Chronic Recalcitrant Bacterial Infection in Steroid Modified Interstitial (Stromal) Keratitis: Presentation and Management

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Objective: *To report histopathologically proven bacterial infection manifested multifocal interstitial (stromal) keratitis (IK) with definite previous history of prolong topical steroid use. Standard managements of bacterial keratitis did not provoke enough benefit.*
Material and Method: *A retrospective analysis of 19 eyes in 15 patients referred to Siriraj Hospital between 2004 and 2010.*
Results: *Multifocal intrastromal infiltration, with relatively quiet ocular reaction and mild inflammation were initially presented in all eyes. They all previously had been diagnosed of presumed viral keratitis, and had been given topical corticosteroid treatment for a prolonged period of time without healing. Autoimmune disease workups were all negative. Corneal scrapings showed negative culture results in all eyes. However, bacteria within stromal lamellae with absent or minimal inflammatory cells were demonstrated in all eyes by corneal biopsies. In addition, cytology results obtained from 16S rDNA sequencing revealed Stenotrophomonas maltophilia in one eye and coagulase-negative staphylococci in two eyes. No case responded well to intensive topical and systemic antibiotics. However, they were successfully treated with penetrating keratoplasty (11 eyes, 57.9%) or intrastromal antibiotic injections (8 eyes, 42.1%).*
Conclusion: *Bacterial infection should be a concern in prolonged chronic IK. This was considered as primary bacterial IK or bacterial superinfection in immunocompromised cornea. Early recognition and appropriately aggressive managements contribute to successful outcome. Corneal biopsy is always essential and 16S rDNA sequencing is useful in this distinct clinical entity.*

Keywords: *Steroid modified keratitis, Interstitial keratitis, Bacterial keratitis*

J Med Assoc Thai 2012; 95 (11): 1425-32
Full text. e-Journal: *http://jmat.mat.or.th*

The normal cornea and conjunctiva are protected by ocular surface defense, such as tear and corneal epithelia. In order to cause infection, the organism has to penetrate into the eye. Although interstitial (stromal) keratitis (IK) with absence of epithelial defect can be the result of autoimmune or microbial process, the most common cause of IK at present is Herpes virus[1], specifically herpes simplex virus (HSV) and varicella-zoster virus (VZV), which accounted for 80% of unilateral cases. In bilateral cases, idiopathic cause was reported to be the most common. The only reports of bacteria contributing to IK were syphilis, which was the leading cause of IK in the past[2,3], mycobacterial infections[4], and Lyme disease[5].

The present study reports a novel observation in 15 patients who (unilateral and bilateral cases) presented with chronic recalcitrant multifocal non-suppurative interstitial keratits caused by bacterial infection. The clinical profile, microbial spectrum, and management modalities were described.

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Material and Method

After the clinical protocol was approved by Siriraj Institutional Review Board, the authors undertook a retrospective analysis of the cases of chronic IK referred to our tertiary eye-care institution between 2004 and 2010. The final diagnosis of bacterial

infection in the cornea in all eyes was based on positive cornea gram stain or positive 16S rDNA sequencing result. Clinical course, demographic features, presence of predisposing factors, corneal characteristics, success of medical therapy, and surgery were evaluated.

Results

Nineteen eyes of 15 patients (six men and nine women) presented with chronic recalcitrant multifocal IK, aged 33 to 85 years were included (Table 1). Four patients had keratitis in both eyes. Ten patients were healthy, whereas three patients had diabetes and two patients had HIV (human immunodeficiency virus) infection. No patient was contact lens user. Two eyes had prior therapeutic keratoplasty for severe keratitis. All eyes were previously diagnosed of presumed viral stromal keratitis or keratouveitis and initially treated with topical corticosteroids for mean duration of 9.2 months (2-24 months). All eyes showed relatively good response with the topical corticosteroids. However, steroid dependence was noted because there were exacerbations of the corneal lesions, conjunctival injection, and anterior chamber reaction when they were tapered. Eight eyes were additionally given topical antibiotics.

