Cerebral aspergillosis and facial acneiform lesions following initiation of ibrutinib in a patient with chronic lymphocytic leukemia

Helbies Bedier a, John Lin b,c, Charles Frenette d, Jean-Pierre Routy a,b,c,*

a Division of Hematology, McGill University Health Centre, Montreal, QC H4A 3J1, Canada
b Chronic Viral Illness Service, McGill University Health Centre, Montreal, QC H4A 3J1, Canada
c Infectious Diseases and Immunity in Global Health, Research Institute of the McGill University Health Centre, Montreal, QC H4A 3J1, Canada
d Division of Infectious Diseases, McGill University Health Centre, Montreal, QC H4A 3J1, Canada

A B S T R A C T

A case of a 67-year-old male with CLL, presented with prolonged pancytopenia after his first cycle of fludarabine, cyclophosphamide, and rituximab (FCR) chemotherapy. He was then treated with ibrutinib oral monotherapy. Shortly after ibrutinib treatment initiation, he developed a brain abscess and pulmonary disease as a part of an invasive aspergillosis. The patient improved after brain abscess drainage and the antifungal therapy voriconazole. Upon resuming ibrutinib four months after his hospitalization, he developed extensive acneiform facial lesions. This case is the first to report on the development of two separate complications in one patient related to ibrutinib, namely, Aspergillus infection, and severe acneiform skin lesions.

Introduction

Chronic lymphocytic leukaemia (CLL), the most common form of adult leukaemia, is characterized by rampant clonal expansion of mature B cells in the blood, bone marrow, and lymphoid tissues. Currently, CLL is most often diagnosed during a routine blood test for the workup of an elevated lymphocyte count. Cell expansion is driven by constitutive B-cell receptor signalling and sustained by overexpression of the anti-apoptotic protein B-cell lymphoma 2 (BCL2) [1]. Bruton’s tyrosine kinase (BTK) is an essential component of B-cell receptor signal transduction expressed by various haematopoietic cells, B-cell lymphomas, and leukaemia. BTK inhibition reduces tumour proliferation and reduces tumour bulk. Therefore, drugs that target either B-cell receptor (BCR) signalling or BCL2 protein have emerged as novel therapies for CLL. These therapies are attractive as they can be given orally in elderly patients, replacing the need for intravenous chemoimmunotherapy.

Ibrutinib is an oral irreversible inhibitor of BTK. Hence, it is indicated for the treatment of certain haematological malignancies, including CLL. Ibrutinib has been given orally as first-line therapy and should be continued indefinitely, or until disease progression.

Most responses to ibrutinib are partial, and with continuous therapy, they may benefit patients for years [1–3]. On the other hand, a critical side effect associated with ibrutinib treatment is increased risk for invasive fungal infection. Herein, we present a case of a 67-year-old male with Aspergillus brain infection and severe acneiform skin lesions a few months after ibrutinib initiation [4].

Case report

A 67-year-old man, with moderate enlargement of cervical lymph nodes, was diagnosed with CLL in 2008. His past medical history included previous colon surgery, left kidney stones, atherosclerotic heart disease, AF, and a history of transient ischemic attack (TIA). Imaging by PET scan showed two groups of cervical and axillary lymph nodes with low metabolic activity. As the patient remained asymptomatic, he was managed by close follow up. In April 2017, he presented with night sweats, weight loss, anaemia, and thrombocytopenia with a lymphocyte count of 304 * 10^9 cells/L. As the patient presented with a Rai Stage VI CLL, he received one cycle of fludarabine, cyclophosphamide, and rituximab (FCR) complicated by prolonged pancytopenia, and did not improve after three infusions of Rituximab (RTX) (450 mg/m2), which were started on the 12th of September 2018, given to treat potential aplastic anaemia related to FCR.

A bone marrow aspiration and biopsy were performed to rule out autoimmune aplasia or Richter transformation into a diffuse large B
cell lymphoma. Results showed sheets of small lymphocytes, confirming the diagnosis of CLL. Fluorescence in situ hybridization (FISH) testing showed the absence of del(17p)/TP53 mutation or other chromosomal mutations and/or translocation. The patient was started on 420 mg daily oral ibrutinib. Subsequently, his lymphocyte count dropped remarkably in three weeks.

