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Progress in Diagnosis and Treatment of Fungal Keratitis

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Abstract

Infectious keratitis is an important cause of corneal blindness all over the world. Although less common in developed countries, fungal keratitis accounts for almost half of all keratitis cases, occurring in developing countries. And early diagnosis and treatment are crucial to improving prognosis. This paper explains the development of diagnosis and treatment of fungal keratitis, and reviews the research progress of diagnosis and treatment of fungal keratitis at home and abroad, in order to provide new ideas for the diagnosis and treatment of fungal keratitis. In recent years, with the development of molecular diagnostic technology and the application of IVCM, the diagnosis methods of fungal keratitis have become more diverse. In addition, new progresses have also been made in the treatment of fungal keratitis, such as the innovation of drug delivery methods, the application of Photodynamic Antimicrobial Therapy (PDAT), and the application of Penetrating Keratoplasty and Corneal cross-linking. This article explains the progress of diagnosis and treatment of fungal keratitis.

Keywords

Fungal Keratitis, Diagnosis of Fungal Keratitis, Treatment of Fungal Keratitis, Infectious Keratitis

1. Introduction

Fungal keratitis (FK) is an ophthalmic disease that seriously damages vision. It often occurs under conditions such as corneal trauma, corneal surgery, chronic ocular surface diseases, local application of corticosteroid hormones, or wearing contact lenses. The source of infection can be filamentous, fungus or yeast, etc. Clinical manifestations are pinnate infiltration at the edge of the corneal, with or without surface bulge, corneal epithelium can be intact but there are deep matrix

infiltration, satellite foci, endothelial plaque, etc., ineffective antibiotic treatment or worsening of the condition after corticosteroid treatment can all indicate fungal keratoitis. Fungal keratitis is one of the major infectious eye diseases caused by blindness in developing countries [1]. It is commonly found in tropical areas and agricultural practitioners and is highly prevalent in India, China and Southeast Asia. Fungal keratitis accounts for about half of microbial keratitis in low- and middle-income countries, and mainly affects the poor rural working population. FK leads to significant morbidity, with most patients suffering from moderate or more severe visual impairment, and approximately 25% require expensive and often unsuccessful surgical interventions [2]. The main risk factors include plant trauma (rice, scratched branches), long-term wear of contact lenses and local immunosuppression caused by glucocorticoid abuse [3]. However, because the laboratory diagnosis positivity rate is relatively low and the few types of effective antifungal drugs available, there are still many difficulties in the diagnosis and treatment of FK [4]. Currently known pathogens that can cause fungal keratitis include 56 bacterial genera and 105 fungi. Since patients with early fungal keratitis have a possibility of complete cure, clinical workers should make clear diagnosis as soon as possible for patients with suspected fungal keratitis [5]. The diagnosis and treatment of fungal keratitis are very difficult. In recent years, with the development of science and technology, new progress has been made in the diagnosis and treatment of fungal keratitis, which has also enabled early diagnosis and early treatment. The following briefly explains both traditional and emerging diagnostic methods.

2. Diagnosis of Fungal Keratitis

2.1. Traditional Diagnostic Methods

The traditional diagnosis methods of fungal keratitis mainly include corneal scraping and finding mycelium and microbial culture. This method is still the gold standard for laboratory diagnosis at this stage [6]. However, both diagnostic methods have very obvious limitations. Corneal scrapers are simple and fast, and do not require special equipment. However, when the lesion develops deep into the corneal or after drug treatment, the positive rate of scrapers microscopy is significantly reduced, and this method requires high requirements for the sample to be tested [7]. If the sample cannot be taken during sampling Mycelium, fungi cannot be detected. The advantages of fungal culture are very obvious. It can identify bacterial species and conduct drug sensitivity experiments to provide a basis for clinical drug treatment. However, fungal culture takes a long time and generally takes 1 week to determine whether it is a fungal infection [8], and it is also affected by the materials and samples sent for testing, and the positive rate of culture is low. These limitations greatly affect the early diagnosis of fungal keratitis. Therefore, it is urgently necessary to shorten the diagnosis time or have higher specificity.

