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Amniotic membrane-covered bio-onlays for treatment of ocular surface disease

Amniotic membrane (AM) transplantation has been used successfully for the treatment of ocular surface diseases for several years.^{1–3} Indications for use of AM at the cornea include persistent epithelial defects, corneal ulcers and chemical burns.^{1–3} Surgical strategies for AM placement onto the cornea are suturing AM onto the corneal surface (“patch”), into a corneal defect (“graft”) or a combination of both strategies (“sandwich”).^{1–5}

All published reports for use of AM in patients are based on the use of sutures. Although most patients can be treated with the suture-based approach, there are several situations in which sutures should be avoided: patients under intensive care, long-lasting corneal epithelial defects causing a cornea too thin to support sutures or sutures may be technically difficult to place in the case of a previous graft, and, in addition, sutures can induce scarring and neovascularisation.⁶ Since the beneficial effects of AM are at least partially mediated by agents released from AM and by AM acting as a natural bandage contact lens,^{1–5} we reasoned that an AM-covered “bio-onlay” may have the same beneficial effects as a sutured graft while avoiding the detrimental effects of sutures. Here we describe a novel sutureless technique using AM to treat persistent corneal epithelial defects.

First, a novel technique for the coating of Illig shells (Müller & Söhne, Wiesbaden, Germany) with AM (bio-onlays) was developed. Initially, the correct size of the Illig shell was determined for each patient (fig 1A). Next, under sterile conditions in the operating room, a sheet of freeze-stored AM (2.5×3.5 cm) was placed around the Illig shell and secured using 8-0 vicryl sutures (fig 1B). The epithelial side of the AM was placed outwards. Suturing takes more time compared with placing just a single AM patch. Finally, the AM-covered bio-onlay was placed onto the eye of the patient using topical anaesthesia (fig 1C). AM-covered bio-onlays were left in place for 2 weeks under topical treatment with lubricants, antibiotics and serum eye drops. After 2 weeks, the device was removed at the slit-lamp examination using topical anaesthesia.

This technique was used in two patients with persistent epithelial defects (after prior informed consent): a 36-year-old patient with neurotrophic keratopathy after keratoplasty (fig 1D) and a 28-year-old woman with chronic graft-versus-host disease. Both defects had not healed with intensive topical treatment, including serum eye drops for several weeks (8 and 6 weeks, respectively). In both patients, AM-covered bio-onlays were tolerated well.

Figure 1 Amniotic membrane (AM)-covered bio-onlays were used for sutureless treatment of persistent corneal epithelial defects. An individualised Illig shell (A) was coated by a single sheet of AM (epithelial side outwards) and sutured at the outer side using 8-0 vicryl (B). This device was then placed onto the cornea under topical anaesthesia (C) and left in place for 2 weeks. A persistent epithelial defect secondary to neurotrophic keratopathy after penetrating keratoplasty (D) healed completely within 2 weeks of bio-onlay treatment (E).

When removed after 2 weeks, AM covering the surface was intact and the persistent epithelial defects were completely healed (fig 1E). There was no evidence for induction of corneal angiogenesis due to the device.

To study the integrity of AM, the membrane was fixed and subjected to histological examination: as can be seen in fig 2A, the AM covering the Illig shell was well preserved (fig 2B). Epithelium and basement membrane of AM appeared intact (fig 2C,D). Using immunohistochemical analysis with CD45 as panleucocyte and CD68 as macrophage marker (Dako, Hamburg, Germany),⁶ we ruled out a significant accumulation of inflammatory cells on the surface of or within the bio-onlay (fig 2E,F). This lack of inflammatory cell “trapping” within the AM-covered bio-onlay is in contrast with previous observations made with AM layered directly onto inflamed corneas,⁷ and may be due to (1) only partial direct contact of the bio-onlay with the ocular surface and (2) lack of an inflammatory, chemotactic stimulus within the bio-onlay attracting inflammatory cells in contrast with

