Endophthalmitis caused by Non-tuberculous Mycobacterium: Clinical features,
Antimicrobial Susceptibilities and Treatment Outcomes

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Short Title - Endophthalmitis caused by Non-tuberculous Mycobacterium

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Introduction

The genus *Mycobacterium* includes more than 50 species including typical (tubercular) and atypical mycobacteria (non-tubercular). Atypical mycobacteria or Non-tuberculous mycobacterium (NTM) have been classified into 4 groups by Runyon in 1959 (Photochromogens, Scotochromogens, Non-chromogens, Rapidly growing mycobacteria).¹ These are aerobic, non-motile, non-spore forming, rapid growing, acid fast bacilli which are widespread in environment. Rapidly growing mycobacteria from Runyon group IV are associated with ocular infections including canaliculitis, dacryocystitis, scleritis, keratitis, uveitis, orbital cellulitis, panophthalmitis, scleral buckle infections and endophthalmitis.²⁻⁷

Endophthalmitis caused by non-tuberculous mycobacterium was first reported in 1989, and was associated with poor visual outcomes.^{6,7} The most common non-tuberculous mycobacterium species isolated from patients with endophthalmitis are *Mycobacterium fortuitum* and *Mycobacterium chelonae*.^{8,9} Rarely endophthalmitis has been reported to be caused by other species of non-tuberculous mycobacterium such as *Mycobacterium hemophilum*,¹⁰ *Mycobacterium goodii*,¹¹ *Mycobacterium avium*,¹² *Mycobacterium gordonae*.¹³ The purpose of this study is to report the clinical features, antibiotic susceptibilities and treatment outcomes of non-tuberculous mycobacterium endophthalmitis cases from our institution.

Methods

The current study is a non-comparative, consecutive case series. A search identifying all culture positive mycobacteria specimens was performed within a computerized database at the microbiology laboratory of Bascom Palmer Eye Institute between December 1990 and June 2014. A retrospective chart review of medical and microbiological records of these patients was performed. Non-tuberculous mycobacterium was isolated in 19/2173 culture positive endophthalmitis patients during this time period. The study was approved by Institutional Review Board (IRB) at University of Miami, Miller School of Medicine, Miami, Florida. The study was performed in accordance with HIPAA regulations. All patients gave informed consent for treatment.

Patient data including age at presentation, gender, history of immunosuppression, etiology, Snellen's best corrected visual acuity at presentation and last visit, clinical features, microbiology findings, management and outcomes were recorded. Clinical diagnosis was confirmed by positive culture of intraocular fluid sample (anterior chamber fluid or vitreous) or cornea by standard laboratory protocol including smear preparation (Gram, Geimsa, 10%KOH wet mount and Ziehl-Neelsen stain if non-tuberculous mycobacterium was suspected) and inoculation of culture media (5% sheep blood agar, chocolate agar, brain heart infusion broth, Sabouraud's dextrose agar and thioglycollate broth and Lowenstein-Jenson medium if non-tuberculous mycobacterium was suspected). Antibiotic susceptibility was determined by obtaining minimum

inhibitory concentrations of various antibiotics using broth microdilution method (as per National Committee for Clinical Laboratory Standards or Clinical and Laboratory Standards Institute guidelines).

Results

The current study included 19 patients with a mean age of the patients at presentation was 62.2 years (range – 23-86 years) and no specific gender predilection (Male:Females=10:9) (Table 1). The mean follow-up duration was 50.4 months (range 1-180 months) (Table 2). The clinical setting of endophthalmitis was as following: post-cataract surgery (7/19, 36.8%), post-glaucoma implant (6/19, 31.6%), post-intravitreal injection (2/19, 10.5%), endogenous endophthalmitis (2/19, 10.5%), post-pars plana vitrectomy (1/19, 5.3%) and post-scleral buckle exposure (1/19, 5.3%). Mean duration of symptoms before presentation was 9 weeks (range – 2 days to 1 year) before the diagnosis of endophthalmitis was made. Chronic recurrent or persisting ocular inflammation was present in 15/19 patients (78.9%). Associated clinical findings included chronic hypotony (6 patients), retinal detachment (1 patient), corneal infiltrates (2 patients), scleral involvement (2 patients), and hypopyon (Figure 1 and Table 1).

