**Title: Novel surgical approaches in complex situations: when ocular cicatricial pemphigoid and glaucoma collide**

Introduction:

We report the case of a 77-year-old woman with ocular cicatricial pemphigoid (OCP) and primary open angle glaucoma (POAG) who suffered from deep corneal calcification (band degeneration) due to phosphate-containing eyedrops and recurring erosion. The therapeutic aim was to quickly achieve disease control and prevent rapid progression in a high-risk situation. Thus, systemic immunomodulatory therapy accompanied by reduction of anti-glaucomatous topical therapy was mandatory. Since invasive glaucoma surgery would usually fail due to disease features, minimally invasive glaucoma surgery (MIGS) was performed. Additionally, the ocular surface needed to be improved without inducing further scarring and to achieve higher visual acuity. To the best of our knowledge, we performed a novel surgical technique including lamellar keratectomy, chelation with topical ethylene-diamine-tetra-acetic acid (EDTA) and using an acellular corneal implant of porcine origin as a corneal graft for the wound.

OCP as a subset of benign mucous membrane pemphigoid (MMP) is a rare but potentially blinding disease with chronic and progressive inflammation affecting the ocular surface. Ocular manifestations include chronic bilateral conjunctivitis with progressive conjunctival fibrosis and shortening of the fornix due to scarring as well as entropion, trichiasis, symblepharon and ankyloblepharon. Typically, women aged ~65 years are predominantly affected by OCP. Major sight-threatening complications due to relapsing and remitting periods of the disease are corneal erosions, ulcerations, neovascularisations, and keratinization. Although parts of the pathogenesis remain uncertain an autoimmune aetiology with a genetic predisposition is highly suspected. Currently systemic immunomodulatory therapy is the standard of care and aims to control disease activity and prevent rapid progression. (1, 2)

Patients with severe ocular surface disease such as commonly seen in OCP are known to have an increased risk for secondary corneal calcification due to recurring corneal ulceration, chronic inflammation and phosphate-containing ophthalmic topical drops and ointments. (3, 4)

Case presentation with illustrations and figures:

A 77-year-old female patient was referred to our outpatient department in November 2020 with severe dry eye disease (DED) since May 2020 and acute corneal calcification of her left eye first noticed 3 days before. She described increasing irritation and ocular pain especially in her left eye with significant photophobia and decreased vision. Ocular surface disease index (OSDI) was 75. POAG was initially diagnosed in 2015. Until the point of admission formerly performed cataract surgery was the only surgical procedure on both eyes. Medical history

included insulin-dependent diabetes type 2, hypothyroidism due to Hashimoto's thyroiditis and antimitochondrial antibody (AMA) negative primary biliary cholangitis.

Best spectacle-corrected visual acuity (BSCVA) was 0.2 log MAR on the right and 1.5 log MAR on the left eye. IOP was 15 mmHg on right and left eye. Topical IOP reducing medication included preservative and phosphate containing latanoprost (50µg/ml) once a day for both eyes. Treatment for the left eye included preservative containing ofloxacin (3mg/ml) eyedrops (once a day), dexamethasone gel viscous eyedrops (1mg/ml) four times a day and dexpanthenol ointment (50mg/g) on demand. At the first presentation, slit lamp examination showed bilateral anterior and posterior blepharitis, conjunctival injection with scarring and predominantly inferior symblepharon with fornix shortening. The left eye showed a complete corneal erosion with deep corneal calcification. There was a subtle corneal epithelial edema and Tyndall effect (Fig. 1).

