CASE REPORT
A case of tuberculous meningitis

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Abstract

In Canada, meningitis is a rare manifestation of Mycobacterium tuberculosis infection. Additionally, a microbiological diagnosis can be difficult because of low sensitivity of mycobacterial tests of cerebrospinal fluid specimens. The typical presentation of meningitis is in the form of subacute meningitis, which is life threatening in the absence of appropriate treatment. Therefore, a high index of suspicion must be maintained. We report a case of tuberculous meningitis highlighting the presentation, workup, and treatment of this serious infection. This report highlights the challenges in identifying cases and establishing a timely diagnosis. Close monitoring of the patient and collecting multiple cerebrospinal fluid samples can improve sensitivity.

A 25-year-old female, originally from India and currently living in Nova Scotia, presented to a community emergency department with headache and chills. Three months prior, she had returned from a four-week trip to rural India, where she visited friends and relatives. She had a self-limited, three-day subjective fever with poorly described gastrointestinal and respiratory symptoms during her trip. Otherwise, she was previously healthy with no history of tuberculosis. In Nova Scotia, she had no direct cattle exposure or consumption of unpasteurized milk.

On initial presentation, she had an eight-day history of headache, chills, and flushing but was afebrile and no meningismus. She was treated for suspected migraine with minimal response and re-presented two days later with worsening headache, alternating chills and sweats, and a fluctuating level of consciousness (LOC). She was given acyclovir and transferred to a nearby tertiary care centre due to worsening confusion and disorientation. The patient was somnolent and unable to follow commands or communicate verbally. Her pupils were equal and reactive with no facial asymmetry or focal weakness. The initial lumbar puncture (LP) revealed a lymphocytic pleocytosis (Table 1). Magnetic resonance imaging (MRI) showed T2 hyperintensities in subcortical and, to a lesser extent, cortical frontal regions, many with nodular enhancement. There was also pial-arachnoid enhancement in the occipital lobe, left greater than right, and the cerebellar hemispheres. There was no basal or diffuse meningeal enhancement. Overall, these findings suggested acute disseminated encephalomyelitis (ADEM).

Her initial treatment included high dose steroids (methylprednisolone 1g/day) for possible ADEM and acyclovir for possible herpes simplex virus (HSV) antidiuretic hormone secretion (SIADH) with urine osmolality 831 mmol/kg, serum osmolality 247 mmol/

Table 1. Lumbar puncture results on three seperate days. Normal values in parentheses.

Test	Sample 1 Admission	Sample 2 PAD 4	Sample 3 PAD 7
Glucose	6.5 mol/L	5.9 mmol/L	2.6 mmol/L
Protein (0.15-0.45)	1.55 g/L	0.98 g/L	1.03 g/L
WBC (0-5)	249 × 10⁶/L	274 × 10⁶/L	776 × 10⁶/L
Lymphocytes	83%	76%	92%
RBC	75 × 10⁶/L	28 × 10⁶/L	114 × 10⁶/L
Gram stain	No bacteria	No bacteria	No bacteria
AFB	- -	- Smear negative - Growth of AFB (positive after discharge, incubation approximately 5 weeks)	- Smear negative - Growth of AFB (PAD20) - Real time PCR positive for *M. tuberculosis**
Other tests	- -	- HSV PCR negative	- Opening pressure 390mmH$_2$O - Crytococcal antigen negative - Enterovirus PCR negative

* referred out to National Reference Centre for Mycobacteriology, result not available until PAD22. AFB = acid-fast bacillus (test) PAD = post-admission day.

kg, and urine sodium 204 mmol/L. She was treated with fluid restriction. Pertinent negatives included blood cultures, vasculitis workup, and syphilis and HIV serology. She had a normal chest x-ray.

Her LOC improved significantly over the next 48 hours, but she continued to have headaches and fevers (39°C). On post admission day (PAD) 6, HSV was polymerase chain reaction (PCR) negative, so acyclovir was discontinued. Subsequently on PAD 7, her LOC decreased to a Glasgow Coma Scale (GCS) of 8 with fever (39.5°C), left cranial nerve six palsy, and meningismus. A third

LP showed an elevated opening pressure, decreased glucose, slightly elevated protein, and increased WBC (Table 1). A computed tomography (CT) scan did not show hydrocephalus, but a repeat MRI showed increased leptomeningeal enhancement affecting the brain, cord, and cauda equina. There was improvement in the foci of enhancement in the brain and no ongoing evidence of ADEM. Given the increased intracranial pressure (ICP), MRI, and clinical deterioration, empiric therapy for tuberculous (TB) meningitis was started with the typical primary regimen: isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), and rifampin (RIF). Since five days of methylprednisolone had just finished, dexamethasone 20 mg IV daily was added. A lumbar drain was placed for increasing neck pain and headache. A tuberculin skin test measured 27 mm and a CT chest (PAD 8) showed clusters of small centrilobular nodules in the upper lobes bilaterally with peripheral tree in bud nodularity in the left upper lobe. At this point, the smear of the cerebrospinal fluid (CSF) was negative for acid-fast bacilli (AFB) and mycobacterial culture was pending.

