

Secondary Keratoconus with Corneal Epithelial Iron Ring Similar to Fleischer's Ring

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Background: Fleischer's ring is considered to be a characteristic of keratoconus, but we have seen a ring similar to Fleischer's ring in patients with secondary keratoconus, in which the cornea becomes thinner secondarily for undetermined reasons.

Cases: We report 6 cases of secondary keratoconus with a corneal epithelial ring similar to the Fleischer's ring pattern.

Observations: In these 6 cases (2 men and 4 women), the causes of secondary keratoconus were trachoma in 2 cases, trauma in 2 cases, keratitis in 1 case and unknown etiology in one case. All showed thinning of the cornea and a corneal iron ring similar to Fleischer's ring pattern. The corneal button obtained after keratoplasty in 1 case showed the deposition of hemosiderin in the corneal epithelium after staining with Prussian blue. At the same time we confirmed the existence of iron in the corneal epithelium by x-ray ultimate analysis.

Conclusions: All 6 patients we encountered had a past history of corneal disease in their childhood except for 1 case with unknown etiology. Primary keratoconus is also considered to develop by the early teens at the latest. These facts led us to an assumption that the occurrence of some abnormalities in the cornea during the growth period may result in iron deposition in the epithelium and thinning of the stroma. In light of these facts, abnormalities of the iron metabolism must be thoroughly investigated in considering the etiology of keratoconus. **Jpn J Ophthalmol 2000;44:381–386** © 2000 Japanese Ophthalmological Society

Key Words: Fleischer's ring, keratoconus, iron metabolism.

Introduction

Primary keratoconus is a disease of unknown origin in which the corneas protrude bilaterally from the early teens or in adolescence. The clinical findings are characterized by conical protrusion and thinning of the central or lower part of the cornea, the keratoconus line, which is considered to result from unbalanced tension of the vertical and horizontal axes of Descemet's membrane, and the Fleischer's ring, which can be observed through a blue filter. We usually diagnose keratoconus on the basis of these findings. The Fleischer's ring found in keratoconus is

a brown oval-shaped ring of 5–6 mm in diameter, the center of which is located at the vertex of the cornea. It has been believed to be unique to keratoconus and caused by hemosiderin deposition in the corneal epithelium. Recently, we discovered that pigmented rings resembling the Fleischer's ring thought to be observed only in cases of primary keratoconus, can also be observed in the partially thinned and protruding cornea caused a corneal disease which we call "secondary keratoconus." We observed this ring also in "secondary thinned cornea," in which thinning of the cornea alone was seen and protrusion was not noted. We report these cases together with some discussion of the causes of primary keratoconus.

Case Reports

We examined 6 cases of secondary keratoconus and thinned cornea (2 men and 4 women). Two pa-

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tients had trachoma, 2 had trauma, and 1 had keratitis as the underlying disease. The underlying disease was unknown in 1 patient (Table 1). All 6 patients showed partial thinning of the cornea near the center, and a Fleischer's ring-like pigmented ring was observed encircling the base of the cone. One of these patients (patient 6) underwent penetrating keratoplasty, and the corneal button of the recipient obtained in this operation was subjected to histopathological examination and x-ray ultimate analysis.

Patient 1. A 26-year-old man sustained trauma at the age of 4 or 5 when a piece of glass entered his right eye; visual acuity: right eye 0.1 (0.1×-3.0 D) ($0.1 \times$ hard contact lens).

The visual impairment of the right eye appeared to be irregular astigmatism and amblyopia.

Slit-lamp examination revealed thinning and opacity of the central part of the cornea, and an almost perfectly round, clear Fleischer's ring-like pigmented ring was observed in the right eye through a blue filter (Figure 1).

Analysis with corneal topography indicated a topical increase in the radius of curvature from the central to the upper part of the cornea, and protrusion was noted.

Patient 2. A 69-year-old man sustained trauma at the age of 5 when a piece of wood injured his right eye. The patient sustained trauma again at the age of 7 when a ruler struck the same eye; visual acuity: right eye 0.01 (0.03×-2.0 D cyl-1.75 D Ax 140°).

The visual impairment of the right eye seemed to be attributable to severe irregular astigmatism and amblyopia.

