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Prevalence and prognosis of corneal perforation in patients diagnosed with fungal keratitis.

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Abstract

This retrospective study was designed to investigate the incidence, clinical characteristics and prognosis of corneal perforation in patients with fungal keratitis. Clinical data of 648 patients who were diagnosed with fungal keratitis in Air Force General Hospital were obtained in this retrospective study. All participants were divided into the corneal perforation (n=156) and non-perforation groups (n=492). The pathogenesis, etiological characteristics, admission date and clinical symptoms were statistically compared between two groups. Clinical prognosis of patients presenting with corneal perforation was retrospectively analysed. The incidence rate of corneal perforation in patients with fungal keratitis was 23.7%. No statistical significance was noted between two groups in terms of history of corneal trauma (r=0.218, P=0.640), contact lens wear (r=0.268, P=0.605) and ocular surface diseases (r=0.353, P=0.553). The proportion of patients who were topically administered with glucocorticoid (χ^2=14.251, P<0.01) and complicated with diabetes mellitus (χ^2=22.365, P<0.01) considerably differed between two groups. The type of pathogenic fungus and duration of onset before admission significantly differed between two groups (both P<0.05). In addition, the size of corneal lesion, infiltration depth and hypopyon in the corneal perforation groups were statistically different from those in the non-perforation group (all P>0.05). Fungal keratitis patients who were administered with glucocorticoid and complicated with diabetes mellitus had a higher risk of corneal perforation compared with their counterparts. Type of pathogenic fungus, admission date, size and infiltration depth of corneal lesion and hypopyon probably served as the risk factors of the incidence of corneal perforation in patients diagnosed with fungal keratitis.

Keywords: Fungal infection, Keratitis, Corneal perforation, Risk factor.

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Introduction

Corneal perforation is an acute blindness-inducing eye disease, which is constantly caused by ocular infection and trauma, etc. If left untreated, corneal perforation probably leads to irreversible glaucoma, endophthalmitis and even blindness [1,2]. Meantime, infectious corneal disease, especially fungal keratitis, is one of the main risk factors of corneal perforation. In recent years, along with the widespread application of broad-spectrum antibiotics and glucocorticoids, the annual quantity of patients diagnosed with fungal keratitis has been steadily increased. However, the clinical prognosis of fungal keratitis is poor and almost all patients are managed by eyeball enucleation of the affected eyes [3]. The incidence of corneal perforation induced by fungal keratitis may provoke endophthalmitis and alternative complications, which are untreated by medical therapy. Nevertheless, surgical procedures probably yield high difficulty and risk of postoperative complications. The surgery is also significantly limited by the availability of donor sources. Thus, efficacious therapy against corneal perforation remains a challenging task for ophthalmologists globally [4]. Consequently, the clinical characteristics and progression status of fungal keratitis were retrospectively analysed in this investigation, aiming to provide reference evidence for the prevention and management of corneal perforation in clinical settings. Moreover, all these efforts are delivered to offer efficacious therapy and minimize the ocular injury.

Materials and Methods

Baseline demographic data

In total, 648 patients (648 eyes) with fungal keratitis, 397 male (61.4%) and 251 female (38.6%), aged ranging from 4 to 80 years, 52.1 years on average, admitted to Air Force General Hospital were recruited in this clinical trial. Regarding the occupation status, 495 of 648 (77.6%) patients were farmers, 64 (10.2%) workers and 76 (12.2%) in other positions. According to the presence of corneal perforation, all patients

were assigned into the corneal perforation (n=156, 23.7%) and non-perforation groups (492, 76.3%). In the corneal perforation group, 89 patients were male (60.1%) and 59 female (39.9%), aged between 14 and 80 years, 53.6 years on average. Among them, 119 (80.4%) were farmers, 20 (13.5%) workers and 9 (6.1%) in other occupations. In the non-perforation group, 293 patients were male (60.1%) and 199 female (39.9%), aged between 4 and 78 years, 52.2 years on average. Among them, 268 (80.4%) were farmers, 69 (13.5%) workers and 25 (6.1%) in other occupations.

The pathogenesis, etiologic diagnosis, clinical admission and therapeutic strategy were retrospectively analysed. The corneal lesion tissue was prepared for corneal scraping examination, inoculated in agar medium and cultured at 25˚Cfor 2 weeks.

Diagnostic criteria

Fungal keratitis: Hypha and/or spore were observed under confocal microscopy. Fungal growth was noted by corneal scraping or postoperative corneal culture. Pathological examination of corneal tissue revealed the signs of hypha. The diagnosis of fungal keratitis was confirmed at least one of the three criteria was satisfied [4].

Corneal perforation: Overall or partial absence of the anterior chamber, constantly accompanied by iris incarceration; pathological section revealed the loss of the entire corneal layer [5].