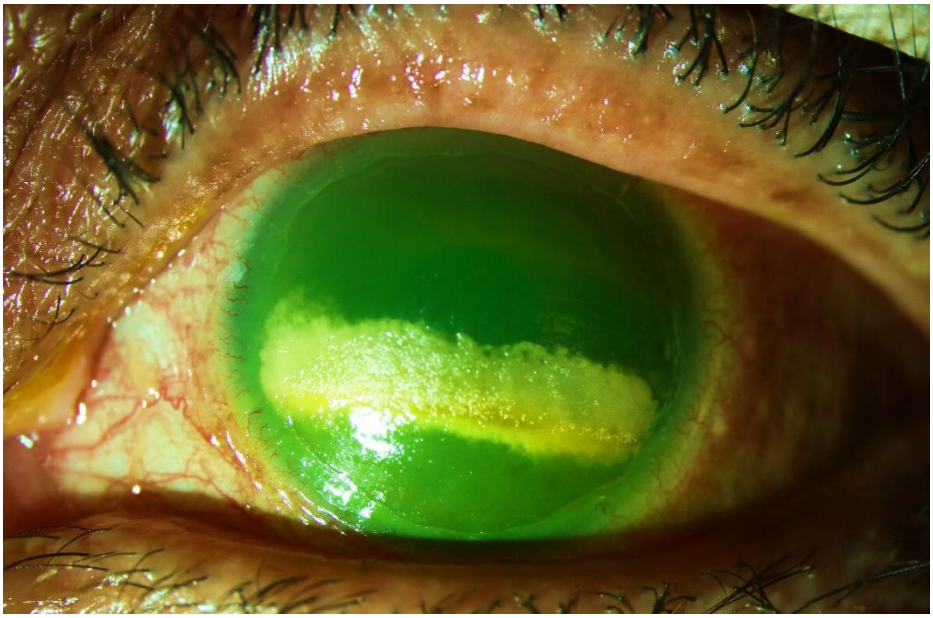

*Figure 1 Left eye with total erosion and horizontal corneal calcification in November 2020.*

Surgery for the left eye was scheduled including chelation with EDTA and amniotic membrane transplantation. Given the typical and severe findings as described before, the suspected clinical diagnosis after consultation of the department of dermatology was OCP. As there was acute progression, we decided not to perform conjunctival biopsy yet and prevent subsequent scarring by minimizing ocular injury in the first place. Additionally, topical therapy was modified without including phosphate- and preservative-containing medication (both eyes: Dorzolamide hydrochloride eyedrops (20mg/ml) 3 times a day) and oral prednisone with an initial dose of 60mg following a reduction scheme were prescribed. Due to deep corneal calcification, chelation with EDTA was not successful.

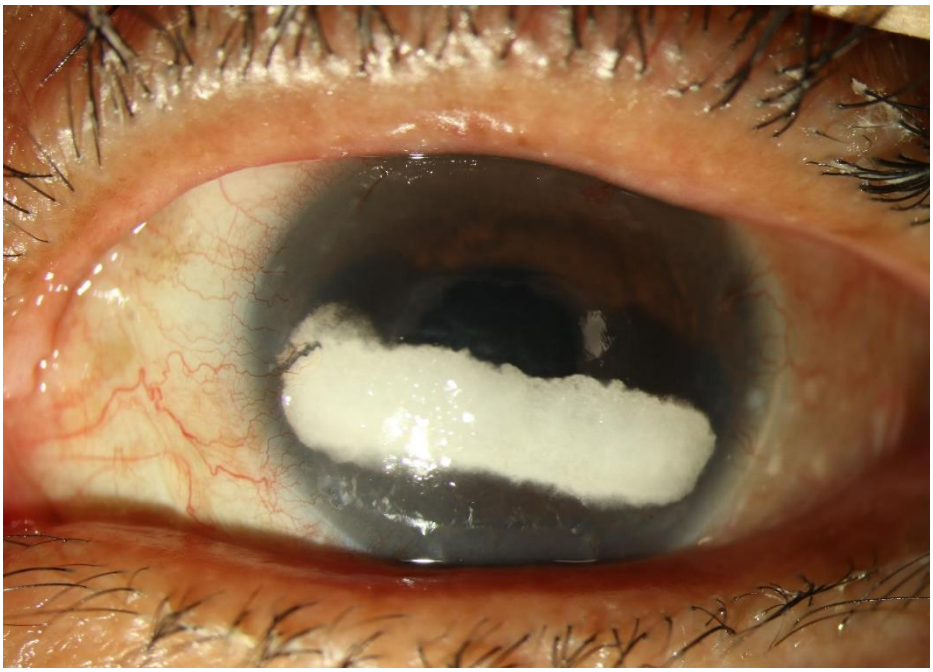

*Figure 2 Persisting corneal calcification after chelation with EDTA and amniotic membrane transplantation.*

