

Scedosporium Brain Abscess: A Rare and Fatal Drawback of Bruton Tyrosine Kinase Inhibitor Therapy

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Abstract

The patient described in this case report was admitted to the San Luigi Hospital in Turin for confusion, drowsiness, and buccal and eye deviation. An acute neurological disease was suspected. He was affected by chronic lymphocytic leukemia (CLL) on active treatment with the novel Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib. Other comorbidities included type II diabetes mellitus, arterial hypertension, and nonalcoholic steatohepatitis. Imaging exams showed multiple brain lesions, which appeared to be of infectious-inflammatory origin. Consequently, therapy with acalabrutinib was withheld. The patient was later transferred to the intensive care unit, because of worsening neurological conditions. The definite diagnosis of fungal abscess was obtained through a stereotactic biopsy of the widest brain lesion. Microbiological tests confirmed *Scedosporium* spp. as the etiological agent. Once a detailed antibiogram had been obtained, voriconazole therapy was started. However, the patient's clinical conditions decayed rapidly and he later died of neurological complications. BTKis represent a milestone in the treatment of CLL; however, little is known about how these molecules act on the immune system. Fungal brain abscesses are rare conditions more commonly seen in heavily immunocompromised patients, such as those affected by acquired immune deficiency syndrome, after bone marrow transplant or treatment for acute leukemia. Whether or not therapy with BTKis can favor opportunistic fungal infections is still a matter of debate. Various reports of Aspergillus infections developing after therapy with ibrutinib exist. Evidence does suggest that an iatrogenic impairment in the innate immune system could favor these infections. In addition,

the patient's comorbidities, such as diabetes mellitus and advancing hematological disease, might create the ideal breeding ground for these microorganisms.

Keywords: Bruton tyrosine kinase inhibitors; Abscess; Opportunistic fungal infection; Immunosuppression

Introduction

Patients affected by chronic lymphocytic leukemia (CLL) are at increased risk of contracting infections sustained by opportunistic microorganisms.

Since the introduction of Bruton tyrosine kinase inhibitor (BTKi), a number of invasive fungal infections have been reported in treated patients. Cases of Aspergillus have in fact been described in patients on therapy with ibrutinib, whereas data regarding acalabrutinib are still scarce [1-4]. Acalabrutinib targets and binds to BTK more specifically than its predecessor, as a result, it causes a lower rate of side effects which are more commonly associated with ibrutinib, such as atrial fibrillation, bleeding, and thrombocytopenia. Still, very little is known about how this latest generation BTKi acts on the immune system and how it contributes to the immunosuppressive state already created by CLL [5].

In this case report, we described a patient affected by relapsed CLL on therapy with acalabrutinib. He was diagnosed with CLL in March 2015 and was treated with a total of six cycles of fludarabine-cyclophosphamide-rituximab (FCR) scheme chemotherapy, which he tolerated well, with a complete hematological response by August 2015. There were no complications during this first treatment cycle, the patient continued attending annual follow-up visits, and no signs of disease relapse were reported.

In February 2022, a bone marrow biopsy was performed after the appearance of enlarged axillary lymph nodes and leukocytosis associated with thrombocytopenia on his routine blood tests. The biopsy demonstrated a relapsed CLL, and computed tomography (CT) scan showed diffuse lymphadenopathies in the abdomen and mediastinal region and splenomegaly. As a result, therapy with second-generation BTKi acalabrutinib was started. A CT scan performed after 1 year confirmed an important reduction in size of his diffuse lymphadenopathies,

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and also his clinical conditions and blood count improved. At the beginning of May 2023, he was diagnosed with bacterial pneumonia and was started on antibiotic therapy with ceftriaxone, and acalabrutinib was not discontinued. No other infectious complications were reported during the treatment.

The patient's comorbidities included type II diabetes mellitus, on therapy with metformin and dapagliflozin, hypercholesterolemia, nonalcoholic steatohepatitis (NASH), and arterial hypertension.

At the time of hospital admission, he was on therapy with acalabrutinib.

He presented to the emergency department on May 21, 2023 for neurological symptoms which were later found to be caused by a brain abscess.

Case Report

Investigations

A 68-year-old male presented to the emergency department of the San Luigi Hospital in Turin for confusion, drowsiness, and buccal and eye deviation. His medical record showed that he was affected by CLL and had previously been initiated on acalabrutinib.

