

Clinical features and treatment outcomes of rare genera of fungal keratitis in China

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Research article

Keywords: fungal keratitis, rare fungal genera, clinical features, treatment outcomes, confocal microscopy

Posted Date: September 11th, 2019

DOI: <https://doi.org/10.21203/rs.2.14305/v1>

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Abstract

Background Fungal keratitis can cause severe corneal blindness, although the major fungal genera in China have been widely reported, however rare genera of fungal keratitis is little known. This study aimed to investigate the clinical features and treatment outcomes of rare genera of fungal keratitis in China.

Methods This retrospective observational study included a total of 1608 patients infected with fungal keratitis and treated at the Shandong Eye Hospital. The risk factors, course of disease, clinical features, confocal microscopy images, histopathological features, in vitro drug sensitivity tests, and treatment outcomes of 16 patients with 8 rare fungal genera were evaluated.

Results No immune rings were observed among the 8 fungal genera studied. *Rhizopus* and *Pythium insidiosum* keratitis presented as endothelial plaque and hypopyon. *Curvularia crescentulum* keratitis presented as endothelial plaque, feathery edges, and raised lesions. *Purpureocillium lilacinum* keratitis showed endothelial plaque, hypopyon, and raised lesions. *Colletotrichum*, *Exserohilum*, and *Bipolaris* keratitis had feathery edges, while *Sarocladium* keratitis had no typical fungal clinical characteristics. In 2/3 cases (12.5%) of *Curvularia crescentulum* keratitis, it was cured with medication, while in 14/16 cases (87.5%), surgery was required, including 3 cases of evisceration. The best-corrected visual acuity (BCVA, LogMAR) of 13 cases was 1.47 ± 0.87 before treatment and 0.64 ± 0.48 after treatment, and the difference was statistically significant [(95% CI, 0.26–1.40) ($P = 0.006$).

Conclusions *Curvularia crescentulum* keratitis showed good results when treated with medicine, while for *Rhizopus*, *Sarocladium*, *Colletotrichum*, *Exserohilum*, *Bipolaris*, and *Purpureocillium lilacinum* keratitis, early surgical intervention shortened the course of the disease. The prognosis of *Pythium insidiosum* keratitis is poor, as medication failed and the recurrence cycle after surgery was short.

Background

Fungal keratitis results in serious visual impairment and affects people quality of life. Fungal infection is mainly concentrated in tropical and subtropical regions in developing countries, such as India and Brazil [1, 2], and it is accountable for 40% to 50% of all isolated keratitis cases [3, 4]. At present, there are more than 70 kinds of pathogen that can cause fungal keratitis [5], but the clinical isolates of these pathogens are mainly concentrated in a few genera. The fungal isolates vary from country to country due to climate and environmental impacts. *Fusarium* and *Candida* are the most common pathogens in developed countries (such as the United States and the United Kingdom) [6], but rare pathogens such as *Rhizopus*, *Sarocladium*, *Colletotrichum*, *Exserohilum*, *Bipolaris*, *Curvularia crescentulum*, *Purpureocillium lilacinum*, and *Pythium insidiosum* have been reported in dozens of cases among both white and black populations. *Fusarium*, *Aspergillus*, and *Alternaria* are the main pathogens in China [7], and the rare fungal genera mentioned above have not been reported among Asian populations.

The different characteristics of host tissue structure and immune status lead to different clinical manifestations of fungal keratitis and different sensitivities to antifungal drugs, which makes it very difficult to treat fungal keratitis. The clinical features and drug sensitivity of common fungal genera have been widely reported, but treatment guidelines for rare genera are lacking. Therefore, the purpose of this study is to gather cases in which rare fungal genera were treated at Shandong Eye Hospital and to analyze the relevant factors predisposing their occurrence, the clinical features, the confocal microscopy images, the drug sensitivity tests, and the treatment outcomes.

Methods

Subjects

The study included a total of 1608 patients with fungal keratitis who were treated at Shandong Eye Hospital between October 2008 and December 2017. Sixteen cases caused by eight rare fungal genera were analyzed. This study was approved by the Ethics Committee of Shandong Eye Hospital. The tenets of the Declaration of Helsinki were adhered to in the conduct of this study, and all surgical patients signed written informed consent forms.

Diagnostic methods

Confocal microscopy, anterior segment coherence optical tomography, corneal scraping cultures, and slitlamp microscopy were performed in all patients. After admission, corneal lesions were examined using cytology smear, and scraped tissues were inoculated into Sabouraud dextrose agar (SDA) and blood agar plate and were cultured in incubators at 28°C and 37°C, respectively. The growth characteristics of the colonies were recorded. Molecular biological methods were used to identify those whose morphology could not be identified.

Four antifungal agents—amphotericin B, fluconazole, itraconazole, and voriconazole (provided by Shandong Boke Biological Co., Ltd.)—were tested for *in vitro* antifungal susceptibility, and the minimum inhibitory concentration (MIC) values were reported. Histopathological examination of corneal tissue excised from surgical patients (hematoxylin and eosin [H&E] staining, periodic acid–Schiff [PAS] staining, and fluorescence staining) were performed to observe the depth of hyphae infiltration, the direction of hyphae growth, and the number of inflammatory cells.

