Pathological aspects of the failed corneal graft

Sonja Klebe

Douglas J Coster

Keryn A Williams

Abstract

The cornea is the clear window at the anterior surface of the eye. Corneal clarity is essential for vision. Corneal transplantation can restore sight when the cornea is diseased, and the cornea is the most commonly transplanted solid tissue. In penetrating corneal transplantation (penetrating keratoplasty), the whole thickness of the cornea is replaced. New surgical techniques of lamellar keratoplasty have been developed in which only the diseased layers of the cornea are replaced, to minimise the risks of graft rejection and optical distortion. Both penetrating and lamellar grafts may fail and need to be replaced. An implication for histopathologists is that the specimen sent for pathological analysis from a patient with a failed lamellar graft will differ from that from a patient with a failed penetrating graft.

Keywords corneal graft failure; corneal transplantation; lamellar keratoplasty; penetrating keratoplasty; rejection

Introduction

The cornea is the transparent window in the front of the eye. Corneal clarity is essential for vision. The shape of the cornea is also important for vision because it is the major refracting element of the eye, contributing 75% of the eye's refractive power. Abnormalities of shape of the cornea, even when it is perfectly transparent, can result in poor vision as occurs in keratoconus, the most frequent indication for corneal transplantation.[1] Corneal transplantation can restore sight when the cornea is diseased. It is thought to be the most common solid organ or tissue transplant and an estimated 120,000 corneal transplantations are performed worldwide every year. Traditionally, the whole thickness of the cornea is transplanted, but new surgical techniques replace only selected layers. As a result the specimen sent for histopathological examination depends on the type of corneal transplantation that has been carried out.

Whilst corneal transplantation is generally successful in the short term, many corneal grafts eventually fail.[1] Despite advances in immunosuppressive agents and new surgical procedures, the long-term prognosis for corneal transplants has not significantly improved over the past 20 years.[1,2] Both penetrating and lamellar grafts may be subject to primary graft failure (i.e. the graft never clears at any stage), or fail later (i.e. the graft clears after surgery but loses clarity at some later time). Any graft may develop opacities or, depending on the indication for transplantation, may be subject to recurrent disease. Many cases of graft failure are caused by immunologically-mediated rejection, which may lead to multiple graft failures and repeated procedures in the same patient. In Australia, more than 1600 grafts are performed per year and failed previous graft is the third most common indication for corneal transplantation. Unlike other solid organs, which may be prone to acute — even hyperacute — rejection, all corneal rejection is late and tends to be slow.

Some surgeons do not submit corneal specimens for histopathological assessment, either believing that the diagnosis has been established clinically, or because they become frustrated with non-specific reports. Nonetheless, pathological assessment serves an important role for quality control and can identify unexpected pathology, which may affect treatment. On the other hand, many histopathologists encounter specimens without clinical information. These specimens may include partial or full thickness corneal specimens, designated by acronyms such as 'PK' or 'DALK'. A list of the commonly used abbreviations relevant to corneal graft specimens is provided in Table 1, but communication between surgeon and pathologist is key. An understanding of the normal corneal anatomy, the type of surgeries performed and their indications is a prerequisite for diagnosis, and is briefly recapitulated here.

Relevant anatomy and relevant of the cornea

The normal adult cornea measures 10.6 mm vertically and 11.7 mm horizontally. It is thinnest in the centre, where it measures between 0.5 and 0.7 mm in thickness. The vast majority of corneal graft specimens are circular and measure between 6 and 9 mm in diameter. On a cross-section of normal human cornea, five layers are seen anteriorly to posteriorly: epithelium; Bowman's layer; stroma; Descemet's membrane; and endothelium.

The non-keratinised corneal epithelium comprises stratified squamous epithelium, which is 5—6 cells thick. This can become attenuated, for example in long-standing graft rejection. The epithelium rests on a collagenous lamina, which is sometimes called Bowman's membrane. However, it is not a true membrane, but rather the outer layer of the corneal stroma, and is more correctly called Bowman's layer. Bowman's layer ends abruptly just before the periphery (limbus) of the cornea.

The corneal stroma accounts for approximately 90% of corneal thickness. It consists of regularly arranged connective tissue surrounded by extracellular matrix and slender fibroblast-like keratocytes. The adjacent Descemet's membrane is a strong basal lamina about 10 μm thick. It increases in thickness throughout life, because it is constantly being laid down by the corneal endothelium, which it supports. Consequently, Descemet's membrane is more homogeneous and thinner in younger individuals.