Given the diagnostic uncertainty, a biopsy of the left superior and middle frontal gyrus was performed, complicated by increased ICP and a frontal bleed. Pathology of the brain tissue showed only inflammatory changes with no infectious organisms found (final culture was negative). After seven days of TB therapy, she was symptomatically improving despite increasing liver enzymes (see Figure 1) so INH, RIF, and PZA were replaced with moxifloxacin and amikacin. On PAD 20, the third cerebrospinal fluid culture was positive for AFB (day 14 incubation), later identified as M. tuberculosis. The direct real time PCR from CSF was sent to the National Reference Centre for Mycobacteriology prior to the culture result and was ultimately positive for M. tuberculosis. The sputum, which was smear negative, eventually grew M. tuberculosis after discharge and incubating for 4 weeks. Infection prevention and control and public health were subsequently notified for contact tracing.

On discharge, 23 days after admission, her liver enzymes were improving and the medication regimen included EMB, RIF, moxifloxacin, amikacin, and dexamethasone. She continued to have a mild headache but normal consciousness. The isolate was susceptible to first line medications (INH, PZA, EMB, RIF) and amikacin was replaced with INH when her liver enzymes normalized (Figure 1). After two months of intensive phase therapy and steroid taper, she was recovering well and her regimen was reduced to RIF and INH for 10 months (12 months total treatment).
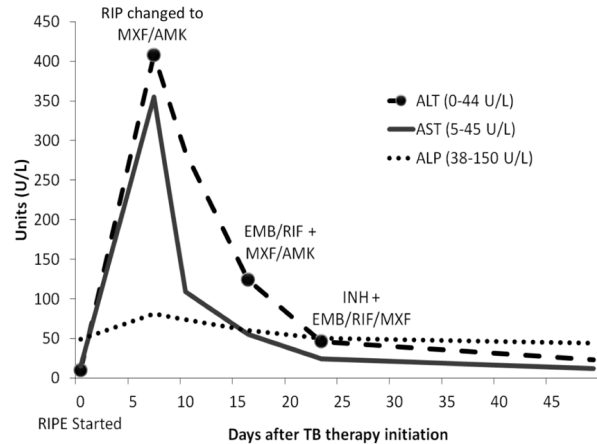

Figure 1. Changes in liver enzymes during TB therapy. ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, INH=isoniazid, RIF=rifampin, PZA=pyrazinamide, EMB= ethambutol, MXF=moxifloxacin, AMK=amikacin, RIP=RIF/INH/PZA. Normal values in parentheses.

Discussion

Tuberculosis, caused by the acid-fast bacillus M. tuberculosis, is a major source of morbidity and mortality globally, with a disproportionately high incidence in lower income countries in Asia and Sub-Saharan Africa.[1] TB typically causes respiratory illness but can manifest in many extrapulmonary forms. TB meningitis is often fatal or results in severe neurological impairment, even with treatment.[2] In 2013, 1640 cases of TB were reported in Canada (incidence rate 4.7/100,000) with central nervous system (CNS) infection in only 27 cases, none of which occurred in Atlantic Canada.[3] Immigrants from high-prevalence areas such as India (2013: incidence 171/100,000)[1] and immunosuppressed individuals (e.g., HIV) are at higher risk. In addition to the rarity of TB meningitis in Canada, the subacute presentation and diagnostic limitations complicate the timely identification and treatment of this life-threatening illness.

After inhaling tubercle bacilli, there is widespread haematogenous dissemination during the primary pulmonary infection resulting in the development of small, subendymal tuberculous foci in the brain.[4] Rarely, subsequent rupture of these foci into the subarachnoid space results in severe inflammation and TB meningitis.[4] The early clinical presentation of TB meningitis is that of a subacute meningitic illness. Unlike typical community acquired bacterial meningitis, there is a period of nonspecific symptoms such as headache, fever, vomiting, and anorexia, lasting anywhere from days to several weeks.[5] As seen in our case, clinical signs then progress to include meningeal stiffness, focal deficits, cranial nerve palsies (most commonly the sixth cranial nerve) and eventually increased intracranial pressure leading to alterations in

level of consciousness and mental state.[6-8] SIADH is a common but non-specific finding.

