

**CASE REPORT****Marchiafava-Bignami & *Mycobacterium tuberculosis***

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**ABSTRACT**

Bacterial meningitis is often considered to be the most likely medical condition in the differential diagnosis for the clinical presentation involving headache, fever, nuchal rigidity, and decreased level of consciousness. Bacterial pathogens most commonly isolated and responsible for meningitis include *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. However, we present a patient with the aforementioned clinical presentation, preceded by a fluctuating encephalopathy, a significant past history of alcohol abuse, demyelination of the corpus callosum noted on CT and MRI, and CSF cultures positive for *Mycobacterium tuberculosis* (M.Tb). To our knowledge, we present the first reported fatal case of tuberculous meningitis (TbM) associated with Marchiafava-Bignami disease (MBD).

**INTRODUCTION**

**M**archiafava-Bignami disease (MBD) is a rare condition involving necrosis, demyelination and eventual atrophy of the corpus callosum (CC). This rare disease was first described by Marchiafava and Bignami in 1903.<sup>1</sup> Approximately 200 cases of MBD have been reported in the literature to date.<sup>2</sup> It typically afflicts middle-aged males and was originally thought to be associated only with alcoholics consuming vast amounts of red wine over 10-20 years.<sup>3-4</sup> MBD was later found to be associated with all types of alcohols and severely malnourished non-alcoholic patients.<sup>2,5</sup>

The histology of MBD has been primarily characterized as a demyelinating process, however the spectrum of histologic changes include acute bleeding, chronic hemosiderin deposits, cavitations and/or cyst formation in the CC.<sup>6</sup> Although the pathogenesis of MBD is unknown, theories include alcohol related toxic metabolite-induced damage to the CC and a more vascular basis of the disease.<sup>2</sup>

A clinical classification of MBD has been developed and includes acute, subacute and chronic presentations for MBD:<sup>4</sup>

- **Acute MBD**

Characterized by sudden onset of impaired level of consciousness (LOC) and seizures, with progression to coma. Most patients die within several days of onset.

- **Subacute MBD**

Characterized by sudden onset of dementia, rapidly progressing to a vegetative state. Patients usually progress to death within a few months of onset.

- **Chronic MBD**

The most frequently recognized clinical presentation of MBD considering the improvements and accessibility to brain imaging, involves a broad spectrum of clinical presentations including: motor (ataxia, apraxia, and gait disturbances), cognitive, and sensory disturbances.

In addition to the diffuse effects of alcohol on the brain, including cortical, cerebellar vermis, and hemispheric atrophy, the following MRI findings are associated with MBD: an acute phase involving diffuse swelling of the CC and a post-acute/chronic phase which involves symmetrical atrophy of the CC with focal hyperintensity on T2 and hypointensity on T1 weighted images.<sup>2</sup>

The differential diagnosis of the radiologic findings associated with MBD include: a demyelinating process secondary to exogenous toxins (i.e. organic solvents), infarction of anterior cerebral arteries resulting in necrosis of the CC, Wernicke's encephalopathy, and Alzheimer's disease with CC atrophy.<sup>2</sup>

The diagnosis of MBD involves a significant past history of alcohol abuse and/or severe malnutrition, in conjunction with a clinical presentation as described above and noted CC lesions on CT or MRI. The only treatment for MBD involves supportive therapy, cessation of alcohol consumption and nutritional support.

### ***Mycobacterium tuberculosis meningitis***

Although *Mycobacterium tuberculosis* (M. Tb) primarily affects the lungs, it can cause disease in almost any tissue, including the brain. Central nervous system (CNS) tuberculosis includes meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis. The first noted description of tuberculous meningitis (TbM) was in Robert Whytt's 1768 monograph, *Observations of Dropsy in the Brain*, and it became a distinct pathological entity in 1836.<sup>7</sup> Currently, Canada has one of the lowest reported incidence rates of M. Tb in the world.<sup>8</sup> The incidence of CNS Tb is directly related to the prevalence of Tb in the community.<sup>8</sup> In Canada, the dominant form of Tb CNS infection is meningitis.<sup>9</sup>

TbM develops most commonly as a complication of post-primary infection in infants and young children and from chronic reactivation bacilleemia in older adults with immune deficiency caused by aging, alcoholism, substance abuse, malnutrition, malignancy, head trauma and HIV infection.

