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Original Article

Classification of Lacrimal Punctal Stenosis and Its Related Histopathological Feature in Patients with Epiphora

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Purpose: To evaluate the classification of punctal stenosis based on the shape of the external punctum, clinical characteristics and histopathologic features.

Methods: Patients who experienced tearing and were diagnosed with punctal stenosis were evaluated in this study. Punctal stenosis was classified according to the shape of the lower external punctum, which included membranous type, slit type, horseshoe type, and pinpoint type. Tear meniscus height, 2% fluorescein dye disappearance test and lacrimal pathway irrigation were measured or performed. For treatment, a punctal snip operation and silicone tube placement were performed, and the peripunctal histopathological findings were evaluated.

Results: Punctal stenosis was classified into four types: membranous type (17 eyes, 21.5%), slit type (11 eyes, 13.9%), horseshoe type (25 eyes, 31.6%), and pinpoint type (26 eyes, 32.9%). The tear meniscus was significantly higher, and the 2% fluorescein dye disappeared significantly more slowly in the punctal stenosis group. However, correlation of the tear meniscus height and 2% fluorescein dye disappearance test with the punctum shape was not statistically significant. A history of previous chemotherapy was significantly associated with the occurrence of punctal stenosis, especially the membranous type ($p < 0.05$). Histopathologic evaluation of the punctum showed differences between the punctum types. Pinpoint puncta exhibited a high density of muscle fibers, while they were faintly visible in the membranous type.

Conclusions: Acquired punctal stenosis has various shapes, and the major types of stenotic puncta exhibited unique histopathologic features. Punctal stenosis and its pathophysiology may be related to multiple factors, such as age and systemic 5-fluorouracil chemotherapy history.

Key Words: Histopathological, Lacrimal apparatus, Lacrimal apparatus diseases

Epiphora is an ocular symptom that develops from a variety of ocular complications, including tear overproduction, irritation-related hypersecretion of the ocular surface, and reduced tear drainage. The lacrimal punctum is the external opening of the lacrimal pathway that is connected to the lacrimal canaliculi, lacrimal sac, and nasolacrimal duct, which are all located within the medial part of the lid margin. The lacrimal punctum is surrounded by a fibrous ring and opens into a tear lake that is larger than 0.3 mm in di-

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ameter [1]. The Riolan muscle and the dense fibrous tissue of the medial eyelid margin insert into the lacrimal punctum and ampulla of the lacrimal drainage system, and together they pull the punctum medially and posteriorly [2,3].

One of the least discussed epiphora etiologies is external lacrimal punctal stenosis, which is caused by an anatomical narrowing or occlusion of the external opening of the lacrimal canaliculi. Epiphora with punctal stenosis can occur congenitally or can be acquired. It can also be accompanied by canalicular or common canalicular ductal stenosis, either of which may make treatment more complicated [3,4]. Numerous agents and conditions have been implicated in the development of punctal stenosis. These include infection, inflammation, systemic diseases, medications, and simple changes associated with aging and gender [3,5-7].

The prevalence of punctal stenosis among the general ophthalmologic population was reported to be 54.3%. While the presence of epiphora is thought to be related to dry eye syndrome [7], it has also been reported that 8% of epiphora is caused by punctal stenosis [8]. The punctum size in Koreans is smaller than in Caucasians. They were measured at an average size of 0.15 ± 0.08 and 0.32 ± 0.16 mm^2, respectively [9,10]. Treatment of punctal stenosis is essential for proper lacrimal clearance and drainage. Several studies have reported on methods for treating and preventing recurrence of punctal stenosis, which include several types of snip operations, punch excisions of the punctum, and electrocauterization [11].

Punctal stenosis is a key, contributing factor to epiphora, especially in Asian populations. Upon slit lamp examination, there are several punctal stenosis shapes, and these forms exhibit definite differences when compared to a normal punctum in size and shape. The types of stenotic puncta may have their own characteristics, and the treatment of punctal stenosis may be adapted to the specific types, which has the potential to alter the prognosis. The objective of this study was to categorize punctal stenosis types based on their macroscopic shape. Additionally, histopathological analysis was performed on peripunctal specimens obtained from punctoplasty to assess the characteristics of each stenotic punctal shape.

