

Disseminated Cryptococcosis With Brain Involvement in Patients With Chronic Lymphoid Malignancies on Ibrutinib

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We report 2 cases of disseminated cryptococcosis with central nervous system involvement in patients with chronic lymphoid malignancies occurring within 1 month of starting on ibrutinib. Characteristically, in both cases, no inflammation was seen in the cerebrospinal fluid. Central nervous system mycoses should be considered as a potential complication of ibrutinib.

Keywords. CARD9; central nervous system mycosis; chronic lymphoid malignancies; cryptococcosis; ibrutinib.

Patients with hematologic malignancies including indolent lymphoproliferative disorders have pleiotropic immune deficits due to their underlying disease, placing them at risk for opportunistic infections, such as invasive fungal infections (IFIs) [1]. Cryptococcosis is an IFI that has previously been described in this patient population, particularly associated with receipt of fludarabine or corticosteroids [2, 3]. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor used to treat lymphoproliferative disorders that has demonstrated significant improvement in progression-free survival in clinical trials [4, 5]. Two cases of cryptococcal infections were reported in the clinical trials for ibrutinib including one death from cryptococcal pneumonia [6, 7]. In this study, we report 2 cases of disseminated cryptococcosis due to *Cryptococcus neoformans* with central nervous system (CNS) involvement but no inflammation in patients with chronic lymphoid malignancies at our center, both occurring within 1 month of starting ibrutinib therapy.

CASE 1

An 88-year-old white man with indolent lymphoma started therapy with ibrutinib 420 mg daily in 2015 due to progressive disease. Initial diagnosis of lymphoplasmacytic lymphoma was made in 1998, and previous therapies included rituximab in 2008 and R-Bendamustine in 2012. Approximately 3 weeks into starting ibrutinib therapy, the patient developed shortness of breath and pleuritic chest pain. He was lymphopenic (total T cells 400/liter) but not neutropenic at that time. A computerized tomography (CT) scan revealed a 1.3-cm, right paramediastinal spiculated lung lesion suspicious for primary lung cancer. The patient did not have any fevers or weight loss at this time, but ibrutinib therapy was withheld in the midst of further evaluation. One week later, he developed fevers up to 39°C and was treated with levofloxacin [8]. However, he then developed worsening fatigue, new nonproductive cough, and headache, which prompted hospital admission. Positron emission tomography-CT scan showed an 8-cm, right paramediastinal mass with increased fluorodeoxyglucose (FDG) activity, multiple enlarged, FDG-avid mediastinal lymph nodes thought to be consistent with progression of his underlying disease. Computerized tomography scan of the brain without contrast did not show an acute intracranial process. For further diagnostic work-up, the patient underwent mediastinoscopy with lymph node biopsy, and pathology showed necrotizing granulomatous lymphadenitis of level 3 and 4R lymph nodes with yeasts morphologically consistent with *Cryptococcus*. Fungal culture from one of the lymph nodes had no growth of organism. Serum cryptococcal antigen titer was positive at 1:40. The patient was started on liposomal amphotericin B (L-AMB) 3 mg/kg daily and flucytosine (5-FC) 25 mg/kg every 6 hours [9, 10]. With an ongoing headache, he underwent lumbar puncture (LP) that showed an opening pressure of 7 cm of cerebrospinal fluid (CSF). Cerebrospinal fluid analysis revealed 3 nucleated cells/mm³ (normal cell count 0–5/mm³), 29 red blood cells (RBCs)/mm³ (normal ≤0 cells/mm³), glucose 57 mg/dL, and protein 43 mg/dL (normal range 15–50 mg/dL). The patient's serum glucose on this day was 158 mg/dL (normal range 70–140 mg/dL) with a resultant CSF to serum glucose ratio of 0.36. Cerebrospinal fluid cryptococcal antigen was negative, but CSF fungal culture grew *Cryptococcus*, and the species, *C. neoformans*, was identified by matrix-assisted laser desorption/ionization time of flight. From follow-up LP results 2 weeks after starting L-AMB/5-FC induction therapy, CSF cryptococcal antigen remained negative, and fungal culture was negative for *Cryptococcus*, so the patient was transitioned to oral fluconazole 400 mg daily [11].

