

Epidemiological Profile of Mycotic Keratitis in a Tertiary Care Center of Iran

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Abstract

The aim of this study was to investigate the epidemiological aspects of keratomycosis in a tertiary care center from northern Iran. This cross-sectional study was conducted on all consecutive patients clinically suspected to keratomycosis that were ultimately diagnosed by positive fungal culture that admitted to Amir-almomenin hospital in Rasht city, Iran, between 2012 and 2020. The sampling method was census. Reviewing the hospital-recorded files collected the required information. Forty-seven patients were examined in the study that 53.2% of patients were men. The most common age of disease onset was 50 to 60 years in women and 60 to 70 years in men. Among the population of women, housewives-farmers with the prevalence rate of 45% and among the population of men, those with farm occupation with the prevalence rate of 52% formed the most common occupational subgroups. Most patients (89.3%) had no history of any ocular surgery or manipulation. *Aspergillus* was the most frequent pathogen (23.4%) followed by *Penicillium* (19.1%) and *Fusarium* (17.0%). History of chronic disorders was also revealed in 44.6%. The results of smear and culture obtained from the study were as follows: in 8.5% of patients as positive smear and positive culture, and in 91.5% as negative smear and positive culture. Only 2.1% used the lens. Ocular trauma in the background of underlying chronic disorders is the most common causal factor for the infection with far less attention to use contact lenses or eye interventions. The most frequent fungal strains responsible for fungal keratitis include *Aspergillus* followed by *Penicillium* and *Fusarium*.

Keywords: Mycotic Keratitis; Epidemiology; *Aspergillus*; *Fusarium*.

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1. Introduction

Various ranges of microorganism can induce keratitis, fungal keratitis or keratomycosis is a type of corneal infection that should be considered in cases of corneal damage caused by plant materials, after corneal surgery, history of topical corticosteroids or contact lenses [1,2,3]. Clinical features including corneal infiltration with plump edges and intact epithelium with severe stromal involvement, satellite lesions, endothelial plaques, lack of improvement with antibiotics, and

worsening with steroids can propose high likelihood of fungal keratitis [3]. Pathologically, more than 70 types of fungal microorganisms have been known to be the major causes for fungal keratitis [4]. Fungi are ubiquitous in the environment, in plants, in soil, in climate, in the form of spores. Yeasts are also widely found in the environment (soil, water, objects, and food), the gastrointestinal tract, or the genitals and skin [5]. The epidemiology of fungal keratitis shows the microorganisms involved as well as the wide geographical diversity. The epidemiology of this

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disease varies around the world and even between different regions of a country. In general, fungal keratitis is more common in hot and humid climates. Infections with filamentous fungi are common in temperate regions such as the southern United States, Mexico, Central America, South America, Africa, the Middle East, China, India, and Southeast Asia [6]. In these areas, fungal keratitis may account for up to 80% of infectious keratitis [7]. Yeast-related keratomycosis often occurs due to *Candida* or *Cryptococcus* leading immune system injuries or local tissue injuries [8]. Yeasts make up about 30 to 52 percent of fungal keratitis in temperate areas including Europe, northern United States, and Australia. In these areas, fungal keratitis includes 1 and 5% of infectious keratitis [9]. The occurrence of a fungal infection means a change in one or more immune components of the surface of the eye and cornea including epithelium tear film, or eyelid. Corticosteroids and other immunosuppressive agents facilitate fungal infections by inhibiting the transcription of cytokines and inflammatory and chemical proteins along with reduce the activity of macrophages and neutrophils [10]. As the first step in disease management, corneal biopsy is necessary and treatment of this lesion with antifungal drops should be started as soon as possible. Surgical interventions are necessary to control the infection in a significant number of cases [11].

Given that very limited studies have examined fungal keratitis among Iranian patients and our epidemiological information in this field is very limited, the aim of this study was to investigate the epidemiological aspects of fungal keratitis in a population sample from northern Iran.

2. Methods

This cross-sectional study was conducted on all consecutive patients clinically suspected to fungal keratitis that were ultimately diagnosed by positive fungal culture that admitted to Amiralmomenin Hospital in Rasht City, Iran, between 2012 and 2020. The Ethics Committee of Guilan University of Medical Sciences approved the protocol of the study. The sampling method was census. Those with systemic fungal infections were not included into our survey.