2.2. Polymerase Chain Reaction Technology

Polymerase chain reaction technology (PCR) uses a conserved sequence shared by all fungi as primers, while other microorganisms and human cells do not contain this sequence to amplify the target gene. This is a molecular biology technology that amplifies and amplifies trace gene extracts and controls them with a database to infer the pathogen species. It only requires a very small number of samples to make the diagnosis faster. Ferrer used smear microscopy, culture and PCR to test 27 corneal samples from 20 patients with confirmed fungal keratitis over 10 years. The positive rate of PCR test was as high as 92.6%, and these positive results were within 4 to 8 hours can be obtained [9]. Therefore, PCR technology has high accuracy in the diagnosis of fungal keratitis and can quickly obtain detection results. However, PCR detection technology also has its limitations. First, it cannot identify fungal strains. Secondly, PCR can only detect organisms with known DNA sequences and primers. Moreover, when PCR amplifiing the pathogenic genes, it replicates and amplifies other genes in the sample at the same time, and there is a possibility of false positives. More importantly, this technology requires higher costs. Therefore, PCR technology is still in the exploration and development stage of diagnosis of fungal keratitis.

2.3. Other Molecular Diagnosis Methods

Metagenome deep sequencing (MDS) is to extract all RNA in the sample, then amplify and amplify it through 16 PCR cycles, and then compare it [10]. It takes about 5 to 7 days, which can improve the sensitivity of the diagnosis of fungal keratitis with accuracy. Lalitha analyzes potential categories, evaluated routine diagnosis, DNA sequence and RNA sequence in sensitivity and specificity. RNA sequence has 100% sensitivity and 97% specificity to fungal cases, much higher than KOH/Gram dyeing (70%), Microbial culture (52%) [11].

There is also a molecular diagnostic method that was used only in bacterial diagnosis in the early stage: MALDI-ToF Mass Spectrometry, identification of microorganisms through different general quality, and it now has been used to identify fungal species. It is especially widely used in the identification of yeast, filamentous fungi, Aspergillus, Penicillium, Fusarium and mucus [12]. It also has limitations in identifying fungal species that can only identify existing mass spectral data. In addition, through tear proteomics, that is, by analyzing tear samples of patients with different treatment stages, comprehensive information on eye surface defense and damage in patients with fungal keratitis can be obtained, which has the following conditions for determining the clinical course and efficacy of fungal keratitis. This has certain significance for the development of diagnosis of fungal keratitis.

2.4. IVCM

Examination in IVCM microscopy is a non-invasive corneal imaging examination, which will make real-time diagnosis. IVCM provides about 500× magnifica-

tion, the horizontal resolution reaches 1 μm. Using this technique, all corneal layers can be examined, even those affected by edema, inflammatory infiltration, and fibrosis. Its sensitivity is about 88.3%, specificity is about 91.1% [13]. Timely diagnosis of FK can prevent irreversible corneal destruction and greatly improve the chance of complete recovery. In recent years, it has become increasingly popular because of its ability to detect larger organisms such as filamentous fungi, apricotum, etc. with rapid and high sensitivity. The basic principle is that light passes through a hole and focuses on a small area of the cornea, and the reflected light is focused through a set second aperture, thereby eliminating out-of-focus light. The term confocal is used because the lighting and detection paths share the same focal plane. On confocal imaging, specific mycelium can be observed in FK, which can distinguish between filamentous fungi and yeast-like fungi [14]. Although IVCM takes a short time, it has the characteristics of inaccurate diagnosis of pathogens. Moreover, IVCM equipment is relatively expensive, and there are still restrictions on its promotion in underdeveloped areas.

3. Treatment of Fungal Keratitis

3.1. Drug Treatment

3.1.1. Local Drug Treatment

Topical drugs used to treat fungal keratitis mainly include 5% natamyci, 0.15% - 0.3% amphotericin B, 1% voriconazole, 1% econazole, 1% Itraconazole, and 1% miconazole. Natamycin is the only local antifungal drug approved by the U.S. Food and Drug Administration for use in the eyes. It has significant efficacy in fungal keratitis caused by various fungi such as Fusarium and Aspergillus [15]. Amphotericin B is a polyene antifungal drug. Although it has potential toxicity, its broad-spectrum activity, low drug resistance and good clinical efficacy. It has been used for more than 50 years to treat invasive fungal infections and is a yeast. The first choice for fungal keratitis caused by bacterial infection [16]. Voriconazole is considered an excellent natamycin alternative, has good ocular penetration, has high bioavailability, and is effective both in the systemic and local areas, but it has caused visual impairment, color vision disorder or photosensitive. Side effects such as sexual increase [17]. In addition to conventional antifungal drugs, some preservatives or disinfectants have broad-spectrum antibacterial activity and can be used to fight bacteria, yeasts, molds and certain viruses in the eyes. The *in vitro* study of Pinna *et al.* evaluated the antibacterial activity of 0.05% hexamidine dihydroxyethyl sulfate solution and 0.6% povidone iodine, were found to have strong antibacterial activity against Candida [18].

