postgadolinium FLAIR images. Blood was negative for rheumatologic testing, human immunodeficiency virus type 1 antibody, human T-cell lymphotropic virus type 1 and 2 antibodies, and Lyme serology. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal (see Supplementary Table 1).

Given the patient's previously negative infectious workups as well as her response to steroids, her symptoms and MRI findings were thought to be secondary to an autoimmune process, perhaps triggered initially by an infection. As she had no response to therapies directed at lymphocytes (methotrexate, mycophenolate), she was given a 1-month trial of the IL-1 receptor antagonist anakinra (up to 200 mg/day), with no improvement in her chronic symptoms. However, about 1 week after discontinuation of anakinra, she developed her typical flare symptoms of malaise and worsening back pain. Her neurologic examination was stable. She had an LP at that time, which showed 156 RBC/μl, 30 WBC/μl (92% lymphocytes, 4% monocytes, 4% neutrophils), total protein 41 mg/dl, and glucose 47 mg/dl. Infectious studies, including mycobacterial culture, histoplasma antigen, and viral PCRs, were negative. She had an elevated IgG index of 2.41 (normal range = 0.26–0.62) and partially identical oligoclonal bands in CSF and serum (pattern 3). She had an elevated blood WBC count of 15,680 cells/μl (94% neutrophils) and normal ESR and CRP. Anakinra was restarted, and her flare symptoms improved over the next several weeks, although her chronic symptoms continued. Several months later, a surveillance lumbar spine MRI showed enlargement and new contrast enhancement of a subarachnoid nodule (see Fig 2E–H).

An additional test was performed, and a diagnosis was made.

Differential Diagnosis Discussion

This is a 41-year-old woman with a 15-year history of relapsing meningitis that progressed to chronic lumbar arachnoiditis, with several notable relapses following episodes of physical stress. Despite multiple investigations, no definitive etiology was identified, and the disease recurred despite multiple empirical treatment regimens for TB, herpesvirus infections, and inflammatory conditions. Several possible diagnoses should be considered at this stage. We focus our discussion around the findings of chronic arachnoiditis and granulomatous disease.

Infectious

The patient's initial presentation at age 26 years was of a subacute prodrome followed by acute meningism. An infectious cause was appropriately at the top of the differential. Given the subacute history and the monocyte-predominant CSF with WBC < 100 cells/μl, bacterial meningitis secondary to typical pathogens, although possible, was less likely.[1,2] Subacute causes of meningitis commonly occur in the setting of viral, parasitic, fungal, or atypical bacterial infections, such as TB.[2] Multiple investigations for these types of pathogens were negative, and there was no evidence of systemic infection by CT or FDG-PET CT. However, TB PCR and culture are insensitive, and up to half of people with TBM have no evidence of systemic disease.[3,4] Given her recent exposure to TB and subsequent PPD conversion, CSF pleocytosis, hypoglycorrhachia, and the poor sensitivity of diagnostic tests for TBM, empiric treatment was appropriate given the disease's high morbidity and mortality.[5–7] Her prolonged remission after empiric TB therapy was also reassuring.

Her second attack 4 years later occurred acutely after an epidural anesthetic in the setting of pregnancy, when she was potentially more prone to infection. MRI showed new lumbar arachnoiditis. Efforts to culture or detect a pathogenic organism from the CSF were again unsuccessful, despite CSF pleocytosis and low glucose. Surgical biopsy revealed a poorly formed non-necrotizing granuloma.

Necrotizing granulomas are a hallmark of TB; however, non-necrotizing granulomas can be found in TB-positive patients, and this finding should not dissuade the clinician from the diagnosis if clinical suspicion is high.[8,9] INH is a cornerstone medication in the therapy of TBM, and patients with INH resistance have significantly worse outcomes.[10–13] The patient's initial TBM treatment did not include an adequate course of INH, and there was concern for recurrence. TB affects the spine predominantly in the form of extramedullary disease.[14] Spinal arachnoiditis can occur as a complication of TBM and can infrequently be an asymptomatic finding.[14–16] Cases of delayed lumbar arachnoiditis, occurring up to 15 years after effective treatment of the initial TBM, have been reported.[17,18]

There are a multitude of infectious, autoimmune, and neoplastic causes of granulomatous disease in the central nervous system (CNS) (Table 1).[19] Most notably in this patient, other infectious etiologies to consider would include fungal infections, neurosyphilis, and a variety of parasitic infections. Many of these conditions can cause chronic meningitis with a relapsing component, and broad diagnostic tests, such as cultures, may detect some (but not all) of these pathogens.[20]

