



## Case Series

## Invasive *Hormographiella aspergillata* infection in patients with acute myeloid leukemia: Report of two cases successfully treated and review of the literature

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## ABSTRACT

*Hormographiella aspergillata* is a rare cause of invasive mold infection, mostly described in patients with hematological malignancies. We describe two cases of invasive *H. aspergillata* infections in patients with acute myeloid leukemia, successfully managed with complete surgical resection of the lesions and antifungal therapy of voriconazole alone or liposomal amphotericin B, followed by voriconazole, highlighting the key role of a multidisciplinary approach for the treatment of this rare and severe invasive mold infection.

## 1. Introduction

The mold *Hormographiella aspergillata* belongs to the *Basidiomycota* division of fungi, and is the asexual form of *Coprinopsis cinerea*, an edible mushroom usually found in compost and other nutrient-rich substrates [1].

*H. aspergillata* has been described as a rare cause of fungal infection in humans. Cases of prosthetic valve endocarditis and intraocular lens-implant-associated endophthalmitis have been described in immunocompetent patients [2,3], but the most severe cases have been reported as lung and disseminated infections in immunocompromised hosts, in particular those with hematological malignancies [4–18]. The elevated mortality rate (around 80%) may result from delayed diagnosis and therapy, in the absence of detection by common fungal biomarkers (e.g. 1,3-β-d-glucan, galactomannan) and sufficient culture yield. Moreover, there are limited clinical data on antifungal treatment efficacy. Most patients in previous case reports and series received multiple lines of antifungal therapy, including amphotericin B formulations in the majority of cases. While breakthrough infections have been reported under azole prophylaxis [5–8,18], the role of this antifungal drug class for the

treatment of *H. aspergillata* infections remains unclear. Antifungal susceptibility testing data are scarce, but suggest a good *in vitro* activity of voriconazole, while resistance or trailing effect have been reported for other mold-active azoles (e.g. posaconazole, itraconazole) [13,14].

## 2. Cases

**Case 1.** A 46-year-old man was diagnosed with acute monoblastic leukemia with a FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) mutation, which was treated with an induction chemotherapy (cytarabine and idarubicin followed by high dose cytarabine and daunorubicin) combined with methylprednisolone and etoposide (at day 1 and 5) for a hemophagocytic syndrome. He was admitted to our hospital for a second cycle of induction therapy using the same regimen (day 0). Antifungal prophylaxis with posaconazole was started on the first day of neutropenia (day +9) and maintained during the entire neutropenic phase. After 10 days of persistent neutropenic fever despite broad-spectrum antibiotics and posaconazole prophylaxis (day +20), a thoraco-abdominal computerized tomography

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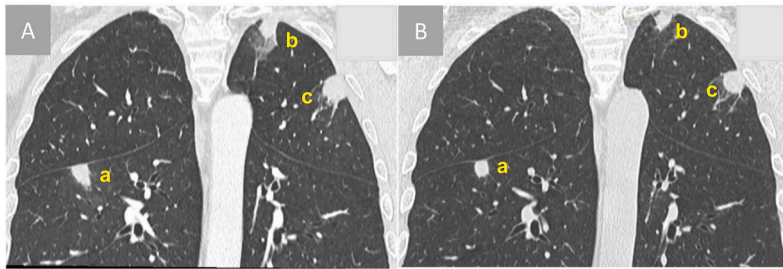
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Mass volumetry of lung lesions



Case 1

Volume [mm <sup>3</sup> ]	Panel A Day 0	Panel B Day 15	Change [%]
Lesion a	2'290	1'029	- 55
Lesion b	204	56	- 73
Lesion c	6'603	4'010	- 39


  
 Antifungal therapy:  
 liposomal amphotericin B

Fig. 1. Radiological assessment of infection at baseline and in follow-up (Case 1).

CT-scan images (sagittal view) of the lung lesions of Case 1. Pictures are taken at initial diagnosis (A) and at day +15 following introduction of liposomal amphotericin B and before the surgical intervention (B).

Volumes of the lung lesion are shown in the table with expression of the changes (in percent) in the follow-up image (B) compared to the baseline image (A).

