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CASE REPORT

Invasive Mucormycosis in a Chronic Lymphocytic Leukemia Patient on Zanubrutinib: A Case Report

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Background: Invasive mucormycosis is a severe fungal infection that predominantly affects immunocompromised and diabetic patients. This case study highlights the importance of early diagnosis and pathogen-specific antifungal therapy in managing invasive mucormycosis among high-risk patients.

Case Description: A 47-year-old male with chronic lymphocytic leukemia (Rai stage IV) on zanubrutinib and with uncontrolled diabetes was admitted to Jiangxi Cancer Hospital on November 7, 2021. Imaging revealed pulmonary infection and splenic infarction, while laboratory findings suggested disseminated intravascular coagulation. Despite empirical broad-spectrum antibiotics, his condition worsened, necessitating an emergency splenectomy. Postoperatively, fluconazole was added to his antimicrobial regimen, but he developed respiratory failure, liver and renal dysfunction, and persistent hyperglycemia. A bronchial alveolar lavage sample was sent for metagenomic next-generation sequencing (mNGS) to identify the pathogen. Despite intensive care, he deteriorated rapidly, developing myocardial injury, metabolic acidosis, and multiorgan failure, leading to death on November 13, 2021. mNGS results, received after the patient's death, identified *Rhizomucor pusillus* as the primary pathogen, with co-infection by *Enterococcus faecium* and *Human betaherpesvirus 7*.

Conclusion: This study presents a case of rapidly progressive mucormycosis co-infected with bacterial and viral pathogens, highlighting the importance of early intervention and accurate diagnosis. Delayed identification of the fungal pathogen significantly hindered timely antifungal intervention, underscoring the importance of appropriate empirical therapies in hematological patients treated with zanubrutinib. Future research should focus on antifungal stewardship and epidemiological surveillance studies to improve early detection and guide targeted empirical treatment for high-risk populations.

Keywords: mucormycosis, chronic lymphocytic leukemia, hyperglycemia, zanubrutinib, *Rhizomucor pusillus*, metagenomic next-generation sequencing, case report

Introduction

Mucormycosis is a severe fungal infection caused by species in the order Mucorales, particularly those within the Mucoraceae family, encompassing the genera *Rhizopus, Mucor*, and *Lichtheimia*.[1] It is the third most common cause of invasive fungal infections (IFIs) globally, accounting for 8% of such infections, following aspergillosis and candidiasis.[2,3] Previous studies have highlighted geographic variation in the annual incidence of mucormycosis, with rates reported as 3.3 cases per 100,000 hospital admissions in Italy,[4] 1.76 per 10,000 hospitalizations in Iran,[5] and 0.12 per 10,000 discharges in the United States.[6] The most frequent clinical manifestations of mucormycosis include rhino-cerebral, maxillofacial, and pulmonary infections. The infection may also affect multiple organs, including the brain, kidneys, liver, and gastrointestinal tract.[7] The incidence of pulmonary mucormycosis has increased with advancements in immunosuppressive medicine. For example, a study from western China reported that pulmonary mucormycosis accounted for 78% of the 59 reported cases.[8] Several predisposing

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clinical factors have been identified, including diabetic ketoacidosis, uncontrolled diabetes mellitus, immunosuppressive therapies, and hematological malignancies (such as lymphoma and leukemia). Diabetes mellitus and hematological malignancies were the most common underlying conditions in cases of mucormycosis, reported in 17 to 88% and 38 to 62% of cases, respectively.[3] Studies stated that in poorly controlled diabetes mellitus, especially during diabetes ketoacidosis (DKA), neutrophil functions such as phagocytosis and chemotaxis are significantly impaired.[9] Moreover, the acidosis due to KDA leads to elevated serum iron levels, which promotes Mucorales species' growth. This immune and metabolic disturbance creates a conducive environment for IFIs.[10]