Materials and Methods

This was a prospective study in patients who experienced tearing and were diagnosed with punctal stenosis between May 2013 and February 2014. All aspects of this research protocol adhered to the tenets of the Declaration of Helsinki. The institutional review board of Dona-A University approved this study (2-1040709-AB-N-01-201404-BR-03-04) and waived the need for informed consent.

A complete ophthalmic examination was performed paying special attention to the tear meniscus, lid margin, skin, and conjunctiva around the punctum. In addition, electronic health records were reviewed for all patients to collect the following clinical data: gender, age, symptom duration, trauma history, use of medications for systemic or ophthalmic diseases, and history of 5-fluorouracil (5-FU) chemotherapy.

For comparison purposes, 30 ophthalmic patients without epiphora symptoms who had a normally shaped lacrimal punctum with a greater than 0.3 mm diameter were used as controls and were evaluated with the same examination as the patient group.

Patients with a previous history of lacrimal passage treatment such as bougination, stent insertion, canalicular laceration reconstruction, facial trauma with suspicious fracture of the nasolacrimal duct, tumor, definite lid malposition such as ectropion or entropion, history of lid malposition correction, congenital agenesis of the punctum and lacrimal passage were excluded.

Punctal stenosis was diagnosed based on the symptoms of epiphora and a narrowing of the punctum to less than 0.2 mm in diameter, as determined by slit lamp examination [1,9]. The punctum was examined to determine its size and shape. It was measured using a standard Ramsden eyepiece with a fixed, transparent, graduated scale positioned at the top fields and fitted to the slit-lamp biomicroscope. The magnification of the optical arrangement was fixed at ×32, resulting in a scale resolution of 0.03 mm [12]. The shape of the punctum was divided into four types (membranous, slit, horseshoe, and pinpoint) based on what was observed on slit lamp examination (Fig. 1). Normal punctual opening was shown in Fig. 1A. If the punctum was covered with a membranous epithelium from the adjacent conjunctiva and if the external orifice of the canaliculum was not visible, the punctum was defined as membranous type (Fig. 1B). If the longest diameter was less than

0.2 mm and the opening was slit-like, the punctum was defined as slit type (Fig. 1C). If the longest diameter was less than 0.2 mm and its external shape appeared to have a horseshoe appearance, the punctum was defined as horseshoe type (Fig. 1D). When the orifice of the punctum was contracted with fibrotic tissue and appeared to have a dot-like opening, it was defined as pinpoint type (Fig. 1E).

Tear meniscus height (TMH) was measured at the midsection along the lower eyelid directly below the center of the pupil. The distance between the upper edge of the lower eyelid and the visible junction between the cornea and the lower tear meniscus was defined as the lower TMH [12]. The TMH was measured using a 1-mm slit beam on a slit lamp biomicroscope between 0 and 1 mm with a 0.1-mm interval (Fig. 2), using the same method that was used for measuring the punctum.

If epiphora was thought to be related to a lacrimal passage problem, a 2% fluorescein dye disappearance test (FDDT) was performed. A 2% diluted fluorescein eye drop (Chauvin Pharmaceuticals, Essex, UK) was instilled into the inferior fornix. The conjunctiva and fornix were then checked after five minutes for any remnant fluorescein dye. The result of the 2% FDDT was divided into five grades, where 0 denoted no remaining dye and 4 denoted the amount of dye present immediately after instillation. Lacrimal irrigation was performed using a 2-mL syringe filled with normal saline and a 27-gauge cannula to evaluate the lower and upper lacrimal system. The cannula was passed through the lower and upper punctum to the inside of the lacrimal sac, and the nasolacrimal duct was irrigated. If the internal canaliculus was severely narrowed such that the cannula tip could not reach the lacrimal sac and saline irrigation saline was ineffective, then the patients were diagnosed with a canalicular obstruction and a nasolacrimal duct obstruction, and they were excluded from the study. Only patients diagnosed with definite punctal stenosis that had an obvious canaliculum and nasolacrimal duct and normal irrigation were included in the study.

