Infective keratitis in advanced glaucoma patients

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Background: To describe a case series of infective keratitis in patients with advanced glaucoma in Selayang Hospital, Malaysia.
Methods: This is a descriptive, retrospective case series. Data from January 2013 to December 2017 was traced from hospital database and analyzed.
Results: A total of 17 eyes of 16 patients was included in this series. Seven were males and nine were females. Mean age group was 64 ± 12 years old (range 48 to 93 years old). Twelve patients had underlying diabetes mellitus. Seven patients (44%) had primary glaucoma (Six POAGs and one PACG), while nine patients (56%) had secondary glaucoma, of which six were due to rubeosis iridis. All patients had premorbid vision of counting fingers or worse. Thirteen patients (81%) were on long term topical anti-glaucoma treatment prior to the development of infective keratitis. Most of the patients had poor IOP control at the time of diagnosis. Painful red eyes were the main presenting symptoms. Corneal scrapings were positive in nine (64.3%) out of the fourteen cases, in which three were Pseudomonas aeruginosa, one Klebsiella sp., three Streptococcus sp., and three others had mixed growth. Majority of the cases were treated medically, but three eyes required evisceration.
Conclusion: Diabetes mellitus, uncontrolled IOP, long term topical anti-glaucoma drops and poor premorbid vision are risk factors for developing infective keratitis in advanced glaucoma patients. Infective keratitis can lead to significant morbidity in this group of patients whose quality of life is already poor.
Conflicts of interest: The authors report no conflicts of interest.
Acknowledgment: We would like to thank the Director General of Health Malaysia for his permission to publish this article.
Keywords: Infective keratitis, Advanced glaucoma
EyeSEA 2019;14(1):29-35
Full text. https://www.tci-thaijo.org/index.php/eyesea/index

Introduction

Glaucoma is a leading cause of visual impairment and irreversible blindness globally.[1] It can lead to significant morbidity and affect patients' quality of life. Patients who are blind from advanced glaucoma can also develop other complications, including infective keratitis. Infective keratitis is a very serious eye condition that can lead to significant corneal scarring and vascularization, or in worst scenarios, corneal perforations which warrant evisceration.

Purposes

1.To describe the incidence of infective keratitis in patients with advanced glaucoma in Selayang Hospital, Malaysia.

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Received: 26 December 2018
Accepted: 25 May 2019
Published: 30 June 2019
https://doi.org/10.36281/2019010202

2.To determine the risk factors for infective keratitis in this group of patients.
3.To determine the causative organisms causing infective keratitis in this group of patients.
4.To determine the ocular outcomes of these patients**.**

Methods

This is a descriptive retrospective case series done from the period between January 2013 and December 2017 in Selayang Hospital, Malaysia. Data collection was done by tracing the electronic patient records and ward admission census. Patients' age, gender, race, diagnosis, glaucoma treatment, visual acuity before developing infective keratitis (premorbid visual acuity), vision at presentation and presenting intraocular pressure (IOP) were recorded. Microorganism culture results and outcome of the treatment were also included in the data collection.

Results

A total of 17 eyes of 16 patients was included in this series. Out of these, 10 patients were Chinese; five were Malay and one was Indian. There were seven males (44%) and nine females (56%). Mean age group was 64 ± 12 years old (range 48 to 93 years old). Ten cases involved the right eye while five cases involved the left eye, one patient had bilateral eye involvement. Twelve patients had underlying diabetes mellitus, twelve patients had hypertension while three patients had end stage renal disease. Seven patients (44%) had primary glaucoma (Six cases of primary open angle glaucoma and one case of primary angle closure glaucoma), whereas nine patients (56%) had secondary glaucoma, of which six were due to rubeotic glaucoma secondary to proliferative diabetic retinopathy (PDR).

All patients had a premorbid vision of counting fingers or worse (counting fingers, hand movement, perception of light or no perception of light). Thirteen patients (81%)were on long term topical anti-glaucoma treatment prior to the development of infective keratitis. Most of the cases (12 patients) had poor IOP control at the time of diagnosis of infective keratitis. Almost all patients presented with painful red eyes. Eleven cases presented with hypopyon, three cases developed corneal melting and perforation (one patient had bilateral eye corneal perforations). Corneal scrapings were sent in 14 cases and out of these, nine (64.3%) were positive for organisms and five (35.7%) had no growth. Of the positive cultures, all were due to bacterial pathogens; four (28.6%) were Gram-negative bacteria (three cases of Pseudomonas aeruginosa and one case of Klebsiella sp.), three (21.4%) were Gram-positive (Streptococcus sp.) while the other two (14.3%) had mixed growth.

