Evaluation of changes in corneal endothelial morphology during the progression of pterygium by specular microscopy

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Abstract

Background/Aim: Corneal endothelial morphology may be corrupted due to pterygium progression. To the best of our knowledge, no study in the literature investigates this. We aimed to evaluate corneal endothelial morphology using specular microscopy (SM) in patients with pterygium.

Methods: In this case-control study, we included thirty-three Type 1 pterygium, thirty-one Type 2 pterygium, thirty Type 3 pterygium patients, and thirty healthy controls. The corneal endothelia of all patients were evaluated by SM, and cell density (CD), hexagonal cell ratio (HEX), corneal thickness (CT), and coefficient of variation (CV) were noted.

Results: While there was no significant difference in corneal thickness (P=0.480) and coefficient of variation (P=0.068) between the groups in SM images, both corneal endothelial cell count (P=0.003) and hexagonal cell ratio (P=0.002) were significantly lower in Type 2 and Type 3 pterygium patients compared to Type 1 and control groups.

Discussion: Corneal endothelial morphology was severely affected in type 2 and 3 pterygium. We think that type 2 and type 3 pterygium patients should be operated on as soon as they are diagnosed to prevent deterioration in corneal endothelial parameters.

Keywords: Pterygium, Specular microscope, Endothelial cell density, Hexagonality, Coefficient of variation
Introduction

Pterygium is a common eye disease characterized by uncontrolled triangular-shaped growth of the conjunctival tissue over the cornea [1]. It can seriously affect vision by inducing astigmatism and in advanced cases, by obstructing the visual axis. Although the etiology of pterygium is not fully known, many factors are suspected in its pathogenesis. While some patients do not have any complaints, many patients may experience symptoms such as burning, stinging, irritation, watering, and foreign body sensation. In addition, it may cause deterioration of the refractive surface of the tear film, astigmatism due to shrinkage on the cornea, and decreased vision due to the closure of the visual axis [2]. Blurred vision or decreased visual acuity, cosmetic problems, chronic inflammation, and irritative symptoms are indications for pterygium surgery. Although degenerated tissue is surgically removed, recurrence may occur [3].

The corneal endothelium predominantly consists of non-regenerative single-layer hexagonal cells. Corneal endothelial cells keep the stroma dry by actively removing water, which is a vital function in maintaining normal corneal transparency. Corneal endothelial cells have very limited mitotic capacity. Therefore, when cell loss occurs, adjacent cells expand and shift to maintain endothelial continuity, which may increase polymegathism and pleomorphism [4]. Cell loss and endothelial status can be determined more precisely based on the evaluation of polymegathism and pleomorphism.

Specular microscopy (SM) is a non-invasive approach for qualitative, quantitative, and morphometric evaluation of corneal endothelial functions [5, 6]. It can assess the corneal thickness, cell density (CD) (the number of cells per mm² of the corneal endothelium), pleomorphism (cell shape variation in the endothelium), and the amount of polymegathism, which shows the variation in the individual cell area. While hexagonal cell ratio is used to evaluate pleomorphism, coefficient of variation, determined by the ratio of standard deviation to the mean cell area, is used to define polymegathism.

Pterygium is divided into 3 subgroups according to its clinical features. Type 1 pterygium involves less than 2 mm of the cornea; Type 2 pterygium advances 2-4 mm on the cornea; and type 3 pterygium, a.k.a., advanced stage pterygium, advances more than 4 mm on the cornea and involves the optic axis [7].

In this study, we aimed to evaluate the changes in corneal endothelial morphology during the progression of the pterygium with SM imaging.

Materials and methods

This case-control prospective study was conducted at our hospital’s ophthalmology outpatient clinic between January 2021 and May 2021. Informed consent was obtained from all participants and ethics committee approval was granted by the Ethics Committee of our hospital (2017-KAEK-189_2021.03.10_02). The Helsinki Declaration Principles were adhered to throughout the study.

A power analysis was conducted using G*Power 3.1.9.2 (Faul, Erdfelder, Lang, & Buchner, 2014). The differences between the four groups were assessed using a one-way ANOVA test, with a low-medium effect size (d=0.5), and an alpha of 0.05. Based on these, a total of 124 participants were required to achieve a power of 0.99. Thirty-three eyes of 33 patients with Type 1 pterygium, 31 eyes of 31 patients with Type 2 pterygium, and 30 eyes of 30 patients with Type 3 pterygium were evaluated. Thirty right eyes of 30 age-and gender-matched healthy individuals were included as controls. Demographic characteristics of all participants, including age, gender, duration of illness, and used medications were recorded.