Blepharitis was defined as an itching or burning sensation on the eyelids, inflammation with crusting on the lid margin, and seborrheic secretions from the meibomian gland [13]. A previous history of systemic 5-FU chemotherapy for cancer treatment was determined by reviewing medical records, and we analyzed the effect of chemotherapy history on the shape of punctum. The analysis of this result was based on the number of eyes, not persons.

Punctoplasty (three-snip operation) and a bicanalicular silicone stent intubation were performed to treat the punctal stenosis. After dilation of the stenotic punctum on the lower lid with a punctal dilator, the punctoplasty and peripunctal conjunctival tissue in contact with the ocular surface were excised (2 × 2 × 2-mm-size). This was performed

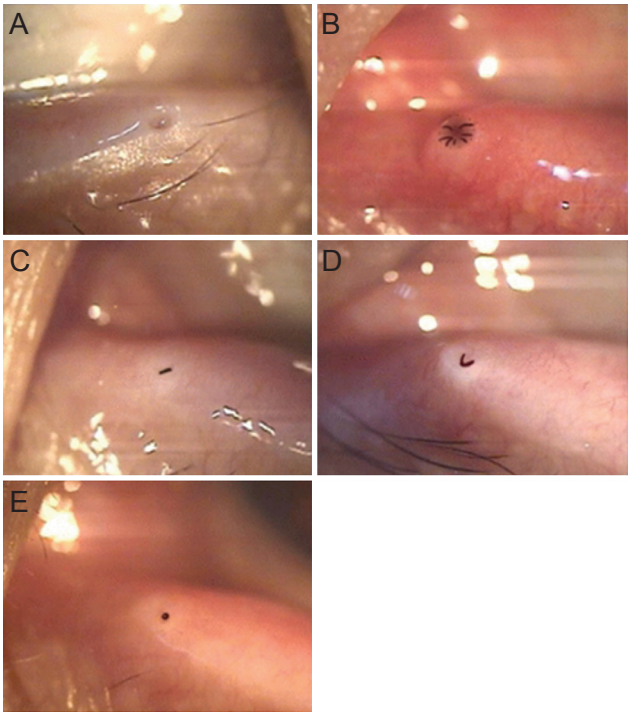

Fig. 1. The shape of a normal punctum and a stenotic or obstructed punctum. (A) Normal punctual opening, (B) membranous type punctum, (C) slit type punctum, (D) horseshoe type punctum, and (E) pinpoint type punctum (×32).

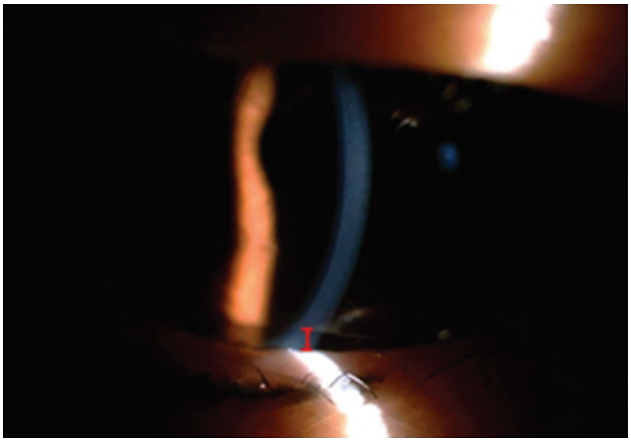

Fig. 2. Measurement of tear meniscus height with slit lamp. Tear meniscus height (vertical red bar) measured with silt lamp midsection along the lower eyelid directly below the center of the pupil (×16).

using Stevens scissors by vertically cutting into the medial and lateral wall of the punctum and removing the interventional tissue with a short horizontal third cut to the base [14]. To maintain an enlarged punctal size, a silicone tube with an outside diameter of 0.94 mm was inserted into the lacrimal pathway through the upper and lower punctum, canaliculum, and nasolacrimal duct.

