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Chapter

How Ocular Surface Disorder Affected Corneal Graft Survival

Sharita Siregar

Abstract

The ocular surface is formed by three component tissues: The cornea, conjunctiva, and limbus all play an important role in keeping a good and clear corneal graft. As part of non-immunological reactions, glaucoma and ocular surface disorders can increase the possibility of corneal graft failure. For that reason, maintaining a healthy and moist ocular surface, depends on an intimate relationship between healthy ocular surface epithelia, the tear film, and the eyelid, which will all increase corneal graft survival. A moist conjunctiva composed of lymphatic tissue as our defense mechanism against infection, will keep the cornea avascular, remaining crystal clear, dehydrated, and protected. Ocular surface epithelium cannot survive without tears. To specified, each component tissue that forms the ocular surface is equally important. Several previous studies revealed that dry eye disease as a form of ocular surface disorders (OSD), can lead to graft rejection. To our knowledge, there are two conditions that cause dry eye syndrome. It can be caused by lipid tear deficiency or aqueous tear deficiency. The severity of dry eye also ranges widely with some mild inflammatory processes leading to severe chronic conditions (i.e., cicatrizing conjunctivitis) that are known to be an absolute contraindication for total or full penetrating keratoplasty. The basic immunological mechanism of dry eye, as one of the most forms of ocular surface disorders that altered corneal graft survival will be discussed specifically in this chapter.

Keywords: Ocular surface disorder, dry eye disease, corneal graft survival, immune privilege, immunopathology, dendritic cells, inflammation, cornea

1. Introduction

Cornea transplantation is considered the most successful form of organ allotransplantation. Immune privilege has been found to be responsible for the high rate of cornea graft survival. Cornea avascularity as well the absence of lymph nodes suppresses antigen transportation and presentation to naive T cells. The spectrum of neuropeptides and complement activation from the cornea combined with aqueous humor immune tolerance - also known as anterior chamber associated immune deviation (ACAID) - will make the cornea tissue become more adaptable and not easily responsive to any foreign antigen from the graft tissue [1, 2]. However, any form of inflammation, vascularization, infection, or previous graft failure will be considered high risk factors that cause rejection due to an adaptive immune response [3]. Loss of graft survival can be defined as a condition where the cornea loses its transparency after two weeks of clarity and is considered a failure if cornea edema persists at six months. Moreover, if in six months persistent

graft edema remains unclear after treatment with a high dose immunosuppressive agent, it should be considered an irreversible rejection. On the other hand, it will be considered a reversible rejection if the graft reaches its clarity after successful treatment [4].

Cornea infection is considered a high-risk factor for corneal transplant rejection. No matter what causes the infection, any form of bacterial, fungal, and viral infection is recognized as factors that increase the risk for graft rejection. Several conditions like a poor ocular surface, coexisting allergies, trauma, or previous intraocular surgeries can disrupt and make conditions worse and accelerate the likely risk of developing graft failure [5–7].

Dry eye disease (DED) that affects tens of millions of people worldwide, is one of the most common types of ocular surface disorders which may initiate graft failure through an immunopathological response [8, 9]. Tear hyperosmolarity is also found to play a major role in the vicious cycle of dry eye disease that is associated with activation of inflammation [10]. Japanese researchers assessed that a DED cornea donor tissue acts as a significant risk factor for subsequent corneal allograft rejection. They found that donor corneas from patients with DED will activate inflammation by augmenting T-cells at the host, promoting dendritic cell maturation in the cornea and draining lymph nodes of the host, increased Th1 and Th17 frequencies and decreased Treg function in the recipient and this activates host T cells through a direct pathway of allosensitization. Therefore, the possibility of a cornea transplant recipient who received donor material from a patient with moderate to severe dry eye disease may predispose higher rejection rates in the grafted host [11].

Recipient characteristics such as the recipient's indication for grafting, previous glaucoma drainage implant surgery and which type of keratoplasty technique performed may profoundly affect the number of endothelial cells lost and graft survival as well. Although there is depth of tissue differences in the amount of implanted cornea tissue between endothelial keratoplasty (EK) and posterior keratoplasty (PK), the endothelial cell loss was found to be similar [12] during 10 years of follow up (71% for EK vs. 78% for PK).

2. Incidence

To estimate the possibility of corneal transplants being rejected, a good explanation about what is allograft rejection and when we can define a condition as a cornea graft failure are needed. The term cornea graft rejection refers to a specific immune response from the recipient after the donor tissue was transplanted and characterized by a successful clear cornea graft condition for two weeks following cornea transplantation. Graft failure is defined as primary graft failure if cornea edema was found to exist immediately after it was transplanted, and it never reached clarity. Any improper cornea tissue storage or surgical trauma can cause graft failure. The immune system is found to give a huge role in the graft tissue to develop rejection or failure. A previous study concluded that cornea transplant success not only depends on the donor and recipient tissue condition, but it also depends on what type of keratoplasty, and which immune pathway is involved (direct or indirect) [13].

