Allograft rejection after living-related simple limbal epithelial transplantation

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A 23-year-old man presented with congestion, peripheral corneal vascularization, an elevated ridge-like epithelial line and cellular infiltration around limbal transplants, 15 months after undergoing living-related simple limbal epithelial transplantation (SLET) for total limbal stem cell deficiency. A diagnosis of acute allograft rejection was made and he was treated with intravenous methylprednisolone, topical and oral prednisolone as well as systemic cyclosporine and azathioprine, leading to reversal of the signs. Similar findings were noted during a later rejection episode. An epithelial rejection line and cellular infiltration of limbal transplants are easily identifiable clinical signs of allograft rejection post SLET.

Key words: Allograft rejection, epithelial rejection line, immunosuppression, simple limbal epithelial transplantation

Limbal transplantation using allogeneic donor limbal tissue is one of the options used to restore the ocular surface in cases of bilateral limbal stem cell deficiency (LSCD).[1] Simple limbal epithelial transplantation (SLET) has largely supplanted earlier techniques of limbal transplantation, as it has proved to be safe, effective, and replicable with minimal costs.[2] Limited information is available on outcomes of allogeneic SLET. Herein, we report clinical features and management of allograft rejection in a case of living-related SLET performed for bilateral LSCD following ocular surface burns.

Case Report

A 23-year-old man underwent allogeneic SLET in the right eye for bilateral total LSCD secondary to ocular surface burns [Fig. 1a]. The surgery was performed one year after the initial injury. Donor limbal tissue was harvested from the right eye of his father, without performing histocompatibility matching. Postoperatively, prednisolone acetate eye drops were used in a dose of 6t/day, tapered and stopped after 6 weeks. The systemic immunosuppression regimen included perioperative intravenous methylprednisolone, oral prednisolone (60 mg/ day), oral cyclosporine (100 mg/ day) and azathioprine (100 mg/day). Oral diltiazem (120 mg/ day) was used to increase bioavailability of cyclosporine. Three months following surgery, a completely avascular, transparent and lustrous corneal surface was restored and the visual acuity in the right eye improved to 20/20 [Fig. 1b]. Oral prednisolone was tapered down to a dose of 5 mg/day at three months, and stopped completely 6 months following surgery. He was maintained on oral cyclosporine and azathioprine with monitoring of blood pressure, complete blood counts, renal and liver function, and followed up uneventfully for one year.

Fifteen months after surgery, the patient reported with complaints of pain, redness and photophobia in the right eye. He had stopped all medication for 2 weeks. The visual acuity in the right eye was 20/30. The eye was congested and showed superficial and deep corneal vascularization along with an elevated ridge-like epithelial line inside the nasal limbus and cellular infiltrates around two limbal transplants [Fig. 2a and c]. The epithelial line and the transplants stained positively with fluorescein [Fig. 2b and d]. A diagnosis of acute allograft rejection was made. The patient was treated with intravenous methylprednisolone (500 mg), followed by oral prednisolone (60 mg/day), oral cyclosporine (100 mg/day) and azathioprine (100 mg/day). He was also started on hourly prednisolone acetate eye drops in the right eye. After one week, the eye was quiet with a smooth corneal surface and no staining with fluorescein. Oral prednisolone was tapered and stopped over the next 7 weeks, while topical prednisolone was tapered slowly and stopped after 6 months. Oral cyclosporine and azathioprine were continued.

One week after stopping topical prednisolone (6 months after the initial rejection episode), the patient presented with a congested eye. The visual acuity was 20/30, and raised epithelial lines were visible inside the superior and inferior limbal areas [Fig. 3a-c]. This was diagnosed as another graft rejection episode, and treated with prednisolone acetate eye drops 6t/day, which led to reversal of signs and symptoms in 10 days. Oral cyclosporine and azathioprine were continued, and prednisolone acetate eye drops were tapered to a twice-daily dose over the next 6 weeks.

Two and a half years following allogeneic SLET, the eye continues to maintain a stable corneal surface, with focal areas of fine pannus across the limbus corresponding to the sites of

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epithelial rejection lines noted earlier [Fig. 3d]. The patient is on oral cyclosporine (100 mg/day), azathioprine (100 mg/day) and twice daily prednisolone acetate eye drops.

