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Drug induced cicatrizing conjunctivitis: A case series with review of etiopathogenesis, diagnosis and management

Swati Singh [a,b], Pragnya Rao Donthineni [c], Swapna S. Shanbhag [c], Sirisha Senthil [d], Hon Shing Ong [e,f], John KG. Dart [e], Sayan Basu [b,c,*]

[a] Ophthalmic Plastic Surgery, Orbit and Ocular Oncology Services, L V Prasad Eye Institute, Hyderabad, Telangana, India
[b] Centre for Ocular Regeneration, L V Prasad Eye Institute, Hyderabad, Telangana, India
[c] The Cornea Institute, L V Prasad Eye Institute, Hyderabad, Telangana, India
[d] VST Centre for Glaucoma Care, L V Prasad Eye Institute, Hyderabad, Telangana, India
[e] National Institute of Health Research (NIHR), Moorfields Biomedical Research Centre, London, UK
[f] Corneal and External Diseases Department, Singapore National Eye Centre, Singapore

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ABSTRACT

Drug induced cicatrizing conjunctivitis (DICC) is defined as a disease in which conjunctival cicatrization develops as a response to the chronic use of inciting topical and, rarely, systemic medications. DICC accounts for up to one third of cases of pseudopemphigoid, a large group of cicatrizing conjunctival diseases sharing similar clinical features to those of mucous membrane pemphigoid (MMP) but generally without the morbidity of progressive scarring or the need for systemic immunosuppression. The preservatives in topical anti-glaucoma medications (AGM) are the most frequently implicated inciting causes of DICC although topical antivirals, vasoconstrictors and mydriatics and some systemic drugs have been implicated. The literature review summarizes the classification, epidemiology, etiopathogenesis, histopathology, clinical presentation, diagnosis, management, and treatment outcomes of DICC in the context of a case series of 23 patients (42 eyes) with AGM induced DICC, from India and the UK. In this series all subjects reacted to preserved AGM with one exception, who also reacted to non-preserved AGM. At diagnosis >70% of eyes showed punctal scarring, inflammation, and forniceal shortening. Pemphigoid studies were negative in the 19/23 patients in whom they were carried out. DICC can be classified as non-progressive, progressive with positive pemphigoid immunopathology or progressive with negative pemphigoid immunopathology. It is unclear whether progressive DICC is a stand-alone disease, or concurrent (or drug induced) ocular MMP. Progressive cases should currently be treated as ocular MMP. The diagnosis can be made clinically when there is rapid resolution of symptoms and inflammation, usually within 1–16 weeks, after withdrawal of suspected inciting medications, ideally by temporary substitution of oral carbonic anhydrase inhibitors. If the response to withdrawal is uncertain, or the progression of inflammation and scarring continues then patients must be evaluated to exclude concurrent (or drug induced) MMP, and other potential causes of CC, for which the treatment and prognosis is different. Management, in addition to withdrawing inciting medications, may require short-term treatment of conjunctival inflammation with steroids, treatment of associated corneal disease with contact lenses or surface reconstructive surgery, control of intraocular pressure with non-preserved AGM and, in some, surgery for glaucoma or for trichiasis and entropion.

1. Introduction

Pseudopemphigoid is a term used to describe ocular conditions that clinically mimic mucous membrane pemphigoid (MMP) [1–7]. The term 'pseudopemphigoid' was originally coined by Patten and coworkers for chronic progressive conjunctival cicatrization secondary to long-term ocular use of topical medications [4]. Unfortunately this term has subsequently been used as an umbrella term that includes many

Abbreviations: DICC, Drug induced cicatricial pemphigoid; OCP, Ocular cicatricial pemphigoid; MMP, Mucous membrane pemphigoid; CC, Cicatrizing conjunctivitis; AGM, Anti-glaucoma medications; DIF, Direct immunofluorescence.

* Corresponding author. Chair of Eye Research, Prof. Brien Holden Eye Research Centre (BHERC), L V Prasad Eye Institute, Hyderabad, Telangana, 500034, India.
E-mail address: sayanbasu@lvpei.org (S. Basu).

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individually well-defined diseases because they share some of the same clinical characteristics as MMP; these have included atopic keratoconjunctivitis, Stevens-Johnson syndrome (SJS), rosacea, trachoma, Sjogren's syndrome, sarcoidosis, and paraneoplastic pemphigus amongst others [1–8]. However, these conditions rarely result either in the progressive scarring that causes much of the morbidity in MMP, or in the need for systemic immunosuppressive therapy, and neither does the term include all of the diseases that are in the differential diagnosis of MMP such as ocular surface squamous neoplasia. For these reasons the term pseudopemphigoid, as a non-specific term covering this disparate group of diseases, can be confusing. In recent years the more descriptive term drug induced cicatrizing conjunctivitis (DICC), the term used in this review, has been used interchangeably with drug induced pseudopemphigoid. DICC can be defined as a disease in which conjunctival cicatrization develops as a response to the chronic use of inciting topical and, rarely, systemic medications; the term DICC has been used throughout this review as being more specific than the term drug induced pseudopemphigoid. DICC accounts for up to a third of all cases reported as pseudopemphigoid and occurs after long-term use of topical ocular medications, most commonly anti-glaucoma medications (AGM) [2]. Less commonly, they can occur after the use of other topical therapies such as antivirals and vasoconstrictors/mydriatics; rarely, they can occur with systemic drugs including practolol (historically) and possibly with pencillamine [6–11]. Recently, two patients who reportedly received the drug Dupilumab for atopic dermatitis developed conjunctivitis, one of whom developed conjunctival cicatrization consistent with DICC [12,13]. Cases of DICC that have the same immunopathological findings and/or disease progression as MMP should be classified as MMP [14]. However, most DICC cases are immunopathology negative and it is critical to distinguish these from MMP because the treatment and prognosis of these two conditions are different. Unfortunately, the literature on DICC is sparse and limited to anecdotal reports. This review addresses the lacuna in the literature by summarizing the etiopathogenesis, histopathological changes, clinical presentation, differential diagnosis, management, and treatment outcomes of DICC in the context of a large case series of AGM-induced pseudopemphigoid.

2. Literature review and case series

A literature search for articles published on pseudopemphigoid in English was performed on PubMed.gov. The search used the terms "pseudopemphigoid", "drug induced cicatrizing conjunctivitis", "drug induced pseudopemphigoid", and "iatrogenic limbal stem cell deficiency". Of the 86 abstracts reviewed, 48 were included for the review. Articles that were non-specific/non-English or included etiologies of pseudopemphigoid other than drug induced were excluded. The references in these articles were also reviewed to make sure no relevant publication was missed. Table 1 provides a summary of the published cases of DICC.

