



## Case report

# Disseminated tuberculosis confounding a co-morbid primary CNS lymphoma

Don Bambino Geno Tai<sup>a,\*</sup>, Christopher S Graffeo<sup>b</sup>, Amy Kotsenas<sup>c</sup>, Fredric B Meyer<sup>b</sup>, Abinash Virk<sup>a</sup>

<sup>a</sup> Division of Infectious Diseases, Mayo Clinic, USA

<sup>b</sup> Department of Neurosurgery, Mayo Clinic, USA

<sup>c</sup> Division of Neuroradiology, Mayo Clinic, USA



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## ABSTRACT

Primary central nervous system lymphoma is notoriously challenging to diagnose in immunocompetent patients as it is an uncommon diagnosis. We present a case of synchronous diagnosis with tuberculosis. A 60-year-old woman presented with cognitive difficulties, memory loss, social withdrawal, unintentional weight loss, and night sweats, the work-up of which ultimately identified multiple brain lesions and mediastinal adenopathy. Brain biopsy showed lymphohistiocytic infiltrate, while mediastinal node histopathology showed necrotizing granulomas, and cultures grew *Mycobacterium tuberculosis*. The patient was initiated on anti-tuberculosis therapy. However, follow-up brain MRI demonstrated disease progression, prompting repeat brain biopsy, which in turn confirmed the diagnosis of diffuse large B-cell lymphoma. Although unrelated synchronous diagnoses are rare, the potential for clinically significant confounding is considerable—particularly where disease markers may overlap, as is often the case with infectious, inflammatory, and neoplastic processes. The present case illustrates the importance of diligence in ruling out competing diagnosis, and timely action when an anticipated finding or response-to-treatment is not observed.

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## Background

Primary central nervous system lymphoma (PCNSL) is rare in immunocompetent patients, constituting only 5% of extra-nodal lymphomas. Most are diffuse large B-cell lymphomas and require biopsy for diagnosis [1]. Central nervous system tuberculosis (TB) can also present as brain tumors called tuberculomas, and diagnosed through tissue cultures [2]. Confounding between the two diseases has clinical implications as treatment strategies are vastly divergent. PCNSL require chemotherapy with high-dose methotrexate that would be anticipated to worsen an infectious process, while anti-TB medications have no impact on PCNSL, and diagnostic delay is associated with a risk of clinically significant disease progression in the setting of malignancy. We present a novel case of concurrent PCNSL and disseminated TB presenting together in an immunocompetent host.