Corneal lesion characteristics: The presence of hypopyon was determined by anterior segment analyser upon the initial admission to our hospital. The lesion diameter and infiltration depth were quantitatively measured.

Parameter measurement: The maximal diameter of the visible lesions was measured and then the maximal width of the infiltrated lesion was quantitatively measured. The mean value of these two values was calculated as the mean diameter of the lesions and classified into three ranges: ≤ 3 cm; 4-6 cm and ≥ 7 cm. Superficial infiltration was defined as the infiltration depth was less than 1/3rd of the corneal thickness and deep infiltration was defined as >2/3 of the corneal thickness.

Statistical analysis

SPSS 17.0 statistical software was utilized for data analysis (SPSS Inc., Chicago, IL). Multiple parameters related to pathogenesis, etiology and lesion characteristics analysis were expressed as frequency and percentage. Clinical data between two groups were statistically compared using Pearson chi-square test. The mean admission time between two groups was analysed by using independent sample F test. A value of $P<0.05$ was considered as statistically significant.

Results

History of corneal trauma

In this study, a total of 648 patients were diagnosed with fungal keratitis and 507 among whom presented a history of corneal trauma. In addition, 156 cases developed fungal corneal ulcer and corneal perforation, and 122 of whom presented with a history of corneal trauma. Among 492 patients without corneal perforation, 385 cases reported a history of corneal trauma. The percentage of corneal trauma history did not significantly differ between two groups ($\chi^2=0.218$, $P>0.05$). The results illustrating the pathogenesis of fungal keratitis were revealed in Table 1.

Corneal contact lens wear and ocular surface diseases

Among 648 patients diagnosed with fungal keratitis, 21 had a history of corneal contact lens wear. In patients with corneal perforation, 6 cases wore the corneal contact lens and 15 for those without corneal perforation. No statistical significance was noted between two groups ($\chi^2=0.268$, $P>0.05$). Moreover, 145 patients were diagnosed with ocular surface diseases, 37 of whom were complicated with corneal perforation and 108 for those without corneal perforation. No statistical significance was documented between two groups ($\chi^2=0.353$, $P>0.05$).

Topical use of glucocorticoids and systematic diseases

Among 648 fungal keratitis patients, 23 cases had a history of topical usage of glucocorticoids. Thirteen cases were complicated with corneal perforation and 10 for those without corneal perforation. Statistical significance was observed between two groups ($\chi^2=14.251$, $P<0.01$). Among all participants, 137 cases, including 36 with corneal perforation and 101 without corneal perforation, had a medical history of hypertension. No statistical significance was noted in terms of this parameter between two groups ($r=0.655$, $P>0.05$). Eighty seven fungal keratitis patients, including 38 with corneal perforation and 49 without corneal perforation, were complicated with a medical history of diabetes mellitus. Statistical significance was documented between two groups ($\chi^2=22.365$, $P<0.05$).

Admission time

Among 648 patients diagnosed with fungal keratitis, 301 cases were admitted to our hospital for the first time and 324 patients were transferred to our hospital from another institution. Patients with fungal corneal ulcer and perforation were admitted to our hospital at 4 to 73 d after onset, (24.5 ± 8.6) d on average. Those without corneal perforation were hospitalized at 1 to 46 d after onset, (12.7 ± 10.3) d on average. Statistical significance was noted between two groups ($t=12.6$, $P<0.05$).

Lesion characteristics upon admission

Upon admission, the size of lesions in patients with corneal perforation was significantly larger compared with that in their counterparts without corneal perforation (P<0.01). The infiltration depth in the perforation group was considerably deeper than that in those without perforation (P<0.01). The incidence of hypopyon in patients with corneal perforation was dramatically higher compared with that in the non-perforation group (P<0.01), as illustrated in Table 2.

Clinical prognosis of fungal keratitis patients

In 156 fungal keratitis patients without corneal perforation, corneal perforation and ulcer was fully healed in 66 cases after simple medication therapy. Twenty cases successfully underwent conventional lamellar keratoplasty with a cure rate of 85%. In total, 24 patients received penetrating keratoplasty and 91.7% of cure rate was achieved. Five cases underwent eyeball enucleation due to ineffective management.

Table 1. Comparison of etiological causes between the perforation and non-perforation groups.

Group	Corneal trauma	Contact lens wear	Ocular surface diseases	Topical use of hormone	Hypertension	Mellitus diabetes
Corneal perforation group (n=156)	122 (82.4%)	6 (4.1%)	37 (25.0%)	13 (8.8%)	36 (24.3%)	38 (25.7%)
Non-perforation group (n=492)	385 (80.7%)	15 (3.1%)	108 (22.6%)	10 (2.1%)	101 (21.2%)	49 (10.3%)
χ^2	0.218	0.268	0.353	14.251	0.655	22.365
P	0.64	0.605	0.553	<0.001	0.418	<0.01

Table 2. Comparison of lesion characteristics between the perforation and non-perforation groups.

