



## Case report

## Cutaneous mucormycosis in a chronic lymphocytic leukemia patient on ibrutinib



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## ABSTRACT

**Background:** Mucorales is a zygomycete fungi known to cause opportunistic infections in immunosuppressed hosts. Spores may be inhaled, causing rhinocerebral or pulmonary infections, or gastrointestinal infections if swallowed. Less often, cutaneous mucormycosis develops after inoculation via broken skin. **Presentation:** A 72-year old male on ibrutinib and prednisone for chronic lymphocytic leukemia (CLL) presented with localized, right forearm cutaneous mucormycosis at the site of a dog-scratch sustained three weeks prior. The patient failed to respond to cephalexin as an outpatient, prompting biopsy showing ribbon-like pseudo septate hyphae and possible vascular invasion suggestive of Mucorales. Treatment course included liposomal amphotericin B 5 mg/kg IV every 24 h for ten days followed by a 90-day course of posaconazole 300 mg daily after general surgery consultation was sought. **Conclusion:** We outline the second reported case of localized cutaneous mucormycosis arising in the setting of ibrutinib use. Because the combination of immunosuppressed states, ibrutinib and skin trauma may serve as a nidus for mucormycosis, practitioners should be vigilant of thorough skin evaluations in these patients and appropriate anti-fungal treatment. Although amphotericin B has been well studied as first line therapy, oral posaconazole has been shown as an efficacious second-line treatment.

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## Introduction

Mucormycosis is a rare but serious infection caused by opportunistic fungi belonging to the subphylum Mucoromycotina and order Zygomycota [1]. Mucormycosis manifests in the immunocompromised setting, most commonly in patients with uncontrolled diabetes mellitus, hematologic malignancies and post hematopoietic stem cell transplantation [1,2]. Zygomycetes are typically isolated from decaying materials, such as soil, foods, and fabrics, with an incidence of 0.3 per 100,000 patients in North America [2,3]. Clinical presentation depends on mode of transmission but predominantly results in pulmonary or rhinocerebral infection through spore inhalation, and less frequently

gastrointestinal infection through spore ingestion [4]. Cutaneous infection may occur through direct inoculation of spores at sites of skin trauma, such as burns, insulin injection sites or scratches, and characteristically presents as a rapidly growing, indurated and necrotic plaque [1]. Diagnosis is sought by polymerase chain reaction (PCR), direct KOH microscopic examination or central lesion biopsy with subcutaneous fat showing thick, non-septated, bifurcated hyphae with necrosis and inflammatory reaction [2].

Ibrutinib (Imbruvica), is a small molecule drug that targets and permanently binds to Bruton's tyrosine kinase, a protein crucial to B-cell function and proliferation. Accordingly, the drug is implicated in treatment of CLL, other lymphomas (small lymphocytic, mantle cell, marginal zone), Waldenstrom macroglobulinemia and graft-versus-host disease [5]. Although cases of ibrutinib-associated cutaneous mucormycosis are rare, its presentation in an immunocompromised state lends to risk of increased morbidity and mortality; 26–43% and 4–10% among those with disseminated and localized cutaneous disease, respectively. Uncontrolled diabetes and metabolic acidosis also served as significant risk factors with an increase in mortality rate to 85% [3,6]. Accordingly, clinicians should maintain high clinical suspicion and know

*Abbreviations:* AFB, Acid-Fast Bacilli; BTK, Bruton's Tyrosine Kinase; CLL, Chronic Lymphocytic Leukemia; CNS, Central Nervous System; IVIG, Intravenous Immunoglobulin; PAS, Periodic Acid Schiff; PCP, Primary Care Physician; PCR, Polymerase Chain Reaction.

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definitive treatments for mucormycosis in these patients. Treatment is multimodal, including antifungals, consideration of surgical debridement, and management of underlying or concomitant conditions. Although amphotericin B has been well studied as first line therapy, oral posaconazole has been shown as an efficacious second-line treatment [1,3,7-9].

