·Clinical Research·

Clinical features and *in vivo* confocal microscopy assessment in 12 patients with ocular cicatricial pemphigoid

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Abstract

• **AIM: To describe the clinical features and microstructural characteristics assessed by *in vivo* confocal microscopy (IVCM) in patients with ocular cicatricial pemphigoid (OCP).**

• **METHODS: A descriptive, uncontrolled case series study. Patients diagnosed with OCP were examined by clinical history, slit-lamp biomicroscopy features and IVCM images. The results of direct immunofluorescence (DIF) biopsies and indirect immunofluorescence (IIF) were also recorded. Local and systemic immunosuppressive therapy were administered and adjusted according to response.**

• **RESULTS: A total of 12 consecutive OCP patients (7 male, 5 female; mean age 60.42±10.39y) were recruited. All patients exhibited bilateral progressive conjunctival scarring and recurrent chronic conjunctivitis was the most frequent clinical pattern. The mean duration of symptoms prior to diagnosis of OCP was 2.95±2.85y (range: 5mo to 10y). The Foster classification varied from stage I to IV and 20 eyes (83%) were within or greater than Foster stage Ⅲ on presentation. Two of the 12 patients (17%) demonstrated positive DIF; 3 of the 12 (25%) patients reported positive IIF. The mean duration of the follow-up period was 20.17±11.88mo (range: 6 to 48mo). IVCM showed variable degrees of abnormality in the conjuctiva-cornea and conjuctival scarring was detected in all the involved eyes. Corneal stromal cell activation and dendritic cell infiltration presented as ocular surface inflammation, ocular surface keratinization along with the destroyed Vogt palisades was noted in eyes with potential limbal stem cell deficiency. After treatment, remission of ocular surface inflammation was achieved in all the patients, 18 eyes (75%) remained stable, 6 eyes (25%) had recurrent conjunctivitis and cicatrization in 2 eyes (8%) was progressing.**

• **CONCLUSION: As an autoimmune disease, OCP manifests as variable degrees of clinical and laboratory abnormalities with both local and systemic immunosuppressive treatment playing important roles in disease therapy. IVCM can be as a valuable non-invasive technique to assess ocular surface changes in a cellular level with a potential value for providing diagnostic evidence and monitoring therapeutic effects during follow-up.**

• **KEYWORDS:** ocular cicatricial pemphigoid; ocular surface disease; *in vivo* confocal microscopy
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INTRODUCTION

Ocular cicatricial pemphigoid (OCP) is an autoimmune disease which clinically develops as progressive subepithelial conjunctival fibrosis and, if not diagnosed and treated early, it usually progresses to severe corneal scarring and neovascularization which can ultimately lead to blindness in up to one third of patients [1-2]. The reported incidence of OCP is about 1:60 000 to 1:12 000 ophthalmic cases or 0.7 per 1 000 000 populations[3-4], but this may be an underestimation since patients in their early stages are likely to be ignored at conventional slit-lamp microscopy examination[5-6].

The gold standard for the diagnosis of OCP is the linear deposition of any one or combination of immunoglobulin (Ig) G, IgA and/or complement component 3 (C3) along the basement membrane zone (BMZ) of the epithelial-subepithelial junction of the conjunctiva or extraocular mucosa using direct immunofluorescence (DIF) biopsies. In addition, a positive indirect immunofluorescence (IIF)

showing circulating anti-BMZ antibodies is considered as diagnostic evidence [7-8]. However, DIF biopsy is an invasive examination which cannot be performed multiple times and a negative DIF or IIF does not exclude OCP, thus, an alternative non-invasive technique needs to be explored.

For OCP patients who develop severe conjunctival inflammation or progressive fibrosis, the treatment strategy based on immunosuppressive therapy is indicated [9-10]. Since optimal regimens have not yet been established, therapeutic timely adjustment according to the ocular surface response is important during follow-up.

