· Case report ·

Successful treatment of a refractory stromal fungal keratitis by intrastromal injection of amphotericin B

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Abstract

• AIM: To report a successful intrastromal injection of amphotericin B 5mg/L in a refractory fungal keratitis.

• METHODS: An interventional case report

• RESULTS: A 48-year-old lady presented with history of redness of the right eye for one week duration followed by decrease in vision and corneal opacity for two days. There was no history of trauma or foreign body. Examination revealed visual acuity of 6/18 with pinhole of 6/12 of the right eye. The conjunctiva was injected with minimal eye discharge. There was a full thickness stromal abscess at the paracentral area of the cornea. It was irregular, feathery margin with few satellite lesions. There was no epithelial defect noted. Hypopyon level was also seen. The left eye was normal. A presumptive diagnosis of fungal keratitis was entertained. Despite three weeks of intensive treatment with topical amphotericin B every 2 hours and natamycin every 4 hours and antibiotic cover, the lesion showed no sign of resolution. It grew larger and a new focal lesion of stromal abscess appeared at the 12 o'clock position. We decided to proceed with an intrastromal injection of amphotericin B 5mg/L in lieu of therapeutic penetrating keratoplasty. The size of the ulcer was substantially reduced with total disappearance of hypopyon. There was no ocular toxicity observed following the intervention. Patient regained her normal visual acuity of 6/6 after 2 months of intervention.

• CONCLUSION: An intrastromal injection of amphotericin B 5mg/L provides an alternative method of treating refractory fungal keratitis. It is also shown to be an effective and safe procedure with promising results.

• KEYWORDS: fungal keratitis; intrastromal injection; amphotericin B

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INTRODUCTION

Fungal keratitis is a well known ocular disease that is difficult to diagnose and treat. Diagnosis is usually delayed due to late presentation and absence of laboratory evidence. Clinical features may provide some clues but most keratitis has mixture of characteristics of both fungal and bacteria. Treatments with topical and systemic antifungal agents are usually prolonged with less satisfactory clinical improvement. Studies showed that 26%-66% of fungal keratitis cases were subjected to therapeutic penetrating keratoplasty[1-5]. Therapeutic penetrating keratoplasty has 84%-94% success rate [4,6] for anatomical integrity but only 51% maintained graft clarity at one year post therapeutic penetrating keratoplasty[4]. Therapeutic penetrating keratoplasty on active fungal keratitis is also associated with higher incidence of reinfection.

This case report provides an insight to a relatively new method of treating refractory fungal keratitis in human which may be beneficial in selective cases. This route of drug delivery method has been tried in animals study before with good outcome[7]. It has also being reported by various authors with varying results[8,9].

CASE REPORT

A 48-year-old lady presented to our eye clinic with history of sudden onset of redness in the right eye for one week duration. It was associated with epiphora and photophobia. She denied any history of trauma or foreign body entry to that eye. Later she developed blurring of vision and noticed corneal opacity of the right eye 2 days before presentation. She had no chronic medical illness such as diabetes or asthma, no underlying malignancy and not on any long term medications. On examination she was afebrile with blood pressure of 120/80 and pulse rate of 72 beat per minute. Ocular examination showed visual acuity of 6/18 with pinhole of 6/12 on the right eye. Visual acuity of the left eye was 6/6.

Slit-lamp examination demonstrated an injected conjunctiva with minimal eye discharge. There was a paracentral stromal abscess with ill-defined, feathery margin and few satellite lesions. The abscess involved the whole thickness of the corneal layers with endothelial plaque. Hypopyon was present measured about 0. 7mm in height and anterior chamber reaction was significantly increased, about 3 +. Pupil and lens examination was unremarkable. Anterior segment examination of the left eye was normal. Intraocular pressures were 13 mmHg on the right eye and 10 mmHg on the left eye. Right eye funduscopy showed cup disc ratio of 0. 5 with normal neuroretinal rim. There was no vitreous haze or opacity detected. The left eye was essentially normal. A presumptive diagnosis of fungal keratitis was made and patient was started empirically with topical antifungal of guttae amphotericin B 1. 5g/L every 2 hourly, guttae ceftazidime 50g/L every 2 hours and broad spectrum antibiotic of moxifloxacin 5g/L (Alcon, USA) every 2 hours. She was also given guttae homatropine 20g/L to alleviate the pain and photophobia.

Despite a week of intensive in-patient treatment with topical antifungal and antibiotics, the lesion grew larger and more anterior chamber reaction was noted. Hypopyon was increased to 2. 5mm in height. She was then started on systemic antifungal of fluconazole 200mg *bd*. At the same time the topical antibiotics were also continued.

In the following week, the stromal abscess had grown even larger with increment of the hypopyon level. Guttae natamycin 50g/L(Alcon, USA) every 4 hours was then initiated in addition to guttae amphotericin B and oral fluconazole. Alarmingly, at day 21 of admission a new full thickness stromal abscess was noted to develop at 12 o'clock position associated with endothelial plaque. The hypopyon had covered the whole pupil and measured around 8. 0mm in height (Figure 1). The vision had dropped significantly to hand movement.

