 10.1111/j.1469-0691.2004.00909.x

Involvement of *Fusarium* spp. in fungal keratitis

I. Dóczi[1], T. Gyetvai[2], L. Kredics[3] and E. Nagy[1,2]

Department of [1]Clinical Microbiology and [2]Opthalmology, Faculty of Medicine, University of Szeged and [3]Hungarian Academy of Sciences and University of Szeged, Microbiological Research Group, Szeged, Hungary

ABSTRACT

Members of the filamentous fungal genus *Fusarium* are among the agents most frequently causing keratomycosis in humans. *Fusarium* keratitis is most common among agricultural workers in geographical regions with hot, humid, tropical or semi-tropical climates, but can occur more rarely in countries with temperate climates, such as Hungary. Keratitis is usually treated with a topical antifungal agent, sometimes in combination with sub-conjunctival injections and/or antimycotic agents, but therapeutic keratoplasty may be needed for patients whose corneal infection does not resolve. Early and accurate diagnosis, coupled with appropriate antifungal therapy, is crucial for improving the chances of complete recovery.

Keywords Epidemiology, *Fusarium*, keratitis, keratomycosis, risk factors, therapy

Clin Microbiol Infect 2004; 10: 773–776

Keratomycosis is a suppurative, usually ulcerative corneal disease [1]. Infection is exogenous, with the organism entering through the corneal epithelium. The most common filamentous fungi involved in mycotic keratitis are *Fusarium* and *Aspergillus* spp.

Fusarium spp. are found commonly in soil, marine or river environments, and on plants throughout the world. Certain species are plant pathogens, while others are soil saprophytes [2]. However, in recent years they have been reported with increasing frequency as aetiological agents in opportunistic infections [3]. Fusariosis occurs most frequently as a localised infection of the cornea, but the incidence of *Fusarium* spp. among culture-proven cases of fungal keratitis varies between different countries (Table 1). *Fusarium* spp. were the predominant aetiological agents of keratomycosis in many surveys [6–8,10,12,13,17, 20–24,26], while *Aspergillus* spp. [4,11,14–16,18,19] and *Candida* spp. [9,25] predominated in other studies. The species reported most often was *Fusarium solani* [13,17,20,23,26,27], and *Fusarium* keratitis may occur as a mixed infection with bacteria, mainly *Streptococcus* and *Staphylococcus* spp. [13,21,27], or herpes simplex virus [27].

The epidemiological pattern of *Fusarium* keratitis varies from country to country, with less developed, tropical and sub-tropical countries being most affected. Climate seems to play an important role in determining the predominance of certain species in fungal keratitis. Particular regions of different continents, e.g., southern Florida, Ghana and southern India, share similar climatic conditions, which seem to favour the predominance of *Fusarium* spp. [10,12,13,26]. In contrast, keratitis caused by *Fusarium* spp. is rare in European countries with temperate climates: only four cases have been reported from Paris, France in 8 years [9], and only a single case has been diagnosed in Hungary (see below). The incidence of *Fusarium* spp. in mycotic keratitis may also vary with climatic conditions within a single country, as demonstrated by data from different parts of China [6–8], Ghana [10] and India [10–18] (Table 1). Where reported, the proportion of farmers and agricultural workers among patients with mycotic keratitis in these studies was relatively high (16–86%). Male patients were more frequent than females, with male:female ratios of between 1.4:1 and 3.5:1, with

Corresponding author and reprint requests: E. Nagy, Department of Clinical Microbiology, Faculty of Medicine, University of Szeged, Somogyi Béla tér 1, H-6725 Szeged, Hungary
E-mail: nagye@mlab.szote.u-szeged.hu

Table 1. Incidence of *Fusarium* spp. among culture-proven cases of fungal keratitis (based on retrospective studies)

