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Research Article / Araştırma Makalesi

Demographic, Epidemiological and Etiological Characteristics of Fungal Keratitis Cases in Southern Anatolia Tertiary Eye Care Center

Güney Anadolu Üçüncül Göz Sağlığı Merkezinde Fungal Keratit Olgularının Demografik, Epidemiyolojik ve Etiyolojik Özellikleri

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Abstract

To evaluate the demographic, epidemiological and etiological charactersisitics of fungal keratitis cases in our tertiary eye care center located in the Eastern Mediterraen coast of South Anatolia.A retrospective review of all culture-proven fungal keratitis seen from May 2017 to May 2019 was performed. The demographic features, predisposing factors, associated systemic and ocular characteristics, and microbiological analysis results of cases were evaluated. The mean age of 15 cases with fungal keratitis was 46±7 years (range: 19-77 years) with a male-to-female ratio of 4:1. The majority of the occupations of the cases were agricultural workers or farmers (73%). The etiology was predominantly trauma mostly with an environmental origin (93.3%). Fungal growth was detected in 15 eyes (38.5%) in a total of 39 microbial positive corneal cultures. Filamentous fungi were responsible for all cases, including Fusarium sp. in 8 eyes (53.3%) and Aspergillus sp. in 7 eyes (46.7%). Species of Fusarium were determined in 4 eyes, namely F. Aquaeductus, F. Chlamydosporum, F. oxysporum and F. solani; whereas species of Aspergillus were determined in 3 eyes, namely A. niger and A. flavus. Bacterial and fungal coinfection was shown in two eyes (Aspergillus sp. with Gram (+) beta hemolytic streptococcus; Fusarium sp. with Pseudomonas orzyihabitans). The results of this study, which determines the characteristics of fungal keratitis cases encountered in the Eastern Mediterranean coasts of Southern Anatolia may be useful in the early diagnosis of the disease, in the timely and appropriate empirical treatment of the patients living in this region.

Keywords: Fungal keratitis, ocular microbiology, filamentous fungi, fusarium, aspergillus

Özet

Güney Anadolu Doğu Akdeniz kıyısında yer alan üçüncü basamak göz sağlığı merkezimizde fungal keratit olgularının demografik, epidemiyolojik ve etiyolojik özelliklerini değerlendirmek. Mayıs 2017'den Mayıs 2019'a kadar görülen, kültürle kanıtlanmış tüm mantar keratitleri retrospektif olarak değerlendirildi. Olguların demografik özellikleri, predispozan faktörleri, ilişkili sistemik ve oküler özellikleri ve mikrobiyolojik analiz sonuçları incelendi. Fungal keratitli 15 olgunun ortalama yaşı 46±7 yıl (19-77 yıl arasında) idi ve erkek/kadın oranı 4:1 idi. Vakaların çoğunluğunu tarım işçileri veya çiftçiler oluşturuyordu (%73). Etyoloji ağırlıklı olarak çevre kaynaklı travmaydı (%93.3). Toplam 39 mikrobiyal pozitif kornea kültüründe 15 gözde (%38.5) mantar üremesi tespit edildi. Fusarium sp. dahil tüm vakalardan filamentöz mantarlar sorumlu olup 8 gözde (%53.3) Fusarium türleri ve 7 gözde (%46.7) Aspergillus türleri saptandı. Fusarium türleri F. Aquaeductus, F. Chlamydosporum, F. oxysporum ve F. solani olmak üzere 4 gözde; Aspergillus türleri ise 3 gözde A. niger ve A. flavus olarak belirlendi. İki gözde bakteriyel ve fungal koenfeksiyon gösterildi (Gram (+) beta hemolitik streptokokla beraber Aspergillus türü; Pseudomonas orzyihabitans ile beraber Fusarium türü). Güney Anadolu'nun Doğu Akdeniz kıyılarında karşılaşılan fungal keratit vakalarının özelliklerini belirleyen bu çalışmanın sonuçları, bu bölgede yaşayan hastaların hastalığın erken teşhisinde ve zamanında ve uygun ampirik tedavisinin başlanmasında faydalı olabilir.