Drugs and surgical procedure

Sixteen patients were given systemic fluconazole sodium chloride injection (0.2 mg/ml intravenous drip) once a day or 200 mg itraconazole orally once a day after admission; polyene (5% natamycin eye drops, 0.25% amphotericin eye drops) and imidazole (0.5% fluconazole eye drops, 10mg/ml voriconazole eye drops) were given topically.

Surgical treatment was used when drug therapy was shown to be ineffective after approximately one week: (1) Focal excision was performed when the lesion was located in the paracentral or periphery, which infection size was less than 5 mm and the depth was less than 1/2 the corneal stroma, as nearly 1/2 of the corneal stroma can be combined with conjunctival flap covering. (2) Lamellar keratoplasty (LKP) was performed when the lesion was located in the optic axis and reached the deep corneal stroma but not the corneal endothelium. (3) Therapeutic penetrating keratoplasty (TPK) was performed when the fungal infection had reached the corneal endothelium. (4) Evisceration was performed when the fungal recurrence after keratoplasty was uncontrollable.

Statistical Analysis Method

Microsoft Excel 2010 was used for data input and management. Changes in the best-corrected visual acuity (BCVA) from the baseline were analyzed with the Wilcoxon signed-rank test. All statistical analyses were performed using Predictive Analytics Software (PASW) version 18.0.

Results

Microbiology

Of 1608 fungal keratitis cases, 857 (53.3%) pathogens were identified as *Fusarium* genera, 377 (23.4%) as *Aspergillus* genera, 202 (12.6%) as *Alternaria* genera, and 172 (10.7%) as other genera. Among 16 rare fungal keratitis cases, 1 case of *Rhizopus* keratitis (6.3%) was identified, as well as 2 cases of *Sarocladium* keratitis (12.5%), 4 cases of *Pythium insidiosum* keratitis (25%), 1 case of *Exserohilum* keratitis (6.3%), 1 case of *Bipolaris* keratitis (6.3%), 2 cases of *Colletotrichum* keratitis (12.5%), 2 cases of *Purpureocillium lilacinum* keratitis (12.5%), and 3 cases of *Curvularia crescentulum* keratitis (18.8%).

Demographics and clinical presentation

Included in this study were 13 males and 3 females, of which 13 were peasants and 3 were workers. The average age was 54.75±12.70 years. Three cases (18.75%) were caused by plant trauma, seven cases (43.75%) due to foreign body scratch, and six cases (37.5%) appeared without inducement. None of the 16 cases had a history of topical steroid use. The onset seasons were mainly summer and winter, and the onset time was 15.14 ±7.22 days. The average duration of illness in all patients was 17.81 ± 8.83 days, with *Exserohilum* keratitis being the shortest (<15 days) and *Pythium insidiosum* keratitis being the longest (>30 days).

The clinical characteristics of fungal keratitis were observed using slit lamp examination. Endothelial plaque and hypopyon were found in the focal area of *Rhizopus* cases, with satellite lesions near to it. One case of *Pythium insidiosum* keratitis resulted in a whole corneal graft infection, and the remaining three cases showed endothelial plaque, hypopyon, and subepithelial and stromal

infiltrations. Three cases of *Curvularia crescentulum* keratitis showed feathery edges. One case of *Purpureocillium lilacinum* keratitis had endothelial plaque and hypopyon, while the other case had raised lesions. Endothelial plaques were observed in all of the four genera mentioned above. *Colletotrichum*, *Exserohilum*, and *Bipolaris* cases also showed feathery edges extending to the periphery, but the above three genera were not associated with endothelial plaque, satellite lesions, or hypopyon. *Sarocladium* cases only showed obvious edema and infiltration in the focal area, without typical fungal clinical characteristics. None of the eight genera in this study showed immune rings (Figure 1).

Confocal microscopy images

Fungal hyphae were found in 16 cases (85.25%) on examination using confocal microscopy, and they were generally changed as follows: the hyphae were highly reflective; they were partially branched and segregated; their diameter was about 2.3–4.4 μm ; their shape was dendritic, linear, or short rod-like; they had an irregular hyphal morphology; the average branching angle was 39.03–46.85 degrees; and their concomitant was a very low spore detection rate. The confocal manifestations of different genera are shown in Figure 2.

Histopathological section results

In the 16 patients, 14 cases had corneal pathological sections, and hyphae structures were found in 8 cases (57.14%) using H&E staining, PAS staining, or immunofluorescence staining. A small number of hyphae and inflammatory cells were observed in *Sarocladium* and *Exserohilum* keratitis. When conducting PAS staining, *Pythium insidiosum* keratitis was not stained; only vacuolar hyphae-like structures were found in the whole stroma, and the inflammatory cells were not obvious. Immunofluorescence staining had positive results for fungi. More hyphae and a few spores were observed in *Purpureocillium lilacinum* and *Curvularia crescentulum* keratitis (Figure 3).

In vitro drug sensitivity tests

In addition to *Pythium insidiosum*, the MIC values of amphotericin B, voriconazole, and itraconazole in seven genera were low (0.016 to >16), indicating that they were all susceptible to the three antifungal agents. Among them, *Rhizopus* was more sensitive to amphotericin B. *Sarocladium* was shown to be equally sensitive to three antifungal agents. *Colletotrichum*, *Exserohilum*, *Bipolaris*, and *Purpureocillium lilacinum* were more sensitive to voriconazole, *Curvularia crescentulum* was more sensitive to itraconazole, and fluconazole was highly resistant in all genera studied (MIC 4 to >256) (Table 1).

