Episodes of corneal allograft rejection are characterized by redness, pain (photophobia), and decreased vision that last more than 12 hours. This triad of symptoms is usually associated with signs of rejection, which may present in several forms. Classically, clinical evaluation often shows endothelial keratic precipitates (KPs) in the lower half of the corneal donor button beginning at the graft-host junction. These KPs may form a visible line on the endothelium (termed the line of Khodadoust), they may be relatively scattered in the lower half of the cornea, or one or a few KPs may be located centrally (Figure 1).1,2

SEVERAL FORMS OF IMMUNE REJECTION

Immune rejection episodes occur in several forms. Surprisingly, epithelial rejection occurs in approximately one-third of patients who develop graft rejection episodes after penetrating keratoplasty (PKP). There are two types of epithelial rejection. The first begins as a line located near engorged limbal vessels, which may travel across the graft-recipient interface. This line may be highlighted using vital stains such as lissamine green. Histologically, the line consists of lymphocytes, plasma cells, and neutrophils. Within the rejection line are damaged and dead epithelial cells. We observe most epithelial rejection lines in the first year after grafting. These lines are usually followed days or weeks later by endothelial rejection. The second type of epithelial rejections are similar in appearance to the infiltrates in epidemic keratoconjunctivitis but may be slightly deeper. Subepithelial rejections are randomly distributed in the central cornea (Figure 2). They may present with an epithelial rejection line or, more frequently, alone. Subepithelial infiltrates are thought to be due to rejection of the stromal keratocytes. They must also be considered a harbinger of an endothelial graft rejection, and they may occur as early as 6 weeks or as late as 2 years after transplantation.2,3

ENDOTHELIAL REJECTION

The most common and important type of corneal graft rejection is endothelial rejection, which occurs primarily because of human lymphocyte antigen incompatibility on the surface of endothelial cells. Rejection episodes have occurred as early as 2 weeks or as late as 31 years after corneal transplantation surgery. Most commonly seen endothelial rejections consist of a line of KPs beginning inferiorly at the graft-host junc-

Figure 1. Inferiorly located Khodadoust line seen 3 months after PKP.
tion and marching superiorly (Figure 3). The cornea is frequently edematous between the line and the graft-host junction. The limbus becomes hyperemic, and cells are frequently present in the anterior chamber. KPs may also occur without a line as mentioned previously. In some cases, not only is there not a rejection line, but KPs or iritis may not be visible through the graft, which may be diffusely edematous. Therefore, any postgraft edema must be considered a sign of rejection and treated as such (Figure 4).4

Theoretically, Descemet’s stripping automated endothelial keratoplasty (DSAEK) surgery should have a lower rate of rejection than PKP because of the absence of an epithelial layer and less stromal tissue in the donor button. Indeed, some early studies suggested a lower rejection rate.5 As more definitive and larger studies have been published and presented, however, the rejection rate of DSAEK surgery has been shown to approach that associated with PKP.6-8

Graft Rejection in DSAEK
To date, no study has rigorously compared inciting factors for graft rejection in DSAEK cases and correlated them with similar types of factors in PKP rejections. At best, present studies reflect the importance of endothelial rejection as the main factor in corneal graft failure from an immunoreactivity standpoint. This is not unexpected, as the greatest immunogenicity of the cornea lies in its endothelial cell layer once stimulated.9 Interestingly, there is a qualitative difference in rejection episodes in DSAEK when compared with PKP. Two studies have pointed out the tendency for DSAEK rejections to be silent.7,8 DSAEK rejection episodes may be found on routine postoperative examinations without symptoms in 33% to 70% of cases (Figure 5). Another characteristic is that they occur without an endothelial rejection line.

Protection of the Cornea
How can surgeons protect the cornea from immune-modulated responses? The answer lies in realizing that the mechanism of action of endothelial rejection is always cell mediated, a fact leading investigators to question the role of inflammatory factors. Common sense implies that corneas that are vascularized present larger numbers of immunocompetent cells than nonvascularized corneas. Extensive evidence supports that vascularized grafts are five to 10 times more likely to suffer rejection episodes than nonvascularized grafts. Chronic uveitis also increases the frequency of rejection, as do corneas that have been attacked by herpes simplex virus.10 More subtle but no less important factors include conditions that affect the ocular surface. Dry eye disease and chronic blepharitis alone or associated
CONTROL OF INFLAMMATION

We feel strongly that any cause of inflammation affecting the ocular surface should be treated aggressively and controlled, if not eradicated, before corneal transplantation. Patients should be carefully evaluated for meibomian gland disease and its degree recorded and treated. Similarly, dry eye disease should be carefully graded and treated. Associated dermatological conditions must be controlled or in remission before surgery is attempted, and systemic immunosuppression should be used perioperatively without hesitation in these patients. We routinely administer intravenous corticosteroids at the time of surgery and prescribe high doses of topical steroids during the first 6 months after transplantation, when the risk of immunologic rejection is greatest.

EDUCATION

Most important is educating patients on the signs and symptoms associated with episodes of corneal graft rejection. At each visit during the immediate postoperative period and at follow-up visits, we give all of our patients an instruction sheet characterizing the signs and symptoms of corneal graft rejections (see For Our Corneal Transplant Patients). This sheet also lists our home phone numbers, which we hope conveys to patients the seriousness of these symptoms and the fact that early treatment leads to improved outcomes. Unfortunately, with the growing popularity of DSAEK surgery, we have noticed that the majority of patients with rejection episodes are asymptomatic and identified during routine follow-up visits. This is in sharp contrast to the classic PKP patients who usually present with both symptoms and signs of an immune-mediated rejection. This observation has led us to increase the frequency of our postoperative visits to at least monthly for the first 6 months and to prescribe significant doses of topical corticosteroids for extended periods of time. Indeed, patients often use at least one drop of a strong steroid indefinitely. If the patient is phakic, we usually switch him or her to topical 0.05% cyclosporine (Restasis; Allergan, Inc., Irvine, CA) after 6 to 8 months. For patients who have a corticosteroid-induced ocular hypertensive response and for those with glaucoma, we prescribe topical cyclosporine at a 0.5% concentration for the first 6 months before switching to topical 0.05% concentration cyclosporine.

New agents that may prove efficacious at preventing graft rejections are currently being evaluated for immune modulation. At this time, however, a careful...
In an effort to increase the success of your transplant, we wish you to know the warning signs of corneal graft rejection episodes. If caught early, over 90% of rejections are reversible by medical means (ie, drop medication).

**CONSIDER ANY EYE PAIN, DECREASED VISION, OR REDNESS THAT LASTS 12 HOURS TO BE A GRAFT REJECTION AND CALL IN AS AN EMERGENCY:**

Drs. Perry, Donnenfeld, Sachs, and Fiore, office: (516) 766-2519  
Dr. Perry, home: (xxx) xxxx-xxxx  
Dr. Donnenfeld, home: (xxx) xxxx-xxxx  
Dr. Sachs, home: (xxx) xxxx-xxxx  
Dr. Fiore, cell: (xxx) xxxx-xxxx

If no response, use the numbers below and ask for the eye resident on call:  
Nassau (516) 562-0100 North Shore Univ. Hosp.  
Nassau (516) 572-0123 Nassau Univ. Medical Center  
New York (212) 979-4000 New York Eye and Ear Infirmary

The treatment for corneal rejection is Pred Forte, Decadron, or cyclosporine, 1 drop every hour to the affected eye.

*Editor’s note: Pred Forte is manufactured by Allergan, Inc. (Irvine, CA), and Decadron is manufactured by Merck & Co., Inc. (Whitehouse Station, NJ).*

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