Once a patient is suspected to have any type of meningitis, a LP for analysis of CSF should be performed. In immunocompetent patients with TB meningitis, CSF analysis often shows an increased opening pressure (>250 mmH$_2$O), high white cell count (100-500 x10^6 cells/L) with a lymphocytic predominance (rarely polymorphonuclear leukocytes predominate early), high protein levels, and decreased CSF:blood glucose ratio.[2,5,9] However, these findings are not exclusive to TB meningitis and may be seen in subacute meningitis syndromes due to viruses, crypto-coccosis, syphilis, Borrelia burgdorferi, or malignancy.[6] HIV co-infected patients may have atypical findings such as normal cell count and glucose.[6] Therefore, a high degree of suspicion must be maintained to pursue appropriate microbiology analysis including culture and staining for AFB.[6] In this case, the patient's previous immigration, as well as her recent travel to India were key pieces of information on history in placing TB meningitis high on the differential, particularly after the clinical deterioration on treatment for ADEM.

The tests for CNS TB lack sensitivity and the slow-growing nature of the bacterium results in prolonged turn-around time of culture.[10,11] The low concentration of M. tuberculosis in CSF usually necessitates higher volumes (10-20 mL) and multiple samples to improve the sensitivity of stains and culture.[12,13] This is apparent in the presented case, where the second and third CSF samples were AFB smear negative and cultures did not become positive until after discharge and PAD 20, respectively. In one study, TB meningitis was confirmed by culture and microscopy in 52% and 37% of first samples, respectively.[13] With repeated sampling, 83% of patients had positive CSF culture and 87% had positive smears.[13] The sensitivities in another large case series were 27% for staining with Ziehl-Neelsen and 82% for automated liquid culture systems.[14] Nucleic acid amplification tests can provide a rapid diagnosis and detect dead bacteria (after treatment initiation) with a sensitivity reported between 57% and 94% for CSF samples.[14,15] As seen in this case, real time PCR can be positive with smear negative CSF samples. Therefore, a combination of rapid tests with confirmatory culture from multiple samples is required to obtain a definitive diagnosis.

As in other manifestations of active TB, a negative tuberculin skin test does not rule out TB meningitis. Approximately 22-24% of patients with TB meningitis will have active pulmonary disease and 30-50% may have an abnormal chest x-ray.[2] The patient in the presented case had minimal respiratory symptoms and a normal chest x-ray on initial work-up but was eventually found to have an abnormal CT chest and culture positive sputum. Findings on brain MRI may further support a diagnosis of TB meningitis and include the presence of basal exudates, basilar meningeal enhancement, and hydrocephalus.[9,16] As in this case, these findings may not be noted on initial presentation and require repeated imaging.

Regarding treatment, it has become common practice to treat TB meningitis with adjuvant corticosteroids. A 2008 Cochrane review on patient outcomes supports this practice by suggesting that HIV-negative TB meningitis patients should receive corticosteroid treatment in addition to standard TB treatment to reduce death and disabling neurological deficits.[17] Otherwise, the choice of first line therapy is the same as pulmonary TB: INH, RIF, PZA, and EMB.[2,18] While the latter two drugs can be discontinued at two months in fully susceptible TB, the INH and RIF are typically continued for an additional ten months in CNS infections. Disseminated rash, especially with mucous membrane involvement, hepatitis, or resistance may warrant the use of second line agents such as moxifloxacin and/or amikacin.

Importantly, infection control precautions should be considered when TB is in the differential diagnosis. Patients with pulmonary TB are infectious by aerosolization of mycobacteria.[2] The transmission risk varies depending on patient factors such as smear positivity, cough, HIV status, and treatment. Environmental factors such as crowding, appropriate infection control measures, and duration of exposure are also important.[2] Routine practices alone are required for TB meningitis provided there is no pulmonary disease. In this case, there was initially low likelihood of pulmonary TB given the absence of cough for two to three weeks and a normal chest x-ray. However, the findings on CT and concern of TB meningitis at that time would have precipitated airborne isolation and three sputum samples for AFB smear and culture. While this patient was less infectious than a smear positive patient the risk of transmission was not zero. Once the sputum was positive for culture, infection control and public health officials would perform contact tracing and testing for exposure as necessary. If three samples of sputum are negative, isolation can generally be discontinued unless pulmonary TB is still strongly suspected. In the latter case two weeks of isolation with effective TB treatment and clinical improvement is typically required.[2]

Conclusion

TB meningitis is a relatively rare diagnosis in Canada, but carries a high rate of morbidity and mortality. This report highlights the challenges in identifying cases and establishing a timely diagnosis. Historically, TB meningitis is more commonly missed and diagnosed

on autopsy compared to pulmonary disease.[19] The reasons for a late diagnosis are likely multifactorial including delayed patient presentation, failure to obtain an epidemiologic history, subacute nature of the presentation, and difficulty obtaining a timely microbiological diagnosis. While the clinical presentation in isolation is non-specific, an appropriate history of TB risk factors should raise the suspicion of TB meningitis. In addition, the clinician should not rely on a single patient encounter, radiological image, or CSF sample. Instead, patients need close monitoring and multiple CSF samples to improve sensitivity. Consideration for direct CSF PCR should be discussed with microbiology. Finally, the infection control issues of TB should always be contemplated when TB is in the narrow differential diagnosis.

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