Two weeks later, he presented to the ER with confusion. His neutrophil count was at 0.96 g/L, hemoglobin 80 g/L, platelets 28 \* 10^9 g/L, and had hypogammaglobulinemia. Testing for plasma levels of galactomannan was negative. His chest radiography was consistent with left lower lobe pneumonia with small left pleural effusion (Fig. 1). The CT scan confirmed pneumonia with small bilateral pleural effusion and showed patchy opacities with scattered sub-centimetric pulmonary nodules and bilateral paratracheal and hilar lymph nodes (Fig. 2). Bronchoalveolar lavage (BAL) bacterial cultures were negative for both bacterial and fungal growth. His head MRI showed a left frontal lobe abscess for which a neurosurgical procedure was carried out for surgical removal (Fig. 3). CT for sinuses was not performed, however, his head MRI didn’t show any sign for sinusitis or sinus infection as a potential source for the spread of the infection.

Microbiological cultures from the brain abscessed tissue showed the growth of Aspergillus fumigatus. (Fig. 4). After his brain surgery, the patient rapidly improved with voriconazole 450 mg given intravenously every 12 h and was discharged on voriconazole 250 mg twice daily orally with regular monitoring to ensure the drug plasma level remained in the therapeutic zone. Despite the discontinuation of ibrutinib since admission, the patient maintained a haematological response for six months. In June 2019, his lymphocyte count increased to his pre-treatment level, and ibrutinib was resumed at a lower dose of 140 mg daily due to concomitant use of voriconazole, a moderate CYP3A4 inhibitor. He maintained grade 2/3 neutropenia (as per CTCAE V.5) since starting ibrutinib in September 2018 all through his treatment until August 2019, and otherwise maintained a good hematological response (Table 1). However, in October 2019, he developed severe acniform lesions on his face and torso which proved negative for microbiological cultures. Empirically, he was prescribed a topical cortisone cream and antibiotic therapy of cefadroxil for 14 days.

**Outcome and follow-up**

The patient remained on voriconazole throughout the end of the follow-up with sustained improvement in imaging by MRI of both central nervous system (CNS) lesions and pulmonary lesions. As of September 23, 2020, he did not show any neurological abnormalities, his skin lesions had healed, and his lymphocyte count was normal with ibrutinib given at 140 mg daily.

**Discussion**

Although novel agent therapies have recently improved the management of patients affected by CLL, infectious complications remain an important contributor to morbidity and mortality. Recently, growing numbers of opportunistic infections including Pneumocystis jirovecii pneumonia and other invasive fungal infections like aspergilliosis have been reported in CLL patients treated with BTK inhibitors (BTKis). However, the use of BTKis has recently become more widespread, with the emergence of greater than expected adverse events. This phenomenon has proven more challenging than initially anticipated from previous clinical trials [5].

Conventional fludarabine-based chemotherapy, one of the frontline standards of care therapies, has improved disease response and prolonged the survival in patients younger than 65 years of age with CLL. However, its use in elderly patients was restricted by substantial myelosuppression and infection. Therefore ibrutinib oral chemotherapy is now largely used [6]. Several studies showed the association of introducing ibrutinib treatment with increasing rates of opportunistic invasive fungal infections (IFIs) caused by Pneumocystis jirovecii (P. jirovecii), Cryptococcus neoformans, and ubiquitous airborne filamentous fungi (Aspergillus, Fusarium, and Mucorales); these often present with atypical manifestations, including central nervous system (CNS) aspergillosis, extrapulmonary P. jirovecii, and disseminated cryptococcosis, and all are associated with substantially increased mortality rates (Table 2) [6–10]. The associated IFIs, particularly invasive aspergillosis (IA), tend to occur within the first months of treatment of ibrutinib. A study by Ruchlemer et al., reported that the median duration of ibrutinib treatment before the onset of IFIs was 45 days. Aspergillus species were identified in 22 (63%) and Cryptococcus species in 9 (26%) of 33 patients with IFI. Pulmonary involvement occurred in 69% of patients, cranial in 60%, and disseminated infection in 60%. Thus, the majority of these IFIs were due to Aspergillus with a trend towards CNS involvement [11].