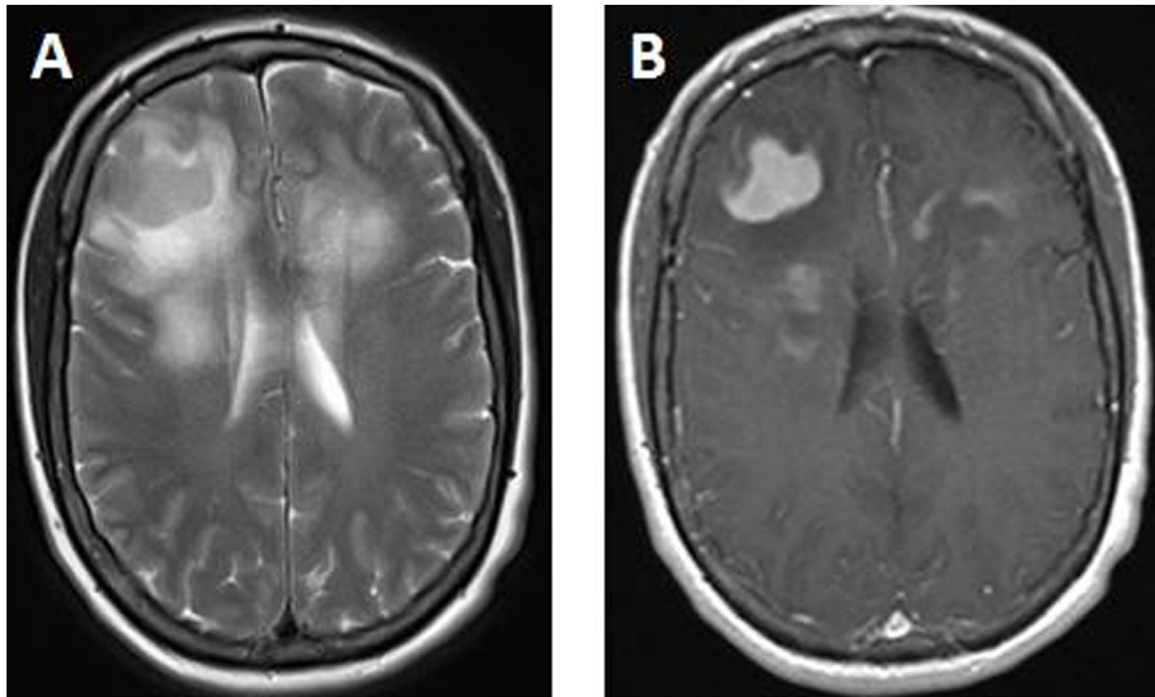
### Case Report

A 60-year-old previously healthy female presented to her local health care providers with cognitive difficulties, memory loss, and social withdrawal, associated with unintentional 40-pound weight loss, and new night sweats. Brain MRI demonstrated multifocal mass lesions (Fig. 1). Stereotactic needle biopsy showed nonspecific perivascular lymphohistiocytic infiltrates. PCNSL could not be confirmed, and no microbiologic studies were performed on the brain tissue. Of note, she was a long-term Oklahoma resident with unremarkable social and personal history.

HIV, syphilis, *Histoplasma* serum and urinary antigen, cryptococcal serum antigen, *Aspergillus* antigen, *Blastomyces* antibodies, *Coccidioides* antibodies, *Tropheryma whipplei* serum PCR, and tuberculosis interferon gamma release assay (TB-IGRA) were negative. Blood cultures were negative. CSF analysis showed a white blood cell count of four lymphocytes, with no malignant cells identified, and CSF cultures for bacteria and mycobacteria were also negative. CT-scan of chest, abdomen, and pelvis was unremarkable.

The patient was initiated by her local doctor on empiric course of corticosteroid therapy. An updated MRI at two weeks demonstrated interval decrease in brain lesions. She came to our institution for a second opinion and underwent repeat lumbar

\* Corresponding author at: Mayo Clinic, 200 1st street SW, Rochester, MN, USA.  
E-mail address: [tai.don@mayo.edu](mailto:tai.don@mayo.edu) (D.B.G. Tai).



**Fig. 1.** Axial T2 weighted (A) and axial contrast-enhanced T1-weighted (B) MRI obtained at presentation demonstrates multifocal, bifrontal poorly margined enhancing mass lesions with surrounding vasogenic edema.

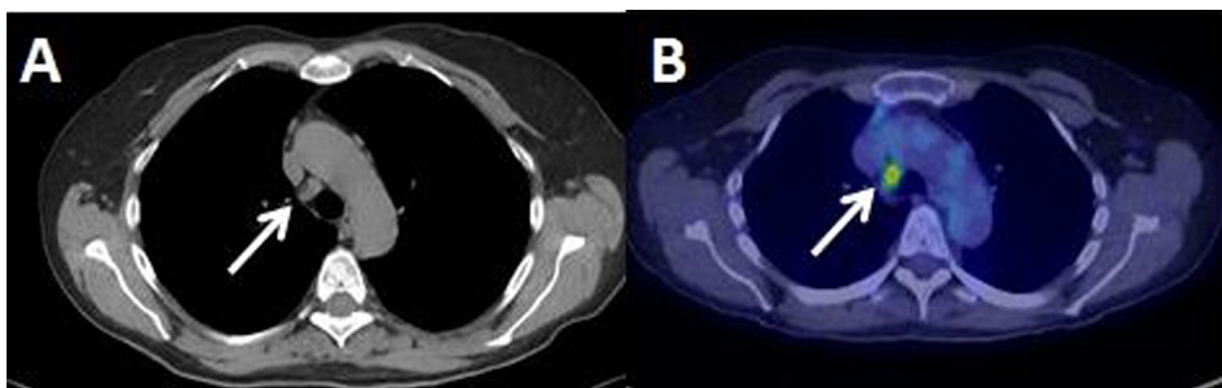
puncture. Total nucleated cells in CSF were 13, 98 % lymphocytes, total protein 42 mg/dL, and glucose 59 mg/dL. Additional infectious work-up was negative, including CSF bacterial, mycobacterial, and fungal cultures, meningitis-encephalitis multiplex PCR, Epstein Barr Virus (EBV) PCR, and free-living amebae PCR were negative. Autoimmune encephalopathy panel, oligoclonal bands, and IgG index were also negative. Outside histopathology underwent direct review by our pathology team, who concurred with the result. TB-IGRA was positive twice this time and she had not been exposed to TB in the interim. A repeat CT chest and PET-CT demonstrated several scattered FDG-avid sub-centimeter mediastinal lymph nodes (Fig. 2), which underwent subsequent mediastinoscopic biopsy, ultimately revealing necrotizing granulomas. Tissue cultures grew pan-susceptible *Mycobacterium tuberculosis* (MTB). Three serial induced sputum cultures were negative.