All cases were treated with empirical topical antibiotics; three cases were treated with topical anti-fungals (amphotericin B 0.15% and fluconazole 0.2%) and systemic anti-fungal (oral fluconazole 200 mg OD) based on the clinical presentation (fluffy edged infiltrates with endothelial plaques). One patient developed endophthalmitis and was treated with intravitreal antibiotics (vancomycin 1mg in 0.1ml and ceftazidime 2 mg in 0.1ml). Majority of the cases (12 patients) were prescribed a combination of topical ceftazidime 5% and fortified gentamicin 0.9%. Three patients were started on fluoroquinolone monotherapy of either topical moxifloxacin 0.5% or ciprofloxacin 0.3%. Systemic antibiotics (intravenous or oral ciprofloxacin) were started in four patients as they developed corneal perforation and endophthalmitis. Despite intensive anti-microbial therapy, three eyes had to be eviscerated following corneal perforation and melting. Eight cases had healed from infective keratitis with corneal scarring and vascularization, three cases

developed decompensated corneas while four cases were lost to follow up.

Discussion

Glaucoma is one of the leading causes of visual impairment and irreversible blindness worldwide, with an estimated 8.4 million people getting blindness from glaucoma.[1] Infective keratitis can develop in patients with advanced glaucoma, leading to significant morbidity and further affecting patients' quality of life. This case series describes the incidence of infective keratitis in patients with advanced glaucoma in Selayang Hospital, Malaysia.

In this series, Gram-negative organisms were the commonest organism cultured; there were three cases of Pseudomonas infection and a case of Klebsiella infection, followed by three cases of Gram-positive organisms, all of which were Streptococcus infection. There were no fungal organisms which were cultured. Interestingly, there are geographic variations in bacterial keratitis, with Paraguay reporting the highest number of Staphylococcal infections (79%), Bangkok reporting the highest prevalence of Pseudomonas infections (55%), and Tamil Naidu more prevalent with Streptococcal infections (47%).[2]

Diabetes mellitus seems to be an important causative factor for corneal ulcers. Diabetes can lead to poor tear film quality, ocular surface disease, diabetic keratopathy and neurotrophic keratopathy.[3] Diabetic keratopathy can lead to fragile corneal epithelium and poor healing of epithelial defects. This condition is made worse by corneal hypoesthesia as seen in neurotropic keratopathy, which ranges from punctate keratopathy, epithelial irregularity to epithelial breakdown and even corneal ulcers which can melt and perforate.[3] On the other hand, endothelial cell dysfunction could lead to corneal decompensation and development of bullous keratopathy.[3]

Contamination of anti-glaucoma drops may also contribute to infective keratitis. A study done by Teuchner et al. showed that the contamination rate of topical antiglaucoma is significantly higher than of antibiotics or anesthetic eye drops. In the same study, it was also found that the tip of the medication bottle was more frequently contaminated as compared to the eye drops themselves.[4] Another study also showed that advanced glaucoma patients with poor vision or severe visual field defects had higher failure rates of eye drop instillation.[5] Frequently, the tip of medication bottles touches the bulbar conjunctiva, cornea, eyelid or eyelashes during drug instillation, and this might lead to unintentional injury of the ocular surface.[5] Together with the contamination of eye drops, they may contribute to infective keratitis especially in this group of patients. Therefore, the presence of an assistant to help instill eye drops could be beneficial.

Another causative factor is the long-term use of topical anti-glaucoma eye drops, which can lead to tear film instability and ocular surface disorders.[6] A study has shown that latanoprost causes significant reduction in tear break-up time, and brimonidine causes significant reduction in the basal secretion of tears.[6] In another study done by Baratz et al., chronic use of topical anti-glaucoma eye drops also leads to a reduction in the number and density of corneal sub-basal nerve fibers, which could worsen cornea hypoesthesia as described above.[7]

In this series, most of the affected patients had suboptimal IOP control despite being on medications. Uncontrolled intraocular pressure could lead to corneal decompensation and hence predispose the patients to corneal ulcers. In a study by Martin et al., the authors showed high success rates of cyclodiode laser treatment for IOP reduction and pain relief in blind glaucomatous eyes.[8] Hence in eyes with poor visual prognosis, cyclodiode laser treatment could be

performed for IOP control and pain relief, as well as to reduce the need for topical anti-glaucoma eye drop usage.