2.1. Classification

There is ambiguity in the literature regarding the appropriate distinction between pseudopemphigoid and drug induced pseudopemphigoid. There are currently 3 categories of DICC that can be identified from the literature [15] and from our experience:

i. **Non-progressive DICC:** those in which the cicatrization (and inflammation) stabilises or regresses following withdrawal of the inciting medication.
ii. **Progressive DICC** which can be further sub-classified as:
   a. Progressive DICC with positive immunopathology. These cases may have either a stand-alone disease or have drug induced ocular monosite MMP or ocular monosite MMP concurrent with, but independent of, medication use.
   b. Progressive DICC with negative immunopathology but who have progressive inflammation and scarring. This may also be a stand-alone disease or be drug induced or concurrent immunopathology-negative ocular MMP [1,16,17].

Future studies reporting the clinical course, outcomes and current or new immunopathology investigations using this classification may improve our understanding of this enigmatic condition.

2.2. Epidemiology

In the largest published series of 231 patients with cicatrizing conjunctivitis (CC), from a specialized US clinic reporting from 1985 to 2001, there were 86/231 (37.2%) subjects with ocular MMP and 145/231 (62.8%) pseudopemphigoid cases associated with 17 different diseases of which DICC due to AGM was the most common in 41/145 (28.3%) cases [2]. **Supplementary Table 1** summarizes a similar series of CC from Moorfields Eye Hospital (UK) for 36 months (March 2013–April 2016) including 224 subjects of whom 137/224 (61.2%) had

Table 1
Summary of articles published on drug induced pseudopemphigoid.

Study/year	Age/Sex (No. of patients)	Type of AGM	Histopathology	Management
Leonard JN et al., /1988 [27]	68/M; 58/F; 79/M; 69/F; 24/F	Topical glaucoma medication unspecified details	2 both DIF positive and IIF positive; 1 IIF positive; 2 negative on both DIF and IIF	No comment. Cases said to be indistinguishable from MMP
Patten et al., /1972 [4]	70/M (2)	Echothiophate iodide	DIF positive (1) Chronic inflammation	Non-progressive
Fiore et al., /1987 [32]	71.5/F (5)	Timolol, epinephrine, pilocarpine	DIF negative (5/5)	4- status quo after stopping AGM 1- Progressive
Hirst et al., /1992 [29]	78/F (2)	Pilocarpine, demecarium	IgA DIF positive (1/2), Chronic inflammation	Status quo after stopping AGM
Pouliquen et al., /1996 [22]	70/7F (10)	Pilocarpine, timolol, epinephrine	Chronic inflammation (80%)	NA
Butt et al., /1998 [30]	65/4F (8)	Timolol, pilocarpine, dipivefrine	Lymphoplasmacytic Infiltrate DIF positive (3/4)	NA
Thorne et al., /2002 [2]	NA (41)	Timolol, brimonidine, epinephrine, pilocarpine, latanoprost, dorzolamide	DIF negative	NA
Gibran et al., /2004 [31]	85/F (1)	latanoprost, Iopidine	DIF negative, Chronic inflammation	NA
Kahana et al., /2007 [35]	60/M (1)	Timolol, brinzolamide, dorzolamide bimatoprost pilocarpine	Granulomatous conjunctivitis	Resolved with preservative free beta blockers

AGM = anti-glaucoma medications; M = male; F = female; DIF = direct immunofluorescence; NA = not available.

MMP with ocular involvement and 87/224 (38.8%) with CC (pseudopemphigoid) caused by 16 other diseases of which the two most common were rosacea/blepharoconjunctivitis in 26/87 (29.9%) and DICC due to AGM in 9/87 (10.3%). In a two-year cross-sectional study of patients with CC from India, SJS was the most common cause, noted in 43/75 (57.3%) cases followed by 19/75 (25.3%) cases of MMP with ocular involvement, 3 cases each of bullous pemphigoid and linear IgA disease, 2 cases of secondary Sjogren's syndrome and 1 case each of SLE, epidermolysis bullosa, scleroderma, granulomatosis with polyangiitis and Behcet's disease [18]. Although these findings are different, reflecting the bias associated with case series from specialist clinics, they show that both MMP and DICC are amongst the most common causes of scarring eye disease in countries with well-developed public health systems and predominantly Caucasian populations, whereas SJS is more common in Indian Asian populations [18]. More reliable figures, for predominantly White British populations, are available from the two prospective national surveys of new cases of CC. In the UK 2008 survey, there were 82 new cases of CC of which 50/82 (60.9%) were due to MMP; of the 32 cases of pseudopemphigoid, 16/32 (19.5%) were SJS and 3/32 (9%) were DICC caused by AGM. In an Australia & New Zealand 17-month survey (2011–2013), using the same methodology as the UK survey, 18/35 (51.4%) were due to MMP and of the 17 cases of pseudopemphigoid, 3/17 (17.6%) were due to SJS and the same number due to DICC. These findings are likely to be very different in other parts of the world where, although glaucoma is common, MMP and the other causes of CC are likely to vary substantially in incidence.

2.3. Possibly implicated drugs and pathogenesis

There are several ways in which AGM and other topical medications can cause ocular surface disease. These include a) chronic cicatrizing conjunctivitis; b) anaphylactoid (allergic) acute or chronic conjunctivitis (type I hypersensitivity); c) allergic contact dermato-conjunctivitis (type IV hypersensitivity); and d) non-specific (folliculo-papillary) irritative/toxic conjunctivitis (immunological or toxic irritation to factors such as pH, tonicity, preservatives, and the drugs themselves) [10]. Long-term use of topical AGM can result in histological changes in the conjunctival epithelium even in the absence of clinically visible conjunctival cicatrization [19]. The commonly used preservatives in topical ocular medications are benzalkonium chloride (BAK), phenylmercuric nitrate, thimerosal, and ethylenediaminetetraacetic acid (EDTA). BAK is the principal preservative used in most anti-glaucoma preparations. Although the incidence of AGM side-effects has declined with the introduction of newer preservatives like stabilized oxychloro complex (SOC) or SofZia (borate, zinc and sorbitol formulation), one patient in our series was using AGM containing SOC as preservative and one patient was on preservative free AGM. This implicates the possible role of the AGM salt itself in inducing conjunctival cicatrization. *In vitro* experiments studying the effect of topical beta blockers (with and without BAK) on fibroblast culture showed no direct stimulatory effect of either drug or preservative on fibroblasts, indicating a different mechanism of inciting fibrosis due to chronic inflammation [20]. The mechanism by which corneal pathology develops relates to a disrupted tear lipid layer, decreased mucin due to damaged goblet cells, thinning of the precorneal tear film leading to superficial punctate keratitis (SPKs), and epithelial erosions, which can be complicated by sterile corneal infiltrates, secondary microbial keratitis and melting [21–23]. The mechanism by which conjunctival pathology develops is an immunological and inflammatory process that causes subconjunctival fibrosis, limbal stem cell deficiency, forniceal shortening and pemphigoid like changes [24].