The decision to intervene with intrastromal injection of the amphotericin B 5mg/L was made and the patient agreed and consented to it. This was in lieu of therapeutic penetrating keratoplasty. The procedure and the possible risks such as corneal melting, corneal perforation, possible failure and eventual therapeutic penetrating keratoplasty were explained to patient. The procedure was done in the operating theater (OT) under full sterile technique and under the microscope. The amphotericin B 5mg/L was diluted under aseptic technique in the OT. Solution of amphotericin B 5mg/L was prepared by adding 10mL of 50g/L dextrose solution to a vial containing 50mg amphotericin B. Then, 0. 1mL of this solution containing 0. 5mg amphotericin B was diluted with 10mL of 50g/L dextrose solution. Finally, 0. 1mL of the solution was diluted with 10mL of 50g/L dextrose, which give rise to a concentration of 5mg/L[7].

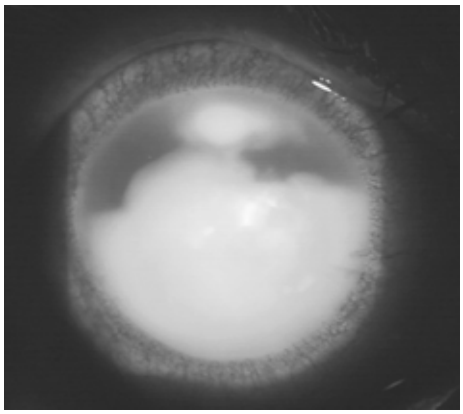

Figure 1 Stromal abscess and hypopyon following 3 weeks of guttae amphotericin B 1. 5g/L 2 hourly and systemic fluconazole 200mg twice daily.

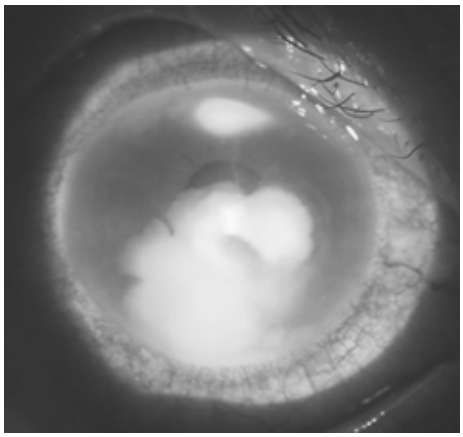

Figure 2 Reduction of stromal abscess and hypopyon after 7 days post intrastromal amphotericin B 5mg/L injection.

About 1. 0mL of amphotericin B 5mg/L was drawn in the tuberculin syringe and connected to a 30G needle. After instillation of the topical anaesthesia with propacaine hydrochloride 5g/L (Alcon-Couvreur, Belgium), the lid speculum was applied. The needle was introduced from a clear periphery area for better visualization of the needle. It was positioned in a beveled down and parallel to the corneal curvature to prevent perforation of the cornea. The injection was given at the midstromal layer and a great care is taken to prevent intracameral infiltration. The drug was injected at 2 sites; 4 and 7 o'clock positions. A total of 0. 5mL of amphotericin 5mg/L was injected. The procedure was uneventful with patient feeling no pain. The topical and systemic antifungal medications were continued as previously indicated. At 7 days post injection, the hypopyon level decreased to 7. 0 mm and superior border of the pupil was able to be seen (Figure 2). Subjectively the vision was improved to 6/36. Further reduction in the hypopyon level was noted with improvement of the patient's visual acuity. At 3 weeks post injection, the vision was improved to 6/18 with pinhole 6/9. The hypopyon level decreased markedly with reduction in the size of the stromal abscess (Figure 3). At day 50 post injection, the size of the ulcer and the hypopyon level was

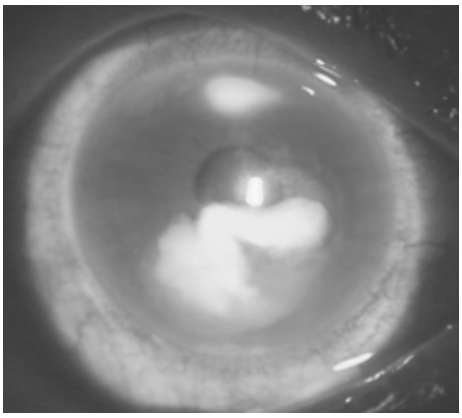

Figure 3 Keratitis at 3 weeks post injection.

