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Short communication

Clinical features of *Streptococcus pyogenes* keratitis: Case series

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ABSTRACT

Purpose: To characterize the risk factors, clinical presentations, management, outcomes, and microbiological properties of *Streptococcus pyogenes* keratitis.

Methods: Eight culture-proven cases (eight eyes) of *S. pyogenes* keratitis were diagnosed and treated between 2008 and 2018 at the University of Pittsburgh Medical Center (UPMC). Medical records were available for six patients, and these were reviewed to identify demographic information, systemic and ocular history, clinical presentations, antibiotic sensitivity, treatments, and outcomes of *S. pyogenes* isolates.

Results: Of the six charts reviewed, the median patient age was 67 years and all patients were female. Four patients had a history of cataract extraction more than one year prior to presentation, one had a history of improper contact lens use, and one had basement membrane dystrophy. Two patients, who also happened to have the most serious medical comorbidities, presented with corneal perforation on initial examination. The median follow-up length was 90.5 days. Visual outcomes varied greatly between patients. Three patients had visual acuity ranging from 20/30 to 20/70, while the two patients with corneal perforation had a final visual acuity of light perception, and one patient was lost to follow-up. Five of six isolates were susceptible to fluoroquinolones and all isolates were susceptible to cefazolin.

Conclusions: S. pyogenes represented an uncommon ocular pathogen at UPMC eye clinic. However, if left untreated, this infection resulted in severe ocular morbidity. The majority of patients had a benign ocular history, suggesting that *S. pyogenes* can infect healthy corneas in immunocompetent patients. The majority of isolates were susceptible to cefazolin and fluoroquinolones.

1. Introduction

Group A *Streptococcus pyogenes* is a Gram positive, catalase negative bacteria known to cause numerous infectious of the skin, soft tissue, bloodstream, and viscera in humans. *S. pyogenes* is identified by the presence of pyrrolidonyl arylamidase (PYR) and the observance of beta-hemolysis on broth agar supplemented with 5% animal red blood cells. *S. pyogenes* can also cause ocular infections, the most common being blepharitis, conjunctivitis, and keratitis [1]. Case studies have documented *S. pyogenes* endogenous endophthalmitis secondary to hematologic dissemination from diverse and distant sites including the pharynx [2], pelvis [3], skin [4], and bones [5]. *S. pyogenes* keratitis has been diagnosed in patients with concurrent streptococcal pharyngitis [6], corneal graft suture infections [7], Streptococcal Toxic Shock Syndrome [8], and periorbital necrotizing fasciitis [9]. Additionally, exogenous endophthalmitis secondary to *S. pyogenes* has been found in the setting of prior cataract surgery [10] and glaucoma implant surgery [11]. A recent systematic review by Tweldermdhin et al. found that on average 4.3% of ocular infections worldwide with identifiable bacterial isolates were secondary to *S. pyogenes*, with a national prevalence ranging between 0.55% of all ocular infections in India to 14.4% of ocular infections in Ethiopia [1].

Given its uncommon nature, a paucity of data exists regarding *S. pyogenes* ocular infection, specifically *S. pyogenes* keratitis. For example, Fong et al. reported that *S. pyogenes* represents 1.6% of bacterial keratitis in 476 cases at a hospital in Tawian [12]. If cases of *S. pyogenes* keratitis are not detected early, they can result in complications such as corneal scarring, perforation, and endophthalmitis leaving patients with devastating visual outcomes. Compared to infections caused by *Staphylococcus* and other *Streptococcus* species, *S. pyogenes* infections cause particularly severe infections characterized by rapid progression and typically poor visual outcomes [13]. The virulence of *S. pyogenes* has been attributed to its M-proteins, which limit the ability of polymorphonuclear leukocytes to phagocytose the bacteria [14]. Furthermore, while *S. pyogenes* is typically susceptible to penicillin and its derivatives, recent antibiotic susceptibility studies have found isolates

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of *S. pyogenes* resistant to potent antibiotics such as vancomycin [15].