Physical examination was carried out: he appeared alert, well-oriented in space and time, and cooperative, and his Glasgow coma scale (GCS) was 15. His pupils were isochoric and isocyclic, with normal pupillary light reflex. His eyesight was deviated to the right, with limited eye movement to the left during fixation, he did not have ptosis or visual impairment, and the oral fissure was slightly deviated to the left. Mingazzini I sign was positive on his left arm which was also hypoesthetic, whereas Mingazzini II was normal. He did not have any signs of dysmetria and his plantar reflex was normal. The patient did not present meningeal signs (no neck stiffness, Brudzinski and Kernig signs were negative), or headache and emesis.

Pulmonary examination did not reveal abnormal respiratory sounds, and cardiac and abdominal examinations were normal. Routine blood tests were requested and showed: white blood cell (WBC) 6,330/ μ L (4,500 - 11,000/ μ L) (neutrophils 4,420/ μ L (1,900 - 8,000/ μ L); lymphocytes 1,110/ μ L (900 - 5,200/ μ L)), Hb 13.9 g/dL (13 - 17 g/dL), platelet count 194,000/ μ L (150,000 - 450,000/ μ L), normal kidney and liver function, IgG 502 mg/dL (750 - 1,560 mg/dL), IgA 106 mg/dL (80 - 450 mg/dL), IgM 15 mg/dL (40 - 300 mg/dL), C-reactive protein 0.89 mg/dL (< 0.80 mg/dL), procalcitonin (PCT) 0.02 ng/mL (< 0.5 ng/mL), prothrombin time (PT) 1.35 (0.80 - 1.20 INR), activated partial thromboplastin time (aPTT) 30.9 s (22.00 - 34.00 s), and fibrinogen 379 mg/dL (150 - 450 mg/dL).

Suspecting a primarily neurological disease, a head CT scan was performed: the images showed a hypodense area 24 mm wide with surrounding edema occupying the left peritrigonal area; a second lesion was described in the contralateral frontal region and a third in the right basal ganglia. Given the worsening peri-lesional edema and the consequent symptoms of intracranial hypertension, a neurological consult was sought: the patient was started on anti-edema therapy with IV

mannitol. He also underwent an electroencephalogram (EEG) scan, which did not document signs of epileptic fits.

Concomitantly, a chest CT scan was requested and showed multiple consolidated areas in the lungs with a tree-in-bud pattern, compatible with a fungal infection. However, serological tests for galactomannan, (1-3)-beta-D-glucan, and toxoplasmosis, which were later performed, were negative.

He was later admitted to the Internal Medicine/Hematology Ward of the San Luigi Hospital.

Diagnosis

Since an infectious etiology was suspected, therapy with acalabrutinib was withheld. The patient was started on empirical antibiotic and antifungal therapy, first with piperacillin/tazobactam 4.5 g tid which was switched to meropenem 2 g tid, linezolid 600 mg bid, and liposomal amphotericin B.

During the hospital stay, a magnetic resonance imaging (MRI) scan was performed. The exam confirmed the presence of multiple brain lesions, with an appearance and radiological pattern suggestive of an infectious-inflammatory etiology (Fig. 1). Following a neurological consult, an MRI spectroscopic scan was executed, which confirmed the lesion's infectious origin.

However, despite the anti-edema therapy, the patient's neurological status became gradually worse, and he appeared drowsy, spatially and temporally disoriented. Consequently, he was transferred to the hospital's intensive care unit.

Treatment and outcomes

Afterward, a stereotactic biopsy was performed on the widest brain lesion. The histological result confirmed that the abscess was of fungal origin, with *Scedosporium* spp. being identified as the etiological agent. A detailed antibiogram was requested and antifungal therapy with IV voriconazole was started empirically.

The bioptic procedure was complicated by an intracranial hemorrhage, which extended to the area adjacent to the biopsied lesion and the homolateral cerebral ventricle. The patient therefore underwent a surgical evacuation of the intracerebral hemorrhage. Nonetheless, in the following days, he presented with worsening neurological symptoms, emesis, and facial clonus, and a head CT scan demonstrated a diffuse subarachnoid hemorrhage. A new neurosurgical consult was sought, but no further surgical indications were given. A new head CT scan was planned for the following day to monitor the extent of the hemorrhage; however, the patient's clinical conditions rapidly decayed, and he became unresponsive and later died.