The fibrotic changes in DICC are concentrated in the inferior fornix and medial canthi including lacrimal punctal edema, ulceration and occlusion. This indicates damage to areas of the ocular surface that come in maximal contact with the medication as it is cleared from the eye [24]. Echothiopate iodide, idoxuridine, timolol, epinephrine and pilocarpine were the initially incriminated drugs in DICC [25,26]. However, almost all kinds of AGM with or without preservatives have shown DICC changes. The topical AGM received in a series of 34 patients with DICC were topical beta blockers in 87.8%, epinephrine and alpha agonists in 61%, and miotics in 53.6% of cases [2].

The pathogenic process has been proposed to be either toxic or immunological [20,27]. The basal cells of conjunctival epithelium from patients with DICC displayed increased proliferation, which was similar to that in ocular surface inflammatory conditions like SJS, graft versus host disease (GVHD) and superior limbic keratoconjunctivitis [28]. The drug might be toxic in the long term to the basement membrane, altering the antigenicity of membrane and activating the autoimmune process. The other possibility is that the drug acts as a trigger in patients predisposed to develop MMP. Leonard et al. suggested it to be immunological as the process continues in some subjects despite drug withdrawal [27]. The drug molecule might be acting as a hapten and in conjugation with tissue proteins, activates an immunological reaction in the eyes.

2.4. Clinical presentation of our series

In this review, we present a case series of 23 patients (42 eyes) with DICC, who presented to Moorfields Eye Hospital NHS Foundation Trust UK over 36 months from March 2013 (n = 9 patients; 14 eyes), and to L V Prasad Eye Institute, Hyderabad, India over the last 4 years (n = 14 patients; 28 eyes). Detailed case summaries are provided in Table 2 and Supplementary Table 2 (also available online as a spreadsheet https://data.mendeley.com/datasets/w4tdfyyrzf/draft?a=93d7711d-0e57-4487-932e-acd426e515ff). The most common ocular findings at

Table 2
Demographics and ocular findings from 23 patients diagnosed with drug induced cicatrizing conjunctivitis. See Supplementary Table 2 for the complete data.

Variable	Current series	Reported data [2,4,22,27,29-32,35]
Demographics at presentation		
Numbers	23 patients (42 eyes)	75 patients
Mean age (in years)	80	61.3
Bilateral	19/23 patients (82.6%)	60%
AGM details		
Mean duration of ocular symptoms (in years)	6.98 (range 0.08–19.00) for 21/23 patients	Not reported
Mean duration of AGM therapy (in years)	6.98 (range 0.08–19.00) for 21/23 patients	Not reported
Types of AGM	All types of AGM	All types of AGM
Preservative exposure	BAK, SOC, Polyquad	BAK
Persistent disease with non-preserved AGM	1/23 patients (4.3%)	Not reported
Ocular findings		
Punctal scarring	27/30 eyes (90%)	Not reported
Periocular hypo-pigmentation	4/42 eyes (9.5%)	Not reported
Lid margin keratinization	12/42 eyes (28.5%)	NA
Limbal stem cell deficiency	20/42 eyes (47.6%)	4%
Forniceal shortening	30/42 eyes (71.4%)	57%
Obstructed meibomian gland orifices	24/29 eyes (82.7%)*	NA
Distichiasis/trichiasis	2/42 (4.7%)	48%
Entropion	11/42 (26.2%)	30%
Symblepharon	27/42 eyes (64.3%)	48%
Immunofluorescence % positivity	Negative in 19/19 patients	9.1%
Management options		
Non-preserved AGM/oral AGM	32/42 eyes (76.2%) in 18 patients	Not reported
Topical steroid	10/42 eyes (23.8%) in 16 patients	Not reported
Glaucoma surgery	10/42 eyes (23.8%)in 6 patients	Not reported

Abbreviations: BAK= Benzalkonium chloride; Polyquad = Polyquaternium-1; SOC = stabilized oxychloro complex; Conj. = conjunctiva.

diagnosis (>70%) were punctal scarring (27/30 eyes; 90%), inflammation (32/38 eyes; 84.2%) forniceal shortening (30/42 eyes; 71.4%) and obstructed meibomian glands (24/29 eyes 82.8%). The BCVA at presentation was reduced from 20/20 in all except for 3 eyes but may have been confounded by co-morbidity with glaucoma. Other clinical findings at diagnosis were lid margin keratinization (12/42 eyes; 28.6% but only in India patients), limbal stem cell deficiency (20/42 eyes; 47.6% but only in India patients), entropion (11/42 eyes; 26.2%), and symblepharon (27/42 eyes; 64.3%). Both upper and lower fornix shortening was present in 8/40 (20%) eyes, no fornix shortening was identified in 12/42 (28.6%) eyes and there were no cases with isolated upper fornix shortening. Peri-ocular hypopigmentation was found in 4/42 (9.5%) eyes but in India patients only. The differences between the clinical findings in the UK and India patients may relate to the smaller size of the UK series or racial/genetic differences; the time from onset of symptoms to diagnosis and time on glaucoma medication was also longer in the UK series. The findings in our case series are similar to those of previously published studies with forniceal foreshortening (57%), symblepharon formation (48%), trichiasis (48%), and entropion (30%) [2,4,22,27,29–35].

One patient (ID 8) reacted to an AGM preserved with stabilized oxychloro complex (SOC) one of the least toxic preservatives. Another subject (ID 15) reacted to all unpreserved AGM including bimatoprost, dorzolamide with timolol, timolol and apraclonidine causing conjunctival inflammation and discomfort and whose DICC resolved following bilateral shunt surgery with Baerveldt tubes. The long-term management of glaucoma in a majority of patients was with non-preserved topical AGM (28/42 eyes; 66.7% in 16 patients), 4 eyes of 2 patients were managed with oral acetazolamide and 10/42 (23.8%) eyes in 6 patients were managed with glaucoma surgery. Lid surgery for entropion/trichiasis was required in 11/42 (26%) eyes in 7 patients. Figs. 1–5 are the representative images of periocular and adnexal changes summarized in Table 2.

