

Ibrutinib Therapy and *Mycobacterium chelonae* Skin and Soft Tissue Infection

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Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase approved for the treatment of B-cell malignancies. There is growing concern about the risk of opportunistic infections following ibrutinib therapy. Herein, we describe the first case of *Mycobacterium chelonae* skin and soft tissue infection in a patient receiving ibrutinib and recount the challenges in treating this infection.

Keywords. chronic lymphocytic leukemia; ibrutinib; *Mycobacterium chelonae*; nontuberculous mycobacteria; skin and soft tissue infection.

CASE DESCRIPTION

An 85-year-old man with a history of chronic lymphocytic leukemia (CLL) presented with slowly progressing skin lesions on his upper and lower extremities that developed over 5 months. The initial skin lesion was a painful cystic nodule on the dorsum of the wrist that gradually increased in size. The patient had not traveled recently and had no significant animal or unusual water exposure. He was first diagnosed with CLL in December of 2006. He was managed expectantly for 4 years until he developed fatigue and splenomegaly and was then treated with 6 cycles of bendamustine and rituximab, with partial response. One year after completion of therapy, he relapsed and was treated with 6 cycles of fludarabine and rituximab. The patient remained asymptomatic until late in 2016, when he developed increasing fatigue and anemia. In December 2016, his CLL was

restaged as high risk, and he was started on treatment with ibrutinib 420 mg once daily. He tolerated ibrutinib therapy well until 6 months into therapy, when he developed skin lesions on his arms and legs. He had no prior serious, recurrent, or opportunistic infections.

On presentation, he was afebrile and normotensive. Physical examination was notable for multiple skin lesions involving both the arms and legs (Figure 1A–C). An elevated white blood cell count (25×10^9 /L; normal 4500 to 11 000 10/L, 58% lymphocytes) and erythrocyte sedimentation rate (75 mm/h; normal 0–22 mm/h) and C-reactive protein of 20.3 mg/d (normal, <0.5 mg/dL) were the only laboratory abnormalities.

The lesion over the wrist was incised and drained. Gram's stain revealed no bacteria. Culture grew mycobacteria identified as *Mycobacterium chelonae* using 16S ribosomal RNA sequencing that was susceptible to tetracycline, linezolid, and clarithromycin. A chest radiograph was normal. Based on the history and examination findings, we hypothesized that the infection occurred by direct skin invasion as the organism is known to be ubiquitous in soil and water [1].

The patient was treated with linezolid, doxycycline, and clarithromycin. He developed severe thrombocytopenia, and linezolid was discontinued. Doxycycline and clarithromycin were continued. Later, he developed dizziness, which was attributed to an interaction between clarithromycin and ibrutinib leading to increased serum ibrutinib levels. Ibrutinib was held for 1 week. His dizziness resolved and did not recur when ibrutinib treatment was restarted with a dose of 280 mg once daily. During the next 4 months, his skin lesions improved (Figure 2D–F).

DISCUSSION

Mycobacterium chelonae is a rapidly growing nontuberculous mycobacterium (RGM) that is ubiquitous in soil and water. Rates of infections caused by RGM have been increasing in the United States [1]. In humans, *M. chelonae* is an opportunistic pathogen that may cause localized cutaneous infection following incidental inoculation from the environment [2]. Typically, infection is limited to the site of inoculation and manifests as cellulitis or abscess; in immunocompromised patients, however, disseminated skin disease can occur. Disseminated infections with *M. chelonae* have also been associated with diabetes mellitus, malignancy, organ transplants, and treatment with corticosteroids and tumor necrosis factor- α (TNF- α) inhibitors. Less frequently, osteomyelitis, pulmonary disease, corneal ulceration, and lymphadenitis may also occur [3]. For extensive skin, bone, and soft tissue disease, treatment guidelines recommend 4 to 6 months of combination therapy guided by drug susceptibility testing [4].

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Figure 1. Skin lesions due to *Mycobacterium chelonae* infection. A, Right wrist. B, Left arm. C, Left leg.

We describe a patient who developed disseminated cutaneous *M. chelonae* infection while on ibrutinib, an irreversible oral inhibitor of Bruton's tyrosine kinase (BTK) that is approved

for the treatment of several B-cell malignancies. Since accelerated Food and Drug Administration approval in 2013, ibrutinib has revolutionized the treatment of CLL [5, 6]. However, a



Figure 2. Subsequent lesions 4 months after therapy with doxycycline and clarithromycin. D, Right arm. E, Left arm. F, Left leg.

growing concern is emerging as a result of increasing reports of opportunistic infections, particularly invasive fungal infections [7–9], which typically do not occur frequently in patients with BTK deficiency (X-linked agammaglobulinemia). This suggests that ibrutinib may have significant immunomodulatory effects beyond those mediated by BTK inhibition [10]. Ibrutinib inhibits B-cell receptor signaling and replication of leukemic cells in CLL. In addition to tyrosine kinase, ibrutinib also inhibits IL2-inducible T-cell kinase (ITK), which regulates T-cell proliferation and may decrease Th-1 immune responses to fungal and other intracellular pathogens [11]. Most serious infections in patients with CLL treated with ibrutinib have been related to B-cell dysfunction; however, invasive aspergillosis, pneumocystis pneumonia, and other invasive fungal infections have been reported [12].

Disseminated *M. chelonae* infection has been reported in patients with genetic immunodeficiencies and in the setting of immunosuppressive and corticosteroid therapy [3]. No cases of *M. chelonae* infection associated with ibrutinib use have been reported previously. The risk of *M. chelonae* in patients with CLL likely depends on multiple factors, including the underlying disease state, concomitant immunosuppressive therapy, medical comorbidities, and genetic predisposition. Furthermore, the risk of serious infections is substantially higher in patients with relapsed or refractory CLL treated with ibrutinib compared with patients treated with ibrutinib as part of initial therapy [13], as in our patient. Treatment of *M. chelonae* infection in such patients constitutes a significant challenge due to drug interactions. Ibrutinib is exclusively metabolized by cytochrome P450 (CYP) CYP3A; hence, therapy with macrolides may result in an increase in the plasma level of ibrutinib and subsequent toxicity. Ibrutinib dose interruption or modification is warranted when treatment of a patient on ibrutinib requires administration of strong or moderate CYP3A inhibitors [14]. In addition, we monitored his electrocardiogram periodically as both clarithromycin and ibrutinib have been linked to fatal and serious cardiac arrhythmias [15, 16].

Our patient adds to the growing list of opportunistic infections occurring in patients with relapsed CLL treated with ibrutinib. Patients who have been previously treated with multiple courses of chemotherapy for CLL might benefit from risk assessment and increased monitoring and prophylactic

strategies for opportunistic infections [17]. More research is needed in this area.

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