In vivo confocal microscopy (IVCM) is a clinical diagnostic technique that enables *in vivo* analysis of all layers of the ocular surface. Unlike conventional light microscopy, IVCM directs light to pass to the desired focal spot by using a pinhole aperture, which overcomes the problem of light scattering and provides clearer images at the cellular level. Some studies have indicated that IVCM can be valuable in non-intrusively detecting ocular surface microstructure in real time and *in situ* [11-12]. However, only few studies reported using IVCM in the assessment of OCP patients[13].

Therefore, the aim of this study was to describe the clinical features and microstructural characteristic changes assessed by IVCM in patients with OCP, and to explore its potential value for diagnosis and monitoring therapeutic effects during follow-up.

SUBJECTS AND METHODS

Subjects The study protocol was approved by the Institutional Review Board of Peking Union Medical College Hospital, and adhered to the tenets of the Declaration of Helsinki. Patients with diagnosis of OCP presenting attending our Cornea Clinic were prospectively enrolled. Diagnosis was based on demonstrating typical progressive conjunctival cicatrization in the absence of other causes of conjunctival scarring, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), chemical burn, *etc*.

Clinical Assessment On presentation, each eye was staged according to the Foster system under slit-lamp microscopy examination, with stage I being chronic conjunctivitis and sub-epithelial fibrosis, stage II fornix shortening, stage III symblepharon and corneal vascularization, and stage IV, ankyloblepharon and ocular surface keratinization as the end stage[14].

IVCM was performed by one experienced examiner using Heidelberg Retinal Tomograph 3 combined with the Rostock Cornea Module (RCM/HRT 3; Heidelberg Engineering GmbH, Dossenheim, Germany). Cornea and conjunctiva were scanned under topical anesthesia with 0.4% oxybuprocaine after applying one drop of 0.4% oxybuprocaine (Benoxil, Santen, Japan) as the coupling medium and putting a blepharostat in each eye. Proper alignment and positioning of the examined eye was adjusted with the help of a dedicated movable-target red fixation light for the contralateral eye. A digital camera placed on the side of the apparatus provided a lateral image of the examined eye. Corneal images were acquired from different depths, in both the center and the periphery, conjunctival images were also recorded for different depth and positions.

Laboratory Assessment All enrolled patients underwent a detailed clinical examination to determine extraocular mucosa involvement. All of the DIF biopsies and IIF results were recorded. DIF is a method for detecting the antibodies binding to target antigen. Biopsy slides from lesions were incubated with fluorescein isothiocyanate (FITC) conjugated murine anti-human antibodies. IIF is to detect pathogenic antibodies in serum of a patient. Normal human skin slides or monkey esophageal slides were incubated with a patient's serum and then incubate with FITC conjugated murine anti-human antibodies.

Treatment Local and systemic immunosuppressive therapy were administered for all patients after diagnosis and adjusted according to the individual response. In detail, oral corticosteroid (methylprednisolone, medrol, Pfizer Italia S.R.L.) at a dosage of 0.5 mg/(kg•d) was initiated and stepped down gradually after the remission of the ocular surface inflammation, the strategy was as following: reducing 4 mg/d every 2 to 3wk until reaching 20 mg/d, then reducing 4 mg/d every 2 to 3mo until reaching 2 mg/d or 4 mg/d and maintaining the dosage for 2 to 3y. If a poor response was recorded after 1wk treatment, which showed persistent ocular surface inflammation and progressive conjunctival scarring, or side effects of corticosteroid occurred, the dose of corticosteroid was increased to 1.5 times of original dosage and immunosuppressive drug (mycophenolate mofetil, Roche Pharmaceuticals Ltd., Shanghai, China) at a dosage of 1 g two times a day (*b.i.d.*) was added. Ocular treatment was prescribed according to ocular involvement and as per the following strategy: 0.1% fluorometholone (FML, Allergan Pharmaceuticals, Ireland) four times a day (*q.i.d.*) for eyes with mild inflammation, Foster stage I-II; 1% prednisolone (Pred Forte, Allergan Pharmaceuticals, Ireland) *q.i.d.* for eyes with severe inflammation, Foster stage III-IV. Of 0.05% cyclosporine (Restasis, Allergan Pharmaceuticals, Canada) *b.i.d.* for mild cases and 1% cyclosporine (Tiankeming, North China Pharmaceuticals, China) *b.i.d.* for severe cases and if side effects or non-response of topical corticosteroids occurs. 0.05% tacrolimus (FK506, Senju Pharmaceutical Co. Ltd.) three times a day (*t.i.d.*) was prescribed on eyes with poor tolerance and response to topical corticosteroids and cyclosporine. Preservative-free lubricants were given to irrigate the conjunctival sac and relieve dryness. If the eye developed persistent corneal epithelial defects, a contact lens was applied.