Anahtar Kelimeler: Fungal keratiti, oküler mikrobiyoloji, filamentöz mantarlar, fusarium, aspergillus

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1. Introduction

Fungal keratitis, also known for keratomycosis, is the inflammation of the cornea that results from fungal infection. It accounts for more than 50% of cases with corneal ulcers, in especially tropical areas of the world [1]. Classification according to fungal genera was basically made in two groups, filamentous fungi and yeast or yeast-like fungi [2]. The epidemiological and etiological factors differ from country to country and even from region to region throughout the country [3]. Numerous studies have reported that filamentous fungi, particularly *Fusarium sp., Aspergillus sp.* and *Curvularia sp.*, are the main causes of mycotic keratitis worldwide [1]. It has been also shown that fungal keratitis infected with these species is more common in tropical and subtropical regions, while yeasts such as *Candida sp.* have been isolated in cases of fungal keratitis mostly in temperate climates [1-3].

Predisposing factors that contribute to the occurence of fungal keratitis also vary around the world. While corneal trauma with vegetative material was reported most frequently, immunosuppression, contact lens wear and ocular surface disorders were reported as other predisposing factors [3,4].

Typical pesentation of fungal keratitis consists of suppurative and ulcerative lesions, which may progress to corneal perforations and endophthalmitis if the stromal inflammation is not taken under control [4]. Therefore, fungal corneal infections require urgent recognition to initiate appropriate antimycotic therapy and prevent permanent vision loss [5].

Knowing the underlying causes and predisposing factors of fungal keratitis in a specific geographical region would help clinicians living in the same area to make the diagnosis and apply the right treatment in a timely manner [4]. Therefore the present study aimed to evaluate the demographic, epidemiological and etiological characteristics of fungal keratitis cases in our tertiary eye care center located in the Eastern Mediterranean coast of Southern Anatolia.

2. Methods

The design of the study was retrospective and cross-sectional that was conducted in accordance with the principals of the Declaration of Helsinki. Approval was obtained from the University Research and Ethics Committee. The files of 39 patients who applied to the tertiary eye care center with corneal ulcer between May 2017 and May 2019 were reviewed and analyzed.

The demographic features, predisposing factors, associated systemic and ocular characteristics, and microbiological analysis results of cases diagnosed with fungal keratitis were evaluated. Patients with viral keratitis, bacterial keratitis and neurotrophic keratitis, and patients with corneal ulcers that did not show any fungi in cytological samples were excluded from the study.

Microbiological investigations

The base and edges of corneal ulcers were scrapped by a spatula under local anesthesia. Microscopical examination was performed for all corneal scraping specimens after staining by Gram, Giemsa, and calcofluor white with 10% potassium hydroxide. A part of each specimen was also inoculated onto blood agar, brain-heart infusion agar and Sabouraud glucose-neopepton agar plates which were incubated for up to 6 weeks at 30◦C and 37◦C under appropriate atmospheric conditions [6]. All culture plates were examined daily for fungal or bacterial growth. Fungal growth in culture was deemed significant if:

1. it was correlated with the clinical presentation, or

2. the growth of the same fungus was demonstrated on two or more solid culture media in the absence of fungus in smears, or

3. there was a semiconfluent growth at the site of inoculation on one solid medium, or

4. there was growth in the liquid media, consistent with microscopy [6].

Re-scraping was performed in case of insufficient material, or suspicion of contaminated material, or adverse results unrelated to clinical properties. After growth on media the isolated fungi were identified according to their macroscopic and microscopic features. The identification of filamentous fungal colonies was made by conventional methods; microscopically (features of conidiogenous cells and conidiophores, production, morphology and organization of conidia, macro-microconidia and blastoconidia, presence or absence of chlamydospores) and macroscopically (structures and colors of colonies) morphological characteristics, rates and temperatures of growth. [7]. Antibiotic susceptibility testing was performed according to CLSI M38-A2, broth microdilution method for molds.

3. Results

We identified 39 cases with culture positive microbial keratitis, where a fungal cause was isolated from corneal scraping samples of 15 eyes (38.5%) of 15 cases. Hyphae were observed in 17 samples out of 17 cases with keratitis on microscopy; however, no fungal growth was shown in two. The remainder were cases of bacterial keratitis (61.5%).

The age of cases with microbiologically proven fungal keratitis ranged from 19 to 77 years with a mean of 46 ± 7 years. Of the 15 patients, 12 (80%) were men and the male / female ratio was 4:1. There were 1 scrap seller (6.7%), 1 undergraduate student (6.7%), 2 construction workers (13.3%) and 11 agricultural workers (9 farm workers and 2 farm owners) (73.3%). Corneal contact with a herbal material was recorded in 10 cases; the others were soil in 4 patients; lime powder in 1 patient and a metal rod in 1 patient. The undergraduate student who had a history of scratching her eyes while working in a garden was the only case who wore soft contact lenses. None of the cases had a previous history of topical or systemic steroid use.

