CASE REPORT

Double invasive fungal infection due to dematiaceous moulds in a renal transplant patient

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SUMMARY

Alternaria and *Verruconis* are two dematiaceous moulds that occasionally cause disease in immunocompromised hosts. We present the case of a 58-year-old man with history of deceased donor renal transplantation 14 months prior, who presented with fevers and cough. He was found to have right upper lobe pneumonia and a non-healing eschar of his right knee. Dematiaceous fungi grew from bronchoalveolar lavage (BAL) and was sent to reference lab for identification. Meanwhile, the eschar on his right knee was biopsied and grew *Alternaria* spp. Pathology was consistent with invasive mould infection and he was treated as having disseminated *Alternaria* infection with voriconazole and amphotericin B lipid complex. Later on, the dematiaceous mould from a BAL specimen was identified as *Verruconis gallopava*. The patient was discharged on voriconazole awaiting minimal inhibitory concentrations for *V. gallopava* but was readmitted 2 days later with high fevers and died from acute respiratory failure.

BACKGROUND

Alternaria and *Verruconis* spp are dematiaceous fungi or phaeohyphomycosis. They are also known as pigmented fungi due to the presence of melanin in their cell wall. More than a 100 genus have been associated with human disease. Though most infections are non-invasive (onychomycosis, superficial cutaneous infection and chronic allergic fungal sinusitis) and rarely fatal, phaeohyphomycosis can lead to invasive fungal infections (IFIs) including skin and subcutaneous disease, pneumonia, central nervous system disease, fungaemia and multiorgan disseminated disease. This group of organisms has gained notoriety since 2012 when a particular species of this group, *Exserohilum rostratum*, was found to be the aetiological agent of the large outbreak of fungal meningitis associated with contaminated methylprednisolone injections.¹ These infections, though described in immunocompetent hosts, occur to much higher degree in the immunocompromised hosts.^{2,3} We present herein a case of 58-year-old renal transplant recipient who presented with invasive disease caused by two different dematiaceous fungi: *Alternaria* spp and *Verruconis gallopava*.

CASE PRESENTATION

A 58-year-old Filipino man with a medical history of hypertension, diabetes mellitus, latent tuberculosis therapy on immigration 20 years ago,

end-stage renal disease status post deceased donor kidney transplantation on immunosuppression with tacrolimus (6 mg po two time a day), mycophenolate mofetil (360 mg in AM and 180 mg in PM) and low-dose prednisone (5 mg po daily) was admitted for fever and right upper lobe consolidation and pneumonia. He reported recent travelling to the Philippines, where he was hospitalised and diagnosed with community-acquired pneumonia 4 days after arrival. He was treated with cefepime and ciprofloxacin and reports that after 4 days of no improvement, he decided to come back to the USA and presented to our emergency department. His admission labs were notable for leucopaenia, anaemia, creatinine at baseline of 1.93 mg/dL, C reactive protein of 389 mg/L and erythrocyte sedimentation rate of >120 mm/h. A CT scan of the chest was obtained and showed extensive dense consolidation of the right upper lobe with associated lucencies in the posterior segment of the right upper lobe consistent with developing cavitation (figure 1). Shortly after admission and empirical intravenous antibiotics (vancomycin and piperacillin/tazobactam), a bronchoscopy was performed and showed diffusely edematous tracheobronchial tree with multiple mucus plugging. The bronchoalveolar lavage (BAL) cell count was non-specific and cytomegalovirus (CMV) PCR was negative. Bronchial biopsy pathology showed necroinflammatory debris with visualised fungal hyphae. Fungal cultures grew moderately dematiaceous mould unable to be identified by MALDI-TOF and was sent to a reference lab for final identification (figures 2 and 3). The patient was empirically started on voriconazole (po 6 mg/kg for two doses followed by 4 mg/kg thereafter) for presumed IFI. His CMV PCR in blood was positive with 1310 copies/mL. He was treated with valganciclovir (po 450 mg daily adjusted to his renal function) with gradual reduction of his immunosuppression to tacrolimus 0.5 mg po daily and stopping mycophenolate mofetil. Meanwhile, he was found to have an eschar on his right knee that developed following a gardening injury 4 months prior per his reports. This was biopsied and showed numerous fungal elements within ulceration, scale and crust of the epidermis, consistent with invasive mould infection. Fungal cultures grew *Alternaria* spp (figure 4). At this point, patient experienced two distinct episodes of acute shortness of breath requiring additional oxygen and transfer to the intensive care unit where his antifungal regimen was escalated with