Table 1 The demographic and clinical data of 12 OCP cases

Case	Sex/age (a)	Duration	BCVA (pre&post)	FS	EI	Biopsy	DIF	IIF
1	M/55	6mo	OD: HM&HM OS: HM&HM	OD: IV OS: IV	Oral mucosa	Subepithelial blister on labium	P[1]	N
2	F/59	2a	OD: 20/25&20/25 OS: 20/25&20/20	OD: I OS: I	Oral mucosa	Subepithelial blister on gums	N	N
3	M/56	5a	OD: 20/33&20/25 OS: FC&20/500	OD: III OS: III	None	Cleft at BMZ of conjunctiva	P[1]	N
4	M/75	2a	OD: 20/67&20/50 OS: 20/50&20/50	OD: III OS: III	None	No typical findings	N	N
5	F/52	1.5a	OD: 20/33&20/67 OS: 20/200&HM	OD: III OS: III	Oral mucosa	No typical findings	N	N
6	M/70	1.5a	OD: 20/40&20/50 OS: 20/40&20/40	OD: III OS: III	None	No typical findings	N	N
7	M/42	5mo	OD: 20/33&20/20 LE: 20/25&20/20	OD: III OS: III	Oral mucosa	No typical findings	N	N
8	M/73	2a	OD: 20/50&20/33 OS: 20/33&20/33	OD: III OS: III	Oral mucosa	No typical findings	N	P[2]
9	F/73	4a	OD: 20/100&20/800 OS: 20/50&20/40	OD: III OS: II	Oral mucosa	Blister formation at BMZ of oral mucosa	N	N
10	M/52	6mo	OD: 20/25&20/25 OS: 20/25&20/40	OD: I OS: III	Oral mucosa	No typical findings	N	P[2]
11	F/55	10a	OD:20/200&20/67 OS: 20/200&20/100	OD: III OS: III	None	No typical findings	N	N
12	F/63	6a	OD: FC&20/500 OS: 20/67&20/67	OD: III OS: III	None	Subepithelial blister of conjunctiva	N	P[2]

BCVA (pre&post): Best-corrected visual acuity pre and post treatment (last visit); HM: Hand motion; FC: Finger counting; Duration: Time period of symptoms prior to diagnosis; FS: Foster stage; EI: Extraocular involvement; BMZ: Basement membrane zone; DIF: Direct immunofluorescence; IIF: Indirect immuno?uorescence; P[1]: Revealed the linear deposition of IgG, IgM and/or complement component 3 along the BMZ; P[2]: Revealed the linear deposition of IgG and/or complement component 3 along the BMZ; N: Negative; OD: Right eye; OS: Left eye.

