

# Chapter 2

## Corneal Degenerations

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### 2.1 Introduction

*Degenerations* are defined as the gradual deterioration of a tissue or an organ that was previously normal with frequent loss of functional activity. Corneal degenerations are characterized by the deposition of material, thinning of tissue, and vascularization. Contrary to corneal dystrophies, they are not hereditary and could be unilateral. Moreover, because of the continuous exposure to environmental conditions, the cornea might undergo changes related to UV stimulation, and in some cases, oxidative stress might be responsible for the onset of degenerative processes [1, 2].

Corneal degenerations are characterized by a late onset; they can occur in several local diseases with mainly unilateral involvement or result from underlying systemic disorders or age-related processes. In the latter cases, they are bilateral even if asymmetric.

Corneal degenerations can be classified with relation to corneal changes. Generally, forms with abnormal peripheral corneal thinning and those with material deposition are recognized. The thinning processes are mainly of unknown etiology even if some general coexisting disorders were reported. In degenerations characterized by material deposition, the local and systemic causes underlying the corneal involvement could usually be identified [1].

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## 2.2 Age-Related Corneal Degenerations

Age-related corneal degenerations represent rather common ocular conditions in elderly. They appear both as corneal thinning and material deposition and generally do not require any therapy as they could lead to visual disturbances only in sporadic cases [3].

### 2.2.1 *Arcus Senilis*

Arcus senilis is considered the most frequent corneal degeneration in elderly, with a prevalence of above 90 % in over 80-year-old subjects. It is bilateral but frequently asymmetric. Clinically, it is represented by a circular band of extracellular deposits of lipoproteins with an evidently sharp external border separated from the limbus by the clear cornea. The internal border of the arcus is poorly defined, while the central cornea is always clear. Lipids deposition starts superiorly and inferiorly involving the deep stroma in proximity to the Descemet's membrane to extend to the sub-Bowman's superficial stroma and become circumferential (Fig. 2.1).

Beyond senescence, the lipid arcus can be present in young males with hypercholesterolemia and hypertriglyceridemia. In fact, such association is actually considered a sign of cardiovascular diseases, and a special medical care with cardiovascular evaluation should be recommended in the presence of the arcus in the young [3–5].



**Fig. 2.1** Arcus senilis.  
(Archives Dr.  
A.M. Roszkowska)

### 2.2.2 *Vogt Limbal Girdle*

It is represented by limbal semilunar whitish lines that have an onset in the interpalpebral rim with a prevalence on the nasal zone. Limbal girdle is characterized by stromal thinning frequently associated to subepithelial calcium deposition. This common degenerative corneal change is present in 100 % of over 80-year-old subjects [3, 6].

Vogt described two types of girdle: type I, separated from the limbus by a clear zone, includes calcium deposits and is considered an early form of band keratopathy, while type II consists of hyaline degeneration with hyperelastosis in the peripheral Bowman's membrane (Fig. 2.2).

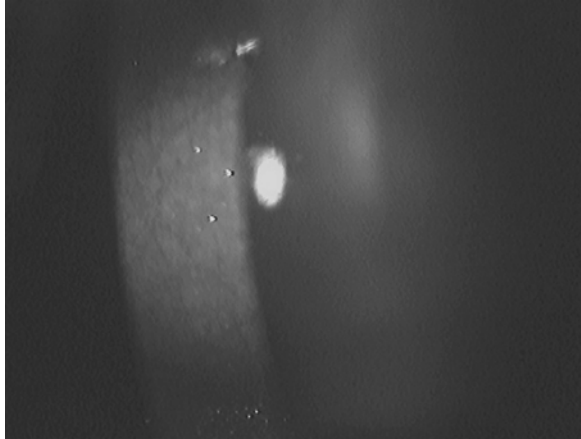
### 2.2.3 *Crocodile Shagreen*

It involves mainly the anterior corneal stroma, but in some rare cases, it can involve the posterior as well. Clinically, it presents evident polygonal cloudities separated by the clear lines that recall the crocodile shagreen (Fig. 2.3). Such clinical manifestation seems to be related to the particular abnormal orientation of the stromal fibers. Electron microscopy revealed the presence of vacuoles throughout the corneal stroma, with some of them containing electron-dense material. Crocodile shagreen corneal degeneration is rather uncommon and can be observed casually during a routine slit-lamp ocular examination. It is considered innocuous, but in its posterior variant, in some cases it can affect visual acuity [7, 8].