Presenting clinical manifestations and investigative results are shown in Table 2. Representative pictures of the various clinical findings at each stage of the disease and histopathological findings are shown in Fig. 1 and 2. The initial presentation of multifocal anterior stromal opacities with relatively normal surrounding tissue was observed. Some eyes previously described as nummular keratitis in the referral medical records. The distributions of the opacities were at localized (central/paracentral) (16 eyes) or diffuse (total) area (3 eyes). Corneal epithelium was intact in the early clinical course in all eyes. Conjunctival injection and anterior chamber reaction were mild in all cases. None of the patients had purulent discharge, corneal edema, suppuration, or melting.

Immunological blood tests (rheumatoid factor (RF), antinuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid (anti-DNA), anti-neutrophil cytoplasmic antibodies (C-ANCA) were taken with negative results in all patients. Corneal scrapings were performed in all eyes, however did not yield any information. Subsequently, corneal biopsies were performed in all cases and histopathological sections demonstrated bacteria infiltrating within the stromal lamellae with absence or minimal inflammatory cells within the surrounding stroma in all eyes. They

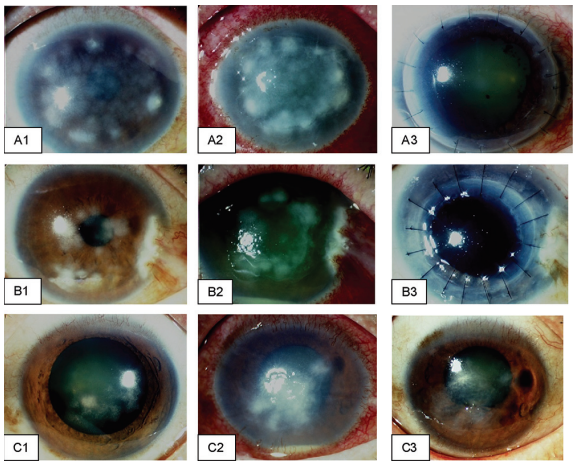

Fig. 1 Diffuse slit lamp photographs of each type of clinical feature of multifocal stromal keratitis. The pictures in the left column show the initial manifestation of multifocal infiltration, A1 at diffuse (total) cornea with relatively clear intervening stroma, B1 at central/paracentral (localized) area with relatively clear intervening stroma, C1 at central/paracentral (localized) area with opaque intervening stroma. There was no significant conjunctival injection or ocular reaction in all eyes. The pictures in the middle column show the later manifestation after discontinuing steroid eye drops. A2, B2, C2 show the stromal infiltration was more progressive with suppurative appearance, corneal epithelial breakdown, anterior chamber reaction and marked conjunctival injection. The pictures in right column are after the successful treatment, A3, B3 of surgery and C3 of medications

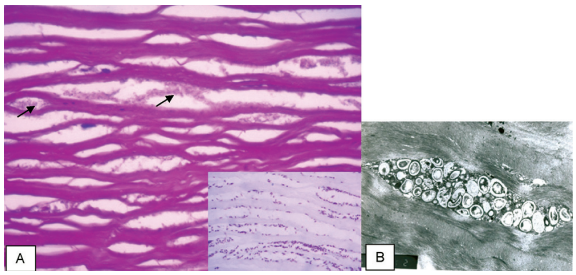

Fig. 2 A) Representative section of corneal button specimen displaying clumps of gram-negative bacteria along the stromal lamellae (arrow) with absence of inflammatory stromal reaction (hematoxylin-eosin stain). B) Transmission electron microscopy showing bacterial biofilm within a degenerative cornea. Relatively normal stromal lamellae, without inflammatory cells surrounding a mass of bacteria

