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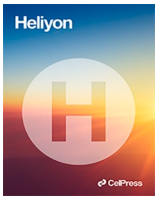

Case report

A case report of successful treatment of pulmonary mucormycosis caused by Cunninghamella bertholletiae infection in a patient with T-lymphoblastic lymphoma

Qing Yang [a], Kang Zhou [a], Yan Shen [a], Rong Huang [a], Li Liu [b], Shengtao Liao [c,*]

[a] Department of Hematology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China
[b] Department of Pathology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China
[c] Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China

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ABSTRACT

Mucormycosis caused by *Cunninghamella bertholletiae (C. bertholletiae)* is a rare opportunistic infection in patients with hematological malignancies (HM), with high mortality rates. Herein, we first report a case of pulmonary mucormycosis (PM) with *C. bertholletiae* in a 25-year-old male recently diagnosed with T-lymphoblastic lymphoma (T-LBL). The diagnosis was established through chest computed tomography (CT), metagenomic next-generation sequencing (mNGS) of blood and bronchoalveolar lavage fluid (BALF), as well as histopathological examination. Hematoxylin and eosin (HE) staining of the surgical specimen revealed the presence of fungal hyphae. He was effectively treated with liposomal amphotericin B (L-AmB) and posaconazole enteric-coated tablets, followed by aggressive surgical debridement. In our case, the fungal infection was initially identified as *C. bertholletiae* using mNGS, which facilitated rapid and accurate diagnosis, enabling clinicians to initiate early intensive treatment. The case also emphasizes the importance of surgical debridement in addressing affected tissues and underscores the significance of a multidisciplinary approach in implementing this treatment strategy.

1. Introduction

The most common pathogens associated with mucormycosis are Rhizopus, Mucor, Lichtheimia, Apophysomyces, Cunninghamella, Rhizomucor, and Saksenaea. This infection primarily affects individuals with weakened immune systems, including those with diabetes, cancer, organ transplants, and those on long-term corticosteroid therapy. PM presents in the lungs, which are the third main location for the infection after the rhino-orbito-cerebral areas and the skin. *C. bertholletiae* is particularly linked to PM and has a higher mortality rate compared to other Mucorales (71 % *vs* 44 %) [1]. Patients with T-LBL often require intensive chemotherapy, leading to severe immunosuppression and increased vulnerability to opportunistic infections. PM involvement in T-LBL is rare and presents significant diagnostic and therapeutic challenges. In this case report, we describe the first documented survival of a T-LBL patient with PM caused by *C. bertholletiae*.

* Corresponding author. Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, No. 74 Linjiang Road, Yuzhong distrinct, Chongqing, China.
E-mail address: jianghe@cqmu.edu.cn (S. Liao).

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2. Case presentation

The patient, a 25-year-old male, was diagnosed with T-LBL without bone marrow involvement. He achieved complete remission after induction chemotherapy with the VDLP regimen (vincristine, daunorubicin, L-asparaginase, prednisone). He then received consolidation chemotherapy with the CAT regimen (cyclophosphamide, cytarabine, 6-mercaptopurine (6-MP). He developed high-grade fever (≥39.5 °C) and severe neutropenia during consolidation chemotherapy. Broad-spectrum antimicrobial therapy was initiated, including imipenem/cilastatin (500 mg intravenously every 8 hours), vancomycin (1000 mg intravenously every 12 hours) and voriconazole (loading dose of 6 mg/kg intravenously every 12 hours, followed by 4 mg/kg intravenously every 12 hours), but the specific pathogen remained unidentified with persistent fever. CT scan revealed multiple patchy and ground-glass opacities with indistinct margins (Fig. 1A). Due to the high risk of bleeding and anesthesia-related complications associated with fiberoptic bronchoscopy, we performed mNGS (Hangzhou Matridx Biotechnology Co.,Ltd.) of blood (Fig. 1H) to identify the causative agent, and the results revealed *C. bertholletiae* (Supplementary materials and methods, Sequencing data in NCBI: PRJNA1113529, 58 reads). And then, L-AmB therapy, initiated through a collaborative, multidisciplinary approach at a dose of 3 mg/kg for PM, effectively reduced the fever (below 38 °C) and improved hemoptysis. However, follow-up CT showed progression of pulmonary lesions and increased pleural effusion (Fig. 1B). After the recovery of thrombocytopenia, we performed mNGS (Hangzhou Matridx Biotechnology Co.,Ltd.) of BALF (Fig. 1I), confirming *C. bertholletiae* as the predominant pathogen (Supplementary materials and methods, Sequencing data in NCBI: PRJNA1113529, 628 reads)). We continued the antifungal treatment, resulting in a normalized temperature and the absence of hemoptysis. However, the third CT scan showed further enlargement of the infected area with consolidation and cavity formation (Fig. 1C). We attempted to increase the dose of L-AmB to 5 mg/kg and added posaconazole enteric-coated tablets at 300 mg/day. However, the patient experienced severe chills and shivering during the higher-dose L-AmB infusion. We then reduced the dose of L-AmB back to 3 mg/kg, and no further infusion reactions occurred. On day 72 of fever, the fourth follow-up CT scan revealed an