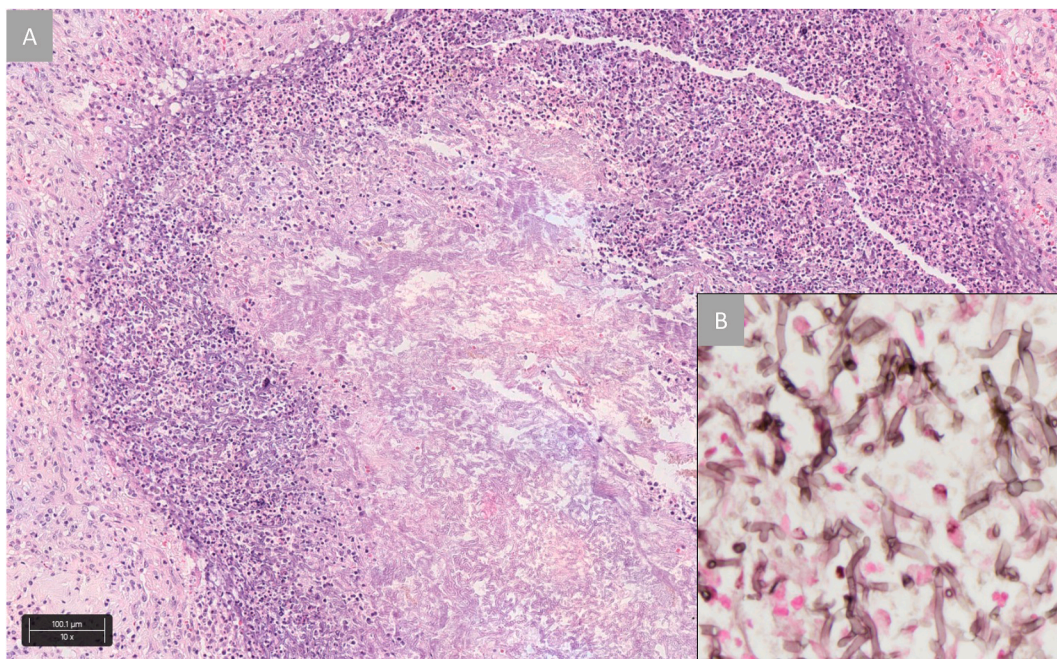


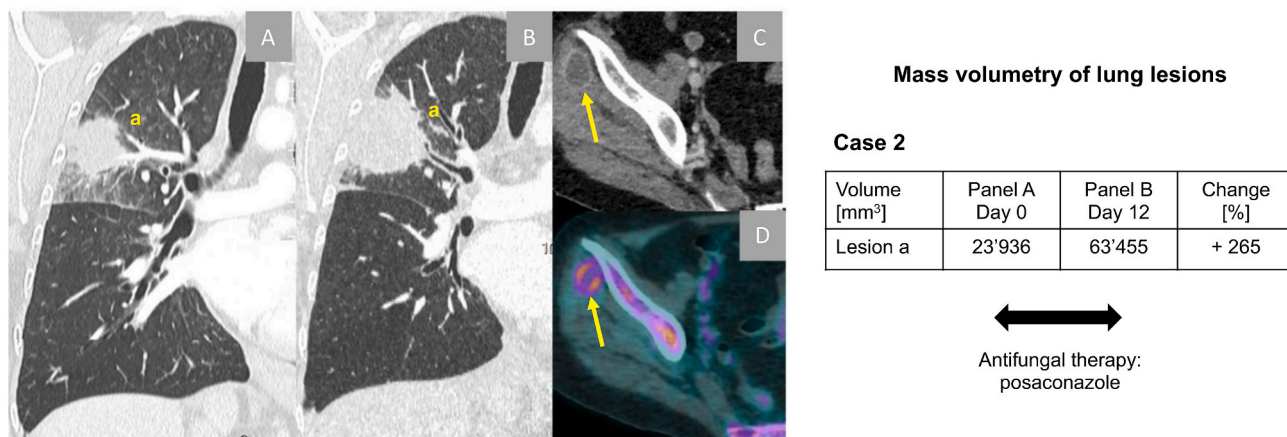
Fig. 2. Histomorphology of the wedge resection with bronchocentric pneumonia (Case 1).

The central necrosis harbors closely packed fungal hyphae and surrounding acute inflammation and organization (A). The hyphae are narrow, septate and branched (B).

Hematoxylin and Eosin, x100 (A), Grocott's methylene silver stain, x400 (B).