The required information including age, sex, occupation, place of residence and history of direct eye injury in the last 6 months, underlying diseases particularly diabetes and hypertension, history of any eye surgery and manipulation, use of contact lenses (type of lens and duration of use) and history of drug use within six months before hospitalization was extracted from patients' hospital records and set in the researcher's checklist. In this study, patients with a history of trauma, use of contact lenses, history of recent

corneal surgeries, use of topical corticosteroids with symptoms of pain, photophobia, redness, decreased vision and tearing, and in the slit lamp examination with sign of suspected fungal keratitis, such as corneal ulcers with fringe-like margins, satellite lesions, and endothelial ring were sampled from the corneal surface by specialists or ophthalmic assistants. Surgical blades or special spatulas were used to sample the corneal surface. Samples were extracted using slit lamps under local anesthesia from deeper layers and edges of patients' corneal ulcers. After preparing the laboratory slides and inducing them in the culture medium, they were carefully examined by microscopic evaluation. Samples were cultured in special culture media including Chocolate agar, Blood agar and Sabouraud dextrose to identify any bacterial and fungal pathogens. The samples were incubated for 24 to 48 hours at the appropriate temperature and incubated for 3 weeks for fungi cultivation. Finally, infectious pathogens related to fungal keratitis were isolated and identified. Microscopic tests and direct smear, 10% KOH staining and gram staining were performed by laboratory experts and the causative agent of fungal keratitis was ultimately diagnosed [2].

The results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. To summarize descriptive information, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used. P values of 0.05 or less were considered statistically significant.

3. Results

From April 1, 2011 to March 20, 2019, out of 53 patients admitted with positive fungal keratitis, 6 patients were excluded from the study due to various reasons such as lack of complete medical information in the recorded file, and thus 47 patients were finally examined in the study. Regarding baseline characteristics (Table 1), 53.2% of patients were men. The most common age of disease onset was 50 to 60 years in women and 60 to 70 years in men. Among the population of women, housewives-farmers with the prevalence rate of 45% and among the population of men, those with farm occupation with the prevalence rate of 52% formed the most common occupational subgroups. Regarding place of residence, 68.1% were in urban areas and 31.9% in rural areas. In terms of history of any surgery and intraocular surgery in the last 6 months, most patients (89.3%) had no history of any ocular surgery or manipulation, while cataract surgery with the rate of 6.3% was more common among patients with a history of manipulation and intraocular surgery. In terms of the causative agents of fungal keratitis

(Table 2), *Aspergillus* was the most frequent pathogen (23.4%) followed by *Penicillium* (19.1%) and *Fusarium* (17.0%). History of trauma to the eyes within the last 6 months was expressed by 59.6%. History of chronic disorders was also revealed in 44.6% as hypertension and/or ischemic heart diseases in 34.0%, diabetes mellitus in 21.3%, neurologic disorders in 4.2%, rheumatologic disorders in 2.1%, and endocrinological disorders in 2.1%. Overall, 42.5% did not have a history of any medication in the last 6 months; while 57.4% had a

history of drug use that the types of medications are shown in Table 1. The results of smear and culture obtained from the study were as follows: in 8.5% of patients as positive smear and positive culture, and in 91.5% as negative smear and positive culture. In this study, the use of contact lenses was also investigated, based on which it was found that out of 47 patients, only 2.1% used the lens and thus 97.9% had no a history of using the lens.

Table 1. Baseline characteristics of study population

| | |
|----------------------------------------------------|---------------|
| Sex | No (%) |
| Male | 25 (53.2) |
| Female | 22 (46.8) |
| Age subgroups (cumulative) | No (%) |
| <40 years | 15 (31.9) |
| <50 years | 23 (48.9) |
| <60 years | 30 (63.8) |
| <70 years | 41 (87.2) |
| Occupational status (women) | No (%) |
| Housewife | 10 (21.3) |
| Housewife-farmer | 10 (21.3) |
| Employed | 2 (4.2) |
| Occupational status (men) | No (%) |
| Employed | 2 (4.2) |
| Worker | 2 (4.2) |
| Self-employed | 3 (6.4) |
| Farmer | 13 (27.7) |
| Unemployed, retired | 5 (10.6) |
| Place of residence | No (%) |
| Urban | 32 (68.1) |
| Rural | 15 (31.9) |
| Eye-related manipulation | No (%) |
| Intraocular injection | 2 (4.2) |
| Cataract surgery | 3 (6.3) |
| Direct eye trauma in the last 6 months | 28 (59.6) |
| History of chronic disease | No (%) |
| Hypertension and/or ischemic heart diseases | 16 (34.0) |
| Diabetes mellitus | 10 (21.3) |
| Neurologic disorders | 2 (4.2) |
| Rheumatologic disorders | 2 (4.2) |
| Endocrinological disorders | 1 (2.1) |
| History of using contact lens, % | 1 (2.1) |
| History of medications in the last 6 months | No (%) |
| Local ocular antibiotics | 5 (10.6) |
| Midriatic-cycloplegic drugs | 2 (4.2) |
| Ocular corticosteroids | 1 (2.1) |
| Artificial tear | 1 (2.1) |
| Antihypertensive drugs | 16 (34.0) |
| Anthyperglycemic drugs | 9 (19.1) |
| Systemic corticosteroids | 1 (2.1) |
| Endocrine drugs | 1 (2.1) |
| Neuropsychological drugs | 5 (10.6) |