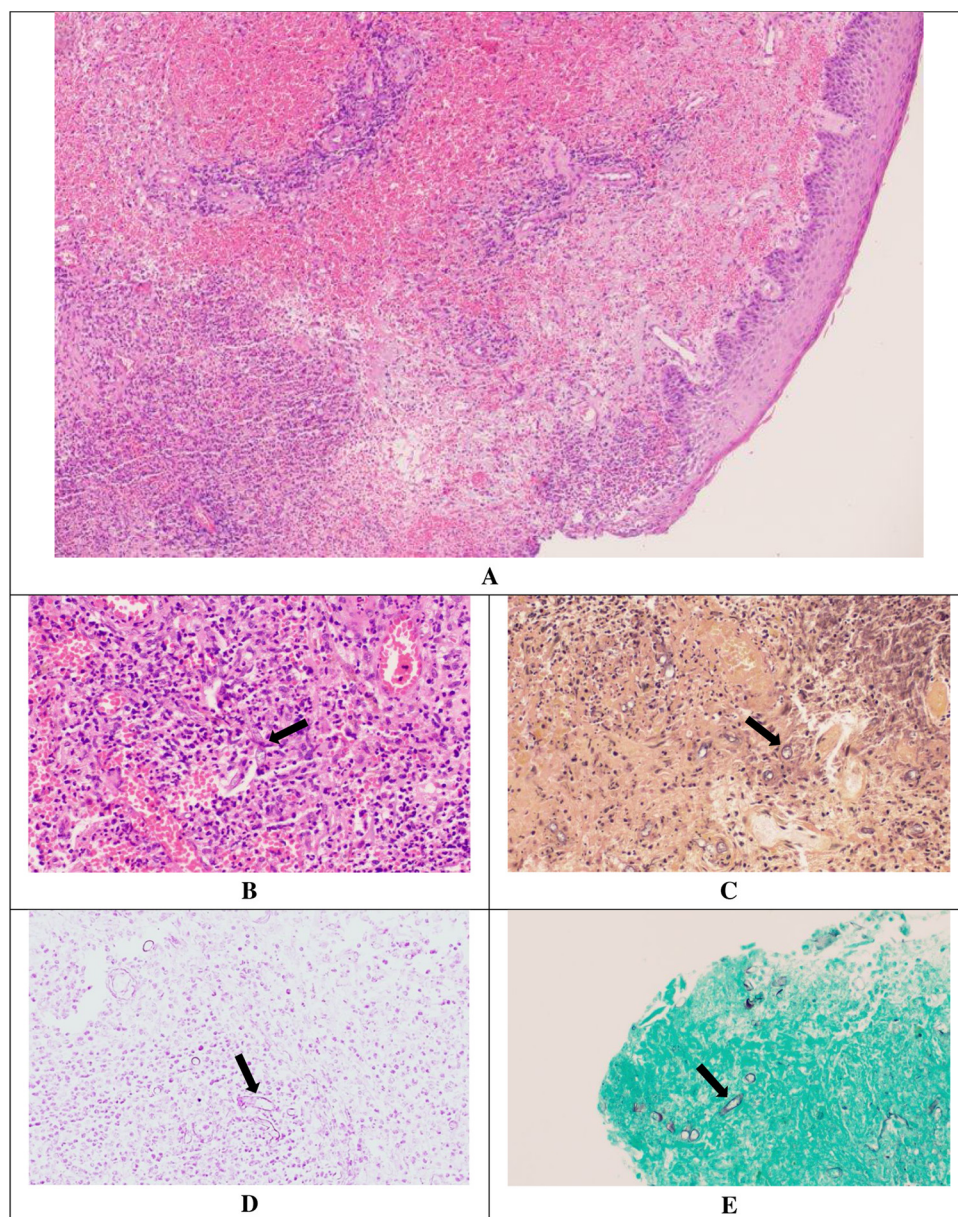
We report a case of cutaneous mucormycosis treated successfully with oral posaconazole in a patient who is immunosuppressed due to treatment for CLL with ibrutinib.

