

**Case Report**
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## Rare Case of Cryptococcal Meningitis in Non-HIV Patient with Mantle Cell Lymphoma Associated with Acalabrutinib (Tyrosine Kinase Inhibitor)

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**ABSTRACT**

Cryptococcus neoformans infections are more common among immunosuppressed individuals, causing the most widespread opportunistic CNS infection among HIV-positive patients [1]. Specifically, those with cellular immunosuppression, such as patients with HIV positive CD4 counts less than 100. When a patient presents with atypical symptoms, it can be difficult to diagnose due to its infrequent presentation in HIV negative patients. Due to the rarity of encounters in HIV-negative patients, when atypical symptoms are present, it poses a diagnostic challenge. Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin B-cell lymphoma that is known to be associated with cellular immunosuppression [2]. This demonstrates the need for early diagnosis and recognition of cryptococcal infections and as a physician should be vigilant to diagnose cryptococcal who is on Acalabrutinib with MCL [3]. CLL patients receiving ibrutinib should be evaluated for cryptococcal infection, which is potentially life threatening if overlooked [4]. Meningitis caused by Cryptococcus mainly presents with fever and altered mental status but in this case, our patient 78-year-old male with mantle cell lymphoma, undergoing a regimen of Rituximab-Bendamustine (BR) in combination with acalabrutinib (TKI), presented with hypotension to ED in June 2021. Cryptococcal infection in patient receiving ibrutinib were mostly reported in patients with Chronic lymphocytic leukemia, who have poor immune reconstitution. Here we are reporting case of cryptococcal meningoencephalitis in patient with MCL on acalabrutinib which is never reported before.

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**Introduction**

Cryptococcal neoformans infections is very common in HIV seropositive patients. Mainly HIV-positive patients with a CD4 count less than 100 or those with cell-mediated immunosuppression. As it is rarely seen in HIV-negative patients, presenting with atypical symptoms makes it a challenge for physicians to diagnose. A rare form of non-Hodgkin lymphoma, Mantle cell lymphoma (MCL) is associated with immune suppression and cryptococcal infections. Here, we report a case of disseminated cryptococcal disease in a patient with MCL (mantle cell lymphoma) on acalabrutinib (TKI).

**Case Presentation**

A 78-year-old man suffering from chronic systolic heart failure with reduced ejection fraction, ischemic cardiomyopathy s/p CABG in 2006 with AICD (st Jude placement in 2009), s/p Coronary angioplasty in 2010 s/p stent in left main coronary & LCX, Dyslipidemia, hypertension, and mantle cell lymphoma [Rituximab-Bendamustine (BR) in combination with acalabrutinib (TKI)] was brought to the Emergency Department of St. Michael's Medical Center in June of 2021 with a complaint of lightheadedness. The patient received last dose of chemotherapy on June 15 (10 days prior to admission). The patient's vitals on admission showed blood pressure 96/47 mmHg, heart rate 110/minute, temperature 98.8 F, and RR 17. All physical exams were within normal limits. Several laboratory results were normal,

except for a serum osmolality of 268 with Mild hyponatremia serum sodium 132. The patient's Hb was 8.8, hematocrit was 26.3, platelet count was  $146 \times 10^3/\mu\text{L}$  and RDW was 17.6. The EKG was sinus tachycardia and the chest x-ray showed no pneumonia, edema, or pneumothorax. Hypotension and tachycardia were initially attributed to hyponatremia due to volume depletion, and IV fluids were administered which responded well. Patient had a NSVT of 20 beats and frequent PVCs. Cardiology was consulted and recommended no active intervention at this time. Echocardiogram showed LVEF 35-40%, severely decreased LV systolic function with global hypokinesis of left ventricle, mild AR & TR, Moderate MR. Patient developed a fever of 101.8 F overnight. The patient underwent a septic workup, ID was consulted, was treated with empiric antibiotics (cefepime and vancomycin), and his electrolytes were replenished. patient had an intermittent course of hypotension during course of admission. We performed head CT without contrast, which showed no acute intracranial abnormalities, mild volume loss, and moderate chronic microangiopathy. Patient's mental status was gradually deteriorated within a week of admission. Neurology was consulted for waxing and waning of mental status and recommended EEG which showed asymptomatic left temporal epileptic discharges and was started on Keppra. As of the sixth day of admission, one out of two bottles of blood cultures showed cryptococcal growth. LP was planned.

