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УСПЕШНОЕ ИЗЛЕЧЕНИЕ ГРИБКОВОГО КЕРАТИТА ПОСЛЕ СКВОЗНОЙ КЕРАТОПЛАСТИКИ

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Инфекционный кератит – наиболее частое осложнение сквозной кератопластики. В статье проанализирован случай успешного излечения грибкового кератита после сквозной кератопластики. Кератопластика выполнялась по поводу эпителиально-эндотелиальной дистрофии роговицы как исхода открытой травмы глаза у пациента 35 лет. Грибковый кератит правого глаза с поражением края донорского лоскута развился спустя 2 недели после вмешательства. Местное применение стероидных гормонов и антибиотиков было прекращено, специфическая терапия включала флуконазол и амфотерицин В. Кератит неоднократно рецидивировал, выполняли скарификацию инфильтратов. Клиническое выздоровление было достигнуто после местного и системного введения вориконазола в сочетании с регулярной скарификацией патологического очага. Применение вориконазола в течение 3-х недель привело к стабильной эпителизации и восстановлению прозрачности роговицы. В течение 3-х лет наблюдения кератит не рецидивировал, острота зрения достигла 1,0.

Ключевые слова: грибковый кератит, грибковая инфекция, пересадка роговицы, инфекционные осложнения.

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SUCCESSFUL TREATMENT OF FUNGAL KERATITIS AFTER PENETRATING KERATOPLASTY

Abstract. Infectious keratitis is the most common complication of penetrating keratoplasty. The article analyzes a case of fungal keratitis after penetrating keratoplasty. Keratoplasty was performed for bullous keratopathy developed after open globe injury in a 35-years old man. The fungal keratitis occurred two weeks later on the edge of the donor flap. The instillation of steroids and antibiotics was discontinued, specific treatment included fluconazole and amphotericin B, keratitis repeatedly recurred, infiltrates were scraped. Topical and systemic voriconazole during 3 weeks resulted in stable corneal epithelialization and corneal transparency restoration. During 3 years of follow-up keratitis did not recur, visual acuity achieved to 1.0.

Key words: infectious keratitis, fungal infection, corneal transplantation, infectious complications.

Infectious keratitis is the most common complication of penetrating keratoplasty (PKP) [1]. Frequency of this complication was 6.5% in the period from 2009 to 2014 that is much less than 11.6% in the period from 1989 to 1994 [1]. Active implementation of antibiotic prophylaxis dramatically changed the microbiological profile of keratitis. Fungal infection was the cause of only 9.8% of infectious keratitis cases in 1989-1994, whereas in 2009-2014 its frequency increased to 66.7% [1]. The risk factors for fungal keratitis include wearing contact lenses, a condition after a PKP, diabetes mellitus, eye trauma by plants [4]. Modern antifungal agents used in ophthalmology include polyenes (amphotericin B, natamycin) and azoles - imidazoles (ketoconazole, miconazole, econazole) and triazoles (fluconazole, itraconazole, voriconazole) [3,7]. The

first-line therapy for fungal keratitis is the topical application of natamycin 5% and voriconazole 1% [7,3]. In Russia, the objective difficulties in the treatment of fungal keratitis are exacerbated by the total absence of officinal ophthalmic antifungal drops. There is also a therapeutic dilemma concerning the administration of steroids [9,10,8]. Discontinuation of steroids is unsafe for immune rejection, but its use can increase the rate of fungal recurrence.

Case presentation

A 35-year-old-man appealed to the Ophthalmology Department complaining of poor vision in the right eye. In 2000, he underwent surgery with the removal of a foreign body (a fragment of glass) from the anterior chamber of the right eye. Subsequently, he was treated for chronic keratouveitis with the development of bullous keratopathy. The best-corrected visual acuity of the right eye was 0.1.