Received 24 October 2016; editorial decision 5 December 2016; accepted 7 December 2016.
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 DOI: 10.1093/ofid/ofw261

Table 1. Demographics of the Invasive Fungal Infections

Clinical Feature	Case 1	Case 2
Underlying disease	Indolent lymphoplasmacytic lymphoma	Chronic lymphocytic leukemia
HIV-1/2 antibody testing	Negative	Negative
Age (years)	88	54
Time from starting ibrutinib to infection presentation	3 weeks	4 weeks
WBC count ^a ($\times 10^9$ /liter) ^b	6.7	74.1
Absolute neutrophil count ($\times 10^9$ /liter) ^c	5.5	11.5
Absolute lymphocyte count ($\times 10^9$ /liter) ^d	0.4	59.2
Serum cryptococcal antigen titer	1:40	Not obtained
Sites of documented cryptococcal involvement	Lung, CSF	Blood, lung, CSF
CSF opening pressure (cm CSF)	7	Not recorded
CSF nucleated cells	1	4
CSF protein (mg/dL)	43	30
CSF glucose (mg/dL)	57	157
CSF India ink stain	Negative	Negative
CSF fungal culture	<i>Cryptococcus neoformans</i>	<i>C neoformans</i>

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; WBC, white blood cell.

^aAt the time of hospital admission.

^bNormal range $3.2\text{--}9.8 \times 10^9$ /liter.

^cNormal range $2.00\text{--}8.60 \times 10^9$ /liter.

^dNormal range $0.60\text{--}4.20 \times 10^9$ /liter.

Follow-up CT chest imaging revealed a decrease in right paramediastinal mass size. The patient ultimately recovered from disseminated cryptococcosis and remains on lifelong fluconazole suppressive therapy (200 mg daily) as he has restarted chemotherapy.

CASE 2

A 54-year-old African American man with a history of chronic lymphocytic leukemia (CLL), bronchiolitis obliterans organizing pneumonia (BOOP), morbid obesity, diabetes mellitus, hypertension, and chronic kidney disease presented with nonproductive cough and fever approximately 1 month after starting ibrutinib therapy (dosed 420 mg daily) in 2016. He was not neutropenic or lymphopenic at this time. The patient was diagnosed with CLL in 2012 and had previously been treated with fludarabine, cyclophosphamide, and rituximab from 2014 to 2015. Upon hospital admission, he denied headache, nausea, vomiting, or visual changes but was febrile to 39.1°C and hypoxic requiring supplemental oxygen. Chest imaging revealed bilateral lower lobe ground-glass opacities consistent with either atypical infection or drug toxicity as well as bulky mediastinal and axillary lymphadenopathy consistent with his underlying CLL. The patient was started on broad-spectrum antibiotics, corticosteroids in view of his history of BOOP, and ibrutinib was withheld pending further work-up of possible drug-induced pneumonitis. He underwent bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL). Pathology from the biopsy demonstrated yeasts on Gomori methenamine silver stain, most consistent with *Cryptococcus*. Blood and BAL cultures grew *C neoformans*. The patient was started on L-AMB 5 mg/kg daily and 5-FC 25 mg/kg every 6 hours for

disseminated cryptococcosis. However, he developed acute respiratory failure and septic shock and was transferred to the intensive care unit (ICU) necessitating mechanical ventilation and continuous veno-venous hemofiltration (CVVH). Computerized tomography scan of the brain without contrast performed before LP did not show an acute intracranial process. Lumbar puncture was performed without a report of an opening pressure, and CSF analysis revealed 4 nucleated cells, 6 RBCs, glucose 157 mg/dL, protein 30 mg/dL, negative CSF cryptococcal antigen, and a fungal culture grew *C neoformans* [12]. In total, the patient was treated with L-AMB for approximately 28 days, 5-FC for 14 days, and fluconazole (dosed 800 mg intravenous daily for CVVH) for approximately 14 days after discontinuation of 5-FC. The L-AMB duration of therapy was extended to 28 days because repeat LP attempts at bedside were unsuccessful, and the ICU team assessed the patient's clinical status to be too tenuous to transport to interventional radiology for an image-guided attempt. Three weeks into his ICU stay, the patient once again developed profound systemic shock, progressive respiratory failure, and lactic acidosis of unclear etiology as blood cultures were negative at this time. His status declined further despite full support, the decision was made to withdraw care, and the patient died. Characteristics from both cases are depicted in Table 1.