The status of donor cornea conditions that are correlated with graft survival rates was studied in 2018. It was reported that donor tissue with a history of dry eye disease will cause a higher number in APCs from the recipient ocular surface draining lymph nodes (dLNs), induce the maturation of dendritic cells and show an increase in the number of CD4 effector T cells produced that will reduce the graft survival rate to 10% [11, 14].

In the same study, at two weeks after surgery, it was also found that an increase in interferon-γ (IFN-γ) and cytokine interleukin 17 (IL_17) secretion and a reduced number Foxp3 expression will interfere with the T regulatory cells ability to protect graft tissue from the recipient's immune response and can lead to rejection [15–18]. In conclusion, cornea graft survival rate is an estimated rate during a period of time that the graft tissue is able to maintain its clarity after transplantation. The successful and high cornea graft survival rate is related not only to its immune privilege but also the status of the recipient bed such as the amount of cornea tissue replaced (penetrating or lamellar keratoplasty), the underlying disease, the amount of vascularization, the presence of glaucoma, inflammation, the number of regrafts performed and larger graft size.

The study done by Eghtedari reported that during a 5-year period, DALK gave better graft survival rates compared to DSAEK and PK in terms of corneal regrafting with a percentage of 1.2% compared to 5% and 8.25%. It is believed because the endothelial layer was not included for the DALK procedure. The primary disease of the cornea that led to transplantation is also proposed to be an important factor in future graft survival and important indicators such as infection (bacterial, herpetic, and fungal) being the major cause of graft rejection and need for repeat grafting (35%), with pseudo phakic bullous keratopathy as the second most common factor with 30.3% chances for corneal regraft. Other risk factors that determine graft survival are as follows: First, the quality of the donor cornea itself where a lower quality donor cornea that was used for tectonic purposes showed a lower survival rate compared to a higher quality donor cornea in keratoplasty for optical reasons. Secondly, glaucoma was found to be responsible for about 13% of regrafts cases. As for corneal vascularization, the existence of pannus was found in 25% of regrafts which is similar to the 10-year previous study that showed the graft survival rates of 35 to 40%. The immune privilege that normally is present in the cornea was interfered with by the lower impression of T regulatory cells caused by a small number of Foxp3 factors expressed [3, 18].

3. The vicious circle of dry eye

Tear hyperosmolarity is the core mechanism of dry eye disease (DED). The cause of DED can be divided into two forms, aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). In ADDE, tear hyperosmolarity results when lacrimal secretion is reduced, with the normal process of evaporation from the eye. In EDE, tear hyperosmolarity is caused by excessive evaporation from the exposed tear film in the presence of a normally functioning lacrimal gland. Since tear osmolarity can only rise because of tear evaporation in both ADDE and EDE, tear hyperosmolarity is due to evaporation from the ocular surface and in that sense, all forms of DED are evaporative. EDE is a hyper-evaporative state. In DED, tear hyperosmolarity is considered to set up a cascade of signaling events within surface epithelial cells, that leads to the release of inflammatory mediators and proteases. Any etiology that induces an increase in tear hyperosmolarity will eventually create an ocular surface disorder. This in turn can activate each inflammatory mediator as a compensatory response.

As a disease caused by multiple factors, dry eye disease is characterized by the loss of homeostasis in the tear film along with ocular symptoms. Intercellular adhesion molecule (ICAM-1) is an over expressed and attracted lymphocyte function associated antigen-1 (LFA-1) receptor that is located at the surface of T cells can either be activated or inactivated. If ICAM-1 binds to LFA-1 receptor, it will release cytokine and cause the inactivated T cell to become activated. The higher amount of cytokine release, the higher number of activated T cells which leads to more severe tissue inflammation occurs [19, 20].

4. Immunopathological mechanisms

There are two kinds of immune systems, the first is also known as an innate immune system consisting of a component that is already in the location and responds immediately after it is exposed, with a general response. As for specific immune system response, it is formed by T cells and B cells that are located far from the exact location of the stimulus and launched with a specialized system after it is triggered after multiple stimuli.