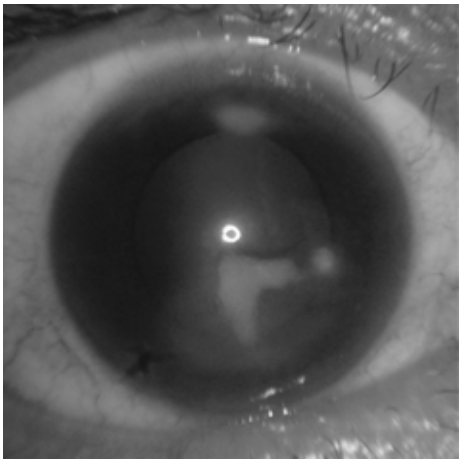

Figure 4 Reduction in stromal abscess and development of corneal scar tissue inferiorly.

reduced substantially resulting in improvement of the vision to 6/6. The rest of the corneal tissue was normal. No scar tissue was seen and the intraocular pressure was normal as well. Patient was discharged and followed up every 2 weeks with medications. At three months after intrastromal injection there was a marked reduction in the size of stromal abscess and development of scar tissue was evident inferiorly away from the visual axis (Figure 4).

DISCUSSION

Fungal keratitis remains a diagnostic and therapeutic challenge to ophthalmologists. It is associated with significant ocular morbidity worldwide especially in the developing countries. Treatment is challenging due to poor ocular penetration of the available commercial antifungal drugs and delay in seeking treatment. This case report describes the use of amphotericin B 5mg/L via the intrastromal route for fungal keratitis refractory to topical and systemic antifungal medications. One week following intervention, the hypopyon has markedly reduced in size and contracted leaving the superficial border of pupil visible and thus improvement in patient's best-corrected visual acuity (BCVA). Intrastromal injection works in this case due to increase in the local concentration of the drug to the site of fungal growth within the stroma. This has been proven by a study of intrastromal amphotericin B in rabbits in this institution[7]. It has also been reported in human to treat a recalcitrant fungal keratitis in patient refusing corneal regrafting [8]. Both studies showed a promising outcome of this surgical intervention. The effect of this intrastromal injection of amphotericin B of such concentration demonstrates no significant corneal toxicity [7].

Corneal ulcers can be classified according to the degree of stromal involvement. Mild ulcer describes a less than $1/3^{rd}$ of the superficial stromal involvement, moderate ulcer describes a lesion of $1/3^{rd}$ to $2/3^{rd}$ stromal involvement and severe ulcers denotes an ulcer involving $2/3^{rd}$ of stromal involvement, ulcer near the limbus, impending perforation or perforated corneal ulcers [10]. Severe ulcers that demonstrate impending perforation or perforated ulcers are not suitable to receive this type of intervention due to compromised corneal thickness and possible toxicity to ocular tissues. In our case, the patient was treated medically with topical natamycin and amphotericin B together with oral fluconazole but shows no improvement or reduction in hypopyon level and size of the ulcer. Usually in cases such as this, patient will have to go through a surgical procedure of tectonic penetrating keratoplasty to remove the infective tissue and to maintain globe integrity. Foster *et al* reported that almost one third of their patient needed surgical intervention where as the rest was successfully treated with topical and systemic antifungal agents. The rate of therapeutic penetrating keratoplasty was higher in eastern regions like Taiwan, 48% [4] and north China, 66% [3]. The reasons are mostly due to higher incidence of fungal keratitis where large numbers of the population are farm workers, delay in presentation to corneal specialist and poor responses to antifungal agents.

Penetrating keratoplasty carries an infectious risk because of its requirement for topical steroid therapy that facilitates fungal growth with resulting recurrence of keratitis. Although further study is required, the intrastromal injection of amphotericin B may offer an alternative treatment to therapeutic PK in refractory fungal keratitis. In conclusion, topical amphotericin B has been largely used worldwide for treatment of fungal keratitis. It is shown to be effective and safe with minimal corneal toxicity. A new method of its delivery to the targeted infected corneal tissue provides an insight to a more aggressive but safer way to combat the disease, in lieu of a more radical surgical treatment. Further trials on human should be explored in a larger study to confirm its safety and effectiveness in treating refractory fungal keratitis.

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两性霉素 B 角膜基质内注射成功治疗真菌性角膜炎 1 例

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摘要

目的:报告 1 例使用 5mg/L 两性霉素成功治疗难治性真菌性角膜炎的病例。

方法:病例报告。

结果:女性患者 1 例,48 岁,以右眼红 1wk,伴视力下降和角膜混浊 2d 入院。否认有外伤或异物史。检查发现:右眼视力:6/12,针孔视力:6/18。注射结膜前使眼分泌物保持最少。角膜旁中央区有一全层基质脓肿-形态不规则且伴有卫星病灶及羽状边缘,不伴有上皮缺损,有前房积脓液平。左眼正常。诊断为真菌性角膜炎。尽管在此前患者经历了 3wk 的局部两性霉素 B 点眼(1 次/2h),那他霉素眼液点眼(1 次/4h),但并无病情恢复的迹象。相反 12 点出现了一个新的更大的基质脓肿病灶。我们应用 5mg/L 两性霉素 B 角膜基质注射联合穿透性角膜移植术治疗后溃疡面积明显减少,前房积脓完全消失,没有毒性反应发生。患者干预后 2mo 视力恢复了正常视力(6/6)。

结论:使用两性霉素 B 5mg/L 基质内注射,使用过程安全有效,是一种治疗难治性真菌性角膜炎的理想方法。

关键词:真菌性角膜炎;角膜基质注射;两性霉素 B