For prognostic reasons and therapy, patients are often categorized on presentation by their clinical stage of TbM:<sup>10</sup>

- **Stage I:** patients are lucid with non-specific symptoms and signs including headache, malaise, fever and anorexia with no focal neurologic signs or evidence of hydrocephalus.
- **Stage II:** patients are confused or have focal signs, such as cranial nerve palsies (VI most frequent followed by III,IV,VII) or hemiparesis.
- **Stage III:** represents advanced illness with delirium, stupor, coma, dense hemiplegia, seizures and/or abnormal movements.

The diagnosis of TbM can be difficult. Maintaining a high index of suspicion is vital in order to initiate prompt therapy. Lumbar puncture (LP) and CSF analysis are essential in diagnosing TbM. CSF pressures are usually higher than normal. CSF analysis usually reveals elevated protein, a low glucose concentration, and a mononuclear pleocytosis.<sup>11</sup> Early in the course of the illness polymorphonuclear leukocytes (PMN) can predominate. This rapidly changes to a lymphocytic response but can briefly revert to a PMN reaction on initiation of therapy, which is associated with transient clinical deterioration.<sup>12</sup> CSF smears for acid fast bacilli (AFB) and culture for M.Tb show significantly increasing yields with repeated sampling (37% on one smear and 87% when four serial specimens are examined).<sup>10</sup>

Other methods to aid in the diagnosis of TbM include: PCR (sensitivity of 60%),<sup>13</sup> a dot-immunobinding assay that measures circulating anti-mycobacterial antibodies in CSF specimens for rapid laboratory diagnosis (although its practical utility requires further studies),<sup>14</sup> and neuroradiology (CT and MRI).

If TbM is suspected, specific antituberculous chemotherapy should be initiated immediately and not delayed until proof of an infection has been obtained. First-line therapy includes isoniazid (INH - 10 mg/kg/day), rifampin (600 mg in adults), and pyrazinamide (PZA - 25 -35mg/kg/day) which can be administered orally and penetrates the CSF readily to achieve levels that exceed the inhibitory concentration of sensitive strains.

These are given for two months followed by INH and rifampin alone.<sup>15</sup> In cases where drug resistance is a concern, a fourth drug (either ethambutol or streptomycin) should be added for the first two months.<sup>16</sup> It is recommended that therapy be administered for a total of twelve months in the usual case of a drug-sensitive infection. In multi-drug resistant infections, the duration of therapy should be extended for a total of 18 to 24 months.<sup>17,18</sup> Corticosteroids can be used adjunctively in stage II and III disease, acute "encephalitis" presentation, cerebral edema, "therapeutic paradox", spinal block, head CT showing marked basilar enhancement and intracerebral tuberculoma with edema.<sup>19</sup>

### **CASE PRESENTATION**

We present a fatal case of suspected Marchiafava-Bignami disease associated with *Mycobacterium tuberculosis* meningitis in a 54 year old white Canadian male with an extensive past medical history including: grade III ischemic cardiomyopathy, chronic atrial fibrillation, elevated cholesterol, hypertension, forty pack-year smoking history, type II diabetes mellitus, Addison's disease, alcohol abuse of > 26 oz/week (discontinued for 18 months), thalassemia trait, and positive Tb skin test but no documented active disease.

His family history was significant for Tb in his mother and one sister.

Medications prior to admission to hospital included: carvedilol 25mg b.i.d., atorvastatin 20 mg o.d., warfarin as per internationalized ratio (INR), repaglinide 2 mg t.i.d, digoxin 0.0625 mg o.d, insulin, prednisone 25 mg qam and 20 mg qpm, ramipril 5 mg o.d., docusate sodium 100 mg b.i.d, and ativan 1 mg qhs.

Initially, the patient presented to a community hospital with signs and symptoms of gastroenteritis and acute renal failure. Both conditions resolved following a four day admission to hospital and intravenous hydration. The patient was subsequently discharged home but soon developed bilateral frontal headaches persisting with no associated symptoms or aggravating factors for two weeks. The patient was then readmitted to hospital with persistent headache and increasing confusion.

A lumbar puncture (LP) revealed a glucose of 6.8 mmol/L, protein of 1.48 g/L and white blood cell count was 518 x 106/L with predominant lymphocytosis. He was diagnosed with viral encephalitis/meningitis and was started on a 14 day course of acyclovir. Metronidazole and cefotaxime were also added as broad-spectrum coverage for bacterial meningitis.

