Infection and Drug Resistance

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CASE REPORT

Successful Treatment of Mucormycosis and Azole-Resistant *Aspergillus* Coinfection in a Diabetic Patient: A Case Report

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Objective: To report a case of coinfection with mucormycosis and azole-resistant *Aspergillus fumigatus* in a patient with poorly controlled type 2 diabetes, highlighting successfully treated with high-dose posaconazole combined with liposomal amphotericin B and lobectomy.

Methods: A 52-year-old man who presented to our hospital with a 1-month history of fever accompanied by productive cough and sputum. He had type 2 diabetes with poor control of glucose level. Chest computed tomography (CT) showed rapidly progressive multiple cavities and consolidation in the lungs. Sputum culture showed azole-resistant *Aspergillus fumigatus*, confirmed by whole genome sequencing, which revealed mutations in non-azole target genes (eg, *CYP51A* was wild-type). Targeted next-generation sequencing (tNGS) of bronchoalveolar lavage fluid (BALF) at admission detected *Aspergillus fumigatus* and *Rhizopus microsporus*, while histopathology of right upper lobe necrotic material on day 18 confirmed mucormycosis. The patients had previously received intravenous voriconazole (400 mg/d) combined with inhaled amphotericin B (10 mg twice daily) for 2 weeks without improvement. Upon admission, initial treatment with isavuconazole, liposomal amphotericin B, and caspofungin was also ineffective. Subsequently, high-dose posaconazole (600 mg/d) combined with liposomal amphotericin B was administered.

Results: Following the initiation of high-dose posaconazole and liposomal amphotericin B, the patient's temperature normalized, and pulmonary exudates significantly improved. Therapeutic drug monitoring (TDM) showed that posaconazole trough concentrations were maintained at 3–4 mg/L without significant hepatic or renal toxicity. The main adverse effects observed were hypokalemia and anorexia. After 102 days of antifungal therapy, the patient underwent successful lobectomy, leading to complete resolution of symptoms.

Conclusion: This case demonstrated the good efficacy and safety of high-dose posaconazole combined with liposomal amphotericin B in the treatment of azole-resistant *Aspergillus* and mucormycosis.

Keywords: invasive pulmonary aspergillosis, mucormycosis, azole-resistant *Aspergillus fumigatus*, high-dose posaconazole, combination therapy

Introduction

The incidence rate of invasive pulmonary aspergillosis (IPA) in severely immunocompromised individuals ranges from 6% to 16%, with published mortality rates reported between 30 and 50%.[1] Azole antifungals are the front-line treatment for IPA, but due to the increase of long-term azole prophylaxis and treatment in immunocompromised patients, azole resistance in *Aspergillus spp*. is increasing,[2] which brings new challenges and difficulties. Mucormycosis is a rare and challenging-to-diagnose fungal infection that often progresses rapidly. In recent years, advancements in molecular biology techniques have enabled increased detection of the disease. Characterized by a high mortality rate, mucormycosis

Received: 1 April 2025
Accepted: 18 July 2025
Published: 25 July 2025

requires timely intervention.[3] When coinfection with two fungal species occurs simultaneously, such as azole-resistant *Aspergillus* and Mucoromycetes, it presents significant diagnostic and therapeutic challenges for clinicians. Uncontrolled diabetes mellitus is a recognized risk factor for both aspergillosis and mucormycosis, primarily due to hyperglycemia-induced immune dysfunction and vascular damage. Here, we reported a complicated coinfection case of azole-resistant *Aspergillus* and mucormycosis, which was successful treatment of antifungal combination therapy with high-dose posaconazole (HD-POS) and liposomal amphotericin B (L-AmB).

Case Report

A 52-year-old man was admitted to our hospital on February 17, 2024, presenting with a one-month history of fever and cough. He had a known medical history of type 2 diabetes mellitus, managed with metformin and glipizide; however, his blood glucose levels remained poorly controlled.

The patient was 170 cm in height and weighed 75 kg. The physical examinations revealed crackles in the right upper lung lobe. Initial computed tomography (CT) imaging revealed groundglass nodules in the bilateral upper lobes (Figure 1A). A follow-up CT scan eight days later showed rapid progression with emerging cavities. Sputum smear tested positive for fungal elements, prompting initiation of intravenous voriconazole (400 mg/day) combined with inhaled amphotericin B (10 mg twice daily) for approximately two weeks. Despite therapy, the patient remained febrile, and subsequent CT imaging revealed enlarged infiltrative shadows and cavitary lesions (Figure 1B). Oral posaconazole (300 mg/day) was administered for three days without resolution of fever.

