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ORIGINAL PAPER

Confocal scanning laser microscopy in patients with postoperative endophthalmitis

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Abstract

Purpose To investigate alterations of corneal layers in eyes treated for acute postoperative endophthalmitis.
Methods In this retrospective, nonrandomized comparative study, eyes treated with 25 gauge pars plana vitrectomy (PPV) for acute post-cataract endophthalmitis (group A) were compared to eyes receiving uneventful cataract surgery (group B) and uneventful 25 gauge PPV for epiretinal membrane (group C). After a minimum follow-up of 8 months from last surgical procedure, laser scanning in vivo confocal microscopy (IVCM) was performed.
Results Twelve eyes for each group were recruited. Comparing study eyes with control eyes of group B and C, no statistical difference was found in corneal epithelial cell density (p = n.s.), in density of nerve fibers (p = n.s.), mean grade of nerve reflectivity (p = n.s.), mean grade of nerve tortuosity (p = n.s.), mean grade of anterior keratocyte activation (p = n.s.), and corneal endothelium cell density (p = n.s.), whereas a statistically higher mean grade of posterior keratocyte activation was found in group A ($p < 0.01$). Epithelial and endothelial corneal morphologies were graded as regular in all groups. Langerhans cells and corneal dendritic-shaped hyper-reflective endothelial deposits were found in group A. Both findings were absent in group B and C, and the difference was statistically significant ($p < 0.01$).
Conclusions IVCM was a useful tool in the detection of microscopic chronic corneal abnormalities caused by postoperative endophthalmitis. These findings confirmed the presence of a subclinical chronic corneal inflammation localized to the posterior stroma that should be related to the infectious process. Future studies might clarify pathological processes in the acute phase of postoperative endophthalmitis.

Keywords Confocal scanning laser microscopy · Confocal microscopy · Endophthalmitis · Postoperative endophthalmitis · Cornea

T. Fiore and G. Torroni equally contributed to this study.

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Introduction

Acute postoperative endophthalmitis following cataract surgery is a devastating condition, despite major advances in medical and surgical treatment in the last decades. With modern cataract surgery, incidence of postoperative endophthalmitis ranges from 0.05 to 0.5%. Rapid treatment to obtain sufficiently high antimicrobial levels in the vitreous is mandatory, because prolonged intraocular infection and inflammation may lead to irreversible structural and functional damage of the retina. Endophthalmitis vitrectomy study [1] has clearly shown the benefit of pars plana vitrectomy (PPV) in eyes with visual acuity (VA) of light perception. However, following technical advances in PPV, recent retrospective studies have shown better visual outcomes also in those cases of acute postoperative endophthalmitis presenting with better than light perception VA [2]. ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery recently supported the idea of a diagnostic and therapeutic vitrectomy as the "gold standard" in most cases [3].

At our institution the standard operating procedure for acute postoperative endophthalmitis is immediate anterior chamber tap with intravitreal injection of vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml). However, when clinical observation suggests an involvement of posterior segment despite VA or when inflammation increases despite medical therapy, a diagnostic and therapeutic 25 gauge PPV is always performed in all eyes followed by injection of vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml).

In the context of intraocular infection, it is often difficult to differentiate between structural damage caused by infection, collateral damage caused by the immune system, and structural changes caused by toxicity. A number of factors are known to influence clinical outcomes after successful management of post-cataract endophthalmitis, and some data were already provided about the microstructural changes in the retina and the choroid long time after this severe postoperative complication [4, 5]. On the other hand, except for a previously reported case of corneal melting [6], nothing is known about long-term structural changes in the cornea after severe acute postoperative endophthalmitis. The aim of this study was to investigate on laser scanning in vivo confocal microscopy (IVCM) potential alterations of corneal layers in eyes treated for severe acute postoperative endophthalmitis and to compare possible findings to those of the opposite healthy eyes.