Table 1. Summary of demographic data, systemic and ocular risk factors

Patient No., gender, age (years)	Lateralilty	Previous diagnosis	Systemic disease	External associated factors				
				Trauma	Topical corticosteroids, duration (months)	Systemic corticosteroids	Antiviral drugs	Antibiotics
1, F, 43	OS	Graft rejection with recurrent herpes keratitis	No	Previous PKP	Yes, 24	Yes	Yes	Yes
2, M, 52	OS	Graft rejection with recurrent herpes keratitis	No	Previous PKP	Yes, 12	Yes	Yes	Yes
3, F, 64	OD	Herpes keratouveitis	No	No	Yes, 10	No	Yes	No
	OS	Herpes keratouveitis	No	No	Yes, 10	No	Yes	No
4, M, 65	OS	Herpes keratitis	No	No	Yes, 12	No	Yes	No
5, M, 53	OD	Herpes keratitis	No	No	Yes, 8	No	Yes	Yes
6, M, 53	OD	Herpes keratouveitis	No	No	Yes, 3	No	Yes	No
7, F, 85	OD	Viral keratitis	No	No	Yes, 2	No	No	No
8, F, 66	OS	Herpes keratitis	DM	No	Yes, 2	No	Yes	No
	OD	Herpes keratitis	DM	No	Yes, 3	No	Yes	No
9, M, 52	OS	Herpes keratitis	No	No	Yes, 6	No	Yes	No
10, F, 50	OD	Viral keratitis	HIV	No	Yes, 24	No	No	No
	OS	Viral keratitis	HIV	No	Yes, 24	No	No	No
11, F, 51	OS	Viral keratitis	No	No	Yes, 12	No	No	Yes
	OD	Viral keratitis	No	No	Yes, 12	No	No	Yes
12, M, 67	OD	Viral keratitis	DM	No	Yes, 6	No	No	Yes
13, M, 33	OD	Viral keratitis	HIV	No	Yes, 12	No	No	Yes
14, M, 67	OD	Viral keratitis	DM	No	Yes, 2	No	No	No
15, M, 60	OD	Herpes keratitis	No	No	Yes, 3	No	Yes	Yes

DM = diabetes mellitus; HIV = human immunodeficiency virus; PKP = penetrating keratoplasty

Table 2. Summary of clinical presentations and clinical findings

Patient No.	Lateralilty	Presenting stromal infiltration	Location	Gram stain	Culture	Molecular detection	Successful therapy	Antibiotics
1	OS	Mutifocal	Diffuse	G negative bacilli	No growth	Negative	PKP	Amikacin, Ceftazidime
2	OS	Multifocal	Central/paracentral	G negative bacilli	No growth	Negative	PKP	Amikacin, Ceftazidime
3	OD	Mutifocal	Diffuse	G positive bacilli	No growth	Negative	PKP	Imipenem, Clindamycin, Penicillin G
	OS	Mutifocal	Central/paracentral	G positive bacilli	No growth	Negative	Intrastromal INJ	Imipenem, Clindamycin, Penicillin G
4	OS	Focal	Central/paracentral	G negative bacilli	No growth	Negative	PKP	Imipenem, Ceftazidime
5	OD	Multifocal	Central/paracentral	G positive bacilli	No growth	Negative	PKP	Imipenem, Vancomycin, Moxifloxacin
6	OD	Focal	Central/paracentral	G negative bacilli	No growth	S. maltophilia	PKP	Moxifloxacin, Ceftazidime, TMP/SMX
7	OD	Multifocal	Central/paracentral	G negative bacilli	No growth	Negative	PKP	Gatifloxacin, Ceftazidime, TMP/SMX
8	OS	Multifocal	Central/paracentral	G negative bacilli	No growth	CMV	PKP	Gatifloxacin, TMP/SMX, Amikacin
	OD	Multifocal	Central/paracentral	G negative bacilli	No growth	Negative	PKP	Gatifloxacin, TMP/SMX, Amikacin
9	OS	Focal	Central/paracentral	G negative bacilli	No growth	Negative	PKP	Gatifloxacin, TMP/SMX, Amikacin
10	OD	Multifocal	Central/paracentral	G negative bacilli	No growth	Negative	Intrastromal INJ	Imipenem, Ceftazidime
	OS	Focal	Central/paracentral	G negative bacilli	No growth	Negative	Intrastromal INJ	Imipenem, Ceftazidime
11	OS	Focal	Central/paracentral	G negative bacilli	No growth	CMV	Intrastromal INJ	Ceftazidime, Amikacin
	OD	Focal	Central/paracentral	G negative bacilli	No growth	Negative	Intrastromal INJ	Ceftazidime, Amikacin
12	OD	Focal	Central/paracentral	G variable coccobacilli	No growth	CNS	Intrastromal INJ	Vancomycin, Ceftazidime
13	OD	Multifocal	Diffuse	G variable coccobacilli	No growth	Negative	PKP	Imipenem, Ceftazidime
14	OD	Focal	Central/paracentral	G variable coccobacilli	No growth	CNS	Medication	Vancomycin, Ceftazidime, Amikacin
15	OD	Focal	Central/paracentral	G variable coccobacilli	No growth	Negative	Medication	Vancomycin, Gatifloxacin, Amikacin