Therapeutic results

Curvularia crescentulum keratitis were treated with routine antifungal drugs for 2–6 days, and in 2/3 cases (66.67%), the ulcer gradually healed. After 1 week of treatment, 14 cases (87.5%) underwent surgical after showing persistent progression or no improvement in symptoms: One case of *Rhizopus* and one case of *Purpureocillium lilacinum* keratitis were treated with TPK. Keratectomy was performed in seven cases (43.75%) of *Colletotrichum*, *Exserohilum*, *Bipolaris*, *Purpureocillium lilacinum*, and *Sarocladium* keratitis (one case of *Sarocladium* combined with conjunctival flap covering), and the average healing time of corneal epithelium was 5.17 ± 0.79 days postoperative. One case of *Curvularia crescentulum* keratitis was treated with LKP. Corneal transplantation was performed in four patients with *Pythium insidiosum* keratitis, of which one case had recurrence after LKP and three cases had recurrence after TPK. The average time of recurrence was 3.33 days. Evisceration were performed in three recurrent cases with uncontrollable infection (Table 2, Figure 4).

Visual acuities

The BCVA (LogMAR) of 13 cases was 1.47 ± 0.87 before treatment and 0.64 ± 0.48 after treatment, and the difference was statistically significant [(95 % CI, 0.26–1.40) ($P = 0.006$)], with an average increase of 4.55 ± 2.62 lines.

Discussion

There are different growth patterns among fungal species, so the clinical features, pathogenic invasiveness, and microbial characteristics of different fungal species are also different. Many studies have reported that *Fusarium* keratitis more commonly

shows feathery edges due to horizontal growth, while *Aspergillus* keratitis more commonly shows immune rings and hypopyon due to vertical growth [8, 9]. In this study, *Rhizopus* keratitis showed endothelial plaque and hypopyon, of which the clinical manifestations were severe. *Rhizopus* belongs to the Mucorales order of fungi, and human infection—such as keratitis—is rarely seen in human eyes. Fewer than five cases have been reported abroad, and there are still no reports in China. Such an infection can rapidly destroy the tissue structure and accelerate the progression of ocular diseases because of its strong pathogenic invasiveness [10].

Pythium insidiosum is classified as an oomycete, which is a fungal-like organism that is seen as branching, sparsely, septate or aseptate filaments; its host animals are mammals, but eye infections are rare. There have been no reports of such an infection in China thus far. Although this study classifies *Pythium insidiosum* as a fungus, its microbial species still requires further discussion. Its clinical features are mainly endothelial plaque, hypopyon, and peripheral reticular infiltration, which indicate that the genus causes strong enzymatic hydrolysis in surrounding and deep tissues, probably because the lack of ergosterol drug targets in the cytoplasmic membrane leads to an insensitivity to antifungal drugs and a difficulty in controlling the disease [11, 12].

Curvularia crescentulum belongs to the family of dematiaceous fungi, and it is the dominant genus in foreign countries. Its clinical features are raised lesions and feathery edges; hypopyon rarely occurs, and the prognosis is quite good. The medication rate of *Curvularia crescentulum* keratitis in this study was 2/3 cases (66.67%). Only one case required LKP, because the ulcer was located in deep stroma after the removal of a corneal foreign body. As such, medication should be recommended as the first choice for *Curvularia crescentulum* patients. *Exserohilum*, *Bipolaris*, and *Colletotrichum* are also dematiaceous fungi, and they are common in patients with low immunity. Human infections mainly invade the skin and respiratory tract, rarely infecting the cornea [13–16]. No cases of such infections have yet been reported in China. In this study, the most common clinical feature of the three fungal genera was feathery edges; they invaded the surrounding corneal tissues in a carpet-like manner, and the main reason for this was the melanin in the cell wall, which can affect the host's immune response to infection and reduce the toxicity of pathogens to deep invasion. In addition, the unique temperature sensitivity of *Colletotrichum* also inhibited its progression to deeper levels ($\geq 35^{\circ}\text{C}$ growth restriction); therefore, the three genera only invaded the superficial stroma without endothelial plaque and hypopyon, which accorded with the low virulence and mild infection. If the infection was diagnosed and treated early, patients were less likely to require TPK treatment [17]. One case of *Purpureocillium lilacinum* keratitis was treated by TPK because of the presence of endothelial plaque, which indicated that if the infection invaded the full thickness of the cornea, treatment using medication would likely be ineffective.

The predisposing factors of fungal infection are mainly a history of plant trauma, the use of steroids, and low immunity. In this study, none of the patients had a history of topical steroid use. One *Rhizopus* patient was scratched by iron foreign bodies. Schwartz [18] and Azari et al. [19] each reported one case of *Rhizopus* keratitis, both of which were caused by metal scratches. As such, scratches caused by metal may be a high risk factor for *Rhizopus* infection. However, the presence of *Rhizopus* infection should be identified as infection with dematiaceous fungi, as it is easy to confuse such an infection with residual metal substances because of pigmentation on the surface of the lesion; detailed inquiries should be made as to whether the patient has such trauma. Foreign bodies or plant trauma are predisposing factors for dematiaceous fungi; in this study, 5/7 cases (71.43%) of *Exserohilum*, *Bipolaris*, *Colletotrichum*, and *Curvularia crescentulum* keratitis had a history of trauma, and this was consistent with relevant reports from other countries [20].

