Letter to the Editor

Concurrent cerebral aspergillosis and abdominal mucormycosis during ibrutinib therapy for chronic lymphocytic leukaemia

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To the Editor

We read with great interest the article from Peri et al. describing a case report of invasive aspergillosis (IA) with primary pulmonary involvement followed by central nervous system (CNS) involvement in a patient treated for chronic lymphocytic leukaemia (CLL) with ibrutinib [1]. The clinical outcome has been reported by Peri et al. during the initial course of pulmonary aspergillosis in the case reported from a patient's temperature was 38.3°C. Cerebral computed tomography (CT) demonstrated a well-defined rim-enhancing lesion with a hypodense centre surrounded by oedema in the left external capsule region complicated by a mass effect on the left ventricle and a subfalcine herniation (Fig. 1a). A stereotaxic biopsy was performed, and mycological cultures were positive for Aspergillus fumigatus with negative direct examination. Antifungal susceptibility tests showed the following MICs (EUCAST method): voriconazole 0.19 mg/L; isavuconazole 0.25 mg/L; posaconazole 0.094 mg/L; itraconazole 0.36 mg/L; caspofungin 0.094 mg/L. Bacterial cultures were also positive for Propionibacterium acnes. No tumour cell was detected on pathological examination.

After the biopsy was performed, she subsequently received cefotaxime and metronidazole for 7 days and a single dose of prednisolone of 1 mg/kg. Intravenous voriconazole (400 mg/12 h at day one then 200 mg/12 h) was started after the result of fungal cultures. Serum galactomannan antigen was negative. (1,3)-β-D-glucan serum titres were 84 pg/mL. Aspergillus fumigatus PCR in serum was negative. Sinus and chest CT scans were normal. A systematic abdominal CT scan revealed a lesion of the upper pole of the left kidney and a lesion of the spleen both consistent with abscesses (Fig. 1c). A CT-guided biopsy was performed of the kidney lesion. The histopathological examination showed ischaemic necrosis associated with non-septate broad hyphae. Fungal cultures

A 52-year-old woman presented with a 5-year history of CLL. In 2015 she received a combination of rituximab, fludarabine and cyclophosphamide with complete remission. She relapsed in September 2017 when a treatment with ibrutinib was started. At that time, she experienced neutropenia (between 0.4 and 0.6 G/L). She presented to the hospital on 16 March 2018 with a 2-week history of confusion, behaviour disorders and aggression. The patient’s temperature was 38.3°C. Cerebral computed tomography (CT) demonstrated a well-defined rim-enhancing lesion with a hypodense centre surrounded by oedema in the left external capsule region complicated by a mass effect on the left ventricle and a subfalcine herniation (Fig. 1a). A stereotaxic biopsy was performed, and mycological cultures were positive for Aspergillus fumigatus with negative direct examination. Antifungal susceptibility tests showed the following MICs (EUCAST method): voriconazole 0.19 mg/L; isavuconazole 0.25 mg/L; posaconazole 0.094 mg/L; itraconazole 0.36 mg/L; caspofungin 0.094 mg/L. Bacterial cultures were also positive for Propionibacterium acnes. No tumour cell was detected on pathological examination.

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To complement Peri et al.’s work, we would like to report a case with primary CNS involvement that has benefited from a systematic screening for extra-neurological involvement and additional invasive tissue biopsies. As ibrutinib-associated fungal infections are an emerging syndrome, we would like to describe clinical issues in the management of these infections.

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remained negative. Mucorales fungal PCR identified *Lichtheimia* spp. on renal biopsy while *Aspergillus fumigatus* PCR was negative. Therefore, voriconazole treatment was stopped on 30 March and a combination of L-AmB (5 mg/kg/day) and isavuconazole was started at standard dosage (200 mg/8 h for 2 days then 200 mg/day). Therapeutic drug monitoring of isavuconazole showed a plasma trough concentration (C0) of 2.9 mg/L. L-AmB was then stopped and isavuconazole was continued as monotherapy. Brain magnetic resonance imaging and abdominal CT performed 6 weeks after initiation of isavuconazole revealed an improvement of perilesional oedema and significant decrease in size of the abscess (Fig. 1b,d). Ibrutinib was discontinued at admission before any antifungal therapy and venetoclax was started 1 month later due to CLL progression. The patient is currently alive without any symptoms after 9 months of treatment. She still receives isavuconazole with significant response on brain and abdominal imaging.

We describe here a case of fungal co-infection caused by moulds with concurrent cerebral IA, renal mucormycosis and probable splenic involvement in a patient with CLL after 6 months of ibrutinib treatment and prolonged neutropenia. This case highlights that invasive screening and diagnostic procedures during the initial course of fungal infection in individuals receiving ibrutinib therapy could be beneficial for the initial management and outcomes.

On the one hand, current IA management guidelines do not recommend systematic screening for asymptomatic CNS involvement [2]. However, given the high mortality rate of CNS aspergillosis, some authors recommend this screening to detect early CNS involvement, which leads to a close monitoring of clinical symptoms, imaging and trough concentrations of azoles [3]. On the other hand, guidelines recommend biopsy of lung or sinus lesions, concomitant with suspected fungal brain lesions. Since the mortality rate of fungal infection remains high and ibrutinib therapy is associated with emerging fungal syndrome...
[4], diagnosis parsimony known as Ockham’s razor is not supported by our case. Kreiniz et al. also reported a case of pneumonia due to concurrent IA and mucormycosis during the course of ibrutinib therapy [5]. In our opinion, systematic full screening including CNS imaging should be performed for every diagnosis of invasive fungal infection, with a biopsy of any suspected lesions, in patients receiving ibrutinib for lymphoid malignancies.

Transparency declaration

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Contribution

AP and RG wrote the first draft of the manuscript. AP, RG and AD performed the literature review. MM and TJM provided radiological and pathological data, respectively. MEB provided mycological expertise. AP, RG, AD, RD, RG and OL took care of the patient’s management. FL and OL made critical revision of the manuscript. All authors read and approved the final manuscript.

References