He was subsequently transferred to the Intensive Care Unit (ICU) at our facility because of a temperature of 38°C, impaired level of consciousness, increasing confusional state, diffuse headache, and neck stiffness with photophobia. In the ICU, the patient's condition rapidly continued to deteriorate and he subsequently required intubation. Multiple serologic, radiologic, and CSF investigations were completed, as outlined in Table 1 to 3 and Figure 1.

Following a CT scan demonstrating no mass effect or mid-line shift, and normal ventricles and basal cisterns, a second LP was done. The CSF was suggestive of a bacterial infection, because of predominant neutrophilia. With continued deterioro-

ration, no response to broad spectrum antimicrobial agents, and considering the patient's strong family history for Tb, pyrazinamide and rifampin were empirically added to cover the possibility of TbM.

Cerebral angiogram, done the following day, revealed no intracranial blood flow. Following a discussion with the family, life-support was withdrawn and the patient expired shortly thereafter. A few days following the patient's death, CSF cultures grew positive for M.Tb, despite the initial CSF sample being negative for acid fast bacilli.

**Table 1.** Pertinent serologic investigations

Investigation	Result (Reference Range/Normal)
Blood Cultures	Negative x three sets
Histoplasmosis immunodiffusion/ complement fixation	Non-reactive
Leukocytes (x10 <sup>9</sup> /L)	10.1 (4.0-11.0)
Absolute Granulocytes (x10 <sup>9</sup> /L)	9.4 (2.0-7.5)
Absolute Lymphocytes (x10 <sup>9</sup> /L)	0.4 (1.5-4.0)
Hemoglobin (x10 <sup>9</sup> /L)	123 (130-180)
Platelets (x10 <sup>9</sup> /L)	198 (150-400)
TSH	0.44 (0.5-4.0)
ANA	Negative
Rheumatoid Factor	< 11 (<11)
C3 (g/L)	1.09 (0.73-1.73)
C4 (g/L)	0.3 (0.13-0.52)
Billirubin, AST, ALT, GGT, ALP	Within Reference Range
Amylase and lipase	Within Reference Range
Calcium, Phosphate, and Magnesium	Within Reference Range

**Table 2.** Pertinent radiologic investigations

Chest Xray	Reticular nodular interstitial disease of the lungs
CT Head with/without Contrast x 3	Mild generalized cerebral atrophy with a focal hypodensity in the splenium of the corpus callosum. No mass effect or midline shift. Ventricles and basal cisterns are within normal limits. No evidence of ventricular hemorrhage.
MRI	Dramatic change from previous CT one day earlier with diffuse cerebral edema, coning and lack of visualization of the intracranial arteries compatible with brain death. Increased signal throughout the body of the corpus callosum, particularly in the splenium.
Cerebral Angiogram	No evidence of intracranial blood flow consistent with angiographically determined brain death.

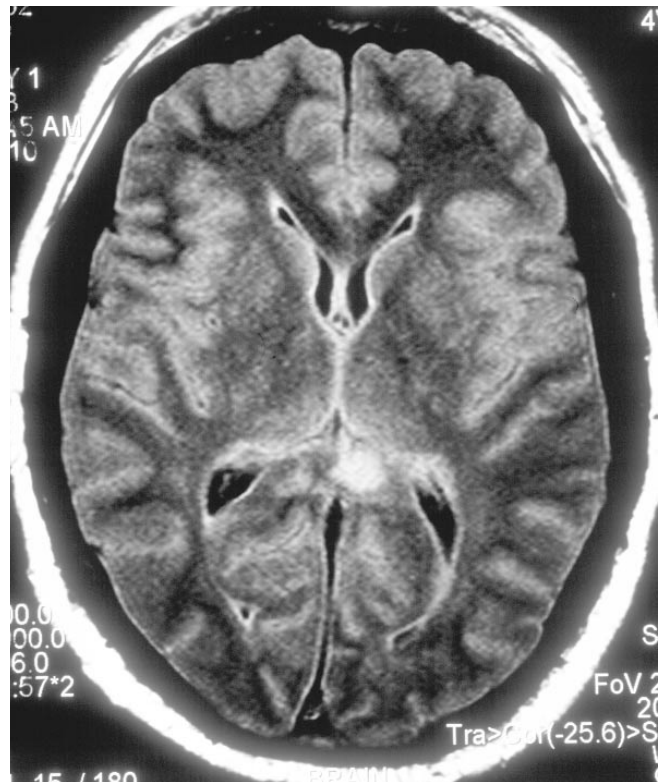
**Table 3.** Pertinent cerebrospinal fluid investigations