Given the presumed diagnosis of disseminated TB with tuberculoma, the patient was initiated on standard-of-care quadruple therapy with isoniazid, rifampin, pyrazinamide, and ethambutol together with a tapered course of corticosteroids. Due

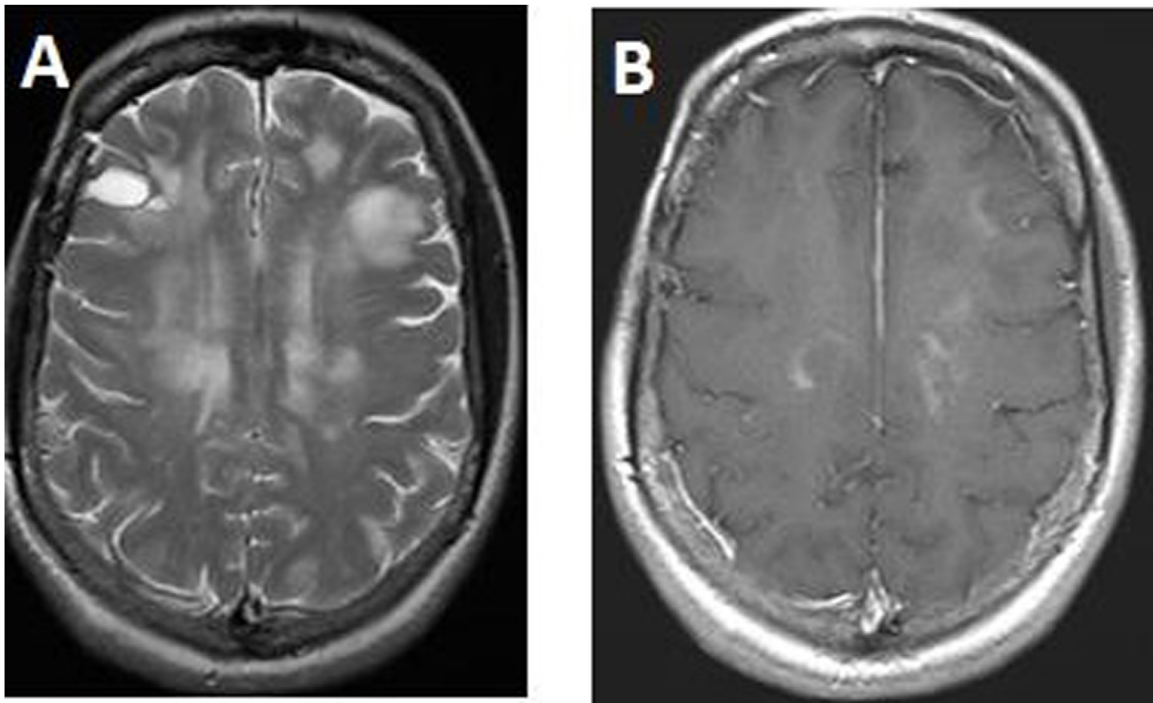
to high degree of suspicion for PCNSL, repeat brain MRI at 8 weeks following initiation of anti-TB treatment was done, demonstrating recurrent multifocal, bifrontal enhancing mass lesions (Fig. 3). Repeat brain biopsy confirmed PCNSL, diffuse large B-cell type. Tissue cultures and PCR were negative for MTB or any other infectious etiology. The patient was referred to hematology and completed eight cycles of methotrexate, rituximab, and temozolomide. She is planned for autologous stem-cell transplantation.