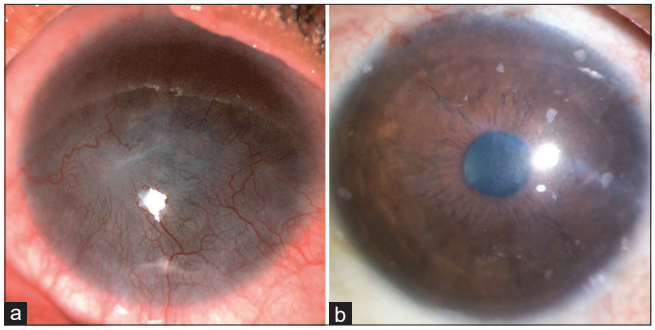

Figure 1: Pre-operative appearance of the right eye with total limbal stem cell deficiency, showing loss of corneal transparency and lustre, along with conjunctivalization of the entire corneal surface (a). A transparent, avascular and lustrous corneal surface was restored 3 months after surgery, with limbal transplants visible on the surface after allogeneic simple limbal epithelial transplantation (b)

Discussion

Allogeneic limbal transplantation is an attractive treatment option for vision restoration in bilateral LSCD secondary to ocular surface burns. Clinical signs of acute allograft rejection after keratolimbal allografts (KLAL) and living related conjunctival limbal allografts (lr-CLAL) have been described earlier.[3] Engorged and tortuous perilimbal vessels, diffuse epithelial haze and vascular ingrowths approaching limbal transplants have been described as clinical signs of rejection after allogeneic SLET using cadaveric donor tissue.[4] To this description, we add the distinct clinical signs of an epithelial rejection line and epithelial breakdown with cellular infiltration at the site of limbal transplants. These features can be easily recognized on slit-lamp examination, and are highlighted by staining with fluorescein. It is intuitive that after allogeneic SLET, the donor limbal tissue would be the primary target of a rejection episode. Therefore, in addition to non-specific features of inflammation such as conjunctival and ciliary congestion, cellular infiltration of the limbal transplants along with cellular aggregates approaching the transplants in the form of an epithelial rejection line provide definitive clinical evidence of allograft rejection. The focal presence of pannus