The genera isolated were *Aspergillus* in 7 eyes (47%) and *Fusarium* in 8 eyes (53%). Among the *Fusarium* species isolated cases, *F. Aquaeductus, F. Chlamydosporum, F. oxysporum and F. solani* were detected from 4 samples (Fig.1). Among the Aspergillus species, *A. niger* (2 samples) and *A. flavus* (1 sample) were isolated. The demographic, etiological characteristics and microbiological spectrum of fungal keratitis cases are shown in Table 1.

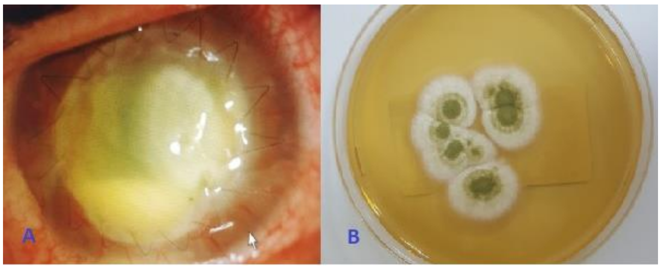

Figure 1. A. Fungal keratitis in the cornea of the left eye of an agricultural worker who underwent penetrating keratoplasty surgery 5 years ago. **B.** Aspergillus flavus growth was seen in the culture of corneal scraping sample.

Table 1. The demographics, epidemiological and etiological features of the fungal keratitis cases

Age / Gender	Occupation	Eye contact	Associated conditions	Fungus
20 / F	Undergrad-gardening	soil	Soft contact lens use	*Aspergillus sp.*
57 / M	Agricultural worker	tree branch	Diabetes mellitus	*Aspergillus sp.*
55 / M	Agricultural laborer	onion skin	-	*Aspergillus sp.*
51 / F	Agricultural worker	tree branch	Diabetes mellitus	*Aspergillus sp.**
35 / M	Agricultural worker	tree branch	-	*Aspergillus niger*
77 / M	Farmer	leaf	Pseudophakia	*Aspergillus niger*

32 / M	Agricultural worker	soil	Keratoplasty	*Aspergillus flavus*
50 / M	Agricultural worker	tree branch	Diabetes mellitus, hypertension, stroke	*Fusarium oxysporium*
57 / M	Agricultural worker	tree branch	-	*Fusarium chlamydosporum*
38 / M	Agricultural worker	tree branch	-	*Fusarium aquaeductum*
19 / M	Agricultural worker	bush	-	*Fusarium solani*
70 / F	Farmer	tree branch	-	*Fusarium sp.*
49 / M	Construction worker	metal rod	-	*Fusarium sp.*
25 / M	Construction worker	lime powder	-	*Fusarium sp.*
50 / M	Scrap dealer	wooden object	-	*Fusarium sp.* †

M: male; F: Female
** Fungal keratitis coinfected with gram(+) beta hemolytic streptococci.*
† Fungal keratitis coinfected with Pseudomonas oryzihabitans.

Antibiotic susceptibility testing of the identified species are given in Table 2. In vitro test results of Caspofungin and Anidulafungin MIC values against *Aspergillus sp.* were found to be very low, while they were found high against *Fusarium sp.* in general.

Table 2. Broth microdilution antifungal susceptibility test results.

Isolates	**MIC values of antifungal drugs (µg/mL)**				
	AmphotericinB	Voriconazole	Posaconazole	Caspofungin	Anidulafungin
A. flavus	1.5	0.5	0.5	0.064	0.003
A. niger* – 1	0.12 g/L	1	0.06	≤0.03	≤0.03
***A. niger* – 2 †**	0.25 g/L	0.5	0.06	≤0.03	≤0.03
F.aquaeductum	1	1	>16	16	>16
F.chlamydosporum	2	4	>16	16	2
F.oxysporum	0.25	8	>16	4	1
F. solani	16	8	>16	16	16

A. Aspergillus; F. Fusarium
** A. niger–1: identified from the corneal sample of the 35-year- old male*
† A. niger–2: identified from the corneal sample of 77-year-old male.

