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Clinical signs in dematiaceous and hyaline fungal keratitis

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INTRODUCTION

Filamentous fungi are important aetiological agents of keratitis globally.¹ Hyaline hyphomycetes including *Fusarium* and *Aspergillus* spp. are most common, but dematiaceous fungi such as *Curvularia* and *Bipolaris* spp. constitute approximately 20% of cases.²³ Commonly reported signs of fungal keratitis include feathery edges, raised lesions, hypopyon, stromal infiltrates and, less frequently, satellite lesions and ring infiltrates.¹ In dematiaceous cases, reported characteristics include raised lesions and macroscopic pigmentation.⁴⁵ In this report, we analyse clinical signs of fungal keratitis, comparing hyaline and dematiaceous fungi, and the hyaline fungi *Fusarium* and *Aspergillus* spp.

METHODS

Clinical examination and microbiological reports were collected prospectively in a clinical trial setting. Methods for the trial have been described previously.⁶ In brief, eligible cases had evidence of filamentous fungus on Gram stain and/or potassium hydroxide. Scrapings were inoculated onto sheep's blood agar, chocolate agar and potato dextrose agar. Fungal cultures were deemed positive with growth on two media or moderate to heavy growth on one media.

After a positive smear, but prior to any fungal identification, clinical examination was performed and ulcers were assessed for feathery edges, raised lesions, ring infiltrates, keratic precipitates, satellite lesions, endothelial plaque, pigment and absence of corneal sensation. Dated, auditable exams ensure that the observers were masked to fungal identification. We performed backwards stepwise regression in the *R* statistical package (<http://www.R-project.org>; Vienna, Austria). Briefly, all covariates were included in the initial model, including age and gender. The covariate whose removal resulted in the lowest Akaike's information criterion (AIC) was deleted from the model until the removal of any remaining covariates no longer improved AIC. Contrasts included dematiaceous versus hyaline fungus,

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Competing interests None.

Ethics approval This study was conducted with the approval of the University of California, San Francisco; Aravind Eye Hospital, Madurai, India; Dartmouth-Hitchcock Medical Center, Hanover, NH.

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Fusarium versus non-*Fusarium* spp. isolates, *Aspergillus* versus non-*Aspergillus* spp. isolates and *Aspergillus flavus* isolates versus non-*Aspergillus flavus*. Mixed infections (N=2) were excluded from the analysis. Ethical approval was obtained from the University of California, San Francisco, and Aravind Eye Care System Institutional Review Boards.

RESULTS

Of the 120 cases enrolled into the trial, 101 had positive cultures. Of these, 37 (37%) were dematiaceous and 64 (63%) were hyaline. Of the hyaline fungal isolates, 44 (69%) were *Fusarium* spp. and 17 (27%) were *Aspergillus* spp., of which 11 isolates were *A. flavus*. Seventy-four cases (73%) had feathery edges: 28 dematiaceous (76%) and 46 hyaline (72%). Forty-three cases (43%) had a hypopyon at presentation: 16 dematiaceous (43%) and 27 hyaline (42%). Forty cases (40%) had a raised lesion: 20 dematiaceous (71%) and 20 hyaline (31%). Six cases (6%) were pigmented, all of which were dematiaceous (figure 1).

Table 1 lists the optimal multivariate models. Dematiaceous fungi were more likely to have a raised lesion than hyaline fungi ($p=0.007$). *Aspergillus* spp. were more likely to have a ring infiltrate ($p=0.042$), and *Fusarium* spp. were less likely to have a raised lesion or an endothelial plaque.

DISCUSSION

Clinical signs have been previously reported as characteristic of fungal keratitis. Here, feathery edges and hypopyon were commonly found in both dematiaceous and hyaline fungal keratitis, with no difference between the two groups. Raised lesions were predictive of dematiaceous fungus, and as expected, all pigmented cases were dematiaceous. No dematiaceous case had a ring infiltrate, consistent with previous reports where this was a rare sign.⁴ Ring infiltrate was predictive of *Aspergillus* spp. and *A. flavus* in particular. Within hyaline cases, raised lesions and endothelial plaques were more common in *Aspergillus* spp. and less common in *Fusarium* spp.

This study suggests that clinical signs can distinguish between hyaline and dematiaceous, and even the genus and species of fungi. Because of the delay in confirming species identification by culture, these clinical signs may help with guiding initial diagnosis and treatment decisions.

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Figure 1.

(A) *Fusarium* spp. keratitis showing neither a ring infiltrate nor a raised lesion. (B) *Aspergillus flavus* keratitis showing a ring infiltrate and feathery borders. (C) Dematiaceous fungal keratitis showing macroscopic pigmentation and a raised lesion.

Table 1

Backwards stepwise regression model, using Akaike's information criterion for clinical signs predicting hyaline fungus (vs dematiaceous); *Fusarium* spp., *Aspergillus* spp. and *Aspergillus flavus* (vs all other fungi)

	<u>Hyaline vs dematiaceous</u>		<u><i>Fusarium</i> spp.</u>		<u><i>Aspergillus</i> spp.</u>		<u><i>A. flavus</i></u>	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Feathery edges	–	–	0.40 (0.13 to 1.24)	0.11	–	–	–	–
Raised lesions	0.28 (0.11 to 0.70)	0.0065	0.20 (0.072 to 0.55)	0.002	2.64 (0.74 to 9.35)	0.13	3.27 (0.77 to 13.57)	0.10
Ring infiltrates	–	–	–	–	14.03 (1.10 to 178.66)	0.042	23.96 (1.67 to 340.58)	0.019
Endothelial plaque	–	–	0.17 (0.031 to 0.97)	0.046	4.73 (0.88 to 25.55)	0.071	–	–
Age	–	–	–	–	0.97 (0.93 to 1.01)	0.14	0.95 (0.90 to 0.99)	0.041