2.5. Diagnosis

An algorithm for evaluating patients with chronic cicatrizing conjunctivitis to arrive at an etiological diagnosis, has been explained in detail by Vazirani et al. [24] Patients with probable DICC have a history of long term unilateral or bilateral topical medication use with disease affecting the treated eye(s) and without any other predisposing scarring diseases, usually identifiable by the medical history. These include Rosacea, AKC, GVHD, SJS, chemical burns, and radiation-induced cicatrization. In the absence of a clear medical history of SJS, a focused history and clinical examination can be used to differentiate SJS from DICC and MMP with >90% sensitivity and specificity [18].

Characteristic clinical signs of DICC include early punctal occlusion, without significant forniceal changes, peri-ocular skin depigmentation changes in some Asian patients resulting from a reaction to the chronic epiphora and spillage of medications onto the lid skin, and inferior forniceal changes that are more prominent nasally than temporally (Fig. 5 A,C) [23]. A diagnosis of unilateral DICC is easier to make in patients with unilateral glaucoma and CC although this must still be differentiated from unilateral MMP which is present in about ~6% of all ocular MMP cases [33]. Furthermore, glaucoma occurs in patients with MMP, reported in 29/111 (26%) in one US series [34], which increases the diagnostic difficulty.

For most presentations of DICC we recommend a clinical approach. For many cases, laboratory investigations (see Supplementary figure) and follow up using quantitative assessments of inflammation and scarring are required to exclude progression of conjunctival scarring, and recurrence or development of inflammation, which may indicate MMP rather than DICC [17,18]. The different presentations of DICC alter the considerations required to confirm the diagnosis:

- In those patients with a provisional diagnosis of DICC and having inflammation as well as scarring the diagnosis can be substantiated by the response to the withdrawal of the potentially inciting topical medications. For this reason, patients on AGM with both inflammation and scarring should have their IOP managed temporarily by using oral carbonic anhydrase inhibitors (CAI's), when these are tolerated. Any type of AGM including non-preserved ones should be avoided in the acute phase. As soon as the topical medications are withdrawn, eyes become rapidly asymptomatic and the conjunctival inflammation resolves within 1–16 weeks. Once resolution is complete, preservative free AGM can be introduced one at a time and

Fig. 1. Peri-ocular skin changes in drug induced cicatrizing conjunctivitis (DICC). Clinical photographs of patients with DICC showing periocular depigmentation, mainly involving the lower eyelid (A to C). Clinical photographs of other patients with DICC with increased pigmentation in the periocular area (D & E).

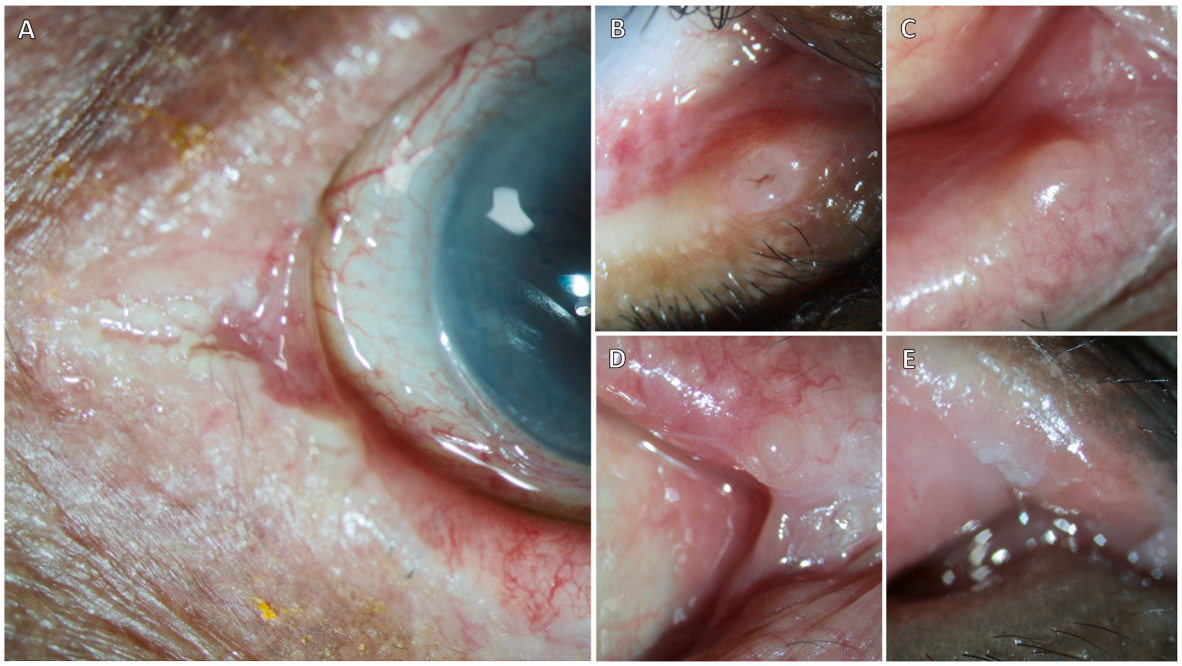

Fig. 2. Punctal and medial canthal changes in drug induced cicatrizing conjunctivitis (DICC). Slit-lamp images of eyelids of DICC patients show complete obliteration of medial conjunctival fornix and canthal fibrosis (A), punctal edema (B) with complete punctal occlusion (C, D) and peri-punctal keratin deposition (E).