Materials and methods

In this retrospective, nonrandomized, comparative study, patients evaluated at the S. Maria della Misericordia Hospital, Perugia, Italy, with an established diagnosis of acute endophthalmitis following cataract surgery were included. The eyes affected by endophthalmitis (group A) were compared to the eyes of patients receiving uneventful cataract surgery (group B) and uneventful 25 gauge PPV for epiretinal membrane (ERM) (group C). This study was performed in accordance with the Declaration of Helsinki after approval by the Perugia Institutional Ethics Committee (IEC), and fully informed written consent was obtained from all study patients prior to scanning with the IVCM.

The clinical diagnosis of endophthalmitis was based on the standard sign and symptoms: pain, loss of vision, lid edema, conjunctival chemosis and injection, corneal edema, anterior chamber flare, hypopyon and vitreous haze. Postoperative endophthalmitis was defined as acute when occurring within 6 weeks from cataract surgery and chronic when occurring after that period of time.

In group A, diagnostic and therapeutic 25-gauge PPV was performed in all eyes when there was an involvement of posterior segment despite VA or when inflammation increased despite medical therapy. An aqueous tap, followed by the injection of viscoelastic material, was performed through an anterior chamber paracentisis, and 2 ml of infected undiluted vitreous sample were thereafter obtained. Anterior chamber was then cleaned up with bimanual irrigation/aspiration followed by a complete vitrectomy. Vitreous removal began behind the lens advancing from posterior to anterior. Posterior vitreous cortex was always detached in case it was attached, and posterior pole underwent further internal limiting membrane (ILM) peeling. At the end of surgery, SO was routinely injected in the eye and subsequently removed during a second surgery within a period of 1–3 months according to clinical conditions.

In group B, phacoemulsification was performed according to our standard procedure that includes stop and chop phacoemulsification and intraocular lens (IOL) implantation through a 2.2 mm clear-cornea temporal incision. All cataract surgeries were performed using the Infiniti Vision System (Alcon Laboratories) by the same experienced surgeon (C. C.) under topical anesthesia. Postoperative medication with topical tobramycin and dexamethasone four times a day was continued for the next 14 days.

In the group C, 25 gauge PPV was performed according to our standard procedure including vitreous removal, posterior vitreous cortex detachment in case it was attached, and further ERM and ILM peeling at posterior pole. At the end of surgery, air was routinely injected in the eye. All PPV surgeries were performed using the Constellation Vision System (Alcon Laboratories) by the same experienced surgeon (T.F.) under local anesthesia. Postoperative medication with topical tobramycin and dexamethasone four times a day was continued for the next 14 days.

Inclusion criteria were: diagnosis of post-cataract endophthalmitis in group A, uneventful cataract surgery in group B and uneventful 25 gauge PPV for ERM in group C. Furthermore, no history of previous corneal surgery was required for each group. Minimum follow-up of 8 months from last surgery was required for inclusion in the study of each group. This was based on previous data showing a recovery of confocal parameter after 8 months from uneventful cataract surgery [7]. At the last follow-up visit, all patients underwent a complete eye examination including BCVA, tonometry, biomicroscopy, fundoscopy and IVCM. Images were excluded from analysis in case of poor quality and preexisting corneal diseases. The cornea's layers evaluated with IVCM were: epithelium, sub-basal nerve plexus, stroma and endothelium.

In vivo confocal microscopy image acquisition and analysis

IVCM was performed on all subjects (Rostock Corneal Module of the Heidelberg Retina Tomograph (HRT) II; Heidelberg Engineering, Heidelberg, Germany) by an expert examiner (G.T.). The technical approach has been previously reported [8]. In brief, after topical anesthesia, the subject was instructed to look straight ahead at a target to make sure that the central cornea was scanned. The objective of the microscope was an immersion lens with 63× magnification covered by a polymethylmethacrylate cap (Tomo-Cap; Heidelberg Engineering, Heidelberg, Germany). Each subject was scanned three times at an interval of at least 15 min, and data were averaged. The laser source is a diode laser with a wavelength of 670 nm. Two-dimensional images, consisting of 384 × 384 pixels covering an area of 400 × 400 µm, were recorded.