Bacterial and fungal coinfection was shown in two eyes (13.3%). *Aspergillus sp.* and *Gram (+) beta hemolytic streptococci* co-infection was detected in a 51-year-old diabetic agricultural worker who was admitted to the hospital with a diagnosis of both keratitis and endophthalmitis with findings of proliferative diabetic retinopathy observed on fundoscopy. The other was *Fusarium sp.* and *Pseudomonas oryzihabitans* co-infection detected in a 50-year-old male. He was a scrap dealer with a corneal ulcer injured by a wooden object.

Among the known systemic factors, diabetes mellitus type II was reported in three patients (20%). A history of hypertension and stroke was determined in a 50-year-old diabetic male agricultural worker. Two patients had previous ocular surgery (13%). One of them was a 77-year-old rancher who had bilateral cataract surgery for senile cataracts 6 years ago. His right cornea was injured by an orange leaf from which *Aspergillus niger* was isolated. The other was an agricultural worker who had penetrating keratoplasty due to trauma 5 years ago. He had a history of soil-related corneal injury while working in a cotton field. *Aspergillus flavus* was isolated from the patient's corneal sample. (Fig.1)

4. Discussion

The results of this study covering a period of two years showed that filamentous fungi were the main etiology in cases with fungal keratitis. *Fusarium* was the most isolated filamentous fungus, followed by *Aspergillus*. Most of the cases had been associated with outdoor activities, where trauma with a herbal substance was the leading susceptibility factor, with structural materials in the second place. It was also observed that the number of affected males was significantly higher than females.

Epidemiological studies have shown that the microorganisms that cause keratitis may vary according to the geographical features and climatic conditions of the countries. Filamentous fungi are the predominant pathogens that have been widely proven to be associated with fungal keratitis in humid and warm climates [1,8]. Provinces of Southern Anatolia are located in the far east of the Mediterranean coast. The climate here is Mediterranean, characterized by hot and humid summers and humid subtropical climate ranging from cold to mild winters [9]. The main pillars of the economy in this region are agriculture and industry [10].

Studies have reported that ocular trauma is the predominant risk factor for fungal keratitis [1-6]. In a 10-year study by Gopinathan et al, it was found that males were affected 2.5 times more than females, and trauma was the etiological factor in more than 50% of infected eyes [6]. Corneal trauma with an organic or herbal substance has been considered the predominant predisposing factor affecting 40-60% of patients with mycotic keratitis [2,11-13]. In line with these facts, Bharathi et al noted in a retrospective review that the highest prevalence of culture-proven cases of fungal keratitis was observed during the South Indian harvest season between June and September [14]. They determined that 92% of patients with fungal keratitis had ocular trauma and 61% of cases were injured by a herbal substance.

In the etiology of corneal damage that causes keratomycosis, leaves, rice grain, cow tail, tree branch, soil and metal objects have been described in various studies [14,15]. Similarly, Ebadollahi-Natanzi et al found that corneal ulcers caused by fungal microorganisms are most common among farmers and construction workers in rural, structural, and roofless areas [16]. In parallel with various studies in the literature, it has been reported that men over the age of 15, especially those working outdoors, are more frequently affected [8,16-19]. Also, in regions where agriculture is the main economy, the highest fungal keratitis is analyzed to be associated with *Fusarium* and *Aspergillus* species [16].

Filamentous fungi, inhabitants of the environment, are widely associated with keratitis caused by ocular trauma, especially in tropical areas containing organic matter [1,8,17]. In some countries with tropical or subtropical regions such as Singapore, Hong Kong, China, East India, South Florida, East Africa, and Northern Tanzania, the filamentous species were mostly isolated fungi and it was *Fusarium sp*. identified as the primary cause, followed by *Aspergillus sp.* [14,18-26]. Similarly, studies from Ghana, Australia, Iran, Brazil, Tunisia, Thailand, Taiwan, Northern China and South India found *Fusarium* to be the most commonly identified species isolated from fungal keratitis cases. On the other hand, studies from India and the rest of Bangladesh showed that *Aspergillus sp.* was the major species detected in cases of fungal keratitis [3].

