CASE REPORT

Intravenous immunoglobulin for antibody-mediated keratolimbal allograft rejection

Victoria Squissato,[1] Jeffrey Schiff,[2] Clara C Chan[3]

[1]McMaster University, Hamilton, Canada
[2]Department of Medicine, University of Toronto, Toronto, Canada
[3]Department of Ophthalmology, University of Toronto, Toronto, Canada

Correspondence to
Professor Clara C Chan, clara.chan@gmail.com

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SUMMARY

A 33-year-old woman with congenital aniridia presented with decreased vision in her right eye. Slit lamp examination revealed diffuse conjunctivalisation of the ocular surface with mild subepithelial fibrosis consistent with aniridic keratopathy secondary to limbal stem cell deficiency. She underwent limbal stem cell transplantation with cadaver donor tissue (keratolimbal allograft (KLAL) surgery) and received systemic immunosuppression. Despite optimal combination immunosuppressive therapy managed by a renal transplant specialist, 2 weeks after the KLAL, the patient developed intractable eye pain, conjunctival injection, dilation of the KLAL graft blood vessels and limbal haemorrhages. There were no epithelial defects noted. Donor-specific antibody testing was positive, and intravenous immunoglobulin therapy was initiated. There was immediate symptomatic and objective improvement. Fifteen months postoperatively, the patient's vision was 20/400 with a stable corneal epithelium and no evidence of inflammation.

BACKGROUND

Congenital aniridia is a panocular disorder characterised by varying degrees of iris hypoplasia, glaucoma and cataract.[1] Aniridic patients experience a gradual decline in visual acuity independent of glaucoma and cataract due to limbal stem cell deficiency, also known as aniridic keratopathy. Over time, the keratopathy progresses from a thickened, irregular epithelium in the peripheral cornea, which has a late staining fluorescein pattern, to neovascularisation or conjunctivalisation involving the entire cornea.[1] End stage changes result in subepithelial fibrosis and stromal scarring.

Keratolimbal allograft (KLAL) is effective for the treatment of aniridic keratopathy.[1 2] Since the allografts are from a cadaver donor with unmatched human leucocyte antigen (HLA), patients are at higher risk of immune rejection. Additionally, the limbal tissue is highly antigenic, rich in Langerhans cells and highly vascularised, allowing for greater access by the immune system.[3] Thus, systemic immunosuppression is crucial for successful allograft longevity.[1 4]

However, even with appropriate systemic immunosuppression, KLAL may be complicated by antibody-mediated rejection (AMR).[5 6] The incidence of AMR among KLAL patients on systemic immunosuppression has been reported to be as high as 24%.[5] In AMR, the body mounts a humoral immune response to the allograft, creating donor-specific antibodies (DSA) against the donor HLA proteins. Unfortunately, visual outcome is poor.[6]

We report an aniridic patient with acute AMR after KLAL surgery who was successfully treated with intravenous immunoglobulin (IVIG) and maintained a stable ocular surface after more than 1 year of follow-up.

CASE PRESENTATION

A patient with aniridic keratopathy underwent uneventful KLAL surgery under general anaesthesia. Briefly, after superficial keratectomy and 360° conjunctival peritomy, three KLAL lenticules from two cadaver corneoscleral rims of the same donor were thinned and trimmed, then secured around the host limbus using 10–0 nylon sutures and tissue glue. Subconjunctival ancef and dexamethasone were injected and a 16 mm bandage contact lens was placed at the end of the surgery.

The immunosuppression regimen was designed by a renal transplant specialist. One hour prior to surgery, the patient received a 20 mg basiliximab infusion and then a second 20 mg infusion 4 days after transplantation. Oral tacrolimus 4 mg twice daily and mycophenolic acid 720 mg twice daily were started 1 week prior to KLAL surgery. Postoperatively, the patient began 20 mg of oral prednisone and the tacrolimus was lowered to 3 mg twice daily to achieve therapeutic serum levels between 8 and 12 ng/mL. Valganciclovir HCl 900 mg daily and trimethoprim/sulfamethoxazole three times weekly were given for prophylaxis against cytomegalovirus and *Pneumocystis jiroveci*, respectively. Postoperatively, the patient also began topical prednisolone acetate 1% and moxifloxacin four times daily, cyclosporine 0.05% two times daily and hourly preservative-free artificial tears.

