CASE REPORT

A masquerader? *Paecilomyces* must be distinguished from *Penicillium* in fungal keratitis: a report of two contrasting cases

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SUMMARY

We describe the clinical outcomes of two contrasting cases of fungal keratitis due to *Paecilomyces* spp. The first case involving a 58-year-old woman was complicated by an initial laboratory misidentification as *Penicillium* and consequently a delay in treatment with an optimised antifungal regimen. The patient had a protracted clinical course that required a total of four penetrating keratoplasties. However, an accurate diagnosis was promptly made in the second case, a 46-year-old woman, which resulted in a satisfactory outcome after penetrating keratoplasty. Our principal aim was to highlight a diagnostic challenge relating to the accurate microbial identification of *Paecilomyces* spp. This can be difficult given its morphological similarity to *Penicillium*, and confusion over the two genera has resulted in misdiagnoses reported previously. Our report aims to raise awareness of this potential laboratory misidentification, which can affect clinical decision-making in guiding antimicrobial therapy.

BACKGROUND

The clinical outcome of corneal ulcers secondary to microbial keratitis is highly variable and can range from mild, transient ocular irritation to loss of the entire eye. These are important entities for clinicians to be aware of as they represent causes of visual loss that are often preventable and treatable with appropriate and timely management. However, identifying the causative organism in cases of infectious keratitis can be extremely challenging.

Fungal keratitis accounts for approximately 9–10% of all infectious keratitis.¹ While subtle clinical findings can help distinguish fungal keratitis from bacterial keratitis, the diagnosis is often unclear from clinical appearance alone. Although cultures can be useful, the positive growth of mere colonising organisms and false-negative culture results for the actual causative microbe can lead clinicians astray. Properly identifying the culprit microbe allows for the selection of effective antimicrobial therapy.

We describe two cases of fungal keratitis secondary to *Paecilomyces* spp, with distinct clinical courses. In the first case, the appropriate management of a *Paecilomyces* infection was delayed by a microbiological misidentification. Specifically, the fungal keratitis from the first patient was initially attributed to *Penicillium* spp. However, a subsequent culture revealed *Paecilomyces* to be the

causative agent. In contrast, *Paecilomyces* was correctly identified without complications in the second case, allowing for the prompt initiation of proper treatment. Prior reports have shown *Paecilomyces* spp to be resistant to polyene antifungals (eg, amphotericin B), highlighting the importance of proper identification and eliciting potential drug sensitivities.^{2,3}

CASE PRESENTATION

Case 1

A 58-year-old woman with a history of contact lens use was referred for a presumed herpes simplex virus (HSV) ulcer of the left eye. She was diagnosed with HSV keratitis 6 months prior to referral and was clinically unresponsive on a regimen of valacyclovir and topical corticosteroids. Her best-corrected visual acuity was 20/20 in the right eye and light perception in the left. Slit-lamp examination of the left eye revealed 4+ conjunctival injection with a dense white central corneal infiltrate and a relatively elliptical epithelial defect measuring 6.4 mm×8 mm. The centre of the infiltrate had thinned nearly to a descemetocoele with a small 1 mm×1 mm area of perforation with iris incarceration and a slow leak. The anterior chamber was shallow without hypopyon, and there was no view to the posterior pole.

After gentle corneal swabbings were obtained, and submitted for bacterial and fungal stains and microbiology culture, the site of perforation was glued and covered with a bandage contact lens. The patient was admitted and treated with hourly fortified vancomycin (50 mg/mL) and tobramycin (14 mg/mL) for presumed bacterial keratitis. After 3 days, her vision slightly improved to hand motion. One week after admission, preliminary culture results grew unspecified 'mould', and her antimicrobial regimen was modified empirically to include topical natamycin and oral itraconazole. The culture report indicated the mould to be *Penicillium* spp and her antifungal regimen was continued.

One month after admission, the patient returned with symptoms of increased pain and discharge out of her left eye. Her vision worsened to light perception and the glued area was again perforated. She had expelled her crystalline lens with vitreous wicking to the edges of the bandage lens with a hypopyon inferiorly. The globe had partially collapsed.