Chronic lymphocytic leukemia (CLL) is a hematological malignancy characterized by the abnormal proliferation of CD5+ B lymphocytes in most cases, which leads to immune dysregulation.[11] CLL cells express immune-suppressing cytokines, and T-lymphocytes often exhibit immune exhaustion, which contributes to the frequent infections observed in these patients.[12] Bruton's tyrosine kinase (BTK) inhibitors, such as zanubrutinib, are the targeted therapies used to treat CLL; however, they disrupt B-cell receptor signaling and may impair immune function, thereby heightening susceptibility to IFIs.[13] Specifically, BTK inhibitors can compromise innate and adaptive immunity, particularly by affecting T-lymphocyte function, reducing antibody production, and decreasing immune surveillance against pathogens.[14] Given the increasing use of BTK inhibitors, healthcare professionals must be vigilant regarding the potential life-threatening IFIs associated with their administration.

The spleen plays a vital role in humoral immunity by producing IgM antibodies and clearing pathogenic microorganisms and cellular debris through phagocytosis. However, in critical care settings such as abscesses and infarction, splenectomy is often performed, which compromises host immunity.[15] This immunocompromised state significantly increases the risk of overwhelming post-splenectomy infection (OPSI) syndrome and IFIs.[15,16] Moreover, the delayed diagnosis of IFIs, particularly mucormycosis, remains challenging in acute clinical scenarios. Conventional culture methods are often slow and may yield false negative results due to the poor growth characteristics of Mucorales species.[17] Advanced diagnostic techniques, such as metagenomic next-generation sequencing (mNGS), offer greater sensitivity and faster detection. However, their limited availability in routine microbiology laboratories and high cost restricts widespread clinical use.[18] Early findings on chest computed tomography (CT) scans, such as the reversed halo sign (RHS), nodules within the halo, and a thick rim of peripheral consolidation, have been associated with pulmonary mucormycosis in immunocompromised individuals.[19] This sign is considered an early but transient sign of pulmonary mucormycosis, which disappears after 15 days of infection. However, despite the diagnostic relevance of RHS, it is frequently overlooked in clinical settings.[20] These limitations often contribute to delayed management of mucormycosis and poor patient outcomes.[18] This case study presents a fatal mucormycosis infection in a zanubrutinib-treated CLL patient, accompanied by a review of relevant literature underscoring the importance of early intervention in these high-risk situations.

Case Presentation

A 47-year-old male with CLL for the past 3 years, classified as Rai stage IV, presented to Jiangxi Cancer Hospital, Nanchang, China, on November 7, 2021, with a one-week history of abdominal pain and fever. The patient had been undergoing treatment for CLL with zanubrutinib at a dose of 160 mg twice daily. His medical history was complicated by uncontrolled diabetes, with an admission glucose level of 17.9 mmol/L, indicating hyperglycemia. On physical examination, he was febrile and exhibited clinical features suggestive of a systemic infection.

Imaging revealed significant findings: chest CT showed patchy shadows in the upper lobe of the left lung and a nodule in the lower lobe of the right lung, with a reversed halo sign, suggesting an infection (Figure 1a). Abdominal CT with contrast demonstrated splenic artery embolism and splenic infarction, leading to a diagnosis of splenic infarction (Figure 1b). Laboratory investigations showed leukocytosis (11.36×10^9/L) with neutrophilia (10.43×10^9/L) and lymphopenia (2.14×10^9/L), suggesting a possible underlying infection. The patient also presented with anemia (hemoglobin: 130 g/L) and thrombocytopenia (56×10^9/L), with elevated inflammatory markers, including C-reactive protein (154.55 mg/L) and procalcitonin (2.78 ng/mL). Coagulation tests showed prolonged prothrombin time (15.9 seconds), hyperfibrinogenemia (7.15 g/L), and elevated D-dimer (9.66 mg/L), indicating disseminated intravascular coagulation (DIC).