On postoperative day 1, the patient's uncorrected vision had improved from counting fingers at three feet preoperatively to 20/400 (figure 1). However, 1 week later, the patient reported of severe eye pain and photophobia. Despite therapeutic tacrolimus blood levels and an increase in topical steroids, her symptoms persisted and the conjunctiva appeared more injected with further dilation of the KLAL graft blood vessels and limbal haemorrhages (figure 2).

INVESTIGATIONS

After the patient developed symptoms, serum was drawn to determine tacrolimus levels, which were found to be therapeutic. DSA testing of the recipient serum drawn prior to transplant was positive for B7, DR15 and DR51 antibodies. These were

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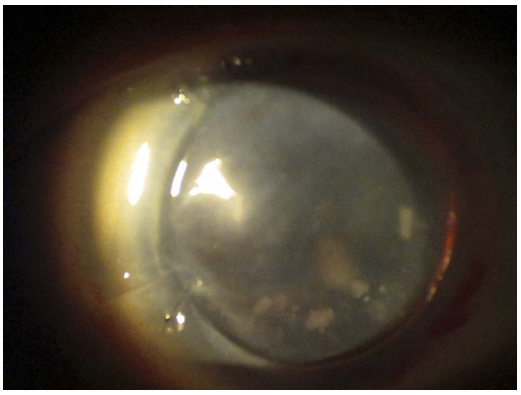

Figure 1 Slit lamp photo of aniridic patient's right eye with epithelialised corneal surface after keratolimbal allograft (KLAL) surgery. Note the absence of iris, cortical flecks of cataract changes and the junction between 2 KLAL segments.

present in the HLA typing results, which were available for the donor, who was an organ transplant donor.

DIFFERENTIAL DIAGNOSIS

Clinical features of acute KLAL rejection has been previously reported.[6] Severe acute rejection presents as moderate to severe pain; intense sectoral or 360° of injection; and/or oedema, haemorrhage, or neovascularisation of the KLAL or living-related conjunctival limbal allograft segments. In later stages, the following clinical findings may be seen as well: epithelial rejection line and/or other signs of abnormal epithelium such as late fluorescein staining, irregular thickened epithelium or conjunctivalisation of the corneal surface.

A simple idiopathic subconjunctival haemorrhage would be painless, focal, more likely to affect only the bulbar conjunctiva where the keratolimbal segments are not attached, spontaneously resolve within a week or two, and would not be associated with signs of abnormal corneal epithelium.

TREATMENT

The patient failed to respond to an increase in topical prednisolone acetate 1% to every hour with no increase in oral prednisone. The renal transplant team recommended an IVIG infusion. Arrangements were made and the patient received 1 g/kg (total 80 g) 20 days after her KLAL surgery.

OUTCOME AND FOLLOW-UP

A week after the IVIG infusion, the inflammation and pain had improved, and by 1 month after the IVIG, the ocular surface was completely quiet and stable (figure 3). Fifteen months after initial KLAL, the patient's vision was 20/400 with a stable corneal epithelium and no evidence of KLAL or conjunctival inflammation. To date, the patient has not experienced any adverse events related to her systemic immunosuppressive medications.

DISCUSSION

Although considered standard treatment for AMR in renal transplant medicine, IVIG has not previously been reported as a treatment for AMR post-KLAL. Unlike true immunosuppressive agents, IVIG does not increase the risk of infection or malignancy. Its side effects are generally mild, and may include headache, oedema and, rarely, a transient haemolytic anaemia. We have reported the use of IVIG for the successful management of AMR in a patient with a KLAL graft.

Acute and chronic episodes of AMR post-KLAL have previously been treated with increased systemic immunosuppression combined with increasing topical and systemic steroids.[5 6] Our patient was optimally immunosuppressed with perioperative basiliximab infusions as well as with tacrolimus and mycophenolic acid. Additionally, her topical prednisolone acetate 1% was increased to hourly without improvement. It should be noted that prednisolone acetate 1% is the strongest topical steroid available in Canada. The lack of response to increased topical and adequate systemic immunosuppression, and the positive DSA testing, prompted the renal transplant team to recommend the use of IVIG. A few days after her IVIG infusion, the patient was clinically much improved.

