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Invasive aspergillosis related to ibrutinib therapy for chronic lymphocytic leukemia

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ABSTRACT

We report a case of invasive pulmonary aspergillosis in a patient taking ibrutinib, a Bruton's tyrosine kinase inhibitor used to treat refractory chronic lymphocytic leukemia. We hypothesize that ibrutinib promoted this infection by suppressing innate immune responses against *Aspergillus*. Clinicians should be aware of potential *Aspergillus* infections in patients treated with this drug.

1. Introduction

Ibrutinib is a novel anti-cancer drug recently approved for the treatment of refractory chronic lymphocytic leukemia (CLL) [1] and other B-cell cancers [2,3]. Ibrutinib selectively inhibits Bruton's tyrosine kinase (BTK), a key enzyme that promotes the survival and proliferation of normal B cells and CLL cells downstream of B-cell receptor activation [4]. Treatment with ibrutinib has not been previously reported to promote invasive *Aspergillus* infections in non-neutropenic patients.

2. Case report

A 62-year-old man was admitted to our hospital with three weeks of non-productive cough, dyspnea, fatigue, and anorexia. He had started ibrutinib six weeks prior to admission for relapsed CLL. He was retired and lived in western Oregon. He reported no exposure to tobacco, dust, birds, or other animals. His tuberculin skin test was negative prior to initiation of ibrutinib. On examination, the patient was afebrile (36.7 C); pulse was 66/min; BP was 82/52 mm Hg; respiratory rate 16/min; and oxygen saturation 96% on room air. Cardiopulmonary examination was normal. Laboratory investigations revealed anemia (Hgb 5.0 g/dL), leukocytosis (21.2 $\times$ 10^3/μl), decreased platelets (140 $\times$ 10^3/μl), and a normal neutrophil count (1.91 $\times$ 10^3/μl). Serum chemistries were notable for a sodium of 129 mmol/L, chloride of 97 mmol/L, bicarbonate of 17 mmol/L, urea nitrogen of 26 mg/dL, and creatinine of 1.2 mg/dL.

Computed tomography scan of the lung showed multifocal upper lobe centrilobular nodules, patchy consolidations with air bronchograms, and small areas of cavitation (Fig. 1A), findings that were not present prior to ibrutinib initiation. Bronchoscopy revealed endobronchial masses in the lingula and right upper lobe (Fig. 1B). Biopsy of the masses showed necrotic mucosa containing septate fungal hyphae with acute angle branching,

Abbreviations list: BAL, Bronchoalveolar lavage; BTK, Bruton's tyrosine kinase; CLL, Chronic lymphocytic leukemia; TLR, Toll-like receptor.

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consistent with *Aspergillus* (Fig. 1C). Bronchoalveolar lavage (BAL) was performed in the right middle lobe. BAL fluid grew *Aspergillus fumigatus* and showed no evidence of acid-fast bacilli or nocardia. BAL galactomannan was positive.

The patient was treated with voriconazole and ibrutinib was briefly discontinued. The patient developed hypercalcemia suspicious for relapsed CLL and ibrutinib was resumed at a lower dose. Serial chest radiographs showed resolution of the multifocal consolidative opacities and nodules over the subsequent two months. The patient's CLL continued to progress despite additional chemotherapy and he died five months after starting ibrutinib.

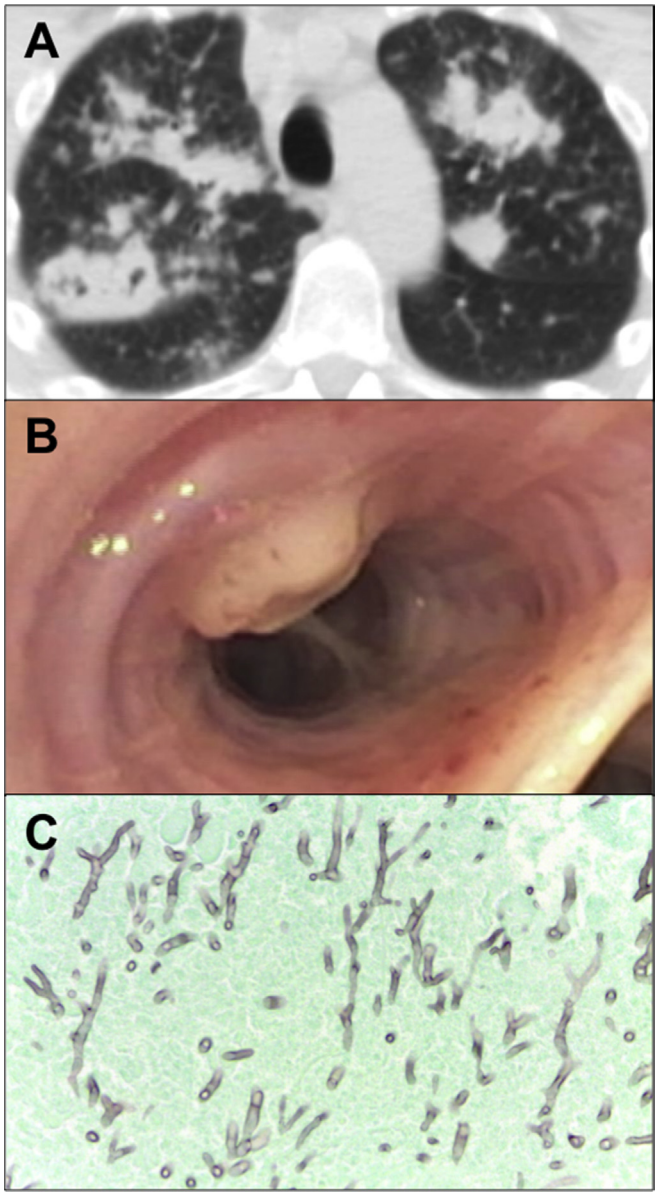

Fig. 1. (A) An axial image from a chest CT shows bilateral upper lobe lung nodules and consolidative opacities. (B) Airway inspection revealed an endobronchial mass in the lingula. (C) The mass contained abundant septate fungal hyphae branching at acute angles within necrotic lung tissue. Photomicrograph is shown at ×63 magnification, Gomori methenamine silver stain.