CMV = cytomegalovirus; CNS = coagulase-negative staphylococci; PKP = penetrating keratoplasty; TMP/SMX = trimethoprim/sulfamethoxazole; Intrastromal INJ = intrastromal antibiotic injection

were gram-negative bacilli in 12 eyes (63.2%), gram-variable coccobacilli in four eyes (21.0%), and gram-positive bacilli in three eyes (15.8%). Even though tissues from corneal biopsies collecting in culture media (blood agar, chocolate agar, thioglycolate broth, Lowenstein-Jensen medium, and sabouraud dextrose agar) were no growth, the tissues sending for molecular detection were positive in three cases. The molecular results revealed *Stenotrophomonas maltophilia* in one eye and coagulase-negative staphylococci in two eyes. The PCR assays for HSV and VZV were negative in all cases.

By the time bacterial infection was suspected, any topical corticosteroids were discontinued and intensive broad-spectrum topical antibiotics were instilled in all cases. Subsequently, the relatively quiet clinical features became more progressive. Secondary epithelial breakdown and more suppurative stromal infiltration were detected. At this stage, the lesions appeared to be more typical for bacterial corneal ulcers. The types of antibiotics were modified depending on the type of organism demonstrated and the clinical response. Systemic antibiotics were added in all eyes for deep and extensive lesions. Despite those medications, good results were not achieved in any eyes. Eventually, 11 eyes (58%) required therapeutic penetrating keratoplasty. After the corneal transplantations, topical corticosteroids were cautiously challenged at one to three weeks and no recurrence of the infection was observed. On the other hand, eight eyes (42%) were successfully treated with medication with slow resolution over several months. In fact, all eyes in this successful medical therapy group, except the left eye of Patient 3, were additionally treated with intrastromal antibiotic injections and noticeably good responses were found.

Discussion

Bacterial keratitis is a potentially sight-threatening condition. Even though a few bacteria, such as *Neisseria gonorrheae*, *Corynebacterium diphtheriae*, *Haemophilus aegypticus*, and *Listeria monocytogenes*, can penetrate an intact corneal epithelium, bacterial keratitis is rarely found in an eye with normal epithelium and usually associated with inflammation and tissue destruction. The present study reported 15 cases (19 eyes) with chronic non-suppurative IK, which later proved to be bacterial infection.

The initial clinical features of IK led to prolonged use of topical corticosteroids in all cases. This can impair ocular defense mechanism[6], alter microbial flora and facilitate the occurrence of secondary corneal bacterial infection. Chronic viral infection of the corneal stroma may also contribute to compromised ocular surface and later causes recurrent epithelial defects. A few studies in 1980s[7-9] reported bacterial super infections in various forms of herpetic ocular diseases including dendritic ulcers and keratouveitis. They found the causative agents of gram-negative rods and gram-positive organisms with similar incidence. Matoba et al[10] later reported polymicrobial kratitis in one patient with herpetic stromal keratitis.

