Commentary: Infectious keratitis after small incision lenticule extraction

Refractive small incision lenticule extraction (Relex-SMILE) is now gaining acceptance and popularity as a ''flap-less" refractive surgery which needs only Femto laser and a single machine, unlike the Femto-LASIK which produces a flap as well as needs an excimer laser to complete the refractive surgery. The number of femto-LASIK along with the microkeratome flap LASIK procedures (started at around 1991) (more than 40 million procedures as of 2016) far outnumber the SMILE procedures (started around 2008–2011) (2 million in 2019) worldwide. The incidence of infections and interface complications of LASIK are well documented in the literature. The Food and Drug Administration (FDA, USA) approved LASIK in 1991 and SMILE in 2016.

There are few reports of infectious keratitis after SMILE [Table 1].[1-7] This issue of the Indian Journal of Ophthalmology features the successful management of Staphylococcal infection after SMILE with interface wash using antibiotics and photoactivated chromophore for keratitis-corneal collagen crosslinking (PACK-CXL).[7] To the best of our knowledge, there are a total of 10 reported cases of infective keratitis after SMILE procedure; however, this is likely to be under-reported.[1-7] Among these, five cases were presumed bacterial;[1,2] one patient had bilateral Pneumococcal infection,[3] two patients had Staphylococcal infection,[4,7] one patient had non-tuberculous Mycobacterial,[5] and another had fungal (Aspergillus)[6] infection [Table 1]. The infection was unilateral in all patients except two[3,5] patients. All cases presented within 1 week after surgery except one patient (with infection due to Mycobacterium)[5] who presented eight days after surgery. The predisposing factor could not be found in all cases except one, in which the fall of a foreign body was suspected.[7] The infection usually manifested at the interface. Epithelial defect[4,5] and endothelial plaque[5] were noted in 2 and 1 case respectively. All patients received medical therapy which was modified according to the sensitivity report of the organism. Four cases healed with medical therapy alone.[2] Most cases received one or repeated interface wash with antimicrobials. One patient recovered with PACK-CXL and medical therapy.[4] The current case received both interface wash and PACK-CXL.[7]

Management of infections after refractive procedures always brings a heightened sense of urgency and responsibility to the refractive surgeon as the patient population for these surgeries is usually young, economically productive, and undergoing what

Table 1: The details of reported SMILE-related corneal infections

Publication	Cases	Age in years/ sex	Preoperative refraction	Ocular history	Time of presentation after SMILE surgery	Description
Vestergaard 2012[1]	1 (1 eye)	NA (Not available)	NA	NA	1 week	NA
Ivarsen 2014[2]	5 cases (?5 eyes) (among which 1 case was previously reported in Vestergaard 2012[1])	NA	NA	NA	During 1 week	1 or more Interface infiltrates
Chehaibou 2016[3]	1 patient (2 eyes)	39/Male	Right eye (RE) -3DS Left eye (LE) -3.75DS	No contact lens use, blepharitis, or dacryocystitis	2-day post-op	RE-'multiple white paracentral infiltrates involving the corneal cap and the underlying stromal bed' LE- multiple corneal infiltrates along the temporal edge of the interface and within the corneal cap opening incision diffuse cellular infiltration at the corneal cap-stromal bed interface. No anterior chamber cells
Chan 2017[4]	1 (1 eye, right eye)	18/ Female	Myopia	NA	5th day. Presented to authors at 1 week.	On 7th day- 'para-axial corneal infiltrate 1.5×1.5 mm in size involving the anterior cap with an overlying epithelial defect. A diffuse cellular infiltration was noted at the cap-stromal bed interface'
Liu 2018[5]	1 patient (both eyes)	21/ Female	RE -6.25DS LE-7.00DS Myopia	NA	8 days. Presented to authors at 2 weeks	RE- 'multiple white infiltrates at the paracentral area and within the corneal incision' LE- 'an infiltrate with a feathery border at the mid-periphery and an overlying epithelial defect'
Sachdev 2019[6]	1 patient (1 eye/right eye)	20/ Female	RE -2.50,-1.50×20 LE- 2.00,-1.00×155	No contact lens use, blepharitis, dacryocystitis, or diabetes Corneal thickness of 547 microns (RE) and 553 microns (LE)	1st postoperative day	"focal paracentral infiltrates involving the interface"
IJO_2418_19R1[7]	1 (1 eye, left eye)	42/ Female	-4DS both eyes	Suspected fall of foreign body	2nd day	On the 2nd day of postop: No foreign body located. "small superficial infiltrate measuring 0.5*0.5 mm in the temporal mid-peripheral cornea at the edge of the sidecut of the lasered area and 2+ reaction in the anterior chamber." On 3rd day postop, 'the left eye developed four new and distinct, white, circular infiltrates of variable sizes (0.5-2 mm)