Group	Lesion diameter (mm)			Infiltration depth		Hypopyon	
	≤ 3	4-6	≥ 7	Superficial layer	Deep layer	Yes	No
Corneal perforation group (n=156)	2 (1.4%)	40 (27.0%)	106 (71.6%)	39 (10.8%)	109 (89.2%)	121 (81.6%)	27 (18.4%)
Non-perforation group (n=492)	96 (20.1%)	152 (31.9%)	229 (48.0%)	213 (44.7%)	264 (55.3%)	256 (53.7%)	221 (46.3%)
χ^2	38.003	15.725	37.231				
P	<0.01	<0.01	<0.01				

Discussion

Fungal keratitis is defined as an infectious process of the cornea induced by multiple pathologic fungi, which are proven to be capable of invading into the ocular surface [6]. Typically, it is a gradual and chronic disease that should be differentiated from alternative types of corneal illnesses with resembling manifestations. Risk factors of fungal keratitis mainly include eye trauma, ocular surface disease and topical steroid use, etc. Risks and types of fungi also sharply vary according to geographic climate and location [7,8]. In warmer climates, the most common organisms consist of filamentous fungi, such as *Fusarium* spp and *Aspergillus* spp. presenting with an intimate association with ocular trauma. Reports from Brazil reveal the most common isolates in descending order were *Fusarium* spp (63%), *Aspergillus* spp (12.2%) and *Candida spp* (13.1%) [9]. Approximately 42% of the infections were related to ocular trauma. In the cooler regions, corneal infection by fungus was more frequent in debilitated or immunocompromised patients. Filamentous fungi in higher latitudes have been then rarely reported. Previous investigations reported a dramatic breakout of Fusarium keratitis associated to a type of contact lens solution displaced yeasts as the most common fungal corneal infection in certain areas [10]. This trend persists in the most recent epidemiological reports. Still they are mainly correlated with contact lens use. It should be noted that the incidence of contact lens-related fungal keratitis was increasing before the *Fusarium* outbreak, indicating that physicians should not rely on the geographical distribution alone to initiate and administer empirical therapy. Broad-spectrum therapy should be administered when a strong probability of a mycotic infection is documented [11,12]. In this study, the pathogenesis, etiology and clinical data of patients diagnosed with fungal keratitis were retrospectively analysed, aiming to identify the risk factors of the incidence of corneal perforation complication in patients with fungal keratitis. In our hospital, the phenomenon of fungal keratitis complicated with corneal perforation was reported to be 23.7%, probably resulting from the delay of early diagnosis and clinical management.

The findings in current investigation demonstrated that patients with fungal keratitis who were complicated with mellitus diabetes, those with a medical history of topical use of hormones and those complicated with systemic diseases, were more likely to develop corneal perforation. These results may be related to the negative effect of hormone use and diabetes

mellitus upon the host immunity, which subsequently lead to an increasing incidence of fungal infection and more severe host inflammation. Previous studies have revealed that the occurrence of diabetes mellitus may provoke corneal abnormality, such as repeated episode of corneal ulcer, persistent epithelial defects, corneal oedema, functional defect and decreasing corneal sensitivity, which collectively aggravate the severity of fungal keratitis and even cause the risk of corneal perforation [13,14]. In addition, albeit history of corneal trauma, corneal contact lens and ocular surface illness were identified as the risk factors of fungal keratitis, these parameters were not correlated with the incidence of corneal perforation and ulcer induced by fungal keratitis.

The pathogenic bacteria of fungal keratitis mainly include *Fusarium*, *Eurotium*, *Mycotoruloides*, *Cephalosporium*, etc. In this study, among all enrolled patients, 397 cases were positive for *Fusarium* culture test, accounting for 51.1% and 31.7% for *Eurotium* infection [15,16]. In patients complicated with corneal perforation, the infection rate of *Fusarium* was significantly higher compared with that in their counterparts without corneal perforation, suggesting a high association between *Fusarium* infection and the incidence of corneal perforation in patients diagnosed with fungal keratitis. The admission time in patients complicated with corneal perforation or ulcer was significantly delayed compared with those without corneal perforation; probably because the poor understanding of fungal keratitis, misdiagnosis, missed diagnosis and drug misuse which collectively prolong the timing of clinical diagnosis and management. Consequently, early diagnosis and timely treatment play a pivotal role in the prevention and treatment of corneal perforation in patients diagnosed with fungal keratitis. Moreover, clinical characteristics of fungal keratitis progressing into corneal perforation should be highly alerted, which contribute to preventing the risk of corneal perforation, mitigating and even averting the progression of corneal perforation in patients suffering from fungal keratitis.

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