

Secondary pseudomonas infection of fungal keratitis following use of contaminated natamycin eye drops: a case series

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Abstract

Aim To report a five case of secondary pseudomonas infection of fungal keratitis following use of contaminated natamycin eye drops.

Methods A retrospective analysis of the course and clinical outcomes of five eyes of five patients with clinical and laboratory-confirmed fungal keratitis species was performed. Clinical worsening despite hourly topical 5% natamycin drops prompted a repeat corneal scraping and microbiological evaluation.

Results The causative fungi for the initial keratitis were *Fusarium* and *Aspergillus* species. All the five specimens obtained from repeat scrapings revealed *Pseudomonas aeruginosa*. The cultures obtained from the natamycin eye drops being used by the patients also grew pseudomonas. On further evaluation, the source of contamination of the natamycin containers was obscure but speculated to be nosocomial, being within the hospital or the pharmacy. All patients had a poor visual outcome with one requiring evisceration because of panophthalmitis, whereas three underwent therapeutic keratoplasty.

Conclusions A high index of suspicion is recommended in all cases of worsening fungal keratitis to identify secondary contamination of antifungal agents with nosocomial infections.

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Keywords: fungal keratitis; pseudomonas; natamycin

Introduction

Fungal keratitis is an important cause of ocular morbidity worldwide. Fungal keratitis accounts for the aetiology in 6–35% of all patients with microbial keratitis in the developed world and from 22 to 50% in the developing world.^{1–6} In southern India, a percentage as high as 42% has been reported.⁵ Filamentous fungi, such as species of *Fusarium* and *Aspergillus*, are the most common isolates.^{2,7}

Pseudomonas species are Gram-negative, aerobic, non-fermentative bacillus frequently found in most hospital environments. They are able to grow in some eye drops (especially quaternary ammonium compounds), saline, and other aqueous solutions.⁸ *Pseudomonas aeruginosa* is the predominant causative agent among Gram-negative organisms causing keratitis.⁹ Here, we analysed the occurrence of secondary pseudomonal infection in five patients with fungal keratitis who had used *P. aeruginosa*-contaminated (confirmed by culture) natamycin eye drops.

Case 1

A 26-year-old male presented with poor vision and pain in his right eye following injury with a sugarcane stick. Ophthalmic examination revealed visual acuities of 6/60 OD and 6/6 OS and a central corneal ulcer measuring 5.5mm × 4.5mm with feathery margins in the right eye. Corneal scraping showed filamentous fungi on a freshly prepared KOH mount and *Fusarium* spp. was cultured from potato dextrose agar (PDA). The patient was treated with 5% natamycin eye drops every hourly. However, on day 4, the ulcer worsened

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clinically. Repeat cultures of corneal scrapings grew *P. aeruginosa*. The natamycin eye drops being used by the patients also grew *P. aeruginosa*. The patient was treated aggressively with topical fortified ceftazidime drops as well as Amphotericin B. However, corneal melting was seen after 1 week and therapeutic keratoplasty was undertaken.

Case 2

A 43-year-old male presented with history of injury to the left eye with paddy husk followed by pain and decreased vision. Examination revealed visual acuity of 4/60 in the left eye with a paracentral corneal ulcer. Corneal scraping showed *Aspergillus flavus* on PDA. Despite treatment with hourly natamycin eye drops, clinical deterioration occurred by day 5. Repeat scraping revealed *P. aeruginosa*. The patient was switched to itraconazole eye drops for the underlying keratitis and hourly Tobramycin for the super added bacterial keratitis. Signs of clinical improvement were evident on the 10th day and by 4 weeks, the keratitis had completely resolved with large paracentral leucomatous opacity.

The clinical profile of all the five patients is summarised in Tables 1 and 2. To avoid the contamination of the drops by the patients themselves, we checked fresh bottles of natamycin drops (five samples chosen randomly from the pharmacy) from the same batch, but the cultures were positive for *P. aeruginosa* in three out of the five patients.