Three weeks after amniotic membrane transplantation there was still corneal erosion measuring 4x8 mm left. Therefore, second and third amniotic membrane transplantation were conducted in December 2020 and February 2021.

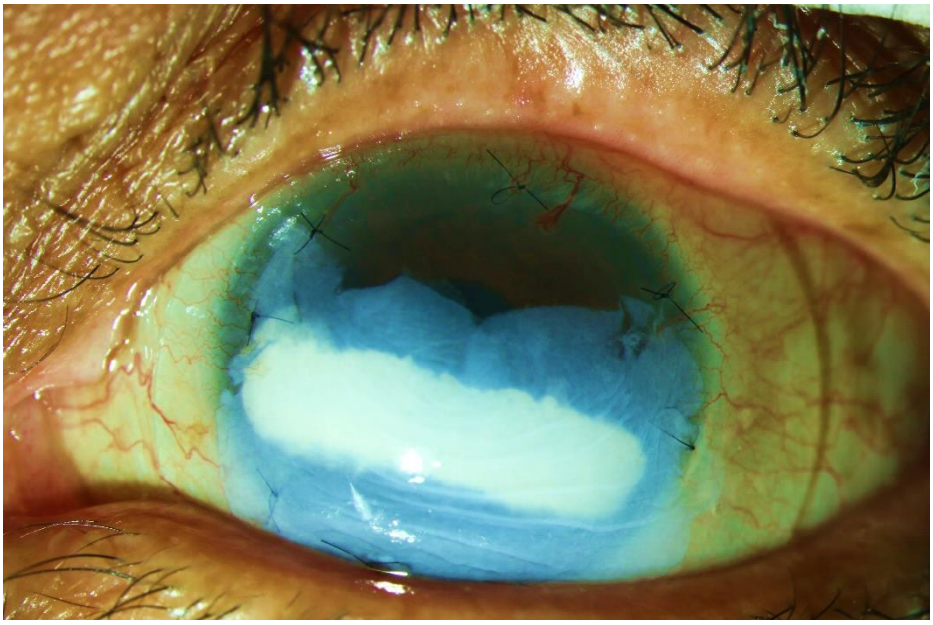

*Figure 3 Left eye with persistent corneal calcification and therapeutic contact lens after amnion membrane transplantation.*

To further improve the ocular surface and reduce anti-glaucoma therapy a Hydrus® Microstent (Ivantis, Inc, USA) as a minimally invasive glaucoma surgery (MIGS) was implanted in the left eye in April 2021. Besides the ocular findings dermatological examination had shown no further extraocular manifestation. Serologically anti-BP (bullous pemphigoid) 180 autoantibodies and

anti-BP230 autoantibodies could not be detected. Indirect immunofluorescence (IIF) on salt-split skin substrate was performed and showed positive results (1:10). Moreover, total serum IgE was elevated (216 kU/l). After discussing the results with our outpatient department for autoimmune skin diseases, our primary diagnosis of OCP was confirmed.
Systemic therapy with Mycophenolate mofetil 1g two times a day and maintenance therapy with 7,5mg oral prednisone was induced. A significant improvement of the ocular surface and disease control was evidenced.