The pathogenesis of infection in CLL is multifactorial with several mechanisms involved in the emergence of invasive aspergillosis. Aspergillus activates BTK in macrophages which in turn leads to downstream macrophage calcineurin-NFAT signalling to recruit neutrophils to the site of infection [14]. However, in the setting of ibrutinib, the downstream NFAT and NFkB response is impaired, resulting in the lack of neutrophil recruitment [15]. Additionally, Blez et al. found that patients treated with ibrutinib have reduced neutrophil function with low oxidative burst and an absence of

![Fig. 1. Chest X-ray September 25th, 2018, Moderate opacification in the inferior left hemithorax likely related to a combination of pneumonia and effusion.](image1)

![Fig. 2. CT-Chest, October 10, 2018: Large consolidation in the left lower lobe and patchy opacities in the right lung. There is also small bilateral pleural effusion as well as enlarged mediastinal lymph nodes.](image2)
interleukin-8 secretion when infected with Aspergillus [16]. As a consequence, for the patient receiving ibrutinib, Aspergillus infection may occur rapidly. Due to the impaired innate response, the fungal infection may invade distant organs via hematogenous dissemination [17]. In CNS Aspergillus infection, in addition to the hematological dissemination, local extension from sinusitis, mastoiditis, and trauma may also occur. In this report, the patient suffered from CNS fungal infection which may have spread from Aspergillus pneumonia. Aspergillus species produce mycotoxins that can alter the blood-brain barrier, evade phagocytosis by microglial cells, and ultimately lead to CNS infection [18]. Additionally, ibrutinib may inhibit macrophages and microglial cells due to its elevated CNS penetration [19]. Consequently, ibrutinib-treated macrophages may transmit Aspergillus organisms across the blood-brain barrier, establishing CNS infection. Moreover, CLL patients may present with impaired T-cell mediated immunity which could also be a contributing factor.

Prentice et al. [17] proposed through a large clinical trial that the severity of neutropenia and its duration, older age, use of corticosteroids, and fludarabine-based combination therapy are risk factors for the development of IFI. In our case, despite his rapid haematological response, the patient developed cerebral aspergillosis, manifesting 3 weeks after the initiation of ibrutinib treatment. Our patient was predisposed by several factors including his previous treatment by FCR with persistent neutropenia. Furthermore, cutaneous manifestations have been reported in 2–27% of patients treated by ibrutinib. The most common cutaneous side effects are rash, petechiae, and bruising [20]. Likewise, upon resuming ibrutinib, the patient developed severe multifocal acneiform lesions. In rare cases, acute generalized exanthemeatous pustulosis, acneiform lesions, and neutrophilic dermatosis cases have been reported with Ibrutinib. Despite these two ibrutinib-related complications, the patient has improved and has maintained partial control of his CLL, enabling him to remain symptom-free.

Fig. 3. A) MRI head October 5, 2018, upon Emergency Room visit for confusion: ring-enhancing lesion at left frontal lobe measuring 3.9 × 3.1 × 2.5 cm diameters. The lesion showed a central bright T2/FLAIR signal with a rim of low T2 signal along with diffusion restriction. Postcontrast administration exhibited smooth rim enhancement associated with surrounding white matter edematous changes. The previously described lesion is in favor of a cerebral abscess causing adjacent mass effect with the involvement of medial anterior right cingulate gyrus. The lesion demonstrates a subependymal extension at the level of the left frontal horn with no signs of ventriculitis. B) MRI head November 10th, 2019, Follow-up postoperative changes of left frontal craniotomy for resection of the left frontal fungal abscess. An enhancing nodule is again noticed in the anterior interhemispheric fissure, slightly predominant on the left side, smaller measured approximately 8 × 9 × 8 mm. There is unchanged T2/FLAIR hyperintensity likely in keeping with gliosis. There is no evidence of diffusion restriction or new areas of abnormal contrast enhancement. There are few scattered foci of T2/FLAIR hyperintensity involving the periventricular and deep white matter of both cerebral hemispheres, likely reflecting mild chronic microvascular ischemic changes. The major intracranial flow voids are unremarkable. The previously described changes indicate favorable evolution of the postoperative changes of abscess resection.