The specimens were fixed in formalin, embedded in paraffin, cut into 4-μm-thick slices, and stained with H&E, Masson trichrome, and elastic stain. A histopathological examination of the peripunctal tissue and adjacent conjunctiva was performed based on age, gender, and punctal type.

Patient history and clinical examination results were retrospectively collected, reviewed, and statistically analyzed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Student's *t*-tests and chi-square test were performed for analysis of demographic data of the punctal stenosis group and control group. Correlations between the punctal shape and the patient's age were verified using a one way ANOVA test. Additionally, a chi-square test was used to analyze the correlation between punctal shape and gender, TMH, 2% FDDT grade, previous systemic 5-FU chemotherapy and inflammation of the eyelid margin. A *p*-value of less than 0.05 was considered statistically significant.

Results

The patient group consisted of 43 patients (79 eyes) with acquired stenosis, and the control group consisted of 30 patients (60 eyes) with a normal punctum shape. In the patient group, the average age was 65.69 ± 7.84 (range, 47 to 78) years old, and the male to female ratio was 27 to 16. The average age and male to female ratio of the control group was 55.3 ± 6.31 (range, 33 to 62) years and 16 to 14, respectively. The difference in age between the two groups was statistically significant ($p < 0.001$), but the difference in the gender ratio was not significant ($p = 0.098$). The female ratio of the patient group (60.8%) was greater than the female proportion of the control group (46.7%) (Table 1).

The distribution of punctal shapes was as followed: 17 eyes (21.5%) with membranous type, 11 eyes (13.9%) with slit type, 25 eyes (31.6%) with horseshoe type, and 26 eyes (32.9%) with pinpoint type. The correlation between age and type of punctum was statistically significant ($p = 0.029$), and it was further examined with a post-hoc comparison that revealed a significant difference between the horseshoe and pinpoint types. The gender ratio was outnumbered for all stenotic punctum group and each 4 types of punctum stenosis, 52.9% (membranous type), 63.6% (slit type), 56% (horseshoe type), 69.2% (pinpoint type) for each type was female. There was no significant correlation between punctal type and gender ($p = 0.696$) (Table 2).

The average TMH and the degree of 2% FDDT was 0.43 ± 0.17 mm with a grade of 2.34 ± 0.81 for all punctal stenosis types in the patient group and 0.17 ± 0.06 mm with a grade of 0.17 ± 0.38 in the control group. The difference in TMH and 2% FDDT between the two groups was statistically significant ($p < 0.001$) (Table 3). The correlation between TMH and 2% FDDT with punctal shape was not statistically significant ($p = 0.798$ and $p = 0.553$, respectively) (Table 4).

Blepharitis accounted for 41.8% (33 / 79 eyes) of all punctal stenosis patients, where 47.1% (8 / 17 eyes) were membranous type, 36.3% (4 / 11 eyes) were slit type, 32% (8 / 25 eyes) were horseshoe type and 50% (13 / 26 eyes) were pinpoint type (Table 3). Blepharitis with a stenotic punctum did not statistically correlate with the type of

Table 1. Demographic data for the punctal stenosis and control groups

Characteristics	Punctal stenosis group (n = 79)	Control group (normal) (n = 60)	*p*-value
Age (yr) (range)	65.69 ± 7.84 (47–78)	55.30 ± 6.31 (33–62)	<0.001*
Sex			0.098†
Male	31 (39.2)	32 (53.3)	
Female	48 (60.8)	28 (46.7)	
Symptom duration (mon)	29.48 ± 9.43	0	

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
*Student's *t*-test; †Chi-square test, statistical significance $p < 0.05$.

punctal stenosis ($p = 0.566$).