4.1 Overview of immune responses in dry eye

4.1.1 Innate immune responses

As mentioned previously, the innate immune response is a fast and nonspecific immune response that is created by the ocular surface as a protection from any microbial invasion or toxin passage across its surface epithelium. Facilitated by the mucin layer of the tears, the glycocalyx changes at the conjunctiva, together with the cornea epithelium, along with production of a stream of antimicrobial defense proteins such as lysozyme, lipocalin, lactoferrin and trefoil peptides, makes the corneal and conjunctival epithelium considered as the "gatekeepers" of the ocular surface [21–25].

The hyperosmolar state of the tear film will also activate MAPK kinases and its master regulator NFkB. This regulator will produce interleukin-1 (IL-1) and TNF-α that will up-regulate matrix metalloproteinase-9 (MMP-9) and associated with disruption of the epithelial cornea barrier [26]. The activation of pattern recognition receptors (PRRs) such as the Toll-like receptors (TLRs) and the NOD-like receptors (NLR) will create an inflammatory response towards DED as part of innate immune response [27]. Induction in chemokines by the ocular surface will attract macrophages, dendritic cells, neutrophils and activated T cells [28–33]. Moreover, blood vessel endothelial cells will produce an adhesion molecule called intracellular adhesion molecule-1 (ICAM-1) in DED [34]. This ICAM-1 will bind to inflammatory cells and express an integrin leukocyte function antigen-1 (LFA-1) causing migration and activation at the site of inflammation and lymphoid organs [35].

4.1.2 Adaptive immune responses

Accumulation of CD11c antigen presenting cells maturation and the activation of antigen specific CD4+ T cells in draining lymph nodes during desiccating stress, with the reduction of CD4+ T cell infiltration numbers in depleted macrophages was found as evidence that can explain why the ocular surface antigen presentation was considered as the first initiator of adaptive immune response [36]. The upregulation in major histocompatibility complex II (MHC II) and primed T cells that are recruited to a patient's cornea and conjunctiva in DED found were also considered as another plausible pathway in local adaptive immune responses [37, 38]. Keep in mind that adaptive immune systems are evolving and becoming more specific through time by memorizing the first encounter antigen.

4.2 Corneal immune responses

4.2.1 Immune privilege of the cornea

Because cornea is avascular and lymphatic free, the graft survival rate for corneal transplantation is the highest among all other organ transplants and this

condition is often referred to as immune privilege of the cornea. Dendritic cells which are also known as the messenger cells of the immune system in cornea graft tissue, exist in an immature inactivated state which will result in immune quiescence in a healthy cornea. All cornea layers are found to have a very low expression of MHC class I and II antigens, limiting immunogenicity to foreign antigens. The transport of antigens and APCs to T cell-rich secondary lymphoid organs as a part of the immune system do not happen in the cornea because of its absence of lymph vessels. Cell membrane bound molecules are also expressed by the cornea - for instance Fas Ligand (FasL), MHC-Ib, tumor necrosis factor (TNF) and complement regulatory protein (CRP). These molecules guard from immune mediated inflammation and induce apoptosis of immune effector cells. FasL expressed by corneal epithelium and endothelium acts as a pro apoptotic molecule. It also will destroy polymorphonuclear neutrophils (PMNs) and effector T cells that express its receptor Fas/CD95, creating immune quiescence while protecting the cornea from immune mediated graft rejection [39, 40]. The corneal epithelium and stroma produce programmed death ligand-1 (PD-L1) which interacts with its receptor PD-1 on the T cells and leads to inhibition of T cells proliferating, induction of apoptosis and suppression of interferon (IFN-γ) secretion [41], promoting graft survival [42, 43].

Soluble immunosuppressive factors inside the anterior chamber will inhibit T cell and complement activation [44, 45]. This alloantigen specific peripheral immune tolerance from aqueous humor is also known as anterior chamber associated immune deviation (ACAID) which modulate the systemic cytotoxic immune response [46, 47] and suppresses delayed-type hypersensitivity. Therefore, ACAID also known as a factor that promote graft survival [48, 49].

4.2.2 Immunopathology of corneal graft rejection

All cells of each living individual express a surface polymorphic protein antigen also known as major histocompatibility complex (MHC) antigens that are located at chromosome 6. The variations in MHC genes are the reason why everyone has their own characteristic hence differentiate people one to another. Therefore, if the antigen between the donor and the recipient was mismatched, the recipient will directly reject the allograft tissue.

Human leukocyte antigen (HLA) is responsible for MHC expression [50]. There are two types of class for MHC expression. MHC type I (MHC-1) is found on all nucleated cells of the body and platelets. In the cornea, its antigens are expressed by corneal epithelial, stromal, and endothelial cells. These transmembrane glycoproteins are coded for HLA-A, -B and -C genes. As for MHC type II (MHC-II) is more specific compared to class I. It was limited only at the cell surface of immunocompetent antigen-presenting cells (APCs) like DCs, macrophages and Langerhans cells [51].