Systemic illness - History of systemic illness was present in 6/19 (31.5%) patients (Table 1). Five of these patients (26.3%) had a history of malignancy and treatment with radiotherapy and/or chemotherapy. One patient (5.3%) had associated cytomegalovirus retinitis. Two patients (10.5%) had received subtenon triamcinolone and may have had a local immunosuppressed environment. Systemic history of diabetes (2/19 patients, 10.5%), arthritis (4 patients, 21.0%), hypertension (3 patients, 15.8%) and cone dystrophy (1 patient, 5.3%) was noted.

Microbiology evaluation - All study patients had a positive culture from intraocular fluid (vitreous-13 and anterior chamber fluid-6). The causative organisms isolated were *Mycobacterium chelonae* in 14/19 (73.7%) patients, *Mycobacterium fortuitum* in 3/19 (15.8%) patients, *Mycobacterium triplex* in 1/19 (5.3%) patients and *Mycobacterium avium intracellulare* in 1/19 (5.3%) patients. Using DNA sequencing, 7 subspecies of *Mycobacterium chelonae/abscessus* were identified. Antibiotic susceptibility was determined for 17/19 (89.5%) patients (test not performed for other two patients). Table 3 shows the rate of antimicrobial susceptibility, intermediate susceptibility and resistance in this cohort of patients. The mycobacterial isolates were susceptible to amikacin in 14/16 isolates (87.5%) and clarithromycin in 12/16 isolates (75.0%). However resistance was seen to ciprofloxacin in 12/15 isolates (80%), to doxycycline in 11/12 isolates (91.7%), and to sulphamethoxazole in 9/11 isolates (81.8%).

Treatment - Systemic antibiotics were administered to 12 patients (oral clarithromycin/azithromycin/ciprofloxacin, intravenous levofloxacin/amikacin, Table 2). During the course of treatment, 14/19 (73.7%) patients underwent one or more pars plana vitrectomy (Table 2). Intravitreal injections of amikacin (0.4mg/0.1ml) were given

in 14/19 patients with an average of 7 injections per patient (range – 1-24 injections). Intraocular lens removal was performed for 6/7 (85.7%) patients with post cataract surgery endophthalmitis. All the patients with glaucoma implant (6/6, 100%) underwent implant removal (Figure 2 and Table 2).

Visual and Anatomical Outcomes - At last follow-up, 6/19 patients (31.6%) had best corrected visual acuity of 20/400 or better. Enucleation was performed in 4/19 (21.1%) patients and 1/19 (5.3%) patients had phthisis bulbi. Visual acuity data has been shown in Tables 4 and 5.

Discussion

Immunocompromised states (eg. use of corticosteroids/ immunosuppressive drugs, malignancy, uncontrolled diabetes) are well-recognized risk factors for development of non-tuberculous mycobacterium infection.² In the current study, patients had a history of malignancy (5/19, 26.3% patients), diabetes (2/19, 10.5% patients), arthritis (4/19, 21.1% patients) and asthma (2/19, 10.5% patients).

Presence of an implant in or around the globe (prosthetics placed after enucleation, nasolacrimal silicone stents, scleral buckles, contact lenses, glaucoma implants and punctal plugs) have been reported to be associated with a risk of non-tuberculous mycobacterium infection.¹⁴ The presence of an implant may act as a scaffold for the formation of biofilm by non-tuberculous mycobacterium. This biofilm provides a survival advantage to mycobacteria by limiting the antibiotic penetration¹⁵ and thus leading to chronic or persisting infection. For eradication of non-tuberculous mycobacterium, multiple intravitreal injections with or without implant removal may be required as demonstrated in the current study.

Commonly, endophthalmitis caused by non-tuberculous mycobacterium manifests with low grade ocular inflammation.³ In the current study, the majority (80%) of patients did present with chronic low grade ocular inflammation. In post-cataract setting, low grade inflammation can be misdiagnosed with *Propionibacterium acnes*, *Nocardia*, *Corynebacterium* or fungal infections.¹⁶ A white plaque between IOL and capsular bag (Figure 3) may indicate organisms clustered inside the capsule which are responsible for the recurrence of inflammation and infection.^{3,5,6,16,17}