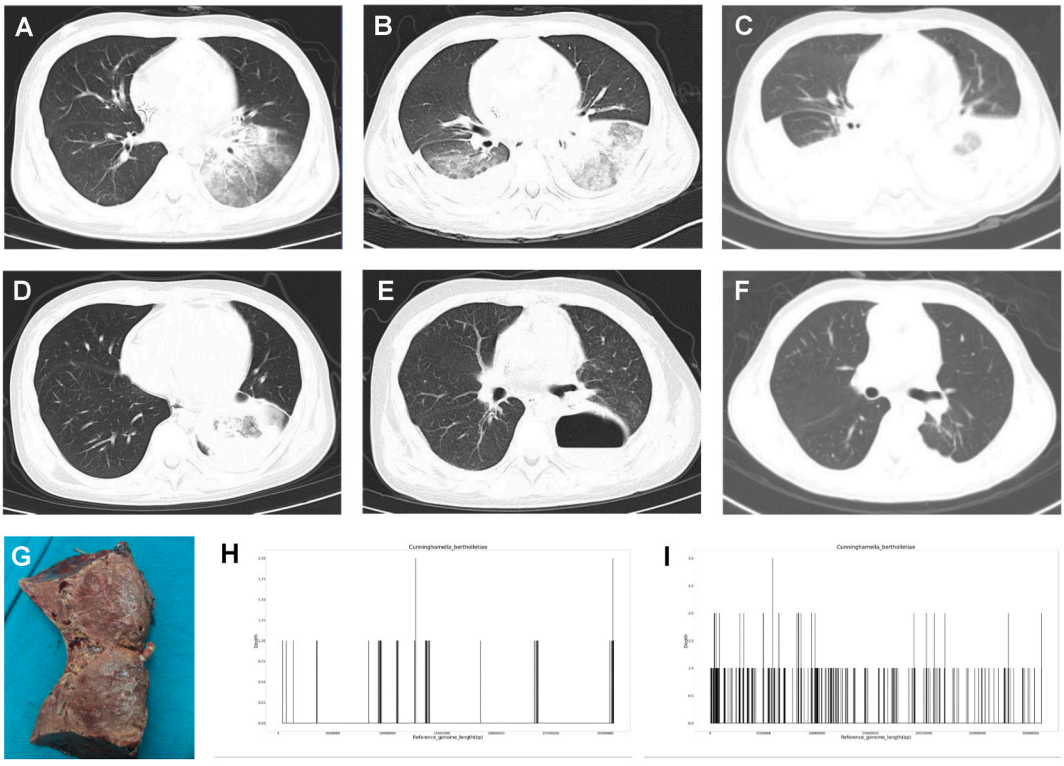

Fig. 1. Chest CT scans, surgical specimens and mNGS of blood and BALF of the patient before and after treatment. Chest CT scans at 13 (A), 21 (B), 33(C), and 72 (D) days post-treatment demonstrated persistent fever and an obstructive mass in the basal segmental bronchus of the left lower lobe. The patient underwent video-assisted thoracoscopic surgery for lung resection (G), and no evidence of PM recurrence was observed on chest CT scan at one month (E) and seven months (F) after lobectomy. (H) The depth coverage distribution plot of the *C. bertholletiae* genome from blood. The X-axis represents the position on the reference genome (in base pairs, bp), while the Y-axis indicates the sequencing depth at each position. The reference genome length is 31,145,096 base pairs. The average depth is 0.01 %, meaning that the total number of bases in the sequencing reads is 0.0001 times the length of the reference genome. The coverage is 0.01 %, indicating that, on average, the sequencing reads cover 0.01 % of the total bases in the genome. (I) The depth coverage distribution plot of the *C. bertholletiae* genome from bronchoalveolar lavage fluid. The reference genome length is 31,145,096 base pairs. The average depth is 0.10 %, meaning that the total number of bases in the sequencing reads is 0.001 times the length of the reference genome. The coverage is 0.10 %, indicating that, on average, the sequencing reads cover 0.10 % of the total bases in the genome.

obstructed bronchus (Fig. 1D).

At this point, we were faced with a treatment dilemma. T-LBL, being an aggressive tumor, required immediate consolidation chemotherapy. However, active pulmonary mucormycosis posed a risk for systemic dissemination during chemotherapy, which could be fatal in severe cases. Following consultations with respiratory medicine, gastroenterology, thoracic surgery, anesthesiology, and hematology specialists, we decided to perform video-assisted thoracoscopic surgery (VATS) to resect the pulmonary lesion. The lesion showed consolidation (Fig. 1G). HE staining (Fig. 2A and B) and PAS staining (Fig. 2C) further confirmed the presence of fungi. During the perioperative period, we continued the antifungal therapy with L-AmB and posaconazole enteric-coated tablets.

