Inonotus in Patient with Hematologic Malignancy

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We report a lung-invasive fungal disease with possible cutaneous needle tract seeding in a patient with a febrile neutropenia caused by the Basidiomycetes mold Inonotus spp. Although rare, Inonotus spp. should be added to the list of microorganisms causing invasive fungal disease in neutropenic patients with hematologic malignancies.

A 33-year-old man in Madrid, Spain, with chronic myeloid leukemia in lymphoid blastic phase underwent allogeneic stem cell transplantation (SCT) from a matched unrelated donor in 2011. Four years later, he had an extramedullary pulmonary relapse, after which he began intensive reinduction chemotherapy. After the second cycle, prolonged severe aplasia developed in the patient. Invasive fungal disease (IFD) was suspected because of the presence of persistent fever despite broad-spectrum antimicrobial drugs and the appearance of a new pulmonary nodule (Figure, panel A; online Technical Appendix, https://wwwnc.cdc.gov/EID/article/24/1/17-1265-Techapp1.pdf) while the patient was receiving prophylactic micafungin (50 mg/d). Serologic fungal biomarkers were negative. A percutaneous pulmonary biopsy sample was taken, and empirical liposomal amphotericin B (3 mg/kg/d) was started (December 2015). Histology showed unspecific inflammatory tissue, and microbiology cultures were negative.

Salvage human leukocyte antigen–haploidentical SCT was performed in January 2016. Fever persisted during conditioning therapy, and a solitary cutaneous millimetric erythematous lesion appeared at the biopsy puncture site (Figure, panel B). Histopathology of the skin lesion showed dermal infiltration by periodic acid Schiff–positive elements compatible with fungal hyaline hyphae with parallel walls, regular septa, and branched hyphae with occasional bulb-like expansions; angioinvasion; and necrosis. Fungal culture of the specimen was negative, but panfungal PCR and further sequencing (1) revealed the presence of Inonotus spp. Voriconazole was added, and the lesion resolved in days. Neutrophil engraftment was achieved on day 12 post-SCT, with complete donor chimerism.

On day 34, the pulmonary lesion progressed, but we could not prove IFD as the cause of concomitant pleural effusion. Despite intensified antifungal therapy, surgical debridement was required to resolve the empyema. The patient was discharged on oral posaconazole (300 mg/d) that was eventually replaced by micafungin.

A computed tomography scan performed 6 months after the SCT showed persistence of a single mass on the left
We performed pulmonary segmentectomy, and lung histology showed mycetoma with fungal elements similar to those observed in the previous skin biopsy. The fungal culture yielded a fluffy, white, slow-growing mold. The lack of sporulation did not permit morphologic identification, although panfungal PCR and further sequencing again revealed the presence of *Inonotus* spp. in the lung tissue sample.

Filamentous Basidiomycetes molds are ubiquitous and able to colonize in patients with chronic pulmonary disease. They cause syndromes comparable to allergic bronchopulmonary or rhinosinus aspergillosis. However, IFD caused by Basidiomycetes molds are extremely rare (2). It has been hypothesized that IFD could occur in patients with mycetoma if they become immunocompromised. Clinical presentation resembles that of other IFDs, with predominantly pulmonary involvement (online Technical Appendix Table 1). Most filamentous Basidiomycetes are susceptible to antifungal drugs except for fluconazole and echinocandins. However, because many isolates do not sporulate, morphologic identification in the clinical microbiology laboratory is difficult without molecular techniques, and antifungal susceptibility testing is impossible to perform (3).

Invasive disease caused by *Inonotus* spp. (*Phellinus tropicalis* and *P. undulatus*) in humans has been described in 1 patient with diabetic nephropathy (3) and 6 patients with chronic granulomatous disease (4–10). Of note, 4 were breakthrough infections in patients receiving prophylactic itraconazole or posaconazole. Local infections had a favorable outcome; however, 1 patient with more extensive involvement had multiple relapses.

The presence of fungal elements invading the tissues supported the diagnosis of IFD; nevertheless, we did not initially consider *Inonotus* spp. to be the causative agent of the IFD in this patient because it rarely causes disease in humans. The clinical significance of the isolation of saprophytic molds in nonsterile clinical samples is difficult to ascertain. However, detection of *Inonotus* spp. in the lung tissue sample taken months after the skin lesion biopsy led us to reassess its potential role as an etiologic agent. In addition, the patient could have acquired the lung infection after inhalation of spores, and selective pressure of previous antimicrobial drugs could have triggered the breakthrough invasive *Inonotus* spp. infection. Antifungal therapy was selected without specific recommendations and without antifungal susceptibility testing (because of the poor sporulation of the isolate). Immunosuppression was more profound and prolonged than in other cases of IFD caused by *Inonotus* spp. Both surgery and antifungal therapy were required, and immunologic recovery, along with a subacute course, were probably essential for the favorable outcome of this patient.