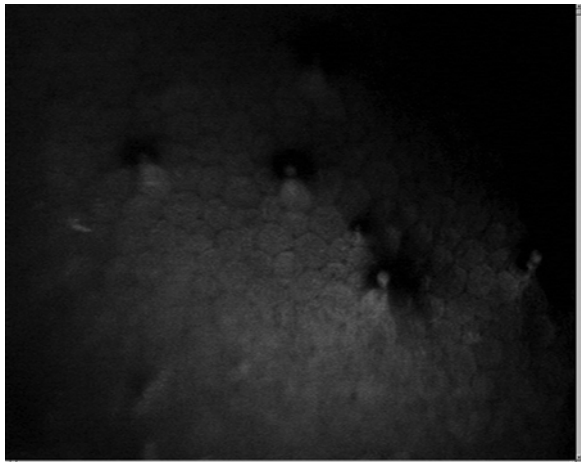


**Fig. 2.2** Vogt limbal girdle.  
(Archives Dr.  
A.M. Roszkowska)

**Fig. 2.3** Crocodile shagreen.  
(Archives Dr.  
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**Fig. 2.4** Hassall-Henle  
bodies. (Archives Dr.  
A.M. Roszkowska)



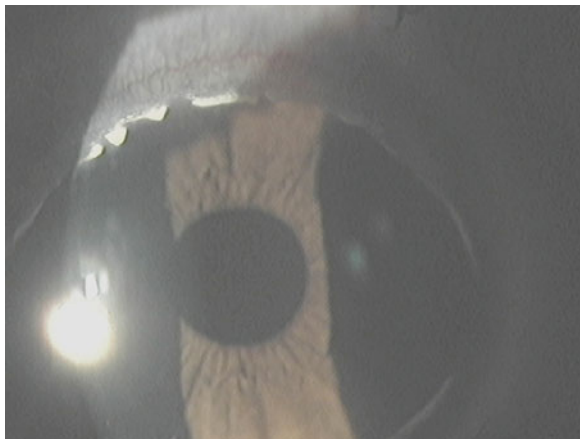
### **2.2.4** *Peripheral Corneal Guttae*

Age-related changes in the corneal endothelium are related above all to the progressive cell loss with reduction of the cell density [9, 10]. The peripheral guttae are also known as Hassall-Henle bodies and are formed by the localized deposition of abnormal collagen secreted by the aging endothelial cells (Fig. 2.4). They consist of sporadic excrescences on the corneal endothelium localized prevalently in the middle periphery. This differentiates them from the Fuchs' endothelial dystrophy, which starts in the center and spreads to the periphery, causing time corneal failure [11]. The number and extension of guttae are limited, so the endothelial cell density and function are not affected. In the pathogenesis of this age-related degeneration, the role of oxidative stress could be considered. In fact, oxidative stress involvement was established at the onset and progression of the Fuchs' endothelial dystrophy, where similar histopathological alterations occur [2].

## 2.3 Corneal Degenerations with Tissue Thinning

### 2.3.1 Terrien's Marginal Degeneration

Terrien described it in 1900 as a noninflammatory, painless, evolutive thinning in the peripheral cornea, and its etiology remains poorly understood. Association with autoimmune disorders was described, so the autoimmune mechanism underlying the pathogenesis was hypothesized. Recently, an association with the chronic inflammatory skin condition known as erythema elevatum diutinum was reported [12]. Terrien's marginal degeneration could be observed at any age, but prevalence in middle-aged males was observed. Generally, it is bilateral but asymmetric. Terrien's degeneration generally starts in the superior area with a local haze separated from the limbus by a clear cornea. Successively, the peripheral stroma thins with typically an intact epithelial layer that characterizes this degeneration. Then the degenerative processes extend in a circumferential manner involving progressively the whole corneal periphery, and in the advanced forms, the degeneration becomes circumferential. Progressive neovascularization could arise, as well as lipid deposits, in the central border of the thinning (Fig. 2.5). Patients are asymptomatic until visual changes occur because of the progressive increment of irregular astigmatism [13, 14]. In some sporadic cases, slight inflammation could be present, as reported by confocal findings, and it responds well to the topical steroid therapy [15, 16]. Histopathological studies showed an increased lysosomal activity together with the absence of the Bowman's membrane in the site of thinning [14]. As to the instrumental findings, the topographical examination demonstrates irregular astigmatism in advanced stages of the disease. The AC-OCT evaluation might be helpful in the evaluation of the peripheral thinning and in differential diagnosis with other peripheral corneal disorders. Recent AC-OCT findings report the stromal cavity formation in the peripheral cornea due probably to the collagen phagocytosis [17]. The differential diagnosis should consider the peripheral corneal melt, Mooren's