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Medical management	Surgical management	Organism	Final UCVA/ BCVA	Outcome	Final follow up time
Eye drops Chloramphenicol and Moxifloxacin	'Flushing the interface with cefuroxime'	No bacterial growth on culture	NA	'When contacted by telephone, the patient wished no further follow-up and said she believed that her visual acuity had improved to the preoperative level with spectacle use. She had no further complaints and was satisfied with the procedure.'	3 months
Eye drops Chloramphenicol and Moxifloxacin	'Flushing the interface with cefuroxime' in 1 case[1]	Treated as bacterial, specific pathogens could not be identified on microbiological investigations	NA	'In all eyes, the infiltrates had cleared without scarring'	3 months
'fortified ticarcillin (7 mg/mL), fortified gentamicin (15 mg/mL), and fortified vancomycin (50 mg/mL) drops given hourly, tapering in frequency every 48 hours' on 4th day after the sensitivity reports changed to 'rifamycin 1.0% and ofloxacin 0.3% every 3 h, and dexamethasone 0.1% was added 3 times daily'	Irrigation and aspiration of infiltrate at the interface by Rycroft cannula, scraping of the infiltrates, interface wash with povidone-iodine 10% and fortified vancomycin 50 mg/ml through the cap opening	Gram-positive cocci, Streptococcus pneumonia sensitive to 'ticarcillin, vancomycin, rifampicin, and fluoroquinolones'	RE 20/40 (20/32 with + 0.25, -1.75×60) LE 20/32 (20/25 with +0.25, -0.25×140)	RE paracentral scar, Le peripheral scars	3 months
'Intensive topical moxifloxacin 0.5% and tobramycin 3%' from postoperative 5th day to the presentation. After PACK-CXL- Hourly Fortified vancomycin (50 mg/mL) and fortified gentamicin (15 mg/mL) drops	PACK-CXL The corneal epithelium was not scraped due to preexisting epithelial defect 0.1% riboflavin for 20 min UV-A (365 nm) at 18 mW/cm^2 for 5 min Illumination ring diameter of 5 mm focused on corneal infiltrate 'patient was reluctant to undergo interface irrigation'	'Staphylococcus haemolyticus and Staphylococcus warneri sensitive to vancomycin but resistant to gentamicin.' Gentamicin was stopped after this report came.	20/20 with --0.50, -0.75×177	Epithelial defect healed over postoperative 48 h. Residual stromal scarring at 2 weeks	2 weeks
Since the 8th day after surgery levofloxacin 0.5% every 4 h. After 2 weeks- fortified cefazolin 33 mg/mL and fortified gentamicin 15 mg/mL hourly. After acid-fast bacilli were noted on 13th day, the therapy was changed to 'topical fortified imipenem 5 mg/mL, fortified amikacin 15 mg/mL, and moxifloxacin 0.5% every 2 h, and oral clarithromycin 1,000 mg daily.' After culture confirmed Mycobacterium abscessus at 4th week postoperatively, 'topical fortified clarithromycin 12.5 mg/mL every 2 h was added for both eyes'. Drops were tapered as per response and continued till 6 months	Bilateral 'interface irrigation of moxifloxacin 0.5% ophthalmic solution' twice between 8th day and 2 weeks. 'The patient was reluctant to undergo stromal cap amputation or interface irrigation.'	'After 4 weeks, scraping culture in the left eye revealed M. abscessus'	BCVA RE 20/32 LE 20/50	At 4 weeks, in corneal infiltrations seemed to reduce in RE and increase in LE. At 6 weeks, there was bilateral worsening (increased infiltrates), endothelial plaque, and increased anterior chamber reaction. At 3 months, bilateral corneal neovascularization, intrastromal hemorrhage, and corneal edema were noted. At 6 months, there were bilateral ghost vessels and corneal opacity which reduced at 12 months.	12 months