Several parameters were recorded: superficial epithelium morphology and density, presence or absence of specific leukocytes (Langerhans cells), sub-epithelial nerve plexus density, tortuosity and reflectivity, activation of anterior and posterior stromal keratocytes, and endothelium morphology and density.

Quantitative analysis

Quantitative changes were recorded and classified using specific grading scales, both in control and in study eyes. In all cases, corneal epithelial cell density and corneal endothelium cell density were determined through the manual cell counting procedure present in the software, taking into consideration the whole area marked as available for the cell count. Cells partially contained in the area analyzed were counted only along the right and lower margins. Results are expressed in cells per square millimeter (cells/mm^2). [8, 9]

The degree of density, tortuosity and reflectivity of the nerve fibers of the sub-epithelial nerve plexus was measured using a rating scale (0–4) performed by comparison with reference images, as proposed by Oliveira-Soto et al. [10]. The best images of the sub-basal nerve plexus were saved as JPEG compressed, monochrome, digital images and selected for the analysis. To determine the sub-basal plexus, the highest number of nerve fibers recognizable was selected from each scan.

The activation of anterior and posterior stromal keratocytes was also assessed by comparison with a grading scale [8, 11].

Qualitative analysis

Qualitative changes were reported in a binary fashion and graded as present or absent in both control and study eyes. Each image from IVCM was carefully evaluated by two independent investigators (G.T. and B.I.), in order to detect the presence or absence of corneal changes. Any possible discordance was resolved by a senior cornea specialist (C.C.). In the corneal epithelium, morphology was graded as regular or irregular. The presence of Langerhans cells (LC) was also recorded. [12–17] Corneal endothelium was assessed, and morphology was evaluated. Furthermore, the presence and shape of hyper-reflective endothelial deposits at IVCM were recorded [13] and measurement of their dimension was performed with the Image J software (public domain software, National Institutes of Health, Bethesda, Maryland, USA) [18, 19].

Statistical analysis

The measurements obtained in group A were compared to those in group B and C by Wilcoxon's matched pair test. The statistical analysis of data obtained was carried out using the ANOVA test. All the data were expressed as the average ± SD, and the level of significance was set at $p < 0.01$.

Results

Twelve Caucasian patients for each group were enrolled in the study. In group A, seven patients were male and five patients were female, and mean age was 64 years (range 42–81 years). Mean follow-up time was 21 months (range 9–41 months). In group B, eight patients were male and four patients were female, and mean age was 68 years (range 56–82 years). Mean follow-up time was 11 months (range 8–13 months). In group C, five patients were male and seven patients were female, and mean age was 63 years (range 48–76 years). Mean follow-up time was 12 months (range 9–14 months).

Quantitative results

IVCM quantitative data analysis is summarized in Table 1 (Confocal Data). Comparing study eyes of group A with control eyes of group B and C (Fig. 1), no statistical difference was found in corneal epithelial cell density ($p < 0.01$), in density of nerve fibers ($p < 0.01$), mean grade of nerve reflectivity ($p < 0.01$), mean grade of nerve tortuosity, and mean grade of anterior keratocyte activation ($p < 0.01$), whereas a statistically higher mean grade of posterior keratocyte activation was found in study eyes ($p < 0.01$). Finally, no difference in corneal endothelium cell density was found between both groups ($p < 0.01$).

Qualitative results

Corneal morphologies of the epithelium were graded as regular in all eyes of each group. The analyses of density, tortuosity and reflectivity of the nerve fibers of the sub-epithelial nerve plexus were evaluated as normal in all eyes of each group. The corneal morphologies of the endothelium were graded as regular in all eyes of each group. Contrarily, the presence of LC and the presence of corneal dendritic-shaped hyper-reflective endothelial deposits were found in all the post-endophthalmitis eyes (Fig. 1). These findings were absent in eyes of group B and C, and the difference was significant for both findings. At the level of the corneal endothelium, hyper-reflective deposits were found in group A. These features were absent in eyes of group B and C, and the difference was significant in both control groups. The mean size of the largest dimension of corneal endothelial deposits was equal to 71.12 micron (SD 15.32; range 49.41–97.21 micron).