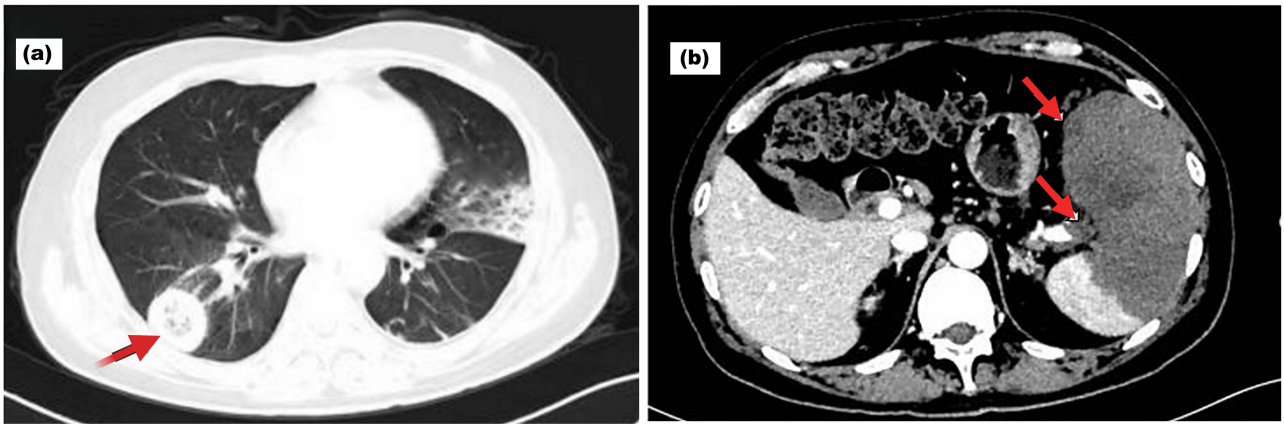

Figure 1 (**a**) Chest computed tomography (CT) scan demonstrating a nodule in the lower lobe of the right lung with a reversed halo sign (arrow), indicative of possible invasive fungal infection. (**b**) Contrast-enhanced abdominal CT revealing splenic artery embolism (lower arrow) and splenic infarction (upper arrow).

The patient was started on empirical broad-spectrum antibiotics, including intravenous cefoperazone-sulbactam (administered every 8 hours, 1 gram per vial, 3 vials per day) and moxifloxacin hydrochloride (50 mL per vial, administered once daily), along with platelet support. However, due to worsening splenic infarction and signs of progressive organ dysfunction, an emergency splenectomy was performed on November 10, 2021. Postoperatively, the patient's condition worsened, necessitating mechanical ventilation for respiratory failure, and was subsequently transferred to the intensive care unit (ICU). Liver enzymes (alanine aminotransferase: 170 U/L; aspartate aminotransferase: 8020 U/L) and renal function markers (urea: 11.4 mmol/L; creatinine: 110 μmol/L) worsened, hyperglycemia persisted despite insulin therapy, and the highest recorded body temperature was 39.5 °C.

Given the patient's declining condition and persistent infection, the antimicrobial regimen was escalated to include intravenous biapenem (0.6 grams every 12 hours), imipenem/cilastatin (1 gram per vial, administered every 8 hours), and fluconazole (100 mL containing 0.2 g per pouch, administered once daily). On November 12, 2021, a bronchial alveolar lavage (BAL) sample was obtained from the patient and sent for metagenomic next-generation sequencing (mNGS) to investigate the exact etiology of the infection. By the third postoperative day, the patient developed signs of myocardial injury, as evidenced by significant ST-segment elevation on electrocardiogram (leads I, II, AVF, V4, V5, and V6), with creatine kinase-myocardial band (CK-MB) levels rising to 82 U/L and troponin I at 0.11 ng/mL. He then developed metabolic acidosis, shock, and multiorgan failure. Despite intensive resuscitation and continued mechanical ventilation, the patient's condition rapidly deteriorated and passed away shortly thereafter on November 13, 2021. The mNGS report, received after the patient's death, identified *Rhizomucor pusillus* as the primary pathogen, with co-infection by *Enterococcus faecium* and *Human betaherpesvirus 7* (HHV-7). A summary of the key laboratory findings is presented in Table S1.