Given the often fulminant nature of *S. pyogenes* infections, early detection and timely antibiotic therapy is crucial to providing patients with the best possible visual outcomes. As a result, this study aimed to characterize the clinical presentations, medical and surgical management, outcomes, and microbiological characteristics of *S. pyogenes* keratitis.

2. Methods

All cases of bacterial keratitis diagnosed at the University of Pittsburgh Medical Center (UPMC) between 2008 and 2018 were reviewed. The Charles T. Ophthlamic Microbiology Lab of UPMC performed all microbiology testing.

The bacterial keratitis cultures submitted to this lab included samples of the cornea, conjunctiva, and eyelid margin on 5% sheep blood supplemented agar, chocolate agar, and mannitol salt agar. Corneal scrapings were stained with Gram and Giemsa. Consisent with the departmental protocol for gram positive organisms, susceptibilities to the following antibiotics were tested on all isolates: bacitracin, cefazolin, ciprofloxacin, gentamicin, moxifloxacin, ofloxacin, polymyxin, sulfa, tobramycin, and vancomycin.

Once cases of S. pyogenes keratitis were identified, the following clinical data was collected from the medical records: age, gender, ocular and systemic history, symptom duration, initial and final visual acuity, intraocular pressure, slit lamp examination findings, follow-up length, medical and surgical management, corneal culture data, as well as isolate antibiotic susceptibility data.

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The Institutional Review Board (IRB) deemed this a case series that does not meet the federal definition of research as defined by 45 CFF 46 102.d. Therefore, IRB oversight was not required.

3. Results

Between 2008 and 2018, a total of 805 culture-positive cases of bacterial keratitis were diagnosed at this facility. Of these, eight cases (0.99%) were secondary to *S. pyogenes*. Medical records were available for six cases. All six patients were female. The median age at presentation was 67 years [range 33–79]. Demographic and medical history data are displayed in Table 1. Five of the patients initially presented to the Emergency Room, while one patient was referred to UPMC clinic from another ophthalmologist.

Regarding systemic medical illnesses, four of the six patients had at least one medical comorbidity. One patient had a history of untreated Hepatitis C infection as well as a history of intravenous drug use. One patient had a history of asthma as well as eczema for which she was on weekly Dupilumab injections. One patient had a history of hypertension and diabetes mellitus. Finally, one patient had a history of hypertension, diabetes mellitus, and intellectual disability that impacted her ability to properly use eyedrops. No patient had an active systemic illness involving *S. pyogenes* at the time of presentation.

Five out of six patients had a past ocular history (Table 1). Four patients had a history of cataract extraction more than one year prior to presentation, one patient had a history of improper contact lens use, and one patient had a history of epithelial basement membrane dystrophy.

At initial presentation, all cases had unilateral involvement. The median time from onset of symptoms to presentation to UPMC clinic was 7.5 days [range 0–30] (Table 2). All patients reported pain or irritation as a presenting symptom. Three patients had already seen an ophthalmologist or optometrist, and each of these patients was treated empirically without obtaining corneal cultures (Table 2). Of these, one patient was treated with moxifloxacin, tobradex, and bromfenac for suspected keratitis. A second patient was given daily neomycin for suspected chalazion, and the third was started on prednisolone acetate for suspected conjunctivitis.

Initial visual acuity on presentation ranged from 20/40 to light perception (Table 2). Intra-ocular pressure ranged from ‘soft’ (unrecordable) to 22 mmHg. At the time of examination, corneal ulcers were found to range from 0.5 to 3 square millimeters in size (Table 2). Three were noted to have central corneal involvement. Furthermore, all corneas demonstrated corneal thinning and two cases presented with frank corneal perforation. One of these patients was found to have a 2 mm x 2 mm corneal perforation with iris plugging the corneal defect. The other was noted to have a corneal perforation with necrosis of the iris and lens. This patient was the only patient to have posterior segment involvement, and was found to have choroidal effusion and retinal necrosis.