IVIG products are derived from pooled human plasma and are known to have powerful immunomodulatory effects on inflammatory and immunodeficiency disorders.[7] Some of the immunomodulatory effects appear to be mediated through anti-idiotypic antibodies that inhibit HLA-specific alloantibodies.[8]

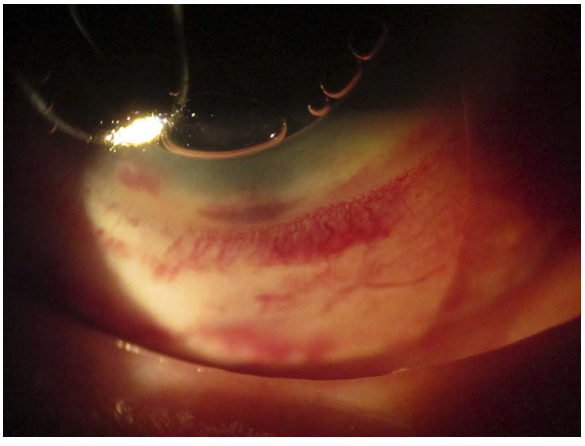

Figure 2 Slit lamp photo of inflamed keratolimbal allograft inferior segment with dilated vessels and limbal haemorrhages accompanied by patient's complaint of severe eye pain consistent with acute rejection 1 week after surgery.

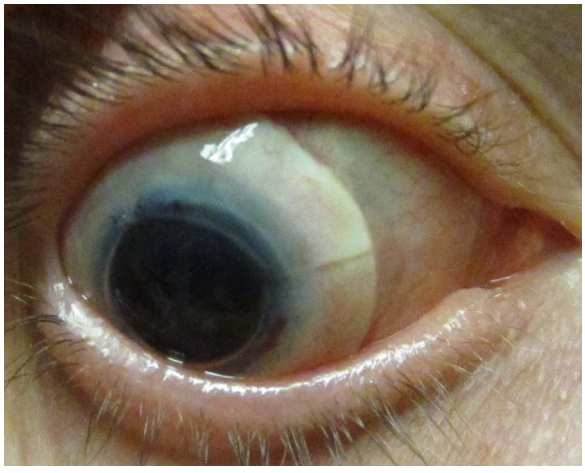

Figure 3 External photograph of keratolimbal allograft and conjunctiva with no inflammation 1 month after intravenous immunoglobulin infusion for the treatment of antibody mediated acute rejection. The corneal epithelial surface was also stable with no epithelial defects or conjunctivalisation.

Essentially, IVIG contains antibodies that can inhibit the HLA-specific antibodies produced by the host to attack the foreign donor tissue. In addition, IVIG also exerts effects on complement activation, B-cell activity and apoptosis and adhesion molecules and cytokines.[9] A multicentre, double-blinded, placebo controlled trial demonstrated that IVIG infusions can reduce the antidonor HLA antibody levels in highly sensitised patients, and increase rates of renal transplantation in this population.[10] Recent data also suggest that IVIG therapy reduces ischaemia-reperfusion injuries; results in fewer acute rejection episodes; and has better long-term outcomes for cardiac and renal allograft recipients.[10]

The renal transplant literature indicates that IVIG may be used alone at high doses (0.5–2 g/kg)[10–12] or at low-doses (100 mg/kg) if combined with plasmapheresis.[13] Our patient received high-dose IVIG alone (1 g/kg, total dose 80 g), 20 days after her KLAL surgery. This was sufficient to reverse the AMR in her KLAL graft prior to any signs of limbal stem cell dysfunction (ie, no late fluorescein staining pattern, epithelial rejection line or defects were noted), and was well tolerated without any systemic adverse events.

Our case demonstrates the novel use of IVIG to treat an episode of AMR in an aniridic patient after KLAL. We recommend close collaboration with a solid organ transplant specialist and consideration of IVIG for the management of AMR.

Learning points

- Collaboration with a transplant specialist is essential to provide adequate systemic immunosuppression to patients undergoing keratolimbal allograft.
- Close follow-up by the cornea and transplant specialist is required to monitor for signs of antibody-mediated rejection including inflammation, allograft dysfunction and severe pain.
- Intravenous immunoglobulin may be used as an adjunctive therapeutic agent in such scenarios in addition to increasing topical and systemic immunosuppressive therapy.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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