Slit-lamp examination of the right eye revealed severe thinning and protrusion at the central part of the cornea, and an oval-shaped clear Fleischer's ring-like pigmented ring was observed through a blue filter (Figure 2).

Analysis with corneal topography showed an area with very strong refractive power near the center of the cornea.

Table 1. Patient Data

Case	Age(y)	Sex	Side/Cause
1	26	M	Right/corneal trauma
2	69	M	Right/corneal trauma
3	70	F	Right/unknown origin
4	58	F	Right/gonorrheal keratitis
5	55	F	Right/trachoma
6	78	F	Right/trachoma

M: Male; F: female.

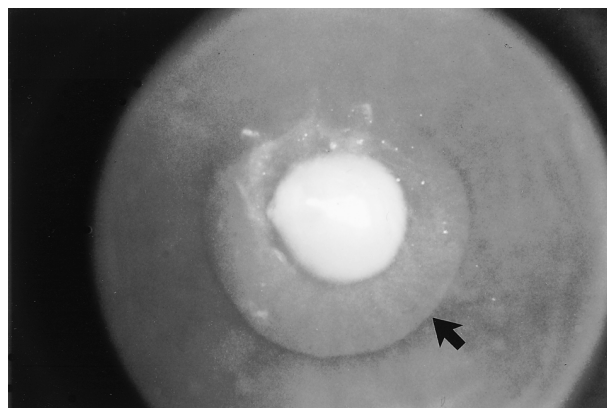


Figure 1. Blue filter photograph of cornea of patient 1. Right eye. Almost perfectly round, distinct Fleischer's ring-like pigmented ring is observed (arrow).

Patient 3. A 70-year-old woman had no underlying disease that could be identified; visual acuity: right eye 0.3 (not corrected).

Slit-lamp examination revealed severe thinning of the central part of the cornea, but protrusion of the cornea was mild in the right eye. The findings resembled those of so-called posterior keratoconus (Figure 3). A Fleischer's ring-like pigmented ring with an obscure upper edge was observed through a blue filter. In addition, cataract was also noted.

Patient 4. A 58-year-old woman had a past history of bilateral gonorrheal keratitis at the age of 2 years, and amblyopia was diagnosed; visual acuity: right eye 10 cm/nd (not corrected).

Slit-lamp examination revealed protrusion, thinning, and opacity of the central to the lower part of



Figure 2. Blue filter photograph of cornea of patient 2. Right eye. Oval-shaped distinct Fleischer's ring-like pigmented ring is observed (arrow).

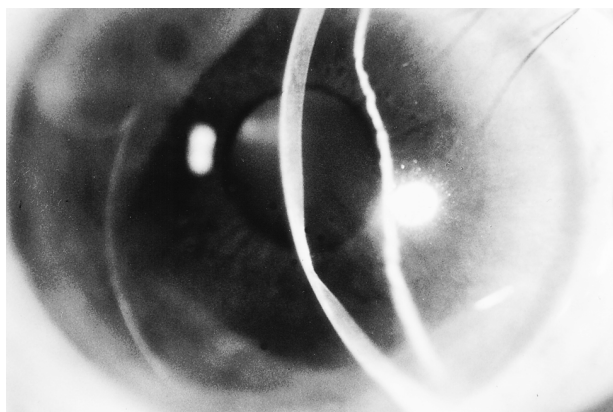


Figure 3. Slit-lamp photograph of cornea of patient 3. Right eye. Severe thinning of central part and posterior keratoconus-like findings are observed.

the cornea, and a Fleischer's ring-like pigmented ring with a slightly obscure lower edge was observed through a blue filter.

Analysis with corneal topography indicated strong refractive power at the center of the cornea, and a relatively large area of protrusion.

Patient 5. A 55-year-old woman had a past history of bilateral trachoma at the age of 6 years, and bilateral amblyopia was diagnosed; visual acuity: right eye 0.01 (0.02×-15.0 D cyl-2.0 D Ax 90°) ($0.1 \times$ hard contact lens), left eye 0.02 (0.02×-15.0 cyl-1.75 D Ax 90°) ($0.08 \times$ hard contact lens).