Discussion

Endophthalmitis is an intra-cavitary accumulation of purulent material. Even if intravitreal antibiotics kill the bacteria, the mixture of organisms, endotoxins and exotoxins, cell wall, and various harmful enzymes is in direct contact with the retina, thus causing continual damage to the retina and limiting visual recovery. For this reason, diagnostic and therapeutic PPV has been increasingly utilized to treat patients with postoperative endophthalmitis [2, 3]. Because inflammatory debris is not limited to the posterior segment, it can cause severe inflammation of the anterior segment. Except for one case of corneal melting, [6] no data are available so far on the effect of postoperative endophthalmitis on the cornea.

IVCM offers many advantages such as high-resolution, superior image contrast and

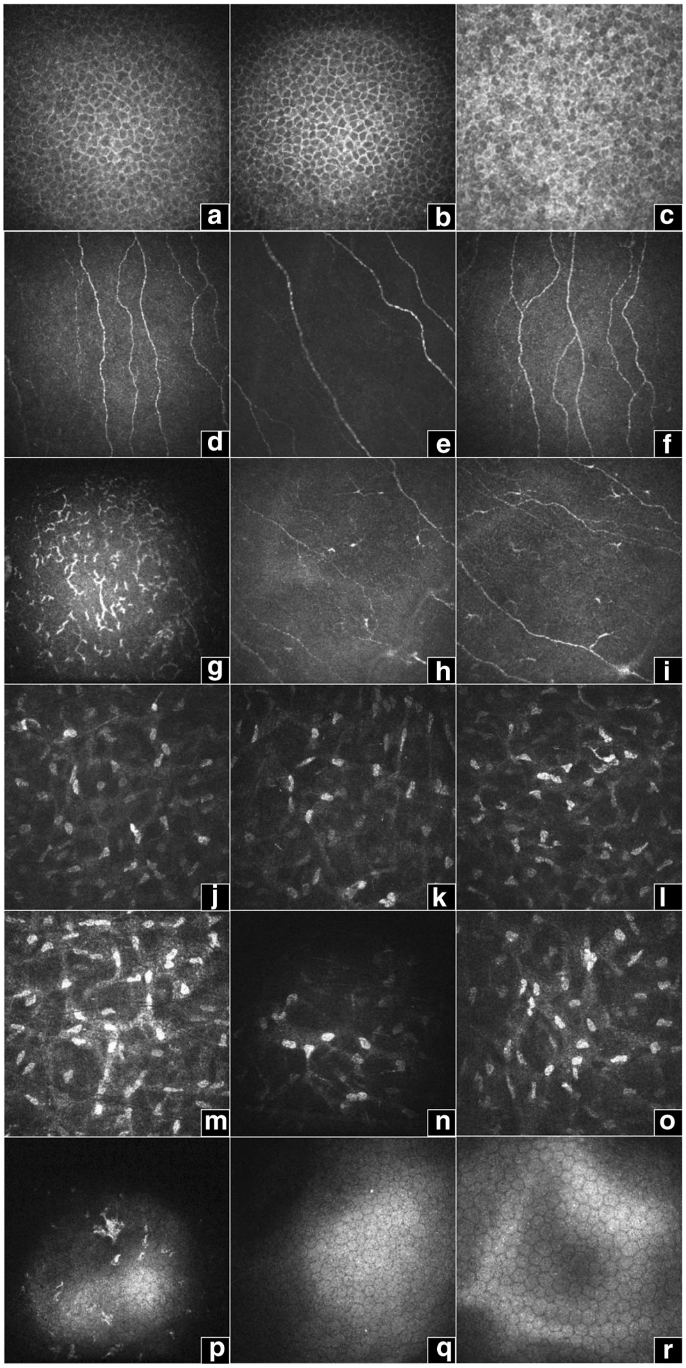
Table 1 Corneal findings on laser scanning in vivo confocal microscopy (mean ± SD) in patients with previous endophthalmitis, uncomplicated cataract surgery or uncomplicated vitrectomy