The frequency of previous systemic 5-FU chemotherapy was 11.4% (9 / 79 eyes) in the punctal stenosis patients, while it was 29.4% (5 / 17 eyes) in the membranous type, 9.1% (1 / 11 eyes) in the slit type, 0% in the horseshoe type, and 11.53% (3 / 26 eyes) in the pinpoint type. Previous chemotherapy treatment significantly correlated with punctum shape ($p = 0.023$) (Table 3).

All 14 specimens (four membranous type eyes, three silt type eyes, three horseshoe type eyes, and four pinpoint type eyes) of punctal and conjunctival tissue taken 2 mm from the punctum and lid margin were examined. The mucosal layer of most specimens showed distinct features from a typical conjunctival epithelium, including a loss of goblet cells with a stratified squamous epithelium, similar to conjunctival metaplasia. The endocanalicular and marginal punctal epithelium that connected to the conjunctiva appeared almost identical to the conjunctival epithelium. The submucosal layer revealed various amounts of connective tissue, and no significant inflammation was observed. The amount of connective tissue observed in female patients was greater when compared to male patients. However, the density and volume of muscle fibers were greater in males when compared to females. The ratio of connective tissue to muscle fiber tended to increase with age but not in all cases.

The Riolan muscle was significantly visible immediately beneath the mucosal layer in the pinpoint type, which also had the least amount of connective tissue compared to the other types. Degenerated muscle fibers were visible as well. In contrast, the muscle fiber tissue was only faintly visible, and there was abundant connective tissue with conjunctival metaplasia and a mucinous gland in the membranous type (Fig. 3A, 3B). There was no significant conjunctival metapla-

Table 2. Distribution of punctal type and demographics based on punctal shape

Characteristics	Membranous type (n = 17)	Slit type (n = 11)	Horseshoe type (n = 25)	Pinpoint type Type (n = 26)	*p*-value
Age (yr)	65.59 ± 6.28 (58–76)	67.55 ± 6.82 (57–76)	68.52 ± 6.76 (57–78)*	62.27 ± 9.08 (47–78)*	0.029†
Sex (male : female)	8 : 9	4 : 7	11 : 14	8 : 18	0.696

Values are presented as mean ± standard deviation (range).
*Correlation between horseshoe type and pinpoint type; †One way ANOVA, statistical significance $p < 0.05$.

Table 3. The results of clinical examinations and the prevalence of blepharitis and systemic chemotherapy (5-FU) in punctal stenosis and control groups

Value	Punctal stenosis group	Control group	*p*- value
TMH (mm)	0.43 ± 0.17	0.17 ± 0.05	<0.001*
2% FDDT (grade)	2.34 ± 0.82	0.17 ± 0.39	<0.001*
Blepharitis (%)	41.8 (33 / 79 eyes)	0	
Systemic 5-FU (%)	11.4 (9 / 79 eyes)	0	

5-FU = 5-fluorouracil; TMH = tear meniscus height; FDDT = fluorescein dye disappearance test.
*Student's *t*-test, statistical significance $p < 0.05$.

Table 4. The results of clinical examinations and the prevalence of blepharitis and systemic chemotherapy (5-FU) according to the shape of the stenotic punctum

Value	Membranous type	Slit type	Horseshoe type	Pinpoint type	*p*-value
TMH (mm)	0.46 ± 0.12	0.41 ± 0.13	0.41 ± 0.14	0.43 ± 0.24	0.798
2% FDDT (grade)	2.59 ± 0.71 (47.1)	2.32 ± 0.80 (36.3)	2.27 ± 0.78 (32)	2.23 ± 0.90 (50)	0.553
Blepharitis (%)	47.1 (8 / 17)	36.3 (4 / 11)	32 (8 / 25)	50 (13 / 26)	0.566
Systemic 5-FU (%)	29.4 (5 / 17)	9.1 (1 / 11)	0 (0 / 25)	11.5 (3 / 26)	0.023*

Values are presented as mean ± standard deviation or % (eyes).
5-FU = 5-fluorouracil; TMH = tear meniscus height; FDDT = fluorescein dye disappearance test.
*Chi-square test, statistical significance $p < 0.05$.

sia or muscle fibers observed in the slit and horseshoe types (Fig. 3C-3F). The Riolan muscle was significantly visible immediately beneath the mucosal layer in the pinpoint type, which also had the least amount of connective tissue compared to the other types (Fig. 3G, 3H).