### Lumbar puncture

Lumbar puncture	1 <sup>st</sup> LP	2 <sup>nd</sup> LP	3 <sup>rd</sup> LP
Serum cryptococcal antigen titer	1:128	1:128	1:128
CSF cryptococcal Antigen Titer	1:128	1:128	1:256
Sites of cryptococcal involvement	Blood, CSF	Blood csf	Blood csf
CSF opening pressure (cm CSF)	24 cm H <sub>2</sub> O	22 cm H <sub>2</sub> O	25 cm H <sub>2</sub> O
CSF nucleated cells (normal cell count 0–5/mm <sup>3</sup> )	2	0	0
CSF protein (mg/dL) (normal range 15–50 mg/dL)	107.7	146.9	120.1
CSF glucose (mg/dL)	28	28	45
CSF India ink stain	Positive	positive	positive
CSF fungal culture	2+ budding yeast	2+ budding yeast	2+ budding yeast
CSF WBC	3	26	26
CSF RBC	4	35	14
CSF Neutrophil	44%	7%	2%
CSF lymphocyte	25%	63%	62%
CSF eosinophils	6%	18%	19%
CSF monocyte	25%	12%	17%

The diagnosis of cryptococcal meningitis was made and Intensive liposomal administration of Amphotericin B and oral 5-Flucytosine were initiated for the patient. Although patients’ mental status improved for 1-2 days after receiving LP and antifungal medication, it deteriorated again on subsequent days. During subsequent LPs, CSF pressure was high, and AMS improved with each LP.

### Outcome & Follow-up

Patient was started on induction therapy (amphotericin-B and flucytosine) for cryptococcal for 12 days. After induction therapy was stopped due to severe cytopenia, consolidation therapy for cryptococcal was begun from the 12th day, but after deteriorating condition, induction therapy for cryptococcal was again initiated.

CBC	On Admission	After Receiving induction Rx
WBC	6.40	2.9
RBC	2.98	2.82
Hb	8.8	8.6
Hematocrit	26.3	24.3
MCV	88.1	86.8
MCH	29.6	30.4
RDW	17.6	21.4
Platelet	146	158

**Medical Abbreviations:** (MCL) Mantle cell lymphoma, (TKI) Tyrosine kinase inhibitor, (CLL) chronic lymphocytic lymphoma, (ID) infection department, (CSF) Cerebro spinal fluid, (RDW) red cell distribution, (WBC) white blood cell, (Hb) Hemoglobin, (RBC) Red blood cell, (CBC) complete blood count, (LP) Lumbar puncture.

### Discussion

The case illustrates a rare complication of TKI treatment, cryptococcal meningitis, and the diagnostic dilemma that it presents. In patients being treated with tyrosine kinase inhibitors or presenting with atypical symptoms like hypotension or no response to antibiotics in the context of sepsis, cryptococcal infection should be high on the differential diagnosis list. Patients who have not responded clinically to empiric antibiotic treatment should have a lumbar puncture as early as possible if they are suspected of cryptococcal meningitis. Patients with MCL are generally not at high risk for cryptococcal meningitis. However, the use of

BTK inhibitor increases their risk of fungal infections [3]. Cell immunity plays an important role in cryptococcal infection and should be relatively intact in MCL patients who are on cytotoxic chemotherapies but the indirect effect of Acalabrutinib (BTK) on immunity might contribute to the infection [3]. BTK has been demonstrated to participate in the regulation of nitric oxide induction and bactericidal functions in macrophages which interact with helper cells and participate in cell immunity [5]. While ibrutinib has demonstrated potential for improving disease progression-free survival in otherwise difficult-to-treat lymphoid malignancies, cases of infection of the central nervous system after ibrutinib use, especially aspergillosis and cryptococcosis, should be taken into account before using the drug [3]. Immunosuppression due to the underlying cancer and chemotherapy increases the likelihood of invasive fungal infection, but we propose that risk may have been exacerbated by introduction of tyrosine kinase inhibitors [3]. The National Comprehensive Cancer Network recommends considering prophylactic fungal therapy in patients

with MCL only during neutropenia and if they anticipate mucositis [4]. Hence, most patient with MCL are unlikely to be on antifungal prophylaxis. Fungal infection can only be detected commercially in neutropenic patients, and there are only a few commercial methods available, these tools are currently less validated in nonneutropenic patients, it may be useful to utilize targeted prophylaxis (or secondary prophylaxis) in these subgroups and should take into account their unique needs [7]. Cryptococcal infections in patients with hematologic malignancies on ibrutinib were primarily reported in patients with CLL [3].

There were some case reported about Ibrutinib, ibrutinib inhibits the signaling of antigen receptors only in B cells and not T cells [6]. Patients with CLL and MCL suffer from a low risk of cryptococcal meningitis, compared with HIV positive patients, yet they are at higher risk of invasive fungal infections when undergoing TKI treatment [4]. With the emergence of TKI & BTK inhibitor drugs (acalabrutinib, ibrutinib) in MCL, it is vital to stay vigilant in keeping cryptococcal infection in differential screening in order to obtain timely diagnosis and treatment [3]. Cryptococcal disease, which could be life threatening if overlooked, could be considered in such patients. The screening of patients on BTK inhibitor can improve patient outcomes by enabling physicians to start antifungal therapy earlier.

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#### **Conflict of interest**

There is no conflict of interest.

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