Geographical location	Time period	Total number of mycotic keratitis cases	Number of cases caused by *Fusarium* spp.	Reference
Bangladesh	11 months	51	10 (19.6%)	[4]
Bangladesh	Unknown	63	22 (34.9%)	[5]
China, Beijing (north)	January 1995 to October 2000	498	321 (64.5%)	[6]
China, Zhengzhou (central)	January 1975 to June 1997	615	NA (65.0%)	[7]
China, Shijiazhuang (north)			NA (33.3%)	
China, Guangzhou (south)			NA (39.2%)	
China, Quingdao (north)	4 years	97	63 (64.9%)	[8]
France, Paris	January 1993 to January 2001	19	4 (21.1%)	[9]
Ghana, Accra (south)	June 1999 to May 2001	43	27 (62.8%)	[10]
Ghana (Ashanti and upper east)	June 1999 to May 2001	48	15 (31.3%)	[10]
India, Tiruchirapalli (south)	June 1999 to May 2001	353	141 (39.9%)	[10]
India, Chandigarh (north)	6 years	61	10 (16.4%)	[11]
India, Hyderabad (south)	January 1991 to December 2000	1360	506 (37.2%)	[12]
India, Madurai (south)	January 1994 to March 1994	155	73 (47.1%)	[13]
India, Madras (south)	1980–1982	68	8 (11.8%)	[14]
India, New Delhi (north)	5 years	211	30 (14.2%)	[15]
India, Patna (east)	2 years	76	6 (7.9%)	[16]
India, Tiruchirapalli (south)	July 1985 to November 1985	40	19 (47.5%)	[17]
India, Mumbai (west)	1988–1996	367	33 (9.0%)	[18]
Nepal	1985–1987	68	8 (11.8%)	[19]
Nigeria	1974–1977	42	15 (35.7%)	[20]
Paraguay	April 1988 to April 1989	26	11 (42.3%)	[21]
Singapore	January 1991 to December 1995	29	15 (51.7%)	[22]
Tanzania	October 1994 to October 1995	32	24 (75.0%)	[23]
Thailand (central)	January 1988 to December 2000	35	12 (34.3%)	[24]
USA, Pennsylvania	January 1991 to March 1999	24	6 (25.0%)	[25]
USA, south Florida	January 1982 to January 1992	125	79 (63.2%)	[26]

NA, specific data not available.

the exception of a study from Nepal, where both sexes were affected equally [19]. The average age of the patients in the studies ranged from 35.8 to 59 years.

Corneal trauma was the most common predisposing factor for keratomycosis, with an incidence ranging from 31.6% to 89.9%, apart from a study from Pennsylvania, in which only 8.3% of the patients reported a recent trauma [25]. The injuries were caused by various traumatising agents, including plant material (paddy, tree branch, thorn, hay, sugar cane, grass, corn stalks, onions, ground nuts, kernel, palm leaf), animal matter (cow's tail, cow dung, insect, cat scratch, hen peck), dust, soil, mud, stones, glass, metal objects and fingernails. Other reported predisposing factors included the use of topical corticosteroids, previous eye surgery, pre-existing ocular diseases (e.g., lagophthalmos, chronic dacryocystitis, corneal scaring or ulcer), systemic diseases such as diabetes mellitus or leprosy, and the wearing of contact lenses. In a study from Tanzania, a positive correlation was found with HIV carriage, in that 81.2% of patients with fungal keratitis were HIV-positive, compared with only 33% of those with non-fungal keratitis [23].

A possible complication after infection of the cornea by *Fusarium* spp. is endophthalmitis, which may result in the deterioration of visual acuities, including the loss of light perception. Of 159 cases of *Fusarium* keratitis in Florida, ten patients progressed to endophthalmitis, suggesting the importance of an early diagnosis and suspicion of endophthalmitis in patients with keratomycosis that does not respond to aggressive topical antifungal treatment [28].

The first sign of fungal keratitis may be the presence of a coarse granular infiltration of the corneal epithelium and the anterior stroma [29]. However, this symptom also occurs with bacterial keratitis; therefore, microbial investigation is necessary to confirm the pathogen. Direct microscopic examination of stained ocular samples can help to detect fungi, but identification to the genus level is generally not considered possible [1].