Discussion

Epiphora can occur when a tear does not drain into the lacrimal pathway due to a stenotic, obstructed punctum or due to an abnormal lid position, even in the presence of a normal punctum.

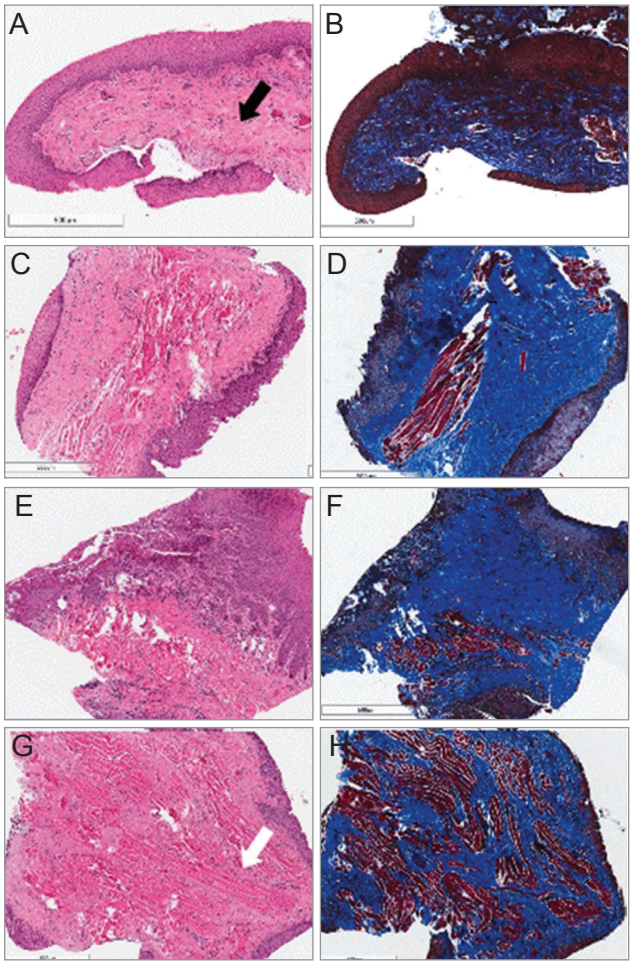

Fig. 3. Representative histopathologic findings according to classification of punctal stenosis. (A,B) Faint muscle fiber and abundant connective tissue (black arrow) of membranous type. (C,D) Moderate amount of connective tissue and muscle fibers of slit type. (E,F) Thick mucosal layer with squamous epithelial cells and a moderate amount of connective tissue with inflammation and muscle fibers of horseshoe type. (G,H) Prominent, high-density muscle fibers (white arrow) beneath mucosal layer of pinpoint type. (A,C,E,G) H&E and (B,D,F,H) Masson trichrome. Bar length = 500 μm.

In this study, patients were classified as having a stenotic punctum based on the shapes observed on slit lamp examination. The distribution of the four types of puncta ranged from 13.9% to 32.9% with the pinpoint type being the most common.

Several reports have described the etiologic factors of punctal stenosis and obstruction, including female gender, blepharitis, tissue atrophy, ectropion, systemic 5-FU chemotherapy, and antiglaucoma eye drops [15-18].