Patients with glaucoma, uveitis, retinal disease, diabetic or hypertensive retinopathy, epiretinal membrane, and retinal detachment, corneal disease, pseudoxefoliation syndrome, high myopia and hypermetropia (>6D), corneal opacity, ocular trauma and surgical history, individuals who could not cooperate during SM imaging, those using eye drops and contact lenses, and those with dementia, Parkinson’s disease, epilepsy, vascular disease, and psychiatric diseases were excluded from the study.

A complete and detailed ophthalmologic evaluation including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement (IOP) with Goldmann applanation tonometry, pachymetry, three-mirror contact lens gonioscopy, and funduscopy were performed in all participants. The sizes of the pterygiums were noted. SM (Specular Microscope CEM-530, NIDEK) images were obtained in all participants and cell density (CD), hexagonal cell ratio (HEX), corneal thickness (CT), and coefficient of variation (CV) of the corneal endothelium were measured.

Statistical analysis

Statistical analysis was performed using the SPSS® 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) package program. Descriptive statistics were presented. The Shapiro-Wilk test was used to evaluate the normality of distribution. The Chi-Square test was used to compare categorical variables. ANOVA and Post-hoc Tukey tests were used to compare normally distributed data, while The Kruskal-Wallis test was utilized to compare non-normally distributed data among the three groups. Mann Whitney-U Test was used for paired comparisons of non-normally distributed data. A P-value of less than 0.05 was considered statistically significant.

Results

Ninety-four eyes of 94 patients diagnosed with pterygium and 30 eyes of 30 healthy controls were included in the study. The patients were divided into three groups according to the size of their pterygium. The mean ages of the patients with Type 1, Type 2, Type 3 pterygium, and that of the control group were 42.93 (13.02) years, 43.80 (11.67) years, 45.20 (11.87) years, and 45.40 (14.77) years, respectively. The groups were similar in terms of age (P=0.855), gender (P=0.979), and intraocular pressure (P=0.732). The sociodemographic data of the patients are summarized in Table 1.

No significant difference was found between the groups in terms of corneal thickness (P=0.480) and coefficient of variation (P=0.068) in SM images. The corneal endothelial cell densities and hexagonal cells ratios of Type 1 pterygium patients and the control group were similar, while those of Type 2 and
Type 3 patients significantly differed from those of the control group and patients with Type 1 pterygium. SM findings are summarized in Table 2.

Table 1: Sociodemographic data of the groups

| Parameter | Control group (n=30) | Type 1 pterygium (n=31) | Type 2 pterygium (n=31) | Type 3 pterygium (n=30) | P-value |
|-----------|---------------------|------------------------|------------------------|------------------------|---------|
| Sex (M/F) | 10/20               | 12/21                  | 12/19                  | 11/19                  | 0.979   |
| Age       | 45.40±(14.77)       | 42.93±(13.02)          | 43.80±(11.67)          | 45.20±(1.87)           | 0.855   |
| IOP (mmHg)| 13.56±(2.86)        | 14.15±(3.07)           | 14.16±(3.12)           | 13.50±(3.17)           | 0.732   |
| Pterygium length | 1.53±(0.24)       | 2.95±(0.51)           | 4.63±(0.46)           | <0.001                |         |

IOP: Intraocular pressure. Continues data are presented mean (standard deviation).

Table 2: Distribution of specular microscopy findings by groups

| Control group (n=30) | Type 1 pterygium (n=31) | Type 2 pterygium (n=31) | Type 3 pterygium (n=30) | P-value |
|---------------------|------------------------|------------------------|------------------------|---------|
| CF                  | 539.00±(10.42)         | 536.00±(13.27)         | 530.90±(32.83)         | 0.489   |
| CD                  | 2440.06±(275.71)       | 2440.07±(225.00)       | 2251.74±(199.13)       | 0.001   |
| CV                  | 28.70±(3.14)           | 29.18±(2.73)           | 30.41±(3.53)           | 0.006   |
| Hex                 | 64.63±(3.56)           | 64.36±(3.65)           | 61.96±(2.08)           | 0.002   |

CT: corneal thickness (µm), CD: the cell density (cell/µm²), CV: coefficient of variation (standard deviation). Hex: percentage of hexagonal cells (%). Results of post hoc analysis: a: different from the control group, b: different from type 1 pterygium patients, c: different from type 2 pterygium patients.