Discussion

Mucormycosis, although rare, is a severe and often fatal complication in immunocompromised individuals, especially those with chronic lymphoproliferative disorders on immunosuppressive therapy like BTK inhibitors.[21] In our case, a 47-year-old male with CLL on zanubrutinib presented with rapid progression of mucormycosis. The patient's disease course from admission to death in a week highlights the aggressive nature of mucormycosis in immunocompromised patients compared to slow and insidious presentations in some other cases. For example, a previously reported case of a 74-year-old female with CLL on zanubrutinib had a slower onset of mucormycosis with cutaneous lesions developing over an extended period prior to diagnosis.[22] Our case emphasizes the rapid progression of mucormycosis in high-risk individuals when diagnosis and treatment are delayed.

Zanubrutinib is an effective treatment for CLL. However, its impact on the impairment of innate immune responses, particularly neutrophil and macrophage functions, and the increased susceptibility to invasive infections should not be overlooked.[23] In our case, the extended administration of zanubrutinib impaired the immune system's ability to

effectively combat the fungal pathogen, even with normal neutrophil counts. The patient's diabetic condition, characterized by hyperglycemia, creates a conducive environment for the development of mucormycosis.[24] Elevated glucose levels in the body create a nutrient-rich environment conducive to the growth and proliferation of Mucorales species.[25] The splenectomy compromised the patient's capacity to filter pathogens effectively. Splenectomy increases the patient's vulnerability to systemic infections due to the spleen's critical role in the innate immune system.[26,27] The patient demonstrated neutrophilia; however, neutrophil-mediated phagocytosis was compromised, which may contribute to the dissemination of the fungal infection.[28]

The clinical presentation of mucormycosis presents considerable challenges, especially in differentiating it from other common infections in immunocompromised individuals.[25] For example, pulmonary mucormycosis exhibits characteristics similar to pneumonia, whereas rhino-cerebral mucormycosis resembles bacterial sinusitis.[29,30] The chest CT of our case revealed a reversed halo sign, which serves as a radiological indicator of IFIs.[19] The reversed halo sign, despite its association with severe infection, was initially not subjected to additional investigation. The clinicians concentrated on other acute issues, such as splenic infarction and respiratory failure, delaying the diagnosis.[31] In suspected mucormycosis, it is important to promptly initiate diagnostic methods such as direct microscopy, histopathology, fungal culture, and molecular assays to confirm the etiological agent.[32] Direct microscopy can provide rapid initial evidence of fungal elements in biological specimens. Fungal culture helps determine the etiology of infection, enables species identification, and allows for subsequent antifungal susceptibility testing.[33] To accelerate the diagnosis of mucormycosis in similar higher-risk patients, clinicians should prioritize early molecular diagnostics such as polymerase chain reaction (PCR) or NGS. These techniques allow for the quick and reliable detection of fungal DNA, particularly in situations when it is difficult to acquire tissue samples or when fungal cultures produce negative results.[34] Unfortunately, in the present case, the NGS results from the patient's alveolar lavage fluid were unavailable before the patient's demise. This underscores the need for rapid diagnostics, particularly in critically ill patients, where clinical deterioration can outpace the availability of test results. New methods are being developed, such as the enzyme-linked immunosorbent assay (ELISA), to detect the highly purified fucomannan wall carbohydrates of *Mucor* species. These methods may be considered upon their availability.[35,36] Emerging tools such as point-of-care antigen detection assays and artificial intelligence-assisted imaging techniques may enable the early identification of mucormycosis.[37,38] When feasible, tissue sampling via bronchoscopy or biopsy remains essential for definitive diagnosis.[39] The suspicion of IFIs in higher-risk groups, such as patients with diabetes, neutrophil dysfunction, or those receiving BTK inhibitors, is essential. Integrating these clinical risk variables into standardized diagnostic algorithms might facilitate timely testing and empirical treatment.[17]

The patient was initially treated with broad-spectrum antibiotics due to his septic presentation, which was appropriate. However, antifungal coverage was not included in the empirical treatment. This was a critical oversight as immunocompromised patients, especially those on BTK inhibitors, are at high risk of IFIs.[40] The exclusion of antifungal agents from initial empirical therapy might be due to the rarity of mucormycosis and its non-specific clinical presentation, often leading clinicians to prioritize bacterial pathogens in septic cases. Later, as the patient's condition worsened post-operatively, fluconazole was added to the treatment plan. However, fluconazole lacks activity against Mucorales and is not recommended for mucormycosis due to intrinsic resistance.[41] This might have contributed to the lack of clinical improvement, emphasizing the necessity of pathogen-specific antifungal selection in high-risk patients.