**Fig. 2.5** Terrien's marginal degeneration. (Archives Dr. A.M. Roszkowska)

ulcer, pellucid marginal degeneration, and dellen. The treatment consists of optical correction of irregular astigmatism. In advanced forms, contact lenses are recommended. The most dreaded complication in severe Terrien's degeneration is related to corneal perforation. Perforation could be spontaneous or could result from any trauma, so the surgical approach should be considered when extreme thinning occurs [18]. Lamellar ring-shaped peripheral corneoscleral grafting is usually considered, but in some cases, tissue excision with appropriated suture could be performed [19, 20].

### **2.3.2 Dellen**

Dellen is a localized area of corneal thinning in the periphery next to the limbus. It is located in proximity to the areas of tissue swelling or inflammation when correct spreading of the tear layer is highly disturbed. Frequently, it follows some surgical procedures that induce conjunctival chemosis with paralimbal elevation, which produces a localized abnormality of the tear film layer with following localized dehydration and thinning [21–24]. This relatively common condition is reversible. In fact, the restoration of the normal film layer spreading and intense lubrication constitute the appropriate therapy for this disorder. Recently, the use of a large-diameter soft contact lens was proven to be an effective therapeutic solution to treat the dellen that arose after a pterygium removal [25].

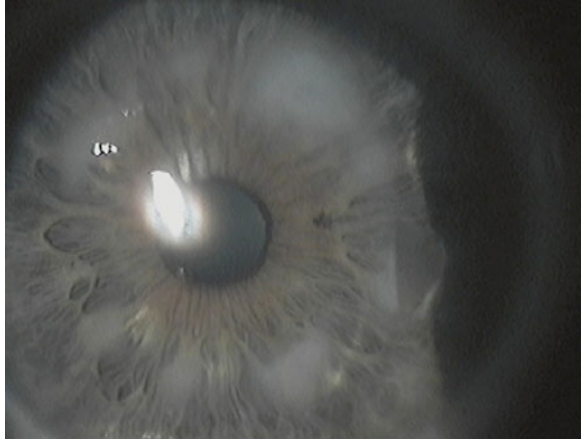
## **2.4 Corneal Degenerations with Material Deposits**

### **2.4.1 Salzmann's Nodular Degeneration**

Salzmann's nodular degeneration (SND) is a noninflammatory, slowly progressive disease characterized by single or multiple whitish-gray subepithelial corneal nodules. Salzmann described it in 1925 in association with keratoconjunctivitis, but with time, several different disorders coexisting with this disorder were detected. To date, its etiopathogenesis remains unknown, but it is considered to be associated with ocular surface inflammation or chronic trauma. However, several cases with no previous corneal pathology have been reported and are considered idiopathic.

Clinically, the typical clinical signs could be observed during slit-lamp examination, with either solitary or multiple nodules elevated on the corneal surface and located in the midperiphery of the cornea. In some cases, single or few nodules are present in one or more quadrants during routine ocular examination in asymptomatic patients, and sometimes, the nodules may invade the central zone. When multiple nodules are present, they have a typical circular arrangement and might be confluent in the advanced stages. A normal clear cornea between the nodules is a characteristic clinical feature (Fig. 2.6). The ocular surface disorders involved in the

**Fig. 2.6** Salzmann nodular degeneration. (Archives Dr. A.M. Roszkowska)



etiopathogenesis of Salzmann's degeneration are Meibomian gland dysfunction and dry eye disease followed by rosacea, phlyctenular keratitis, vernal keratoconjunctivitis, trachoma and interstitial keratitis. The chronic injuries that are most commonly associated with the development of the degenerative changes are extended contact lens use and previous corneal surgery followed by actinic exposure, recurrent erosions, and chemical or thermal injuries [26–29].