Severe bacterial keratitis warrants intensive antibiotic therapy, which usually consists of topical fluoroquinolone monotherapy or aminoglycoside-cephalosporin combination. Prompt empirical treatment is usually required to cover for both gram-positive and gram-negative pathogens while waiting for culture and sensitivity results. In this series, most of our patients were treated with a combination of fortified aminoglycoside-cephalosporin, with a few treated with fluoroquinolone monotherapy. Interestingly, a meta-analysis[9] comparing monotherapy and combination therapy has shown no significant difference in their efficacy. Fluoroquinolones were shown to significantly reduce ocular discomfort and rate of chemical conjunctivitis compared to combination therapy, while fortified combination therapy was said to cause increased corneal irritation and delayed corneal epithelialization.[9] The risk of corneal perforation between the two groups did not differ significantly. However, topical fluoroquinolone especially ciprofloxacin has an increased risk of white precipitate formation.[9]

Conclusion

Diabetes mellitus, suboptimal IOP control, long term topical anti-glaucoma drops and poor premorbid vision are the risk factors for developing infective keratitis in patients with advanced glaucoma. Infective keratitis can lead to significant morbidity in advanced glaucoma patients whose quality of life are already poor. Hence, prevention is better than cure and prompt treatment of infective keratitis is the key.

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Table 1: Demographic Data of Patients

Case	Age (years)	Sex	Race	Co-morbid	Eye	Ocular Diagnosis	Topical Antiglaucoma	Pre-morbid vision
1	53	M	Malay	DM HPT	OD	Rubeotic glaucoma secondary to PDR	Latanoprost Brimonidine	NPL
2	64	F	Chinese	DM HPT	OD	Aphakic glaucoma	Timolol Latanoprost	HM
3	69	F	Malay	nil	OD	Advanced PACG	Timolol Latanoprost	PL
4	66	F	Chinese	nil	OD	Advanced POAG	Timolol Latanoprost Brimonidine Dorzolamide	PL
5	50	F	Malay	DM	OD	Advanced POAG	Timolol Latanoprost Brimonidine Dorzolamide	CF 1ft
6	93	F	Malay	nil	OS	Advanced POAG	NIL	NPL
7	69	M	Chinese	DM HPT	OD	Advanced POAG	Timolol Latanoprost Brimonidine	NPL
8	50	M	Malay	DM HPT	OS	Rubeotic glaucoma secondary to PDR	Timolol Latanoprost	HM
9	78	F	Chinese	HPT IHD	OD	Advanced POAG	Timolol Bimatoprost	PL
10	48	M	Chinese	DM HPT ESRD	OD	Rubeotic glaucoma secondary to PDR	Brimonidine Dorzolamide	NPL
11	63	F	Indian	DM HPT	OS	Rubeotic glaucoma secondary to PDR	Timolol Latanoprost	NPL
12	52	M	Chinese	DM HPT	OS	Rubeotic glaucoma secondary to PDR	Timolol Bimatoprost	HM
13	62	M	Chinese	DM HPT ESRD	OU	Uveitic glaucoma	NIL	OD NPL OS CF 1ft
14	62	F	Chinese	DM HPT ESRD	OD	Rubeotic glaucoma secondary to PDR	Timolol Latanoprost Brimonidine	HM
15	62	M	Chinese	DM HPT	OS	Secondary glaucoma post complicated cataract surgery	Timolol Latanoprost Brimonidine Dorzolamide	HM
16	81	F	Chinese	DM, HPT CRD	OD	Advanced POAG	NIL	NPL

Abbreviations

CRD : Chronic Renal disease
DM : Diabetes Mellitus
ESRD : End stage renal disease
HPT : Hypertension
IHD : Ischemic heart disease
PDR : Proliferative diabetic retinopathy
POAG : Primary open angle glaucoma
PACG : Primary angle closure glaucoma