3.1.2. Intrastromal Injection

Corneal stroma is the middle layer of the cornea ,which accounts for about 90% of the thickness of the entire cornea. Corneal stroma consists mainly of collagen fibers and a small number of cells, and these ingredients provide structural support for the cornea and maintain its transparency. Intrastromal Injection is a treatment that injects drugs or biological materials directly into the corneal

stroma, *i.e.* the matrix layer of cornea, to achieve the goal of local treatment. The advantage of this treatment is that the drug can act directly on the lesion area and can increase the effective concentration of the drug. At the same time, it reduces the side effects of systemic drugs. This treatment is often used to treat deep corneal infections or inflammation that are difficult to treat with eye drops or systemic medication. Injecting antifungal drugs (voriconazole or amphotericinB) into corneal stroma keeps the drug levels in corneal tissue stable, and prevents antifungal drug doses from being below treatment levels. This targeted drug delivery method ensures antifungal drug penetration in the event of deep corneal matrix involvement. The randomized controlled study of Narayana *et al.* evaluated the efficacy of intrastromal injection of 1% voriconazole on moderate to severe filamentous fungal keratitis [19]. Comparing the culture positivity rates and final scar size on day 3 and day 7, the corneal perforation rate was reduced in subjects with intrastromal injection of voriconazole compared with 5% natamycin eye drops alone. Another prospective randomized clinical trial compared the efficacy of intrastromal injection of natamycin, voriconazole, and amphotericin B, where the treatment group with intrastromal injection of natamycin recovered faster [20].

3.1.3. Inject Medicine in Anterior Chamber

In cases of severe fungal keratitis with deep matrix infiltration and ineffective treatment, inject antifungal drugs in anterior chamber may be effective. It delivers high doses of medication to the anterior chamber. Injection should be carried out under strict sterile conditions in the operating room [21]. Additionally, an anterior chamber rinsing can also be performed to remove exudates and pus accumulation in the anterior chamber, but if the infection involves the anterior lens capsule, care must be taken to avoid capsular damage and cataract formation. Many studies have evaluated the application of anterior chamber injection of antifungal drugs in deep corneal mycosciences, and most of them have reported higher success rates and fewer complications. This method of administration can enable antifungal drugs to reach high concentrations in the deep corneal layer, reducing infiltration, and thus eliminating endothelial plaques [22]. Most studies use amphotericin B at a dose of 5 - 10 μg/0.1mL, Voriconazole was used in some studies, dosage is 50 - 100 μg/0.1mL. If the reaction is insufficient, repeat injections can be done up to 13 times. The 91 reported complications of anterior intra-arterial antifungal medications include puerkia and temporary elevated intra-arterial pressure, postoperative pain, and intrastromal bleeding.

3.2. Photodynamic Antimicrobial Therapy (PDAT)

Bascom Palmer Eye Institute initiated a study, using rose red dye as an *in vitro* photosensitive agent, studying its antibacterial effect [23]. Bascom Palmer Eye Institute Biophysics Laboratory has reported PDTA *in vitro* antibacterial effect on Fusarium, *Aspergillus fumigatus*, *Candida albicans* and other fungi. Subsequently, clinical efficacy was determined in patients with Fusarium keratitis who

are resistant to many antifungal agents. The program is performed using 0.1% rose red, then illuminate green light, with a total energy of 2.7 J/cm^2. The patient received this treatment twice. It was reported that the infection was successfully treated within 10 months without complications or recurrence. Therefore, the safety of PDTA *in vivo* has been proven and no drug resistance has been reported [24]. However, there are still many unsolved problems in treating fungal infections in this method. For example, the mechanism of antifungal action is not particularly clear, and how to choose the best photodynamic treatment parameters for specific fungi and multiple fungal infections is still a difficult problem. In addition, the choice of how to choose the best synergistic approach to other treatment modes is also worth further investigation.