Recently, SND in patients with Crohn's disease was reported, and a hypothesis about association with systemic diseases was advanced [30, 31].

Therefore, although the etiology remains uncertain, it is hypothesized that Salzmann's nodular degeneration can be triggered by multiple events that lead to a nonspecific corneal tissue reaction based on individual predisposition. It appears to be more frequent in middle-aged women, and it is bilateral in about 60 % of cases. The main symptoms are visual disturbances and photophobia, ocular discomfort, mainly characterized by dryness, and foreign body sensation. In severe forms, characterized by very elevated nodules, painful epithelial lesions can occur. Visual impairment is progressive and due to an astigmatic defect produced by the nodules. Severe corneal irregularities in advanced stages generate high irregular astigmatism with severe visual loss. Although the diagnosis of Salzmann's degeneration is exclusively based on clinical findings, several instrumental examinations such as corneal topography, anterior segment optical coherence tomography, and confocal microscopy are useful to provide a better understanding of the corneal alterations and to quantify the amount of visual impairment. Corneal topography demonstrates the irregularities of the corneal shape produced by corneal nodules, and the induced surface alteration depends on their number and localization.

AC-OCT allows the evaluation of the nodules' dimension and depth, allowing the investigation of the stromal extension of the nodules that can help decide the surgical approach [32]. Confocal microscopy showed an increased reflectivity of the anterior stroma with abnormal and activated keratocytes and marked stromal scatter corresponding to the nodules as a result of the presence of fibrosis [33–35].

Histopathological studies have revealed that the corneal nodules are located subepithelially but may extend to one-third of the anterior stroma and are formed by a dense connective tissue with hyaline degeneration. The corneal epithelium has an irregular thickness, with extremely increased thinning over the corneal nodules. The Bowman's membrane exhibits disruption, and in the correspondence of the nodules, it is no longer appreciable and frequently replaced by fibrosis. Subepithelial fibrosis is a frequent histopathological finding, with activated fibroblasts beneath the epithelial cells. Increased expression of matrix metalloproteinase-2 (MMP-2) was recently detected in patients affected by Salzmann's degeneration, and this may be responsible for the induction of the basement membrane and Bowman's layer disruption [33, 35–37].

Therapy is related to the symptoms and severity. In early forms, treatment is aimed at reducing the presenting symptoms with conservative therapy concerning eyelid hygiene, lubricants, and anti-inflammatory eyedrops sufficiently to eliminate dry eye symptoms and foreign body sensation. Visual loss is an indication for surgical treatment, which consists of the removal of the nodules and the restoration of corneal surface regularity. In superficial nodules, manual removal with a crescent knife is sufficient and leaves a uniform smooth underlying surface. In the case of deeper ingrowth that involves the anterior stroma, after the nodule's removal, the excimer laser PTK is usually performed to smoothen the surface. In some cases with deep ingrowth, the anterior lamellar becomes necessary [38, 39]. The recurrence of Salzmann's nodules after surgical removal can occur with varying prevalence rates (18–21.9 %) and periods of time to recurrence (1 month to 6 years) [40–42].

### **2.4.2 Band Keratopathy**

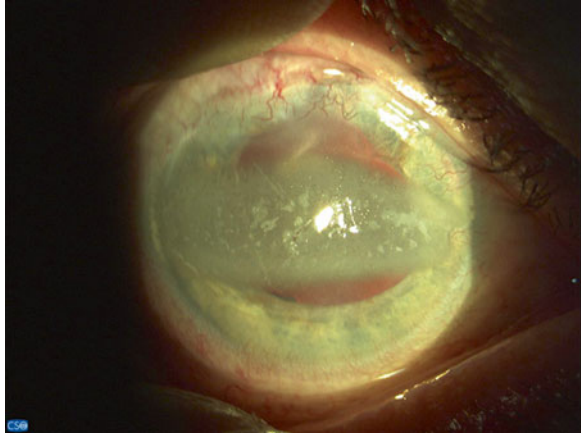
Band keratopathy consists of the deposition of calcium salts in the interpalpebral region. It starts in proximity to the limbus in the corneal periphery nasally and temporally at the same time. Successively, it spreads gradually to the center, forming a band-like whitish-gray plaque. Clear cornea separates the peripheral border of the band from the limbus. Visual acuity decreases with the advancement of deposits. In fact, in the advanced stages, the density of calcium deposition might create a severe visual impairment (Fig. 2.7). Moreover, in severe lesions, the deposits become elevated and produce considerable discomfort because of the ocular surface alterations.