Laboratory confirmation of non-tuberculous mycobacterium may be enhanced by obtaining and culturing a part of the capsular bag where the organisms are thought to be sequestered.¹⁶ Although these are type IV rapid growing non-tuberculous mycobacterium (within a week), there are a high rate of negative cultures initially. Having a high index of suspicion based on clinical presentation and observing the culture plates for more than seven days seems to be helpful in such cases. Performing specific microbiology evaluation such as acid fast staining for acid fast bacilli, Ziehl

Neelsen (ZN) staining or polymerase chain reaction (PCR) for non-tuberculous mycobacterium genomic sequence help in early identification of these organisms.¹⁸

Management strategies for non-tuberculous mycobacterium endophthalmitis are not well defined. Amikacin, clarithromycin, and/ or azithromycin have been considered to be the best antibiotics for non-tuberculous mycobacterium infections.³ Intravitreal moxifloxacin and imipenem, although not used in this series of patients, have been reported to be successful in the management of isolated cases of endophthalmitis.¹⁹⁻²¹ In the current study, susceptibility of mycobacterial isolates to amikacin and clarithromycin was reported in 14/16 (87.5%) and 12/16 (75.0%) isolates respectively. Given the current data, treatment with pars plana vitrectomy, removal of implant (intraocular lens, glaucoma implant or scleral buckle) (Figure 4), serial intravitreal amikacin and systemic azithromycin/clarithromycin (oral) is recommended.

The retrospective nature of the current study, small number of patients, and the lack of standardized treatment protocol are important limitations of current study. However, the current series is the largest clinical study of non-tuberculous mycobacterium endophthalmitis to date (based on a PubMed search using “mycobacterium” and “endophthalmitis” as keywords) and provides important clinical and microbiological information in the management of these patients. Also, this is the first report of non-tuberculous mycobacterium endophthalmitis following pars plana vitrectomy.

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Authors' contributions

MS, NR, AEK collected the data and drafted the manuscript. TAA, AP, JLD and HWF helped to look for relevant literature, understand the concept better and did the critical revision of manuscript. All the authors have read and approved the manuscript submitted.

Captions: Figures

Figure 1 – A 76 year old, pseudophakic female patient (patient number 3) with post glaucoma implant surgery, presented with marked anterior segment inflammation and hypopyon.

Figure 2 – Exposed and infected glaucoma implant in a patient (patient number 3) with marked anterior segment inflammation and hypopyon. Her glaucoma implant was removed, received oral clarithromycin, 24 intravitreal injections of amikacin. Despite all treatment her visual outcome was hand motions at 5 years of follow-up.

Figure 3 – A 69 year old male patient (patient number 10), with white plaque between intraocular lens and posterior capsule presented with low grade ocular inflammation.

Figure 4 – An 80 year old male patient (patient number 5) with history of multiple recurrent retinal detachment surgeries in past, presented post-scleral buckle removal performed for buckle exposure and infection. The patient had conjunctival congestion, chemosis, purulent endoexudates at the back of the cornea, hypopyon, vitritis and retinal detachment.

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Table 1 –History, clinical presentation and causative organism of patients with non- tuberculous mycobacterium endophthalmitis.