Purpureocillium lilacinum and *Pythium insidiosum* are rare in China. There is no obvious common history of trauma for the two pathogens; corneal infection caused by low immunity because of topical steroid application is a common cause of *Purpureocillium lilacinum* abroad [21, 22], and if a patient has a history of topical steroid use and subsequent corneal infection, the possibility of such pathogens may be considered. *Pythium insidiosum* inhabits aquatic and moist soil environments. The main predisposing factors are water exposure, wearing contact lenses, and trauma, which is similar to the *Acanthamoeba* risk factors. In this study, 3/4 (75%) cases of *Pythium insidiosum* keratitis lived in humid areas along rivers, which provided a favorable environment for *Pythium*. If corneal infection patients have the above-mentioned susceptibility factors and living environment, the possibility of *Pythium insidiosum* infection should not be excluded.

Chidambaram et al. [23] reported that the average branching angle of *Fusarium* was 59.7° and that of *Aspergillus* was 63.3° . In our study, confocal microscopy images showed an average branching angle of 39.03° – 46.85° for the eight rare fungal genera, which is

close to that of *Fusarium*. However, it has also been reported that the average branching angle of *Pythium insidiosum* is 78.6°[24], so further observations should be made to increase the number of patients studied and confirm the average branching angle. *Colletotrichum*'s unique cluster-like and *Pythium insidiosum*'s bead-like manifestations were different from those of *Fusarium* and *Aspergillus*, so the genera can be judged preliminarily according to the results of the examination. The positive results of histopathology also showed that most hyphae grew horizontally. The direction of hyphae growth should be judged by clinical features, confocal microscopy images, and pathological findings together, which can provide a reference for the choice of surgical methods in the future.

Polyene and imidazole are still the main antifungal therapies used in China. There was no zoospore in the culture of *Pythium insidiosum* in our study, and no results were obtained in the in vitro susceptibility tests. The other seven species were susceptible to amphotericin B, voriconazole, and itraconazole; among them, voriconazole was more effective against fungi, especially for dematiaceous species. It is impossible to test the susceptibility of natamycin due to lack of test reagents. Sixteen cases were treated with two antifungal drugs after admission, which was beneficial for limiting the lesion.

Seven patients (43.75%) with *Colletotrichum*, *Exserohilum*, *Bipolaris*, *Purpureocillium lilacinum*, and *Sarocladium* keratitis were treated with keratectomy (one case of *Sarocladium* combined with conjunctival flap covering). The average healing time of corneal epithelium was 5.17 ±0.79 days postoperatively, and there was no evidence of fungal recurrence, which significantly shortened the course of the disease. This indicated that if medication was not effective, surgery without delay could be beneficial to control fungal keratitis. Most of the foreign reports of *Purpureocillium lilacinum* keratitis had a poor prognosis because the role of hydrolase progressed deeper more easily. Okhravi et al.[25] reported the cure rate of patients to be about 30% to 40%, but Todokoro et al. [26]reported that two patients were cured completely using only drugs. In this study, the two patients with *Purpureocillium lilacinum* keratitis underwent surgical treatment, which had a good clinical effect; it was considered that this was related to the combination of preoperative antifungal-sensitive drugs and the total eradication of lesions, which effectively controlled fungi recurrence. At present, there is no effective treatment for *Pythium insidiosum* keratitis; antifungal therapy is still the main treatment method used in other countries, but their effect is generally not good. The recurrence rate of fungi after surgery is high, and several foreign studies showed that the evisceration rate in *Pythium* patients was 42.6% [24, 27]. In our study, four cases of *Pythium insidiosum* keratitis were ineffective in antifungal therapy, and three cases (75%) showed fungal recurrence after corneal transplantation. A hyphae-like structure was observed using confocal microscopy, and evisceration was required for an uncontrolled fungal infection. The average time of recurrence was 3.33 days after surgery. Antifungal medication combined with antimicrobial therapy has been used in other countries, and for patients with corneal limbus invasion, it can be combined with cryotherapy [28, 29], which providing a new idea for the targeted treatment of patients with poor surgical outcomes in China.

Conclusions

In this study, the treatment of *Curvularia crescentulum* keratitis with medication showed good results. For cases of *Rhizopus*, *Sarocladium*, *Colletotrichum*, *Exserohilum*, *Bipolaris*, and *Purpureocillium lilacinum* keratitis, early surgical intervention seemed to be effective in shortening the course of the disease. For *Pythium insidiosum* keratitis, medication generally failed, so corneal transplantation after thorough lesion resection remains the primary treatment method. However, because recurrence still occurs and the cycle is short, especially if the infection extends to the limbus, the evisceration rate is high. Therefore, such patients should be closely observed after surgery, the medication and surgical plan should be adjusted in real time to actively respond to fungi recurrence.