On November 23, 2016, PKP was performed according to a standard procedure. The early postoperative period was uneventful; the patient received local antibiotics, steroidal and non-steroidal anti-inflammatory drugs and artificial tears (Fig. 1). On examination 2 weeks after the surgery (05.12.16), the edges of the wound were adapted, the sutures were clean, the donor corneal flap was transparent, and the epithelization was practically complete, visual acuity 0.1. On examination 3 weeks after the surgery (12.12.16) a superficial white infiltrate was found on the edge of the donor flap (Fig. 2B). In a retrospective analysis of earlier photos (Fig. 2 A) dated 05.12.16, a semitransparent yellowish infiltrate was found at this site, but at that time, we did not note it as a pathological sign. As a result, the fungal keratitis was suspected on 12.12.16; the antibiotic was replaced with a local antiseptic, the instillation of dexamethasone was discontinued. On 15.12.16 the lesion was scrapped, the direct microscopic evaluation revealed fungus spores and filaments, but the growth of fungi was not determined in culture.

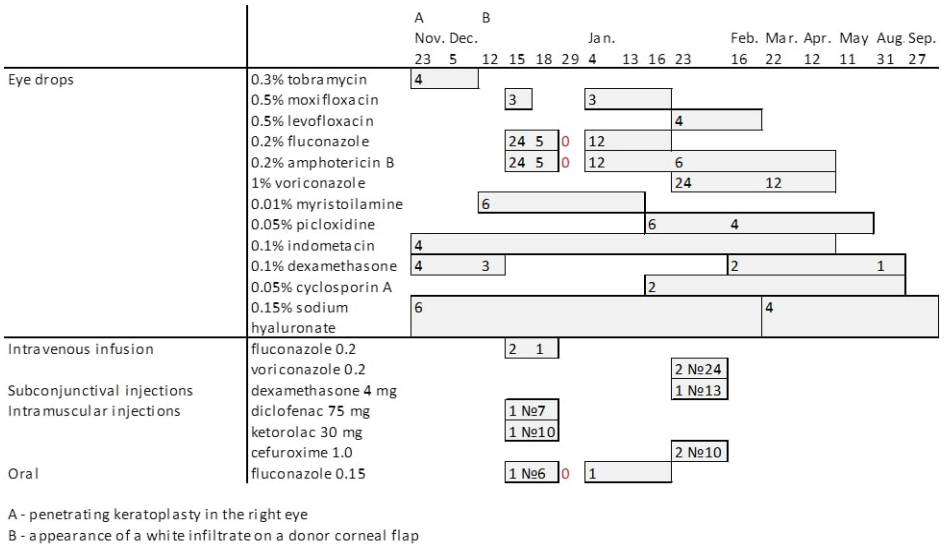

Figure 1. The timeline of the intensive treatment. Numbers opposite to medicines indicate the frequency of application. A - penetrating keratoplasty in the right eye. B - appearance of an infiltrate on the donor corneal flap (see Fig. 2B). Since 29.12.16 till 04.01.17 the patient interrupted the specific treatment

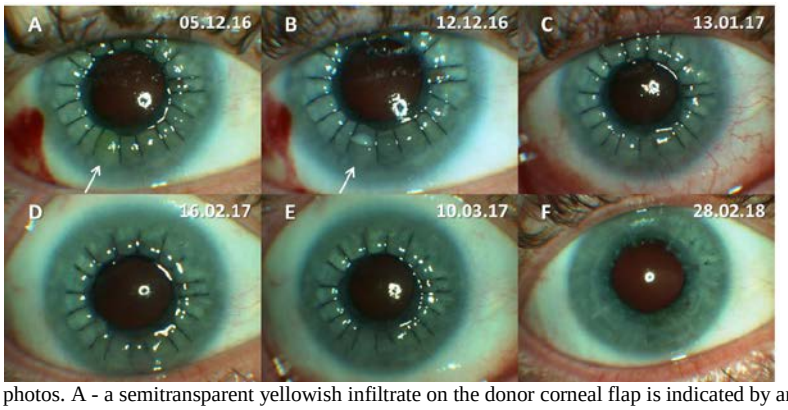

Figure 2. Anterior segment photos. A - a semitransparent yellowish infiltrate on the donor corneal flap is indicated by an arrow. B - white opaque infiltrate of the same localization. C - moderate corneal neovascularization in the lower quadrant, a semitransparent grayish infiltrate of the same localization. D-F - regression of neovascularization, epithelialization of the lesion

In the absence of officinal antifungal eye drops, 0.2% fluconazole solution for intravenous infusion and 0.2% amphotericin B (ex tempore) were instilled. Also, the patient received fluconazole intravenously, fluconazole in capsules, systemic and local anti-inflammatory therapy was performed (Fig. 1). By 29.12.16, epithelialization of the cornea was complete, but on 04.01.17, the keratitis recurred at the former site. Subsequently the keratitis recurred again with a moderate neovascularization of the cornea (Fig. 2C). Topical cyclosporine 0.05% was added to treatment, antiseptic "Okomistin" was replaced by 0.05% picloxidine (Fig. 1). The lesion was scraped every time, the microscopy and culture showed the same results as previously.