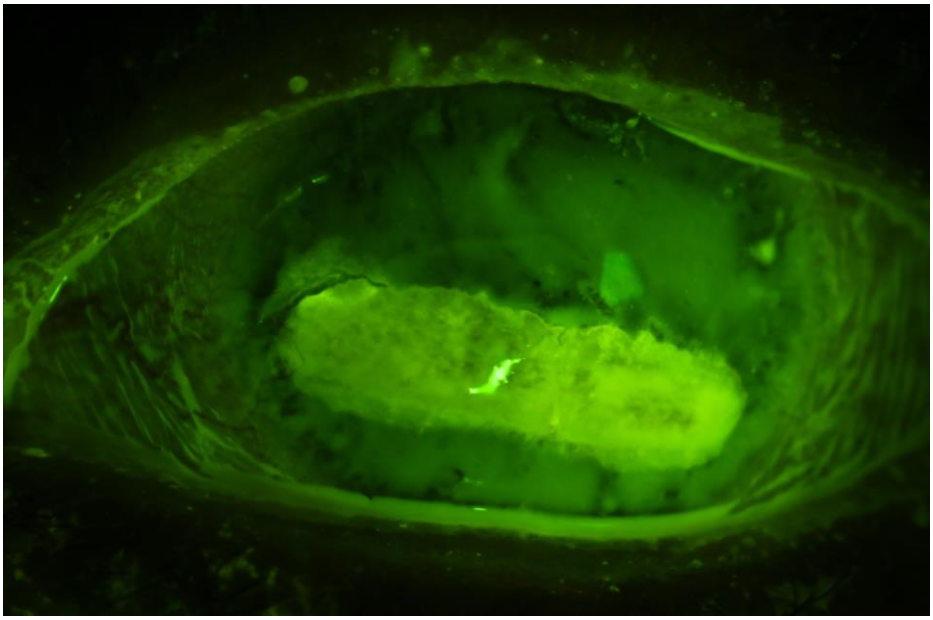

*Figure 4 Left eye with persistent corneal calcification without corneal erosion preoperatively.*

To increase visual acuity and reduce the risk of recurring corneal erosion with minimal surgical trauma after corneal epithelium was finally intact a novel corneal implant (XENIA® corneal implant, Gebauer Medizintechnik GmbH, Germany) was used as a lamellar graft after lamellar keratectomy and chelation with topical ethylene-diamine-tetra-acetic acid (EDTA) on the left eye in August 2021.

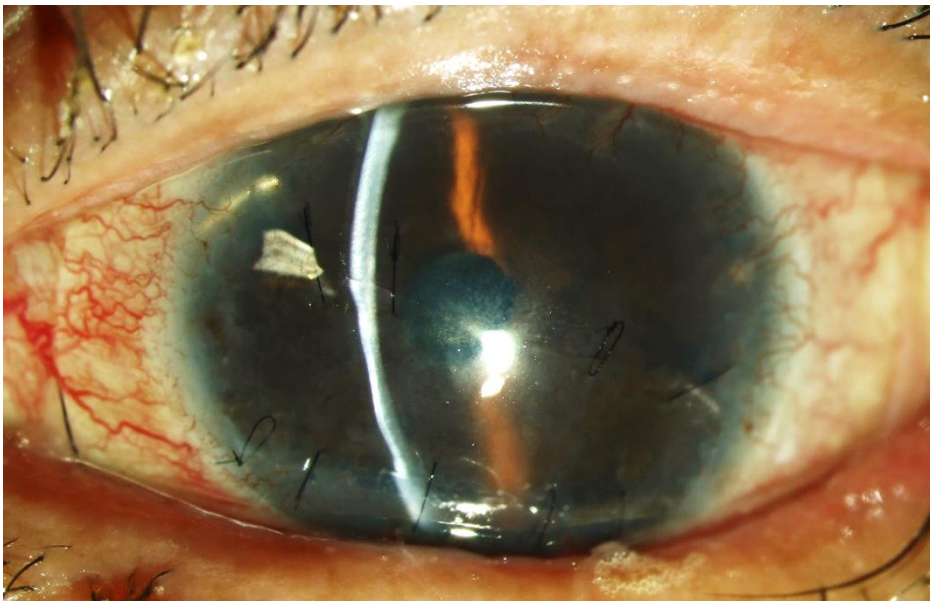

*Figure 5 Left eye with therapeutic contact lens seven days after surgery. Transplant without signs of rejection or infection.*

