Management of Corneal Graft Rejection in High-Risk Patients

An essay
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Abstract

Penetrating keratoplasty is the most common form of solid organ transplantation. Owing to recent developments in surgical techniques, materials and postoperative management, indications for PK have been extended to high risk patients.

Corneal grafting is a successful procedure with a first year survival rate of up to 90%, however a long-term 10 year survival rate drops to 62% and in ‘high risk’ eyes can be as low as 35%. The most common cause of corneal graft failure is allograft rejection and endothelial damage accounts for most of the morbidity. Despite the anterior eye chamber immune privilege, graft rejection is a major complication of penetrating keratoplasty as they facilitate subsequent graft failure.

Acute rejection which may occur weeks to years after transplantation involves both humoral and cell-mediated immune reactions. The pathogenesis of chronic rejection is not clear.

Key Words:

Pathology of corneal graft rejection, risk factors for penetrating keratoplasty, and management.

Contents:

Table of Abbreviations:

AC	Anterior Chamber
ACAID	Anterior chamber–associated immune deviation
APCs	Antigen Presenting Cells
bFGF	Basic Fibroblast growth factor
CCTS	Collaborative Corneal Transplantation Studies
CD	Cluster differentiated
CsA	Cyclosporine A
CTLs	Cytotoxic T cells
DCs	Denderetic Cells
DTH	Delayed-type hypersensitivity
EpRL	Epithelial rejection line
GAG	Glycosaminoglycan
HLA	Human Lymphocyte Antigens
HSV	Herpes simplex virus
IFN	Interferon
IG	Immunoglobulin
IL	Interleukin
KGF	Keratinocyte Growth factor
LCs	Langerhan's Cells
mAbs	monoclonal antibodies
MMF	Mycophenolate Mofitil
MMPs	Matrix metalloproteinase
NGF	Nerve Growth Factor
NV	Neovessels

PKP	Penetrating Keratoplasty
SCID	Severe combined immunodeficient
SEIs	Subepithelial infilterates
TGF	Transforming Growth Factor
Th	T-Helper cells
uPA	Urokinase type plasminogen activator
VIP	Vasoactive interstitial peptide

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INTRODUCTION

The concept of corneal transplantation was first suggested in 1796 by Erasmus Darwin, the grandfather of Charles Darwin, in his influential book Zoonomia. However, theory did not translate into practice until 1835 when an Irish man, Samuel Bigger while he was a prisoner in Egypt successfully transplanted an allogeneic cornea (An allograft is a transplanted organ or tissue from a genetically non-identical member of the same species) into the blind eye of a pet gazelle **(Brent L, 1997).**

In 1838, many years before the invention of anaesthesia, Richard Kissam reported the first corneal transplant in human: this was a procedure in which pig cornea was grafted into a human recipient eye and remained transparent for a couple of weeks. Almost all donor corneas were xenografts (A transplant of organs or tissue from one species to another), until the late 19th century when a successful partial thickness corneal transplant was performed **(Aggarwal, 1997).**

A significant milestone was the first successful full-thickness human corneal graft reported in 1906 by Zirm. Since then corneal transplantation has grown rapidly with the first eye bank established in Moorfields Eye Hospital, London in 1960′s **(Archer and Trevor-Roper, 1967).**

Zirm in 1906 was the first surgeon to perform a successful homologus penetrating keratoplasty (PKP) in a human patient. The operation became more successful with the development of more delicate instruments, use of operating microscopes and the availability of the antibiotics, antivirals and corticosteroids **(Aggarwal, 1997).**

Although the first successful penetrating corneal graft was reported in 1906, it took another half a century before the first description of opacification of a previously clear corneal graft was published. Paufique named this event "maladie du greffon" (graft sickness) and suggested that this clinical finding was caused by sensitization of the donor by the recipient **(Paufique et al., 1948)**.

This description followed the experiments reported by Medawar a few years previously in which differences were observed between rabbit skin grafts of donor and recipient origin giving rise to the term "histocompatibility". Because of the comparatively crude methods of biomicroscopy and the lack of clear diagnostic criteria for rejection, the percentage of these failures that were due to corneal allograft rejection was unknown **(Medawar, 1944).**

In 1948, Paufique and co-workers accurately described what was undoubtedly an acute graft rejection and the associated vascularization of the graft-host interface. Various explanations were given for such opacification, including poor nutrition and bacterial-allergenic inflammation **(Paufique et al., 1948).**

In the early 1950s, graft rejection was hypothesized by Maumenee to be of immunologic origin. Early investigators found that transplanted corneas were more likely to survive than other organs and tissues. Thus the concept arose that the cornea is a "privileged site," protected from rejection by its isolation from the vascular and lymphatic systems of the host. In a rabbit study, Mueller and Maumenee performed a series of successful penetrating keratoplasties and later applied skin grafts from the same donors. They found that 90% of the previously

clear grafts were rejected, suggesting that the lack of host sensitization (afferent blockade) was a major factor in the success of corneal grafts but that avascularity did not absolutely prevent rejection **(Maumenee,1951).**