Foreign antigens carried by APCs and presented to naive T cells with the presence of MHC-II will stimulate molecules and recognize it as a non-self-antigen. Any inflammation, interferon gamma and surgery will induce the expression of MHC II antigens even more in the cornea [52].

Dendritic cells as the messenger of the immune system will bring the foreign antigen from their exact location of inflammation and transport them to the lymph node which will activate B cells at the spleen and T cells at the thymus glands. It is known that corneal DCs play a critical role in graft rejection through their ability to regulate T cell response to both self and foreign antigens of the cornea donor tissue.

Antigen was recognized by the MHC class II at the surface of mature DCs. After it binds to its receptor at the surface of T cell/CD4, they will cause the replication of T cells into several types of T cells. The first type is T helper. Antigen that

was present to it will be recognized by the CD8 and cause cytokine release. After cytokine release, T helper will differentiate into a cytotoxic T cell.

The second type of T cell is found actively in plasma cells differentiation into antibodies and create an immune memory at the first encounter antigen. It will recall a similar response every time the same pathogen exists. The third type is the T cell that will release cytokine to attract monocytes and macrophages at the inflammation site so the phagocytosis process can occur.

The role of dendritic cells in graft rejection was determined by regulating the T cells after the antigen was presented and recognized by the MHC class II antigen receptor at the surface of mature DC. Normally, these central corneal DCs will remain silent, dormant, and undifferentiated. However, any kind of stress like inflammation will activate DCs and after the DC reaches the cornea through bloodstream where the donor alloantigen was captured by lymphoid organs, it will be transported and presented back into T cell for further immune response [53].

5. Dry eye disease predilection to corneal graft rejection

Patients with dry eye disease will complain about foreign body sensation, blurred vision, and redness on their eyes due to the lack of tear production and rapid tear evaporation caused by poor tear stability as their characteristic. The lacrimal gland dysfunction creates an inflamed ocular surface, and it is considered as the pathognomonic sign of DED [54].

Post corneal graft patients often will develop ocular dryness as a side effect from consuming glaucoma medication that can lead to poorer healing process at the ocular surface. The mechanisms of the poorer healing process are as follows. Dryness at the ocular surface activates inflammatory mediators such as collagenase and will create a defect at the epithelium of the cornea if it was not treated which can lead to an infection or induce vascularization that can affect as a high-risk factor for corneal graft rejection [55]. Tear examination may show shorter tear break-up time (BUT) and an unstable tear film.

Glaucoma is the adverse effect because of long-term steroid topical medication usage. Contrarily, steroid eye drops are also very important to prevent graft rejection in post corneal transplant patients. Each glaucoma medication has their own mechanism in causing any cornea or ocular surface disorder. For example, beta blocker eye drops like timolol has been found to act on the beta receptors on lacrimal gland that will reduce basal tear turnover rate after one month of therapy [56]. Prostaglandin analog medication will obstruct the meibomian gland even more [57]. Brimonidine tartrate as the alpha-adrenergic agonist mostly used may predispose the patient into ocular allergy [58]. Although corneal thickness has been found to be related to carbonic anhydrase inhibitor brinzolamide eye drop, further investigation is still needed [59]. Ocular surface disease because of the long-term glaucoma medication use is related to the increment of macrophages found in the conjunctiva. The expression of inflammatory marker like antigen HLA-DR and Immunoglobulin E is higher in patient with prolonged glaucoma topical medication compared to untreated eyes [60–62].

LASIK as one of refractive surgery procedures will cause ocular dryness through the laser dissection at the corneal nerves that will interrupt the corneal reflex arc further and reduce the tear film production with substance P release which will increase the severity of inflammation [63, 64].

The mechanism in DED related post refractive surgery was thought to be similar to DED followed by perforating keratoplasty. The whole dissected corneal nerve using trephination in keratoplasty will release substance P because all corneal

nerves are dissected during trephination. Substance P from keratocytes [65] will induce the secretion of interleukin 8 as a pro inflammatory chemokine. Kuchle et al. demonstrated that dry eye disease is a risk factor for graft rejection in PK through inflammatory mechanisms [66].

6. Treatment of corneal graft rejection

6.1 Provide a healthy ocular surface

A smooth ocular surface can be achieved through intensive and frequent non-preserved tear supplements or hyaluronate eye drops [67]. Frequent drops using non-preserved tears is necessary for managing accumulated inflammatory cytokines. Hyaluronate eye drops have been reported to be effective in managing patients with ocular surface disorders through improving the corneal epithelial barrier function, promoting corneal wound healing, and reducing ocular surface tissue damage as well as minimizing the inflammation process in DED [68].

