Case Report

Disseminated phaeohyphomycosis due to *Ochroconis gallopavum* in the setting of advanced HIV infection

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Disseminated phaeohyphomycosis is a rare and typically fatal infection caused by members of the dematiaceous fungi, and occurs almost universally in the setting of immunocompromise. We herein report a case of systemic phaeohyphomycosis caused by *Ochroconis gallopavum* in a patient with advanced HIV disease. A possible risk factor for this infection in our patient was heavy marijuana use. This case highlights both the diagnostic and management challenges posed by these infections. To our knowledge, this is the first reported case of disseminated phaeohyphomycosis due to *Ochroconis gallopavum* in a patient with HIV.

**Keywords** dematiaceous fungi, HIV, immunodeficiency, phaeohyphomycosis, systemic mycoses

Introduction

Phaeohyphomycosis constitutes an invasive tissue infection caused by dematiaceous, or black, moulds. While dematiaceous fungi are ubiquitously distributed throughout the environment, they infrequently cause disease in humans, and almost universally in the setting of compromised host immunity. *Ochroconis gallopavum* is a rare cause of phaeohyphomycosis in humans, with only 15 documented cases to date. Of the previously reported cases, 14 occurred in individuals with evidence of immunosuppression, though to our knowledge, this case report is the first to describe systemic *O. gallopavum* infection in an HIV-infected person. We herein provide a brief topical overview of human *O. gallopavum* infections, and describe the diagnostic and therapeutic challenges commonly encountered in the management of systemic phaeohyphomycosis.

Case report

A 28-year-old native Canadian man presented to the emergency room with a 4-week history of worsening cough productive of green sputum, exertional dyspnea, fever, sweats, non-bloody diarrhea, persistent left groin pain, and a 40-lb weight loss. He also complained of a 2 day history of left anterior pleuritic chest pain.

Past medical history was notable for HIV infection diagnosed 4 years earlier. He had had irregular follow-up and had received no prophylaxis or anti-retroviral therapy. His last known CD4 count from 7 months prior to presentation was 294/µl. His HIV viral load was unknown. He had a history of heavy alcohol and marijuana use, took no regular medications, had no drug allergies, and smoked cigarettes occasionally.

Physical examination was notable for fever (temperature 38.6°C), tachycardia (HR 103), and exertional hypoxia (oxygen saturation 88% on room air). Blood pressure was 115/70 mmHg with no pulsus paradoxus. Chest examination was remarkable for coarse rales in the right middle lobe (RML) distribution and diffuse wheezes. Examination of the head and neck, precordium, abdomen, and skin revealed no abnormalities. Neurologically, the patient was intact. Musculoskeletal...
exam revealed decreased range-of-motion of the left hip, and diminished weight-bearing capacity.

Initial blood laboratory investigations revealed a total leukocyte count of $21 \times 10^9/l$ with a neutrophil count of $20 \times 10^9/l$. Hemoglobin was 120 g/l and platelets were $632 \times 10^9/l$. Serum electrolytes were normal, but the patient’s serum creatinine level was elevated at $131 \, \mu$mol/l. Liver profile revealed an elevated alkaline phosphatase of 369 U/l, but was otherwise normal. The serum lactate dehydrogenase level was 216 U/l, and his cardiac enzymes were within normal range. His electrocardiogram revealed diffuse ST elevation with PR elevation in AVR (Fig. 1A). Chest radiograph was notable for patchy bilateral opacities, most prominent in the RML distribution (Fig. 1B).

The patient was admitted with a diagnosis of community-acquired pneumonia, pericarditis, as well as left hip pain and diarrhea of unclear origin. He was started on ceftriaxone and azithromycin for typical causes of community-acquired pneumonia and treatment doses of trimethoprim-sulfamethoxazole for possible *Pneumocystis jiroveci* pneumonia (PCP) along with fluconazole prophylaxis. He was given indomethacin for his pericarditis. Blood and urine cultures were taken, and sputum was sent for acid-fast bacilli (AFB), PCP, and culture and sensitivity (C&S), all of which were negative. A transthoracic echocardiogram revealed a left ventricular ejection fraction of $>60\%$ with no evidence of pericardial effusion. Stool studies for *Clostridium difficile*, ova and parasites, and C&S were negative.