Slit-lamp examination revealed opacity; thinning of the central to the lower part of the cornea in the left eye, but obvious protrusion was not observed. An oval-shaped, clear Fleischer's ring-like pigmented ring was observed through a blue filter.

Patient 6. A 78-year-old woman had a past history of trachoma in the right eye when she was in the upper grades of elementary school; visual acuity: right eye 0.03 (not corrected).

Slit-lamp examination revealed opacity; thinning of the cornea was not observed. A faint Fleischer's ring-like pigmented ring was observed through a blue filter (Figure 4). Cataract was also noted.

Clinical course. The patient underwent penetrating keratoplasty, extra-capsular cataract extraction, and intraocular lens implantation (triple procedure) in the right eye on April 3, 1993. After surgery, the corneal button was obtained and used with the patient's permission for histological analysis.

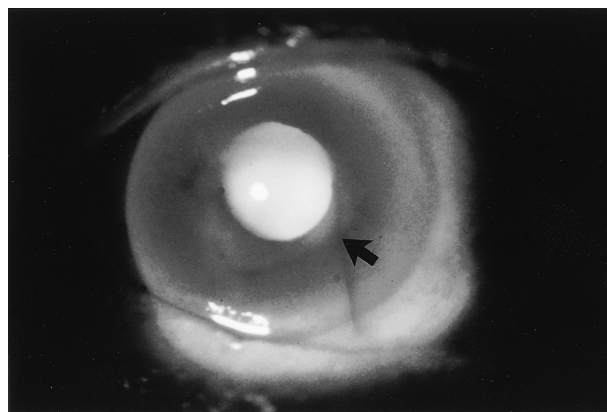


Figure 4. Blue filter photograph of cornea of patient 6. Right eye. Faint Fleischer's ring-like pigmented ring is observed (arrow).

Histological Observations of Corneal Button

Optical microscopic findings. The thickness of the corneal epithelium was irregular, and even a site of perfect defect was noted at the center. Local thickening of Descemet's membrane (retrocorneal membrane) was observed on the endothelial side. As a result of Prussian blue staining of the area that was believed to be the border of the thinned cornea, the entire epithelium was stained blue, and hemosiderin deposition was confirmed (Figure 5).

Electron microscopic findings. The epithelial cells in the thinned area were irregular, and some parts of the epithelial basement membrane were found to be missing. The basal cell process of the epithelial layer was observed to be invading the stroma at this site.



Figure 5. Light microscopic image of corneal button obtained during keratoplasty of right eye of patient 6. Hemosiderin deposition stained blue is observed in entire epithelium (arrowheads). Prussian blue staining. Bar = 50 μ m.

Partial degeneration of Bowman's membrane was also noted.

Microparticles with high electron density, which appeared to suggest hemosiderin, were noted in the intercellular space of the corneal epithelial basal cells (Figure 6). X-ray ultimate analysis findings: We attempted identification of the metal by scanning electron microscopy. As a result, a reflected image of a metallic substance was obtained at the site corresponding with the Prussian blue-positive epithelial cells (Figure 7). X-ray ultimate analysis of this area exhibited a peak at the site of the Fe element (Figure 8A). The intact part of the corneal button of the same patient showed Prussian Blue-negative (Figure 8B).

Discussion

We defined secondary keratoconus as a condition in which a part of the cornea becomes thin and protrudes secondarily to some other corneal disease. However, the term, "secondary keratoconus," cannot be found in the literature from Europe and the United States. Accordingly, this term may not represent an internationally established clinical entity. However, we believe that "secondary keratoconus" is an appropriate and convenient term to refer to a condition with thinning and protrusion of the cornea such as observed in our cases. Therefore, we decided to use this term in this report. We used the term, "secondary thinned cornea," to refer to the cases in which thinning of the cornea alone was observed, and protrusion was not noted.

