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## **Panorama of limbal changes**

Julie Gueudry (1)\*, François Majo (2), Agnès Delcampe (1), Marc Muraine (1)

(1) Ophthalmology service, Hôpital Charles Nicolle, Rouen University hospital, 1 rue de  
Germont, 76000 Rouen

(2) COG Ophthalmology Center, Lausanne, Suisse

\*Corresponding author:

Julie Gueudry

Service d'ophtalmologie, CHU de Rouen

1 rue de Germont, 76000 Rouen

Email: [julie.gueudry@chu-rouen.fr](mailto:julie.gueudry@chu-rouen.fr)

Tel: +33 2 32 88 80 57 Fax: +33 2 32 88 80 46

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## **ABSTRACT**

The corneal limbus is a privileged region on the border between two quite different microenvironments, where corneal epithelial stem cells, numerous melanocytes, and antigen-presenting cells are all concentrated within a richly vascularized and innervated stroma. This situation within the ocular surface confers on it the key functions of barrier, epithelial renewal and defense of the cornea. As an immunological crossroads and since the corneoscleral limbus is directly exposed to external insults such as caustic agents, ultraviolet radiation, microbial agents, and allergens, it is the potential site of many tumoral, degenerative or inflammatory pathologies and may progress under certain conditions to limbal stem cell deficiency.

**Key words:** corneoscleral limbus; cornea; conjunctiva; limbal epithelium; stem cell; ocular surface tumors

## INTRODUCTION

In astronomy, the word “limbus” represents the edge of the disc-shaped image of a star. Its parallel use in ophthalmology is easily understood, since the limbus defines the border between the transparent cornea and the opaque sclera. Its privileged location on the ocular surface confers to it key functions as a barrier, source of epithelial renewal and defense of the cornea. It is thus easy to understand that it is also the site of numerous pathologies, which we will present in this chapter in the form of a panorama, with emphasis on visual recognition. We refer the reader to various reference articles in which each specific pathology is detailed, particularly in the various treatises of the Medical-Surgical Encyclopedia (EMC) of Ophthalmology.

## THE LIMBUS

### **Anatomy of the limbus**

The limbus designates the anatomic border between the transparent, avascular cornea and the white sclera covered with richly vascularized conjunctiva. For surgeons, it corresponds to the macroscopic zone of color change from the sclera to the cornea, which goes from white to blue or gray, over a length of about 1.2 mm before reaching the transparent cornea [1]. This is where the transition between the bulbar conjunctival and corneal epithelium occurs.

### **Histology and functional anatomy**

#### *Limbal epithelium*

The limbal epithelium is a transitional epithelium between the conjunctival and cornea epithelium, in other words between two fundamentally different biologic micro-environments – the vascularized, lymphoid conjunctival environment on one side, and the very innervated, avascular corneal environment on the other side. The limbal epithelium is a multi-layered squamous epithelium, non-keratinized and without mucous cells, although they are present throughout the rest of the conjunctival epithelium. It is thicker than the central corneal epithelium and the rest of the conjunctival epithelium with ten to fifteen cell layers.

The underlying stroma contains a dense vascular network and is organized in a series of radial elevations centered about a fibrovascular axis known as the palisades of Vogt. These elevations are oriented radially, perpendicular to the limbus. These palisades form undulations on the limbal surface, especially visible superiorly and inferiorly, more easily

seen in more darkly pigmented subjects (Fig. 1). Between the palisades of Vogt, the crypts are home to the corneal stem cells, more deeply embedded [2].

Melanocytes are present in the basal layer of the conjunctival epithelium, especially at the limbus. Just as with epidermal melanocytes, they transfer their melanin granules to the epithelial cells [3]. Their primary role is to protect tissues from ultraviolet radiation. More recently, a role has been identified within the “limbal stem cell niche;” through their interaction, they are said to permit maintenance of the stem cell character of certain limbal cells as well as their multipotent character [4].

The limbus is a richly vascularized zone. Its arterial supply is achieved through anterior conjunctival arteries which arise from the anterior ciliary arteries, which in turn arise from the ophthalmic artery. These anterior conjunctival arteries head radially toward the cornea within the episcleral tissue and insure vascularization of the limbal conjunctiva via a direct branch, which ends in a terminal meshwork, forming the limbal vascular arcades. From the terminal meshwork, venous return occurs through the corresponding conjunctival veins [5].

The anterior ciliary nerves, coming from the ophthalmic branch of Willis of the trigeminal, collect sensory information from the limbal conjunctiva. The limbus is the site of passage of the long ciliary nerves, which radiate toward the center of the cornea. There is also vegetative innervation to the limbus, notably parasympathetic [6].