Glucose (mmol/L)	2.3 (2.2-3.9)
Protein (g/L)	1.55 (<0.45)
Leukocytes (x10 <sup>6</sup> /L)/Neutrophils (%)	246 (0-5)/74%
Erythrocytes (x 10 <sup>6</sup> /L)	15
Culture for Tb	Positive
Xanthochromia, Stain for Acid Fast Bacilli, Cryptococcus latex Antigen, Virology, and CMV IgM antibody	Negative
VDRL and Toxoplasmosis latex agglutination	Non-reactive

## DISCUSSION

According to Sir William Osler, most clinical presentations can be explained by a single disease. However, we presented a fatal case of a patient with both, TbM and suspected MBD.

Considering the patient's past history of significant alcohol abuse and suspicious CC lesion noted on both MRI (Figure 1) and CT, a diagnosis of Marchiafava-Bignami disease was considered to be a strong contributory factor to the etiology of his death. While the histology of the CC lesion could not be elucidated as his family had refused an autopsy, it was hypothesized that he had suffered from an acute presentation of MBD involving altered level of consciousness progressing to a comatose



**Figure 1.** MRI of the cranium showing increased signal throughout the body of the corpus callosum, particularly in the splenium.

state and death. There are no published data to help explain why people with MBD and the classic CC lesion progress to coma and eventually expire. It was not until the CSF cultures grew positive for M.Tb, that the cause of this man's death was fully understood.

While Canada has one of the lowest reported incidence rates of Tb in the world, the patient that we present did have a strong family history for Tb in his mother and sister, and was noted to have a positive Tb skin test in the past. The patient was also immunocompromised due to his daily prednisone and multiple co-morbidities including a long history of alcohol abuse and type II diabetes mellitus. Prior to his admission to the community hospital, he was most likely experiencing signs and symptoms consistent with TbM clinical Stage I, as he was lucid with only a mild, but persistent headache. As his TbM progressed, he developed signs and symptoms consistent with Stage II, including increasing confusion, headache, and fever.

Upon admission to hospital, initial LP revealed a lymphocyte predominant CSF, consistent with both viral encephalitis/meningitis and TbM. However, Tb was not considered to be a likely pathogen at this point and only acyclovir and broad-spectrum antibiotics were initiated. As he continued to deteriorate into a comatose state, displaying signs consistent with TbM clinical stage III, antituberculous chemotherapy was initiated. His second LP was again negative for AFB and was PMN predominant, highly suggestive of a bacterial meningitis, but also consistent with the PMN reaction seen following initiation of antituberculous chemotherapy.<sup>14</sup> An additional feature possibly accounting for the PMNs may be necrosis of the CC. PCR and Dot-Iba were not conducted to assess for the possibility of TbM. CTs and MRI did not reveal classic changes consistent with TbM.

It is hard to establish a clear connection between TbM and MBD. One could speculate that the high metabolic demand posed by TbM in a patient with multi-system disease could have created a form of nutritional imbalance in a toxic-like state similar to what can potentially induce MBD. The MRI did not show involvement of brainstem or paraventricular areas suggestive of other entities such as central pontine myelinolysis which has been reported in association with TbM.<sup>20</sup>

## CONCLUSION

When patients present with gradually progressive neurologic deterioration, fever, and headache, a subacute or chronic meningeal infectious process should be entertained. While

Canada has one of the lowest incidence rates of Tb meningitis, it should still be considered a potential pathogen, especially in a patient with a strong family history of Tb. If Tb is suspected, then repeated LPs for both Tb cultures and AFBs, in conjunction with PCR, can significantly increase the diagnostic yield of TbM. The diagnosis of TbM requires a high index of suspicion and empiric therapy should be initiated as soon as possible to ensure favorable outcomes. †

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### Author Biographies

**J-D Schwalm** holds an MD from McMaster and is currently in his first year of the McMaster University Cardiology Residency Program.

**Callista Phillips** holds a medical degree and specialty training in Pathology from Bombay University, India. She was selected through the IMG program and is currently a PGY4 in internal medicine specializing in medical oncology.

**Jaime Silva** is a consultant in neurology and a consultant for the MS clinic at the Hamilton Health Sciences. He is also assistant professor of medicine, Division of Neurology at McMaster University, Director of the Stroke Research Program, and co-director of the Acute Stroke Unit at the Hamilton General Hospital.