No	Age/ Sex	Etiology	Presentation (Acute/Chronic)	Mycobacteria species ^a (Isolated from)	Associated systemic Illness
1	76/M	Post-cataract surgery	Chronic (H)	<i>M. chelonae</i> (Vit)	-
2*	68/F	Post-GDI and PK	Chronic	<i>M. chelonae</i> (Vit)	-
3	76/F	Post-GDI	Chronic(H)	<i>M. chelonae</i> (AC)	Asthma, Arthritis, Anemia, Hysterectomy, Cancer
4	80/F	Post-cataract surgery	Acute	<i>M. chelonae</i> (Vit)	-
5	80/M	Post-scleral buckle removal	Chronic	<i>M. chelonae</i> (AC)	-
6	23/M	Post-GDI	Chronic(H)	<i>M. chelonae</i> (Vit)	-
7	65/M	Post-GDI	Chronic	<i>M. chelonae</i> (Vit)	-
8	71/F	Post-cataract surgery	Chronic (H)	<i>M. chelonae/abscessus</i> (Vit)	Arthritis
9*	62/M	Post-IVTA	Chronic	<i>M. chelonae/abscessus</i> (Vit)	DM, HTN
10	69/F	Post-cataract surgery	Chronic	<i>M. chelonae/abscessus</i> (Vit)	RT, CT, Low platelet, Arthritis, Asthma
11	69/F	Post-intravitreal bevacizumab	Chronic(H)	<i>M. chelonae/abscessus</i> (AC)	Low grade leukemia, CT, RT, Lung lobectomy
12	53/F	Post-cataract/pupilloplasty surgery	Chronic	<i>M. chelonae/abscessus</i> (Vit)	HTN
13	54/M	Post-cataract surgery (traumatic cataract)	Chronic	<i>M. chelonae/abscessus</i> (AC)	HTN, Arthritis, DM, Insulin
14	74/M	Post-cataract surgery	Acute	<i>M. chelonae/abscessus</i> (AC)	-
15	35/F	Post-GDI	Chronic	<i>M. fortuitum</i> (Vit)	Kidney & Pancreas transplant
16	55/F	Post-vitreectomy	Chronic	<i>M. fortuitum</i> (Vit)	Breast CA, CT and RT, Hysterectomy
17	86/M	Post-GDI	Chronic (H)	<i>M. fortuitum</i> (AC)	-
18	33/M	Endogenous	NA	<i>M. triplex</i> (Vit)	-
19	53/M	Endogenous	Acute	<i>M. avium intracellulare</i> (Vit)	HIV and CMV retinitis

AC-anterior chamber, CA-carcinoma, CT-chemotherapy, CMV-cytomegalovirus, DM-diabetes mellitus, F-female, GDI-glaucoma drainage implant, (H)-hypotony, HIV-human immunodeficiency virus, HTN-hypertension, IOL-intraocular lens, IVTA-intravitreal triamcinolone, M-male, NA-information not available, PK-penetrating keratoplasty, RT-radiotherapy, Vit-vitreous,

^a – Mycobacterium species isolated from vitreous or anterior chamber fluid or intraocular lens

(* – Patient number 2 and 9 previously were reported by Scott et al, 2004 (Reference number 5).

Table 2 –Systemic and surgical treatment (including surgical procedures, intravitreal amikacin injection and implant removal) of patients with non-tuberculous mycobacterium endophthalmitis.

No	Systemic Therapy (duration)	Primary Treatment	Implant removal ^a	Number of additional surgeries ^b	Number of Intravitreal Amikacin
1	None	PPV+ Capsulectomy+ IOAB (V+D)	IOL-R	3 ^c	1
2*	None	GDI-R + IOAB (V+C)	GDI-R	1	0
3	Oral Clarithromycin (4 weeks)	Revision of GDI + IOAB (V+A)	GDI-R	1 ^c	24
4	Oral Clarithromycin (4 weeks)	PPV + IOAB (V+C)	IOL-R + PK	1 ^c	7
5	Oral Clarithromycin (4 weeks)	PPV + Lensectomy + gas exchange	SB-R	1 ^c	3
6	Oral Clarithromycin (1 week)	Tube revision + AC tap	GDI-R	1	0
7	None	AC tap + IOAB (V+C+D)	GDI-R	2	2
8	None	PPV + IOAB (A)	IOL-R	1 ^c	7
9*	Intravenous Amikacin (1 week)	PPV	Enucleation	2 ^c	5
10	Oral Clarithromycin (3 weeks) Oral Rifampin (2 Week) Oral Azithromycin (4 weeks)	PPV + Capsulectomy + IOAB (V+C+D)	IOL-R	2 ^c	9
11	Oral Clarithromycin (4 weeks)	PPV + IOAB (V+G)	-	3 ^c	8
12	Oral Azithromycin (1 week)	VIT tap + IOAB	IOL-R	4 ^c	13
13	Oral Azithromycin (2 weeks)	AC tap + IOAB (V)	-	2	2
14	None	AC wash and biopsy	IOL-R	2 ^c	0
15	Oral Ciprofloxacin (2 weeks)	Vitreous tap + IOAB (V+C+D)	GDI-R + IOL-R	1 ^c	4
16	None	Vitreous tap + IOAB (V+C)	-	1 ^c	9
17	Intravenous Levofloxacin (weeks)	GDI-R + IOAB (V+C+D)	GDI-R	6 ^c	1
18	None	NA	Systemic a/b	NA	NA
19	Oral Clarithromycin (3 weeks)	PPV (diagnostic)	Retinal biopsy	1 ^c	0

A-amikacin, AC-anterior chamber, a/b-antibiotic, C-ceftazidime, D-dexamethasone, F-female, G-gentamycin, GDI-R-glaucoma drainage implant removal, HM-hand motions, IOAB-intraocular antibiotic, IOL-R-intraocular lens removal, IV-intravenous, LP-light perception, M-male, NA-information not available, PPV-pars plana vitrectomy, PK-penetrating keratoplasty, SB-R-scleral buckle removal, V-vancomycin.