Upon admission, laboratory tests showed elevated C-reactive protein (81 mg/L) and *Aspergillus* IgG antibody levels (128.0 IU/L). During bronchoscopy, fungal elements were visualized through brush cytology and microscopic examination (Figure 2). Targeted next-generation sequencing (tNGS) of bronchoalveolar lavage fluid (BALF) identified *Aspergillus fumigatus* (5227 reads, average depth 373) and *Rhizopus microspores* (1366 reads, average depth 195), which was performed on the DIFSEQ-200 platform with 50bp single-end sequencing. Galactomannan antigen (GM) testing of BALF was elevated at 3.4. Both BALF and sputum cultures grew *Aspergillus fumigatus* resistant to voriconazole (MIC = 4 mg/L) and itraconazole (MIC = 16 mg/L), with reduced susceptibility to posaconazole (MIC = 1 mg/L). Whole genome sequencing (Average sequencing depth 48X) of the isolate revealed mutations, but none in the azole target gene CYP51A (Table 1).

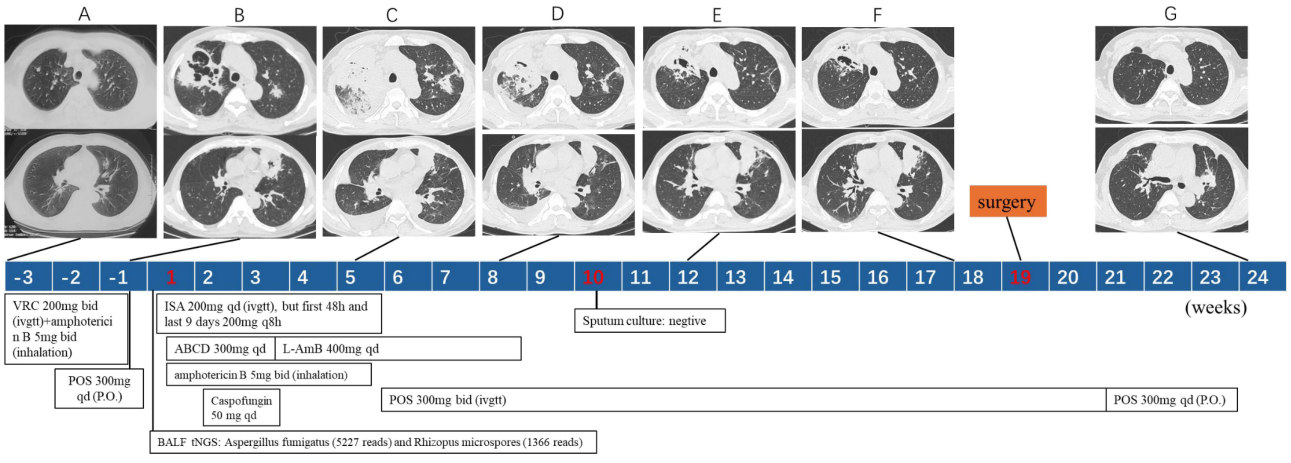

Figure 1 The patient's clinical course. (**A**) Initial CT scan: groundglass nodules in the bilateral upper lobes; (**B**) 3 weeks of treatment (02–14,3 days before admitting): the appearance of cavities in the bilateral upper lobes; (**C**) CT scan when hemoptysis (03–18): the infiltrative shadow worsened and right pleural effusion appeared; (**D**) After 17 days of HD-POS treatment (04–08): improvement of the infiltrative shadows in right upper lobes; (**E**) 1 month after a monotherapy of HD-POS (05–08): infiltrative shadows was further improvement, and pleural effusion disappeared; (**F**) 2 months after a monotherapy of HD-POS (06–14): consolidation was similar to the images from May. In 19th week, surgical resection of the infected parenchyma was performed. After surgery, HD-POS was still used for 10 days, then reduced to 300 mg per day for 3 weeks. (**G**) 1month after surgery: CT view showed postoperative changes (07–29).