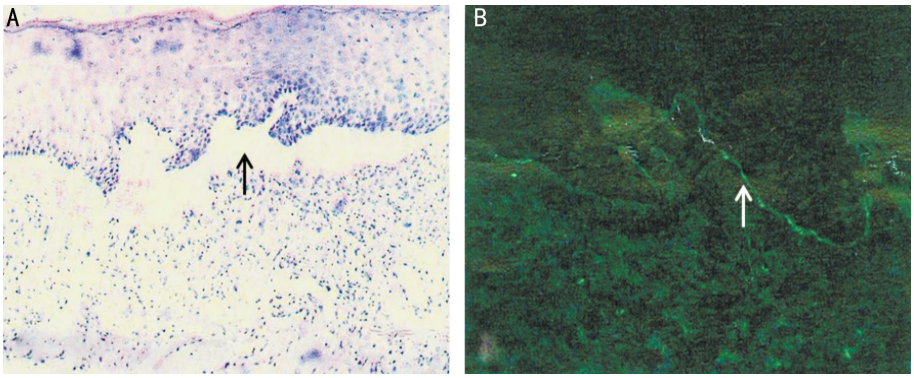

Figure 1 Biopsy and direct immunofluorescence findings A: Blister formation at the basal membrane zone (arrow, ×400) ; B: Linear immunoglobulin G deposition along the BMZ (arrow, ×400) .

RESULTS

Patients´ General Data Our series comprised 12 consecutive patients with OCP. Of these 12 patients, 7 were male and 5 were female, with a mean age of 60.42±10.39y (range: 42 to 75y) at enrollment. The mean duration of symptoms prior to diagnosis of OCP was 2.95±2.85y (range: 5mo to 10y). All patients exhibited bilateral progressive conjunctival scarring on presentation. The Foster stages varied from stage I to IV, 3 eyes presented Foster stage I, 1 eye with stage II, 18 eyes with stage III and 2 eyes with stage IV. A total of 5 patients showed abnormal mucosal biopsy, mainly blister formation at BMZ (Figure 1A); 2 of the 12 patients (17%) demonstrated positive DIF (Figure 1 B); 3 of 12 (25%) patients reported positive IIF. The mean duration of the follow-up period was 20.17±11.88mo (range: 6 to 48mo). The detailed demographic and clinical data are summarized in Table 1.

In total, recurrent conjunctivitis with subepithelial fibrosis was the most common initial symptom and clinical pattern. Within the 24 examined, 17 eyes (71%) presented moderate to severe dry eye, 12 eyes (50%) had different degrees of corneal neovascularization, and corneal conjunctivilazation was noted in 4 eyes (17%). Fornix foreshortening and symblepharon were typical phenotypes in the recruited OCP patients. There was no past history of systematic immune disease in any cases. Figure 2 shows the main clinical manifestations of the OCP patients in this study.

***In vivo* Confocal Microscopy Assessment** Overall, IVCM showed variable degrees of abnormality in the conjuctiva-cornea. Subepithelial conjunctival fibrosis was detectable in all of the studied eyes at the first visit. Inflammatory cells and dendritic cell infiltration revealed ocular surface inflammation, ocular surface keratinization along with the destroyed Vogt palisades indicated potential