Table 1
Invasive fungal infections in patients receiving ibrutinib.

Organism	Description	Clinical Course
Aspergillus		
Phase 3 trial [13]	Two patients with bronchopulmonary aspergillosis.	
Follow-up of phase 2 trial [14]	One patient with "extensive aspergillosis" after two months of treatment with ibrutinib AND rituximab.	Ibrutinib discontinued.
Case series [15]	Three patients with invasive aspergillosis and CNS involvement within two months of starting ibrutinib AND corticosteroids.	Patient one: ibrutinib discontinued, infection resolved. Patient two died. Patient three: critically ill, outcome unspecified.
Case report [16]	One neutropenic patient with multifocal pneumonia due to invasive aspergillosis and mucormycosis after seven months of ibrutinib therapy.	Patient died.
Cryptococcus neoformans		
Phase 2 trial [17]	One patient with "cryptococcal infection."	
Phase 1b-2 trial [1]	One patient with cryptococcal pneumonia.	
Case report [18]	One patient with disseminated infection without CNS involvement.	Ibrutinib discontinued, infection resolved. Therapy resumed at lower dose with fluconazole prophylaxis.
Case series [19]	Two patients with disseminated infection with CNS involvement within one month of starting ibrutinib.	Patient one: ibrutinib discontinued, infection resolved. Patient two died.
Pneumocystis jirovecii		
Phase 2 trial [17]	One patient with "pneumocystis infection."	
Case series [20]	Five patients with PJP pneumonia after 2–24 months of therapy despite CD4 > 500. Estimated incidence 2 cases/100 patient-years.	Ibrutinib continued, pneumonias resolved with oral antibiotics. Ibrutinib continued without prophylaxis in three patients without recurrent infection.
Histoplasma		
Phase 2 trial [17]	One patient with "histoplasmosis infection."	
Fusarium solani		
Case report [21]	One patient with disseminated infection, fevers, and multiple skin abscesses after six weeks of treatment.	Ibrutinib continued, infection resolved.
Other		
Follow-up of phase 1b-2 trial [14]	One patient with extensive fungal pneumonia after 20 months of treatment.	Ibrutinib discontinued, patient died.

3. Discussion

Members of the genus *Aspergillus* are ubiquitous fungi that grow in soil. *Aspergillus* spores are regularly inhaled, but the fungi have almost no ability to invade hosts with adequate neutrophil and macrophage phagocyte function [5]. While CLL is characterized by defects in humoral immunity and T-cell function, phagocyte function is relatively preserved in CLL and invasive aspergillosis is uncommon [6]. Eventually, most CLL patients experience neutropenia, the most important risk factor for invasive aspergillosis, because of bone marrow involvement or myelosuppressive chemotherapy. However, the patient in this case was not neutropenic on presentation and had no clinical or radiographic evidence of pneumonia prior to receiving ibrutinib, suggesting that ibrutinib promoted invasive aspergillosis in this

patient.

B cells do not play a major role in anti-fungal immunity, arguing against blockade of B-cell receptor signaling as a cause of ibrutinib-related *Aspergillus* infection. Notably, neutrophils and macrophages, innate immune cells that phagocytose and kill fungi, have been shown to express the ibrutinib target BTK [7,8]. In these cells, BTK activation increases levels of reactive oxygen species, nitric oxide, and proteases [7,8], substances that directly kill fungi. In macrophages, binding of fungal components to dectin-1 [9], the major pattern recognition receptor involved in anti-fungal immunity, and to Toll-like receptor 9 [10], activates BTK. In turn, BTK has been reported to be an essential part of the inflammasome [11], a protein complex that converts pro-IL-1beta into mature IL-1beta in response to *Aspergillus* infection [12]. Thus, there is growing evidence that BTK plays an important role in innate immune responses against *Aspergillus*.

In patients receiving ibrutinib for refractory CLL, invasive *Aspergillus* infection has been reported only in those who were neutropenic or receiving concomitant rituximab or corticosteroids (see Table 1). The patient we describe had impaired immunity due to CLL itself and related to his prior treatment for CLL with fludarabine and rituximab, and he was neutropenic in the months prior to starting ibrutinib. However, he was not neutropenic when ibrutinib was initiated or when he presented to hospital and he had not received additional immunosuppressive therapies. We hypothesize that ibrutinib promoted invasive pulmonary aspergillosis in this case via suppression of BTK in macrophages and neutrophils. As ibrutinib becomes more widely used in B-cell cancers, clinicians should be aware of the potential for decreased anti-fungal immunity and for opportunistic *Aspergillus* infections in patients treated with this drug, even in the absence of neutropenia or combination therapy.

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Conflicts of interest

None.

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