4. Discussion

The present study was one of the first reports on epidemiological aspects of fungal keratitis in northern Iran. Due to this fact that the global prevalence rate of this infection is exclusively divergent and in fact different epidemiological behaviors of fungal agents can be revealed in different geographical areas, minutely assessing fungal infections and its trend over the years is critical because of scheduling better managerial and therapeutic approaches. It has been well demonstrated that fungal keratitis can be influenced by different genetic, environmental and even iatrogenic factors that the impact of such factors can be very different in various populations.

Table 2. Pathogens related to fungal keratitis

| Pathogen | Frequency (%) |
|----------------------|---------------|
| Aspergillus | 11 (23.4) |
| Penicillium | 9 (19.1) |
| Fusarium | 8 (17.0) |
| Alternaria | 3 (6.4) |
| Candida | 3 (6.4) |
| Cladosporium | 2 (4.3) |
| Pseudallescheria | 1 (2.1) |
| Scopulariopsis | 1 (2.1) |
| Geothermal | 1 (2.1) |
| Philadelphia | 1 (2.1) |
| Acremonium | 2 (4.3) |
| Fungi with bacteria | 2 (4.3) |
| Unknown fungal agent | 3 (6.4) |

In the present observation, we attempted to provide a clear picture of the epidemiological situation of this disease in one of the major cities in northern Iran. According to our observation, the disease affects almost both sexes equally; however its prevalence has been mainly related to the sixth and seventh decades of life, which mainly coincides with a decrease in immune system capability. Regarding its association with occupational state, about half of the male and female populations were housekeeper and farmer respectively because most of the men in this area are farmers and a significant part of the women are farmers-housewives. Among underlying causes for creating fungal keratitis, a small number of patients reported ocular-related manipulations or surgery emphasizing this fact that these interventions did not significantly affect the incidence of this infection, but ocular trauma was revealed in more than half of the affected patients that points it as a main cause for infection. Along with ocular trauma, the presence of chronic disorders mainly associated with immune deficiency can be considered as another causal factor. With respect to fungal strains associated

with fungal keratitis, *Aspergillus* and *Penicillium* were the most prevalent causes for this infection. Reviewing the literatures showed the highest incidence rate of fungal keratitis among Asian, African, and the Middle East regions, while European countries have shown the lowest incidence of this infection. In this regard, different factors including the variations in climatic differences, comprehensive different management programs in the diagnosis and screening of the disease and even genomic divergent have all been evaluated as the cause of this difference.

Comparing our results with other studies highlights significant differences in epidemiological aspects of fungal keratitis across the societies. In our study, the prevalence of disease was slightly higher in men than in women. The results of our study were consistent with most studies, so that in the Rathi and colleagues study [12], about 70% of men were affected, which was more than the female group. The results of this study regarding sex distribution were also consistent with Ghosh and colleagues [13] and Ebadollahi and colleagues [14] studies, so that in Ghosh study, about 80% of patients were men, and in Ebadollahi study conducted in Iran, the prevalence of this disease was higher in men. It seems that since men have more high-risk jobs than women, they are more exposed to high-risk factors such as trauma, which can play a role in the development of this disease. Additionally, in our study, the most common age of onset in women and in men was the sixth and seventh decades of life, respectively, and in general, the most common age of onset was in the age range of 60 to 70 years followed by 30 to 40 years. The results of most studies were inconsistent with our study, so that in Rathi and colleagues study [12] the most common age was related to fifth decade of life. In another study [15], which examined the epidemiology of fungal keratitis in northern Vietnam, a large proportion of patients with fungal keratitis were in the middle decades of life (40 to 60 years). In our study, in terms of occupation, most women were in the household-farmer group followed by in the housewife group and most of men were farmers and thus agriculture was the most common occupation among the patients studied. Nhung and others study conducted in Vietnam [15], it was shown that most of the patients were farmers and had a history of farm work and damage caused by contact of plant material with the eyes that was consistent with our study. In addition, in our study, most patients had a history of trauma. These results were consistent with most studies, so that in a study [16] conducted in China; corneal lesions were reported as the most important predisposing factors in the development of fungal keratitis. In another study conducted in 2015 on 1542 patients in India, there was a history