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Medical management	Surgical management	Organism	Final UCVA/ BCVA	Outcome	Final follow up time
Stopped routine postoperative regimen of steroid. Started hourly "topical fortified vancomycin 5% and fortified tobramycin 1.4% eyedrops." Infiltrate at the cap gradually increased and UCVA reduced to 20/200 at postoperative day 4. KOH mount of corneal scraping showed septate fungal elements- 'antibiotics were withdrawn and topical voriconazole 1% and natamycin 5% were initiated on an hourly basis, along with cycloplegic drops (homatropine hydrobromide) twice a day.'	"Interface wash with an antifungal solution (voriconazole 1%) was performed daily" for 5 days starting on 7th postoperative day when the culture was positive for Aspergillus species.	Aspergillus species	UCVA 20/60, BCVA 20/45 with -1.00×10	Central fibrotic stromal scar	3 months
On day 2- Gram staining of corneal scrape showed Gram-positive cocci- "fortified cefotaxime: 50 mg/mL and vancomycin: 50 mg/mL topical drops (Q 1 hourly alternately) was started along with topical homatropine (2%) for cycloplegia." Stopped topical steroids. Postoperative day 3- UCVA worsened to 20/80 and LE "developed four new and distinct, white, circular infiltrates of variable sizes (0.5-2 mm), and involving the interface." The interface wash was done on the 3rd day and 5th day. On 3rd day, PACK-CXL was also performed. Fluorometholone 0.1% was started on 10th-day postop and tapered over three weeks.	On day 3- Interface was opened with blunt dissection. 26G needle was used to scrape the undersurface of the cap. The interface was washed with 'vancomycin (1 mg in 0.1 ml solution) and moxifloxacin' (0.5%). Then PACK-CXL was performed ('using2.5% riboflavin reconstituted in normal saline, applied in the interface for 1 minute, followed by UV-A exposure at a fluence of 30 mW for 3 min, delivering total energy of 5.4J/cm^2'). Interface wash was repeated after 48 h.	*Staphylococcus aureus*, sensitive to vancomycin, cefotaxime, and moxifloxacin. No fungal growth.	UCVA 20/30, BCVa 20/20 with 0.7×140.	Reduced scar	3 months

is essentially a cosmetic procedure with preoperative excellent BCVA which is 20/20. Adding to the woes of the surgeon, the infecting organism which has made its way to the interface is not as easily scraped and it is pharmacologically challenging to deliver the therapeutic drug concentration to the interface.

Flap lifting and scraping the bed or as in the case of SMILE, enlarging the incision and using a 26 G needle to scrape under the cap may be done for the microbiological workup.[7] Interface wash with antimicrobials delivers the drug to the site of infection. Scraping of the undersurface of the cap needs to be gentle to avoid perforation.

The results of additional procedures such as PACK-CXL in infectious keratitis need further evaluation. In a randomized control trial by Prajna *et al*.[8] the authors did not find any additional benefit of PACK –CXL in the management of fungal keratitis. The current article,[7] however, presents the successful use of PACK-CXL as an additional procedure to the interface wash with antibiotics. Proposed mechanisms include limited microbial replication due to the intercalation of riboflavin with nucleic acids, damage to the pathogen cell walls by reactive oxygen species, and increased corneal resistance to enzymatic degradation.[4] Also, the inflammatory response may reduce due to CXL-induced apoptosis.[4]

The addition of topical corticosteroids after the initial phase of treatment may be appropriate in a case of bacterial infection and may help to counter inflammation after a refractive procedure.

As more SMILE procedures are done, further cases may be reported in future.

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