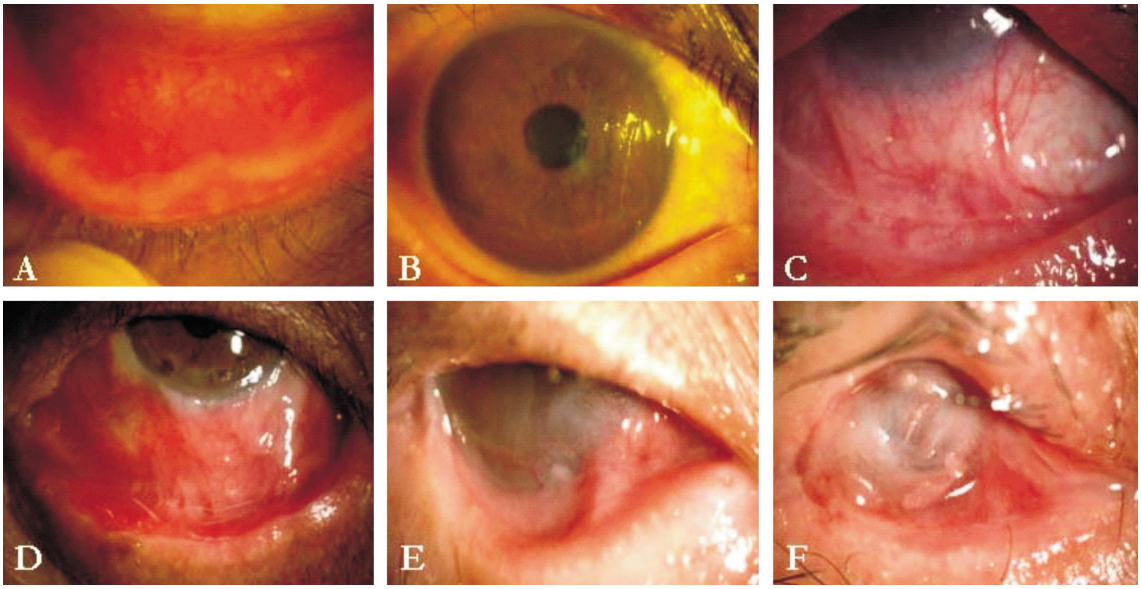

Figure 2 Slit-lamp microscopy images of the ocular surface of the patients with OCP A: Conjunctivitis (case 2, left eye); B: Dry eye (case 10, right eye); C: Subepithelial fibrosis (case 4, right eye); D: Fornix foreshortening (case 6, left eye); E: Symblepharon with corneal neovascularization (case 9, right eye); F: Total limbal stem cell deficiency with corneal conjunctivilazation (case 1, right eye).