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Figure 1 Histopathology of the host cornea in case 1. (A) Low-power view showing acute ulcerative keratitis with perforation. Arrowheads mark perforation site, while arrows indicate a mixture of hypopyon and iris tissue prolapsing through the perforation, with a portion (perhaps artefactually) extending onto the corneal surface (H&E stain, original magnification, $\times 20$). (B) High-magnification view of the area outlined by box in A, demonstrating stromal necrosis/hypopyon at perforation site, with abundant neutrophils (H&E stain, original magnification, $\times 400$). (C) Grocott-Gomori methenamine silver stain showing septated filamentous fungi (arrows; original magnification, $\times 400$).

The patient underwent an emergent therapeutic penetrating keratoplasty (PKP) and anterior vitrectomy. Evidence of fungal ulcerative keratitis was seen on histopathological examination of the corneal button including fungi present in the hypopyon (figure 1). Cultures from a postoperative swab at 2 weeks grew no fungal organisms. The patient continued to receive topical prednisolone, natamycin and oral itraconazole, but returned 6 weeks post-PKP with stromal necrosis in the graft with an inferior endothelial plaque (figure 2).

She underwent another emergent therapeutic PKP with intravitreal injection of amphotericin B ($0.5 \mu\text{g}$ in 0.1 mL). Half of the resected failed graft was sent for histopathological examination, which showed fungal organisms to the edges of the resected corneal button. Fungi could be seen invading the posterior stroma and Descemet's membrane, including a few fungi present in the anterior chamber (figure 3). The other half was submitted for microbial evaluation that included testing for drug sensitivities. One week following the patient's second PKP, the mycology laboratory reported growth of *Paecilomyces*, contradicting the prior reported culture of *Penicillium*. In accordance with susceptibility results that showed resistance to natamycin but susceptibility to voriconazole, she was then

started on an aggressive antifungal regimen that included oral and hourly topical voriconazole (1%).

The patient's clinical course saw further complications over the next year. She had a retinal detachment, which was managed with silicone oil tamponade; she experienced recurrent bouts of fungal endophthalmitis despite multiple intravitreal voriconazole injections, and ultimately underwent pars plana vitrectomy. She was continued on topical and oral voriconazole with minimal topical prednisolone but eventually required two additional PKP's (totalling four). The final corneal button showed acute and chronic stromal keratitis with vascularisation. Of note, there were no fungi seen on histopathology, indicating elimination of the pathogen. To date, she is 24 months out from initial presentation to us. Her graft has remained clear without recurrence in a 10 month follow-up period since her most recent PKP. Her eye remains hypotonous with silicone oil in place. There has been no recurrence of endophthalmitis or retinal detachment. Her best-corrected vision is hand motion.

Case 2

A 46-year-old woman was referred to us with a 1-month history of a corneal ulcer presumably related to contact lens use. Her referring ophthalmologist had ordered a Gram stain, which revealed yeast with pending culture results from corneal swabbings. At the time, she was placed on topical gatifloxacin (0.3%), amphotericin (0.15%), loteprednol, and oral fluconazole. On slit-lamp examination, her right eye was notable for 2+ conjunctival injection, a dense central corneal infiltrate and a $4.7 \text{ mm} \times 4.5 \text{ mm}$ epithelial defect. Additionally, there was a hypopyon present in the anterior chamber. Her best-corrected vision was 20/200 in her right eye and 20/20 in the left. One day after referral to our service, the growth of *Paecilomyces* spp was reported from prior cultures, and the patient was started on topical voriconazole (1%) and oral itraconazole.

Four weeks after presentation to our service, the patient's vision had improved slightly to 20/80 in her right eye. She no longer had a hypopyon, but the dense corneal infiltrate was still present with a smaller epithelial defect. Seven weeks after referral, she returned emergently for increased pain in her right eye. On slit-lamp examination, the epithelial defect measured

Figure 2 Slit-lamp photograph of the left eye of case 1 showing a new inferior infiltrate at the deep corneal stroma and graft-host interface 4 weeks after the first corneal transplantation.