	Endophthalmitis eyes	Cataract eyes	Vitrectomy eyes	Endophthalmitis versus cataract (*p*)	Endophthalmitis versus vitrectomy (*p*)	Cataract versus vitrectomy (*p*)
Cell density of the intermediate epithelium (cells/mm^2)	3190.00 ± 322.66	3132.00 ± 34.34	3099.00 ± 20.22	0.08	0.09	0.14
Density nerve fibers (fibers/ROI)	4.2 ± 0.10	4.1 ± 0.31	4.1 ± 0.11	0.16	0.32	0.42
Nerve fibers tortuosity	1.49 ± 0.20	1.44 ± 0.21	1.51 ± 0.17	0.09	0.23	0.08
Nerve fibers reflectivity	1.81 ± 0.20	1.89 ± 0.13	1.94 ± 0.2	0.13	0.08	0.56
Anterior keratocytes activation	1.61 ± 0.13	1.76 ± 0.09	1.82 ± 0.12	0.18	0.09	0.34
Posterior keratocytes activation	3.81 ± 0.10	1.21 ± 0.01	1.45 ± 0.20	< 0.001	< 0.001	0.16
Cell density of the endothelium (cells/mm^2)	1785.31 ± 294.03	1789.82 ± 120	1801 ± 184.35	0.59	0.53	0.60

noninvasiveness, enabling in vivo analysis of all corneal cellular levels in exquisite detail and allowing detection of even subtle microstructural changes of the cornea under pathological conditions [8, 20, 21]. Particularly, in our study it was possible to analyze each corneal layer and to highlight qualitative and quantitative changes directly related to the postoperative endophthalmitis inflammatory process (or to the surgical procedure itself). None of these corneal abnormalities could be disclosed under slit-lamp examination.

Concerning the analysis of the epithelium, no reduction in the number of epithelial cells and no changes in their morphology was found comparing affected eyes to the control eyes. IVCM was also used to investigate the sub-epithelial nerve plexus. In fact, changes of density, tortuosity and reflectivity are considered the best parameters to study in vivo the inflammatory damage of the sub-basal nerve plexus. [8, 22–24] Such changes were not reported in all the study eyes probably due to the absence of an active inflammation at the level of the corneal epithelium.

The imaging of the stroma disclosed the presence of activated keratocytes in group A. None of these lesions was disclosed in group B and C. Activated keratocytes are a sign of an ongoing inflammatory process and are thought to correspond to keratocytes in a particular state of metabolic activation. [25] The presence of activated keratocytes was already reported in inflammatory pathologies such as dry eye [8, 11], keratitis [26], vernal kerato-conjunctivitis [27, 28], or after surgical procedures such as cross-linking treatment in patients with keratoconus [29, 30] and Lasik treatment. [31, 32] In our study, a higher degree of activated keratocytes was found in the posterior stroma of all study eyes. This supports the hypothesis that the infection and the subsequent inflammation, developed inside the eye, extended from the anterior chamber to the cornea through the endothelium, and subsequently reached the posterior stroma. Therefore, prompt PPV could be useful either to control the



infection and inflammation in the vitreous cavity [33], or to reduce the corneal inflammation, limiting in our eyes the number and location of activated keratocytes to the posterior stroma.

Analyzing the corneal endothelium, no change in morphology and density of hexagonal cells was observed, whereas hyper-reflective endothelial deposits were present in all the study eyes. None of these lesions was disclosed in control eyes. These hyper-