### ***Renewal of the corneal epithelium***

The corneal epithelium is a tissue with rapid renewal, which occurs, according to the predominant theory, from corneal epithelial stem cells situated within the limbus. The basal epithelial cells migrate continuously from the limbus toward the central cornea like an escalator from the basal layer. The more superficial cells then migrate vertically by “pushing off” from the basal “escalator.” This model is the basis of our current understanding of corneal pathologies known as “limbal stem cell deficiency.” According to this pathologic model, if there are no more stem cells within the limbus, or if the limbus is destroyed, there are no more epithelial cells left to renew the corneal epithelium, and this is then replaced by the nearest epithelium – the conjunctival epithelium.

## **LIMBAL PATHOLOGIES**

As indicated in the introduction, we have taken the liberty to present here all of the limbal pathologies in the form of a rich panorama of photographs. For each of them, we cite references to specific corresponding chapters in the EMC treatise. Diseases of the trabecular meshwork, which belongs to the anatomic limbus, will not be addressed in this chapter.

## **Limbal tumors**

### *The limbus as a specific site for carcinogenesis*

The presence of epithelial stem cells might in part explain the preferential presence of conjunctival carcinomas within the limbus. In effect, the protective process of desquamation is less active here. On the other hand, rapidly renewing epithelial cells desquamate rapidly and would theoretically be protected against phenomena of carcinogenesis, which may explain the rarity of carcinomas in the central cornea. In addition, the limbus is one of the ocular surface zones most exposed to ultraviolet rays, which constitute an additional risk factor. Finally, one hypothesis suggests that transitional epithelia might be specific sites for the occurrence of carcinomas due to their location between several different micro-environments and their reception of possibly conflicting biologic signals. This phenomenon might induce a deregulation of the cellular machinery, with a secondary increased risk of metaplasia and carcinoma [7].

Limbal tumors are varied, with various prognoses. The clinical appearance is often insufficient to characterize these various lesions as benign, precancerous or malignant [8, 9]. It is thus recommended to be relatively systematic when in the slightest doubt, by performing an excisional biopsy so as to obtain a histologically certain diagnosis and thus be able to appropriately customize management.

The evaluation of 5002 conjunctival tumors by Shields *et al*, in an American tertiary care center for ophthalmologic oncology, has shown that the limbal location was the most frequent localization, since 2370 lesions were localized to the limbus, i.e. 47.4% of cases. The large number of melanomas and squamous cell cancers in this study is very probably related to the specific recruitment at this referral center (Table 1) [10].

### *Benign lesions*

We typically distinguish acquired benign tumors from congenital tumors, in particular dermoids, located mostly at the limbus. Histologically, dermoids are choristomas, defined as

congenital proliferations of tissue of normal structure, but in a site where they should not be located. Their presence must trigger an attentive examination looking for a congenital malformation syndrome, in particular Goldenhar syndrome. Surgical excision may be considered in the case of functional, visual or aesthetic compromise (Fig. 2). Acquired tumors may be melanotic (Fig. 3, 4), epithelial, some of which are considered precancerous (Fig. 5), or stromal (Fig. 6) (Table 1).

### ***Malignant lesions***

In this situation, one must distinguish between melanocytic lesions, epithelial or conjunctival stromal lesions and metastases. These malignant lesions have a tendency to occur in elderly patients; the majority of conjunctival lesions in children, whether limbal or not, are benign [10, 11]. Primary acquired melanosis is a flat pigmentation of variable extent, most often unilateral, appearing relatively late between 40 and 60 years of age, and with a progressive course. We distinguish primary acquired melanosis without cytologic atypia from primary acquired melanosis with cytologic atypia, which are considered precancerous. All areas of the conjunctiva may be affected, but in the case of limbal localization, the pigmentation is particularly visible and may result in diffusion of pigment into the corneal epithelium. (Fig. 7). Classically, melanomas have no specific conjunctival localization, but their localization at the limbus is not rare (Fig. 8). Malignant epithelial tumors, essentially intra-epithelial (or *in situ*) or invasive squamous cell tumors are difficult to diagnose clinically, which justifies surgical excision to obtain a confirmed diagnosis (Fig. 9, 10, 11).