**Case**

A 72-year-old Caucasian male presented to his primary care physician (PCP) for complaints of a rapidly progressing, non-healing right forearm wound arising at the site of a dog-scratch sustained 3 weeks prior. The patient denied any concomitant fevers, chills, bowel or urinary symptoms, other constitutional symptoms or sites of skin change. Past medical history was notable

for CLL treated with ibrutinib (Imbruvica, 140 mg oral nightly) and prednisone (10 mg oral daily), hypertension, hyperlipidemia, diverticulosis, nonalcoholic steatohepatitis, and paroxysmal atrial fibrillation. The patient was rate/rhythm controlled with metoprolol tartrate and anticoagulated with apixaban. He initially received a 7-day course of oral cephalexin (Keflex) which resulted in no improvement in symptoms, accordingly dermatology referral was placed and a skin biopsy was pursued. Several stains were completed, including gram, acid-fast bacilli (AFB), mucicarmine, and Periodic acid-Schiff (PAS), showing ribbon-like pauciseptate hyphae suggestive of Mucorales (Fig. 1). Of note, gram stains were weakly PAS positive, and slides were reviewed by two pathologists: Mayo Clinic (Rochester, MN) and UnityPoint (Des Moines, Iowa) (Fig. 1).

The patient was admitted to a tertiary care facility, treated with IV amphotericin B (490 mg in 250 mL 5% dextrose) and topical silver sulfadiazine 1% cream. On and throughout admission, the patient remained hemodynamically stable. Initial examination



**Fig. 1.** Histopathology sections showing A. 10x magnification H and E epidermal ulceration and granulation tissue. B. 40X magnification ribbon like organisms amid inflammation. C. 40x magnification mucicarmine stain with organism. D. 40X, PAS stain with arrow pointing to organism. E. 40X, GMS stain.





**Fig. 2.** Temporal representation of right forearm lesion. A. Day of presentation. B. One week from initial presentation. C. One month from initial presentation. D. Two months from initial presentation. E. Six months from initial presentation. (Please use color).

showed a 4.0 × 2.5 cm erythematous, heme-crusted plaque of non-healing tissue (Fig. 2A). Differentials for the patient’s wound included squamous and/or basal cell carcinoma, ecthyma gangrenosum, pyogenic granuloma, tinea corporis, polymicrobial non-healing ulcer or osteomyelitis. Initial basic metabolic panel was notable for a creatinine of 1.23 mg/dL (normal 0.8–1.3 mg/dL) and glucose 135 mg/dL (normal 70–99 mg/dL). Complete blood count was notable for hemoglobin of 12.0 g/dL (normal 13.0–17.0 g/dL) and platelets of 66 × 10<sup>3</sup>/uL (normal 150–450 × 10<sup>3</sup>/uL). Upper extremity MRI was attempted but unsuccessful due to patient movement; no additional diagnostic imaging was pursued. Fungal and bacterial wound cultures were also obtained and positive for

*Pseudomonas aeruginosa*, with IV cefepime (2 g every 24 h) added accordingly.

After consultation with Infectious Disease, the patient’s fungal infection was attributed to his CLL and ibrutinib medication. Hematology and Oncology was subsequently consulted and modified the ibrutinib treatment to “every-other-day” regimen, but a higher daily dose of 280 mg. New-onset acute kidney injury later developed, and was attributed to amphotericin B but continued due to the acute nature and severity of disease. To prophylax against nephrotoxicity, the patient was placed on 125 cc/hr normal saline per Nephrology recommendations. General Surgery recommended against initial debridement and elected to

pursue medical management. By hospital day 7, wound healing was noted (Fig. 2B) and ibrutinib was held. He completed a total of ten days of amphotericin B, seven days of cefepime, and eight days of stress-dose steroids with hydrocortisone sodium succinate IV with notable improvement in his wound. He was discharged home on oral posaconazole (300 mg daily for 90 days), prednisone steroid taper, and ibrutinib to be taken at decreased frequency of every other day. At 6-month reevaluation, the patient's lesion had completely healed and he denied any new lesions or symptoms (Fig. 2E).

**Discussion**

Greater than 90 % of invasive fungal infections arise from species in five principal genera: Candida, Aspergillus, Mucor, Cryptococcus and Pneumocystis [10]. Due to the growing number of fungal infections arising in patients with B-cell malignancies on ibrutinib, Chamilos et al. and other infectious disease physicians

pushed for publications of these cases beginning in 2017 [11]. A number of cases have since been published, including sinus, disseminated, abdominal, CNS, and thyroid manifestations, as well as cutaneous seeded from a distant focus of infection (Table 1) [12–18]. To our knowledge, there are only two reported cases of cutaneous mucormycosis in patients on ibrutinib for CLL: one patient presenting with localized disease from accidental skin trauma and a second with disseminated skin involvement in the setting of a bullous pemphigoid flare [12,13].