The patient remained febrile and achieved only minimal subjective improvement with the above interventions. CD4 count from admission was 79/μl. Repeat chest radiograph on day 6 of admission showed worsening bilateral airspace disease (Fig. 1C). A computed tomography (CT) of the chest confirmed panlobar consolidation with significant parenchymal destruction (Fig. 1D). A CT abdomen revealed a complex collection in the left obturator internus which tracked into the left hip joint causing an effusion (Fig. 1E). Because of the deterioration in the patient’s respiratory status, he was switched from ceftriaxone to piperacillin-tazobactam, and bronchoscopy was arranged. At bronchoscopy on day 8 of admission, frank pus was noted in the airways, and bronchoalveolar lavage (BAL) washings were sent for AFB, C&S, and KOH preparation with fungal culture.
On day 8 of admission, the sputum culture from day 6 was positive for heavy growth of *Aspergillus* species. In addition, the KOH of BAL fluid revealed hyaline, septate hyphae, and the transbronchial biopsy specimen also noted fungi with hyphae and granulomatous inflammation (Fig. 1F,1G). Ultrasound-guided drainage of the hip abscess yielded purulent material, which also revealed hyaline, septate hyphae on KOH preparation.

The patient was started on oral voriconazole 200 mg BID for invasive pulmonary aspergillosis and antibiotics were discontinued. The patient defervesced and achieved moderate clinical improvement with voriconazole. However, on day 13 of admission, his fever recurred. At the same time, culture of the BAL fluid revealed hyaline, septate hyphae on KOH preparation. Inoculated media were examined weekly for growth. At 1 week, moderate growth of a dry, flat, brown-black fungus with diffusible brown pigment was noted on pyruvate and Leonian’s agar up to 45°C. No growth was observed on cycloheximide or benomyl agar, nor was there growth on Leonian’s agar at 52°C. Microscopically, branched, hyaline septate hyphae were noted, with clavate, 2-celled, smooth, thin-walled conidia with septal constriction and frilled denticles. Differentiation from other species of *Ochroconis* was based on the presence of clavate, asymmetric, septate conidia, lack of growth on cycloheximide and benomyl agar, and growth tolerance of temperatures up to 45°C.

**Discussion**

Phaeohyphomycosis refers to a local or systemic tissue infection caused by members of the dematiaceous, or black, fungi. *Ochroconis gallopa* (previously named *Dactylaria gallopava*) is one such species, and is a rare cause of phaeohyphomycosis in humans. The case reported herein highlights both the diagnostic and management challenges posed by these infections.

Dematiaceous fungi are widely distributed in the environment, isolated often from soil and wood, and are found worldwide [1]. They are a rare cause of disease in humans, with one population-based surveillance study in San Francisco reporting an incidence of black mould infection of 1 case per million per year [2]. However, the number of reported cases has increased over the past decade [3]. Altered host immunity in the form of depressed cell-mediated immune function is perhaps the largest contributor to the rising incidence [3,4], with phaeohyphomycosis caused by *Ochroconis* spp. occurring almost exclusively in the immunocompromised [5]. Documented risk factors for phaeohyphomycosis include hematologic malignancy, bone-marrow or solid-organ transplantation, AIDS, agranulocytosis, diabetes mellitus, steroid use, and chronic granulomatous disease [1,3,5,6]. Of the 15 reported cases of human *O. gallopava* infection to date, eight occurred in transplant recipients [5,7–13], 5 in those with hematologic malignancies [14–18], one in a patient with pemphigus [19], and one in a healthy individual with a significant environmental exposure history [20] (Table 1). Dematiaceous moulds other than *O. gallopava* have been reported in patients with underlying HIV infection and include *Hormonema dematioides* [21], *Scytalidium dimidiatum* [22], and *Scedosporium prolificans* [23].

In our patient, another possible risk factor for disseminated phaeohyphomycosis was heavy marijuana use. Marijuana leaves are known to be contaminated with fungal spores [24], and marijuana smoking has been documented to be a risk factor for invasive aspergillosis in a variety of immunocompromised hosts [25–27]. Specific counseling of patients with depressed
cell-mediated immunity or neutropenia who use street-grade marijuana for recreational or medicinal purposes may therefore be indicated. From a single random sample of street-grade marijuana in Toronto, we were able to culture several species of potentially pathogenic fungi including *Scopulariopsis* spp., *Penicillium* spp., *Cladosporium* spp., and *Ulocladium* spp. (unpubl.data).

While we were unable to isolate *O. gallopa* from this single sample, it is reasonable to believe that this species may also contaminate street-grade marijuana. Substantiation of this hypothesis through a larger prevalence series would be of interest.