Abbreviations: VRC, Voriconazole; POS, Posaconazole; ISA, Isavuconazole; ABCD, Amphotericin B Colloidal Dispersion; L-AmB, Liposomal Amphotericin B; bid, Bis in Die; ivgtt, intravenous guttae; qd, Quaque Die; q8h, Quaque 8 Horas; PO, Per Os.

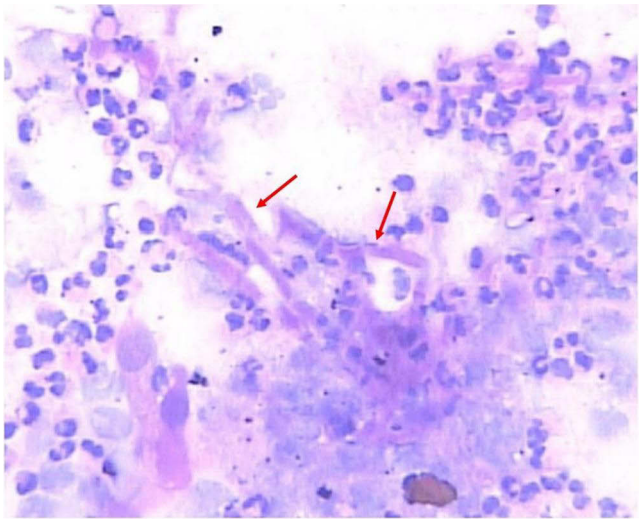

Figure 2 Bronchoscope brushing cells in cytological diagnosis: fungal hyphae can be seen (red arrow).

Antifungal therapy was escalated to intravenous amphotericin B colloidal dispersion (ABCD; 5mg/kg/d, 300 mg/day), inhaled amphotericin B (10 mg/day), and isavuconazole (600 mg/day for 48 hours, then 200 mg/day). Fever transiently resolved but recurred at 39°C in the second week. Caspofungin was added as combination therapy without clinical improvement. Repeat bronchoscopy on hospital day 18 identified necrotic debris obstructing the right upper apical and left upper lobe bronchi (Figure 3A and B). The histopathology of necrotic material showed mucormycosis. Endobronchial instillations of amphotericin B deoxycholate were performed for 3 times, but this approach did not appear to work. On day 19, ABCD was substituted with L-AmB (6mg/kg/d, 400 mg/day) due to severe nausea, vomiting, and hypokalemia. GM of BALF was also elevated at 3.36 on day 18 and 1.45 on day 24. Isavuconazole was increased to 600 mg/day on day 26, resulting in mild fever reduction but exacerbated gastrointestinal toxicity. By day 31, hemoptysis developed alongside worsening infiltrates and pleural effusion (Figure 1C). Surgical resection was declined due to bleeding and infection risks.

On day 35, the antifungal strategy was adjusted to the intravenous injection of high-dose posaconazole (HD-POS, 300 mg bid) combined with L-AmB. The patient's hemoptysis improved and body temperature gradually dropped to normal after 1 week. The follow-up CT revealed improvement of the infiltrative shadows (Figure 1D). The patient then continued HD-POS on 51st day as a monotherapy. The main side-effect was anorexia and hypokalemia. The therapeutic

Table 1 Mutations of This Strain of *Aspergillus Fumigatus*

Genes	Mutations	Mutations of Amino Acid
Cyp52A	c.1279A>G	p.Lys427Glu
Cyp54A	c.765G>C	p.Glu255Asp
Cyp55A	c.743C>A	p.Thr248Asn
Cyp56A	c.514G>A	p.Val172Met
Cyp60A	c.137A>T	p.Tyr46Phe
AtrF	c.115A>G	p.Met39Val
HMG-CoA/hmg1	c.961G>A	p.Ala321Thr
HMG-CoA/hmg1	c.1012C>A	p.Pro338Thr
HMG-CoA/hmg1	c.1499C>T	p.Ala500Val
HMG-CoA/hmg1	c.2905_2906+2delAAGT	p.Asn969fs
HMG-CoA/hmg1	c.634T>C	p.Ser212Pro
Cdr1B	c.407A>G	p.Lys136Arg
Cdr1B	c.2033T>A	p.Ile678Asn

