The ROYAL COLLEGE of OPHTHALMOLOGISTS

focus

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Ocular Graft vs Host Disease

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A 62 year old man was referred for urgent assessment by his haematologist. He had previously undergone haematopoietic stem cell transplantation (HSCT) 5 years before for Non-Hodgkin's Lymphoma, and had developed Graft vs Host Disease (GVHD) affecting the eyes a few months later.

The referral was prompted by a worsening of dry eye symptoms. Examination showed severe dry eyes, with punctate epithelial erosions throughout both cornea and subconjunctival fibrosis. He was managed with punctal plugs and copious lubrication.

4 months later, his left BCVA fell from 6/6 to 6/12. He was noted to have worsening conjunctival inflammation, with mucoid discharge, ongoing epitheliopathy, and a new area of central corneal thinning. Dexamethasone drops were added in order to address the inflammation, thought likely to be due to active GVHD. Following discussion with his haematologist, systemic immunosuppression was commenced.

Over 4 weeks, the thinning progressed, leading to perforation and emergency penetrating keratoplasty (Figure 1).

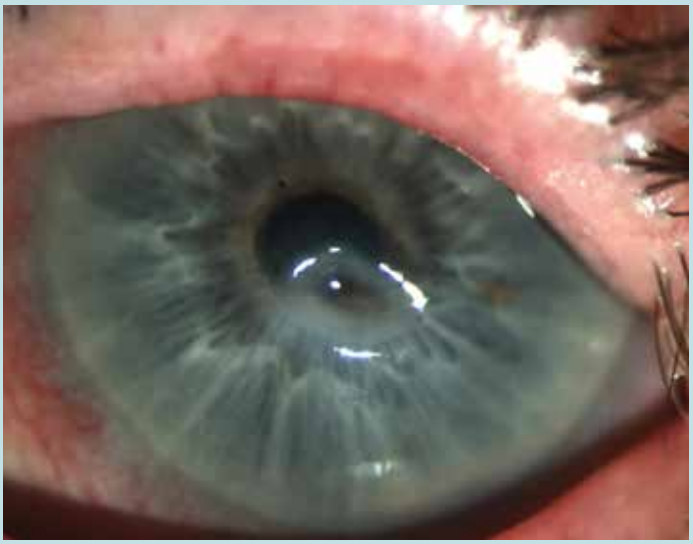

Figure 1. Central corneal thinning and perforation

Graft vs Host Disease

The indications for HSCT are wide ranging, from malignancies to metabolic disorders. It has the potential to be curative, but its application is limited by GVHD; a common complication (25-70% patients after allogeneic HSCT [1]) with significant morbidity and mortality.

Acute GVHD (aGVHD) is a multi-organ inflammatory syndrome; donor T cells recognise recipient antigens and mount a response, whilst the recipient lacks the immunological ability to eliminate them. This is essentially a normal, yet exaggerated response. Whilst eyes may be affected, the primary targets are the skin (maculopapular rash), liver (cholestatic bile duct injury), and gastrointestinal tract.

Chronic GVHD (cGVHD) is clinically reminiscent of a mixed autoimmune-like disease, and a major cause of late non-relapse death [2]. cGVHD can occur as a progression of aGVHD, or de novo. It is characterised by excessive fibrosis, stenosis, and atrophy of tissue in the skin, lungs and mucous membranes (manifesting in eyes as dry eye syndrome).

Whilst the effects of GVHD are clearly deleterious, such graft activity produces a concurrent 'graft vs tumour effect' which is desirable; this effect is associated with a reduced relapse rate of the original disease. A delicate balance must therefore be struck by the haematologist in managing these competing processes.

Ocular GvHD

Ocular GVHD affects 40-60% of patients after allogeneic HSCT [3]. In systemic GVHD, eye involvement is common (60-90% with acute and chronic GVHD[3]). Timely identification of ocular GVHD enables prompt treatment to minimise long term irreversible damage, but additionally, provides information on general GVHD activity with wider implications to the patient. Eye symptoms may be the first presentation of systemic GVHD; ocular involvement (particularly pseudomembranous conjunctivitis, Figure 2) can be a poor prognostic indicator for mortality [4].

All ocular tissue levels may be targeted, from periocular skin and lids though to the choroid. However, the predominant manifestations of ocular GVHD are conjunctival inflammation and dry eye syndrome (DES).

Figure 2. Psedomembranous conjunctivitis can be a poor prognostic indicator for mortality.

Conjunctival inflammation

The severity of acute ocular GVHD is generally in line with that of systemic GVHD. It is particularly associated with skin and mouth involvement. Importantly, for a given grade of aGVHD, those with conjunctival inflammation have a higher mortality rate compared to those without [4].

Signs of conjunctival inflammation can vary in severity from hyperaemia with serosanguinous chemosis through to conjunctival sloughing and pseudomembranous conjunctivitis (Figure 2). Conjunctival scarring and symblepharon may ensue; such cicatricial changes, as well as superior limbic keratoconjunctivitis can signify progression to (or development of) cGVHD.

Dry eye syndrome

Dry eye syndrome (DES) is the most frequent ocular manifestation [5] and occurs in 40-76% of patients with systemic GVHD [5]. It is particularly associated with cGVHD where it can herald the development of systemic disease. DES may also be the sole manifestation of GVHD [3]. Onset of symptoms can range from a few weeks to 100 months after HSCT (median 6 months [6]).

Histological changes to cornea and conjunctiva are similar to skin GVHD (keratinisation, epithelial thinning and squamous metaplasia), whilst observations in lacrimal glands echo that in cholestatic liver GVHD (ductule distension and obliteration of lumina) [3]. Meibomian gland atrophy contributes to tear-film instability.

Dry eye in GVHD commonly progresses [5]. Tear physiology in cGVHD is more severely disrupted than in Sjogrens syndrome (with lower tear turnover rate, higher evaporation and osmolality, and less stable lipid layer [7]) (Figure 3). Aqueous tear dysfunction in most patients does not recover [4]. DES in GVHD may be complicated by secondary infection, severe non-healing corneal ulceration and perforation.

There are no symptoms or signs specific to chronic ocular GVHD; however, a new onset severe dry eye on a background of HSCT should strongly suggest a diagnosis of ocular GVHD.

Figure 3. Extensive ocular surface Lissamine green staining in GVHD dry eye syndrome.

Treatment approach

Ocular GVHD should be managed in close liaison with the patient's haematologist as severe disease may require an increase in systemic immunosuppression, which may in turn affect treatment of the original disease.

Tear function is addressed whilst controlling inflammation to maintain the ocular surface, much like any other very severe dry eye; the mainstay for achieving this are preservative free lubricants, punctal occlusion and topical anti-inflammatory treatment. There should be a low threshold for the latter and topical steroids are usually first line. Topical ciclosporin is increasingly utilised for its effects on the immune response (including inhibition of T cell proliferation, and downregulating pro-inflammatory cytokines) and may have fewer long-term side-effects.

Further epithelial support provided through Autologous Serum is often helpful. The use of Autologous Serum has been described as having an 80% success in refractory cGVHD[8], and is increasingly being advocated in milder disease[5] (though this use may be limited by cost).

Patients with significant ocular GVHD should be monitored in liaison with their haematologist, informing them of changes in ocular GVHD activity which may reflect active systemic disease.

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Editor, Focus

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