Ecthyma gangrenosum is a cutaneous manifestation of bacteremia that presents with an ulcer similar to that seen in Fig. 2. Though it can be associated with other bacteria, it is most often associated with *Pseudomonas aeruginosa* infection [19]. As bacterial wound culture was positive for *P. aeruginosa*, ecthyma gangrenosum is a differential for the case presented here. However, our patient lacked both *P. aeruginosa* bacteremia, as well as the classic vesicular or pustular lesion prior to ulcer development. This, together with the pathology findings shown in

**Table 1**  
Literature review: cases of mucormycosis arising in the setting of ibrutinib use. Column four highlights treatments used in sequential order for chronic lymphocytic leukemia (CLL) (above dashed line) followed by the hospital treatment course for the mucormycosis (below dashed line). Medications followed by a "/" and second medication signifies those two medications were used concomitantly during the treatment course.

Authors (1)	Sex & Age (2)	Associated Diagnoses (3)	Cancer Treatment(s) (4)	Infection Treatment(s)	Infection Sites (5)
Fehr et al. [18]	71 (M)	CLL CNS	Ibrutinib -----		CNS
Mascarella et al. [15]	79 (M)	Aspergillus Rhizomucor CLL	Amphotericin B Posaconazole Ibrutinib -----		Thyroid
Pouvaret et al. [14]	52 (F)	CLL CNS Aspergillus	Piperacillin-tazobactam/Vancomycin Amphotericin B Posaconazole Rituximab Fludarabine Cyclophosphamide Ibrutinib -----		Cerebral, left kidney, spleen
Stein et al. [13]	M (68)	CLL Bullous Pemphigoid	Cefotaxime/Metronidazole Voriconazole/Amphotericin B Alsavuconazole/Amphotericin B Rituximab Cyclophosphamide Vincristine Prednisone Fludarabine Ibrutinib -----		Disseminated Cutaneous
Mir et al. [16]	M (61)	CLL Sarcoidosis	IVIG Vancomycin/Meropenem Acyclovir Fluconazole Amphotericin B Posaconazole Bendamustine Rituximab Ibrutinib -----		Pulmonary mucormycosis (Right upper lung consolidation)
Grossi et al. [17]	M (70)	CLL Disseminated Lichtheimia Corymbifera	Voriconazole Amphotericin B Posaconazole Fludarabine Cyclophosphamide Rituximab Ibrutinib -----		Cerebral (left caudate) Pulmonary (right inferior) Splenic/Hepatic (several nodules)
Figueroa Castro [12]	M	CLL	Meropenem/Amikacin Amphotericin B Ibrutinib ----- Amphotericin B Posaconazole		Localized Cutaneous

**Fig. 1**, speak against ecthyma gangrenosum as the etiology of our patient's lesion.

The rarity of cutaneous mucormycosis reports in CLL patients on ibrutinib also suggests the importance of intact mucosal and skin barriers. A retrospective study by Varughese et al. (2018) identified a 37.2 % rate of fungal infections in CLL and mantle cell lymphoma patients, of whom 62.5 % lacked significant risk factors (neutropenia, lymphopenia, or concomitant steroid use) [20]. In this patient demographic, Ghez et al. (2018) also identified aspergillosis as the predominant species; their study showed 82 % (27 cases) of aspergillus and just one case of mucormycosis. They also recognized 85 % of fungal infections arose within six months of ibrutinib initiation, and identified five major predisposing factors: chemotherapy within 6 months of ibrutinib use, neutropenia, and corticosteroids with or without concomitant rituximab or other immunochemotherapy [21].

To date, only seven cases of localized and disseminated mucormycosis have been reported in CLL patients treated with ibrutinib (Table 1). A single case details localized mucormycosis after left leg trauma in a CLL patient on ibrutinib [12]. Stein et al. (2018) also reported the first case of disseminated cutaneous mucormycosis in the same population but arising in the setting of a bullous pemphigoid flare [13]. Research on ibrutinib disease associations have identified a prevalence of fungal infections among CLL and lymphoma patients [20]. Although the mechanism is not fully elucidated, authors suggest fungal infections arise from a compromised innate/adaptive antifungal immune response during the early phase (first 6 months) of ibrutinib-immune reconstitution [21,22].