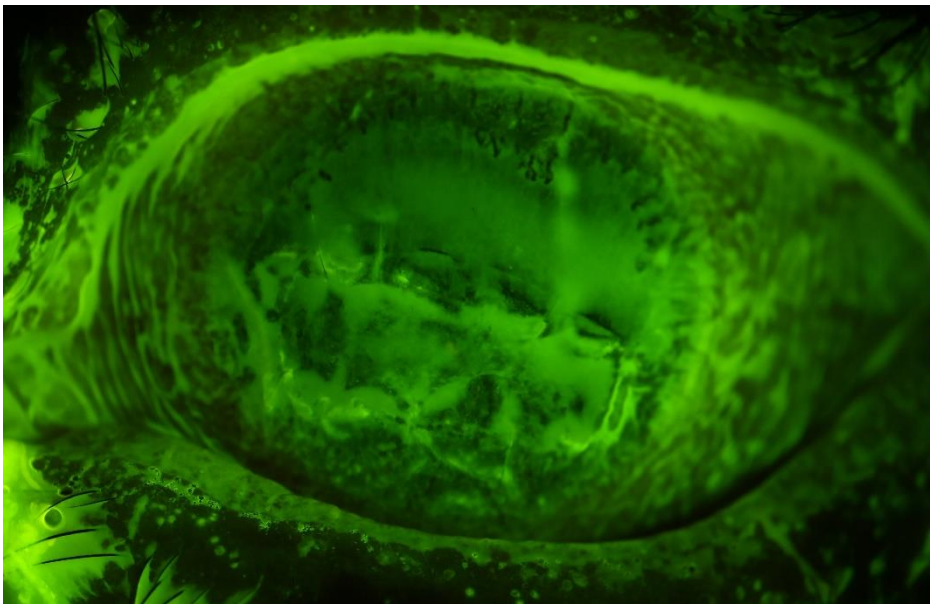

*Figure 6 Left eye seven days after surgery. No corneal erosion due to early epithelialisation.*

Postoperative follow ups revealed increased visual acuity and early epithelization after 6 days. The graft was in place without any signs of rejection or infection. Several small cavities filled with fluid in the interface between cornea and graft decreased and vanished over time (Fig. 7). Systemic immunomodulatory therapy could stabilize disease activity successfully. Moreover, ocular pain and irritation decreased noticeably with intense lubrification. OSDI was 32 and significantly improved compared to the initial examination. The IOP was regulated without pressure-lowering local therapy and the last corneal sutures were removed without complications 7 weeks after surgery. BSCVA of the left eye improved to 0.8 logMar.