All patients were started on empirical topical antibiotics with additional adjunctive therapy while awaiting culture and susceptibility data (Table 2). Four patients were placed on a regimen that included hourly fortified antibiotic drops: one patient was given moxifloxacin and fortified cefazolin and three patietns were started on fortified tobramycin and fortified cefazolin. The other two patients were started on hourly moxifloxacin.

The microbiological data and isolate susceptibilities are presented in Table 3. Four cultures demonstrated only *S. pyogenes*, while one patient had concomitant infection with *methicillin-resistant Staphylococcus aureus* and one patient had concomitant infection with m*ethicillin-susceptible Staphylococcus aureus*. A standardized gram positive organism antibiotic susceptibility panel was performed. All isolates were susceptible to bacitracin, cefazolin, gentamicin, and vancomycin. One isolate was resistant to sulfa. One isolate was resistant to polymyxin and sulfa. One isolate was resistant to ciprofloxacin, moxifloxacin, ofloxacin, sulfa, and tobramycin. Three isolates were resistant to polymyxin, sulfa, and tobramycin. The isolates from the patients presenting with corneal perforation were identical, and demonstrated resistance to polymyxin, sulfa, and tobramycin.

Median follow-up time was 90.5 days [range 4–157] (Table 4). The patient with four days of follow-up transferred their care to an ophthalmologist closer to their home. The four patients who were initially managed medically did not require surgical intervention at any point in time. However, adjunctive medical therapies included a combination of antibiotics based on susceptibility data, prednisolone acetate to reduce inflammation, and adjunctive oral doxycycline and vitamin C to aid in corneal wound healing.

The two patients presenting with corneal perforation required surgical intervention within 24 h of presentation (Table 4). One patient required cyanoacrylate glue followed by Gunderson flap two weeks

Table 1
Demographic Data of patients with *Streptococcus pyogenes* keratitis.

Patient	Gender	Age	Past Ocular History	Past Medical History
1	Female	33	Contact lens use; No prior surgery	None
2	Female	79	Pseudophakia OU; Primary open angle glaucoma	Hypertension, Diabetes Mellitus
3	Female	70	Pseudophakia OU	Hypertension, Diabetes Mellitus, Hyperlipidemia, Intellectual Disability
4	Female	64	Pseudophakia OU, Epithelial basement membrane dystrophy OU	Asthma, Eczema on Dupilumab
5	Female	43	None	Hepatitis C (Untreated), IV Drug Use
6	Female	74	Pseudophakia OD	None

Table 2
Corneal Examination and Initial Management of cases with *Streptococcus pyogenes* keratitis.

Patient	Symptom Duration (days)	Prior Therapy	Initial VA	IOP	Corneal Ulcer Description	Corneal Perforation	Initial Management	Initial Antibiotics	Adjunctive Therapy on Presentation
1	5	Moxifloxacin, Bromfenac, Tobradex	HM	20	0.5 mm ulcer with ring infiltrate, stellate stromal edema with 5% thinning	No	Medical	Moxifloxacin + fortified Cefazolin	Vitamin C
2	0	None	CF	19	1.5 mm x 1.5 mm inferior ulcer with bullous keratopathy	No	Medical	Moxifloxacin	None
3	10	Neomycin	CF	12	Perforated 2.0 mm x 2.0 mm superior ulcer with iris plugging the wound	Yes	Medical and surgical	Fortified Tobramycin + fortified Cefazolin	Doxycycline, Vitamin C
4	4	Prednisolone Acetate 1% q2hrs	20/40	12	3.0 mm x 3.0 mm ulcer with 30% thinning	No	Medical	Moxifloxacin	None
5[a]	14	None	LP	Soft	Perforated corneal ulcer with necrosis of cornea, iris, and lens	Yes	Medical and surgical	Fortified Tobramycin + fortified Cefazolin	Doxycycline, Vitamin C
6	30	None	CF	22	Central 1.5 × 1.5 mm ulcer with 20% thinning	No	Medical	Fortified Tobramycin + fortified Cefazolin	None

VA: visual acuity; IOP: intraocular pressure; HM: hand motions; CF: counting figures; LP: light perception.
[a] Choroidal effusion, retinal necrosis.