### **Pterygium and pinguecula**

Pterygium is a benign conjunctival fibrovascular lesion, spreading progressively onto the cornea, in a potentially disabling fashion [12]. Exposure to ultraviolet rays represents the main risk factor. The limbal location is explained by the Coroneo effect, corresponding to the focusing of reflected light rays coming from the temporal region onto the nasal limbus. Pinguecula is a yellowish degenerative lesion of conjunctival elastic tissue, adjacent to the nasal or temporal limbus, which does not invade the cornea. It has the same pathophysiologic origin as a pterygium (Fig. 12).

### **Immune and infectious lesions**

The limbus is also the site of immune inflammatory and infectious pathologies [13]. In effect, the corneal-conjunctival epithelium constitutes the final barrier to the entry of pathogenic

agents into the deep ocular structures after the lids and the tear film. The conjunctiva possesses a network of intra-epithelial immunologic cells, in particular the Langerhans cells. These cells are antigen-presenting cells, which enables them to be recognized and then eliminated by subepithelial immunocompetent cells. In the case of ocular surface inflammation, their density increases considerably [14]. The conjunctival stroma is extremely rich in immunocompetent cells. Lymphatic drainage proceeds to the parotid, pretragal and submaxillary nodes [5]. Due to its abundant supply of vessels and lymphatics, the limbus is a veritable immunologic crossroads. It is indeed possible to imagine that the limbus plays a role as guardian of the cornea, which is very poorly defended by the immune system, since such a reaction would be harmful to its integrity and transparency. Thus, in the case of keratitis, limbal inflammation occurs, with dilation of the vessels and migration of inflammatory cells into the extracellular space, which then migrate into the normally avascular cornea. An auto-amplification of the inflammatory process through the involvement of secreted pro-inflammatory substances favors its extension to the entire ocular surface [15].

A limbal location of an ulcer is very suggestive of an inflammatory cause, although this is not a given (Table 2) [16]. Thus, in rosacea or Meibomian gland dysfunction, the infiltrates are probably a type III hypersensitivity reaction (immune complex deposits) and phlyctenular keratoconjunctivitis and type IV hypersensitivity reaction (cell-mediated immunity) to staphylococcal antigens colonizing the lids in these situations (Fig. 13). In the limbal form of vernal keratoconjunctivitis, a limbal gelatinous bead-like appearance is seen, within which one may sometimes see white nodules known as Trantas dots, which represent the accumulation of eosinophils (fig. 14). This form is most frequently encountered in black subjects, thus sometimes known as tropical endemic limbo-conjunctivitis. A limbal bead may also be identified in atopic keratoconjunctivitis [17].

One must be aware that an autoimmune peripheral ulcerative keratitis may be the first manifestation of a systemic disease. Mooren's ulcer, an idiopathic peripheral ulcerative keratitis, is a diagnosis of exclusion which requires other diseases causative of peripheral corneal ulcers to be ruled out (Fig. 15). An underlying systemic disease is found in about one half of cases, and a fourth of predisposing conditions are unknown at the time of ophthalmologic symptoms [18]. Rheumatoid arthritis is the main cause, found in 38%, then, next most frequently, Wegener's granulomatosis or granulomatosis with polyangiitis [19]. Other systemic conditions associated with peripheral ulcerative keratitis include other ANCA

positive vasculitis (Churg-Strauss syndrome and microscopic polyangiitis), polyarteritis nodosa, chronic atrophic polychondritis and systemic lupus erythematosus. Certain ocular surface infections may present in a manner which mimics an autoimmune condition, particularly herpetic limbal epithelial keratitis (Fig. 16). In the case of chronic conjunctivitis and a limbal bead, chlamydia must also be considered.

### **Limbal stem cell deficiency**

Regardless of the theory of epithelial renewal, this can only produce an epithelium with a corneal phenotype (transparent, non-keratinized) if the environment is healthy (quality of the tears and lids, absence of conjunctival inflammation). In the case of a chronic alteration of this micro-environment, the corneal epithelium transforms and takes on the phenotypical appearance of conjunctiva or epithelial metaplasia [20]. The corneal epithelium is invaded by the conjunctival epithelium or changes phenotype to appear vascularized with the presence of goblet cells. This situation occurs in several pathologic conditions and results in limbal stem cell deficiency (LSCD), which occurs not only by destruction of the limbal cell reserve in a strict sense (Table 3) [21]. In the largest series published to date, a retrospective series of 1512 eyes, the most frequent causes are, in decreasing order, chemical or thermal burns (54%), atopic and vernal keratoconjunctivitis (18%), Stevens-Johnson syndrome and toxic epidermal necrolysis (15%), congenital aniridia (5%), and mucous membrane pemphigoid (3%) [22]. Clinically, one of the first signs may be the disappearance of the normal limbal architecture (palisades of Vogt). Then, the corneal surface neovascularizes and opacifies. This syndrome may be complicated by chronic or recurrent corneal ulcers which may eventually progress to perforation. In the end stage, the corneal surface may keratinize, be invaded by a fibrovascular pannus and develop calcium deposits (Fig. 17, 18, 19, 20).