In conclusion, *Inonotus* spp. should be added to the list of potential causal agents of IFD in neutropenic hematological patients. Systematic use of panfungal PCR targeting the internal transcribed tracer regions coupled with sequencing in patients at a high risk for IFD may be helpful for diagnosing rare invasive fungal infections.

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The subject of the case report signed an informed consent document for publication.

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References

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Corrections
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An incorrect word in a sentence in Escherichia coli O157 Outbreaks in the United States, 2003–2012 (K.E. Heiman et al.) inadvertently changed the meaning. The sentence should have read, “The median annual number of outbreaks reported during 2008–2012 was higher than during 2003–2007 (45 vs. 33, p = 0.12) (Figure 1).” The article has been corrected online (https://wwwnc.cdc.gov/eid/article/21/8/14-1364_article).

Vol. 23, Supplement

The name of author Melanie E. King was incorrectly listed and several items in the text were unclear in Surveillance Training for Ebola Preparedness in Côte d’Ivoire, Guinea-Bissau, Senegal, and Mali (V.M. Cáceres et al.). The article has been corrected online (https://wwwnc.cdc.gov/eid/article/23/13/17-0299_article).
## Inonotosis in Patient with Hematologic Malignancy

### Technical Appendix

#### Technical Appendix Table. Invasive fungal infections caused by Basidiomycetes in neutropenic hematological patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Place</th>
<th>Age, Sex</th>
<th>Species</th>
<th>Diagnostic technique</th>
<th>Underlying disease</th>
<th>Infection site</th>
<th>Therapy</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nenoff P (1)</td>
<td>1997</td>
<td>Germany</td>
<td>40F</td>
<td><em>Coprinus</em> <em>spp</em> (<em>Hormographiella aspegilliata</em>)</td>
<td>Histology, culture</td>
<td>Relapsed ALL</td>
<td>Lung</td>
<td>AmB</td>
<td>Fatal</td>
<td>Coinfection with <em>A. flavus</em></td>
</tr>
<tr>
<td>Verweij PE (2)</td>
<td>1997</td>
<td>Netherlands</td>
<td>24M</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>Relapse ALL; HSCT</td>
<td>Lung-multiple</td>
<td>AmB</td>
<td>Fatal</td>
<td>Breakthrough while on fluconazole</td>
</tr>
<tr>
<td>Surmont I (3)</td>
<td>2002</td>
<td>Belgium</td>
<td>34F</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>NHL (lymphoblastic)</td>
<td>Lung abscesses</td>
<td>AmB, AmB Itraconazole</td>
<td>Favorable</td>
<td>Postmortem diagnosis.</td>
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<tr>
<td>Buzina W (4)</td>
<td>2005</td>
<td>Austria</td>
<td>9F</td>
<td><em>Irpex lacteus</em></td>
<td>Histology, culture, PCR</td>
<td>Lung abscesses</td>
<td>Lung</td>
<td>Caspofungin</td>
<td>Favorable</td>
<td>Postmortem diagnosis.</td>
</tr>
<tr>
<td>Lagrou K (5)</td>
<td>2005</td>
<td>Belgium</td>
<td>34M</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>Lung abscesses</td>
<td>Lung</td>
<td>LAmb+caspofungin</td>
<td>Fatal</td>
<td>Mixed infection: first, palatal <em>Rhizomucor variabilis</em></td>
</tr>
<tr>
<td>Abuali M (6)</td>
<td>2009</td>
<td>NY (USA)</td>
<td>14F</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>AML; HSCT</td>
<td>Lung</td>
<td>LAmb+surgery</td>
<td>Favorable</td>
<td>Breakthrough while on posaconazole and caspofungin</td>
</tr>
<tr>
<td>Conen A (7)</td>
<td>2010</td>
<td>Switzerland</td>
<td>41F</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>AML; double HSCT</td>
<td>Lung nodules, eye, brain</td>
<td>Voriconazole, Caspofungin</td>
<td>Fatal</td>
<td>GVHD Postmortem diagnosis.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>63F</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>AML</td>
<td>Lung nodules</td>
<td>Caspofungin</td>
<td>Favorable</td>
<td>blood from underlying disease</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>55M</td>
<td><em>Hormographiella aspegilliata</em></td>
<td>Histology, culture, PCR</td>
<td>AML; HSCT (double cord)</td>
<td>Lung nodules</td>