Discussion

Fungal keratitis is an increasing cause of concern. Bacterial coinfection with fungal keratitis has been

documented in the past with prevalence of 20%, occurring more commonly in association with candidiasis.¹⁰ On the basis of an extensive search in the PubMed and Medline databases, however, we believe that ours is the first report of a series of patients with fungal keratitis who developed secondary *P. aeruginosa* infection because of the use of natamycin eye drops contaminated with this bacterium. Microbial contamination of preservative-free eye drops in multiple application containers has been reported in the past, the commonest organism being *Staphylococcus aureus*.¹¹ The answer to the question ‘how did this contamination occur?’ is difficult to explain. The bacterial contamination of the culture plates was thought to be a source. We investigated this possibility by incubating five empty blood culture plates for 48 h as recommended by the International Society of Microbiology.^{12,13} However, these culture plates did not reveal any positive results. The pharmaceutical company that manufactured the drops

Table 2 Sensitivity pattern of Pseudomonas isolates in the five cases Kirby–Bauer disc diffusion method

Drug	Case I	Case II	Case III	Case IV	Case V
Gentamicin	+	–	–	–	+
Tobramycin	+	+	+	+	+
Amikacin	+	+	–	+	–
Ciprofloxacin	+	+	–	+	+
Ofloxacin	–	–	+	–	+
Gatifloxacin	+	–	–	+	+
Ceftazidime	+	+	+	+	+
Cefoperazone	+	+	–	+	+
Netilmicin	+	+	+	+	–
Imipenam	+	+	+	+	+
Meropenam	+	+	+	+	+

Table 1 Clinical profile of the five patients with secondary pseudomonas infection from contaminated natamycin eye drops

Category	Case I	Case II	Case III	Case IV	Case IV
Age in years	26	43	34	38	52
Sex	Male	Male	Female	Male	Female
Initial Fungus isolated	<i>Fusarium</i> spp.	<i>Aspergillus flavus</i>	<i>Fusarium</i> spp.	<i>Fusarium</i> spp.	Undefined hyaline filamentous
Initial treatment (one hourly)	Natamycin	Natamycin	Natamycin	Natamycin	Natamycin
Clinical worsening appreciable (days from natamycin initiation)	4 days	5 days	3 days	4 days	3 days
Timing of repeat scraping	Day 5	Day 6	Day 4	Day 5	Day 4
Organism isolated from repeat scrapings	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>
Antibiotic used for super-infection management	Fortified Ceftazidime	0.3% Tobramycin	Fortified Ceftazidime	0.3% Tobramycin	Fortified Ceftazidime
Visual acuity at presentation	6/60	4/60	5/60	6/36	6/60
Final visual acuity at 4weeks	PL	4/60	PL	No PL	1/60
Additional procedure undertaken	TPK	Nil	TPK	Evisceration	TPK

Abbreviations: *P. aeruginosa*, *Pseudomonas aeruginosa*; PL, perception of light; TPK, therapeutic keratoplasty.

did not report any other similar cases. None of the five patients were immunocompromised or diabetic and none had any bacteraemia as evidenced by negative blood cultures in all of them. The five patients were seen over a period of 4 weeks, in quick succession to each other. This triggered the search to find the cause for such an unusual occurrence and clinical acumen, and a high level of suspicion helped us trace the source to the natamycin eye drops. During the interim period of 4 weeks, natamycin eye drops were prescribed to many other patients as well; however, only the five patients being reported developed infection causing us to believe that contamination occurred during the hospital stay or from the pharmacy. The antibiotic sensitivity of *P. aeruginosa* has been extensively reported in literature.^{14–18} Topical tobramycin, amikacin, ceftazidime, and fluoroquinolones like ciprofloxacin, gatifloxacin, and moxifloxacin have been found to be effective in most of the cases, yet resistance to these have been periodically, although sporadically demonstrated.^{14–18} The susceptibility patterns of our *P. aeruginosa* isolates were similar to those reported in the literature, and no unusual resistance pattern was noted.

Conclusion

In conclusion, a high level of suspicion is recommended in all cases of clinically worsening fungal keratitis. If repeat cultures yield a bacterial element, the culture of the topical antifungal medications being used is essential in management of these cases.

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