One month after the surgery, a follow-up CT scan showed no evidence of PM recurrence (Fig. 1E). Subsequently, he received one cycle of high-dose methotrexate (MTX), two cycles of autologous stem cell transplantation and low-dose MTX and 6-MP orally for maintenance therapy. He continued oral posaconazole enteric-coated tablets for secondary prophylaxis. Currently, seven months after the lobectomy, the CT scan shows no signs of lymphoma or PM relapse (Fig. 1F). The patient has resumed his college studies.

3. Discussion

Recent studies have identified HM as the main cause of PM, including acute leukemia (24 %), hematopoietic stem cell transplant (HSCT) (21 %), lymphoma (13 %), and others (4 %) [2,3]. The occurrence of PM in T-LBL patients infected with *C. bertholletiae* is actually rare. Early diagnosis of PM poses huge challenges, which was predominantly confirmed through postmortem examinations in the past [4]. Isolation of Mucorales from clinical specimens is difficult, with positive cultures observed in only 15 %–25 % of cases [5]. Efforts should also be directed towards obtaining specimens for non-culture methods, such as tissue puncture or excisional biopsy and mNGS of blood or BALF. However, invasive examinations or surgical procedures are contraindicated in patients with low platelet counts ($<$50,000/mm^3), which is very common in hematological diseases, thus increasing the difficulty of diagnosis of PM [6]. mNGS provides a comprehensive approach to identify causative agents, with a significantly higher pathogen detection rate compared to traditional methods (80.21 % *vs* 25.00 %) [7]. Additionally, in patients with febrile neutropenia, it also shows a significantly higher fungal detection rate compared to the non-febrile neutropenia group (32.35 % *vs* 12.22 %) [7,8]. In this case, both blood and BALF mNGS identified *C. bertholletiae* (Fig. 1H and I), which played a crucial role in determining the cause of PM and initiating timely antifungal therapy. Fungal hyphae were also detected in the histopathological examination of the surgically resected lung tissue specimen.