Fig. 4. Microscopic examination of deep culture from brain October 7th, 2018, Fungal hyphae are seen; 1 + Aspergillus fumigatus.

Table 1 Summary of the patient’s haematological test results showing case progress (2018–2020) Ibrt = ibrutinib; HB = haemoglobin; WBC = White Blood Count.

| Lab Test result and date | HB (g/L) | WBC (10^9/L) | Platelets (10^9/L) | Neutrophils (10^9/L) | Lymphocytes (10^9/L) |
|-------------------------|----------|--------------|------------------|----------------------|----------------------|
| 19-Sep. 2018 (Relapse/before Ibrt) | 92       | 320          | 50               | 3.60                 | 314.15               |
| 25-Sep.2018 (after Ibrt) | 53       | 35.2         | 24               | 0.78                 | 18.03                |
| 05-Oct. 2018 (brain abscess) | 80       | 5.3          | 28               | 0.96                 | 4.27                 |
| 04-Dec. 2018 Post surgical | 76       | 14.9         | 48               | 0.66                 | 14.9                 |
| 30-Jan-2019 FU | 113       | 24.6         | 38               | 0.93                 | 23.41                |
| 20-Nov-2019 1st Resp-restart Ibrt. | 93       | 48.5         | 63               | 4.63                 | 30.09                |
| 17-Sep 2020, Follow up | 118      | 8.80         | 65               | 2.71                 | 5.53                 |
| 21-Jul 2021, Follow up | 115      | 5.10         | 72               | 3.31                 | 1.22                 |
This described case widely contributes to the management of CLL cases (the commonest adult leukemia) by raising the clinical index of suspicion of invasive fungal infection, particularly aspergillosis in CLL patients treated with ibrutinib, who present with persistent fever of unclear origin and/or unexplained respiratory signs or symptoms.

**CRediT authorship contribution statement**

Helbies Bedier (HB) and Jean-Pierre Routy (JPR) devised the project, main ideas and proofs. HB wrote the manuscript with the supervision of JPR. HB acquired all the images. JPR and John Lin (JL) provided critical review and helped shape analysis and the manuscript. Charles Frenette (CF) provided critical review of the manuscript.

**Conflict of interest**

The authors declare no conflict of interest.

**Ethical approval**

Not applicable.

**Patient consent**

The authors obtained a written informed consent from the patient for the publication of this report.

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**Table 2**

Summary of publications on Aspergillosis infection in CLL patients, its frequency, the predisposing factors, the treatment given and the outcome of their treatment.

| Study | Patient age and sex | Prior lines of treatment | Associated Pulmonary aspergillosis | Serum Neutropenia at time of diagnosis | Time from Ibrutinib initiation to diagnosis of CNS Aspergillosis (months) | Galactomannan test | Asp Treatment | Outcome at the time of publication |
|-------|---------------------|--------------------------|-----------------------------------|--------------------------------------|------------------------------------------------------------------------|------------------|-----------------|----------------------------------|
| Gaye et al. [2] | 75-Years-old male | Obinutuzumab, bendamustine, rituximab | Present | Positive | Not Available | < 1 | Voriconazole; ibrutinib discontinued | Alive |
| Beresford et al. [3] | 65-Years-Old Male | Corticosteroids based treatment | Absent | Positive | Absent | 2 | Voriconazole and amphotericin B; ibrutinib continued | Alive |
| Lionakis et al. [4] | 66-Years-Old Male | Fludarabine, CP, bendamustine, rituximab | Absent | Negative | Absent | 1 | Voriconazole subseq uently switched to posaconazole; ibrutinib discontinued | Alive |
| Eichenberger [5] | 62-Years-Old Male | None | Present | Negative | Present | < 1 | Voriconazole, ibrutinib | Alive |
| Present Case | 66-Years-Old-Male | fludarabine, cyclophosphamide, and rituximab | Present | Negative | Present | < 1 | Surgery, Voriconazole, ibrutinib | Alive |
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