Arachnoiditis is a rare condition characterized by chronic inflammation of the arachnoid and pia mater with increased production of collagen deposition between the two layers, leading to adhesions. Anatomically related cranial and radicular nerve roots become edematous and hyperemic before being entrapped and clumped together

TABLE 1. Causes of Central Nervous System Granulomatous Disease

Infectious[19,70]	**Immune**[19,71–76]
Bacteria	Common variable immunodeficiency
Bartonella henselae	Chronic granulomatous disease
Brucella sp.	Idiopathic pachymeningitis
Listeria monocytogenes	Kikuchi–Fujimoto disease
Mycobacterium leprae	Neurosarcoidosis
Mycobacterium tuberculosis	Rheumatoid arthritis
Nocardia sp.[a]	Vasculitis[44,45]
Treponema pallidum	Eosinophilic granulomatosis with polyangiitis
Tropheryma whipplei	Giant cell arteritis
Fungi	Granulomatosis with polyangiitis
Aspergillus sp.[b]	Primary angiitis of the central nervous system
Candida albicans[b]	Takayasu arteritis
Coccidioides sp.[c]	ANCA-associated vasculitis
Cryptococcus neoformans	**Malignancy**[77–79]
Histoplasma capsulatum	Lymphomatoid granulomatosis
Mucormycosis[a]	Langerhans cell histiocytosis
Paracoccidioides brasiliensis[4]	Erdheim–Chester disease
Parasites	
Acanthamoeba sp.[b]	
Balamuthia mandrillaris	
Echinococcus sp.[4]	
Naegleria fowleri	
Paragonimus westermani[c]	
Plasmodium sp.[c]	
Schistosoma sp.[c]	
Taenia sp.[c]	
Toxoplasma gondii	
Trypanosoma cruzi	

[a]In immunocompromised or diabetic people or intravenous drug users.
[b]In immunocompromised hosts.
[c]In people with history of travel to endemic areas.
[4]In people with prolonged residence in endemic areas.
ANCA = antineutrophil cytoplasmic antibody.

in the adhesive leptomeninges. Over time, the nerves atrophy due to diminished blood supply.[21] Intracranial arachnoiditis can lead to cranial nerve abnormalities, with blindness possible in cases of optochiasmatic arachnoiditis.[22] Lumbar arachnoiditis can cause back and lower limb pain, variable neurological deficits, and partial cauda equina syndrome. However, the clinical manifestations depend on the severity and location of disease.[23]

Any irritant or pathogen that causes chronic inflammation of the arachnoid mater can lead to adhesive arachnoiditis, and therefore, despite the rarity of the syndrome, the potential etiologies are broad. Older contrast agents used in CT myelograms (particularly ethyliodophentylate, which is no longer used), blood breakdown following subarachnoid hemorrhage, older anesthetic preservatives, and lumbar surgery have all been implicated.[23] Other causes include infections, autoimmune conditions, and malignancy, as described below. Despite an extensive workup, a causative organism may not be found, due to poor sensitivities of diagnostic assays or unintentional omission of appropriate pathogen-specific investigations.

Fungal infections such as *Cryptococcus* and *Candida* species can cause chronic meningitis and arachnoiditis.[15,22,24,25] However, this patient was not known to be immunocompromised or to have engaged in intravenous drug use, making fungal meningitis less likely. In addition, her clinical course and CSF profile were not consistent with coccidioidomycosis, which was suspected because she had lived in Arizona. Neurocysticercosis (NCC) can cause spinal arachnoid disease, usually in patients with basal arachnoid disease, and can be asymptomatic, although this was not considered in this patient (although she grew up in a country where NCC is endemic) because no parenchymal or subarachnoid cysts were detected on at least 8 brain MRIs over 15 years.[26] She did have a cyst adjacent to the lumbar cord seen on MRI in 2015; however, in light of her overall presentation and lack of brain cysts, NCC was not investigated as a possible cause. Syphilis can rarely cause subacute meningitis with optochiasmal arachnoiditis and has also been implicated in lumbar arachnoiditis.[27,28] Schistosomiasis can manifest with spinal cord disease, either with transverse myelitis commonly involving the conus medullaris or with lumbar arachnoiditis.[29] Neuroschistosomiasis occurs in endemic regions, such as Egypt, but neither India nor the USA is considered a high-risk area.[30] Meningitis can also be seen in angiostrongyliasis, gnathostomiasis, and sparganosis parasitic infections, but usually with a much more acute course.[31,32] Case reports of vertebral disease and lumbar arachnoiditis secondary to *Echinococcus granulosus*, a zoonotic parasitic infection transmitted from dogs, have also been described.[33,34] Amoebic infections such as *Balamuthia mandrillaris* can cause granulomatous meningitis, but the course is usually much more rapid.[35] An occult or indolent infection in her lumbar canal may have incited a larger-than-expected immune response after the introduction of an epidural needle, which would otherwise cause only a mild local inflammatory response.