DISCUSSION

The association between ibrutinib and risk for IFI with a propensity for CNS invasion has previously been reported, and it is not limited to *Cryptococcus*. Specifically, Ruchlemer et al [13] reported 3 cases of invasive aspergillosis with CNS predilection

in patients on ibrutinib within 2 months of drug initiation and concurrent glucocorticoids. The authors noted that 2 patients had documented *Aspergillus* brain abscesses, and 1 patient had documented sinusitis with suspected CNS involvement. Here, we described for the first time 2 cases of disseminated cryptococcosis with CNS involvement but a noninflammatory CSF analysis and negative CSF cryptococcal antigen titers, both presenting approximately 1 month after starting ibrutinib. The poor outcome of the second case reflects an overwhelming infection and cryptococemia. Cryptococemia has been long described as a marker of high fungal burden and a poor prognostic factor in cryptococcosis [14].

Okamoto et al [15] have reported a case of disseminated cryptococcosis due to *C neoformans* in a patient with CLL approximately 1 month after starting ibrutinib with documented blood and suspected lung involvement. The early onset of disseminated cryptococcosis after the initiation of ibrutinib is similar to what occurred in our 2 cases and suggests that these patients had preceding pulmonary colonization with *C neoformans*. Of note, patients with chronic lymphoid malignancies are already at risk for disseminated infection due to immunosuppression from their underlying diseases and chemotherapy, but we propose that this risk may have been exacerbated by the initiation of ibrutinib. Whether the amplification of the risk is directly due to BTK inhibition or an off-target effect of ibrutinib requires further evaluation.

One potential mechanism is the role of caspase recruitment domain (CARD) homologs in facilitating entry and propagation of infection by fungal organisms in the CNS. The CARD homologs (CARD9, 10, and 11) form heterotrimers with B-cell lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma-translocation gene 1 (MALT1) to produce CARD-BCL10-MALT1 (CBM) complexes [16]. The CBM complexes activate nuclear factor $\kappa\beta$, which plays a critical role in regulation of the innate and adaptive immune systems and apoptosis [17]. CARD11, found in lymphocytes, is a key player in the CBM complex downstream of the B-cell receptor and BTK, the target for ibrutinib [18]. CARD9, found in myeloid cells, is a signaling adaptor used by C-lectin receptors, which are types of pattern recognition receptors and are involved in neutrophil recruitment and proinflammatory cytokine production in antifungal immunity [19]. Patients with CARD9 deficiency are uniquely susceptible to invasive fungal infections of the CNS due to diminished neutrophil accumulation in the brain [20]. Therefore, CARD9 could be essential for a complex similar to CBM in CNS macrophages and microglial cells, which is potentially affected by ibrutinib.

An unusual feature of the present cases is the noninflammatory CSF profile. In fact, the yeasts may have arrived quickly in the CNS after the start of ibrutinib because there was a negative CSF cryptococcal antigen despite positive CSF cultures for *C neoformans*. A similar finding of noninflammatory CSF with

negative India ink stain and negative CSF cryptococcal antigen has been reported in a case of cryptococcal meningitis in a patient with Hodgkin's lymphoma [21]. One possible explanation of the noninflammatory CSF profile was that the disseminated infection was detected relatively early in the course before a detectable level of antigen could be achieved in the CSF. In contrast, the noninflammatory CSF analysis may be due to an immune defect similar to that seen in acquired immunodeficiency syndrome, where 25%–30% of patients will have normal CSF profiles despite CNS infection documented by positive fungal cultures [22, 23].

CONCLUSIONS

Ibrutinib shows promise for improving disease progression-free survival in otherwise difficult-to-treat chronic lymphoid malignancies, but cases of IFI with CNS involvement, specifically aspergillosis and cryptococcosis, seen shortly after drug initiation should raise caution to use of ibrutinib. The extent of immunosuppression and immunogenetic risks for this complication of ibrutinib therapy are unknown. Clinicians should be vigilant, and IFIs should be included in the differential diagnosis in patients with suspected infectious complications on ibrutinib therapy. Further study of the potential association between ibrutinib and IFI could offer insight into the immune implications of ibrutinib as well as host-pathogen interactions of disseminated cryptococcosis.

Acknowledgments

Financial support. J. A. M. is supported by the National Institute of Allergy and Infectious Diseases Grant 5T32AI100851-03.

Potential conflicts of interest. A. S. receives research funding from Astellas, Scynexis, MiraVista, and IMMY and consulting fees from Astellas and MiraVista. D. P. K. has received research support from Merck, Pfizer, and Astellas and has received honoraria from Merck, Astellas, Gilead, Pfizer, F2G, and Cidara, Inc. J. R. P. has served on advisory committees, honorariums, performed consulting, and has received research support from Astellas, Merck, Vical, Cidara, Viamet, F2G, Scynexis, Matinas, and TEVA.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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