There is a lack of prospective studies to determine the optimal treatment strategy for this rare infection. Current management primarily follows the guidelines for diagnosing and treating mucormycosis. Successful treatment of mucormycosis relies on three essential factors: surgery, antifungal therapy, and the management of underlying risk factors. The guideline group strongly recommends early and complete surgical resection of mucormycosis whenever feasible, along with systemic antifungal therapy [9]. Timely initiation of antifungal therapy is crucial, as a delay of 3 days in starting amphotericin B can increase the mortality rate (72 *vs* 33 %) [10]. In this case, the primary predisposing factor was neutropenia, which required active efforts to promote granulocyte recovery through appropriate supportive care measures. L-AmB is the recommended first-line treatment for mucormycosis at a dose of 5$\sim$10 mg/kg/day. A high dose of L-AmB (10 mg/kg) is suggested for central nervous system infection, while 5 mg/kg/day is advised for PM. In real-world scenarios, patient tolerance to L-AmB dosages varies significantly. In our case, the patient was unable to tolerate a moderate dose of 5 mg/kg due to recurrent chills and high fever. According to the guideline recommendation, if a patient exhibits intolerance to L-AmB, reducing the dosage and considering the addition of isavuconazole or posaconazole may be appropriate. However, further research is needed to establish the optimal combination therapy regimen. The duration of therapy required to treat mucormycosis is uncertain. In our case, after two months of combined antifungal treatment, the dissemination of mucormycosis was effectively controlled. However, complete eradication was not achieved, resulting in residual consolidative lesions. The most common histopathologic findings in patients with pulmonary mucormycosis who underwent autopsy or lung biopsy include angioinvasion (100 %), hemorrhagic infarction (90 %), coagulative necrosis (85 %), and intra-alveolar hemorrhage (85 %) [11]. These changes impair the continuous fungicidal action of medications, leading to irreversible necrosis of lung tissue. Therefore, timely surgical resection of the lesions becomes crucial. Surgical resection of localized pulmonary lesions is an important therapeutic modality in the management of PM. In this case, we performed VATS, which resulted in the successful resection of the affected lung lobe. Surgical intervention allows for the elimination of the infectious focus, reducing the risk of dissemination and improving overall treatment outcomes.

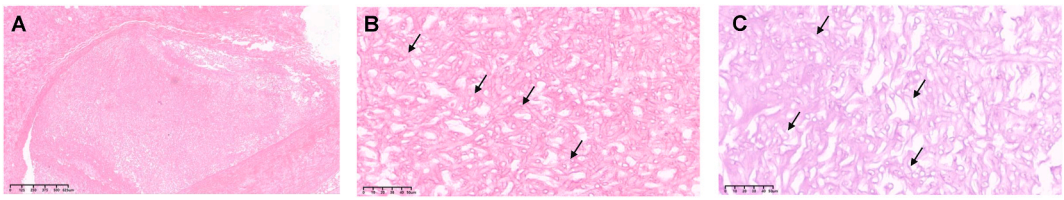

Fig. 2. Lung tissue HE and PAS staining. (A) HE staining at 40 × magnification demonstrates the lumen uniformly filled with evenly distributed fungal hyphae. (B) Higher magnification (400 ×) of the HE-stained section reveals hyphae of consistent thickness, displaying septa and acute-angled branching. Spores are often located at one end of the hyphae, forming a racquet-like structure. (C) PAS staining at 400 × magnification highlights the hyphae, which are stained rose-red. Black arrows indicate the presence of fungi. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Conclusions

In sum, the successful management of PM in a T-LBL patient highlights the crucial importance of early pathogen detection through mNGS of blood and BALF, prompt correction of underlying conditions, surgical intervention, and secondary prophylactic antifungal therapy. These findings emphasize the need for a multidisciplinary approach and personalized management strategies to optimize outcomes in complex cases involving hematological malignancies and invasive fungal infections.

5. Supplementary statement

In regard to the section on relevant past interventions with outcomes (5d), it is important to note that the patient in this case had no prior history of pulmonary mucormycosis infection. As a result, there were no previous medical records or interventions related to this specific condition. This case represents the patient's initial occurrence of pulmonary mucormycosis, and therefore, no relevant past interventions or outcomes are available for discussion or comparison.

6. Patient perspective

I feel extremely fortunate throughout the treatment of pulmonary mucormycosis. With accurate diagnosis and comprehensive treatment from my doctors, my condition has been effectively controlled. The utilization of mNGS technology swiftly identified the *C. bertholletiae* infection, providing a basis for prompt intervention. Additionally, surgical debridement played a significant role in my recovery. This experience has deeply emphasized the importance of multidisciplinary collaboration, and I am grateful to the medical team for their expertise and care, which helped me overcome the illness.