(CT) scan showed 3 nodular lung lesions (Fig. 1A). Serum galactomannan and 1,3-β-d-glucan were negative at this time. A bronchoscopy was performed on the following day (day +21), with sterile fungal culture and negative galactomannan on the bronchoalveolar lavage (BAL) sample. Empirical antifungal therapy with liposomal amphotericin B (L-AMB, 5 mg/kg/day) was initiated immediately after the bronchoscopy. A new chest CT performed two weeks after initiation of L-AMB (day +36) showed a reduction of all three lung lesions (73%, 55%, and 39% reduction, respectively, according to mass volumetry, Fig. 1A and B). Following neutrophil recovery, complete removal of the three lung lesions was performed by wedge resection of the right and the left lungs at week 2 (day +38) and 3 (day +44) after the start of L-AMB, respectively. The histopathological exam of the lung lesions showed bronchocentric pneumonia with narrow septate and branched mycelia compatible with an *Aspergillus* spp. (Fig. 2). Despite sterile fungal cultures, the panfungal PCR (targeting the 18S rDNA) [19] on the resected

lung tissue was eventually positive for *H. aspergillata* on both the right inferior lobe and the left superior lobe lesions. Assessment of disease extension (abdominal and cerebral CT) did not show any other lesion. The antifungal therapy was changed to oral voriconazole (6 mg/kg twice a day on the first day, followed by 4 mg/kg twice a day) after 6 weeks of L-AMB (day +66) because of acute kidney injury attributed to L-AMB toxicity. Voriconazole therapy was continued for a total duration of 5 months without evidence of recurrent fungal disease on radiological follow-up (day +217). Voriconazole therapeutic drug monitoring was performed every two weeks and dosing was adjusted accordingly for a targeted trough concentration of 1 to 5 mg/l. In the meantime, the patient experienced relapsed AML, which was treated by two cycles of high dose cytarabine combined to cladribine and the FLT3-ITD inhibitor sorafenib, followed by a haploidentical allogeneic hematopoietic stem cell transplantation 4 months later (day +152). After 3 years, the patient is still alive and in complete remission.



**Fig. 3.** Radiological assessment of infection at baseline and in follow-up (Case 2) CT-scan images (sagittal view) of the lung lesions of Case 2 (A and B), as well as PET-CT imaging of the right *gluteus minimus* abscess (C and D). Chest CT pictures are taken at initial diagnosis (A) and at day +12 following introduction of posaconazole therapy and before the surgical intervention (B). Volume of the lung lesion is shown in the table with expression of the changes (in percent) in the follow-up image (B) compared to the baseline image (A).

**Case 2.** A 70-year-old woman was diagnosed with AML with mutated runt-related transcription factor 1 (RUNX1). The induction chemotherapy included fludarabine, high-dose cytarabine and idarubicin. Because complete remission was not achieved after the first cycle, she was admitted to our hospital (day 0) for a second cycle of chemotherapy including high-dose cytarabine and clofarabine with the addition of the B-cell lymphoma 2 (BCL2) inhibitor venetoclax. Antifungal prophylaxis with fluconazole (400 mg/day) was started on the first day of neutropenia (day +5). On the 13th day of neutropenia (day +17), a thoraco-abdominal CT-scan was performed because of persistent fever despite broad-spectrum antibiotics, which showed a lung mass in the right apex with a halo sign (Fig. 3A). The fluconazole prophylaxis was stopped and posaconazole was started (300 mg twice a day on the first day, then 300 mg once a day). A first bronchoscopy was rapidly performed (day +18) with negative fungal cultures and galactomannan in BAL, followed by a second bronchoscopy with ultrasound-guided transbronchial biopsies 5 days later (day +23). A CT of the chest, abdomen and pelvis performed 12 days after initiation of posaconazole therapy (day +29) showed a progression of the lung mass with a volume increase of 265% of the lesion (Fig. 3B), a new right pleural effusion, as well as a right gluteus minimus muscle abscess (Fig. 3C). The muscle abscess was drained by interventional radiology (day +29) and a lung wedge resection was performed four days later (day +33). An assessment of disease extension was made afterward with a normal brain magnetic resonance imaging (day +36) and a PET-CT (day +40) showing a persistent hypermetabolism around the right gluteus minimus muscle abscess (Fig. 3D). The histopathological analysis of both the lung tissue and muscle abscess showed branched septate mycelial elements and the panfungal PCR was positive for *H. aspergillata*, which was subsequently also recovered on culture. Antifungal susceptibility testing was performed by microbroth dilution method using the Sensititre YeastOne™ kit (Trek Diagnostics Systems, ThermoFisher Scientific, Cleveland, OH). Minimum inhibitory concentrations (MIC) for amphotericin B, voriconazole, posaconazole were 0.5, 0.5 and 2 mg/L, respectively. Based on these results, anti-fungal treatment was changed (day +31) to voriconazole (6 mg/kg twice a day on the first day, followed by 4 mg/kg twice a day). Voriconazole therapy was continued and the patient was eventually transferred home with a palliative treatment plan because of progression of the leukemia after 2 cycles of intensive chemotherapy. Eight months afterward, the patient is still alive with no clinical or radiological signs of recurrence of the fungal infection under voriconazole therapy.