Band keratopathy can affect a single eye when it arises after local disorders such as chronic anterior uveitis, interstitial keratitis, severe injury, chronic corneal inflammations, and phthisis bulbi. It is bilateral when generated by a general disorder. Systemic conditions underlying the band keratopathy onset are chronic renal failure, juvenile rheumatoid arthritis, and hyperuricemia.

Histology shows calcium salt deposits localized in the Bowman's layer, basement membrane of epithelium, and anterior stroma [43].



**Fig. 2.7** Band Keratopathy.  
(Archives Prof. E. Wylegala)



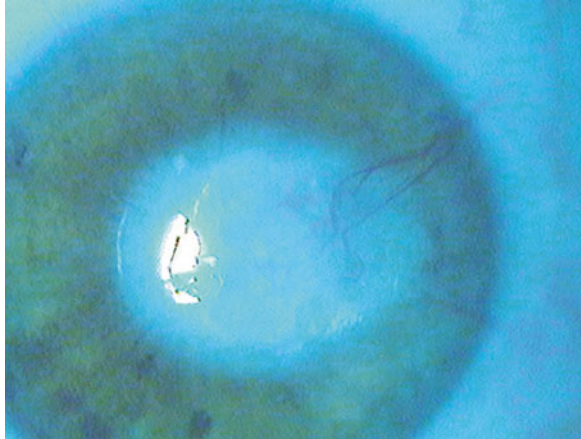
As for the treatment, the cause of band keratopathy should be addressed. The coexistence of an underlying systemic or local disorder must be recognized and treated first. Successively, calcium deposits are treated with a chelation procedure, which has been proven to be effective and easy to perform. Mechanical debridement was demonstrated to be effective as well in early stages. In case of dense and thick deposits, the manual scraping is necessary prior to chelation. Chelation is performed using a 1.5–3.0 % solution of ethylenediaminetetraacetic acid (EDTA) for 15–20 min. If required, the corneal surface might be further smoothed by excimer laser phototherapeutic keratectomy. Epithelial layer restoration could be enhanced by amniotic membrane application, which may help optimize the clinical outcome. Only in very advanced cases with severe visual impairment could the lamellar keratoplasty be considered a therapeutic option [43–45].

### 2.4.3 Lipid Keratopathy

Lipid keratopathy can occur spontaneously or may be a consequence of a previous ocular injury or inflammation. The first form is a primary one, rather infrequent, because of stromal deposits of cholesterol, fats, and phospholipids. It is not associated with vascularization.

The second form occurs as a secondary disorder associated to previous ocular diseases or injury. The secondary lipid keratopathy is much more common, and it is typically associated with corneal vascularization (Fig. 2.8). The most frequent corneal pathologies underlying the secondary lipid keratopathy are herpetic infections, both simplex and zoster. Treatment should focus on the underlying disease first. Successively, abnormal vascularization should be eliminated by argon laser photocoagulation or needle point cautery to induce the absorption of the lipids through the destruction of the feeder vessels.

**Fig. 2.8** Lipid keratopathy.  
(Archives Dr.  
A.M. Roszkowska)



Corneal grafting remains the last treatment option, but it needs a relative quiescence, and the clinical outcome is rather poor because of the corneal thinning, hypesthesia, and persistent vascularization [46, 47].