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Figure 1 CT scan of the chest showing extensive dense consolidation of the right upper lobe (A and B) with associated lucencies in the posterior segment of the right upper lobe consistent with developing cavitation (arrow head in panel A).

the addition of amphotericin B lipid complex. No clear aetiology for these acute events could be identified. He was then de-escalated to voriconazole monotherapy and was stable for about a week before discharge. His BAL cultures later were identified as *V. gallopava* and he continued voriconazole on discharge while awaiting minimal inhibitory concentrations (MICs) of *V. gallopava*.

OUTCOME AND FOLLOW-UP

He came back 2 days later with high fevers and respiratory failure. He passed away soon after electing comfort care. At readmission, his serum CMV PCR was not detectable and fungal blood cultures were negative. This was thought to be

due to his recently diagnosed fungal pneumonia as repeat CT scan of the chest was showing similar to slightly progressing consolidation, though autopsy was not performed to confirm cause of death.

DISCUSSION

Dematiaceous moulds have been recognised as causative of various human infections, especially in the immunocompromised hosts.²⁻⁴ Less commonly implicated in human disease, phaeohyphomycosis constitute about 2.6% of all IFIs in patients who had transplants.² Solid organ transplant recipients seem to be at increased risk, especially lung transplants. Infection sites vary, and environmental fungi isolated from immunocompromised hosts are potentially pathogenic. *Alternaria*

Figure 2 Sabouraud's dextrose agar showing darkly pigmented growth of *Verruconis gallopava*. Note the dark discolouration of the agar as well.

Figure 3 Lactophenol cotton blue-stained smear showing the microscopic characteristic of *Verruconis gallopava*. Note the two-celled smooth-walled conidia at the tip of conidiophores.

Figure 4 Lactophenol cotton blue smear showing the microscopic characteristics of *Alternaria* spp smear. Note the prominent, multicelled macroconidia.

genus are melanised hyphomycetes containing several species. They have been described in over 210 human cases since 1933,⁵ mostly associated with hypersensitivity reactions⁶ and infections in solid and stem-cell transplant recipients.⁷ Treatment is often challenging and depends largely on the infection site. Most reported therapies for cutaneous and subcutaneous tissue infections due to *Alternaria* spp included a combination of local interventions or steroids reduction and use of different antifungals (amphotericin B, different azoles and terbinafine). Itraconazole is the antifungal mostly used for this indication since 1990.⁵ *V. gallopava* is a newly recognised mould. Previously part of the *Ochroconis* genus, it is now a separate genus owing to its thermotolerance.⁸ Reports of *V. gallopava* infections are not numerous. Jennings *et al* published a case of endovascular and cardiac infection with dissemination following renal transplantation with unfavourable outcome.⁸ Another report of *V. gallopava* published in 2015 describes necrotising pulmonary infection in an immunocompetent patient with clearance failure despite multiple courses of antifungals stretching over >5 years.⁹ These reports emphasise the aggressive nature of infection when caused by *V. gallopava*. MIC breakpoints are not yet available for this phaeohyphomycete, but ranges have been reported as follows: amphotericin B 0.125–4.0 mg/L, anidulofungin 0.016–0.25 mg/L, caspofungin 0.25–1.0 mg/L, fluconazole 4–>64 mg/L, flucytosine 0.125–>16 mg/L, itraconazole <0.016–>16 mg/L, posaconazole <0.016–0.25 mg/L and voriconazole 0.125–8 mg/L.¹⁰ Our isolates' MICs fell into these ranges and are reported in table 1. Our isolate's MIC to isavuconazole, a novel triazole antifungal, is the first reported in the medical literature. Our choice of continuing voriconazole was largely based on

