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Cranial aspergillosis in a patient receiving ibrutinib for chronic lymphocytic leukemia

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ABSTRACT

Cerebral abscess due to *Aspergillus species* is a relatively uncommon presentation, even amongst immunocompromised patients. However it is increasingly being recognized as a complication of ibrutinib therapy in patients with chronic lymphocytic leukemia. We present a case of cerebral abscesses caused by *Aspergillus felis* in a patient receiving ibrutinib for chronic lymphocytic leukemia.

1. Introduction

Central nervous system (CNS) aspergillosis is an uncommon presentation, but has been seen in immunocompromised patients [1]. Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) increasingly being used in the management of chronic lymphocytic leukemia (CLL), a hematological malignancy which has generally been viewed as low risk for invasive fungal disease. As such, antifungal prophylaxis is not routinely recommended for CLL patients. There have been multiple reports of patients treated with ibrutinib, who have developed invasive fungal disease, with a noted predilection for the central nervous system [3–8].

We present a case of cerebral aspergillosis in a patient with CLL receiving ibrutinib without other risk factors for invasive aspergillosis, and review the literature that suggest an association between ibrutninb therapy and an increased risk of invasive fungal disease, particularly affecting the central nervous system. Furthermore we discuss the isolation of a newly recognized species of *Aspergillus* section *fumigati*, *Aspergillus felis*, and the implications for treating this species, given its frequent association with high minimum inhibitory concentration (MIC) levels for triazoles.

2. Case

A 66 year old male presented to hospital with new onset confusion and expressive dysphasia over several days, on a background of CLL, and a previous excision of cutaneous melanoma one year previously with clear margins. His background history also included mild stable asthma, hypertension, and allergic rhinitis. His CLL treatment over several years had included: fludarabine, cyclophosphamide, bendamustine and rituximab. However, over the 12 months prior to presentation, he had been established on monthly intravenous immunoglobulin (IVIG) and ibrutinib. Of note, his lowest recorded neutrophil count in the previous 12 months was 1.5×10^9/L and he was not receiving concurrent corticosteroids or prophylactic antimicrobials.

The patient was afebrile on presentation, and apart from an expressive dysphasia, a neurology examination was unremarkable. Initial blood tests revealed a total white cell count of 4.7×10^9/L, with a neutrophil count of 2.6×10^9/L. A brain magnetic resonance imaging (MRI) scan with gadolinium enhancement demonstrated multiple rim-enhancing hemorrhagic lesions, the largest of which was located in the left parieto-temporal region (Fig. 1). A presumptive diagnosis of metastatic melanoma with hemorrhagic cerebral metastases was made and the patient was commenced on dexamethasone. He subsequently underwent craniotomy and excision of the left parieto-temporal lesion. Intra-operatively, the lesion was noted to have a thick fibrous capsule containing purulent material within, consistent with an abscess.

Histopathological examination of the tissue demonstrated gliosis and filamentous septate hyphae with acute angle branching (Fig. 2); with no evidence of malignant cells. Culture of the tissue demonstrated growth of white fungal colonies with blue-green reverse color. Microscopically, singly borne conidiophores with uniseriate phialides arising from the upper two thirds of the terminal vesicle were seen, consistent with *Aspergillus fumigatus* complex. A serum galactomannan (Platelia-Aspergillus Ag, Bio-Rad Laboratories, Hercules CA USA) was negative, as were fungal blood cultures. A computerised tomography (CT) scan of the chest and abdomen revealed a 5mm pulmonary nodule and

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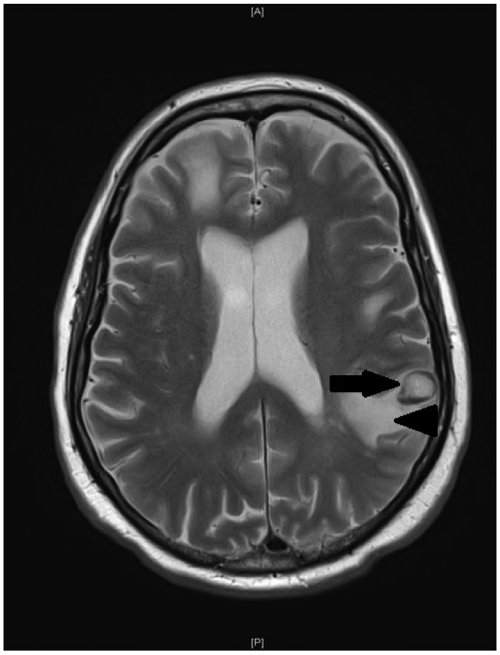

Fig. 1. MRI scan T2 weighted (axial) with 14mm rim-enhancing left parieto-temporal lesion (arrow) and perilesional edema (arrowhead).

