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Peripheral Ulcerative Keratitis

A Comprehensive Guide

Springer

Essentials in Ophthalmology

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Preface

This textbook, Peripheral Ulcerative Keratitis, came about in 2014, when the topic was covered in the Cornea Subspecialty Day at the AAO meeting in Chicago and we realized that this was a clinical area that required an updated textbook of its own. Though not that common, the disease is of sufficient importance to merit special attention by virtue of it being sight threatening and a complex disorder with an interplay of systemic and local pathologies and advances in therapeutic strategies that should be highlighted.

The book has a galaxy of contributing authors who are all clinical luminaries in the field and were kind enough to join the journey of reposing their knowledge in the form of a book. The book has been designed to serve as a simple practical guide to understanding the disease in a basic and clinical sense with a view to help both general ophthalmologists and cornea specialists have a ready reference at hand to guide their clinical practice in dealing with such patients. In addition, ophthalmology residents and cornea fellows would find it useful to read as valuable study material to build their basic knowledge and enhance clinical skills.

The chapters deal with different aspects of the illness and all facets of diagnosis and management are well represented in the different sections. The text has been supplemented with useful references and the appendices provide a useful guide by simple step-by-step algorithms which are easy to comprehend and follow. Both medical and surgical treatment options are mentioned and the approach to management is covered in a style which is comprehensive and easy to understand.

The erudite authors are from different corners of the globe and we are most grateful that they were very forthcoming in their contributions and helpful with adherence to timelines. We are indeed indebted to them for the excellent contributions they have made in providing their expertise for this venture. The textbook is supported by illustrative examples and figures to enable the reader to apply the information gained in a practical and effective manner.

It has been an honor and privilege to work on this project with all the contributors and the team from Springer. We would like to acknowledge the aid provided by Rebecca and Tracy from Springer in coordinating the editorial efforts and that of Dr. Arun D. Singh in overall conception and design of the book.

We trust that libraries will take this volume to be a valuable asset on their bookshelves and the readers will find this compendium a useful addition to their personal collection and carry useful take home messages every time they go through it. We hope you enjoy absorbing the contents provided as much as we did in compiling all the information within the confines of the covers and wish you success in handling patients you may encounter from time to time.

New Delhi, India — Radhika Tandon
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Part I
Basics

1 Anatomical Considerations

Saranya Devi, Anin Sethi, Noopur Gupta, Seema Sen and M. Vanathi

Introduction

Cornea is a transparent area which makes one-sixth of the outer circumference of the eye. **At the periphery is a transition zone 1–1.5 mm**, **limbus where corneal stroma is bonded to the sclera**. The adult cornea is 10.5 mm vertically and 11.5 mm horizontally. The anterior and posterior surfaces are parallel to each other in the central 4 mm spherical-shaped “optical zone” where the cornea averages 0.52 mm in thickness. **The peripheral cornea is slightly flattened**, **anterior and posterior surfaces are no longer parallel and corneal thickness increases to 0.65 mm**. Even though central cornea is responsible for the formation of sharp retinal image as it lies in the visual axis, studies have proven that peripheral cornea also has significant role in affecting the optical quality of the image formed [1].

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Anatomy

The central cornea is divided into five distinct layers proceeding from without inwards: epithelium, Bowman’s membrane, stroma, Descemet’s membrane, and endothelium. The peripheral cornea requires specific mention as its anatomy and microscopic appearance differ from the remaining cornea.

The corneal epithelium is stratified squamous consisting of five or six layers of cells. **Towards the periphery**, epithelial cells are concentrated where these cells undergo proliferation [2, 3] **and the number of cells increases to 8–10** in the periphery. This explains the role of limbal vasculature in healing after surgery. The deepest or basal layer rests directly on the Bowman’s membrane as a single layer of polygonal cells with flat bases and round heads. These cells are considerably large with pale-staining cytoplasm and oval nucleus lying perpendicular to the corneal surface. The thin basement membrane (480 Å) is seen on periodic acid-Schiff (PAS) stain. The basement membrane is composed of type IV collagen, proteoglycans, fibronectin, and laminin. Ultrastructurally hemidesmosomes are seen to lie along the attachment of the basal cell layer to its basement

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membrane. The posterior portion of the basement membrane blends with the Bowman's layer. Various membrane associated mucins, which are important components of the tear film, as MUC 1 and 16, are found to be dispersed throughout the peripheral cornea. Also MUC 4 is found in higher levels at the peripheral region [4] which is associated with the serum albumin in the surrounding capillaries. This differential expression of the mucins affects the clinical manifestations of those with dry eye disease.

The Bowman's layer is 8–14 µm acellular structure that merges with the superficial stromal lamellae to which it is firmly attached. Bowman's layer is composed of type V collagen. Numerous pores in the inner portion provide passage for terminal branches of the corneal nerve. The peripheral margins of the Bowman's layer demarcate the anterior boundary of the limbus.