Phaeohyphomycosis has been attributed to over 100 species and 60 genera of dematiaceous fungi [3]. There are 4 clinical classifications of phaeohyphomycosis: superficial, cutaneous, subcutaneous, and systemic, the latter of which occurred in our patient. Inhalation of conidia with subsequent dissemination is thought to be the pathogenesis of systemic disease1. Dematiaceous fungi are particularly neurotropic, and CNS phaeohyphomycosis is a common systemic form [3]. Involvement of the lungs, endocardium, bones, joints, eyes, and gastrointestinal tract have all been reported. Amongst cases of disseminated disease, documented fungemia occurs frequently [3]. Our patient likely had involvement of the lungs, pericardium, joints, and CNS. Involvement of his gastrointestinal tract was also a possibility, given his diarrhea.

The diagnosis of phaeohyphomycosis is challenging due to the rarity of disease and ubiquity of causative

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### Table 1  REPORTED CASES OF *OCHROCONIS GALLOPA* INFECTION IN HUMANS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Risk factor</th>
<th>Site of involvement</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>This report</td>
<td>28</td>
<td>M</td>
<td>Advanced HIV, CD4 79 cells/μl</td>
<td>Disseminated: Lungs, left hip joint, brain</td>
<td>Voriconazole 200 mg BID × 7d, then 300 mg BID × 9d + Caspofungin 50 mg OD × 9d 5FC × 4 mos</td>
<td>Died</td>
</tr>
<tr>
<td>[14]</td>
<td>58</td>
<td>F</td>
<td>AML</td>
<td>Subcutaneous nodules</td>
<td>None</td>
<td>Survived</td>
</tr>
<tr>
<td>[15]</td>
<td>62</td>
<td>M</td>
<td>CLL</td>
<td>Disseminated: Lungs, liver, kidney, brain</td>
<td>Surgery (craniotomy + resection), Amphotericin B 0.5 mg/kg + 5FC 150 mg/kg × 2 wks</td>
<td>Died</td>
</tr>
<tr>
<td>[16]</td>
<td>60</td>
<td>M</td>
<td>LBCL</td>
<td>Cerebral abscess</td>
<td>Amphotericin B 1 mg/kg/d + one of 5FC 8 g/d, Itraconazole 200 mg/d, or Terbinafine 250 mg/d × 4 mos</td>
<td>Died</td>
</tr>
<tr>
<td>[17]</td>
<td>66</td>
<td>F</td>
<td>CLL</td>
<td>Disseminated: Brain, Lungs, Femoral Mass</td>
<td>Fluconazole 400 mg/d + intravitreal Amphotericin B 0.05 mg/ml × 2, then 0.2 mg/ml × 1, followed by Itraconazole 200 mg BID</td>
<td>Died</td>
</tr>
<tr>
<td>[18]</td>
<td>69</td>
<td>M</td>
<td>CLL</td>
<td>Endophthalmitis</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>[7]</td>
<td>30</td>
<td>M</td>
<td>Heart Transplant</td>
<td>Pulmonary nodule</td>
<td>Amphotericin B 0.7 mg/kg (811 mg total)</td>
<td>Survived</td>
</tr>
<tr>
<td>[8]</td>
<td>46</td>
<td>M</td>
<td>Heart Transplant</td>
<td>Cerebral abscess</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>[13]</td>
<td>58</td>
<td>M</td>
<td>Heart Transplant, IDDM</td>
<td>Pulmonary nodule</td>
<td>Itraconazole 200 mg BID × 15 wks + Amphotericin B 400 mg total over 7d</td>
<td>Survived</td>
</tr>
<tr>
<td>[9]</td>
<td>68</td>
<td>M</td>
<td>Liver Transplant</td>
<td>Pulmonary abscesses</td>
<td>Amphotericin B (colloidal) 8.5 g total + 5FC × 4 wks, then Itraconazole 200 mg OD × 1 yr</td>
<td>Survived</td>
</tr>
<tr>
<td>[5]</td>
<td>63</td>
<td>M</td>
<td>Liver Transplant</td>
<td>Disseminated: Brain, lungs</td>
<td>Surgery (craniotomy), Amphotericin B 1 mg/kg × 10d, then Itraconazole 400 mg OD</td>
<td>Died</td>
</tr>
<tr>
<td>[10]</td>
<td>58</td>
<td>F</td>
<td>Single-lung Transplant</td>
<td>Pulmonary nodule</td>
<td>Amphotericin B 620 mg total over 2d, then Itraconazole 300 mg TID × 8 mos</td>
<td>Survived</td>
</tr>
<tr>
<td>[11]</td>
<td>32</td>
<td>F</td>
<td>Single-lung Transplant</td>
<td>Shoulder joint abscess + enhancing lesions right frontal &amp; parietal lobes</td>
<td>Surgery (I&amp;D shoulder), Amphotericin B 7.5 g over 22d + 5FC 1500 mg TID × 14d, then Itraconazole 200 mg BID</td>
<td>Survived</td>
</tr>
<tr>
<td>[12]</td>
<td>13</td>
<td>M</td>
<td>Renal Transplant</td>
<td>Disseminated: Brain, lungs, spleen</td>
<td>Amphotericin B + Itraconazole, then Voriconazole</td>
<td>Died</td>
</tr>
<tr>
<td>[19]</td>
<td>68</td>
<td>M</td>
<td>Pemphigus</td>
<td>Pulmonary cavity</td>
<td>Liposomal Amphotericin B 50–100 mg/d × 1 mos, then Itraconazole × 1 yr</td>
<td>Survived</td>
</tr>
<tr>
<td>[20]</td>
<td>38</td>
<td>M</td>
<td>Wood pulp worker</td>
<td>Pulmonary nodules</td>
<td>Surgery (right lobectomy), Itraconazole × 6 mos</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; LBCL, large B-cell lymphoma; 5FC, flucytosine; I&D, incision and drainage; IDDM, insulin-dependent diabetes mellitus.
organisms, which are often considered laboratory contaminants. Disease, when it occurs, tends to be non-specific with an insidious onset. Currently, there are no commercially available molecular techniques that can rapidly and reliably diagnose these infections [6], thus, culture and microscopic exam remain the gold standard for diagnosis. Macroscopically, dematiaceous fungi form dark grey to black, heaped, velvety colonies on Sabouraud agar [1]. *O. gallopava*um is tolerant of temperatures up to 45°C, and fails to grow on benomyl or cycloheximide agar. Microscopically, they have an irregular, toruloid hyphal structure, with yeast-like forms as well [1]. Microscopically, *O. gallopavum* um has characteristic two-celled, clavate, nearly hyaline conidia, and thick-walled brown hyphae. In tissue, the Masson-Fontana melanin-specific stain permits the detection of the brown hyphal walls typical of dematiaceous fungi. As illustrated by our case, morphology can be non-specific, and dematiaceous fungi can resemble hyaline, septate moulds, such as *Aspergillus*, using routine histopathology fungal stains, leading to inappropriate empiric therapy. This emphasizes the importance of Masson-Fontana staining to distinguish between hyaline and dematiaceous fungi, which was not performed in this case. In addition, faster growing species such as *Aspergillus* can dominate a culture and obscure the true pathogen. In the case described, *Aspergillus* was a likely colonizer of the respiratory tree, and was probably non-invasive, although invasive aspergillosis cannot be ruled out completely.

