Combination Topical Heparan Mimetic with Amniotic Membrane Transplantation for Non-healing Herpetic Neurotrophic Corneal Ulcer

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Case Report

A 74-year old woman was referred to an ophthalmologist for 'non-healing conjunctivitis' in her left eye. Past medical history included diabetes, hypothyroidism and shingles of the right thigh.

Visual acuity was 6/9 OD and hand movements (HM) OS with findings of an 8x7mm corneal ulcer, keratic precipitates, 3+ cells in the anterior chamber and an IOP of 30mmHg with a moderately dense age related cataract. The patient was commenced on topical ciprofloxacin (Ciloxan), bimatoprost (Lumigan) and prednisolone acetate (Predforte) drops. After 2 months, the ulcer reduced to 4.5x3mm, however vision remained HM and the patient was referred to our service.

Examination at this point (Figure 1) revealed absent corneal sensation, signs of limbal stem cell failure, marked peripheral corneal vascularisation and dry eye with lagophthalmos and poor blink reflex. Her uveitis and ocular hypertension had settled. Preserved medications were ceased and she began intensive treatment with preservative-free (PF) carbomer 2mg/g (Viscotears) 2hourly, dexamethasone 0.1% PF od, oral acyclovir 800mg 5xdly and doxycycline 100mg od. Botulinum chemodenervation-ptosis and punctal occlusion were also performed.

Abstract

A rural based 74-year-old female patient developed a persistent herpetic epithelial ulcer after prolonged hospitalisation for heart failure, with no improvement despite 4 weeks of topical antibiotic and artificial tears. Heparan sulfate mimetic (RGTA, Cacicol20®) was then used, with a dosage of two eye drops per week for 3 weeks followed by cryopreserved amniotic membrane graft transplant (AMT). Improvement was observed within 2 weeks of RGTA, complete healing with 6/12 improvement of vision post-AMT within a total of 5 weeks with no side effects. This sequential use of RGTA followed by AMT in the treatment of rural patients with severe neurotrophic ulcers is a practical therapy showing promising results.

Keywords: Resistant herpetic neurotrophic ulcer; Matrix regenerating agent; Heparan sulfate; Amniotic membrane graft

Figure 1: Fluorescein-stained central neurotrophic ulcer with marked peripheral corneal vascularisation.
Unsuccessful attempts to procure autologous serum drops rurally led to alternative treatment with heparan sulfate mimetic RGTA (Cacicol20®) while awaiting amniotic membrane transplant (AMT).

Upon administration, improvement was seen by two weeks with a reduction of the ulcer to 3mmx2mm, reduced corneal vascularity and a diffuse epithelial healing pattern nasally (Figure 2).

Three weeks following RGTA, a small central ulcer of 1.5x1.5mm remained with an adjacent greyish white subepithelial opacity. This remained indolent - showing no tissue reaction, and was thought to represent extracellular fibrin, a RGTA complex.

The cryopreserved AMT involved subtenons anaesthesia followed by a multilayer technique of two 3x4mm sutureless inlay grafts placed stromal side down and one 10x12mm patch graft stromal side down secured by running 10.0 nylon suture. No attempt was made to bury the periphery of the AMT.

The graft dissolved over several weeks and 6 weeks postoperatively, the ulcer had healed completely. The patient remained on unpreserved lubricants and VitA-POS ointment. At 12 months’ follow-up, the cornea remained clear (Figure 3) with best corrected visual acuity of 6/12 OS following cataract removal and lens implant five months after treatment cessation.

Discussion

Post-herpetic neurotrophic ulcers in a rural setting pose a challenge for effective treatment, given the need for frequent visits and paucity of specialised treatments available. Delayed presentations and prior topical treatments with benzalkonium chloride (BALK) containing topical medications exacerbate limbal stem cell failure [1]. Conservative therapies initially involve cessation of such preserved medications and commencement of copious non-preserved lubricants. Temporary tarsorraphy or chemodenervation-induced ptosis are important adjuncts in preventing delayed epithelialisation post-AMT [2].

If significant limbal stem cell failure is present (risk factors include severe herpes zoster ophthalmicus, copious BALK toxicity, diabetic neuropathy or severe dry eye), augmented treatment with autologous serum or AMT have proven to be effective treatments [3]. There are practical limitations in the use of autologous serum in our rural setting as it is a specialised product to manufacture (requiring preparation by the Red Cross Blood Bank in Australia) with risk of infection linked both to its preparation and the active growth factors contained within. Equally, AMT is not readily available to rural patients as it is a hospital based procedure involving the use of exogenous human tissue (with co-inherent risks of cross-infection and contamination) requiring its procurement from a reputable source such as a city based eye bank. Heparan sulfate mimetic (RGTA, Cacichol20®), which may stimulate extracellular matrix healing, has already been suggested as alternative therapy to autologous serum or AMT in severe neurotrophic ulcer [4], and is thought to perform well in the presence of inflammation (unpublished data) with few side effects. The unique properties of RGTA® (resistance to degradation, binding and protection of ECM structural and signaling proteins, like heparin sulphate) permit the reconstruction of the ECM, restoring both structural and biochemical functions to this essential substrate, and facilitating the processes of tissue repair and regeneration.

Although a host of conservative management reduced the size and limited superadded infection of the ulcer, ultimately our patient required AMT to fully heal. AMT has many unique properties making it an ideal intervention in neurotrophic corneal ulceration and even in bacterial keratitis healing [5]. It resembles the structural composition of corneal tissue and serves as a biological bandage. It provides a thick basement membrane to facilitate epithelial migration and reinforces the adhesion of basal epithelial cells for rapid epithelialisation. It also promotes epithelial differentiation and prevents epithelial apoptosis through the expression of mRNAs for several growth factors.

RGTA has been successful in treating chronic non-healing ulcers resistant to amniotic membrane graft delivered in a post-graft setting [6]. Our case report suggests RGTA may also be administered before AMT, as a useful adjunct contributing to the overall success of the therapeutic regime without impacting negatively on subsequent AMT healing.

Patients do, however, need to be fully informed of the risks of using amniotic transplant tissue (transmission of infectious disease) and novel recombinant technologies such as heparan sulphate mimetics (unknown but considerably low toxicity potential for the individual). The combined simultaneous or crossover use of AMT and recombinant therapeutic technologies
may also theoretically lead to a reduction in efficacy of either one and although this was not seen in our case study should also be addressed with the patient during informed consent. Further studies are needed to validate our observations.

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References