Antimycotic treatment was changed since 23.01.17. The second scheme included corneal scraping every 3 days, topical voriconazole 1% (we gave new ex tempore solution to the patient every 5 days) and systemic voriconazole, topical amphotericin B and levofloxacin. Systemic cefuroxime was used to prevent mixed infection. By 16.02.17 (Fig. 2 D-F) there was no infiltrate, the corneal epithelization was complete, the cornea was transparent, and neovascularization regressed. Topical dexamethasone 0.1% was added to treatment, the course of topical antimycotic therapy continued: amphotericin B up to 4 months and voriconazole up to 2.5 months (Fig. 1). As a result, during the next 14 months, there were no recurrences, all drugs were gradually discontinued. The corneal sutures were removed on 10.01.18; residual fragments remained due to long-term preservation and partial degradation of sutures. On examination, 17.04.18 best-corrected visual acuity reached 1.0 (with correction sph 0 cyl -6,0D ax62°). During the next 2 years of follow-up keratitis did not recur.

Discussion

Fungal keratitis after PKP deserves special attention of surgeons and eye banks specialists, because it is a devastating disease. In the presented case, the material for transplantation was obtained from the eye bank, which sterility conditions correspond to ISO 14644. The remnants of the donor cornea after the transplantation were not examined so we could not state whether the disease was iatrogenic. Fungal keratitis was clinically suspected early enough due to frequent monitoring of the patient. Diagnosis of fungal keratitis was routinely based on the results of the smear microscopy, but the culture was negative as it occurs in 52-68% [9]. The lack of officinal ophthalmic antifungal drugs in Russia made us seek an alternative solution to the problem [5]. In the presented case, we used ex tempore preparations of specific drugs.

The first treatment regimen (Fig. 2 B-E) included corneal scraping and antimycotic drugs of two different groups. Amphotericin B is a polyene, effective against Aspergillus and Candida and less effective against Fusarium. In case of systemic use, it poorly penetrates the eye and is nephrotoxic. In this regard, amphotericin B was used topically. Fluconazole is a fungistatic antibiotic of the azoles group with proven local and systemic safety. It penetrates the cornea well and is most effective in the treatment of Candida-associated infection. Systemic use of antimycotics is recommended only in cases of severe fungal infection, in the presented case, the condition after PKP was regarded as an additional risk factor requiring the most intensive treatment regimen [2,7].

The recurrence of fungal keratitis required a change in the treatment regimen. First-line therapy in the treatment of fungal keratitis includes topical natamycin and voriconazole [2,3,7,9]. Natamycin is absent in Russia in the form of a solution or powder, therefore, we couldn't use it. Voriconazole is presented as a powder for infusion preparation. There is also a cheap alternative to the specific antimycotics – 0.2% chlorhexidine gluconate. It is shown to be as effective as topical 2.5% natamycin, however, we did not use it [6]. A long course of treatment with voriconazole and amphotericin B led to recovery without relapse within 3 years of follow-up.

Discontinuation of local corticosteroids less than a month after PKP did not result in graft disease; however, neovascularization of the cornea soon developed. The use of antimycotics combined with cyclosporin A resulted in a regress of neovascularization. Instillations of steroids was resumed after clinical recovery and did not result in infection recurrence, as shown previously [10].

Conclusion

Patients who had undergone PKP are at risk of developing fungal keratitis. Frequent monitoring of such patients contributes to the early diagnosis of infectious complications. The fungal culture is often negative and the planning of antimycotic therapy must be carried out empirically. The treatment regimen for fungal keratitis in Russian reality includes regular corneal scraping and topical 1% voriconazole, 0.2% amphotericin B and 0.2% fluconazole. Early temporary discontinuation of steroids may be safe in such cases. The efforts in the long-term struggle with corneal fungal infection, difficulties associated with ex tempore drugs preparations are justified by clinical recovery, restoration of the corneal transparency and visual acuity of the patient.

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