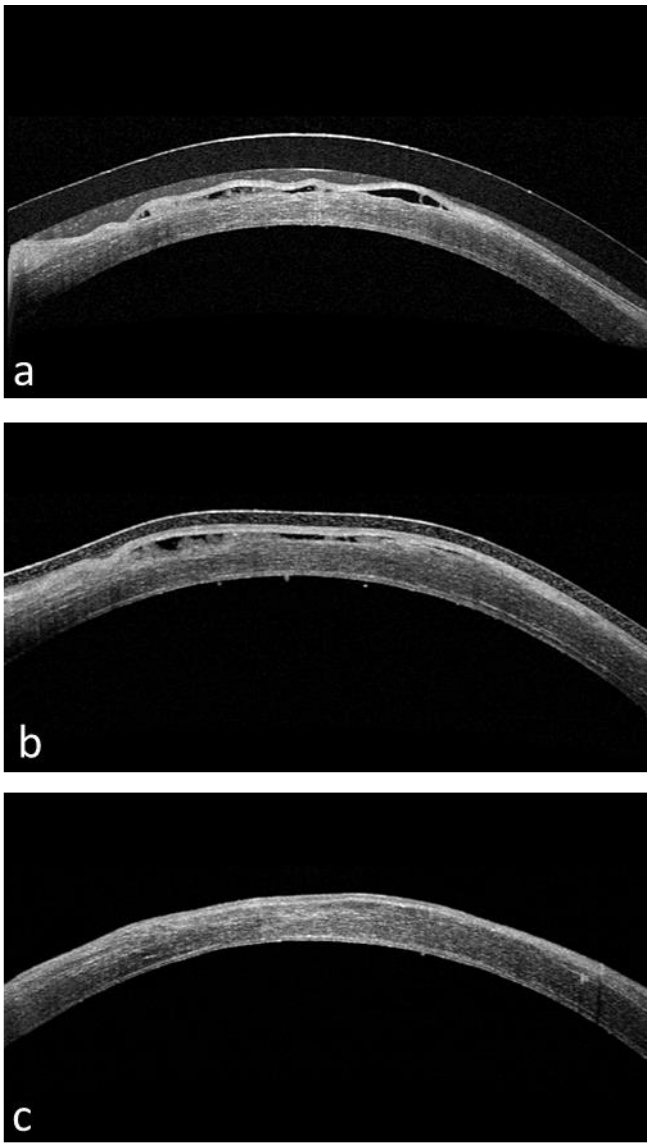


*Figure 7 Anterior segment spectral domain optical coherence tomography (SD-OCT) of the left eye. a: Fluid under uneven implant 6 days after surgery. b: Decreased fluid 2 weeks after surgery. c: No fluid left 1 month after surgery.*

Discussion:

In this case report we present the use of a novel medical device and emphasize the importance of several aspects of ocular surface disease and glaucoma.

First, the diagnosis and therapy of OCP. Definite diagnosis of MMP requires typical findings as well as histopathological and immunopathological examination of a conjunctival biopsy. The record of linear hyperfluorescence in direct immunofluorescence (DIF) results from linear deposits of immunoglobulin (Ig) G, IgA or complement factor C3 at the basement membrane zone. However, the diagnosis of OCP is often primarily based on clinical findings due to a high false negative rate of diagnostic biopsies. Although there is a variable sensitivity, conjunctival biopsy remains the gold standard. Therefore, it has recently been discussed to emphasize the

importance of DIF negative ocular only MMP. Since early diagnosis and treatment are essential to prevent further complications, the diagnostic dilemma after negative DIF remains a crucial aspect in patients with clinical MMP. It has previously been shown that half of the patients with ocular only MMP have intermittent or repeatedly negative DIF. This could often lead to inadequate topical therapy rather than systemic immunomodulatory treatment due to a delayed or false diagnosis. The reported case emphasizes the clinical importance of DIF negative ocular MMP in favour of patients' treatment decisions and successful disease management. (1, 5-9).

Secondly, the relevance of careful decision making regarding topical treatment in patients with glaucoma and ocular surface disease is emphasized. Topical anti-glaucomatous therapy deteriorates the mucosal changes. As it has been described before, patients with ocular inflammation and corneal erosion are at higher risk for developing band keratopathy and stromal calcification (3), which could contribute to additional loss of vision and higher disease burden. Especially corneal ulcerations seem to increase the incidence of stromal calcification, which might not be available for chelation with EDTA or phototherapeutic keratectomy (PTK) and therefore require extended surgical procedures such as penetrating or lamellar keratoplasty. Since these involve higher surgical trauma and risk, it is mandatory to evaluate the best intervention individually for every patient. Although phosphate associated calcification is still extremely rare, to prevent this cascade, topical medication for patients with several ophthalmic diseases including glaucoma and DED should be prescribed cautiously as it is known that topical steroids and intraocular pressure (IOP) reducing drops are often phosphate- or preservative-containing. (4, 10)