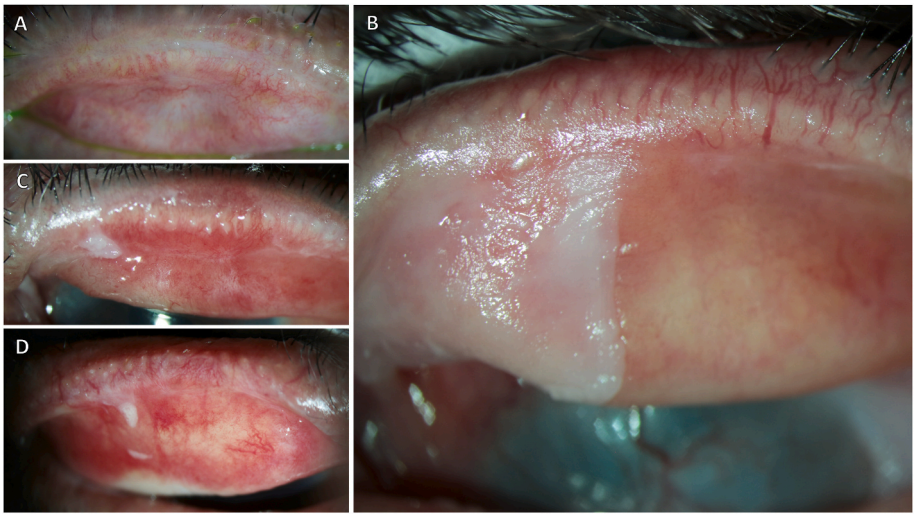

Fig. 3. Superior lid-margin and upper tarsal conjunctival changes in drug induced cicatrizing conjunctivitis. Slit-lamp images of the everted upper eyelids show occlusion of meibomian gland orifices (A to D), inflammation and scarring of tarsal conjunctiva (A to D), and focal or diffuse keratinization of palpebral conjunctiva (B to D).

monitored. Patients who react to non-preserved AGM are very uncommon but this may occur. One of 23 patients (ID 15 in Supplementary Table 2) in our series also reacted to non-preserved AGM and another patient (ID 8) reacted to AGM's preserved with stabilized oxychloro complex, which is inactivated on exposure to air.

- In those patients who cannot tolerate CAI's for more than a few days, if symptoms have improved this may indicate DICC. In those cases that are still symptomatic but cannot tolerate oral CAI, substitution of topical non-preserved apraclonidine 1%, may help in resolution of symptoms and inflammation temporarily. In these eyes glaucoma surgery may be needed for long term benefit. (see section on management below).
- In those patients in whom withdrawal of AGM, using the approach described above is not tolerated, an alternative is stepwise withdrawal of existing medications and substitution of new non-preserved AGM, to which the patient has not been exposed. However, this approach can take longer to establish whether or not the cause is DICC or another cause of CC. In addition, some DICC patients may have granulomatous inflammation that resolves with the addition of topical steroids and the use of preservative free AGM [35].
- For patients with probable DICC associated with drugs other than AGM, of which idoxuridine, vidarabine, trifluridine (all without BAK) and phenylephrine (or adrenergic vasoconstrictors) are the only currently reported causes, the effect of withdrawal of the potentially inciting drug is likely to be easier as alternatives are readily available [10].
- In these four groups of subjects, laboratory investigations to exclude MMP are unnecessary if the response to withdrawal/substitution is

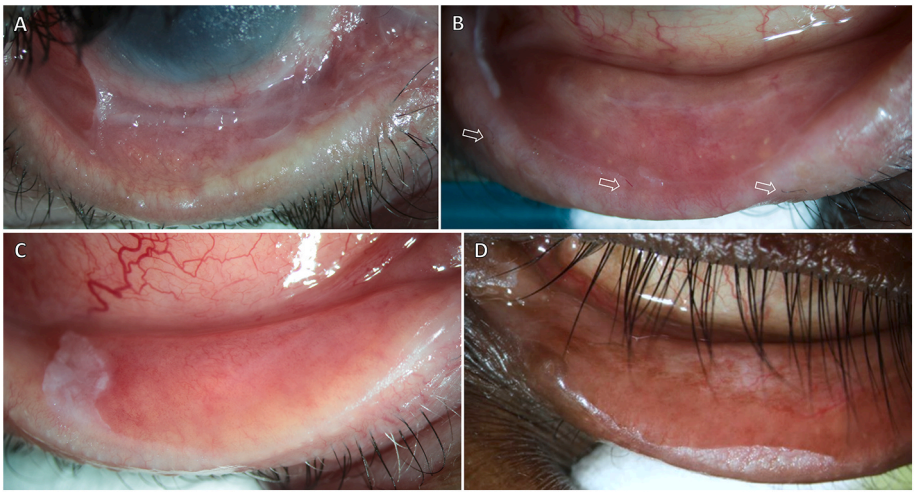

Fig. 4. Inferior lid-margin and lower tarsal conjunctival changes in drug induced cicatrizing conjunctivitis. Slit-lamp images showing thickened lid margins with inflamed, scarred and keratinized tarsal conjunctiva (A), meibomian gland drop-out with distichiasis (B, white arrows) and focal patches of tarsal keratinization (C, D).

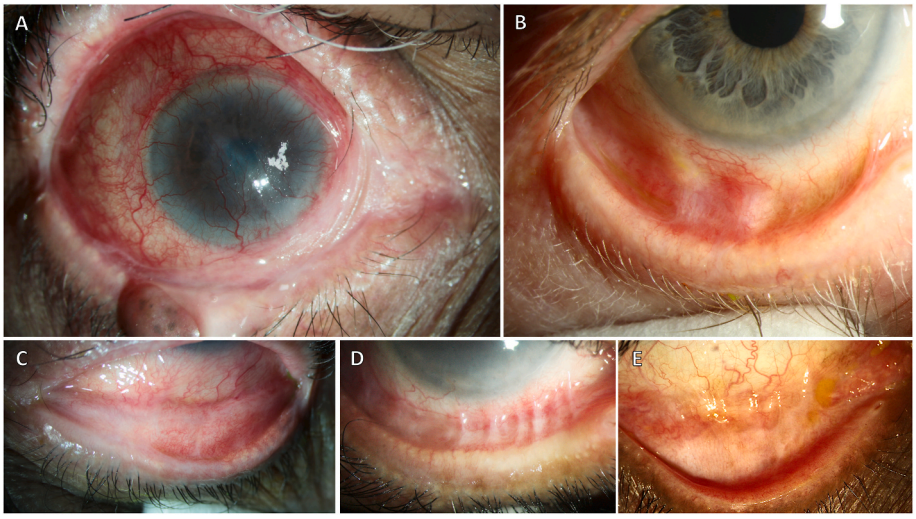

Fig. 5. Inferior forniceal changes in drug induced cicatrizing conjunctivitis (DICC). Slit lamp images of DICC patients show medial ankyloblepharon with diffuse bulbar conjunctival inflammation complicated by corneal scarring and vascularization (A), and different patterns of whitish bands of symblephara with shortening of the inferior fornix (B to E).

clear cut; follow up, using a quantitative assessment tool, to exclude progression will confirm whether or not there may be progressive disease [36]. However, if either the response to drug withdrawal is not clear cut, or if there is progression on follow-up, then we recommend that the diagnostic tests described in Supplementary figure are carried out. These are done both to exclude other causes of CC and, in immunopathology-positive ocular MMP, to provide additional reassurance that the benefits of immunosuppression are likely to outweigh the risks. However, providing other causes of CC have been excluded, and the criteria for immunopathology test negative MMP have been met, then we recommend that this category of progressive DICC cases are treated as immunopathology-negative ocular MMP.