https://doi.org/10.2147/IDR.S530615

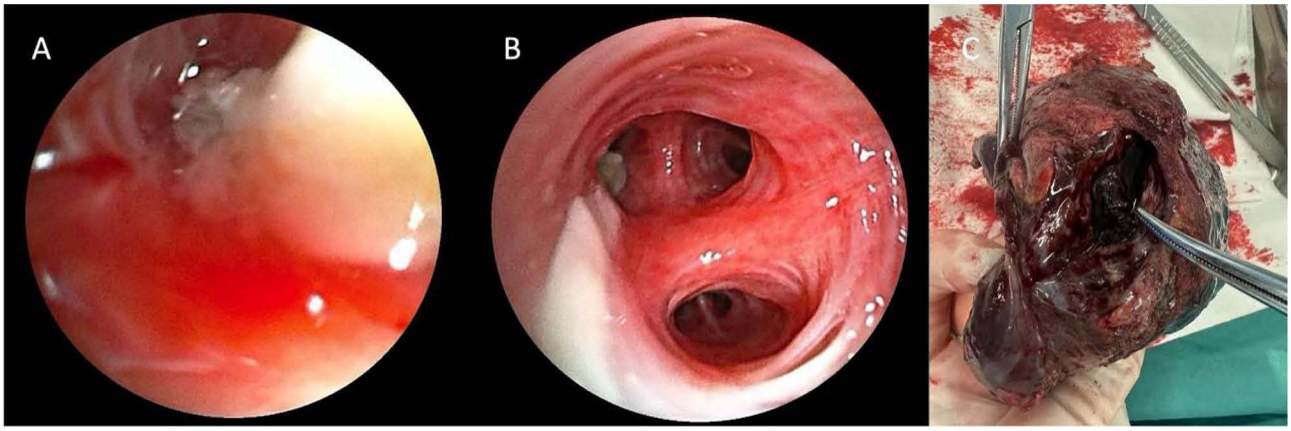

Figure 3 Images of bronchoscopy on March 18th: necrotic matter blocking the bronchi of right upper tip segment (**A**) and left upper lobe proper segment (**B**). (**C**) Resected right upper lobe: a large mass of fungus hypha.

drug monitoring (TDM) of POS was administrated. The POS trough concentrations maintained 3–4mg/L. On day 70, sputum culture had finally turned negative. A follow-up CT scan on day 81 demonstrated continued improvement (Figure 1E). The patient's physical condition was further improving, and surgical resection will be performed after the further reduction in size of consolidation. By day 126, a subsequent CT scan (Figure 1F) revealed stabilization of the consolidation, which was comparable in size to the findings observed on day 81. Given the patient's significantly improved clinical status, a left lingular segmentectomy and right upper lobectomy (Figure 3C) were performed via video-assisted thoracoscopic surgery (VATS) on June 25 (137 days after initial admission). Postoperatively, the patient received a high-dose posaconazole (HD-POS) regimen for 10 days, followed by a standard dose of posaconazole (300 mg once daily) for 3 weeks. Follow-up radiological evaluation one month later showed no evidence of active infection (Figure 1G), and the patient was deemed cured. Notably, after admission to our hospital, blood glucose levels were managed with Insulin Aspart and Insulin Glargine. Fasting blood glucose ranged from 4.7 to 9.3 mmol/L, and postprandial blood glucose ranged from 5.1 to 14.8 mmol/L.

Discussion

Aspergillus fumigatus is a ubiquitous pathogen which can cause aspergillosis, especially in immunodeficient patients. Azoles have been the frontline of therapy in infections with *Aspergillus fumigatus*. In recent years, the emergence of azole resistance in *Aspergillus fumigatus* has become a serious problem worldwide.[4] The frequency of itraconazole resistance in *Aspergillus fumigatus* isolates was 4.4% in China.[5] The development of resistance may be linked to either long-term use of azole antifungals in patients, but it can also occur in newly treated patients which is associated with selection pressure of the fungicides in the environment.[6] In azole-naive patients, the resistance maybe responsible to the extensive use of azole fungicides in the environment.[7] Mucormycosis, a rare fungal infection primarily affecting the lungs or the rhino-orbital-cerebral area, particularly occurs in immunocompromised individuals or those with diabetes mellitus.[8] Within the Mucorales order, Rhizopus species are the most frequent etiology of mucormycosis, with *Rhizopus microsporus* being a significant pathogen. It can induce acute invasive infections in humans by germinating and evading the host's immune defenses.[9] The patient we reported was newly diagnosed and suffered from co-infection of Aspergillus and mucormycosis (*Rhizopus microspores*), which posed a greater therapeutic challenge.