Discussion

To our knowledge, very few studies have investigated the risk of contracting opportunistic infections in patients treated with a BTKi.

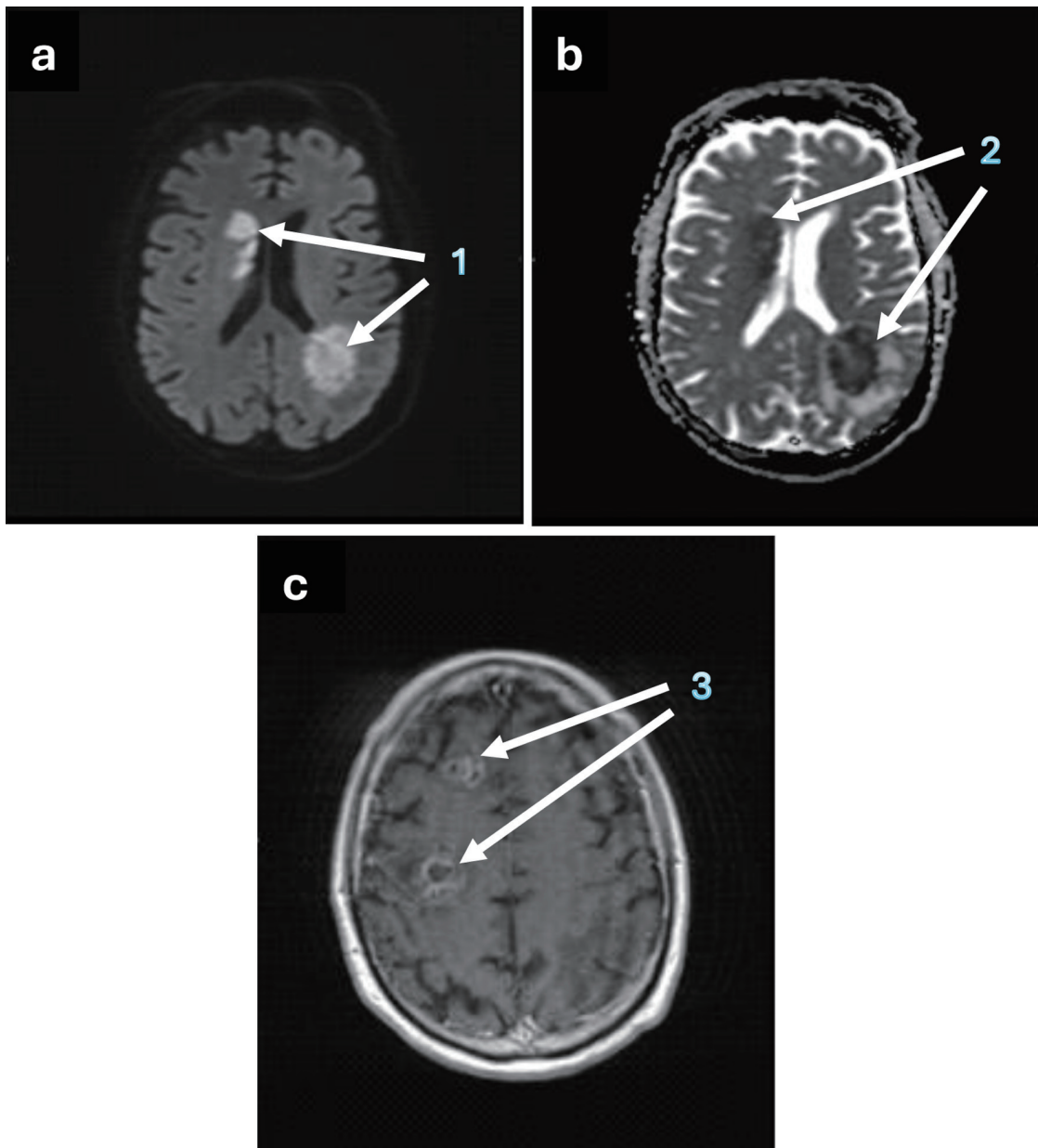


Figure 1. Brain MRI showing the axial view of the abscessual lesions. (a) 1 - hyperintense nodular lesions, compatible with abscessual lesions, on DWI mapping; (b) 2 - abscessual lesions with an hypointense appearance on ADC mapping; (c) 3 - nodular lesions, with contrast enhancement, ring enhancement and peri-lesional oedema after paramagnetic contrast agent injection, on T1-weighted image. ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; MRI: magnetic resonance imaging.