A clinical diagnosis is difficult to establish in patients with probable DICC without conjunctival inflammation because this group may also have MMP in a period when the latter is relatively inactive. In this subset of patients both biopsies and blood tests to exclude MMP, and follow up to detect progression, are mandatory.

2.6. *Histopathological findings*

The conjunctival cellular infiltrate in DICC is similar to that in conjunctival MMP. The subepithelial infiltrate is composed of active fibroblasts, lymphocytes, plasma cells and mast cells [22,37]. The increase in the macrophage population in the conjunctiva of eyes with MMP results in a fibrogenic process secondary to cytokines like transforming growth factor beta, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and tumor necrosis factor alpha (TNFa) [10].

Histopathological study of conjunctival specimens from eight patients of the current case series revealed a chronic subepithelial band-like inflammatory infiltrate composed of lymphocytes and plasma cells (Fig. 6). Squamous metaplasia of conjunctival epithelium with loss of goblet cells was seen in all cases and conjunctival keratinization was noted in 80% of specimens. Congested blood vessels and perivasculitis were present in subepithelial small vessels.

In our series DIF of conjunctival biopsies was performed in all affected eyes of 19/23 patients (34/42 eyes). All biopsies were negative.

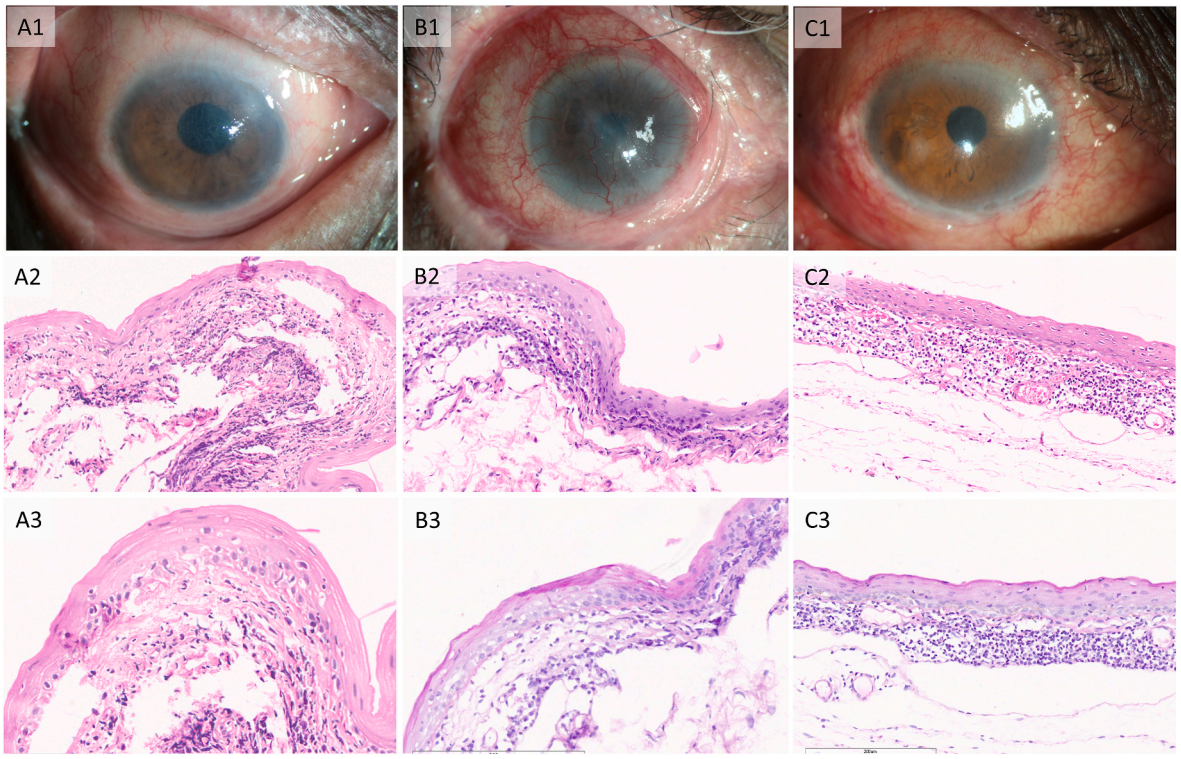

Fig. 6. Histopathology findings in drug induced cicatrizing conjunctivitis (DICC) . Slit-lamp photographs of three eyes with DICC and their corresponding conjunctival biopsies stained with hematoxylin-eosin (middle row) and periodic acid-Schiff (bottom row) staining. Photomicrographs (X100) show subepithelial chronic inflammatory infiltrate with squamous metaplasia on hematoxylin-eosin-stained sections (A2 to C2). PAS staining shows the disrupted basement membrane (A3), loss of goblet cells (A3 to C3), and reduplication of basement membrane (C3).

DIF is usually negative in DICC, however, rarely positive biopsies have also been reported [24,27]. In one study, indirect immunofluorescence was positive in 3/5 patients, whereas DIF was positive in two out of these three biopsies [27]. All 5 patients were non-reactive for skin and oral mucosal biopsies. Patients with DICC who have positive DIF have developed MMP and it is currently recommended that these should be treated as such.

A study on the electron microscopy findings of the conjunctiva obtained from 10 pseudopemphigoid patients revealed squamous metaplasia, increased numbers of desmosomes, basal lamina discontinuation and reduplication, subepithelial inflammatory cell infiltration, and diminished intravascular space within the stroma [22]. The changes in the basal lamina of epithelium and stromal blood vessels are suggestive of reparative process in response to chronic inflammation. There was no increase in neutrophil or eosinophil numbers. Effects of long-term use of topical AGM in eyes (without any DICC) has revealed subclinical inflammation and loss of goblet cells when used for 3 years or more irrespective of the type of AGM [19]. These changes were found to be more pronounced in patients who were on multidrug therapy. The numbers of macrophages, plasma cells, fibroblasts and mast cells showed an increase with increasing duration of drug use.