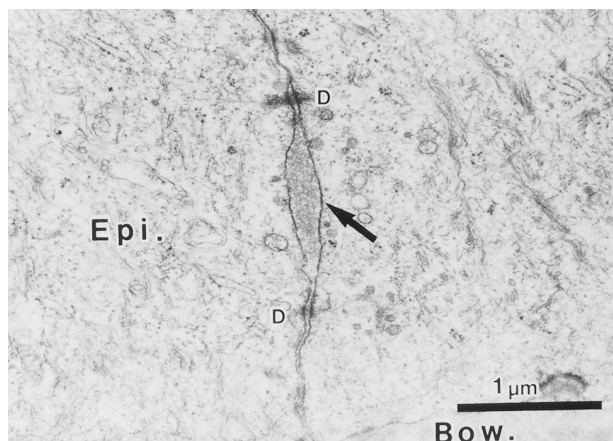


Figure 6. Electron microscopic image of corneal button obtained during keratoplasty in patient 6. Microparticles with high electron density, suggesting hemosiderin, are noted in intracellular space of corneal epithelial basal cells (arrow). Epi.: Corneal epithelium, Bow.: Bowman's membrane, D: Desmosome. Bar = 1 μ m.

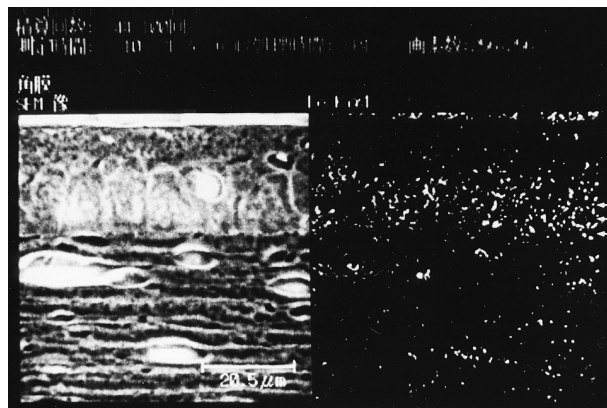


Figure 7. Metal identification by scanning electron microscopy in corneal button from patient 6. Reflection image of metallic substance (white arrow) is observed corresponding to site of Prussian blue-positive epithelial cells.

The most common underlying disease for secondary keratoconus is corneal ulcer.¹ In addition, rupture of Descemet's membrane induced by forceps delivery, trabeculectomy, interstitial herpetic keratitis, and long-term wearing of hard contact lenses by allergic people have also been reported as possible

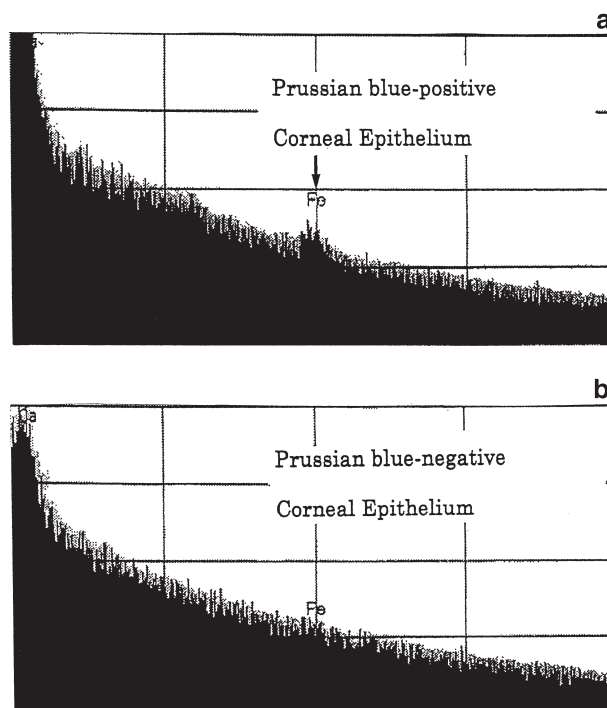


Figure 8. X-ray ultimate analysis finding. (A) Peak (arrow) is noted at site of iron element in Prussian blue-positive corneal epithelium. (B) Intact part of corneal button of patient 6 shows Prussian blue-negative.

causes. The appearance of the cornea is similar to primary keratoconus, but it can be differentiated from primary keratoconus in that the onset is confined to a single eye in most cases, the age of onset varies, the position and depth of corneal opacity are diversified, and the protrusion may not always be conical or the shape of the conus may be irregular. Moreover, it can be differentiated from descemetocele because the cornea is thinned but the parenchymal tissues are still remaining. The 6 patients presented herein all showed partial thinning of the cornea due to some corneal disease, but obvious conular protrusion was observed only in patients 1, 2, and 4 (secondary keratoconus). Patients 3, 5, and 6 had only a small area of thinning, and this might be the reason why they did not show a tendency toward protrusion (secondary thinned cornea).