Abbreviations

BCVA: Best-corrected visual acuity

LogMAR: the logarithm of minimal angle of resolution score

SDA: Sabouraud dextrose agar

MIC: minimum inhibitory concentration

H&E: hematoxylin and eosin staining

PAS: periodic acid–Schiff staining

LKP: Lamellar keratoplasty

TPK: Therapeutic penetrating keratoplasty

PASW: Predictive Analytics Software

Declarations

Acknowledgments

The author thank the imaging department and clinical laboratories of Shandong Eye Hospital for their help in collecting information of this manuscript.

Authors' contributions

XW is responsible for the acquisition of clinical data and the writing of manuscripts. XHL participates in the preparation of culture medium and identification of fungal pathogens. SXL, TW and YNJ guided the data analysis. STW, JTW and CXD performed data collection. WYS reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

This work was partially supported by the National Natural Science Foundation of China (81530027, 81470611); W. S. are partially supported by the Taishan Scholar Program (20150215) and the Innovation Project of Shandong Academy of Medical Sciences.

Availability of data and materials

The datasets used and/or analyzed to support the findings of this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study followed the tenets of the Helsinki Declaration on ethical principles for medical research involving human subjects and was approved by the ethics committee of Shandong Eye Hospital, Shandong Provincial Key Laboratory of Ophthalmology, China. Written informed consents were obtained from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Drug sensitivity of different fungi genera (MIC)

	<i>Rhizopus</i>	<i>Sarocladium</i>	<i>Exserohilum</i>	<i>Bipolaris</i>	<i>Colletotrichum</i>	<i>Purpureocillium lilacinum</i>	<i>Curvularia crescentulum</i>					
Amphotericin B (0.002-32)	1	0.25	4	0.25	1.2	0.25	0.25	8	2	0.25	0.5	0.5
Fluconazol (0.016-256)	256	64	64	25	32	16	24	64	256	4	32	64
Voriconazole (0.002-32)	8	0.25	1	0.05	0.12	0.016	0.05	0.25	0.05	0.032	1	1
Itraconazole (0.002-32)	16	0.25	16	0.25	0.125	1.5	1.2	1	4	0.125	0.25	0.25

* The MIC value of the genera are only provided in this experiment. The results are for reference only.

Table 2 Drugs and surgical methods of different fungi genera keratitis

Genus	Drugs	Surgical
<i>Rhizopus</i>		V+I TPK
<i>Sarocladium</i>		V+N Keratectomy+Conjunctival flap covering
		V+N Keratectomy
<i>Colletotrichum</i>		V+N Keratectomy
		V+N Keratectomy
<i>Exserohilum</i>		V+A Keratectomy
<i>Bipolaris</i>		V+N Keratectomy
		V+N LKP
<i>Curvularia crescentulum</i>		V+N --
		V+N --
<i>Purpureocillium lilacinum</i>		V+N Keratectomy
		V+N TPK
		V+N LKP/TPK/ Evisceration
<i>Pythium insidiosum</i>		V+N TPK/outside hospital/TPK/ Evisceration
		V+A TPK/ Keratectomy / Evisceration
		V+N TPK

* I Itraconazole/ V Voriconazole/ N Natamycin/ A Amphotericin B.