Figure 3 Histopathology of the excised failed graft from case 1. (A) H&E stain demonstrating acute inflammatory cells at the edge of the corneal button. The epithelium is eroded. (The absence of Descemet's membrane at this edge of the button was consistent with artefact, original magnification, $\times 100$). (B) Grocott-Gomori methenamine silver stain showing septated filamentous fungi (arrows), similar in morphology to those seen in the original corneal button (original magnification, $\times 400$).

2.1 mm $\times$ 3.5 mm, but an infiltrate with stromal thinning was noted. When the area of corneal thinning worsened 3 days later, she underwent a therapeutic PKP with a total of 0.2 mL of voriconazole (100 μ g in 0.1 mL) and 0.2 mL of amphotericin B (5 μ g in 0.1 mL) injected into the anterior chamber. Preoperative corneal swabbings and the resected host corneal tissue both grew *Paecilomyces* spp. Histopathological examination of the resected corneal button revealed septated filamentous fungi extending to one edge and also invading Descemet's membrane, with several fungi spilling into the anterior chamber (figure 4). One week post-PKP, the patient's best-corrected vision in the right eye was 20/50. She was continued on topical voriconazole and tobramycin six times a day, alongside oral intracranial, but was weaned off of these antibiotics within 6 weeks of her PKP. She continued to receive topical loteprednol to prevent graft rejection.

The patient is currently over 12 months out from initial presentation to our service. At her most recent visit, best-corrected vision was 20/30 in the right eye, and her graft remains clear to date without evidence of keratitis (figure 5).

DISCUSSION

There are a number of factors that may have contributed to the markedly contrasting clinical courses of these two cases. The first case had more risk factors associated with fungal keratitis, including chronic topical corticosteroid use and pre-existing HSV keratitis.⁴ However, the risk factor identified in case 2 was a history of refractive contact lens wear.⁴ Prior reports have shown that outcomes for *Paecilomyces* infections can be highly variable, despite similar treatment approaches.^{2 3} Both cases progressed to corneal perforation; however, one additional distinguishing aspect was the length of time that elapsed before optimal management for a *Paecilomyces* infection was begun. In our first case, the patient was symptomatic for 6 months prior to referral, and the initial misidentification further delayed treatment with voriconazole by an additional 2 months. In contrast, the patient in the second case was started on voriconazole within 4 weeks of symptom onset. We speculate that the increased delay in proper treatment for the patient in our first case may have contributed to her more complicated clinical course. The microbiological misidentification was a poignant

Figure 4 Histology of excised corneal button from case 2, H&E (A) and Grocott-Gomori methenamine silver (B–D) stains. (A) Low-power view showing acute and chronic ulcerative keratitis, with re-epithelialised portion centrally exhibiting compensatory epithelial thickening. (Only a portion of Descemet's membrane is visible, possibly due to artefactual turning of the tissue, original magnification, $\times 40$.) (B) GMS stain under higher magnification showing filamentous fungi extending to left edge of corneal button and invading deep stroma and Descemet's membrane (d) (original magnification, $\times 100$). (C) Higher magnification of posterior cornea demonstrating filamentous fungi invading Descemet's membrane (d), with several fungi spilling into anterior chamber. Endothelial cell loss is also apparent (original magnification, $\times 400$). (D) Higher magnification showing fungi with septations (arrowhead; original magnification, $\times 600$).

Figure 5 Slit-lamp photograph of the right eye in case 2 with a history of *Paecilomyces* spp keratitis after receiving a therapeutic corneal transplantation. The corneal graft has been clear of keratitis for over 12 months.

realisation when discovered, and important lessons can be learned from it.

The misidentification of *Paecilomyces* as *Penicillium* should not be entirely unexpected. The mycological distinction between the two genera is non-trivial and has been historically controversial among mycologists. Their morphological features are similar enough to have once raised doubts about the need for a generic separation.^{5 6} These two cases bring into light how this subtle academic distinction played a role in the management of our patients.