3.3. Penetrating Keratoplasty

Penetrating Keratoplasty (PK) plays a vital role in keratitis that is ineffective in antimicrobial treatment, which can also restore complete anatomy and effective vision. This kind of surgery is of great significance to the treatment of severe and refractory keratitis [25]. Yusuf K. L *et al.* gave this treatment to 25 patients diagnosed with fungal keratitis, which included 13 female patients and 12 male patients. Finally, the cure rate for early treatment of PK is 100%, the cure rate of this treatment in the late stage is 83.3%. And the recurrence rate in the early treatment group was 0, two cases (16.7%) recurred in late stages [26]. Therefore, the earlier the treatment is, the better the prognosis. In the early stages of the disease, the lesion does not reach the corneal margin and the cornea is not perforated before the cornea is perforated, PKP may provide a solution for better clinical efficacy and reduction of postoperative complications in drug-ineffective fungal keratitis [27].

3.4. Corneal Cross-Linking

Corneal cross-linking (CXL) is a new treatment for corneal diseases such as keratoconus, excimer laser surgery, and refractory corneal ulcers, keratitis, etc. that have emerged in recent years. It induces the cross-linking of collagen fibers in the corneal matrix through segment A and the photosensitive agent riboflavin to increase corneal hardness, [28] enhances the biochemical and mechanical stability of corneal quality, thereby preventing keratoconus, corneal expansion, and refractory corneal cornea. Progress of corneal diseases such as ulcers [29]. Some scholars gave drugs combined with ultraviolet light-riboflavin collagen cross-linking therapy to 8 patients with fungal infection and ineffective comprehensive drug treatment. Seven patients achieved clinical recovery in 2 weeks after the operation, ulcers healed, eyelid redness, conjunctival congestion reduced or disappeared, corneal transparency increased, and corneal scar remained at different degrees. After the operation, 7 patients with deep and anterior central stromal layer were infected. The ulcer was cured, and inflammatory cells were reduced, and high-reflective sediments, fibroblasts appeared on the anterior corneal stromal layer,

scar formation, and endothelial cell morphology rules [30]. From the above studies, it can be seen that corneal cross-linking has a good therapeutic effect in relieving eye symptoms and corneal ulcers with relatively superficial depth and range of ulcers [31]. Corneal collagen cross-linking has been proposed as an adjunctive therapy for either independent therapy or antifungal drugs for fungal keratitis. Although collagen crosslinking has been extensively studied in the past few years, its protocol still requires many modifications to optimize UV flux levels, irradiation time, and riboflavin concentrations to achieve 100% microbial killing for operators and surgical instruments. At present, this treatment technology still has great potential for development [15] [32].

4. Summary

Fungal keratitis is a disease that is relatively difficult to diagnose and treat in ophthalmic infectious keratopathy, and is also an important cause of corneal blindness in developing countries. Untimely diagnosis and lack of effective antifungal drugs often lead to undesirable prognosis, due to the development of diagnosis and treatment methods of fungal keratitis in recent years, the diagnosis and treatment methods are also more diverse. In terms of diagnostic technology, in addition to the corneal scraping and pathogen culture methods that are widely used, molecular biological technologies such as polymerase chain reaction technology, metagenomic deep sequencing can be used, which greatly improves the positive rate of examination and shortens the examination. However, this method has the shortage of false positive rate and expensive price, which still has a lot of room for improvement and development of this method. Corneal laser confocal microscopy can observe specific mycelium, which can distinguish filamentous fungi from yeast-like fungi, and has the advantage of short time, but it cannot accurately diagnose the characteristics of pathogenic species. Moreover, IVCM equipment is relatively expensive, there are still restrictions on promotion in underdeveloped areas. There have also been many progresses in the treatment of fungal keratitis. For example, in addition to local eye drops, drug treatment has also further developed the traditional drug treatment methods. In addition, there are other alternative treatments for fungal keratitis during rose red photodynamic antibacterial therapy, corneal cross-linking therapy, and penetrating keratoplasty. When choosing a diagnosis and treatment plan, ophthalmologists can target and understand the indications and contraindications of disease progression and treatment methods in order to choose the optimal plan for the patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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