### Discussion

Lymphoma and TB are among the most storied of medicine's "great mimics," often mimicking not only one another, but a wide protean swath of other common and rare diagnoses. The presence of numerous overlapping features further confounds definitive diagnosis, with a range of non-specific clinical symptoms and radiographic findings characterizing both, as well as the pathologic finding of necrotizing granulomas. Misdiagnosis is widely reported, and numerous preceding studies have highlighted the specific and general challenges



**Fig. 2.** Axial non-contrast chest CT (A) and PET (B) an FDG-avid mediastinal lymph node (arrows).



**Fig. 3.** Axial T2 weighted (A) and axial contrast-enhanced T1-weighted (B) MRI obtained after initiation of RIPE therapy demonstrate recurrent multifocal, bifrontal poorly marginated enhancing mass lesions with surrounding vasogenic edema.

**Table 1**  
Cases of misdiagnosis of PCNSL and CNS TB.

Age / Sex / Comorbidity	Presentation	Initial diagnosis / treatment	Basis of diagnosis	Final diagnosis	Definitive diagnostic test
19 / M / Healthy	multiple enhancing brain lesions on MRI	CNS TB / Anti-TB drugs	Clinical	diffuse cerebral lymphoma	Autopsy
50 / M / AIDS	bright intramedullary lesion at T9/T10 levels with cord expansion on MRI	PCNSL / radiation therapy	CSF EBV PCR	CNS tuberculosis	Biopsy
58 / F / Diabetes	diabetes insipidus and panhypopituitarism, suprasellar mass on MRI	CNS TB / Anti-TB drugs, steroids	CSF MTB PCR	PCNSL	Biopsy

inherent to diagnostically differentiating between these two entities [3].

Three cases were reported in literature describing misdiagnosis of PCNSL and TB. All cases highlighted that clinicians were misled to think one for another. There was a delay in definitive diagnosis resulting to deaths (Table 1) [4–6]. Although exceedingly rare, co-morbid lymphoma and tuberculosis presents perhaps an apical challenge within this diagnostic niche—and one with significant clinical implications, given the opposed nature of the preferred treatments in each disease. There was only one other case of concurrent PCNSL and TB reported in literature. It was in an immunocompromised, renal transplant patient with CNS T-cell lymphoma and disseminated TB. Both conditions were diagnosed in time and resulted in favorable outcome [7].

Indeed, for other cases of coexistent lymphoma and opportunistic infections in the same organ, clarity is often reached when patients either do not improve on empirical therapy or deteriorate in spite of it, prompting consideration of another treatment that ultimately reveals the true diagnosis. Even more often, repeat biopsy or additional invasive work-up is required beyond the first “diagnostic” test to establish true identity of the underlying disease [8]. Still further confounding is introduced by patient-specific complicating factors, such as non-infectious

co-morbidities, particularly those with significant impacts on their immune status.

From a practical perspective, if a patient is being worked up for PCNSL and TB, confirmation of TB via a secondary site warrants expedited anti-TB treatment. If brain biopsy is inconclusive, a trial of anti-TB drugs may be considered. Brain biopsy may be inconclusive if tissue size is not enough. When this route is chosen, close follow-up with repeat imaging is mandatory. Repeat tissue diagnosis should be done as soon as clinical improvement is not noted following an appropriate trial of empiric therapy.

Particular care is needed in patients undergoing induction therapy for suspected PCNSL when TB remains under consideration as an alternative or concomitant diagnosis. In contrast to the current patient, individuals initiated on chemotherapy prior to anti-TB treatments may develop serious disease exacerbations due to compromised immune status. Fortunately for our patient, several months of anti-TB treatment had elapsed prior to induction chemotherapy for PCNSL, providing a critical buffer in controlling the TB before potentially weakening her immune response. Tuberculosis cannot be ruled out with negative mycobacterial cultures owing in part to administration of anti-TB treatment.

The present case emphasizes the importance of considering not just multiple items on the differential for each patient, but the

possibility of multiple co-morbid diseases—including those with overlapping clinical features. PCNSL and TB are rarely observed in tandem; however, as the present case demonstrates, they highlight the importance of establishing a diagnostic framework in considering these rare cases.

#### Author contribution

All authors have contributed to writing of manuscript

#### Consent

The case does not have personal identifying detail. Under state law, medical records are authorized by patients for research unless declined in writing.

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#### Declaration of Competing Interest

Nothing to declare.

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