Paecilomyces and *Penicillium* are both septated, hyphal fungi with specialised sporing structures called conidiophores. In both genera, the conidiophore structure can be strikingly similar in appearance, but subtle morphological differences, if visible, can allow mycologists to distinguish the two (figure 6 for comparison; photos are from unrelated isolates at Washington University microbiology laboratory). Their conidiophores have secondary branches called metulae, from which phialide cells protrude to generate the mitogenic spores (conidia). In exemplar specimens, *Paecilomyces* can be histologically distinguished from *Penicillium* by the shape of their phialide cells. The terminal portion of the phialide cells in *Paecilomyces* appear tapered and slightly more elongated than those belonging to *Penicillium*. However, this hallmark contrasting feature may be challenging to appreciate in certain cases. For instance, the phialide cells of *Paecilomyces lilacinus* can be variable in appearance, with some resembling the shorter cells of *Penicillium* and others being longer, as in the *Paecilomyces* type. Owing to its ambiguous appearance, *Paecilomyces lilacinus* was known as *Penicillium lilacinum* until reclassification in 1974.⁵⁻⁷

Figure 6 Micrographs of *Penicillium* and *Paecilomyces* from unrelated isolates. *Penicillium* spp (A) has broad and then blunted phialids (brackets) with generally circular conidia (arrows). This differs slightly from the tapered phialids in *Paecilomyces* spp (B).

Although subtle, this distinction among genera was pertinent to the initial choice of antifungals for our patients. Whereas *Penicillium* spp is typically sensitive to polyenes (eg, amphotericin, natamycin), *Paecilomyces* spp is notoriously resistant to this class of antifungals.^{2 3} Even though the *Paecilomyces* spp in our first case were mildly sensitive to the itraconazole that we used empirically, optimal care with voriconazole was not initiated until 8 weeks after presentation to our service and was only employed after a second perforation.⁸ While we contend that a delay in recognising the fungal infection and drug optimisation may have contributed to the patient's complicated clinical course, we recognise that outcomes of *Paecilomyces* keratitis are variable and that a number of complications occurred in prior reported cases even when an appropriate antimicrobial regimen was initiated.^{2 3 9-13}

In reviewing our initial case, the first culture identified as *Penicillium* was logged in the laboratory note as 'questionable *Paecilomyces*' at the time of initial reporting. Since this was an internal laboratory note, it was not documented in the electronic medical record, consequently delaying optimal treatment. The misidentification of *Paecilomyces* as *Penicillium* by the microbiology laboratory was not an issue unique to our case. A previously published case of fungal keratitis similarly involved the misidentification of *Paecilomyces* as *Penicillium*, leading to a fungal endophthalmitis requiring three PKPs.¹³ Given the fact that morphological criteria are routinely employed to distinguish these organisms, it is not surprising that this confusion of *Paecilomyces* for other fungal genera has complicated diagnoses as well as the treatment of infections in the eye and elsewhere in the body (eg, in cases of fungal sinusitis).¹⁴

Given the difficulty of treating *Paecilomyces* infections in comparison to the readily responsive nature of *Penicillium*,^{2 15} it is clinically useful for ophthalmologists to be aware of this potential laboratory misidentification. To assist in making the proper diagnosis and avoiding delays in treatment, the following

Learning points

- ▶ Since the identification of *Paecilomyces* spp from fungal cultures is made on the basis of microscopic examination, the similar morphological features it shares with *Penicillium* spp can result in misdiagnoses.
- ▶ Distinguishing *Paecilomyces* from *Penicillium* can be clinically important for properly tailoring antifungal therapy.
- ▶ In circumstances where the exact organismal identification affects clinical decision-making, it may be helpful for the clinician to open discussion with laboratory personnel who may otherwise be removed from key aspects of the case.

measures may be taken: the clinician might open discussion with the mycologist, who is often removed from the clinical history. And while the value of in vitro drug sensitivity analyses remains controversial, it may be prudent to request antifungal susceptibilities for tailoring therapy, especially in cases with a protracted clinical course.

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