2.7. Management

The management of DICC involves discontinuing the inciting topical medications. In general, this includes preserved and/or non-preserved AGM, certain antivirals, and vasoconstrictors or other drugs suspected of causing toxicity. Ocular surface inflammation may subside rapidly on drug withdrawal but may benefit from treatment with non-preserved topical steroids. However, once cicatrization has developed it is rarely reversible. In our clinical series, management modalities consisted of stopping topical AGM in all patients, substituting with preservative free or oral AGM in 32/42 eyes (76.2%), and a short course of topical steroids in 10/42 eyes (23.8%). Eight of 42 eyes (19%) with uncontrolled IOP despite oral AGM required trabeculectomy, 1/42 (2.3%) required Baerveldt tube (shunt) surgery and another 1/42 (2.3%) transscleral laser photocoagulation; all procedures resulted in control of IOP without AGM. The ocular surface signs dramatically improved in some patients (Fig. 7), and all patients reported a subjective improvement in symptoms. Reversal of cicatricial ectropion was noted in both eyes of one patient. Of 5 patients who underwent a scleral lens trial for poor vision (n = 3) and severely dry ocular surface (n = 2), three patients reported better vision and ocular comfort. Eyes with corneal involvement, scarring and an irregular surface can benefit from large corneoscleral conventional rigid gas permeable contact lenses which are less expensive and easier to fit than scleral lenses, unless the dryness is very severe in which case scleral lenses are the only option. Topical and systemic treatment is supportive and targets ocular surface inflammation. No available topical drug is antifibrogenic.

2.7.1. Inflammation

For ocular surface inflammation, topical anti-inflammatory drugs offer some relief but for long-term use, a calcineurin antagonist (e.g. cyclosporin) is recommended. In one study, withdrawal of the inciting drug stopped the progression of the disease in 4/5 patients but continued to progress in one patient despite drug withdrawal, probably reflecting drug-induced or concurrent MMP [32]. Low-dose (5–25 mg) oral methotrexate monotherapy in 5 patients with drug-induced MMP (one biopsy positive) controlled ocular surface inflammation and prevented cicatrization progression [38]. These subjects have what we have termed progressive DICC which we currently consider to be synonymous with drug-induced/associated immunopathology negative ocular MMP [1] and which should be treated in the same way. The use of AGM is also associated with the development of dry eye disease that can exacerbate the inflammation on the ocular surface [39,40].

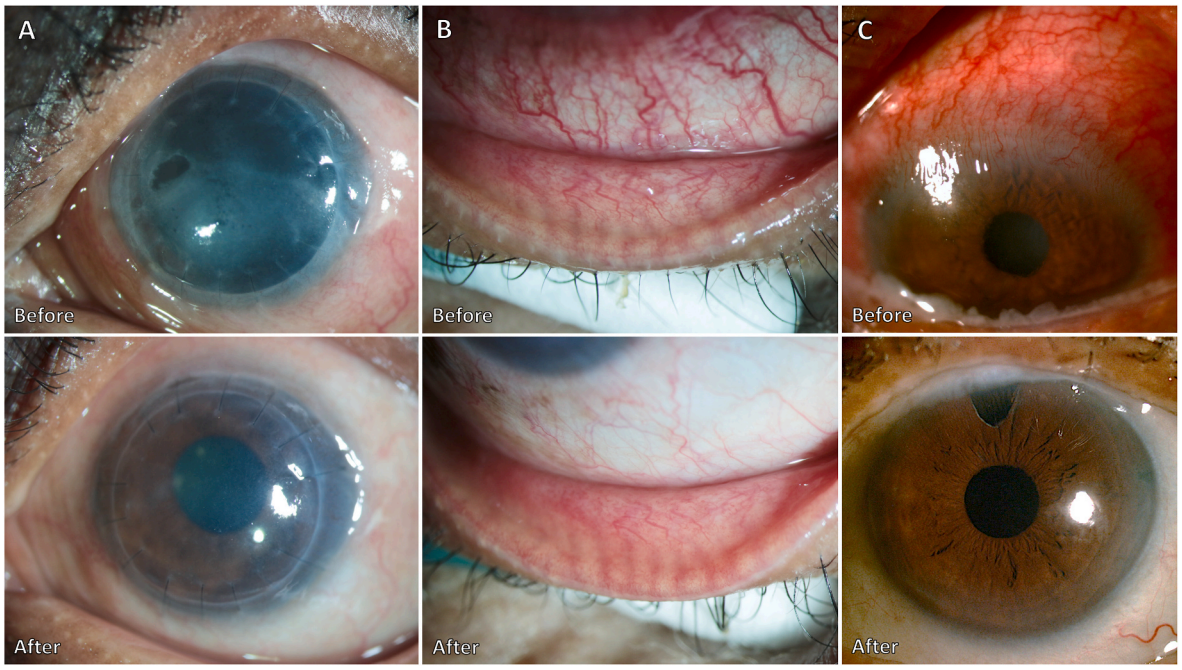

Fig. 7. Improvement in ocular surface disease with anti-glaucoma medications withdrawal and medical or surgical therapy. Slit-lamp images at presentation in 3 different cases (A to C) with corresponding photographs (bottom row) after the withdrawal of the inciting topical anti-glaucoma medications, in cases A &B, and trabeculectomy, in case C.

2.7.2. Surface reconstruction

In severe cases of limbal stem cell deficiency (LSCD), the management depends on the laterality and severity [41]. Penetrating keratoplasties usually fail due to the associated LSCD and dry eye disease [42]. In mild LSCD corneoscleral or scleral lenses may be effective. For severe LSCD, lamellar keratoplasty with cultivated limbal epithelial stem cell transplantation can be tried. Corneal vascularization can improve post-surgery but improvement in vision can be minimal, e.g. from hand motions to counting fingers close to face [43]. The outcomes of allogeneic cultivated limbal epithelial stem cell transplantation in DICC are not favourable [44]. In one case report, conjunctival limbal autograft with amniotic membrane transplantation, performed in a 71-year-old with LSCD and recurrent epithelial erosions, restored the epithelial integrity [45]. Topical retinoic acid (currently having very limited availability) has also been used for treating surface keratinization but appears to have no effect on disease progression [46–48].

