SCIENTIFIC REPORT

Early pathological features of the cornea in toxic epidermal necrolysis

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Aim: To describe the early pathological changes in the cornea during toxic epidermal necrolysis (TEN).

Method: Demonstration of histological features of sequential corneal samples taken during management of complications of TEN in a young adult.

Results: Early vacuolation of basal keratinocytes and late infiltration of the cornea with CD 8 lymphocytes were observed. These changes are similar to those found in cutaneous TEN and may represent weakening of the stromal–epithelium interface with resultant recurrent erosion and chronic inflammation.

Conclusions: Similar changes were found in avascular corneal tissue to those previously described in skin. The initial insult may be traumatic. We propose that a cytokine-mediated response contributes to the initial insult, either in response to and/or by accelerating severe inflammation. This precedes a cytotoxic infiltration which may exacerbate episodes of recurrent erosion. This provides a new insight into the mechanism of disease in the cornea following TEN.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening mucocutaneous blistering disorders. TEN is the more severe manifestation with a mortality rate of 34%.¹ The immunological pathogenesis has been previously reported in the skin.^{2–6} There are few pathological data regarding the early corneal changes, however. We report the histological features of sequential corneal samples taken during management of complications of TEN in a young adult.

MATERIALS AND METHODS

Case report

A 33-year-old man was admitted to intensive care with TEN secondary to a respiratory infection or acute drug reaction (amoxicillin or ibuprofen). His multiple problems included extensive skin sloughing and mucous membrane destruction requiring intubation, ventilatory support, aggressive fluid replacement and sandoglobulin.

He developed bilateral blepharo-conjunctivitis within 24 hours of presentation. This was treated with intensive topical preservative-free lubricants and dexamethasone. The eyelids rapidly became erythematous and friable (fig 1a) with sloughing of skin (Nikolsky's sign). Acceleration of conjunctival inflammation led to temporal symblepharon formation requiring daily glass-rod forniceal 'sweeping'. Inflammation was compounded by development of an extremely dry ocular surface (fig 1b) and subsequent corneal abrasions. Autologous serum drops were prepared and urgent bilateral amniotic membrane grafting (AMG) carried out. The first corneal specimen was taken at the time of surgery (fig 2).

After two months systemic improvement allowed extubation and transfer to a ward, facilitating detailed ocular examination. The patient's acuity at this stage was counting fingers OD and

6/5 OS. His poor vision related to right corneal haze, diffuse epithelial staining and inferior vascularisation. The corneal surface was thickened and irregular with evidence of superior conjunctival down-growth. The left cornea had a crescent of stromal scarring inferiorly with localised vascularisation. The anterior chambers were quiet and fundoscopy unremarkable.

Ocular surface problems were exacerbated by upper and lower lid cicatricial entropions. An oculoplastic consult was requested and bilateral grey line splits with everting sutures were undertaken. Despite improvement in lash misdirection, lid swelling and tendency to forniceal adhesion, repeated episodes of right corneal epithelial erosion occurred with progressive corneal vascularisation. Poor tear film stability undoubtedly contributed to these problems with resultant fluctuation in VA. A superficial keratectomy was undertaken with repeat AMG (four months after the original procedure). Repeat corneal samples were taken at this time (fig 3, 4).

Figure 1 (A) Colour photograph demonstrating skin sloughing and lid margin disorganisation. (B) Colour photograph of the left eye demonstrating extremely dry ocular surface.

Abbreviations: AMG, amniotic membrane grafting; IL1, interleukin 1; MMP, matrix metalloproteinases; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

Figure 2 Haematoxylin and eosin section of corneal epithelium. This demonstrates vacuolation of the basal keratinocyte cytoplasm (arrow). No intraepithelial lymphocytes are identified.

RESULTS

Pathological findings

Histological sections from day 7 showed loosely adherent tissue to the underlying stroma. Basal cell intracellular oedema, vacuolation and occasional apoptotic keratinocytes were demonstrated (fig 2). There was no evidence of intraepithelial lymphocyte attack or necrosis at this stage.