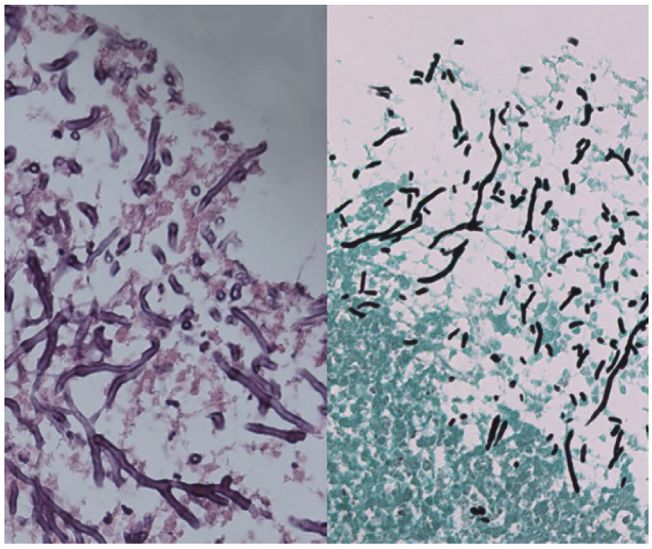

Fig. 2. Histopathology of left parieto-temporal lesion demonstrating septate fungal hyphae with acute angle branching on iron and hematoxylin (left) and Grocott's methenamine silver (right) stains.

widespread lymphadenopathy consistent with the diagnosis of CLL (which were unchanged from previous imaging). A *trans*-esophageal echocardiogram did not demonstrate any definite evidence of endocarditis.

The patient was commenced on voriconazole with achievement of therapeutic drug levels, and the ibrutinib was ceased. He had a good clinical response to surgery and initiation of voriconazole and was discharged from hospital. His treatment course was complicated by the development of a photosensitivity rash, resulting in a switch from voriconazole to oral posaconazole. DNN sequence analysis of internal transcribed sequence 1, 5.8S and ITS2 regions was performed using published primers and standard sequencing methodologies, identified the fungus as a member of the *Aspegillus felis* complex within *Aspegillus* section *Fumigati* [9]. The sequence showed 100% identity (480 base pairs) to numerous reference strains in the Westerdijk Fungal Biodiversity Institute database including *Aspegillus felis* (CBS 130244), *Aspergillus parafelis* (CBS 140763) and *Aspergillus pseudofelis* (CBS 140763). Susceptibility testing by broth microdilution using the SensititreTM YeastONE YO10 plates (Thermo Fisher) revealed non-Wild-Type minimum inhibitory concentrations (MICs) for all tested triazoles (Table 1). In view of the marked clinical and radiological improvement on triazoles despite elevated MICs, and the lack of alternative oral antifungal options, the patient was maintained on posaconazole, which he continues to tolerate well. However, his CLL progressed after cessation of the ibrutinib, and he is currently being treated with rituximab. Given his ongoing immunosuppression he is expected to require indefinite antifungal therapy.

Table 1
Antifungal susceptibility testing of *Aspergillus felis* isolate by broth microdilution.

Antifungal	MIC (ug/mL)
Amphotericin B	2
Anidulafungin	0.06
Itraconazole	> 16
Voriconazole	4
Posaconazole	1

MIC, Minimum inhibitory concentration.

3. Discussion

We present a case of a patient with CLL, without classic risk factors for invasive fungal disease, who develops cerebral aspergillosis whilst receiving ibrutinib. Patients at highest risk of developing invasive fungal disease include: those receiving intensive chemotherapy for acute myeloid leukemia or myelodysplastic syndromes; and those requiring corticosteroids for graft-versus-host-disease following allogeneic hematopoietic stem cell transplantation (AHSCT) or with prolonged neutropenia post-AHSCT. There are no current recommendations for routine antifungal prophylaxis in CLL patients, a group considered to be low risk for invasive fungal disease, or in patients receiving ibrutinib [2].

Ibrutinib is a newly approved treatment for CLL which selectively inhibits BTK, an enzyme that promotes survival and proliferation in normal B cells and CLL cells. Several reports have highlighted a possible link between ibrutinib therapy and the development of invasive fungal disease [3,4], with a distinct predilection for invasive cerebral disease [6–8]. *Aspergillus* species, *Cryptococcus neoformans* [7,8], and *Pneumocystis jirovecii* [7] causing invasive fungal disease have all been identified in patients on ibrutinib therapy. Onset of the invasive fungal infection can be seen early in ibrutinib therapy, without any other identifiable risk factor for fungal infection [7]. The mechanism by which BTK inhibition by ibrutinib results in a propensity for fungal disease is unclear. One proposed mechanism is the suppression of the activation and normal function of macrophages and neutrophils expressing BTK [6], thereby interfering with the host's primary lines of defense against fungal pathogens. Predilection for CNS involvement has been postulated to result from inhibition of CNS macrophages [6].

Aspergillus felis is a newly recognized member of *Aspergillus* section *fumigati* that has been isolated predominantly from cats, but also from dogs and humans [10]. *Aspergillus felis* differs morphologically from other *Aspergillus* section *fumigati* by its ability to grow at 45 °C; however it is only reliably identified by ITS sequencing. Notably this species may have high MICs to antifungal drugs, including triazoles, which was seen in our patient. This raises concerns that antifungal treatment may be more likely to fail in these patients, and therefore early identification of this organism may prompt avoidance of the triazole class until susceptibility is confirmed. In the case of our patient, by the time the *Aspergillus* identification and susceptibility was confirmed, he had clearly

improved on triazole therapy.

With the increasing use of ibrutinib for CLL, it is important to be aware of a possible association with development of invasive fungal disease, particularly cerebral disease. Further study is required to determine if ibrutinib use warrants antifungal prophylaxis. Additionally, early identification of less commonly encountered *Aspergillus species* may be important in order to guide appropriate empiric antifungal therapy.

Conflict of interest

None of the authors have conflicts of interest to declare.

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