2.7.3. Ocular adnexal issues (trichiasis, entropion and fornix shortening)

The outcomes of electroepilation or entropion correction for trichiasis in DICC have not, to our knowledge, been reported. In our personal experience, the recurrence rate for trichiasis or distichiasis is close to 40–50% and multiple sessions induce lid margin inflammation and scarring, which can lead to entropion [49]. Similarly, entropion correction surgeries are quite challenging and are often associated with recurrences. Trichiasis is usually associated with entropion and mild degrees can be managed by self-epilation or assisted epilation. Small numbers of recurrent lashes can be treated with electrolysis but electrolysis may fail and, if extensive, may scar the lid. Surgical management of the entropion will also control the trichiasis but may be challenging to perform and result in recurrences. Anterior lamellar repositioning and levator recession with or without a posterior lamellar graft for the upper eyelid and Jones procedure for the lower eyelid are the preferred techniques. In eyes with severe, recurrent cicatricial entropion, segmental resection of eyelashes along with skin is a viable option [50]. In lid-related keratopathy, as well as in recurrent trichiasis, corneoscleral or scleral lenses may benefit and can be tried before lid-margin mucous membrane grafting. Mucous membrane grafting has been shown to improve symptoms, corneal health and vision in patients with SJS and it seems reasonable to extrapolate this to DICC as well with the caveat that continuing the use of the inciting agent may result in a recurrence of keratinization in the mucosal graft [51,52].

2.7.4. Glaucoma

After discontinuing topical AGM, the IOP should be controlled with oral CAIs; some patients tolerate long-term use of oral CAIs well and they can be maintained on this therapy with a check on potassium levels. However, in others preservative free AGM can be prescribed, although 1/23 patients in the Author's series have shown that preservative free AGM may also result in persistent DICC, although the disease was precipitated by preserved AGM at the onset. If the IOP remains elevated, or the patient cannot tolerate oral AGM, then glaucoma surgery is advisable. Conjunctival cicatrization or inflammation renders trabeculectomy at high-risk of failure. Hence the use of antifibrotic agents during trabeculectomy is expected to be helpful as well as a short course of preservative free topical steroids to control ocular surface inflammation before surgery. In the presence of severe conjunctival fibrosis, in whom filtration surgery failure rates are high, glaucoma drainage devices or tube shunts may have advantages as shown in one of our cases. Other options like laser cyclo-photocoagulation may be used when conjunctival incisional surgery is not possible. If available, endocyclophotocoagulation would be a better option compared to *trans*-scleral cyclophotocoagulation as the latter can induce significant surface and intraocular inflammation. Managing the IOP is probably the most difficult component in the management of DICC.

2.7.5. Visual rehabilitation

Both early and late disease often show an improvement with drug withdrawal, lubrication, with or without topical steroid therapy. However, some of these patients have a dual cause for visual loss: keratopathy and glaucoma. It may be impossible to know the relative contribution of each factor, and this presents a significant challenge in accurately prognosticating the visual potential with medical or surgical therapy. Often medical therapy with cataract surgery, if indicated, is sufficient and the patients can be visually rehabilitated with spectacles.

In more advanced cases, Vazirani et al. have recommended the use of scleral contact lenses or corneoscleral lenses for those with mild to moderate keratopathy, while those with advanced keratopathy may need a corneal rehabilitation procedure depending on the dryness of the ocular surface especially in progressive DICC [24]. If the surface is relatively wet and systemic immunosuppression is not contraindicated, allogeneic limbal epithelial stem cell transplantation can be performed for eyes with LSCD that are not improving with or not tolerating scleral contact lenses [41,53]. Eyes with dry ocular surfaces or disorganized anterior segments will need a keratoprosthesis implantation [54–56]. However, it is important to understand that there are no published series with long-term outcomes of these reconstructive procedures specifically in DICC and while it may be reasonable to a certain extent to extrapolate the experience of these procedures in MMP to cases with DICC, the clinical outcomes particular to this condition are unknown.

3. Summary

The term DICC is preferred as being more specific, compared to the alternatives of pseudopemphigoid or drug induced pseudopemphigoid, for the description of this disease entity in which conjunctival cicatrization develops following chronic use of topical and rarely systemic medications. Based on the literature and our experience we have classified DICC into three categories: Non-progressive DICC: in which the cicatrization (and inflammation) resolves following withdrawal of the inciting medication. Progressive DICC which can be further subclassified as: a. Progressive DICC with positive immunopathology. These cases may have either a stand-alone disease or have drug-induced ocular monosite MMP or ocular monosite MMP concurrent with, but independent of, medication use. b. Progressive DICC with negative immunopathology but who have progressive inflammation and scarring. This may also be a stand-alone disease or be drug-induced or concurrent immunopathology negative ocular MMP [1,16,17].

Where symptoms and conjunctival inflammation both resolve rapidly (1–16 weeks) on removal of the inciting medications there is no need to proceed with the laboratory investigations to exclude MMP and other causes of CC. However, if the effect of withdrawal of the potentially inciting medications on symptoms and signs of CC is unclear OR if on follow up scarring progresses and/or inflammation relapses these cases must be investigated further, using the laboratory tests outlined in the Supplementary figure, to distinguish between (a) DICC/MMP with positive immunopathology (b) progressive DICC with negative immunopathology consistent with immunopathology-negative MMP OR one of the other causes of CC that may be concurrent with DICC.

The only systemic medications that have been identified as causing DICC are practolol, now withdrawn, Dupilumab, and (possibly) penicillamine, but clinicians must be alert to the possibility that other systemic medications may precipitate CC in the future. Besides topical AGM, topical antivirals and topical vasoconstrictors have also been identified as potential causes of DICC. One of our cases with DICC reacted to AGM's preserved with stabilized oxychloro complex, a lower risk preservative which has not until now been reported as causing significant ocular surface disease. Physicians should be alert to the potential of any topical medication whether preserved or otherwise, used for prolonged periods, as a cause of DICC. Solutions to the challenges of managing glaucoma in patients with probable DICC due to AGM are outlined above; this is a relatively common condition and will be encountered by all experienced in the management of glaucoma and external eye disease. Rehabilitation includes stopping the inciting medication, using lubricants and topical steroids as required to control the surface inflammation and optimizing vision with spectacles or contact lenses. In more advanced cases of corneal involvement complex reconstructive procedures like stem cell transplants or keratoprosthesis may be indicated but the risks versus benefits of these in DICC is unknown. Future experimental and clinical studies evaluating the inciting potential of different AGM and preservatives would help clinicians manage the risks associated with long-term topical therapies.

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Declaration of competing interest

None of the authors have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2022.02.004.

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