**Table 1**  
Literature review of invasive *Hormoglyphiella aspergillata* infections in patients with hematological cancer (n = 20).

General demographic characteristics	N patients = 20
Male / Female	10 (50%) / 10 (50%)
Age (median, range)	44 (14 – 70)
<b>Hematological disease</b>	
Acute myeloid or lymphoid leukemia	16 (80%)
Other <sup>a</sup>	4 (20%)
Allogeneic stem cell transplantation	14 (70%)
<b>Site of infection</b>	
Localized / disseminated (more than one site)	14 (70%) / 6 (30%)
Lung	19 (95%)
Brain	4 (20%)
Skin and soft tissues	3 (15%)
Other <sup>b</sup>	3 (15%)
<b>Microbiological identification of <i>H. aspergillata</i></b>	
Postmortem (autopsy)	5 (25%)
Antemortem - biopsy sample only	11 (55%)
Antemortem - non-biopsy sample <sup>c</sup>	4 (20%)
<b>Antifungal drugs</b>	
Ongoing antifungal prophylaxis at time of diagnosis <sup>d</sup>	5 (25%)
<b>First-line treatment</b>	
Amphotericin B formulation	7 (35%)
Amphotericin B formulation + echinocandin	2 (10%)
Voriconazole	6 (30%)
Posaconazole	1 (5%)
Echinocandin	4 (20%)
<b>Subsequent treatment lines</b>	
Amphotericin B formulation	7 (35%)
Voriconazole	7 (35%)
Posaconazole	3 (15%)
Itraconazole	1 (5%)
Echinocandin	3 (15%)
<b>Outcome</b>	
Overall mortality	14 (70%)
Attributable to IFI	9 (64%)
Partially attributable to IFI	3 (21%)
Not related to IFI	2 (14%)

Literature review including previously published cases (4–18) and the two present case reports.

<sup>a</sup> Refractory anemia with excess blasts (1), chronic myeloid leukemia with B-cell lymphoid blast phase (1), lymphoma (1), X-linked adrenoleukodystrophy (1).

<sup>b</sup> Sinus (1), eye (1), intestine (1).

<sup>c</sup> Bronchoalveolar lavage fluid (3), sinus fluid (1).

<sup>d</sup> Posaconazole (2), voriconazole (1), itraconazole (1), caspofungin (1).

**Table 2**Antifungal susceptibility profile of *Hormoglyphiella aspergillata* clinical isolates reported in the literature (n = 16).

1st author [ref]	Present case	Gené (1)	Suarez (5)	Nanno (8)	Bojic (12)	Conen (13)	Verweij (14)	Isabel Cristina (18)
N isolates	1 isolate SYO	7 isolates BMiD	1 isolate EUCAST	1 isolate NA	1 isolate	3 isolates CLSI	1 isolate	1 isolate EUCAST
Testing method					E-test		Agar / BMaD	
<b>Itraconazole</b>	2	0.51 ± 0.1	≥8	0.25	–	–	32 / 8	–
<b>Voriconazole</b>	0.5	–	1	0.015	0.125	0.125 - 0.25	0.5 / NA	0.06
<b>Posaconazole</b>	2	–	–	–	0.064	2	–	0.06
<b>Caspofungin</b>	0.5	–	2	–	–	≥32	–	32
<b>Anidulafungin</b>	0.12	–	–	–	–	–	–	–
<b>Micafungin</b>	0.25	2.3 ± 1.5	–	≥16	–	–	–	–
<b>Amphotericin B</b>	0.5	0.5/2.3	2	0.125	0.094	0.5	0.03 / 0.5	32

Values are minimum inhibitory concentration (MIC) expressed in mg/L.