The stroma forms 90% of the corneal thickness. It is avascular and consists of collagenous lamellae interspersed with keratocytes and ground substance. The collagen fibrils are parallel to one another and to the surface. Majority of the stroma has type I collagen. The keratocytes in between the lamellae are like flattened and compressed fibroblasts. Stroma in the peripheral cornea forms a transition zone between cornea and sclera. Collagen fibers are loosely arranged in this area [5, 6]. The nutritional supply to this area is derived from the capillaries at the periphery of cornea [7]. Diffusion of various molecules occurs from these capillaries to the peripheral cornea resulting in higher concentration of serum albumin in the periphery which later diffuses to the central cornea [8]. This limited diffusion results in higher concentration of Langerhans cells, IgM and complement factor C1 [9]. Because of its proximity to the conjunctival tissue; peripheral cornea has access to the lymphatics and to both afferent and efferent arms of the immune system [10, 11].

The Descemet's membrane lies on the posterior aspect of the stroma. It is a true basement membrane formed by corneal endothelial cells. It contains type IV collagen. At the periphery Descemet's membrane terminates at the junction between trabecular and corneal endothelium. Descemet's membrane is acellular, faintly eosinophilic, and PAS positive. It is 3–4 µm at birth and 10–124 µm at 50 years.

The endothelium is a single layer of polygonal cells extending over the inner surface of Descemet's membrane. The cells appear rectangular with pale-staining granular cytoplasm and centrally located nucleus. This layer is derived from the neural crest. Unlike the epithelium it hardly undergoes mitotic division in normal eye. Corneal endothelial cells have maximum mitogenic activity in the peripheral area [3]. These cells might migrate towards the center to facilitate the healing after any damage [12].

These anatomical and physiological characteristics of the peripheral cornea make it vulnerable to various diseases such as:

(i) local infectious diseases or hypersensitivity reactions
(ii) systemic reactions such as vasculitides, autoimmune diseases, and metabolic disorders or
(iii) noninflammatory peripheral degenerations [11, 13, 14].

Limbus proper

Limbus is the peripheral area, 1 mm wide which forms a transition between the transparent cornea and conjunctiva/opaque sclera. Although it is transparent like the cornea, it is rich in blood vessels and nerve endings like the conjunctiva. It is further divided into anatomical, histological, and surgical limbus [15]. **Anatomical limbus** is formed by the junction of the conjunctival and corneal epithelia where multipotential limbal stem cells undergo differentiation [16]. Histologic limbus is defined as the junction of cornea and sclera documented in histological cross-sectional views. The microscopic anatomy of the limbus is depicted in Fig. 1.1.

The limbus is composed of only two layers namely the epithelium and the stroma, because

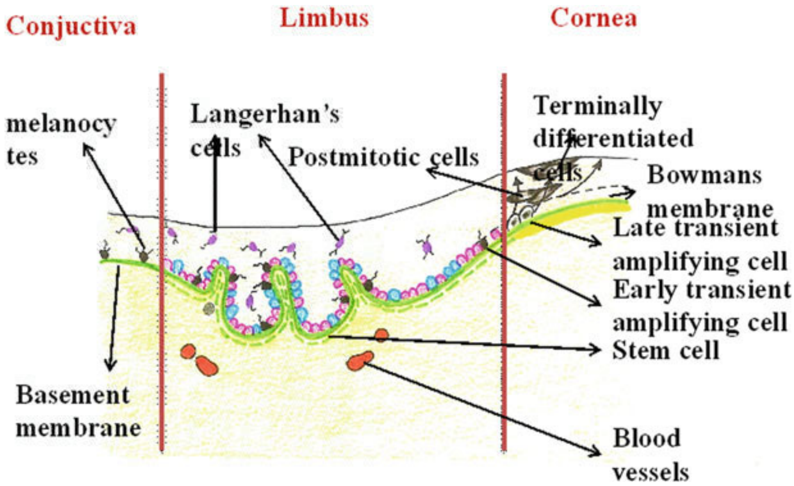

Fig. 1.1 Anatomy of the limbus

the Bowman's membrane stops abruptly and Descemet's membrane merges into the meshwork at the angle. **The epithelium is still stratified squamous but has 10 or more layers with the basal layer cells being smaller, more closely packed with scant cytoplasm**. The stroma loses its regular arrangement and becomes normal connective tissue with numerous blood vessels which are anastomosing branches of the anterior ciliary artery that terminate in the loops of the marginal plexus and then drain back into conjunctival venules. The limbus consists of stem cells which undergo slow cycling and are capable to undergo proliferation and differentiation. Each stem cell divides into a daughter stem cell and transient amplifying cell. These transient amplifying cells lie in the basal layer where they further divide to produce post-mitotic cells. These post-mitotic cells undergo further differentiation to produce terminally differentiated cells. These cells reach the superficial layers where continuous sloughing of the epithelium occurs.