Culturing of scrapings or a tissue biopsy from the infected area can yield the fungus. In this case, the cultures are used for susceptibility testing. *Fusarium* spp. grow rapidly on Sabouraud dextrose agar plates, forming colonies that are usually 'woolly', with a white, yellow, pink or purple colour on the surface. The underside is palered, violet or brown. Typically, these organisms produce curved, multicellular macroconidia. However, negative culture results can be obtained following previous antifungal therapy, or if there has been difficulty in obtaining the specimen from a deep infection. PCR-based tests can also be used to detect fungi in infected corneas [30].

Usually, keratitis is treated with a topical antifungal agent, sometimes in combination with sub-conjunctival injections of the same drug and/or oral antimycotic agents [29]. Natamycin is the preferred initial agent for the treatment of filamentous fungal keratitis. Amphotericin B lipid complex, voriconazole and oral or topical ketoconazole, are also effective in the treatment of fusarial keratitis [1,28,29]. Therapeutic keratoplasty may be needed for patients whose corneal infection does not resolve during antifungal therapy [8,27].

In our own experience, a case of keratomycosis caused by a mixed infection involving *Fusarium verticillioides* was diagnosed in a 47-year-old Hungarian man. In addition to a trauma in his left eye, another potential predisposing factor was untreated diabetes. After the injury, the corneal epithelial lesion developed into a severe visual impairment, despite local antibiotic (ciprofloxacin) and steroid (prednisolone, dexamethasone) treatment. After 4 weeks, a dense, mesh-like structure in the anterior chamber attached to the posterior surface of the cornea was revealed by ultrasound biomicroscopy. Local natamycin therapy was started, but the mesh-like structure progressed, filling almost the entire anterior chamber. Penetrating keratoplasty was performed as the only possible treatment. Intra-operative samples taken from the cornea and the anterior chamber yielded bacteria (*Staphylococcus epidermidis*, an α-haemolytic streptococcus and *Propionibacterium acnes*) and a filamentous fungus (*F. verticillioides*). Local steroid (prednisolone) and antibiotic (neomycin and tobramycin) treatment, combined with oral itraconazole therapy, were started post-operatively. The diabetic status improved following the initiation of insulin therapy. Three months later, the host and graft cornea were transparent without inflammatory signs, and the best corrected vision was 0.9.

In conclusion, *Fusarium* keratitis is rare in temperate climates, but frequent in agriculture-based geographical regions with hot, humid, tropical or sub-tropical climates. Those at highest risk are young and middle-aged farmers, as they are more exposed to the possibility of corneal trauma with infected material. Early and accurate microbiological diagnosis, coupled with appropriate treatment, is crucial for increasing the chances of complete recovery.