Figures

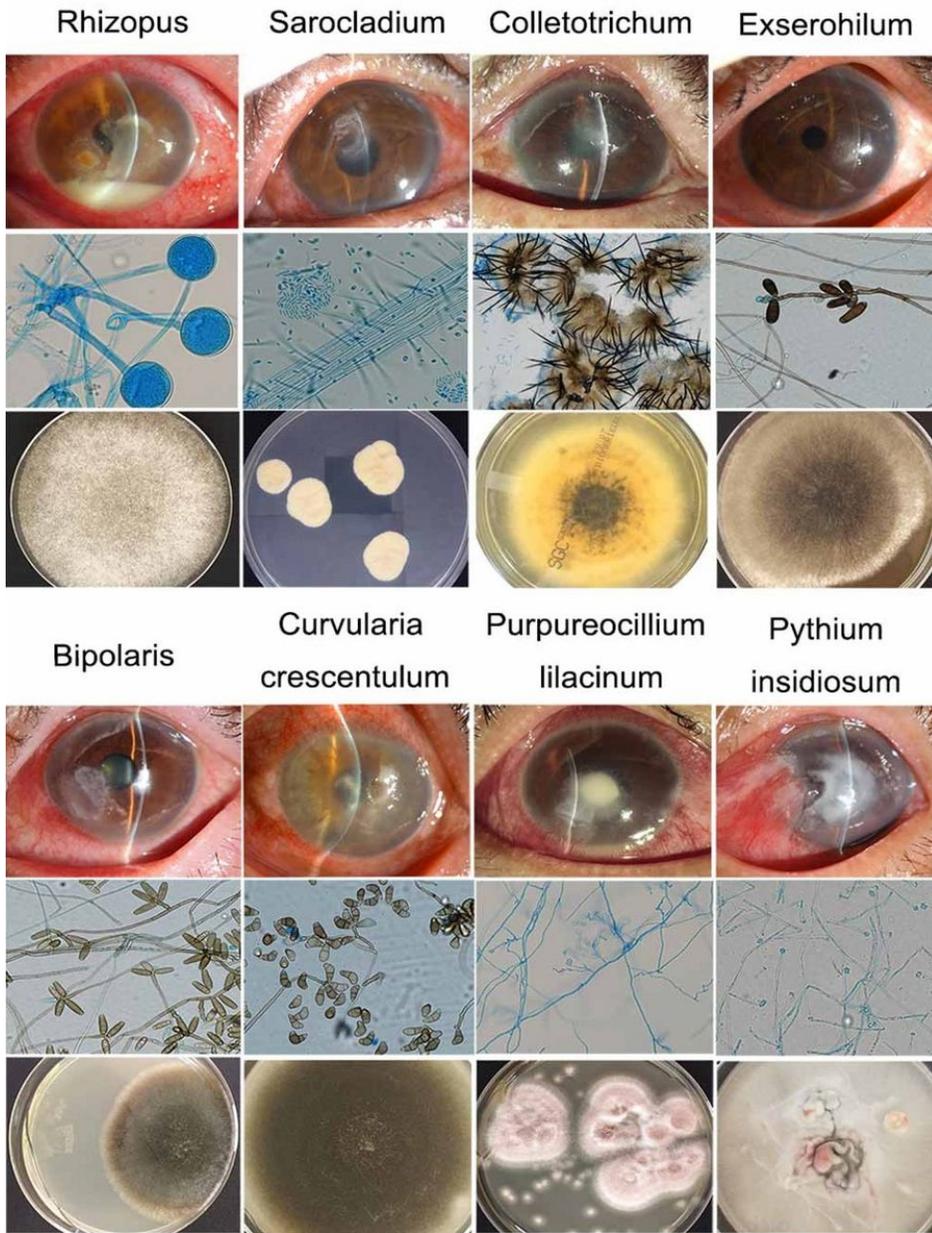


Figure 1

Slit lamp biomicroscopy photography, tape smear, and culture pictures of different species of fungal keratitis (SDA medium, 28°C, 5–9 days).