Epidemiological studies of fungal keratitis cases in the Eastern Mediterranean Coast of Southern Anatolia have not been conducted yet. Therefore, this study has been compared with studies conducted in other regions of Anatolia where geographical and demographic factors are similar. The available data obtained are similar to these studies in some respects. For instance, in a study conducted in a province of Southern Anatolia, 11 out of 20 fungal keratitis cases had a history of trauma due to plant or soil material [27]. In this 3-year retrospective study, there were five patients with a previous history of topical steroid use, but similarly, the cases were predominantly male, and filamentous pathogens were seen in the microscopy of all corneal scrapings. In another study retrospectively investigating the etiological factors and clinical features of microbial keratitis cases admitted in Western Anatolia over a 16-year period, it was found that approximately half of the eyes had a history of ocular trauma with herbal substance. The fungal pathogens isolated from these traumatized eyes were found to be predominantly filamentous and 43.5% of fungal keratitis cases were agricultural workers or farmers [28]. Unlike our study, it was determined that corticosteroid therapy was the second most common risk factor for fungal keratitis. *Fusarium sp* were identified as the most isolated fungal species but different from our study they were followed by *Candida sp*.

Unlike filamentous fungi, it has been reported that corneal infections with *Candida sp.* are more common in temperate climates and are less associated with vegetative matter and trauma. In a large analysis conducted in New York, *Candida sp.* was found to be the most common fungal agent (48%) among 5083 cases with keratitis [29]. Ocular surface diseases such as dry eye syndrome and corneal ulcer, systemic immunosuppressive diseases such as diabetes mellitus and the use of steroids and broad-spectrum antibiotics have been shown to be important predisposing factors for *Candida*-induced keratitis [1,17,18,29]. In addition, previous ocular surgeries, especially penetrating keratoplasty, a pre-existing epithelial defect due to herpes keratitis and contact lens abrasions have been also found as risk factors for *Candida* keratitis [1,29]. In the present study, there were cases with diabetis mellitus, previous history of ocular surgery and contact lens use, however, *Candida sp.* was not isolated from any of them. It may be because all of these cases had a history of corneal contact with an environmental agent.

There are extensive retrospective studies defining contact lens use as an important predisposing risk factor for fungal keratitis in studies where fungal etiologies differ by species [18,21-24]. Filamentous fungi have been reported as one of these etiological factors for contact lens-associated keratitis [30]. In this study, *Aspergillus sp.* grew up in a corneal scraping culture of a case using contact lenses and she had a history of scratching her eye while working in a garden. In a 5-year hospital-based retrospective study in which the microbial and clinical characteristics of cases with fungal keratitis were determined in Singapore, where the climate is warm and tropical, 2 cases using contact lenses were reported. Similar to the current study, more than half of the patients in this study had trauma and *Fusarium sp.* was the leading cause of fungal keratitis, followed by *Aspergillus* [22].

When compared to the studies on antibiotic susceptibility of fungal pathogens isolated from patients with keratitis in the literature, the lower number of Fusarium and Aspergillus species in the present study limits the evaluation of this study in this respect. For example, drug susceptibility differences between Fusarium and Aspergillus species were similar in our study compared to the study of Lalitha et al. [31]. However, unlike our study, the sensitivity of fungal agents to different drugs such as Natamycin and Itraconazole was also investigated in the study of Lalitha et al. , which had a much larger sample size (41 Aspercillus spp and 38 Fusarium spp).

The most significant limitations of the present study were the retrospective design and relatively small number of patients. In addition, there were cases where subspecies could not be detected. Adding to this, the inclusion of only culture-positive cases of fungal keratitis may have led to a biased prevalence. That is, there may be some patients with high suspicion of fungal keratitis where fungal growth was not demonstrated in cultures of corneal specimens and microbiological studies were not repeated enough. Furthermore, although important information was provided to guide the treatment of fungal keratitis, the clinical picture, treatment methods and responses to these treatments were not included due to the lack of follow-up information of the patients. For this reason, the current study chose to focus more on the predisposing and etiological factors of the cases with fungal keratitis.

5. Conclusions

Our study, despite all its limitations, provides reliable preliminary information on this subject, showing that agricultural activity and associated eye trauma are the main cause of fungal keratitis caused by filamentous fungi in the Eastern Mediterranean coast of South Anatolia. Since corneal infections need to be recognized urgently to prevent permanent vision loss by facilitating complete recovery, the characteristics of fungal keratitis cases described in this retrospective review may be helpful in early diagnosis of the disease and initiating appropriate early empirical treatment by clinicians working in this geaographic region.

Ethical Approval

All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (ethics committee approval date-decision number: 23/05/2019-10).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The authors affirm that human research participants provided informed consent for publication of the images in Figures 1A and 1B.

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