Changes due to aging as well as tissue atrophy can cause dense fibrous structures in the punctum to become less resilient and the surrounding orbicularis fibers to become atonic, resulting in punctal stenosis [5]. In addition, the shape of the punctum changes and becomes less circular, gradually leading to complete closure with age [9]. In our study, there was a significant correlation between the shape of the stenotic punctum and age. In addition, when comparing histologic features, the pinpoint type was found to have a high density of muscle fibers with faint connective tissue, while the other types had plentiful connective tissue. Therefore, compared to older punctal stenosis patients, younger patients had more a pinpoint shaped punctum and a different pathophysiology compared to other punctual shapes.

Chronic blepharitis is a well-known predisposing factor found in 41.7% to 97% of punctal stenosis cases [6,7,19]. In this study, 47.06% of all patients and about 50% of patients with the membranous type and pinpoint type had chronic blepharitis.

Epiphora with stenosis of the punctum and canaliculum has been reported as a side effect of systemic 5-FU therapy [17,20,21]. In this study, 11.39% of punctal stenosis patients had a previous history of systemic 5-FU chemotherapy. In addition, chemotherapy significantly correlated with punctal stenosis in shape, especially with the membranous type (29.41%). There may be a correlation between stenotic punctal shape and the pathophysiology of systemic 5-FU. Additionally, systemic 5-FU may have an effect on the occurrence of membranous punctal stenosis.

The pathogenesis of punctal atresia with membranes is unknown, but several studies have described that pathogenesis of punctal atresia with membrane is correlated with failed dehiscence of the epithelium. Others have classified this as a part of punctal stenosis [22-26]. However, in

this study, the membranous type exhibited district features of punctal agenesis with a membrane. Most cases of punctal dysgenesis were diagnosed at a younger age, and the membrane that covers the punctum appears translucent. Also, the membranotomy specimens had fibro-collagenous tissues [22]. In contrast, patients in this study with the membranous type were of older age and had a punctum covered with obscured vascularized tissue, like conjunctival mucosa. Also, the punctum was easily perforated, and a blunt tipped cannula passed into the canaliculum without resistance. On pathology, the peripunctal and conjunctival tissue from punctoplasty had a definite peripunctal anatomical structure, conjunctival metaplasia, submucosal connective tissue and a small amount of muscle fiber. Acquired punctal obstruction with membranous features can be distinguished from membranous punctal dysgenesis.

Peripunctal specimens were examined in more detail to determine the anatomy of the punctum and adjacent tissue. The Riolan muscle extended medially over the lacrimal punctum, and the vertical canaliculum was connected to the tarsal plate [1]. In addition, the tissue around the lacrimal punctum and the vertical canaliculum was continuous with the tarsal plate [25]. Our study showed a predominant Riolan muscle close to the punctum. Looking into a more detailed and magnified structure around the punctum, we observed some degenerated muscle fibers depending on the punctum type. In these specimens, the punctum was closely surrounded by the Riolan muscle and not only by the vertical canaliculum. Port et al. [27] showed that histopathologic specimens from punctal stenosis revealed findings consistent with inflammation, fibrosis, or both. However, in this study, dense fibrotic connective tissue with no or minimal residual inflammation was observed in spite of the significant proportion of blepharitis (47.06%) in the punctal stenosis group.

Limitations of this study are as follows: (1) the small number of patients in each punctal stenosis group; (2) selection bias because of insufficient age-matching between patient and control groups; (3) insufficient specimens for generalizing these results; and (4) the absence of the effect and prognosis of treatment. In future studies, quantification of histopathologic findings for each type of stenotic punctum will be carried out. Further exploration into the etiology, pathogenesis and distribution of punctal problems will also be undertaken. The prognosis of treatments based on the shape of punctal stenosis will be analyzed. However, to the best of our knowledge, this study presents for the first time the major shapes and distribution of punctal stenosis and their related histopathologic findings.

In conclusion, stenosis of punctum and its pathophysiology may be related to age and systemic 5-FU chemotherapy history. Acquired punctal stenosis exhibits various shapes with the major types displaying their own histopathologic features.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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