Table 1 *V. gallopava* isolate MICs to various antifungals

Antifungal	MIC (mg/L)
Fluconazole	>64
Itraconazole	0.5
Posaconazole	0.5
Voriconazole	1
Isavuconazole	16

MIC, minimal inhibitory concentration; *V. gallopava*, *Verruconis gallopava*.

Learning points

- ▶ Invasive dematiaceous moulds are increasingly reported pathogens in human. They cause a broad spectrum of diseases, especially in immunocompromised and transplanted hosts.
- ▶ Clinicians should have a low suspicion threshold and cultures growing these moulds should be interpreted with caution before being labelled as contaminants.
- ▶ Even though they are still considered rare infections, it is possible to have two phaeohyphomycetes simultaneously infecting a patient, as described in our case.
- ▶ Treatment is often challenging and relies largely on source control when possible. Most frequently used antifungals are fluconazole, voriconazole, posaconazole and amphotericin B owing to relatively low MICs, though no clear breakpoints are available to guide therapy.
- ▶ Outcome depends on prompt source control and antifungal initiation, although *Verruconis gallopava* seems to be very challenging to treat.

Alternaria literature discussed above, as the literature for *V. gallopava* was scarce. Though MICs for our *Alternaria* isolate were not available, reported voriconazole MICs in published literature were low and clinical outcomes were favourable. We had planned on revising therapy on follow-up based on clinical status and MICs.

Contributors GEH and MN: took part in caring for and treating patient with the infectious diseases department. EP: is head of the microbiology lab and offered great help in identifying the different molds. All authors: contributed in this manuscript through writing and editing.

Competing interests None declared.

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REFERENCES

- Kauffman CA, Pappas PG, Patterson TF. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med* 2013;368:2495–500.
- McCarty TP, Baddley JW, Walsh TJ, *et al*. Phaeohyphomycosis in transplant recipients: Results from the Transplant Associated Infection Surveillance Network (TRANSNET). *Med Mycol* 2015;53:440–6.
- Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: current epidemiological trends. *Clinical Infectious Diseases* 2006;43:S3–14.
- Santos DW, Camargo LF, Gonçalves SS, *et al*. Melanized fungal infections in kidney transplant recipients: contributions to optimize clinical management. *Clin Microbiol Infect* 2017;23:333.e9–14.
- Pastor FJ, Guarro J. *Alternaria* infections: laboratory diagnosis and relevant clinical features. *Clin Microbiol Infect* 2008;14:734–46.
- Cantani A, Ciaschi V. Epidemiology of *alternaria alternata* allergy: a prospective study in 6840 Italian asthmatic children. *Eur Rev Med Pharmacol Sci* 2004;8:289–94.

- 7 Boyce RD, Deziel PJ, Otley CC, *et al.* Phaeohyphomycosis due to *Alternaria* species in transplant recipients. *Transpl Infect Dis* 2010;12:242–50.
- 8 Jennings Z, Kable K, Halliday CL, *et al.* *Verruconis gallopava* cardiac and endovascular infection with dissemination after renal transplantation: case report and lessons learned. *Med Mycol Case Rep* 2017;15:5–8.
- 9 Geltner C, Sorschag S, Willinger B, *et al.* Necrotizing mycosis due to *Verruconis gallopava* in an immunocompetent patient. *Infection* 2015;43:743–6.
- 10 Seyedmousavi S, Samerpitak K, Rijs AJ, *et al.* Antifungal susceptibility patterns of opportunistic fungi in the genera *Verruconis* and *Ochroconis*. *Antimicrob Agents Chemother* 2014;58:3285–92.

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