On a single LP in 2002, our patient had CSF eosinophilia, with eosinophils making up 1% of 147 WBC/μl. Eosinophilic meningitis, which is defined as the presence of at least 10% eosinophils of CSF WBC or at least 10 eosinophils/μl, is most often caused by a helminthic infection, most commonly *Angiostrongylus catonensis*. However, a wide variety of other infections as well as malignancy and autoimmune disease, including sarcoidosis, can also cause CSF eosinophilia, with variable blood eosinophilia.[31]

Inflammatory Conditions

Postinfectious autoimmune neurological conditions are common. Paradoxical worsening of TBM is an immune-mediated response that can present up to a year after effective treatment, with 4% of patients developing spinal arachnoiditis.[36] Postinfectious inflammatory lumbar arachnoiditis can also be seen following cryptococcal meningitis secondary to a postinfectious inflammatory response syndrome. Most cases have negative cryptococcal cultures in CSF.[37]

Neurosarcoidosis is an autoimmune non-necrotizing granulomatous condition that can present with both systemic and neurological disease.[38] Neurosarcoidosis commonly causes a relapsing chronic meningitis, and chronic lumbar arachnoiditis has been described.[39,40] Neurological symptoms can be the initial presentation of neurosarcoidosis in 50% of patients, with 85% ultimately developing systemic disease but with a significant percentage continuing to have isolated CNS involvement.[41] Features that prompt the consideration of neurosarcoidosis in our patient were her presentation with chronic meningitis and arachnoiditis, CSF pleocytosis, low CSF glucose (which can occur in 14% of patients), non-necrotizing granulomas on biopsy, and the relapsing nature of the disease in the same region of the CNS.[41–43] Despite extensive investigation including CT of the chest, abdomen, and pelvis as well as FDG-PET/CT, there was no evidence of systemic sarcoidosis. Her later relapses responded extremely well to steroid therapy, and she became dependent on steroids, further implicating an autoimmune etiology. Primary CNS vasculitis can also present with granulomatous inflammation, but it rarely involves the spinal cord,[44,45] and blood vessel wall inflammation was not identified on biopsy. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis can also have CNS involvement, but repeat serum ANCA testing was negative.

Malignancy

Invasive malignancy of the subarachnoid space is another important diagnostic consideration. Despite the patient's strong family history of cancer, there was no evidence of malignancy in repeated CSF cytology and flow cytometry examinations, on lumbar meningeal biopsy, or by whole body imaging. In addition, the sheer length of the 15-year disease course with no manifestations of systemic malignancy make the diagnosis less likely. However, this diagnostic possibility should always still be considered,

especially given that systemic glucocorticoids can temporarily improve hematologic malignancies, and CSF cytology is notoriously insensitive.

Research CSF Metagenomic Sequencing

Despite the presumption of an autoimmune etiology, lingering concerns about an occult infection prompted enrollment of the patient in a research study at University of California, San Francisco to investigate her CSF with metagenomic next generation sequencing (mNGS), an unbiased approach to the identification of neuroinfectious diseases. The use of mNGS has gained momentum over the past several years, with several notable case reports and case series showcasing mNGS's ability to capture a broad range of infections with a single assay.[24,46–52] Total RNA is extracted from a patient's CSF, and complementary DNA (cDNA) is generated by reverse transcription with random hexamer primers. The cDNA is then converted into a library of random fragments, which is then sequenced on a massively parallel scale.[53] The resulting genomic data are then processed through a bioinformatics pipeline, which removes human, low-complexity, redundant, and poor-quality sequences. The remaining sequences are searched against all known organisms in the National Center for Biotechnology Information's GenBank database to identify the source of the high-quality, nonredundant, high-complexity, nonhuman sequences.[54–56] As a result, it is possible to identify the vast majority of known organisms, including viral, fungal, bacterial, and parasitic infections, whether or not they are being considered as part of the treating physician's differential diagnosis.