Discussion

In their SM study, Sousa et al. compared eyes with pterygium with the contralateral healthy eyes and found a negative correlation between pterygium size and endothelial cell density, with no difference in the other parameters [8]. Similarly, in the study by Hsu et al. [9] in which 90 patients with unilateral pterygium were evaluated and eyes with pterygium were compared with other normal eyes, there was a significant decrease in the number of corneal endothelial cells in eyes with pterygium. In our study, we divided patients into three groups based on the size of their pterygium and found no significant difference in any of the parameters between patients with Type 1 pterygium and the healthy controls. However, both the corneal cell density and the hexagonal cell ratio of pterygium patients with Types 2 and 3 differed from those of Type 1 patients and healthy controls. There was no significant difference between the groups in terms of corneal thickness, which was similar to findings reported by Hansen et al. [10], Gros-Otero et al. [11], and Kılıç et al [12]. In addition, no significant difference was found between any of the groups in terms of the coefficient of variation.

Although the pathophysiology of pterygium is still unknown, the involvement of genetic factors, proinflammatory cytokines, and ultraviolet (UV) light is suspected [13]. The incidence of pterygium is increased in individuals and populations exposed to excessive solar radiation. The ultraviolet light (UV) that causes this radiation affects the DNA, RNA, and extracellular matrix by initiating a chain reaction both inside and outside the cell. Kennedy et al. [14] reported that UV light induces mutations in the TP53 tumor suppressor gene in limbal basal cells in the cornea and causes the secretion of various cytokines, angiogenic and fibrogenic growth factors such as IL-1, IL-6, IL-8, and tumor necrosis factor-α. Girolamo et al. [15] reported that UVB stimulates the induction of matrix metalloproteinase-1 (MMP-1) in human ocular surface epithelial cells. Moreover, it has been reported that the expression of matrix metalloproteinases disrupts the basal membrane, causing an increase in the anterior margins of the pterygium [16].

Nolan et al. [17] found that UVB causes overexpression of heparin-binding epidermal growth factor (HB-EGF), which is a powerful mitogen and is considered a major driving force in the development of pterygium. Tsai et al. [18] investigated oxidative DNA damage and noted that UV radiation can damage conjunctival tissue directly through phototoxicity or indirectly through the generation of radical oxygen species (ROS). In particular, they found hydroxydeoxyguanosine (8-OHdG), which shows DNA damage, in pterygium tissue. Kau et al. [19] reported that there is a connection between oxidative stress caused by UV, conjunctival damage, and pterygium development.

Marcovic et al. found that vascular endothelial growth factor (VEGF) and von-Willebrand factor (VWF) were overexpressed in pterygium tissue and suggested that this is evidence of the vascular proliferative process that plays a role in the development of pterygium [20]. In another study on angiogenesis, Ozdemir et al. reported lower nitric oxide (NO) levels in pterygium tissue compared to conjunctival tissue. They noted that this occurs due to the rich vascular structure in the pterygium tissue, which is the opposite of the NO increase that occurs under ischemic conditions [21].

Mootha et al. [22] reported that in long-term nasal pterygium, the underlying Bowman layer of the pterygium can dissolve due to fibroblast infiltration of the anterior stroma, and subsequently, Descemet's membrane and endothelial damage may occur in the cornea.

Based on these, we observe three main factors in the formation of pterygium: Mitogenicity, formation of a new vascular network, and remodeling of the extracellular matrix. Together, they stimulate aggressive growth on top of the cornea, creating new vascular and fibrotic tissue. Currently, surgery is the only option in pterygium treatment.

There were several limitations in our study, such as the low number of patients and difficulties in performing specular microscopy, especially in patients with type 3 pterygium. However, the fact that there is no previous study in the literature with a similar design increases the importance of this study. Further, extensive studies are warranted.

Conclusion

There was a significant decrease in corneal endothelial cell density and hexagonal cell ratio in Type 2 and 3 pterygium patients. This poses a serious risk for postoperative edema and decreased vision, especially among patients that require cataract surgery. We believe that while patients with Type 1 pterygium only require close follow-up, patients with Types 2 and 3 pterygium should be operated on as soon as they are diagnosed to prevent further damage to the corneal endothelium.

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