Management of phaeohyphomycosis is challenging due to a lack of evidence around treatment strategies and the high mortality rate, which in two large series, approached 80% [3,6]. To date, there are no published trials of pharmacotherapy for phaeohyphomycosis. Amphotericin B, which is the historical first-line therapeutic agent, has shown limited success in systemic phaeohyphomycosis, but remains the drug-of-choice for life-threatening disease [1,3,4]. Itraconazole has shown the most consistent and potent *in vitro* activity against dematiaceous fungi [28], has been used successfully in cutaneous and subcutaneous infection, and is the first line agent for treatment of non-life-threatening disease [1,3,4]. Newer tertiary azoles, such as voriconazole, are potent with broad-spectrum *in vitro* activity against dematiaceous fungi [29], though clinical experience is extremely limited. Among the cases of human *Ochroconis* infection, only two were treated with voriconazole, and both had fatal outcomes (Table 1). However, these drugs achieve excellent CSF and tissue concentrations [30], and therefore hold promise in the management of phaeohyphomycosis. Echinocandins, such as caspofungin, demonstrate much lower *in vitro* activity than either itraconazole or tertiary azoles [31], and again clinical experience is limited in the setting of phaeohyphomycosis [1,3,6]. Their role in the treatment of these types of infections remains unclear [3,31]. While terbinafine demonstrates significant *in vitro* activity against dematiaceous fungi [32], its clinical successes have been limited to cases of cutaneous rather than systemic phaeohyphomycosis [33,34]. There is no single agent which shows clinical superiority in the management of systemic phaeohyphomycosis, and combination therapy confers no mortality benefit [3,6].

In summary, systemic phaeohyphomycosis is a rare but deadly disease in humans caused by dematiaceous fungi. The case of human *O. gallopava*um infection in an HIV-positive person reported herein, highlights the diagnostic and management challenges presented by phaeohyphomycosis, and underscores its grave prognosis. Isolation of a black mould from a patient specimen should be considered seriously, particularly in the setting of known defects in cell-mediated immune function. Current treatment options are limited, and there is a dire need for empiric evidence surrounding therapeutic strategies.

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**References**