Immunocompromised individuals are at increased risk of developing invasive fungal infections. Favoring conditions include undergoing high-dose chemotherapy for hematological malignancies, allogeneic stem cell transplantation, prolonged immunosuppression, persistent neutropenia, corticosteroid therapy, and acquired immune deficiency syndrome. However, even if these conditions are satisfied, infections by *Scedosporium* remain very rare. *Scedosporium* is a ubiquitous mold, whose entry route in the human body is commonly via the upper airways. From the respiratory tract, it may spread to other sites, including the central nervous system (CNS), a

localization associated with a very poor prognosis. Therapeutic options include voriconazole, posaconazole and liposomal amphotericin B [6].

Pharmacological inhibition of BTK, as caused by acalabrutinib, alters B-cell function and the adaptive immune system, resulting in an acquired state of immunosuppression. A similar effect could be expected in a “natural” BTK inactivation. Bruton’s agammaglobulinemia is an inherited condition characterized by the mutation of the BTK gene, as a result, B cells do not mature properly and their action is impaired. Those affected are at high risk of contracting infections, these however are mainly

sustained by viruses and capsulated bacteria [7].

The reason for increased susceptibility to fungal infections could be sought in the involvement of different cellular types, for instance, those belonging to the myeloid-macrophage lineage. Evidence does suggest that BTK is also expressed on neutrophils and macrophages, both part of the innate immune system, which represents the first line of defense against microorganisms like fungi. In these cells, BTK activates a molecular pathway responsible for neutrophil-macrophage chemotaxis, oxidative burst activation, and microbial phagocytosis [8]. Interestingly, a condition known as chronic granulomatous disease, which is characterized by the inability of phagocytic cells to destroy microorganisms because of an inherited defect, poses those affected at a greater risk of developing invasive fungal infections [9].

The artificial inhibition of BTK might affect neutrophils and macrophages and their ability to efficiently contrast these microbes in a similar way to what occurs in the inherited condition [10].

In addition, the combination with the progressing hematological disease could represent an even greater risk factor for contracting invasive infections.

Furthermore, the individual's baseline characteristics are particularly relevant: the patient in this case report was affected by type II diabetes mellitus, a known risk factor for fungal infections. Upon hospital admission, he did not present with neutropenia and he had not recently received prolonged steroid therapy. However, the hematological disease had relapsed after the first treatment cycle, resulting in an even more impaired immune system and higher susceptibility to infectious events.

Based on current guidelines, once the patient had been started on acalabrutinib, he had not been given anti-fungal prophylaxis. In fact, in the eventuality of starting anti-fungal treatment or prophylaxis, an issue could be represented by the pharmacological interactions: azoles inhibit cytochrome P450, which metabolizes acalabrutinib [11]. For this reason, their concomitant use should be avoided, as it could result in the increased bioavailability of acalabrutinib [12, 13].

In the case of this patient, acalabrutinib was withheld as soon as he was admitted to the hospital and an infectious etiology had been suspected. The fungal abscess was biopsied, in order to define a diagnosis, obtain an antibiogram, and start a tailored anti-fungal therapy. Nevertheless, given the infection's very poor prognosis and the patient's decaying general conditions, the therapy was not successful and he later died of neurological complications.

Learning points

BTKis currently represent an important therapeutic option for the treatment of CLL. Acalabrutinib offers a more selective and potent inhibition of BTK, while causing a lesser degree of side effects, which are more commonly associated with ibrutinib. However, it contributes to a state of immunosuppression which may already have been generated by the hematological disease.

We believe that, before BTKi administration, each patient's individual characteristics and risk factors should be kept carefully into consideration, so as to maximize the therapeutic ben-

efits and minimize the probability of contracting opportunistic infections. Additionally, careful clinical monitoring for prompt diagnosis of fungal infections should be carried out regularly.

