Medical Mycology Case Reports 27 (2020) 14–16

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Multi-fungal sepsis and mucormycosis of the central nervous system in a patient treated with ibrutinib, a case report and review of the literature

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ARTICLE INFO

Keywords:
Ibrutinib
Chronic lymphocytic leukemia
CLL
Aspergillosis
Mucormykosis
Cerebral infection

ABSTRACT

We report the case of a 71 years old patient with chronic lymphocytic leukemia (CLL), who developed a rapidly progressing multi-fungal infection including mucormycosis of the central nervous system (CNS) during treatment with ibrutinib.

On autopsy mucorales species were demonstrated intravascularly by histomorphology of several organs and lymph nodes and were characterized as *Rhizomucor pusillus* by polymerase-chain reaction (PCR) – analysis. In addition, invasive pulmonary *Aspergillus fumigatus* was found and also confirmed by PCR. To the best of our knowledge, this is the first confirmation of a multi-fungal sepsis and invasive CNS-infection with mucorales species under ibrutinib. Knowing the risk for invasive fungal disease in patients under ibrutinib, identifying the pathogen and early initiation of specific treatment is crucial for a good clinical outcome especially in mucormycosis.

1. Introduction

Ibrutinib is an inhibitor of brutons tyrosine kinase (BTK) and has been paradigm-shifting in the treatment of a number of B-cell malignancies [2]. Although well tolerated in the majority of patients a few troublesome adverse events have become apparent, as the use of the drug has expanded. One of the adverse events is a relatively high risk of fungal infection, such as Aspergillosis, but also other opportunistic fungal infections such as Cryptococcosis or *Pneumocystis Jirovecii* infections are increasingly reported [2–6]. We report the case of a patient with chronic lymphocytic leukemia (CLL), who developed a multi-fungal infection including invasive pulmonary aspergillosis and synchronous mucormycosis of the central nervous system (CNS) with rapid deterioration during first line treatment with ibrutinib.

2. Case

A 71 years old male patient was initially diagnosed with CLL, Binet A, Rai 0 with moderate lymphocytosis (62 G/l) and no other symptoms. 13 months later he presented with significant weight loss, fatigue and new palpable splenomegaly and lymphadenopathy. Biopsies of the largest inguinal lymph node and bone marrow re-confirmed the diagnosis of CLL with absence of deletion 17p, mutation of p53 or transformation into high-grade lymphoma. He received investigational treatment with the monoclonal CD20-antibody obinutuzumab 3 times in weekly intervals the first cycle (days -25, -18 and -11), daily ibrutinib as of the first day of the treatment (day -25) and addition of venetoclax three weeks later (day -3).

During the first three weeks of the CLL-directed treatment the neutrophil counts and immunoglobulin levels were within normal limits. The patient received single doses of 20 mg dexamethasone with obinutuzumab weekly for 3 times (days -25, -18 and -11).

The initial treatment with obinutuzumab and ibrutinib was well tolerated with early signs of clinical benefit such as decrease of lymphadenopathy and leucocytosis, stop of weight loss and improvement of fatigue.

After 3 weeks venetoclax was added in a ramp-up dosing-schedule without any signs of tumor-lysis after the first dose (day -3). Three days after the start of venetoclax he was admitted to the emergency department with a clinical picture of sepsis due to pneumonia and pleural effusion (day 0). Cultures were performed, broad-spectrum antibiotics and inotropic, cardio-circulatory support was initiated. All cultures (blood, pleural effusion) remained negative throughout the disease-course. Within hours after admission the neurological status