The *Rhizomucor pusillus* was the primary pathogen in our case; however, the co-infection due to *E. faecium* and HHV-7 may have contributed to the rapid clinical deterioration. *E. faecium* is a known cause of severe bloodstream infections in immunocompromised patients and often exhibits multidrug resistance, complicating the empirical antibiotic selections.[42] Similarly, HHV7 may occur in immunosuppressed patients and has been associated with encephalitis, rash, and persistent fever. While the pathogenic role of HHV-7 remains unknown, its existence could be a sign of underlying immunological malfunction.[43] For high-risk patients, early identification of these co-pathogens using blood cultures and molecular diagnostics is important for targeted antimicrobial therapy.

Liposomal amphotericin B is the standard of care for mucormycosis, with isavuconazole considered in certain cases. Liposomal amphotericin B is the first-line therapy for mucormycosis due to its broad-spectrum activity against fungal species and lower nephrotoxicity compared to conventional amphotericin B.[44] Isavuconazole is used as an alternative treatment when amphotericin B is unavailable or poorly tolerated, and some studies suggest it offers comparable efficacy.[45,46] Similarly, posaconazole can also be considered; however, due to its varying efficacy against different Mucorales species, it is not

recommended as the primary treatment option.[41,47] The observation of respiratory symptoms and radiological findings suggestive of IFIs should prompt the initiation of early empirical antifungal therapy, even before diagnostic confirmation. Given the high mortality associated with mucormycosis in immunocompromised hosts, including those receiving BTK inhibitors, the early administration of liposomal amphotericin B as empirical therapy could be lifesaving.[48]

The limitation of this study is that it is a single case and has a retrospective design, as the information was collected after the patient's death. Moreover, the autopsy of patients was not conducted, which might provide answers to specific clinical questions of cases having no definitive diagnosis. Despite these limitations, this case report highlights the gaps in current clinical practices. It stresses the need for earlier suspicion, improved diagnostic methods, and appropriate empirical therapies to improve outcomes in similar scenarios. Future studies focusing on regional epidemiological surveillance and antifungal stewardship programs are essential to guide targeted empirical therapy in high-risk populations. Additionally, institutional protocols that account for immunosuppressive therapies, underlying comorbidities, and local fungal profiles should be developed to support timely intervention and potentially reduce mortality.

Conclusion

This case report underscores the importance of early recognition and prompt antifungal intervention in high-risk patients, particularly those with CLL receiving BTK inhibitors such as zanubrutinib. Radiological findings, especially the reversed halo sign, should not be overlooked, as they may indicate IFSs and warrant immediate fungal workup, including molecular diagnostics via PCR and NGS. Although diagnosis delays are often unavoidable in complicated cases, a multidisciplinary approach, including timely consultation with infectious disease specialists, may have enhanced the management of such cases.

This case study yields several important lessons. Clinicians must maintain high vigilance for fungal infections in immunocompromised patients, particularly those on BTK inhibitors. When radiological signs suggest IFIs, early initiation of targeted diagnostic and empirical antifungal therapy is crucial. In suspected cases of mucormycosis, liposomal amphotericin B or isavuconazole should be prioritized over fluconazole, which lacks activity against Mucorales.

Data Sharing Statement

This study did not involve the creation or analysis of new data, so data sharing does not apply.

Ethical Statement

The authors take full responsibility for the work, ensuring that any concerns about accuracy or integrity are properly addressed. All procedures followed ethical guidelines set by the institutional or national research committee(s) and complied with the Declaration of Helsinki (2013 revision). Institutional approval for publication was obtained from the Human Research Ethics Committee of the Jiangxi Cancer Hospital and Institute (Approval No. 2024ky078). Written informed consent was obtained from the patient's relatives to publish this case report and related images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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