To our knowledge, this is one of the few existing reports describing an opportunistic infection by *Scedosporium* spp. in a patient on treatment with acalabrutinib. Further studies are needed to ascertain a possible link between targeted molecular therapies and the resulting increased infectious risk.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

MD and MP wrote the manuscript; MD, MP, GR, SC, TTB, PN, MDG, and AM evaluated the patients at the Division of Internal Medicine - Hematology; FP assessed radiological images; PC evaluated the patients at the ICU. MDG and AM reviewed manuscript and data.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

BTKi: Bruton tyrosine kinase inhibitor; CLL: chronic lymphocytic leukemia; FCR: fludarabine-cyclophosphamide-rituximab; NASH: nonalcoholic steatohepatitis

References

1. Marchesini G, Nadali G, Facchinelli D, Candoni A, Cattaneo C, Laurenti L, Fanci R, et al. Infections in patients with lymphoproliferative diseases treated with targeted agents: SEIFEM multicentric retrospective study.

- Br J Haematol. 2021;193(2):316-324. [doi](#) [pubmed](#) [pmc](#)
2. Faisal MS, Shaikh H, Khattab A, Albrethsen M, Fazal S. Cerebral aspergillosis in a patient on ibrutinib therapy- A predisposition not to overlook. *J Oncol Pharm Pract*. 2019;25(6):1486-1490. [doi](#) [pubmed](#)
3. Gaye E, Le Bot A, Talarmin JP, Le Calloch R, Belaz S, Dupont M, Tattevin P. Cerebral aspergillosis: An emerging opportunistic infection in patients receiving ibrutinib for chronic lymphocytic leukemia? *Med Mal Infect*. 2018;48(4):294-297. [doi](#) [pubmed](#)
4. Reynolds G, Slavin M, Teh BW. Ibrutinib and invasive fungal infections: the known, the unknown and the known unknowns. *Leuk Lymphoma*. 2020;61(10):2292-2294. [doi](#) [pubmed](#)
5. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, Chaves J, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323-332. [doi](#) [pubmed](#) [pmc](#)
6. Seidel D, Meissner A, Lackner M, Piepenbrock E, Sal-manton-Garcia J, Stecher M, Mellingerhoff S, et al. Prognostic factors in 264 adults with invasive *Scedosporium* spp. and *Lomentospora prolificans* infection reported in the literature and FungiScope((R)). *Crit Rev Microbiol*. 2019;45(1):1-21. [doi](#) [pubmed](#)
7. Corneth OBJ, Klein Wolterink RGJ, Hendriks RW. BTK signaling in B cell differentiation and autoimmunity. *Curr Top Microbiol Immunol*. 2016;393:67-105. [doi](#) [pubmed](#)
8. Lionakis MS, Levitz SM. Host control of fungal infections: lessons from basic studies and human cohorts. *Annu Rev Immunol*. 2018;36:157-191. [doi](#) [pubmed](#)
9. Yu HH, Yang YH, Chiang BL. Chronic granulomatous disease: a comprehensive review. *Clin Rev Allergy Immunol*. 2021;61(2):101-113. [doi](#) [pubmed](#)
10. Varughese T, Taur Y, Cohen N, Palomba ML, Seo SK, Hohl TM, Redelman-Sidi G. Serious infections in patients receiving ibrutinib for treatment of lymphoid cancer. *Clin Infect Dis*. 2018;67(5):687-692. [doi](#) [pubmed](#) [pmc](#)
11. Chen L, Li C, Bai H, Li L, Chen W. Use of modeling and simulation to predict the influence of triazole anti-fungal agents on the pharmacokinetics of zanubrutinib and acalabrutinib. *Front Pharmacol*. 2022;13:960186. [doi](#) [pubmed](#) [pmc](#)
12. Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G, Brander D, et al. NCCN Guidelines(R) insights: chronic lymphocytic leukemia/small lymphocytic lymphoma, Version 3.2022. *J Natl Compr Canc Netw*. 2022;20(6):622-634. [doi](#) [pubmed](#)
13. Criscuolo M, Fracchiolla N, Farina F, Verga L, Pagano L, Busca A. A review of prophylactic regimens to prevent invasive fungal infections in hematology patients undergoing chemotherapy or stem cell transplantation. *Expert Rev Hematol*. 2023;16(12):963-980. [doi](#) [pubmed](#)