◀**Fig. 1** Corneal confocal microscopy obtained from an eye treated for acute postoperative endophthalmitis (left column) and from patients who underwent uncomplicated cataract surgery (middle column) or uncomplicated vitrectomy surgery (right column). **a** Cell density of the corneal intermediate epithelium of an eye treated for acute severe postoperative endophthalmitis and of two eyes after cataract surgery (**b**) or vitrectomy (**c**). **d** The density, reflectivity and tortuosity of the sub-basal nerve plexus fibers of the study eye is equal to those who underwent uncomplicated surgeries (**e**, **f**). **g** The presence of Langerhans cells was observed in the cornea of the study eye, **h**, **i** whereas they were absent after cataract surgery or vitrectomy. **j** Image of anterior corneal stroma shows an equal keratocyte activation in the post-endophthalmitis eyes compared to the anterior keratocyte activation in control eyes (**k**, **l**). **m** The image of the posterior corneal stroma shows a significantly higher keratocyte activation in the cornea of the study eye compared to the controls (**n**, **o**). Corneal endothelium cells with hyper-reflective endothelial deposits were present in the study eyes (**p**), whereas they were not visible after cataract surgery (**q**) or pars plana vitrectomy (**r**)

reflective endothelial deposits share the same dendritic morphology of those found in Fuchs' uveitis. [18] This morphology is strongly suggestive of an infectious etiology [34–36] and is different from that one of the hyper-reflective silicone oil droplets. [20, 37] Furthermore, when endothelial deposits found in our study eyes were compared to similar deposits found in Fuchs' uveitis, they were smaller and not visible by standard slit-lamp biomicrosccopy.

Finally, at the level of the basal corneal epithelium, we observed LC which play a key role in the nonspecific innate immune response. In fact, they have a role in the capture, uptake and processing of tissue antigens, and to subsequently present this processing antigens to specific cells, or lymphocytes. [38, 39] This induces a shift from a nonspecific innate immune response to a specific lymphocyte T-mediated immune response, and therefore supports the idea that at this stage the corneal inflammation should be considered chronic. In agreement with previous studies [38, 39], IVCM showed that LC bodies are located in the basal cell layer of the corneal epithelium, whereas LC dendrites extend toward the ocular surface with no connection with the epithelial tight junctions. This finding indicates that LC cannot directly interact with antigens of the ocular surface and that their presence should be related to antigens located in the corneal stroma. [38, 39]

In patients treated with silicone oil tamponade after PPV, Qihua et al. [20] and Szaflik et al. [37] reported corneal changes such as decreased cellular density, increased polymegathism and pleomorphism, hyper-reflective silicone oil membrane or droplets adhering to the endothelium, and silicone oil deposits in both posterior and anterior stroma, along with the infiltration of Langerhans cells beneath the epithelium. The absence of all these findings, except for the presence of LC, support the hypothesis that the inflammatory markers observed in our study eyes should be related to the infectious process, as already strongly supported by the presence of dendritic-shaped hyper-reflective endothelial deposits and not to the use of silicone oil as endotamponade.

Limitations of the present study are mainly due the small number of subjects included and to the different follow-up time of patients included in group A. Both limitations are related to the low rate of post-cataract endophthalmitis [3, 40] that prevents a greater and more homogeneous study sample. The presence of two control groups was planned to minimize these drawbacks. Moreover, the absence in group B and C of all confocal findings observed in all eyes of group A seems to confirm the results of our study.

In conclusion, IVCM was a useful tool in the detection of microscopic chronic corneal abnormalities caused by postoperative endophthalmitis, including the presence of LC at the level of the basal corneal epithelium, activated keratocytes in the posterior stroma, and dendritic-shaped hyper-reflective endothelial deposits. The presented findings, although not specific to endophthalmitis [7, 8, 11, 18, 26–28, 31, 32, 38], represent a sign of long-lasting inflammatory condition related to the infectious process. IVCM proved to be a valuable tool to explore and detect post-endophthalmitis keratopathy (SK). Because all patients affected by postoperative endophthalmitis can be treated with SO endotamponade at the end of PPV, timing for SO removal should be based on both retinal and corneal conditions. It is unclear whether ocular surface symptoms are at least partially related to the corneal inflammation. Future studies might clarify pathological processes in the acute phase. We finally assume that the presence of a subclinical chronic corneal inflammation is due to the early PPV that, in such way, could be helpful in preventing not only retinal complications but also corneal ones.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Perugia IEC) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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