the scenario of an AM placed onto an inflamed corneal stroma.⁷

In summary, we demonstrate a novel sutureless method of application of AM onto the ocular surface using AM-covered bio-onlays. A small pilot study provides proof of concept and demonstrates that the technique was well tolerated. AM-covered bio-onlays seem to be beneficial because they act as a natural bandage contact lens and, in addition, exert trophic and anti-inflammatory effects. More patients will have to be studied under controlled conditions to further evaluate this promising new technique. Our pilot study paves the way towards non-surgical use of AM components for surface reconstruction and for anti-inflammatory/anti-angiogenic treatment.^{6, 8}

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Figure 2 Amniotic membrane (AM) sutured around an Illog shell and left in place on the eye for 2 weeks does not show signs of mechanical irritation or enzyme degradation or inflammation. The photograph of the bio-onlay after 2 weeks on the ocular surface (A,B) does not show signs of destruction or severe inflammation. Histological examination for acid mucopolysaccharides (using Alcian blue staining; C) and periodic acid-Schiff (D) demonstrates intact anatomy of amniotic membrane. Immunohistochemical analysis does not reveal significant accumulation of CD45 leucocytes (E) or CD68 macrophages (F) on the surface or within the bio-onlay.

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Ocular myasthenia: a rare presentation with MuSK antibody and bilateral extraocular muscle atrophy

Atrophic extraocular muscles are rarely observed¹⁻³ and bilateral extraocular muscle (EOM) atrophy is extremely rare.³ It has been reported in chronic progressive external ophthalmoplegia (CPEO) related to mitochondrial myopathies,⁴ myotonic dystrophy type 1⁵ and in three other cases of myasthenia gravis (MG).⁴ This report is an atypical presentation of ocular MG with positive muscle-specific kinase (MuSK) antibodies and bilateral EOM atrophy.

Case report

A 49-year-old man presented with a 12-year history of slowly isolated progressive external ophthalmoplegia. His medical history was unremarkable and he did not take any drugs, smoke or drink alcohol. Examination revealed limitation of gaze in all directions to 3°-5° with bilateral ptosis and no exophthalmos. He had no other facial, bulbar or peripheral weakness. His acetylcholine receptor ϵ subunit-specific antibodies and γ subunit-specific antibodies were negative, but his anti-MuSK antibody level was increased at 32 693 pg/ml (normal values 249-264 pg/ml). Single-fibre electromyography revealed jitter and blocking that confirmed his diagnosis of MG. Complete blood count and routine chemistry laboratories were normal. Sedimentation rate, rapid plasma reagin, rheumatoid factor, antinuclear antibody, anti-Hu, anti-Lambert-Eaton myasthenic syndrome, anti-Yo and anti-MaTa antibodies were all negative. Thyroid testing and mitochondrial DNA rearrangement analysis for Kearns-Sayre syndrome were negative. MRI of the orbits revealed severe wasting of all extraocular muscles, except for the inferior oblique muscle (fig 1). Chest CT scan with contrast was normal. Even after 6 months of pyridostigmine and prednisone treatment, followed by thymectomy, his extraocular motility did not improve for 2½ years.

Comment

We have found no previously published cases of bilateral EOM atrophy in MuSK antibody-positive patients with myasthenia. The diagnosis of MG was confirmed by single-fibre electromyography to rule out the possibility of a false-positive increased level of anti-MuSK antibodies. Although >50% of patients with MG present with symptoms and signs related to EOM weakness,⁶ such as diplopia or ptosis, bilateral EOM atrophy is unusual. Unlike the three patients reported by Bau *et al*⁷ and Caress *et al*,⁸ who had anti-MuSK-positive ocular myasthenia with normal extraocular muscles on MRI, our patient had bilateral EOM atrophy. Unlike

Figure 1 On axial postcontrast T1-weighted MRI of the orbits, the rectus muscles seem to be "string-like pulleys". These muscles lost their normal fusiform shape and became thin ribbon-like bands.