Table 3
Corneal Cultures and Sensitivities of *Streptococcus pyogenes* corneal ulcers.

Patient	S. Pyogenes Culture	Additional Isolates	Sensitivities	Resistances
1	Light *S. pyogenes*	–	Bacitracin, Cefazolin, Ciprofloxacin, Gentamycin, Moxifloxacin, Ofloxacin, Tobramycin, Vancomycin.	Polymyxin, Sulfa
2	Moderate *S. pyogenes*	–	Bacitracin, Cefazolin, Ciprofloxacin, Gentamycin, Moxifloxacin, Ofloxacin, Vancomycin.	Polymyxin, Sulfa, Tobramycin
3	Heavy *S. pyogenes*	–	Bacitracin, Cefazolin, Ciprofloxacin, Gentamycin, Moxifloxacin, Ofloxacin, Vancomycin.	Polymyxin, Sulfa, Tobramycin
4	2 colonies *S. pyogenes*	2 colonies *Methicillin-Sensitive S. Aureus*	Bacitracin, Cefazolin, Ciprofloxacin, Gentamycin, Moxifloxacin, Ofloxacin, Polymyxin, Tobramycin, Vancomycin.	Sulfa
5	Moderate *S. pyogenes*	Light *Methicillin-Resistant S. Aureus*	Bacitracin, Cefazolin, Ciprofloxacin, Gentamycin, Moxifloxacin, Ofloxacin, Vancomycin.	Polymyxin, Sulfa, Tobramycin
6	Light *S. pyogenes*	–	Bacitracin, Cefazolin, Gentamycin, Vancomycin.	Ciprofloxacin, Moxifloxacin, Ofloxacin, Sulfa, Tobramycin

Table 4
: Outcomes of *Streptococcus pyogenes* Corneal Ulcers.

Patient	Surgical Intervention	Details of Surgical Intervention	Last Recorded Follow Up	Final Visual Acuity
1	No	–	18 days	20/30
2	No	–	4 days	Count Fingers[a]
3	Yes	Within 24 hours of presentation: Cyanoacrylate gluing; Continued leakage from site and with Gunderson flap placed 2 weeks later	57 days	Light perception
4	No	–	157 days	20/30
5	Yes	Within 24 hours of presentation: Penetrating keratoplasty with anterior vitrectomy to remove necrotic cornea, iris, lens	142 days	Light Perception
6	No	–	124 days	20/70

[a] Associated bullous keratopathy.

later. The second patient with corneal perforation had posterior segment involvement and required penetrating keratoplasty along with anterior vitrectomy. The corneal graft eventually failed due to poor compliance with post-operative care.

Final visual outcomes were measured at the last recorded clinic visit (Table 4). Three patients maintained functionally useful vision ranging from 20/30 to 20/70. However, the vision of the remaining three patients ranged from count fingers at face to light perception only. Both patients presenting with corneal perforation had a final visual outcome of light perception.

4. Discussion

S. pyogenes is a rare cause of keratitis. Previous studies have included only isolated case reports, typically in the setting of recent surgery or underlying systemic infection. However, eight cases of culture-proven *S. pyogenes* corneal ulcers were diagnosed and treated at the University of Pittsburgh Medical Center over a 10-year period, representing the first case series of *S. pyogenes* keratitis in the literature thus far.