Deep to Descemet's membrane and in direct contact with the aqueous humour at the interior aspect of the cornea is the corneal endothelium. This is a single layer of post-mitotic, neural crest-derived hexagonal flat cells, responsible for controlling the

Sonja Klebe *PhD Department of Anatomical Pathology, Flinders University; SA Pathology, Department of Surgical Pathology, Flinders Medical Centre, South Australia, Australia. Conflicts of interest: none.*

Douglas J Coster *Department of Ophthalmology, Flinders University, South Australia, Australia. Conflicts of interest: none.*

Keryn A Williams *Department of Ophthalmology, Flinders University, South Australia, Australia. Conflicts of interest: none.*

Glossary of terms and common abbreviations relevant to corneal specimens

ABK	Aphakic bullous keratopathy — cataract surgery has been done, but no intraocular lens (IOL) is in place corneal oedema resulting from endothelial damage after cataract surgery but without a prosthetic lens
AC	Anterior chamber
A chaud	Surgery, usually keratoplasty, into an inflamed graft bed, does not imply a specific cause of inflammation, could be infection, or rejection
Anterior synechia	Adhesion of iris tissue to endothelium, may result in endothelial failure or raised intraocular pressure (IOP)
Band keratopathy	Calcific band keratopathy, band-like area of dystrophic calcification on cornea confined to Bowman's membrane, usually treated with debridement, rarely grafted
Bullous keratopathy	Clinical sign of endothelial cell failure, resulting in stromal oedema and basal edema and bullae between epithelium and Bowman's layer
Calcific band keratopathy	Same as band keratopathy
CHED	Congenital hereditary endothelial dystrophy
Clefting	Stromal discohesion, usually artefactual
DALK	Deep anterior lamellar keratoplasty
Dellen	Localized areas of thinning in the peripheral cornea due to local drying
DMEK	Descemet's membrane endothelial keratoplasty
DLEK	Deep lamellar endothelial keratoplasty
DSAEK	Descemet stripping automated endothelial keratoplasty
DSEK	Descemet stripping endothelial keratoplasty
Descemeto-cele	An area of exposed Descemet's membrane — the overlying stroma has been lost to destructive inflammation. Often seen with HSV, sometimes with other infections
EK	Endothelial keratoplasty
Endothelial failure	End-result of any condition with loss/lack of endothelial cells, characterized by epithelial edema, stromal edema
Epithelial edema	Small vacuoles in the basal cell layer of the epithelium, sign of endothelial cell failure
Epithelial ingrowth	Epithelial cells deep to Bowman's layer, suggestive of previous trauma, e.g. surgical tract may epithelialise
Facet	Depression in corneal surface often associated with irregularity/defect in Bowman's layer, suggestive of previous trauma
Fuchs' dystrophy	Endothelial dystrophy characterised by endothelial failure and thickening of Descemet's and endothelial cell loss
Hassal-Henle warts	Focal thickening of Descemet's, may be seen in the periphery of elderly corneas, if in central cornea, suggestive of Fuchs' dystrophy
HSV K	Herpes simplex virus keratitis
ICE	Irido-corneal endothelial syndrome, a rare form of glaucoma, endothelial failure and iris atrophy in varying proportions
IK	Interstitial keratitis
IOL	Intraocular lens
IOP	Intraocular pressure
Khodadoust line	Endothelial rejection line, caused by a cluster of lymphocytes attached to the endothelium and visible at the slit-lamp
KP	Keratic precipitates, clusters of any white cells adherent to the corneal endothelium as part of intraocular inflammation
LASIK	Laser assisted stromal in situ keratomileusis
Mooren's ulcer	Sterile peripheral corneal ulcer
OSSN	Ocular squamous neoplasia
PAM	Primary acquired melanosis
Pannus (histology)	Break in Bowman's layer with anterior stroma abutting epithelium
Pannus (clinical)	A patch or front of new vessels — usually complicating inflammation or post-inflammatory
PBK	Pseudophakic bullous keratopathy — cataract surgery with lens replacement in situ, followed by loss of endothelium, features of endothelial failure causing stromal and epithelial oedema
PEX	Pseudoexfoliation syndrome — proteinaceous deposits on the lens which may also be associated with glauocma
PK or PKP	Penetrating keratoplasty
PPV	Pars plana vitrectomy
PRK	Photorefractive keratectomy
Retrocorneal membrane	Organising fibrin adherent to endothelium, may result in endothelial cell failure or raised IOP
RK	Radial keratotomy
SPK	Superficial punctate keratopathy

Table 1