Epithelial rejection occurred at the first three months after surgery can be seen as a linear opacification at the cornea surface which stains with fluorescein. Although the dead epithelial cells are replaced rapidly by recipient epithelial cells, it is important to remember that these recipient epithelial cells have been sensitized by the donor which can progress to deeper rejection such as stromal or endothelial rejection in the future. It can be seen as a nummular infiltrate if the rejection reaches the stroma. However, endothelial rejection can be shown as keratic precipitates where the inflammatory cells adhere to the endothelial graft [69].

6.2 Immunosuppressive agents

Topical steroid eye drops such as dexamethasone 0.1% or prednisolone acetate 1% are given every three hours per day for the first 2–3 months, then tapered gradually until it reaches zero in one year. These steroid drop regimens are different for each center. The purpose of steroid drops is to prevent and reverse any rejection episodes and avoid more endothelial cell loss. Lack of detecting signs of rejection will postpone graft treatment initiation. Delay in diagnosing or treating rejection will reduce graft sensitivity towards the treatment and may develop to an irreversible rejection [70, 71].

6.3 HLA matching

HLA matching is shown to be effective in predicting graft survival rates in a vascularized organ allotransplantation. However, the benefits from tissue matching in cornea transplantation are still debatable since the cornea has its own immune privilege as a non-vascularized tissue. Nevertheless, it was found that an active graft rejection is related to the donor HLA class I specific cytotoxic T cells.

The greater number of mismatches between HLA-A and HLA-B shows a higher risk of corneal tissue developing into graft rejection. These tissue mismatches are considered as a high-risk factor for rejection after corneal transplantation [72–76]. Whilst Collaborative Corneal Transplantation Studies (CCTS) suggest the necessity of HLA matching in corneal transplantation remains doubtful, it may be useful for high-risk patients although it is still not considered to do the tissue matching as part of routine preoperative assessment due to the donor cornea tissue available [77].

Minor histocompatibility antigens such as ABO blood antigens are a different class of cell surface proteins that are also expressed by the corneal epithelium. It

is coded throughout the genome at various loci [78]. CCTS concluded with ABO blood matching, the possibility for someone having graft rejection is 41% if the ABO antigens are incompatible and 31% may experience rejection for the compatible ABO antigens. The study concluded ABO matching may still be considered useful in predicting corneal graft rejection. However, doing HLA matching is still debatable - not only because of the lack in the availability of cornea tissue globally but also its very expensive [79].

7. Conclusion and future prospects

Cornea graft survival rates are influenced by many factors. Dry eye as part of ocular surface disorders is one important thing that we should care for. The aim for dry eye or OSD management is to treat the hyperosmolarity condition of the tear film to reduce the expression of a response from our immune system to any foreign antigens from desiccating stress or inflammation. Although the cornea has immune privilege due to being avascular and lymph node free, a successful prevention of immune rejection is better compared to immune suppression by immune modifying treatments such as gene therapy post transplantation. Minor histocompatibility complex tissue matching can be done due to its low cost. However, ABO antigens testing is not as specific as major histocompatibility tests.

Cornea as the only organ that has its own immune privilege is still in doubt for testing major histocompatibility complex tissue matching. Mainly, because most of major histocompatibility testing only work for class II but not shown effective for class I. Unfortunately, due to human major histocompatibility complex genes are highly polymorphic, any random allocation of HLA will achieve the required matching level in a very long time which are very unethical for our patients. If in the future, there will be a HLA matching that is highly specific, low cost and only needs a period of time to get the test result, probably the HLA testing can be applied as a routine evaluation to provide higher number of graft survival in the future.

As mentioned in the literature, a high-risk condition such as corneal vascularization, DED and prolonged use of antiglaucoma medication can reduce the corneal graft survival rate. Therefore, the application of anti VEGF through injection on the subconjunctival, an adjunct non-preservative topical lubricant in glaucoma medication and the use of lifitegrast as the antagonist of LFA-1 and inhibits T cell formation in dry eye management will probably useful and create a promising result related to a higher graft survival rate in the future.

To conclude, a prospective clinical trial to investigate the role of preexisting DED in the context of corneal transplantation and its influence on graft survival is needed. Understanding the role of HLA in corneal graft rejection from an immunological point of view as well as the necessity of conducting a comprehensive knowledge of the HLA tissue matching will create other options to prevent graft rejection. Future pharmacotherapies for DED with novel targets are the focus of ongoing research, and several promising treatment options are expected.

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Conflict of interest

The author declares no conflict of interest.

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