In this case, mNGS of total RNA extracted from 500 µl of the patient's CSF generated 5,750,572 pairs of 135 nucleotide sequences. After computational filtering, there were 67,334 pairs of high-quality, nonhuman, and nonredundant sequences. Of these, 2,725 sequence pairs unambiguously aligned to the genus *Taenia* with 99 to 100% similarity to *Taenia solium.* Based on a *z* score–based statistical model comparing the abundance of organisms in the sample to "no template" water controls and uninfected CSF samples, *T. solium* was the highest ranking organism, with all other identified microbes consistent with frequent environmental contaminants.[24] The diagnosis of NCC was confirmed with a clinical CSF cestode antigen assay and serology, which previously had not been performed.[57] Retrospective review of the patient's earlier meningeal biopsy did not reveal evidence of cysticerci.

Discussion of Pathology and Diagnosis

NCC is caused by infection with *T. solium*, the pork tapeworm. The condition leads to single or multiple intraparenchymal, ventricular, and subarachnoid cysts. NCC is endemic to Central America, South America, Sub-Saharan Africa, and Asia.[58] The hallmark of parenchymal NCC is the formation of a vesicular cyst that degenerates from a viable to a calcified form. During the viable stage, the parasite is thought to evade host defenses, and there is minimal to no immune response.[59] Cyst degeneration occurs when the immune system detects the parasite. The pathogen can no longer evade the immune system, and a robust granulomatous inflammatory response occurs, which can lead to significant neurological morbidity.[60,61] The final, calcified stage contains a dead parasite and creates minimal inflammatory response.[58,62] In subarachnoid NCC, the parasite can lack typical cystic structures, making it more challenging to identify on imaging. Subarachnoid NCC can also cause pronounced inflammation, which can be difficult to control and treat.[63,64] Spinal NCC is a rarer manifestation of NCC, with extramedullary arachnoid disease constituting the majority of cases.[26] Intracranial disease is also evident in most cases, but our patient only had subtle leptomeningeal enhancement on brain MRI and no intraparenchymal or intraventricular lesions.[26] In retrospect, the cyst seen on the patient's lumbar spine MRI in 2015, and the enhancing intradural extramedullary lumbar nodule seen in 2017, likely represented degenerating cysts, although even after the diagnosis was made there was debate among neuroradiologists about whether the findings on MRI in 2015 represented a *Taenia* cyst versus arachnoid scarring. At the time, these were not identified as parasitic, given the lack of more typical brain cysts, as well as the larger clinical context of recurrent fever and constitutional symptoms, which are unusual features of NCC.[65,66] Nevertheless, NCC should be considered in any patient with chronic meningitis who has spent time in an endemic area, even without typical MRI findings.

Follow-up

After the NCC diagnosis, the patient was started on dual antihelminthic therapy with praziquantel and albendazole. She was also started on the tumor necrosis factor α inhibitor etanercept to protect against an inflammatory reaction to degenerating cysts.[67] On this therapy, she tolerated a steroid taper for the first time in 2 years, and after a year was able to discontinue steroids completely. Following 3 months of treatment, her MRI remained stable, CSF demonstrated reduced leukocytosis (10 WBC/µl; 91% lymphocytes, 7% monocytes, 2% neutrophils) with normal protein and glucose, and the CSF cestode antigen was no longer detectable. CSF cestode antigen was again undetectable after a year of treatment, and so antihelminthic treatment and etanercept were stopped, with the intention of stopping anakinra in the coming months. She continues to have fatigue and low back and buttock pain but

has been able to increase her daily activities and has not had a severe symptom flare since starting specific therapy.

This case thus highlights the utility of mNGS for the diagnosis of atypical presentations of common infections.[24,68,69] The case also vividly illustrates that either improvement or lack of clinical deterioration in the setting of immunosuppression does not rule out an underlying infectious etiology, even after years of treatment.

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Author Contributions

E.S.B., A.V., A.N., J.L.D., and M.R.W. contributed to the conception and design of the study. E.S.B., E.M.O., T.N., D.S.R., A.V., A.N., L.M.K., H.A.S., K.C.Z., J.L.D., and M.R.W. contributed to the acquisition and analysis of data. E.S.B., P.S.R., and M.R.W. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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