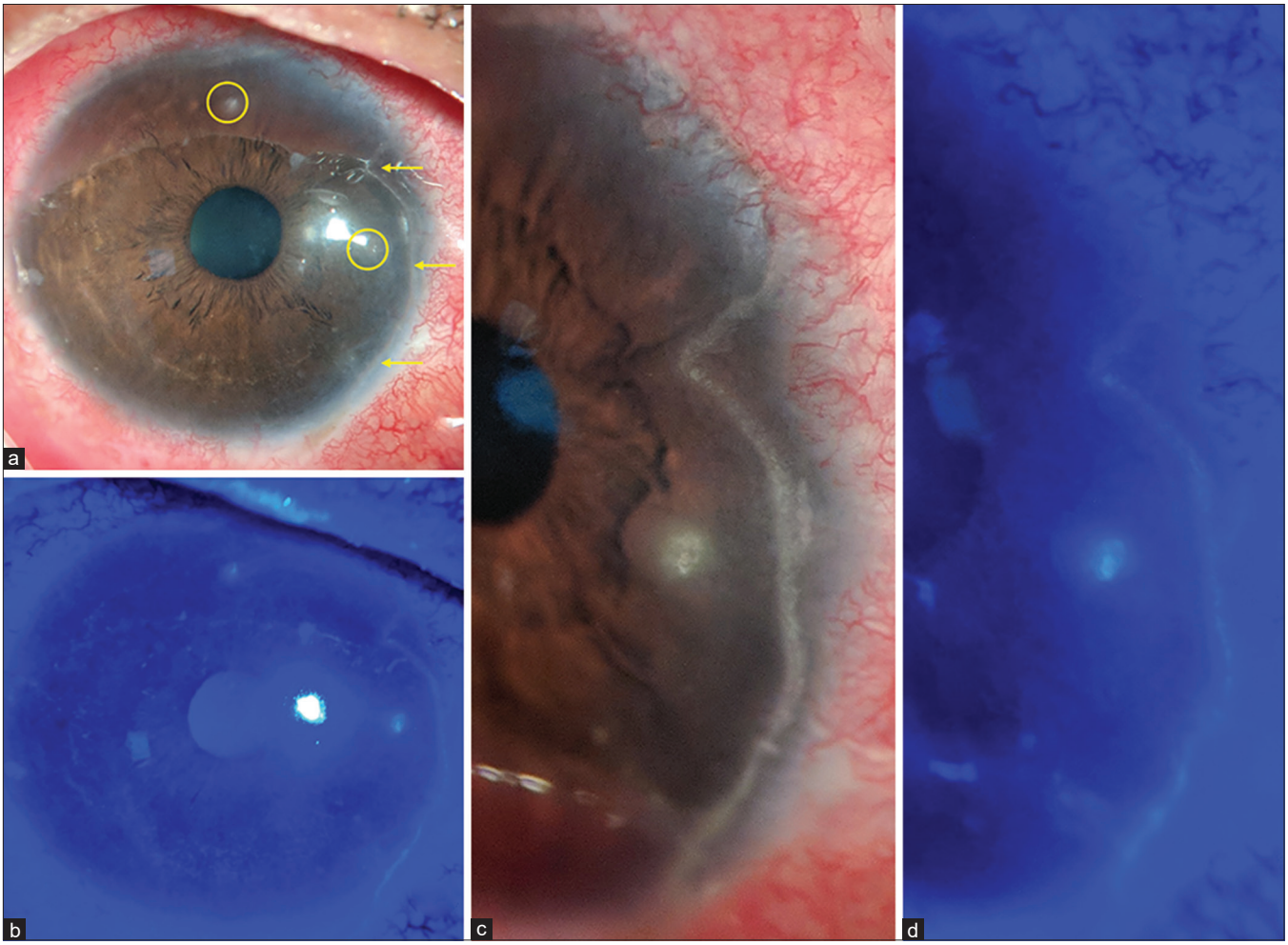

Figure 2: Acute allograft rejection episode. The right eye shows diffuse congestion, peripheral corneal vascularization, cellular infiltration at limbal transplant sites (circles) and an elevated epithelial line inside the nasal limbus (arrows) in diffuse illumination (a). The epithelial rejection line and limbal transplants stained with fluorescein are visible with a cobalt blue filter (b). High magnification images of the nasal cornea show the epithelial rejection line adjacent to an infiltrated limbal transplant (c and d)

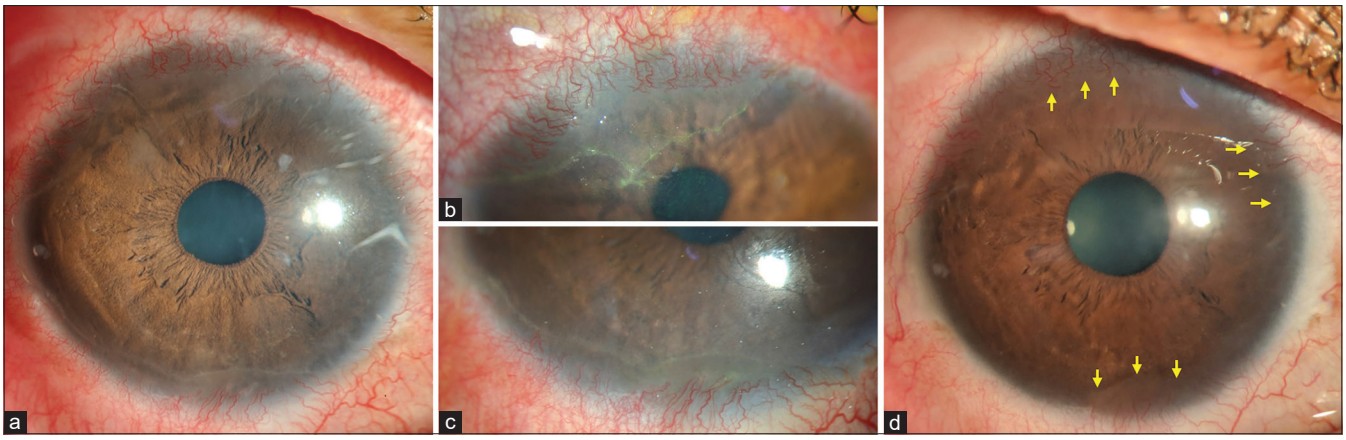

Figure 3: Second allograft rejection episode and recovery. The right eye shows congestion and peripheral vascularization (a). High magnification images show epithelial rejection lines on the superior (b) and inferior (c) cornea. Two and a half years after simple limbal epithelial transplantation, the corneal lustre and transparency is maintained (d), with focal areas of pannus inside the limbus (arrows)

after reversal of the rejection episodes indicates replacement of corneal epithelium with host conjunctiva at these sites.

Outcomes after allogeneic limbal transplantation have been shown to be better with the use of living-related donor limbal tissue compared to use of cadaveric limbal tissue.[5] Although there is no consensus on the ideal protocol for immunosuppressive therapy following allogeneic limbal transplantation, a triple-drug regimen similar to that used for solid organ transplants is often used.[6] In our patient, we used systemic corticosteroids, cyclosporine and azathioprine for immunosuppression. As long as the patient was on medication, the eye was quiet. Soon after stopping the medication, he suffered rejection episodes. The first rejection episode was managed successfully by reinstating systemic immunosuppression, along with intravenous and topical steroids. We hypothesize that this episode led to sensitization of the host immune system to the allogeneic tissue, and therefore a second rejection episode occurred on stopping topical steroid therapy.

It has been surmised that compared to KLAL and lr-CLAL, allogeneic SLET may be relatively less prone to rejection as less tissue is transplanted and the transplants are placed on the cornea, away from the host vasculature. In a recent report, allograft rejection was noted in 2 out of 30 eyes at a median follow-up period of 28 months following allogeneic SLET.[7] With the growing popularity of SLET, we expect more data on rejection rates after allogeneic SLET to emerge with time.

Conclusion

To conclude, we report cellular infiltration at the site of limbal transplants and an epithelial rejection line as novel clinical signs of allograft rejection after living-related SLET. These clinical signs should alert the clinician to a diagnosis of allograft rejection. Prompt recognition and appropriate therapy can reverse the rejection episode and restore function of the transplants. We believe long-term systemic immunosuppressive therapy is essential for rejection-free graft survival after allogeneic SLET, even with the use of living-related donor tissue.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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