As recommended by Ullmann et al, combination therapy with HD-POS and L-AmB is a viable strategy for azole-resistant aspergillosis.[10] In this case, the combination therapy was started immediately after the co-infection was confirmed, and L-AmB was given in high dose (400mg/d), but the therapeutic response was suboptimal. In the absence of effective antimicrobial agents, escalating drug doses to achieve higher plasma concentrations may be a viable strategy. In a case report with a lung transplant recipient, the concentration of isavuconazole did not achieve steady state plasma concentration with 600 mg/d within first 2 days and maintenance dose of 200 mg once daily. Then the daily dose was increased to 600 mg/d for 2 weeks, achieving a steady-state level and demonstrating good efficacy and safety.[11] In our

case, the patient's body temperature normalized within the first week, likely due to elevated plasma concentrations of isavuconazole. However, when the dose was increased to 600 mg/day in the fourth week, only a slight reduction in body temperature was observed, while chest imaging and symptoms remained unchanged. Additionally, the patient experienced severe nausea and vomiting, prompting consideration of posaconazole (POS).

POS is characterized by its high tissue concentration, with intracellular levels reported to be 40- to 50-fold higher than extracellular levels in previous studies.[12] This suggests that POS can achieve higher concentrations in lung tissue. Schauwvlieghe et al retrospectively evaluated the use of oral HD-POS (600 mg/day, with an interquartile range of 400–750 mg/day) in patients with azole-resistant aspergillosis and other refractory mold infections, demonstrating favorable efficacy and tolerable side effect.[13] They reported trough plasma concentrations of POS reaching 3–4 mg/L, significantly higher than the guideline-recommended levels (>1 mg/L).[14] According to this case, HD-POS (600 mg/day) was initiated on day 35 after admission, with continued administration of L-AmB. TDM confirmed a steady-state plasma concentration of POS at 3–4 mg/L. Subsequently, the patient's body temperature gradually normalized, and CT imaging showed significant improvement. The primary adverse events (AEs) were anorexia and hypokalemia, consistent with previously reported findings.[13]

Resistance mechanisms of *Aspergillus* involve *Cyp51* genes, efflux pumps and other signaling pathways related to biofilm formation, mitochondrial or stress response, while which factor plays a major role, more isolates are needed to study.[15] The large majority of azole-resistant *Aspergillus fumigatus* isolates harbour TR34/L98H or TR46/Y121F/T289A mutations in the *Cyp51A* gene,[13,16] but no mutations were found in the *Cyp51A* gene in our report. The gene *hmg1* has been involved in the ergosterol biosynthesis pathway which is similar to *Cyp51* genes.[4] *Cdr1B* gene and *AtrF* gene are both ATP Binding Cassette transporters which mediate the efflux of toxic compounds associated with azole resistance.[7] Other mutations in our case including *Cyp52A, Cyp54A, Cyp55A, Cyp56A, Cyp60A* have not been reported. The resistance mechanism needs further study.

Conclusion

For patients with *Aspergillus* infection who are failed in initial treatment, drug resistance testing should be performed immediately and mixed infection should be considered at the same time. This case of co-infection with azole-resistant *Aspergillus* and *Rhizopus microsporus* underscores the need for comprehensive microbial profiling in refractory fungal infections. Combination therapy with HD-POS and L-AmB may be a viable treatment strategy in such cases. Additionally, TDM for posaconazole is crucial to prevent drug-related AEs. This case highlights the importance of microbial documentation, including culture, serum, and tNGS, in guiding therapy for fungal co-infections. Further investigation into the resistance mechanisms of Aspergillus is necessary to inform optimal treatment approaches.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for Publication

This case was a part of routine clinical practice at our institution and didn't require specific approval to publish the case details. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Acknowledgments

We sincerely thank Dinfectome Inc., Nanjing, China for providing the help in targeted next-generation sequencing.

Funding

This work was supported by the Project of Natural Science Foundation of China (82270019, 82070011), and General Program of Clinical Research, Nanjing Drum Tower Hospital (2023-LCYJ-MS-18).

Disclosure

WWW is the employee of Dinfectome Inc. The remaining authors declare that they have no competing interests.

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