#### **2.4.4 Spheroidal Keratopathy**

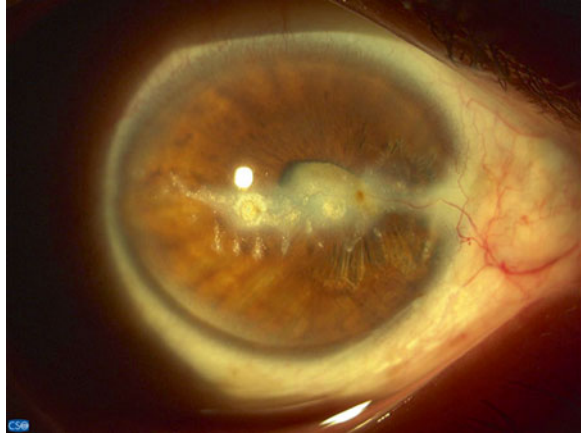
Spheroidal corneal degeneration is also known as corneal elastosis, Labrador keratopathy, climatic droplet keratopathy, Bietti's nodular dystrophy, proteinaceous corneal degeneration, elastotic degeneration, Fisherman's keratopathy, and Eskimo's corneal degeneration. It was described by Bietti in 1955 and is characterized by oil-like, amber-colored, spheroidal deposits at the limbus and in the peripheral interpalpebral cornea.

It arises typically in outdoor workers, and the main causing factor is ultraviolet exposure. It is more frequent in populations living in zones with high climatic UV exposure, and the severity is correlated positively with the time of exposure (Fig. 2.9).

With time, the corneal opacification increases, and deposits spread toward the center of the cornea. The advanced lesions are associated with localized haze. Sometimes the corneal changes coexist with the same conjunctival deposits. Spheroidal keratopathy is more frequent in males; it is bilateral and relatively innocuous, although in some cases, visual impairment might occur.

Histologic examination showed extracellular protein deposits in the anterior corneal stroma with elastotic degeneration. They are formed by UV-degraded protein materials that originated from the plasma through the limbal vessels. Progressively, such deposits slowly replace the Bowman's membrane [47–50]. In patients with spheroidal degeneration, protection against ultraviolet damage with sunglasses is mandatory. In advanced forms with central involvement, the various grades of visual impairment might occur, requiring appropriate therapeutic options. In such cases, superficial keratectomy and PTK are recommended, and good clinical and visual outcome could be expected.

**Fig. 2.9** Spheroidal keratopathy, (Archives Prof. E. Wylegala)



### 2.4.5 Vortex Keratopathy

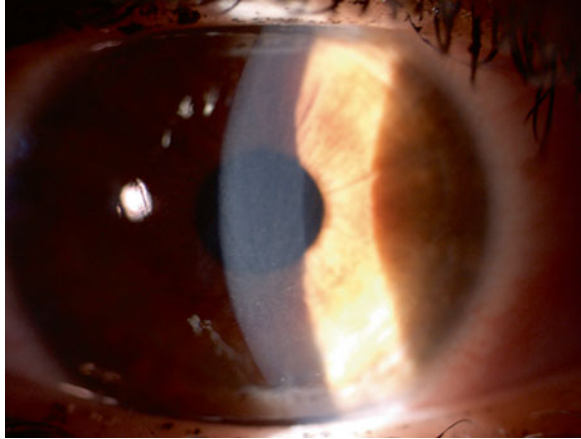
This corneal degeneration is also known as cornea verticillata. It is bilateral and characterized by the whitish-gray or golden-brown deposits that form a whorl-like pattern in the inferior hemicornea. Its typical clinical appearance makes it easily recognizable (Fig. 2.10).

Vortex keratopathy is a form of drug-induced lipidosis because it results from chronic prolonged systemic therapies with amiodarone, chloroquine, hydroxychloroquine, indomethacin, and phenothiazine with deposition in the cornea of phospholipids not metabolized by lysosomal phospholipases. The vortex keratopathy is also typical for a lipid storage disorder called Fabry disease caused by genetically determined enzymatic deficiency. Corneal lipid depositions are localized in the basal epithelial cells [51–53]. Recent confocal investigation showed deeper stromal deposits in advanced forms, suggesting a higher toxicity than was thought until now in long-term treated patients [54]. Generally, no visual alterations are present. However, in the extended drug-induced keratopathy, some visual disturbance might occur, indicating a high toxicity. In such case, the modification of systemic therapy could be considered. Vortex keratopathy is reversible and decreases when systemic therapy is switched or reduced.