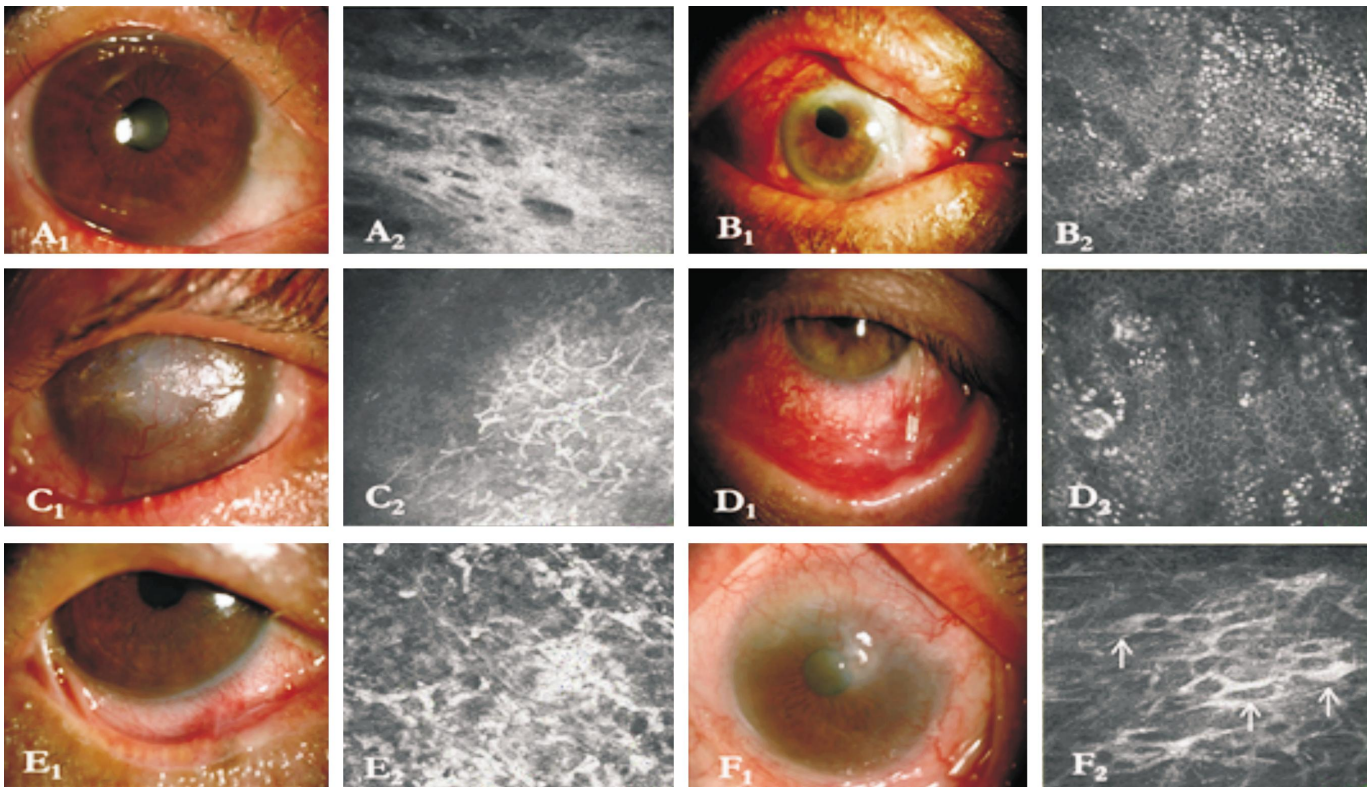

Figure 3 Slit-lamp microscopy images and IVCM images of the patients with OCP $A_{1\text{-}2}$: Conjunctival fibrosis (case 5, right eye); $B_{1\text{-}2}$): Inflammatory cells infiltration in the corneal epithelium (case 8, right eye); $C_{1\text{-}2}$: Dendritic cells infiltration in the corneal stroma (case 5, left eye); $D_{1\text{-}2}$: Destroyed Vogt palisades in the corneal limbus (case 10, left eye); $E_{1\text{-}2}$: Activated keratocytes in the corneal stroma (case 5, right eye); $F_{1\text{-}2}$: Membrane bridge-like structures in the corneal stroma (arrow) (case 4, left eye). Bar=50 μm.

limbal stem cell deficiency; membrane bridge-like structures (MBS) between activated keratocytes were seen in 9 cases (17 eyes), and the amount of MBS seems positively correlated with the severity of inflammation and the duration of ocular symptoms. Figure 3 shows the IVCM images of the ocular surface of the OCP patients in this study. Several eyes showed clear corneas at slit-lamp examination however enlarged and highly reflective corneal epithelial cells with inflammatory cells infiltration and activated heteromorphic keratocytes were visible on IVCM. These findings indicate a potential activation of the immune system of the cornea (Figure 4). After therapy, remarkable improvement was detected using IVCM, including reduced reflectivity of corneal epithelial cells and decreased activation of stromal