The present study reported gram-negative bacilli in 12 eyes (63%) as the most common bacterial infection in stromal keratitis, followed by gram-variable coccobacilli in four eyes (21%), and gram-positive bacilli in three eyes (16%). Some gram-positive bacteria may lose the stain easily and therefore appear as a mixture of gram-positive and gram-negative bacteria (gram-variable). Moreover, gram-positive cells affected by cell wall active agents such as lysozyme or antibiotics may become gram-negative. Certain group of bacteria can display variable response to the stain, which can be due to growth stress (*e.g.*, unsuitable nutrients, temperatures, pHs, or electrolytes).

The histopathological findings of bacteria within the corneal stromal lamellae with relatively pauci-inflammatory reaction and the feature of stromal keratitis occurring after long-term use of topical corticosteroid in the present study were similar to the distinct histological findings of infectious crystalline keratopathy (ICK) which was firstly reported in 1983[11]. Depending on variability in bacterial virulence and altered host defense mechanism, atypical clinical presentations may occur. This explanation may imply to the authors' novel clinical finding as a specific primary clinical presentation of bacterial IK caused by chronic bacterial colonization in the stroma. Instead of characteristic crystalline branching intrastromal opacities, the cases in the present study were manifested as non-suppurative non-crystalline IK. Biofilm, bacterial colonies surrounded by polysaccharide-rich bacterial extracellular matrix (glycocalix), described as the possible pathogenic mechanism for ICK was similarly found in the present report. This explained the lack of inflammatory response and resistance to antimicrobial therapy[12-14]. It was found in a wide range of organisms[12,13,15,16]. Since organisms themselves have slower growing rate within the biofilm, this also possibly explained the negative culture result[17-20].

Because of negative investigative results and limited response to therapies, corneal biopsies were

undertaken in all cases. Even though the corneal tissue cultures were negative, the organisms were identified by molecular methods in three eyes in the present study (*Stenotrophomonas maltophilia* one eye, coagulase-negative staphylococci two eyes). PCR (polymerase chain reaction) analysis has been reported to detect microbial DNA in the majority of corneal ulcers and identify pathogenic organisms in a high proportion of culture-negative cases[21-23]. It is in particular useful if only a small amount of pathogens are available or if the eye has been treated by antibiotics prior to the microbiological diagnosis.

Successful medical therapy of eight eyes (42.1%) in the present series was relevant to the severity at presentation when all eyes in this group were at localized location. In addition, this group of the patients noticeably found in later years when the authors were capable of early recognition of this atypical bacterial infection and when the additional treatment of intrastromal antibiotic injections were initiated. The eyes demonstrated favorable response after the treatment with no need of keratoplasty. Although, intraocular medical treatment is off-label, it has been investigated for the safety profile in human and animal model[24-27]. Intracameral antibacterial injection has been shown in studies to be effectively used as prophylaxis and treatment of intraocular bacterial infection[24,28-30]. Intrastromal antifungal agents have been used effectively for deep and localized intrastromal location when inadequate treatment with topical drugs[31-34].

A case of *Stenotrophomonas maltrophilia* failed to respond to medical therapy. This organism has been rarely reported to cause keratitis including ICK[35,36]. Despite being bacteriostatic, TMP/SMX is the combination of choice[37]. Characteristically, ocular isolates of this gram-negative bacilli were resistant to aminoglycosides, quinolones and most beta-lactam antibiotics and trimethoprim/sulfamethoxazole (TMP/SMX). A combination of ticarcillin and clavulanic acid was one of the most active compounds against *S. maltophilia in vitro*[38].

In conclusion, the authors suggest to be aware of atypical bacterial infection in IK especially when presumed herpetic IK is in chronic form and not responsive well to standard treatment. Use of corticosteroids should be discontinued. Aggressive investigations should be done. Corneal biopsy is always essential when corneal scraping is insufficient for the deep lesion. Molecular method is particularly useful when culture result is negative.