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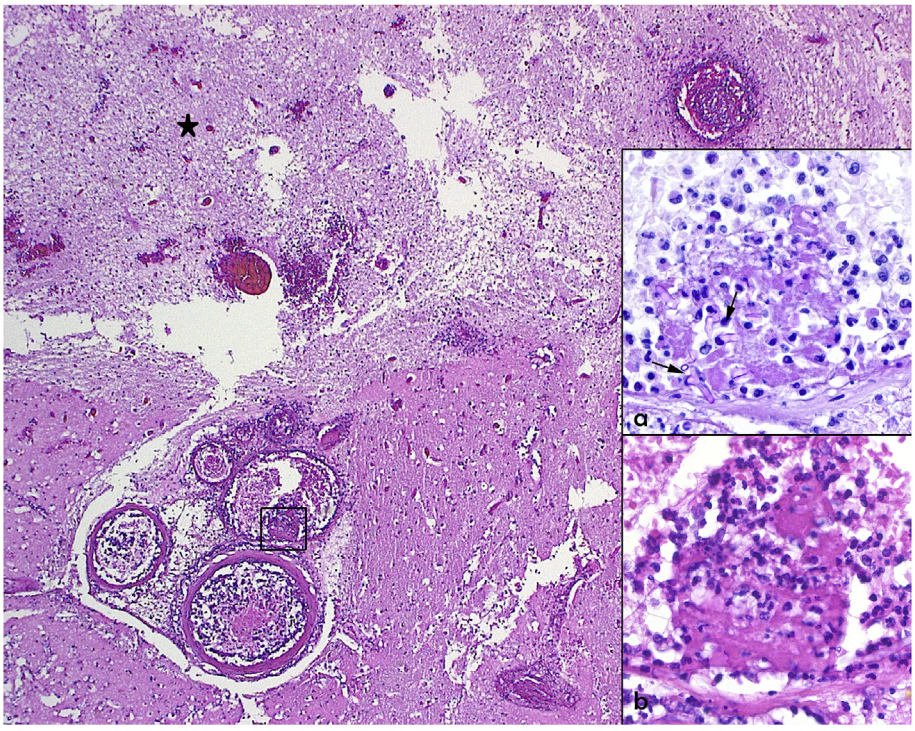
https://doi.org/10.1016/j.mmcr.2019.12.005
Received 28 October 2019; Accepted 2 December 2019
Available online 03 December 2019



Legend Image 1. Histopathology of cerebral infection by Rhizomucor pusillus: Perivascular/vascular inflammation with thrombosis and subsequent necrosis (*)(Hematoxyline & Eosin, H&E; 2.5x). Insert (rectangle): The fungal are hardly seen by H&E (insert a, 40x) but can be visualized by Periodic acid-Schiff reaction, PAS (insert b, 40x).

deteriorated – initially with a sudden onset of right-sided hemiplegia and progressive decrease of consciousness followed by a generalized seizure and coma (days +1 and + 2).

Repeated cross-sectional imaging revealed abdominal lymphadenopathy and a cerebral lesion in the left basal ganglia, which increased rapidly and extended to the left hemisphere. The patient died 4 days after admission due to uncontrollable central nervous pressure (day +4). Autopsy revealed angioinvasive fungal sepsis with fungal meningoencephalitis as cause of death. Histologically, mucorales species were demonstrated intravascularly, in several organs and lymph nodes [Image 1]. These were characterized as *Rhizomucor pusillus* by polymerase-chain reaction (PCR) - analysis from pancreas-, kidney-, lung- and brain-tissue.

In addition, *Aspergillus fumigatus* was found in lung tissue by histomorphology and molecular analysis [Image 2].

Of note, no evidence of remaining CLL was found neither in the sections from bone marrow nor lymph-nodes consistent with a complete remission.

The molecular analysis consists of three different PCR reactions: A specific mucorales PCR, a specific aspergillus PCR and a panfungal PCR. The mucorales PCR amplifies the 18s ribosomal RNA region using primers Z1 and Z3 with minor changes and additional internal primers to obtain a specific nested PCR [1]. The nested aspergillus PCR amplifies the 5.8s ribosomal RNA region (unpublished data) and the single run panfungal PCR the variable region ITS2 (Graber A, manuscript in preparation). The obtained PCR products were sequenced and blasted at NCBI Nblast suite. Rhizomucor pusillus with the following sequence IDS: JX644489.1, HQ845297.1, HQ845296.1, HM234128.1, AF113434.1 was identified with 79 of 79 homolog base pairs, 100% identity and 100% query coverage. Aspergillus fumigatus (sequence IDS: e.g. MG459154.1, MH745427.1, MH729807.1) was identified with 149 of 149 homolog base pairs, 100% identity and 100% query coverage in the lung.

To the best of our knowledge this is the first report of an invasive multi-fungal infection confirmed by histology and PCR in a patient treated with ibrutinib. In addition, it is the first confirmation of invasive cerebral infection with mucorales species under ibrutinib.