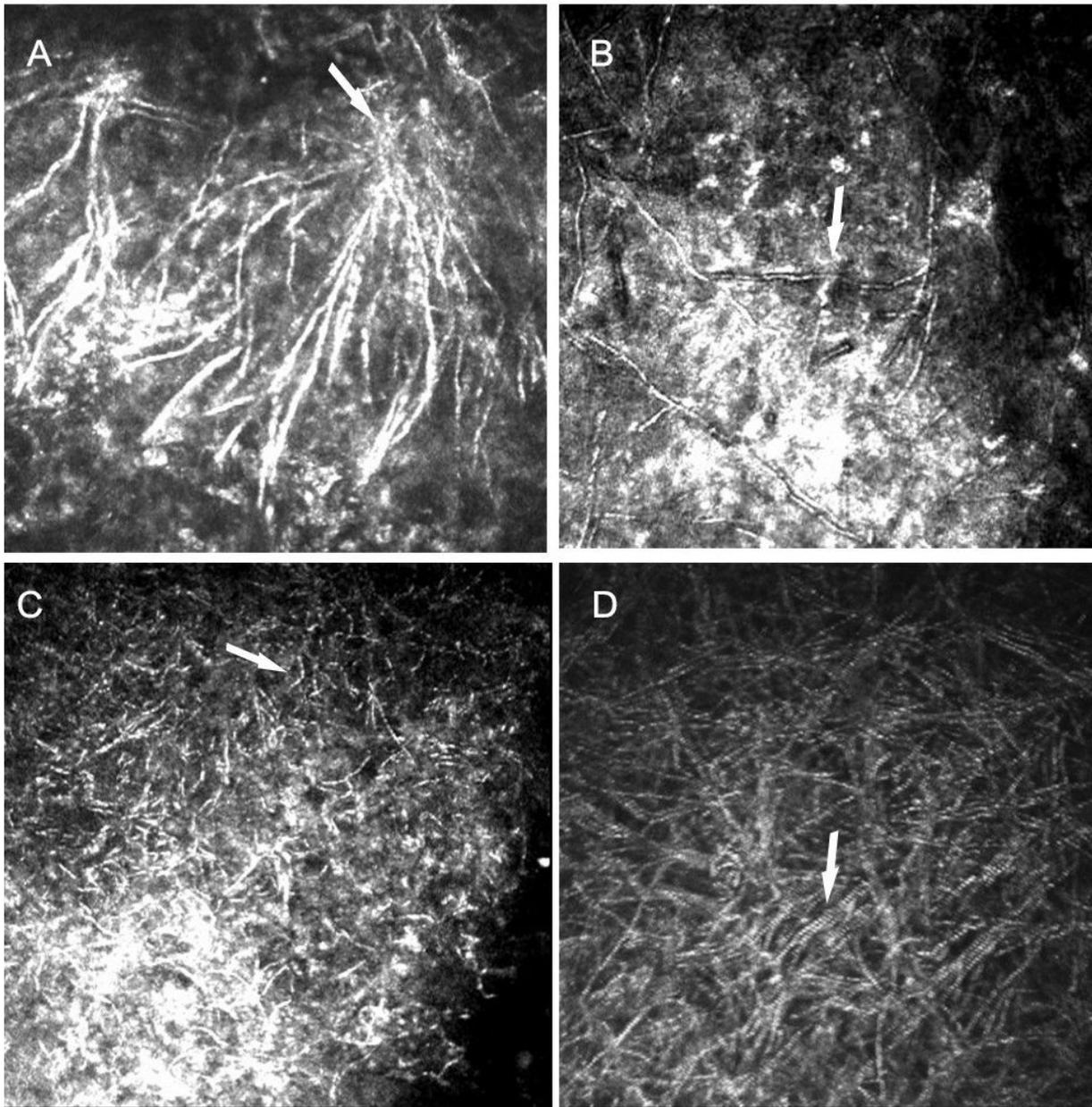


Figure 2

Confocal microscopy images of different fungal genera keratitis. A: Colletotrichum keratitis showed hyphae densely distributed in clusters and scattered inflammatory cells. B: Exserohilum keratitis showed slender hyphae overlap distribution, with sheath wall and segregation, a few spores, and inflammatory cells. C: Purpureocillium lilacinum keratitis showed a large number of curved short rod-like hyphae structures with branches and segregation and a small number of spores. D: Pythium insidiosum keratitis showed densely distributed hyphae that were beaded, and few inflammatory cells (arrow point, magnification of 400×400).

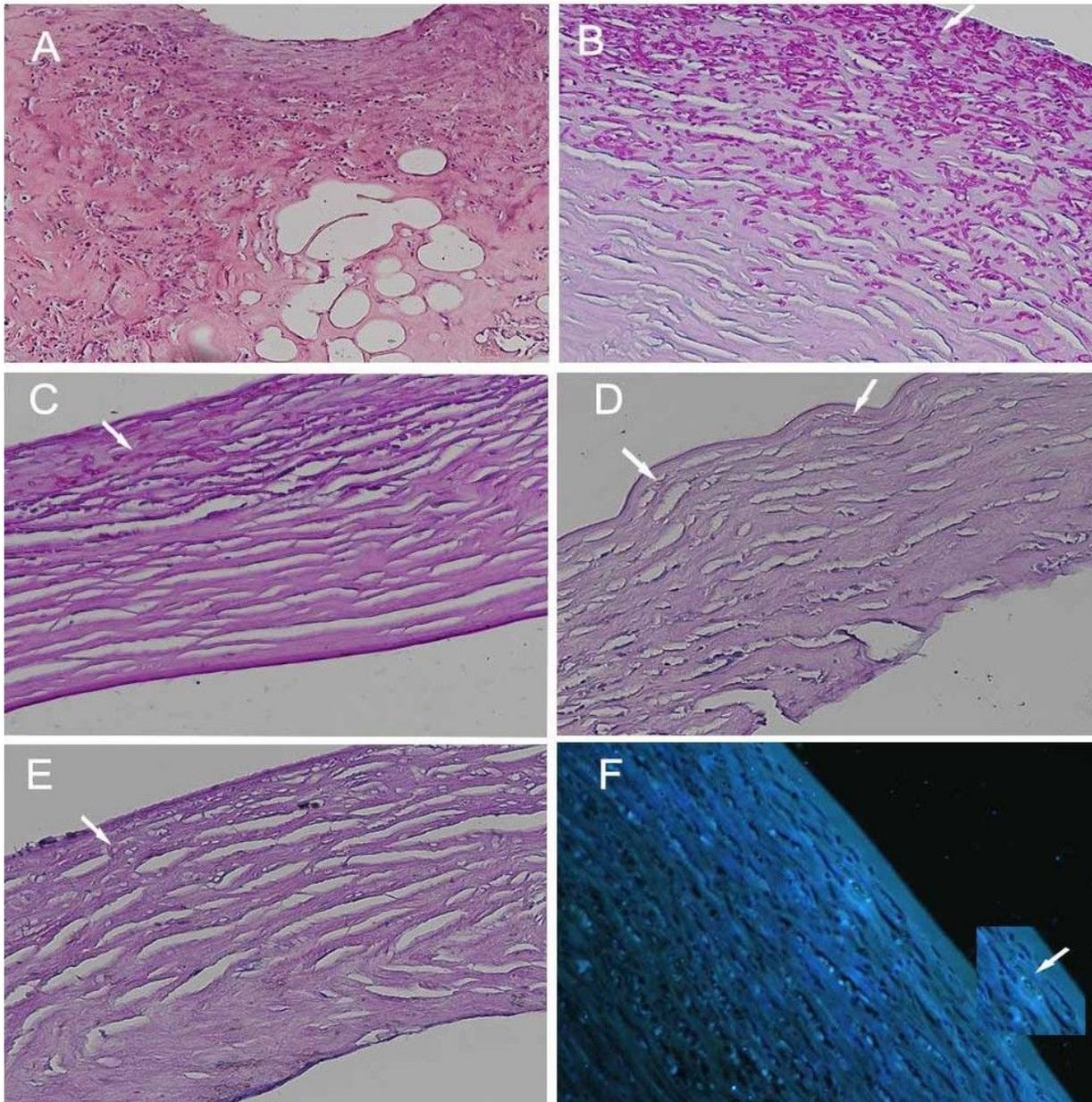


Figure 3

Histopathological manifestations of different fungal genera. A: Sporadic inflammatory cells and no obvious hyphae were observed in Colletotrichum keratitis (H&E staining, 200 × magnification). B,C: Hyphae and a few spores were found in Purpureocillium lilacinum and Curvularia crescentulum keratitis, which invaded the shallow and medium stroma and showed mainly horizontal growth (PAS staining, 200×magnification). D: A small number of hyphae and inflammatory cells were observed in Exserohilum keratitis, and mainly horizontal growth was observed (PAS staining, 200×magnification). E: A large number of vacuolar hyphae-like structures were found to invade the whole cornea of Pythium insidiosum keratitis, and no obvious inflammatory cells were seen (PAS staining, 200×magnification). F: For Pythium insidiosum keratitis, immunofluorescence staining showed that the hyphae grew horizontally (200×magnification).