^a – Removal of implant such as intraocular lens, glaucoma drainage implant or scleral buckle

^b – Additional procedures excluding IOAB (14/19 patients underwent PPV)

^c – Patients who underwent PPV during the course of treatment.

(* – Patient number 2 and 9 previously were reported by Scott et al, 2004 (Reference number 5).

Table 4–Visual acuity distribution (initial and last visit), and duration of follow-up of patients with non-tuberculous mycobacterium endophthalmitis.

No	Age/Sex	Initial visual acuity	Final visual acuity	Duration of follow-up (months)
1	76/M	20/200	5/200	48
2*	68/F	HM	3/200	84
3	76/F	20/100	HM	60
4	80/F	HM	20/100	33
5	80/M	20/800	pthisis	3
6	23/M	2/200	20/300	84
7	65/M	HM	HM	72
8	71/F	HM	20/400	6
9*	62/M	HM	enucleated	24
10	69/F	20/100	20/25 (+10D)	48
11	69/F	20/400	20/400	12
12	53/F	20/400	enucleated	120
13	54/M	4/200	enucleated	18
14	74/M	LP	enucleated	1
15	35/F	HM	20/60	180
16	55/F	20/50	20/40	54
17	86/M	HM	HM	24
18	33/M	-	-	-
19	53/M	HM	2/200	36

F-female, HM-hand motions, LP-light perception, M-male.

(* – Patient number 2 and 9 previously were reported by Scott et al, 2004 (Reference number 5).

Table 3 –Rates of antibiotic susceptibility, intermediate susceptibility and resistance, among isolates obtained from patients with non-tuberculous mycobacterium endophthalmitis, using broth microdilution method of antimicrobial susceptibility testing.

Drug	Susceptibility		Intermediate susceptibility		Resistance	
	%	n/N	%	n/N	%	n/N
Amikacin	87.5%	14/16	6.3%	1/16	6.3%	1/16
Clarithromycin	75.0%	12/16	6.3%	1/16	18.8%	3/16
Ciprofloxacin	20.0%	3/15	0%	0/15	80.0%	12/15
Cefoxitin	14.28%	2/14	57.1%	8/14	28.6%	4/14
Doxycyclin	0%	0/12	8.3%	1/12	91.7%	11/12
Sulphamethoxazole	18.2%	2/11	0%	0/11	81.8%	9/11
Linezolid	40.0%	4/10	50%	5/10	10%	1/10
Tobramycin	22.2%	2/9	0%	0/9	77.8%	7/9
Moxifloxacin	14.3%	1/7	0%	0/7	85.7%	6/7
Imipenem	14.3%	1/7	42.9%	3/7	42.8%	3/7
Gatifloxacin	33.3%	1/3	0%	0/3	66.7%	2/3
Levofloxacin	0%	0/2	0%	0/2	100%	2/2
Vancomycin	0%	0/2	0%	0/2	100%	2/2
Tetracyclin	0%	0/2	0%	0/2	100%	2/2
Erythromycin	100%	1/1	0%	0/1	0%	0/1

n-number of patients with the positive finding, N-total number of patients in the group tested for antimicrobial susceptibility.

Table 5 –Visual acuity (at initial and last visit) of patients with non-tuberculous mycobacterium endophthalmitis.

	Number of patients at Presentation (18 total)^a	Number of patients at last Visit (18 total) ^a
> 20/100	3 (16.7%)	4 (22.2%)
20/100 - 20/400	3 (16.7%)	3 (16.7%)
20/400 -HM	3 (16.7%)	3 (16.7%)
HM/LP/NLP	9 (50.0%)	3 (16.7%)
Enucleation/Pthisis	-	5 (27.8%)

HM-hand motions, LP – Light perception, NLP-no light perception

^a - Visual acuity data were not available for one patient.