Table 2: Clinical presentations of patients

Case	Presenting Vision	Presenting IOP (mmHg)	Symptoms	Signs
1	NPL	38	Pain and redness x 5/7	Hypopyon, dense stromal abscess
2	HM	13	Pain and redness x 3/7	Paracentral infiltrate, hypopyon
3	PL	33	Pain, redness, discharge x 3/7	Paracentral infiltrate
4	NPL	27	Pain and discharge x 4/7	Hypopyon, corneal melting
5	CF 1ft	26	Pain and redness x 1/52	Paracentral infiltrate, hypopyon
6	NPL	23	Pain and discharge x 1/12	Perforated corneal ulcer
7	NPL	27	Pain and redness x 2/52	Central infiltrate, hypopyon
8	HM	27	Pain and redness x 3/7	Paracentral infiltrate, endothelial plaque
9	PL	20	Pain and redness x 1/52	Hypopyon, central infiltrate
10	NPL	8	Pain x 3/7	Total hypopyon, corneal thinning
11	NPL	49	Pain and redness x 3/7	Central infiltrate, hypopyon
12	HM	8	Redness and discharge x 4/7	Paracentral infiltrate, hypopyon
13	OD NPL OS PL	30	Pain and redness x 1/52	Perforated corneal ulcer
14	NPL	30	Pain and discharge x 2/52	Paracentral infiltrate, hypopyon
15	PL	8	Redness and discharge x 3/7	Central infiltrate, endothelial plaque
16	NPL	36	Redness and discharge x 2/7	Central infiltrate, hypopyon

Table 3: Treatments and outcome of patients

Case	Microorganism culture	Treatment	Final Vision	Outcome
1	Streptococcus group C	Gtt. CAZ 5% Gtt. GEN 0.9%	NPL	Corneal scar, vascularization
2	Pseudomonas aeruginosa	Gtt. CAZ 5% Gtt. GEN 0.9%	HM	Decompensated cornea
3	Klebsiella sp.	Gtt. CAZ 5% Gtt. GEN 0.9%	NPL	Corneal scar, vascularization
4	Pseudomonas aeruginosa	Gtt. CAZ 5% Gtt. GEN 0.9%	-	Eviscerated
5	No growth	Gtt. MXF 0.5%	CF 2ft	Corneal scar
6	Not sent	Gtt. CIP 0.3% Tab. CIP 250mg BD	NPL	Tarsorrhaphy done Loss to follow up
7	No growth	Gtt. CAZ 5% Gtt. GEN 0.9% Gtt. AMB 0.15% Gtt. FLC 0.2%	NPL	Corneal scar, vascularization
8	No growth	Gtt. CAZ 5% Gtt. GEN 0.9% Gtt. AMB 0.15% Gtt. FLC 0.2% IVit VAN 1mg in 0.1ml IVit CAZ 2mg in 0.1ml Tab. FLC 200mg OD Tab. CIP 500mg BD	HM	Endophthalmitis, Decompensated cornea
9	Pseudomonas aeruginosa	Gtt. CAZ 5% Gtt. GEN 0.9%	NPL	Corneal scar, vascularization
10	Mixed growth	Gtt. CAZ 5% Gtt. GEN 0.9% IV CIP 200mg OD	NPL	Corneal perforation, loss to follow up
11	Streptococcus pneumoniae	Gtt. CAZ 5% Gtt. GEN 0.9%	NPL	Corneal scar, vascularization
12	Not sent	Gtt. CXM 5% Gtt. GEN 0.9% Tab. CIP 750mg BD	CF 1ft	Loss to follow up
13	No growth	IV CIP 250mg OD Gtt. MXF 0.5%	-	BE eviscerated
14	No growth	Gtt. CAZ 5% Gtt. GEN 0.9%	NPL	Bullous keratopathy, decompensated cornea
15	Mixed growth	Gtt. CAZ 5% Gtt. GEN 0.9% Gtt. AMB 0.15% Gtt. FLC 0.2% Tab. FLC 200mg OD	HM	Corneal scar, vascularization
16	Streptococcus pneumoniae	Gtt. CAZ 5% Gtt. GEN 0.9%	NPL	Corneal scar, vascularization

Abbrevitations

AMB	: Amphotericin B	FLC	: Fluconazole	IVit	: Intravitreal
CAZ	: Ceftazidime	GEN	: Gentamicin	MXF	: Moxifloxacin
CIP	: Ciprofloxacin	Gtt	: Gutta	Tab	: Tablet
CXM	: Cefuroxime	IV	: Intravenous	VAN	: Vancomycin