Thirdly, we want to introduce and elucidate the use of the XENIA® corneal implant as a corneal graft and possible future surgical alternative for corneal ulcer repair and to prevent increased surgical trauma. In contrast to amniotic membrane the corneal graft is optically clear but lacks trophic factors. Prior to surgery the implant undergoes biochemical decellularization to reduce postoperative rejection. The implant consists of porcine corneal collagen and was customized for our patient in size and thickness. The lenticule is firm and less flexible than human corneal donor tissue due to a crosslinking process during implant preparation, but it could be easily secured with sutures in the resulting wound after keratectomy. The unpredictable intraoperative change in corneal thickness after keratectomy limits the balancing of postoperative astigmatism. As early epithelialization is required for best results preoperative disease control was necessary.

Conclusion:

Given the remarkable course of our patient we emphasize the importance of interdisciplinary care and treatment management especially in patients with DIF negative ocular only MMP.

Although rare, corneal calcification due to phosphate containing topical medication should be kept in mind. Especially patients with multiple ocular diseases such as glaucoma and ocular surface disease often present physicians with the challenge of an optimized and individualised treatment.

The combination of minimally invasive glaucoma surgery and the implantation of optically sophisticated biomaterials under good systemic anti-inflammatory control has allowed control of the disease and partial improvement of visual performance early after the surgical procedures. Nevertheless, this therapeutic option needs further investigation.

References


1. Branisteanu DC, Stoleriu G, Branisteanu DE, Boda D, Branisteanu CI, Maranduca MA, et al. Ocular cicatricial pemphigoid. Experimental and Therapeutic Medicine. 2020;20(4):3379-82.
2. Chang JH, McCluskey PJ. Ocular cicatricial pemphigoid: manifestations and management. Current allergy and asthma reports. 2005;5(4):333-8.
3. Schlötzer-Schrehardt U, Zagórski Z, Holbach LM, Hofmann-Rummelt C, Naumann GO. Corneal stromal calcification after topical steroid-phosphate therapy. Archives of Ophthalmology. 1999;117(10):1414-8.
4. Popiela MZ, Hawksworth N. Corneal calcification and phosphates: do you need to prescribe phosphate free? Journal of ocular pharmacology and therapeutics. 2014;30(10):800-2.
5. Ong HS, Setterfield JF, Minassian DC, Dart JK, Booth D, Reid E, et al. Mucous membrane pemphigoid with ocular involvement: the clinical phenotype and its relationship to direct immunofluorescence findings. Ophthalmology. 2018;125(4):496-504.
6. Mondino BJ, Brown SI. Ocular cicatricial pemphigoid. Ophthalmology. 1981;88(2):95-100.
7. Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Archives of dermatology. 2002;138(3):370-9.
8. Dart JK. The 2016 Bowman Lecture Conjunctival curses: scarring conjunctivitis 30 years on. Eye. 2017;31(2):301-32.
9. Rashid H, Lamberts A, Borradori L, Alberti-Violetti S, Barry R, Caproni M, et al. European guidelines (S3) on diagnosis and management of mucous membrane pemphigoid, initiated by the European Academy of Dermatology and Venereology–Part I. Journal of the European Academy of Dermatology and Venereology. 2021;35(9):1750-64.
10. Jhanji V, Rapuano CJ, Vajpayee RB. Corneal calcific band keratopathy. Current opinion in ophthalmology. 2011;22(4):283-9.

Abbreviations

| | |
|---|---|
| AMA | antimitochondrial antibody |
| BSCVA | best-spectacle corrected visual acuity |
| BP | bullous pemphigoid |
| EDTA | ethylene-diamine-tetra-acetic acid |
| DED | dry eye disease |
| DIF | direct immunofluorescence |
| Ig | immunoglobulin |
| IOP | intraocular pressure |
| MMP | mucous membrane pemphigoid |
| MIGS | minimally invasive glaucoma surgery |
| OCP | ocular cicatricial pemphigoid |
| POAG | primary open angle glaucoma |
| PTK | phototherapeutic keratectomy |