At 4 months, histological sections confirmed as stratified squamous non-keratinised epithelium positive for cytokeratin 3 and negative for cytokeratin 19, indicating a corneal epithelium phenotype. Clusters of basally sited intraepithelial cytotoxic lymphocytes were seen (fig 3), resulting in epithelial cell discohesion, vacuolar change and condensation of the epithelial eosinophilic cytoplasm (fig 4).

Follow-up

The ocular surfaces remain extremely dry and the right cornea has developed a keratin plaque in response to chronic lid margin and eyelash irritation, with the left eye developing inferior stromal vascularisation. There have been no further episodes of epithelial erosion and the most recent acuities were 6/12 OD and 6/60 OS. The combination of initial glass-rodging, intense lubrication, AMG, superficial keratectomy and lid surgery has thus far retained functional vision in a severe and sight-threatening illness.

DISCUSSION

This case offers a unique insight to the corneal pathological sequelae during the acute stages of SJS–TEN. Clinically and histologically the epithelium was damaged at an early stage. It was also debrided with ease, implying loose hemidesmosome adhesion, analogous to changes in recurrent-erosion syndrome or diabetes mellitus. The mechanism for this early breakdown is not fully understood. Corneal epithelial tight junction integrity depends on the interaction between cytokines derived from epithelial cells, stromal keratinocytes, immune cells and lacrimal fluid and damage to tight junction integrity may disrupt this equilibrium.⁷ Ocular surface damage may be induced by severe inflammation and dry eye; this is modulated by cytokine interaction with keratinocytes.⁸ TEN, as in our patient, is

characterised by severe inflammatory changes and this may have had a direct role in ocular surface damage.

The early vacuolation of basal keratinocytes in our patient occurred in the absence of a lymphocytic infiltrate. Given the importance of pro-inflammatory cytokines in severe ocular inflammation and dry eye, it seems plausible therefore that they contributed to the epithelial damage seen or their normal balance was severely disrupted. There is evidence that these cytokines may in part be derived from conjunctival tissue.⁹ The key cytokines involved in surface repair and damage include $\text{TNF}\alpha$, interleukin 1 (IL1) and matrix metalloproteinases (MMP).^{7 10 11} IL1 is a key inducer of other inflammatory cytokines including $\text{TNF}\alpha$ and MMP and is upregulated in dry eye states such as keratoconjunctivitis sicca.¹⁰ Induction of dry eye in mouse models results in upregulation of mitogen-associated protein kinase expression, which is known to stimulate inflammatory cytokines and MMP-9 (which cause corneal basement membrane and tight junction lysis).¹¹ Once the initial epithelial damage took place, our clinical findings were similar to recurrent erosion syndrome. Cytokines also play an important role in the pathogenesis of this disease and again MMP is found to be upregulated in this condition.^{12 13}

There is also evidence for the role of cytokines in cutaneous TEN. There is initially minimal inflammatory cell infiltrate² with vacuolar attenuation along the dermal–epidermal junction.³ In cutaneous epithelial tissue it has been found that $\text{TNF}\alpha$ and interferon- γ are found at high concentrations in TEN together with cytotoxic T cells.¹⁴ Recruitment, however, is thought to be derived from peripheral blood cells¹⁵ and it is argued that $\text{TNF}\alpha$, Fas/Fas ligand and IL10 may act as a defence mechanism against cytotoxic T cell induced apoptosis.¹⁴ It is not known if this represents a difference in cutaneous tissue.

We cannot determine with certainty if Bowman's membrane was effaced at the time of biopsy or indeed as a result of drop installation/glass-rodging. It is therefore conceivable that minimal initial disruption is enough to damage the epithelium while it is extremely vulnerable to further cytokine-mediated disruption. Our patient also underwent a sustained period of induced eyelid closure while paralysed and sedated. It has been suggested that prolonged eyelid closure may contribute to recurrent erosion.¹⁶ The effect therefore may be direct damage to the corneal epithelium by inflammatory cytokines or trauma and subsequent stromal/Bowman's membrane trapping of cytokines and resultant cytotoxicity.