### **Miscellaneous**

#### ***Terrien's marginal degeneration***

Terrien's marginal degeneration is a rare bilateral peripheral corneal limbal degeneration of unknown cause. It is characterized by a non-inflammatory thinning of the peripheral cornea (Fig. 21).

#### ***Corneal Dellen***

The corneal Dellen is characterized by a corneal thinning typically at the limbus, in association with an elevation, most often conjunctival, causing a reduction in the spreading of

the tear film at its base, which results in stromal dehydration and thus visible thinning of the limbus or peripheral cornea (Fig. 22).

## CONCLUSION

The anatomic and physiologic configuration of the corneoscleral limbus explains the specificity and rich panorama of pathologies which may affect it. A more precise knowledge of the phenomena of cellular regeneration and the various intercellular interactions or those with the extracellular matrix may be able to improve medical and surgical management of these apparently definitive changes in the limbal epithelium [23].

## Disclosure of interest

The authors have no conflicts of interest to disclose in relation to this article.

## Further reading

See this article, unabridged, illustrated and detailed, with electronic enhancements, in EMC-Ophtalmologie : Gueudry J, Majo F, Delcampe A, Muraine M. Panorama des altérations limbiques cornéennes. EMC - Ophtalmologie 2018;15(4):1-13 [Article 21-200-C-20].

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		Total number (n) of patients	Limbal localization
<b>Melanocytic</b>	Nevus	1163	42%
	Primary acquired melanosis	623	62%
	Melanoma	601	61%
<b>Epithelial</b>	Papilloma	77	14%
	Carcinoma <i>in situ</i>	275	88%
	Invasive carcinoma	440	76%
<b>Lymphoid</b>	Benign lymphocytic hyperplasia	107	12%
	Lymphoma	358	11%
<b>Stromal</b>	Dermoid	46	39%
	Dermatolipoma	41	2%
	Pyogenic granuloma	66	20%

<b>LSCD secondary to chemical, physical or mechanical destruction</b>
<b>Table 2. Etiologies of peripheral ulcerative keratitis according to [16]</b>
<ul style="list-style-type: none"> <li>• Chemical or thermal burns</li> </ul>
<b>Non-infectious ocular causes</b>
<ul style="list-style-type: none"> <li>• Radiotherapy</li> <li>• Idiopathic or Mooren's ulcer</li> <li>• Surgical trauma: history of surgery (peritomy) or cryotherapy involving the limbus, surgical excision of limbal neoplasm</li> <li>• Exposure, post-traumatic, toxic keratopathy</li> </ul>
<b>Local infectious causes</b>
<ul style="list-style-type: none"> <li>• Mechanical trauma: trichiasis, prolonged contact lens wear</li> </ul>
<b>LSCD of infectious origin</b>
<ul style="list-style-type: none"> <li>• Bacterial (<i>Staphylococcus</i>, <i>Streptococcus</i>, <i>Gonococcus</i>)</li> <li>• Viral (Herpes simplex or varicella-zoster virus)</li> <li>• Severe bacterial keratitis, trachoma, herpes, mycoses</li> <li>• Parasitic (<i>Acanthamoeba</i>)</li> </ul>
<b>LSCD of inflammatory origin</b>
<ul style="list-style-type: none"> <li>• Stevens-Johnson syndrome and toxic epidermal necrolysis</li> <li>• Mucous membrane pemphigoid</li> <li>• Atopic keratoconjunctivitis, ocular rosacea, Sjögren's syndrome</li> <li>• Connective tissue diseases</li> <li>• Rheumatoid arthritis (frequent)</li> </ul>
<b>LSCD of genetic origin</b>
<ul style="list-style-type: none"> <li>• Granulomatosis with polyangiitis (Wegener's Granulomatosis)</li> <li>• Congenital aniridia</li> <li>• Periarteritis nodosa</li> <li>• Hereditary epidermolysis bullosa</li> <li>• Microscopic polyangiitis</li> <li>• Congenital erythrokeratoderma</li> <li>• Churg-Strauss syndrome</li> <li>• Hereditary multiple endocrinopathy</li> <li>• Chronic atrophy polychondritis</li> </ul>
<b>LSCD and surface dysplasia or dystrophies</b>
<ul style="list-style-type: none"> <li>• Bleydenma</li> <li>• Exanthematous keratitis (very rare)</li> </ul>
<b>Idiopathic LSCD</b>
<b>Autoimmune diseases</b>
<ul style="list-style-type: none"> <li>• Aniridic keratitis</li> <li>• Chronic inflammatory bowel disease</li> <li>• Cicatricial pemphigoid</li> </ul>
<b>LSCD by destruction of a component of the corneal matrix</b>
<ul style="list-style-type: none"> <li>• Sjögren's syndrome</li> <li>• Neurotrophic keratitis (herpes, diabetes)</li> <li>• Leukemia, sarcoidosis (very rare)</li> </ul>