Prior to the publication of this case report, informed consent was obtained from the patient for the publication of all clinical information, images, and other data included in this manuscript. The patient was fully informed about the nature of the publication and its potential implications. Confidentiality was ensured, and all identifying information has been appropriately anonymized to protect the patient's privacy.

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Ethics approval and consent to participate

The study was approved by the Second Affiliated Hospital of Chongqing Medical University.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [Shengtao, Liao], upon reasonable request. Additionally, the mNGS data has been uploaded to the NCBI database (NCBI: PRJNA1113529).

Ethics declarations

Ethical approval was not required for the publication of this manuscript. The authors obtained informed consent from the patient.

CRediT authorship contribution statement

Qing Yang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kang Zhou:** Writing – original draft, Visualization, Validation, Supervision, Investigation. **Yan Shen:** Writing – original draft, Investigation, Formal analysis, Data curation. **Rong Huang:** Writing – original draft, Formal analysis, Data curation. **Li Liu:** Writing – original draft, Formal analysis. **Shengtao Liao:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36244.

References

[1] W. Jeong, C. Keighley, R. Wolfe, et al., The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports, Clin. Microbiol. Infect. 25 (1) (2019) 26–34, https://doi.org/10.1016/j.cmi.2018.07.011.
[2] A. Coste, A. Conrad, R. Porcher, et al., Improving diagnosis of pulmonary mucormycosis: leads from a contemporary national study of 114 cases, Chest 164 (5) (2023) 1097–1107, https://doi.org/10.1016/j.chest.2023.06.039.
[3] Z.M. Hu, L.L. Wang, L. Zou, et al., Coinfection pulmonary mucormycosis and aspergillosis with disseminated mucormycosis involving gastrointestinalin in an acute b-lymphoblastic leukemia patient, Braz. J. Microbiol. 52 (4) (2021) 2063–2068, https://doi.org/10.1007/s42770-021-00554-8.
[4] R.E. Lewis, L. Cahyame-Zuniga, K. Leventakos, et al., Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study, Mycoses 56 (6) (2013) 638–645, https://doi.org/10.1111/myc.12081.
[5] C. Lass-Florl, Zygomycosis: conventional laboratory diagnosis, Clin. Microbiol. Infect. 15 Suppl 52009) 60-65, https://doi.org/10.1111/j.1469-0691.2009.02999.x.
[6] C. Lass-Florl, G. Resch, D. Nachbaur, et al., The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients, Clin. Infect. Dis. 45 (7) (2007) e101–e104, https://doi.org/10.1086/521245.
[7] M. Zhang, Z. Wang, J. Wang, et al., The value of metagenomic next-generation sequencing in hematological malignancy patients with febrile neutropenia after empiric antibiotic treatment failure, Infect. Drug Resist. 152022) 3549-3559, https://doi.org/10.2147/IDR.S364525.
[8] S. Feng, G. Rao, X. Wei, et al., Clinical metagenomic sequencing of plasma microbial cell-free dna for febrile neutropenia in patients with acute leukaemia, Clin. Microbiol. Infect. (2023), https://doi.org/10.1016/j.cmi.2023.05.034.
[9] O.A. Cornely, A. Alastruey-Izquierdo, D. Arenz, et al., Global guideline for the diagnosis and management of mucormycosis: an initiative of the european confederation of medical mycology in cooperation with the mycoses study group education and research consortium, Lancet Infect. Dis. 19 (12) (2019) e405–e421, https://doi.org/10.1016/S1473-3099(19)30312-3.
[10] R. Ben-Ami, M. Luna, R.E. Lewis, T.J. Walsh, D.P. Kontoyiannis, A clinicopathological study of pulmonary mucormycosis in cancer patients: extensive angioinvasion but limited inflammatory response, J. Infect. 59 (2) (2009) 134–138, https://doi.org/10.1016/j.jinf.2009.06.002.
[11] O.A. Cornely, R.F. Duarte, S. Haider, et al., Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease, J. Antimicrob. Chemother. 71 (3) (2016) 718–726, https://doi.org/10.1093/jac/dkv380.