The late infiltration with CD8 lymphocytes represents a cell-mediated reaction in the epithelium. These subtle changes are similar to epidermal findings in cutaneous TEN⁴ and may have contributed to epithelial damage. Direct attack through cytotoxic T cells could be mediated by $\text{TNF}\alpha$.^{2 14} There is evidence that $\text{TNF}\alpha$ is released by keratinocytes or monocyte–macrophage cells² and these cells play an important role in corneal wound healing.¹⁷ The absence of these cells in our patient may reflect an important difference in the immune response in TEN. The alternative possibility for CD8 T cell infiltration is that initial damage leads to delayed cell-mediated cytotoxic attack.⁴ In the case of the cornea, this may have contributed to the episodes of recurrent erosion and poor healing. Intriguingly in conjunctival/dermal tissue during SJS, the predominant lymphocytes are CD4.^{5 18}

Finally, the contribution of blink microtrauma to the chronic inflammation and ocular surface damage is well recognised in SJS/TEN.^{8 19} A relative reserve of limbal stem cells can allow squamous metaplasia and pannus following chronic micro-trauma.¹⁹ Poor stem cell reserve (a feature of SJS/TEN) may, however, lead to conjunctivalisation as in our patient.²⁰ Crucially, it is thought that stem cell destruction in SJS may contribute to episodes of recurrent erosions.²⁰

Figure 3 Corneal epithelium showing (A) intraepithelial lymphocytes (arrow) on H&E section and confirmed by (B) the presence of CD45 (leucocyte common antigen) membrane-positive lymphocytes. (C) The subtype is demonstrated as a cytotoxic T cell by its CD8 marker (brown arrowed cells).

We have found similar changes in avascular corneal tissue to those previously described in skin. The exact mechanism which leads to epithelial vacuolation/shearing and subsequent recurrent erosions is unknown. The initial insult may be iatrogenic trauma or a blink-related phenomenon. We propose that a cytokine-mediated response contributes to the initial insult, either in response to and/or by accelerating severe inflammation. This precedes cytotoxic T cell infiltration which then compounds poor healing and erosions. Our report has limitations in that we were unable to quantify cytokines in the initial and late samples and that this is an isolated histological sequence. Nonetheless the findings offer important information regarding the cornea in the early stages of the disease. The low incidence precludes large-scale case series but the opportunity to assay inflammatory cytokines from corneal tissue and tears may shed yet more light on the corneal changes in this devastating condition.

Figure 4 The cytopathic effect of intraepithelial cytotoxic lymphocytes (white arrow) manifests as discohesion, vacuolar change and condensation of the epithelial eosinophilic cytoplasm (black arrow). This indicates early apoptotic changes.

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VIDEO REPORT

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Detached Descemet's membrane

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Introduction: Post operative complications following cataract surgery can present following a seemingly normal procedure, with few clues as to cause.

Case Description: A 62-year-old female had cataract surgery on her left eye. The surgery was uncomplicated until the end of the procedure. When the surgeon inserted a small cannula with balanced salt solution, to refill the anterior chamber just prior to checking the wound, the cornea gradually turned somewhat translucent. The following morning the cornea was cloudy and the visual acuity was count fingers.

The patient was referred and found to have visual acuity of count fingers without pain and normal intraocular pressure. An Ultrasound Biomicroscopic Examination (UBM) was performed, revealing a detached Descemet's membrane, which could be seen in the anterior chamber waving within the aqueous. Five days later, reattachment of Descemet's membrane was performed with air without complication. Within 4 weeks, the visual acuity was 6/12 with retinal pathology accounting for the remaining reduction in visual acuity.

Discussion: This patient was referred with a diagnosis of endothelial decompensation. The surgeon assumed that he had injected a toxic solution into the anterior chamber. The use of UBM allowed the diagnosis of Descemet's detachment to be made in the setting of an opacified cornea. Repair with the use of air to re-approximate the membrane with its complement of endothelium led to visual recovery in four weeks.

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