of trauma in most cases (80.9%) and most patients (72.3%) had central or para-central wounds [12]. The results of a study in Iran [14] also showed that a large number of fungal keratitis due to trauma is seen in farmers and construction workers. Trauma seems to play a very important role in the development of ocular keratitis, especially in farmers who suffer from many wounds and injuries due to contact with wood and plant materials due to working in the field. More important, regarding the use of contact lenses in this study, only 1 patient (2.1%) used the lens and 46 patients (97.9%) did not have a history of using the lens. It seems that according to the results of our study, contact lenses had a lesser role in the development of keratitis in this region, but this is while the results of many similar studies were inconsistent with our study. These studies have identified contact lenses as a major risk factor for fungal keratitis. In Walter and co-workers study of patients with keratitis in Germany, the use of contact lenses was a major risk factor [17]. In the Iseline and co-workers study [18], the most important risk factor was use of contact lenses in 65%. In another study [19] in the United States on 528 eyes with microbial keratitis, patients were divided into two groups of general hospital and private hospital. The results of this study were also inconsistent with our study, so that contact lenses were the most common risk factor in the general hospital group. In addition, the Lin and colleagues study [20] was conducted in 2015 in China on 558 patients showed that contact lenses were considered the most common and as the first predisposing factor (31.4%) in the incidence of keratitis. It should be also noted that with the growth of urban population and the advancement of technology, the use of contact lenses and consequently the incidence of infectious keratitis associated with lenses is increasing every year.

As an important finding, the results of smear and culture obtained from most patients (91.5%) were reported as negative smear and positive culture. *Aspergillus* was the most common fungal pathogen. The results of the Ghosh et al study [13], which examined fungal keratitis in 2459 patients in northern India, *Aspergillus* was reported to be the most common pathogen in fungal keratitis. *Aspergillus Flavus* Keratitis was also reported as the most common pathogen in the study of Jafarinasab and others [21]. However, the results of other similar studies are inconsistent with our study, so that in some of these studies, *Fusarium* has been known as the most common cause and *Aspergillus* is the second most common cause. The results of Ebadollahi and colleagues study in 2016 [14] that examined the prevalence of fungal keratitis in 121 patients with corneal ulcers in Farabi Eye Hospital in Tehran, it was shown that the most fungi isolated from the samples belonged to

Fusarium with 49% and then *Aspergillus* with 26%. The Nhung and colleagues [15] study also examined the epidemiology of fungal keratitis in northern Vietnam in 2012 showed the predominant fungal species of *Fusarium* followed *Aspergillus* spp. Therefore, from different epidemiological, pathophysiological and even causal aspects, there is a significant difference between the communities and even different regions in a country regarding the occurrence of fungal keratitis. Therefore, accurate determination of the characteristics of the disease and evaluation of its trend of the changes in each region to achieve the minimum outbreak of the disease and control of its complications and morbidity is essential in the structure of infection control in each country.

Our study had some potential limitations. First, due to employing small sample size, the sex and age analysis of the disease rate or its correlated was not possible requiring further studies with larger sample sizes. Second, our results focused on a sample of northern Iran area and thus our results could not be generalized to other country regions, especially considering this fact that our country is multiracial and multi-climatal.

5. Conclusion

It can be finally concluded that fungal keratitis affects our male population slightly high than females with the highest overall prevalence rate in the sixth and seventh decades of life. Ocular trauma in the background of underlying chronic disorders is the most common causal factor for the infection with far less attention to use contact lenses or eye interventions. The most frequent fungal strains responsible for fungal keratitis include *Aspergillus* followed by *Penicillium* and *Fusarium* that is consistent with most reports released from other regions in the world.

Conflicts of Interest

There are no conflicts of interest

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