Figure 1. Palisades of Vogt superiorly (a), better seen in black patients due to the accumulation of melanocytes in this location, here inferiorly (b).

Figure 2. Limbal dermoids (a, b).

Figure 3. Conjunctival nevi are the most frequent tumors of the ocular surface. They are typically located in the bulbar conjunctiva and frequently at the limbus. They frequently contain inclusion cysts, which is a feature suggestive of their benign nature. Limbal nevi (a,b,c); achromatic limbal nevus (d).

Figure 4. Ethnic melanosis. This is a flat, bilateral pigmentation predominantly at the limbus in a black subject, appearing in childhood and non-progressive.

Figure 5. Actinic keratosis is an epithelial lesion considered precancerous and having a characteristic wet sugar appearance.

Figure 6. Corneal xanthoma is a deposition of cholesterol-rich material and appears as a yellowish lesion. It is frequently excised due to diagnostic uncertainty. Appearance before and after central corneoscleral lamellar keratoplasty (a,b).

Figure 7. Primary acquired melanoses with cytologic atypia (a, b). Primary acquired melanosis with cellular atypia before (c) and after treatment with two 2-week courses of mitomycin 0.04% spaced two weeks apart (d).

Figure 8. Invasive limbal conjunctival melanomas of variable pigmentation (a,b).

Figure 9. Squamous cell carcinoma *in situ* with gelatinous invasion of the cornea (a,b,c,d).

Figure 10. Squamous cell carcinoma *in situ* in its papillomatous form (a). Squamous cell carcinoma *in situ* in its pigmented form of a patient of African origin (b).

Figure 11. Appearance of an invasive squamous cell carcinoma of the limbus. On histology, the edges of the tumor have crossed the epithelial basement membrane with a resultant risk of distant metastasis, which is not the case for carcinoma *in situ*.

Figure 12. Characteristic triangular appearance of pterygium. Note the limbal location of early cases (a). Pinguecula; note the absence of corneal invasion (b).

Figure 13. Rosacea and Meibomian gland dysfunction. Catarrhal infiltrates (a). Phlyctenular keratoconjunctivitis (b).

Figure 14. Vernal keratoconjunctivitis. Limbal bead (a). Trantas dots (b).

Figure 15. Peripheral ulcerative keratitis. Perforated Mooren's ulcer (a). Peripheral ulcerative keratitis seen in the context of rheumatoid arthritis (b).

Figure 16. Peripheral or limbal epithelial herpetic keratitis. Diagnostic delay in this form is frequent, since the clinical symptomatology is very similar to autoimmune peripheral

ulcerative keratitis, including a corneal epithelial and often a stromal involvements (a).

Proximity to the limbus may result in a marked adjacent stromal infiltrate (b).

Figure 17. Syndrome of limbal stem cell deficiency and aniridia keratopathy (a). Appearance on retro-illumination. Note absence of iris (b).

Figure 18. Syndrome of limbal stem cell deficiency and chemical burn of the ocular surface. Initial appearance, after amniotic membrane graft performed 4 days after the burn (a) and at 6 months (b).

Figure 19. Syndrome of limbal stem cell deficiency and Stevens-Johnson syndrome and toxic epidermal necrolysis. Appearance 2 years after toxic epidermal necrolysis (a); patient fitted with a scleral lens for sequellae of toxic epidermal necrolysis (b).

Figure 20. Syndrome of limbal stem cell deficiency and mucous membrane pemphigoid. Inferior neovascularization and epithelial ulcer (a), corneal neovascularization and inferior symblepharon (b).

Figure 21. Terrien's marginal degeneration. Peripheral corneal thinning and lipid deposits, without epithelial ulceration.

Figure 22. Corneal Dellen caused by an adjacent limbal lesion.

























































