Though the sample size is not large enough to make definitive conclusions, important demographic trends were identified. First, it is interesting to note that all six patients in this study were females. Larger case series are required to better understand the relationship, if any, *S. pyogenes* infection has with gender.

Further, half of the patients had serious systemic comorbidities. This included Hepatitis C and intra-vitreous drug use, eczema requiring monoclonal antibody immunosuppression, and intellectual disability delaying presentation and interfering with treatment adherence. The patients who had more serious medical comorbidities also tended to have worse outcomes, as two of them presented with frank corneal perforation, and were only able to regain vision to the level of light perception despite timely surgical intervention.

Additionally, it is noteworthy that the majority of patients in this series had a relatively benign ocular history. While the only risk factor present in the majority of patients (four out of six) was history of cataract surgery, given the prevalence of cataract surgery in the population, this more likely represents an association with, rather than a true risk factor for, *S. pyogenes* keratitis. One patient had a history of improper contact lens use and another had epithelial basement membrane dystrophy. Poor ocular surface is a known risk factor for bacterial keratitis, and it appears *S. pyogenes* keratitis is no exception. None of the patients had recently undergone intra-ocular surgery. Additionally, none of the patients were septic on presentation or had systemic manifestaions of *S. pyogenes* infection such as pharyngitis, cellulitis, impetigo, erysipelas, bacteremia, toxic shock syndrome, or scarlet fever. These results suggest that one cannot rely on the absence of these classic *S. pyogenes* infections to rule out *S. pyogenes* as a cause of bacterial keratitis on first presentation. Although not relevant to any patients in this report, an uncommonly reported source of infection is transfer of the organism to the eyes by using saliva to lubricate the eye. Carriage of S. pyogenes in the throat is common in asymptomatic subjects. Therefore it is important that patients are warned against rubbing their eyes with saliva contaminated fingers. The need for good personal hygiene with frequent hand washing following surgery needs to be stressed before discharge of patients.

Consistent with prior studies, *S. pyogenes* caused particularly fulminant ocular infections in this series. The median time to presentation was 7.5 days. However, there was a marked difference in visual outcomes between those who presented within one week of symptom onset versus after one week of symptoms onset. Excluding the patient with incomplete follow-up, those presenting within one week of symptom onset both had visual acuity of 20/30 at most recent follow-up, while those presenting after one week were 20/70 and light perception at the conclusion of the study. In addition to delayed time to presentation, the two patients requiring surgical management had medical comorbidities that further compromised their care: one had intellectual disability limiting her ability to instill eye drops and the other had a history of intra-venous drug use and poor adherence to medical advice. It is interesting to note that these two patients had isolates with the same antimicrobial susceptibilities, possibly representing a more virulent strain of *S. pyogenes*,that caused both corneal perforation and posterior segment involvement.

A few additional trends regarding *S. pyogenes* susceptibilities emerged when analyzing these cases. While tobramycin was prescribed as empiric therapy in three patients, resistance to tobramycin was present in three out of six isolates. Given these results, empiric treatment with tobramycin for suspected *S. pyogenes* infection may be ineffective. Five out of six isolates were susceptible to fluoroquinolones. All isolates were susceptible to cefazolin. Given the fulminant nature of *S. pyogenes* keratitis, it would be reasonable to empirically prescribe topical fluoroquinolone and fortified cefazolin while awaiting culture data and susceptibility studies.

S. pyogenes keratits is a rare but aggressive infection that can be complicated by diagnostic delays and posterior segment involvement in otherwise healthy eyes. Together, these features can lead to devastating consequences for patients. Classic examination findings have not yet been established. However, the finding of corneal perforation at presentation suggests a truly virulent pathogen such as *S. pyogenes.* As outlined in this case series, a team-based approach with a specialized ocular microbiology laboratory is paramount for proper diagnosis and treatment. Larger studies are needed to better understand the clinical course of *S. pyogenes* keratitis and to establish formal treatment guidelines.

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Conflict of interest statement

None.

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