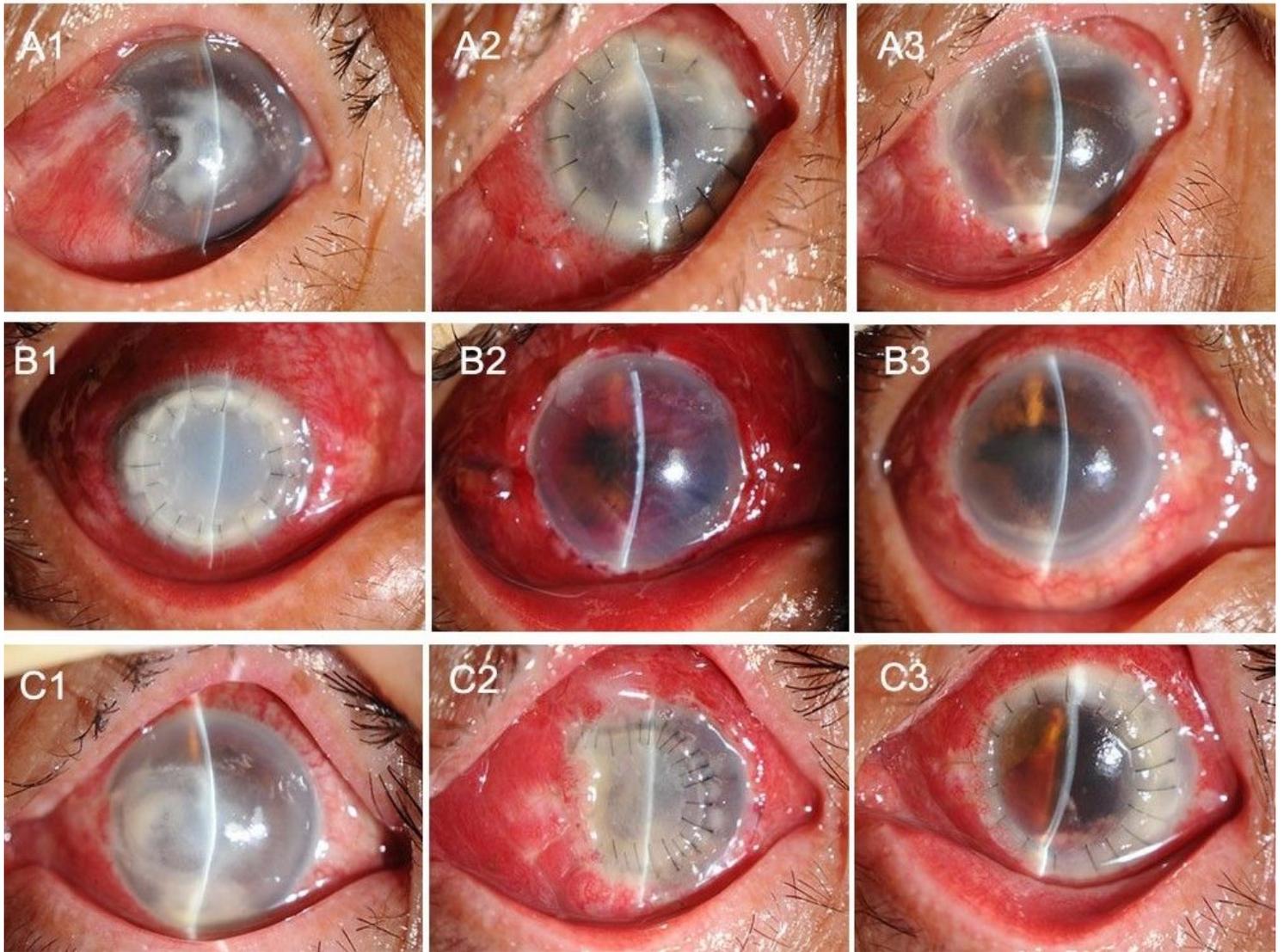


Figure 4

*The treatment process of three evisceration cases of *Pythium insidiosum* keratitis. A1,B1,C1: Slit lamp biomicroscopy photography. A2: Fungal recurrence was observed four days after LKP, and the whole corneal graft was infiltrated. A3: Fungal recurrence was observed two days after TKP, accompanied by hypopyon. B2: Hypopyon occurred five days after TPK. B3: Hypopyon increased half a month after surgery. C2: Corneal graft, implant bed infiltration, and hypopyon were observed three days after TKP. C3: Whole corneal graft infiltration was observed three days after keratectomy.*