### 2.4.6 Pigment Deposition Keratopathies

These corneal degenerations consist of deposition of different pigmented substances in corneal layers. The most frequent are due to the epithelial iron deposits. Beyond the Hudson–Stahli line observed sporadically in normal corneas of aged individuals, the iron deposits are typically present in particular corneal conditions when the regular corneal profile is modified. This can be observed in the cases of pterygium,

**Fig. 2.10** Vortex keratopathy.  
(Archives Prof. E. Wylegala)



keratoconus, previous corneal refractive surgery, corneal scars, and filtering blebs [55, 56]. In these conditions, the common finding is related to the high variation of corneal shape, and the deposits are localized typically in the zones where such changes occur. Corneal profile variations generate alteration of the physiological lacrimal film distribution that probably underlies this keratopathy. Histologically, the deposits are formed by intraepithelial hemosiderin in the basal cells.

#### **2.4.6.1 Pterygium**

In the advanced forms, the iron deposits separate the advancing head of pterygium exactly where the corneal surface undergoes variations. In this case, the deposits form the so-called Stocker-Hali line [57].

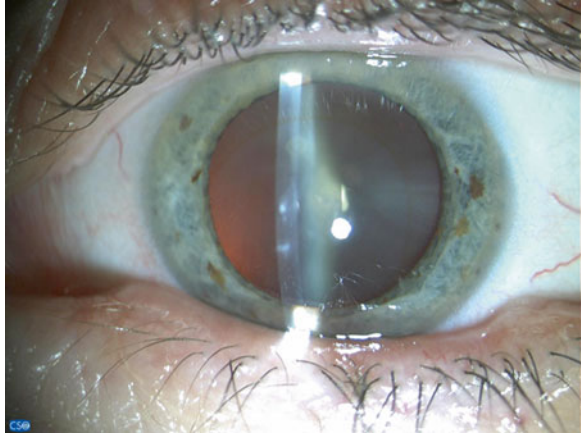
#### **2.4.6.2 Keratoconus**

In keratoconus, circular iron deposits surround the base of the cone where extreme variations of the corneal curvature could be detected, and they are commonly known as Fleischer ring [58, 59] (Fig. 2.11).

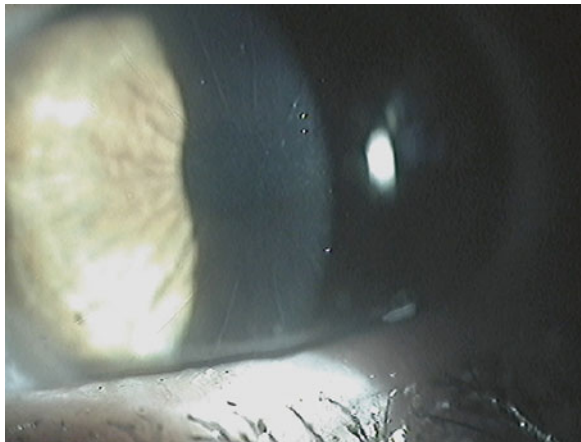
#### **2.4.6.3 Refractive Surgery**

Central corneal iron deposits in corneal epithelium are a common side effect of corneal refractive surgery, both incisional and excimer laser (Fig. 2.12). Corneal refractive procedures change corneal curvature by inducing central flattening or steepening. As previously mentioned, the important changes in corneal profile, induce alteration in tear film dynamics that promote epithelial deposition of iron. So

**Fig. 2.11** Fleischer's ring in keratoconus. (Archives Prof. E. Wylegala)



**Fig. 2.12** Central corneal iron deposits in eye with previous radial keratotomy . (Archives Dr. A.M. Roszkowska)



in eyes that have undergone hyperopic refractive corneal procedures with laser-induced excessive central corneal steepening pseudo-Fleischer ring, could be observed. In myopic correction, the iron lines could be appreciated in the central cornea where the surgically induced flattening occurs [60–62].

## 2.5 Conclusions

In this chapter, the main corneal degenerations were considered. Such corneal disorders are not hereditary, have a late onset, and might be related to local or systemic diseases or can arise with aging. In the first case, degenerations occur only in the affected eye, while in the last, the bilateral involvement is present. Some forms of degeneration might induce severe visual impairment, and appropriate therapy is

necessary to recovery and maintenance of visual acuity. Therapy is aimed to resolve the underlying disorder first and only successively to treat the corneal changes. The age-related degenerations are bilateral, usually innocuous for visual capacity. Correct diagnosis is mandatory for therapeutic choice and the efficacy of clinical outcomes.

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