SYO: Sensititre YeastOne™; BMiD: broth microdilution; NA, not available; EUCAST: European Committee on antimicrobial susceptibility testing; CLSI: clinical and laboratory standards institute; BMaD: broth macrodilution.

### 3. Discussion

*Hormoglyphiella aspergillata* is a rare, but possibly underreported cause of invasive fungal infection in neutropenic patients with hematological malignancies. Eighteen cases have been reported so far in this population with an associated mortality rate of 78% (14/18 cases, Table 1). Disseminated infection was observed in 30% of these cases with relatively frequent localization in brain or skin/soft tissues. The diagnosis was made on *postmortem* tissues or biopsy samples in most cases, stressing the difficulty to identify this pathogen and to initiate prompt appropriate antifungal therapy.

We described here two cases of invasive *H. aspergillata* infection in patients with AML that were successfully managed with early surgery and antifungal treatment. Some key interventions were probably determinants for the favorable outcome of these fungal infections.

First, we performed a prompt and invasive diagnostic strategy with bronchoscopy and lung tissue biopsy. In our experience, mini probe-guided transbronchial lung biopsies can be performed safely in neutropenic and thrombocytopenic patients using platelet transfusion during the procedure, and is associated with a better yield than BAL alone for the diagnosis of invasive fungal diseases [19]. Molecular diagnostic tools, such as our broad panfungal PCR targeting the 18S rDNA [20], were used in addition to standard cultures for the rapid detection of the causal fungal pathogen. Indeed, *H. aspergillata*, as most other basidiomycetous molds, are usually not detected by fungal biomarkers, such as galactomannan or 1,3-β-d-glucan.

Second, the surgical approach consisting of complete wedge resection of the lesions was probably a key element in the successful outcome of these cases. This experience supports the crucial role of surgery following neutrophil recovery in the management of rare and fastidious mold infections in general, including *H. aspergillata* and other non-*Aspergillus* molds that are relatively resistant to antifungals and notoriously difficult to treat [21]. Indeed, previous reports of *H. aspergillata* invasive infections were associated with a very high mortality and it is noteworthy that surgical interventions were performed in a minority of cases (33%, Table 1).

Our review of literature showed that multiple lines of antifungal therapy were often used (Table 1). Most patients received first-line or second-line treatments of amphotericin B formulations, for which *H. aspergillata* exhibited relatively low MIC in most cases except one (Table 2). In our first case-report, liposomal amphotericin B was associated with a favorable response as illustrated by the significant reduction of the lung lesions after two weeks of therapy and before the surgical intervention.

The role of azoles in this setting is more debatable. Some breakthrough *H. aspergillata* infections have been reported under mold-active azoles (Table 1) and *in vitro* susceptibility of this mold to azoles is variable (Table 2) [5–8,18]. Notably, posaconazole MICs are relatively high and a trailing effect has been described, which suggests some level of tolerance of *H. aspergillata* to this drug [13]. Indeed, we observed a

progression of the lung mass under posaconazole therapy in our second reported case. However, we observed a favorable outcome in the absence of relapsing infection with maintenance voriconazole therapy following surgery in both cases. In contrast to posaconazole, voriconazole displayed good *in vitro* activity against all tested isolates of the literature and in the present case for which antifungal susceptibility testing could be performed (i.e. median 0.125 mg/L, range 0.015 – 1 mg/L, Table 2) [1,5,8,12–14,18]. Use of voriconazole as first-line or second-line treatments has been associated with variable outcomes [6, 13,15,16]. Indeed, progression of the fungal disease under voriconazole therapy was observed in some cases [13,15] and one breakthrough *H. aspergillata* infection under voriconazole prophylaxis has also been reported [13]. Our data however suggest that voriconazole may have a place for the treatment of this rare mold disease, provided that an optimal source control is achieved by surgery. Whether the novel broad-spectrum azole drug isavuconazole could be used in this setting remains to be determined.

The present cases of *H. aspergillata* invasive fungal infections in leukemic patients are among the rare ones reported in the literature that were successfully treated. While we cannot draw firm conclusions and recommendations on the basis of only two cases, we attributed this therapeutic success to the extensive diagnostic work-up for early detection of the pathogen using mini probe-guided transbronchial lung biopsies and molecular diagnostic tools, and the aggressive surgical management of the lesions in conjunction with antifungal therapy of liposomal amphotericin B and/or voriconazole. Based on this experience, we suggest that similar approach could be used in the future for the management of such cases.

### Declaration of competing interest

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