Because Mucorales is typically an aggressive and often angioinvasive fungi, quick diagnosis and treatment are imperative in medical complex and immunocompromised patients [11]. Physical examination with careful attention to skin, pulmonary and neurologic signs should be implicated with a low threshold for paralleled diagnostic evaluation with head CT (computerized tomography) or chest radiograph. Any wound or lesion site should undergo biopsy and PCR, if available, provides the highest sensitivity and specificity [3]. Regardless of organ site involvement, first-line treatment for mucormycosis is amphotericin B, either deoxycholate (1–1.5 mg/kg/day) and liposomal form (5–10 mg/kg/day), the latter formulation being less nephrotoxic [7]. Although duration of therapy is unclear, a 6–8-week course has been recommended in literature [7].

For those intolerant of amphotericin B, growing data have shown posaconazole (400 mg twice daily for several months) and isavuconazole as efficacious second line agents [1,3,8,9]. Because of its oral dosing and safer drug profile, including less renal toxicity, posaconazole has become an attractive alternative to amphotericin B, particularly in the context of discharge planning. However, because posaconazole inhibits CYP34A, elevations in serum ibrutinib may result, and therefore concomitant use of these drugs should be avoided as to not impact CLL management [12]. As highlighted in Table 1, all CLL patients were treated with ibrutinib before or after use of additional immunotherapies. Similarly, all cases of Mucorales were ultimately treated with brief courses of amphotericin B and a second antifungal, such as posaconazole. Similar to our patient, the case reports of patients with cutaneous mucormycosis above were initially treated with amphotericin B and then posaconazole, at which time the ibrutinib was held to avoid drug-drug interactions [8,12,13]. In contrast, Stein et al. (2016), Pouvaret et al. (2019) and Mascarella et al. (2019) reported several failed antibiotics prior to use of antifungals [13–15].

The few studies highlighted in Table 1 lend to the difficult diagnosis and lack of treatment guidelines for mucormycosis. Mucor is at least 5- to 10- fold less common than the other genera of Candida, Aspergillus, Mucorales, Cryptococcus and Pneumocystis [10,11].

Accordingly, the research community has not yet obtained a “critical mass” of case reports and studies on clinical signs, diagnosis and treatment for both invasive and cutaneous mucormycosis [11].

This case details the second reported patient with localized cutaneous mucormycosis in the setting of ibrutinib treatment for CLL. The patient underwent a 10-day course of IV amphotericin, seven days of IV cefepime, and 90-days of oral posaconazole following discharge with successful infection resolution and wound healing (Fig. 2A,B). The case provides several clinical pearls for physicians. Hematologic malignancies and uncontrolled diabetes mellitus (type II) provide the greatest risk factors for mucormycosis in the setting of ibrutinib treatment, and concomitant skin trauma or disease (e.g. bullous pemphigoid) can be an inciting factor for skin manifestations of the opportunistic infection. In cases of amphotericin B intolerance, physicians should be aware that posaconazole exists as a viable oral alternative for extended treatment. Treatment of this fungi in these patient populations requires a collaborative effort, often requiring Hematology/Oncology, Infectious Disease, Nephrology, Surgery, and Hospitalist teams. We hope this case report contributes to the knowledge base regarding mucormycosis in the immunocompromised setting, especially CLL patients receiving ibrutinib treatment, as well as aid in future consensus regarding treatment guidelines for the invasive fungus.

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#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### CRediT authorship contribution statement

**Katherine R. Sittig:** Conceptualization, Writing - original draft. **Leah G. Laageide:** Writing - original draft, Visualization. **Zaheer Akhtar:** Conceptualization, Writing - original draft. **Geoffrey C. Wall:** Conceptualization, Writing - review & editing, Supervision. **Sudhir C. Kumar:** Conceptualization, Writing - review & editing, Supervision.

#### Declaration of Competing Interest

The authors have no conflicts of interest to declare. The authors received no financial support for this manuscript.

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