Since the work of **Khodadoust and Silverstein (1969),** experimental attention has been drawn to the relative importance of the role that each cell layer of the cornea plays in inducing sensitization to donor alloantigens and in serving as a target of alloimmune rejection. Much evidence points to a potent role for corneal epithelial cells as a source of immunizing alloantigens in corneal grafts placed orthotopically (grafts placed in the normal anatomic location in recipients) **(Khodadoust and Silverstein, 1969, Hori and Streilein, 2001)** and heterotopically [cutaneous surface **(Streilein et al., 1996),** subcutaneous pouches **(Peeler and Niederkorn, 1986),** and beneath the kidney capsule **(Hori et al., 2000)].**

Although the corneal stroma has also been found to be alloimmunogenic, corneal endothelial cells appear to play only a minor role as graft-derived immunogens. On the contrary, corneal endothelium has been found to confer immune privilege on corneal tissues, protecting them from immune rejection by efficacy of constitutive expression of CD95 ligand (a cell-surface protein on the killer cell, with its receptor Fas on the target cell) **(Hori et al., 2000).**

In 1972 Khodadoust and Silverstein found that, despite the added sensitization obtained with a skin graft, only 25% of subsequent penetrating keratoplasties failed in the avascular host cornea, compared to a 100% failure rate in the vascularized host. They concluded that the lack of corneal vascularity interferes with the efferent arm of the immune response (efferent blockade).

These authors also reported that corneal epithelium, stroma, or endothelium alone, transplanted in the avascular cornea, can be rejected. Because distinct clinicopathologic patterns of allograft rejection reactions were readily identifiable, definite diagnostic criteria for graft rejection, such as the presence of rejection lines, were established **(Khodadoust and Silverstein, 1969).**

The above mentioned data indicate that the immunologic "privilege" of the cornea is explained by a combination of afferent and efferent blockade of the immune response based on a lack of vascularization of the cornea.

It is important to report that corneal grafting is a successful procedure with a first year survival rate of up to 90% **(Barker and billingham,1997 & Williams et al.,1997)** however a long-term 10 year survival rate drops to 62% and in 'high risk' eyes can be as low as 35% **(Hill et al., 1991)**. The most common cause of corneal graft failure is allograft rejection, and endothelial damage accounts for most of the morbidity **(Vail et al., 1994).**

IMMUNOLOGY OF GRAFT REJECTION

I. Ocular immune privilege:

Corneal transplantation, which is also known as penetrating keratoplasty, is the most common form of tissue allotransplantation. In the USA alone, nearly 40 000 cases are performed annually. In uncomplicated first grafts, the two-year graft survival rate under cover of local immune suppression is over 90% **(Rocha et al., 1998).** This extraordinary rate of success, which can be achieved in other solid grafts only with profound systemic immune suppression, has been related to various features of the cornea and ocular microenvironment that together account for its immune-privileged status.

Immune privilege is a dynamic phenomenon in which the destructive effect of a "Normal" immune response to a particular antigens is either altered or absent in order to protect the microanatomy of highly organized tissues in the eye. Both (1) the recipient corneal bed and anterior chamber and (2) the transplanted tissue have features of immune privilege. These features include:

1- The blood eye barrier. The normal cornea is avascular. Only the peripheral cornea depends directly on the vasculature. The central cornea depends on the tear film and the aqueous humor for metabolic requirements. The aqueous humor is secreted by the ciliary body and there is normally no leakage of cells or proteins across the vessels of the tissues lining the anterior chamber such as those in the iris. The separation of the intravascular space and the ocular tissues is referred to as the blood-eye barrier **(Kuchle et al., 1994).**

2- Absence of blood vessels and lymphatics. The cornea is normally avascular and devoid of lymphatics. This is an impediment to both the afferent and efferent limbs of corneal allograft rejection **(Barker and Billingham,1973 and Collin,1996).**

3- Modest expression of HLA **(Streilein et al., 1979).**

4- Relative absence of mature antigen-presenting cells. Antigen-presenting cells are necessary to initiate the corneal allograft response. Cells with antigen-presentation capability are virtually absent from normal cornea. There are few interstitial dendritic cells in the peripheral corneal stroma and Langerhans cells in the peripheral epithelium**.** These are outside the operative field for most corneal grafts **(Jager, 1998)**.

5- The cornea [and other anterior chamber (AC) tissues] constitutively expresses Fas ligand (Fas L, CD95L), which plays a pivotal role in protecting the eye from cell-mediated damage. It is proposed that Fas+ T cells, which enter the eye during inflammation, interact with FasL within the eye and are eliminated by apoptosis (programmed cell death) with no ensuing inflammatory damage **(Stuart et al., 1997).**

6- Immunosuppressive cytokines in aqueous humor. Transforming Growth Factor (TGF-b) and Vasoactive interstitial peptide [VIP] are present in normal aqueous fluid **(Taylor et al., 1994)**.

7- Anterior chamber –associated immune deviation. Antigen introduced into the aqueous humor results in antigen-specific suppression of delayed hypersensitivity **(Streilein, 1996).**