One of the typical findings of primary keratoconus is Fleischer's ring. This is an oval-shaped brown ring surrounding the site of conical protrusion. Histologically, it is known to consist of hemosiderin deposition in the epithelial intercellular space or in the epithelial cells. Recently, we discovered a pigmented ring similar to the Fleischer's ring, which is considered to be unique to primary keratoconus, also in the cases of secondary keratoconus and thinned cornea. This pigmented ring was in a round or oval shape surrounding the area of thinned corneal stroma in all our cases, and could be easily observed through a blue filter. These findings were clinically very similar to that of the Fleischer's ring in primary keratoconus. Moreover, no obvious differences in the shape of Fleischer's ring were observed between the cases with protrusion and those without protrusion. Histological examination and x-ray ultimate analysis were conducted in one of these cases, and the substance deposited among the epithelial cells was confirmed to be iron. Thus, the ring we observed was revealed to consist of the same substance as Fleischer's ring.

A variety of hypotheses have been proposed as the etiology of primary keratoconus. However, there have been no reports on the relationship between keratoconus and iron metabolism as far as we could learn. Deposition of pale yellowish-brown particles can occur in various shapes in the corneal epithelium as a result of iron deposition, irrespective of clinical symptoms.

In 1906, Fleischer first reported deposition of iron in a characteristic shape in the corneal epithelium in keratoconus, and since then there have been several reports. Hudson-Stahli line, which is believed to be an age-related change, Stocker's line observed at the head of pterygium, and Ferry's line observed in the cornea near the filtering bleb after trabeculectomy,

are widely known. Since the 1980s, unique corneal iron lines after radial keratotomy² and immediately after penetrating keratoplasty³ have been reported, and detection of a Hudson-Stahli pattern iron line after the intrastromal corneal ring insertion has been reported in recent years.⁴ These reports appeared to imply a close association between the iron deposition line in the corneal epithelium and morphological changes in the corneal surface. The possible origins of the iron which deposits in the epithelium include tears, limbal vessel, aqueous humor, and cytochrome.⁵ At any rate, it has been revealed that iron deposition in the corneal epithelium occurs in association with thinning of the corneal stroma in cases of both primary and secondary keratoconus.

The relationship between thinning of the corneal stroma and iron deposition in the epithelium, however, remains unknown. One possible explanation may be that abnormality in the corneal epithelium leads to iron deposition in the epithelium, while impairment of the interaction between the epithelium and stroma results in abnormality in the metabolism of collagen fibers and thinning of the stroma. Another explanation may be that abnormality of the iron metabolism occurs in the epithelium, triggered probably by different factors in primary and secondary cases, and results in thinning of the stroma. Hydroxylysine, which affects the diameter of collagen fibers in the cornea, is generated by hydroxylation of lysine in molecules of the collagen fibers, and iron ion is necessary as a co-factor in this process.⁶ The hydroxylysine level in the stromal collagen fibers in patients with keratoconus has been reported to be significantly lower than in normal subjects.⁷ If this report is correct, it may also be possible that hydroxylation of lysine is not promoted, and thus, iron ions that should be consumed as co-factors under normal conditions are not consumed in the corneal stroma and are accumulated in the epithelium. Thus, there are various possible hypotheses, but nothing has been determined at present with respect to the relationship between thinning of the stroma and iron deposition in the epithelium.

All 6 patients we encountered had a past history of corneal disease in their childhood, except for 1 case with unknown etiology. Primary keratoconus is also considered to develop by the early teens at the latest. These facts led us to an assumption that occurrence of some abnormalities in the cornea during the growth period may result in iron deposition in the epithelium and thinning of the stroma.

In light of these facts, abnormalities of the iron metabolism must be thoroughly investigated in considering the etiology of keratoconus.

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