Although both cornea and sclera consist of collagen fibers, corneal collagen is relatively less eosinophilic and is regularly arranged contributing to its transparency. These corneal collagen fibers are 600 Å in diameter whereas scleral fibers are 700–1000 Å in diameter. Scleral fibers are more branched and extend anteriorly on the external surface further than on the internal surface of the corneoscleral junction. This diagonal arrangement of the interface relates to the appearance of surgical limbus and is associated with the structures of the anterior chamber angle.

Clinically, the **surgical limbus** (Fig. 1.2) is appreciated as the blue-gray transition zone appearing after reflecting the conjunctiva away from the limbus. The classical blue-gray appearance of this zone results from the scattering of light through the oblique interface between the cornea and sclera. Surgical limbus is approximately

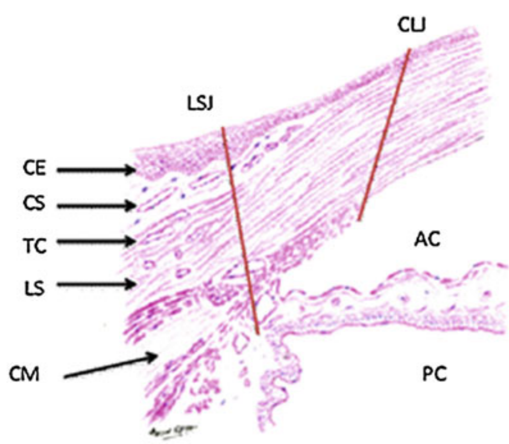

Fig. 1.2 Histological section showing the limbus. *CE* Conjunctival Epithelium; *CS* Conjunctival Stroma; *TC* Tenons Capsule; *LS* Limbal Stroma; *CM* Ciliary Muscle; *LSJ* Limoscleral Junction; *CLJ* Corneolimbal Junction; *AC* Anterior Chamber; *PC* Posterior Chamber

1.2 mm wide but is narrower in the horizontal meridian owing to less obliquity of this diagonal interface in the horizontal meridian. The posterior border of this blue zone corresponds to the location of trabecular well. The posterior border of this blue zone corresponds to the location of trabecular meshwork internally. Thus surgical incisions located anterior to this blue zone would enter well away from the trabecular meshwork [17].

On advancing towards the cornea, another well-delineated white line is noticed which corresponds to the location of scleral spur internally. After crossing this region, tissue appears grayish corresponding to the location of Schwalbe's line. The limbus contains the aqueous outflow pathway system consisting of:

(i) trabecular meshwork,
(ii) Schlemm's canal and
(iii) aqueous collector channels.

The ***trabecular meshwork*** consists of three components (Fig. 1.3). The *uveal meshwork* is the innermost part extending from uveal tissue to trabeculum and the contribution of this part of the meshwork to the outflow resistance is very minimal. Next is the *middle trabecular component* which consists of fenestrated collagen bundles. This part of the extracellular matrix undergoes phagocytic activity under the influence of appropriate stimulus [18, 19]. The *juxtacanalicular meshwork* lies adjacent to the Schlemm's canal and consists of loosely arranged connective tissue.

The ***canal of Schlemm*** is single layer of endothelial-lined channel which plays a major role in the collection of aqueous humor. It is located in the groove formed by internal sclera sulcus which is sandwiched between the scleral spur posteriorly and by the sclera collagen fibers superiorly. Aqueous from the Schlemm's canal is drained externally by the aqueous collector channels. These collector channels in turn join the intrascleral and episcleral veins [20].

Vascular supply

Limbal vessels supply peripheral cornea, conjunctiva, episclera, limbal sclera, and peripheral uvea. The limbal vessels receive arterial supply from the anterior ciliary arteries [21]. Arterioles from these arteries supply the peripheral cornea and some of the terminal arterioles reach the Palisades of Vogt. The venules from the peripheral cornea drain into the orbital veins along with the venules from episclera. The deep scleral plexus and the intrascleral plexus drain into the episcleral veins. The aqueous collector channels may drain directly into the deep scleral vein or alternatively pass through the sclera into the aqueous vein [22].

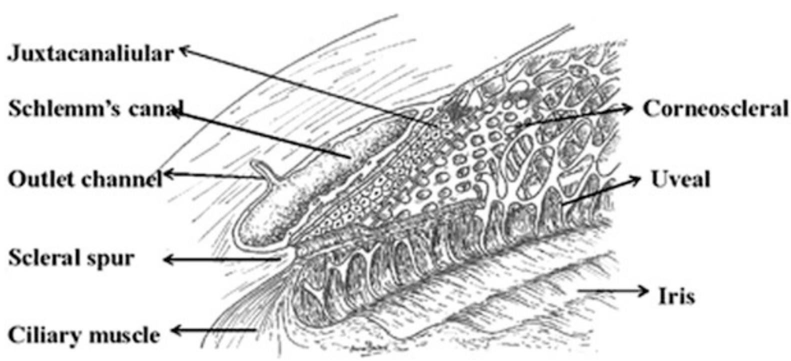

Fig. 1.3 Anatomy of the trabecular meshwork components