Potential conflicts of interest

None.

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กระจกตาอักเสบชนิด interstitial keratitis เรื้อรังสาเหตุจากเชื้อแบคทีเรียในตาที่ได้รับยาหยอดสเตียรอยด์ระยะยาว: ลักษณะทางคลินิกและการรักษา

สุขศรี โชติกวณิชย์, ณัฐพร เทศะวิบุล, มงคล อุยประเสริฐกุล, อมรรัตน์ ลีลาภรณ์, ภิญนิตา ประภาสะวัต

วัตถุประสงค์: *ศึกษากระจกตาอักเสบเรื้อรังชนิด interstitial (stromal) keratitis ที่มีประวัติเคยได้รับการรักษาด้วยยาหยอดสเตียรอยด์ระยะยาว ต่อมาพบว่ามีสาเหตุจากการติดเชื้อแบคทีเรีย พิสูจน์โดยการตรวจทางพยาธิวิทยา กระจกตาอักเสบดังกล่าวไม่ตอบสนองด้วยการรักษาแบบกระจกตาอักเสบติดเชื้อแบคทีเรียโดยทั่วไป*

วัสดุและวิธีการ: *ทำการศึกษาแบบวิเคราะห์ย้อนหลังใน 19 ตา จากผู้ป่วย 15 ราย ที่ได้รับการส่งตัวมารักษาที่โรงพยาบาลศิริราช ช่วงปี พ.ศ. 2547 ถึง พ.ศ. 2553*

ผลการศึกษา: *แรกรับทุกรายพบกระจกตามีลักษณะ multifocal intrastromal infiltration โดยมีตาแดงและการอักเสบในตาเพียงเล็กน้อยร่วมด้วย ผู้ป่วยทุกรายมีประวัติเคยได้รับการวินิจฉัยและรักษาแบบการติดเชื้อไวรัสที่กระจกตา โดยได้รับรักษาด้วยยาหยอดสเตียรอยด์ระยะยาวแต่กระจกตาอักเสบไม่หายขาด ผลการตรวจ autoimmune disease ทุกรายอยู่ในเกณฑ์ปกติ การขูดผิวกระจกตาส่งตรวจไม่พบเชื้อในทุกตา สุดท้ายทุกรายได้รับการตัดชิ้นเนื้อที่กระจกตาส่งตรวจทางพยาธิวิทยา และพบเชื้อแบคทีเรียในกระจกตา โดยพบเม็ดเลือดขาวบริเวณรอบ ๆ เพียงเล็กน้อย ส่วนชิ้นเนื้อกระจกตาที่ส่งเพาะเชื้อไม่พบเชื้อใด ๆ ชิ้นเนื้อกระจกตาที่ส่งตรวจ 16S rDNA sequencing พบเชื้อ Stenotrophomonas maltophilia 1 ตา และ coagulase-negative staphylococci 2 ตา ทุกตาไม่ตอบสนองต่อยาหยอด ยากิน หรือ ยาฉีดฆ่าเชื้อแบคทีเรีย แต่หายได้ด้วยการผ่าตัดเปลี่ยนกระจกตา (11 ตา, 57.9%) หรือ การฉีดยาฆ่าเชื้อแบคทีเรีย เข้าที่กระจกตาโดยตรง (8 ตา, 41.2%)*

สรุป: *การติดเชื้อแบคทีเรียควรได้รับการนึกถึงไว้ด้วยในกระจกตาอักเสบชนิด interstitial keratitis เรื้อรัง การติดเชื้อนี้อาจมีสาเหตุจากแบคทีเรียโดยตรง หรือ มีการติดเชื้อแบคทีเรียแทรกซ้อนในตาที่ได้รับยาหยอดสเตียรอยด์ระยะยาว การตัดชิ้นเนื้อกระจกตาส่งตรวจพยาธิวิทยา และการตรวจ 16S rDNA sequencing อาจมีความจำเป็นที่ช่วยในการวินิจฉัยและการรักษา*