<td>LAmb+wedge resection, Voriconazole</td>
<td>Fatal</td>
<td>Breakthrough while on voriconazole</td>
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<tr>
<td>Salit RB (8)</td>
<td>2010</td>
<td>Bethesda, MD, USA</td>
<td>41F</td>
<td><em>Volvariella volvacea</em></td>
<td>Histology, culture, PCR</td>
<td>HL; HSCT (cord)</td>
<td>Lung wedge infiltrates and CNS focal lesions</td>
<td>Voriconazole+LAmb</td>
<td>Fatal</td>
<td>Previous proven aspergillosis.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Place</td>
<td>Age, Sex</td>
<td>Species</td>
<td>Diagnostic technique</td>
<td>Underlying disease</td>
<td>Infection site</td>
<td>Therapy</td>
<td>Outcome</td>
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<tr>
<td>Pang KA (9)</td>
<td>2011</td>
<td>Strasbourg</td>
<td>25F</td>
<td>Hormographiella aspergillata</td>
<td>Histology, culture</td>
<td>ALL</td>
<td>Lung</td>
<td>Voriconazole, LAmB</td>
<td>Favorable</td>
<td>Breakthrough while on caspofungin</td>
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<tr>
<td>Suárez F (10)</td>
<td>2011</td>
<td>Paris</td>
<td>23F</td>
<td>Hormographiella aspergillata</td>
<td>Histology, culture</td>
<td>Acute biphenoxytipic</td>
<td>Lung</td>
<td>Voriconazole, LAmB</td>
<td>Favorable</td>
<td>Breakthrough while on caspofungin</td>
</tr>
<tr>
<td>Bojic M (11)</td>
<td>2013</td>
<td>Austria</td>
<td>61F</td>
<td>Hormographiella aspergillata</td>
<td>Histology, culture</td>
<td>Adrenoleukodystrophy;</td>
<td>Skin, lung</td>
<td>LAmB</td>
<td>Fatal</td>
<td>Postmortem diagnosis.</td>
</tr>
<tr>
<td>Toya T (12)</td>
<td>2013</td>
<td>Japan</td>
<td>23F</td>
<td>Schizophyllum commune</td>
<td>Culture, PCR</td>
<td>ALL, SCT (cord)</td>
<td>Maxillary and etmoidal sinusitis</td>
<td>Voriconazole, LAmB</td>
<td>Favorable</td>
<td>Breakthrough while on Itraconazole followed by micafungin</td>
</tr>
<tr>
<td>Heiblig M (13)</td>
<td>2015</td>
<td>France</td>
<td>19M</td>
<td>Hormographiella aspergillata</td>
<td>Histology, culture</td>
<td>Mitochondrial cytopathy</td>
<td>Lung</td>
<td>LAmB</td>
<td>Fatal</td>
<td>Reduction of involvement, death from bacterial septic shock</td>
</tr>
<tr>
<td>Corzo-León DE (14)</td>
<td>2015</td>
<td>Mexico</td>
<td>52F</td>
<td>Hormographiella aspergillata</td>
<td>Culture, PCR</td>
<td>MDS-AML; AlloHSCT</td>
<td>Lung</td>
<td>Voriconazole, LAmB + caspo</td>
<td>Favorable, but died</td>
<td>Improvement, but died of unspecified cause Postmortem diagnosis, although previously detected in transbronchial biopsy, but not identified</td>
</tr>
<tr>
<td>Nanno S (15)</td>
<td>2016</td>
<td>Japan</td>
<td>51M</td>
<td>Hormographiella aspergillata</td>
<td>Histology, culture</td>
<td>SMD-EB; Cord HSCT</td>
<td>Small intestine, lung and brain</td>
<td>LAmB + caspo</td>
<td>Fatal</td>
<td></td>
</tr>
<tr>
<td>Lim DS (16)</td>
<td>2017</td>
<td>Singapore</td>
<td>1 M</td>
<td>Earliella scabrosa</td>
<td>Histology, culture</td>
<td>Aplastic anemia emboli (multiple purpuric skin lesions), disseminated (pulmonary nodules)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Fatal</td>
<td></td>
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<td>Godet C (17)</td>
<td>2017</td>
<td>France</td>
<td>36M</td>
<td>Hormographiella aspergillata</td>
<td>Histology, PCR</td>
<td>AML, Cord HSCT</td>
<td>Lung nodule</td>
<td>Voriconazole, LAmB + Nebulized LAmB</td>
<td>Favorable</td>
<td>Surgical resection</td>
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<tr>
<td>Fernández-Cruz A (this study)</td>
<td>2017</td>
<td>Spain</td>
<td>33M</td>
<td>Inonotus spp</td>
<td>Histology, culture</td>
<td>ALL</td>
<td>Lung nodule, skin</td>
<td>LAmB+vori Surgery Micafungin</td>
<td>Favorable</td>
<td>Breakthrough while on micafungin</td>
</tr>
</tbody>
</table>

*ALL, acute lymphoblastic leukemia; AlloHSCT, allogenic hematopoietic stem cell transplantation; AmB, amphotericin B deoxicolate; AML, acute myeloblastic leukemia; HL, Hodgkin lymphoma; HSTC, hematopoietic stem cell transplant; LAmB, liposomal amphotericin B; MDS, myelodysplastic syndrome.
References


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