REFERENCES

1. Thomas PA. Current perspectives on ophthalmic mycoses. *Clin Microbiol Rev* 2003; **16**: 730–797.
2. Guy St-Germain BS, Summerbell R. *Identifying filamentous fungi*. Belmont, CA: Star Publishing Co., 1996.
3. Nelson PE, Dignani MC, Anaissie EJ. Taxonomy, biology, and clinical aspects of *Fusarium* species. *Clin Microbiol Rev* 1994; **7**: 479–504.
4. Dunlop AA, Wright ED, Howlader SA *et al*. Suppurative corneal ulceration in Bangladesh. A study of 142 cases examining the microbiological diagnosis, clinical and epidemiological features of bacterial and fungal keratitis. *Aust NZ J Ophthalmol* 1994; **22**: 105–110.
5. Rahman MR, Johnson GJ, Husain R, Howlader SA, Minassian DC. Randomised trial of 0.2% chlorhexidine gluconate and 2.5% natamycin for fungal keratitis in Bangladesh. *Br J Ophthalmol* 1998; **82**: 919–925.
6. Zhang W, Pan Z, Wang Z *et al*. The variance of pathogenic organisms of purulent ulcerative keratitis [in Chinese]. *Zhonghua Yan Ke Za Zhi* 2002; **38**: 8–12.
7. Wang L, Zhang Y, Wang Y, Wang G, Lu J, Deng J. Spectrum of mycotic keratitis in China [in Chinese]. *Zhonghua Yan Ke Za Zhi* 2000; **36**: 138–140.
8. Xie L, Dong X, Shi W. Treatment of fungal keratitis by penetrating keratoplasty. *Br J Ophthalmol* 2001; **85**: 1070–1074.
9. Rondeau N, Bourcier T, Chaumeil C *et al*. Fungal keratitis at the Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts: retrospective study of 19 cases [in French]. *J Fr Ophtalmol* 2002; **25**: 890–896.
10. Leck AK, Thomas PA, Hagan M *et al*. Aetiology of suppurative corneal ulcers in Ghana and south India, and epidemiology of fungal keratitis. *Br J Ophthalmol* 2002; **86**: 1211–1215.
11. Chander J, Sharma A. Prevalence of fungal corneal ulcers in northern India. *Infection* 1994; **22**: 207–209.
12. Gopinathan U, Garg P, Fernandes M, Sharma S, Athmanathan S, Rao GN. The epidemiological features and laboratory results of fungal keratitis: a 10-year review at a referral eye care center in South India. *Cornea* 2002; **21**: 555–559.
13. Srinivasan M, Gonzales CA, George C *et al*. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. *Br J Ophthalmol* 1997; **81**: 965–971.
14. Sundaram BM, Badrinath S, Subramanian S. Studies on mycotic keratitis. *Mycoses* 1989; **32**: 568–572.
15. Panda A, Sharma N, Das G, Kumar N, Satpathy G. Mycotic keratitis in children: epidemiologic and microbiologic evaluation. *Cornea* 1997; **16**: 295–299.
16. Kumari N, Xess A, Shahi SK. A study of keratomycosis: our experience. *Indian J Pathol Microbiol* 2002; **45**: 299–302.
17. Thomas PA, Abraham DJ, Kalavathy CM, Rajasekaran J. Oral itraconazole therapy for mycotic keratitis. *Mycoses* 1988; **31**: 271–279.
18. Deshpande SD, Koppikar GV. A study of mycotic keratitis in Mumbai. *Indian J Pathol Microbiol* 1999; **42**: 81–87.
19. Upadhyay MP, Karmacharya PC, Koirala S *et al*. Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal. *Am J Ophthalmol* 1991; **111**: 92–99.

20. Gugnani HC, Gupta S, Talwar RS. Role of opportunistic fungi in ocular infections in Nigeria. *Mycopathologia* 1978; **65**: 155–166.
21. Mino de Kaspar H, Zoulek G *et al*. Mycotic keratitis in Paraguay. *Mycoses* 1991; **34**: 251–254.
22. Wong TY, Fong KS, Tan DT. Clinical and microbial spectrum of fungal keratitis in Singapore: a 5-year retrospective study. *Int Ophthalmol* 1997; **21**: 127–130.
23. Mselle J. Fungal keratitis as an indicator of HIV infection in Africa. *Trop Doct* 1999; **29**: 133–135.
24. Boonpasart S, Kasetsuwan N, Puangsricharern V, Pariyakanok L, Jittpoonkusol T. Infectious keratitis at King Chulalongkorn Memorial Hospital: a 12-year retrospective study of 391 cases *J Med Assoc Thai* 2002; **85**(suppl): S217–S230.
25. Tanure MA, Cohen EJ, Sudesh S, Rapuano CJ, Laibson PR. Spectrum of fungal keratitis at Wills Eye Hospital, Philadelphia, Pennsylvania. *Cornea* 2000; **19**: 307–312.
26. Rosa RH, Miller D, Alfonso EC. The changing spectrum of fungal keratitis in south Florida. *Ophthalmology* 1994; **101**: 1005–1013.
27. Gupta V, Dada T, Vajpayee RB, Sharma N, Dada VK. Polymicrobial keratitis after laser in situ keratomileusis. *J Refract Surg* 2001; **17**: 147–148.
28. Dursun D, Fernandez V, Miller D, Alfonso EC. Advanced *Fusarium* keratitis progressing to endophthalmitis. *Cornea* 2003; **22**: 300–303.
29. Klotz SA, Penn CC, Negvesky GJ, Butrus SI. Fungal and parasitic infections of the eye. *Clin Microbiol Rev* 2000; **13**: 662–685.
30. Gaudio PA, Gopinathan U, Sangwan V, Hughes TE. Polymerase chain reaction based detection of fungi in infected corneas. *Br J Ophthalmol* 2002; **86**: 755–760.