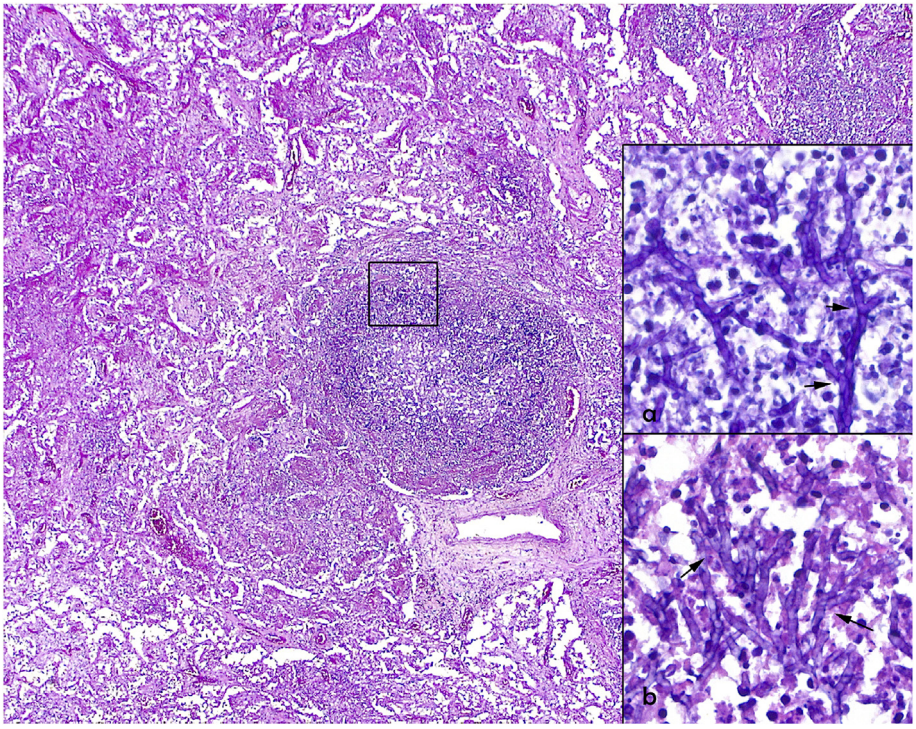
3. Discussion

Ibrutinib-associated fungal infections are characterized by a rapid clinical course and a high mortality rate [3–6]. Diabetes, chronic liver disease, multiple prior therapies including corticosteroids and neutropenia are currently regarded as risk factors [2]. Several defects of innate and acquired immunity are supposed to be responsible for ibrutinib-associated fungal infections. These include the modulation of the function of neutrophils, macrophages and T-cells influenced by effects of BTK-inhibition or other pathways such as toll-like receptor-9, Calcineurin- and TEC-family kinases [7]. Recently, it has been demonstrated that ibrutinib also impairs the activation of macrophages, usually induced by fungal infections, by inhibition of the transcription factors NFAT and NF-κB [8]. Furthermore the production of TNF-α and galactomannan is inhibited in ibrutinib-treated human monocyte-derived macrophages [9].

Molds such as *Aspergillus sp* or Mucorales are ubiquitously found in the environment, predominantly in soil. Infection mainly occurs by inhalation of spores followed by secondary dissemination as most molds are angioinvasive. Direct inoculation through disrupture of the skin is also possible, but in such cases recognized early by local clinical signs.

Rapid clinical courses of multi-fungal infections would normally be expected in severely and long-term immunocompromised patients, such as patients with long periods of aplasia or in patients with advanced AIDS in the era before HAART-therapy [10]. In our patient no pre-existing immunodeficiency or known risk factors for ibrutinib-associated fungal infection were obvious, except for 20 mg dexamethasone administered before obinutuzumab in weekly intervals for 3 times (days -25, -18 and -11) and the potentially impaired immune function by the underlying CLL per se. More clinical data are necessary to evaluate whether the bcl-2 inhibitor venetoclax could have added to the off-target effects of ibrutinib on the function of phagocytotic and antigen presenting cells. In addition to its role as regulators of apoptosis, the bcl-2 family of proteins has also functions in non-tumor cells, including autophagy, antigen-presentation and interferon-alpha production [11].

We presume that the infection of our patient occurred through inhalation but it remains speculative whether it was related to gardening as leisure activity or to molds from the cellar of our patient's house.



Legend Image 2. Histopathology of pulmonary infection with Aspergillus fumigatus: Vascular involvement by fungus, easily seen by H&E (insert a) and PAS (insert b)(2.5x and 40x, respectively).

Aspergillus ochraceus, *Penicillium brevicompactum* and *Penicillium corylophilum* were isolated from the cellar walls, but the species identified in our patient (*Rhizomucor pusillus, Aspergillus fumigatus*) differed from the species found on the cellar walls.

This case may have therapeutic implications as it highlights the possibility of ibrutinib-associated, simultaneous multi-fungal infection with a rapid clinical deterioration in the absence of conventional risk factors for invasive fungal infections. Therefore, in patients treated with ibrutinib, invasive fungal disease must be taken into consideration in case of clinical deterioration. Early diagnostic procedures to identify the pathogen are necessary and in case of possible fungal disease early empiric antifungal treatment should be discussed. Identifying the pathogen and early initiation of specific treatment is crucial for a good clinical outcome especially in mucormycosis [12]. Knowing the risk and risk factors for invasive fungal disease in patients under ibrutinib and counseling of patients for emerging risk factors such as increased patient-specific environmental exposure appears important.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

All contributors met the criteria for authorship.

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