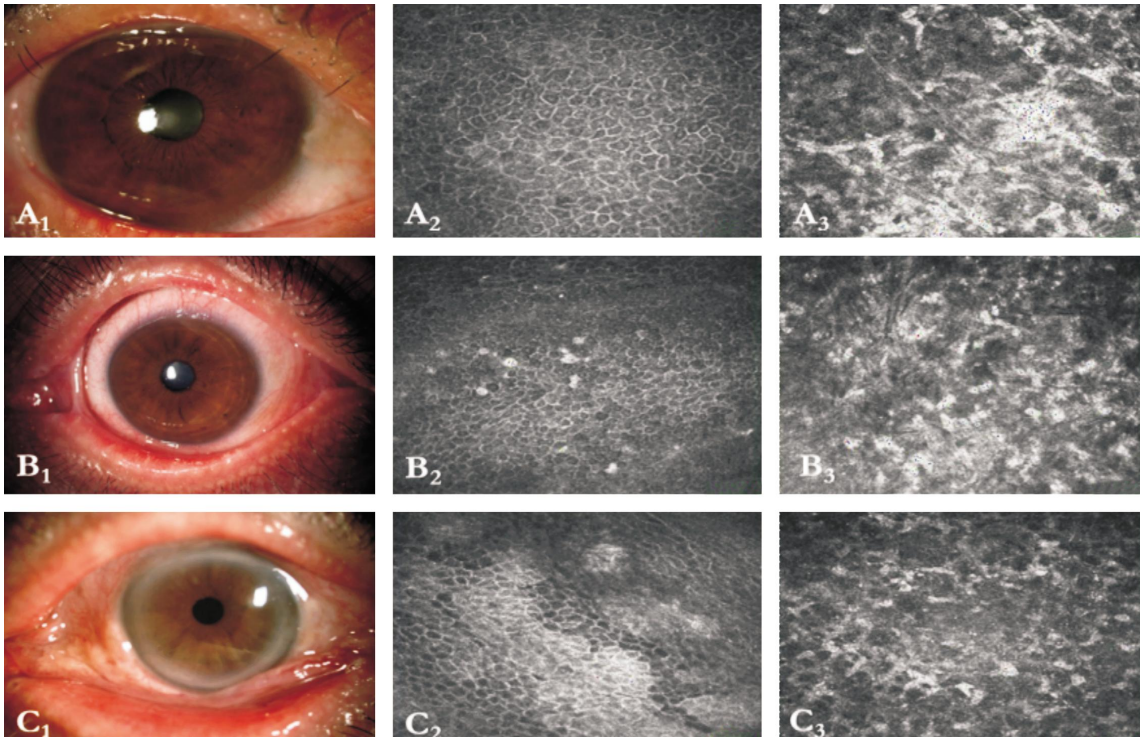

Figure 4 The abnormalities noted in the transparent corneas by IVCM A_{1-3}, B_{1-3} and C_{1-3} show the right eye of case 5, the left eye of case 7 and the left eye of case 8, respectively. Note the enlarged and highly reflective corneal epithelial cells with inflammatory cells infiltration (A_2, B_2, C_2) and heteromorphic activated keratocytes (A_3, B_3, C_3). Bar=50 μm.

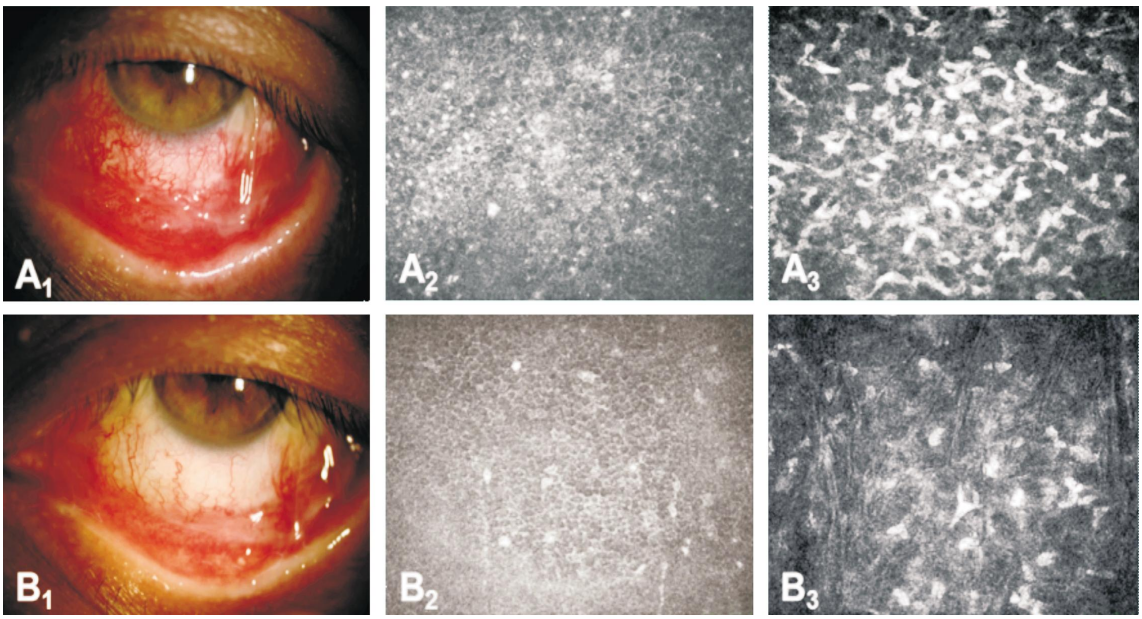

Figure 5 A comparison before and after immunosuppressive treatment on the left eye of case 10 After treatment, remarkable improvement was noted at slit lamp examination compared to that of before treatment (B_1 versus A_1), accompanied with detectable improvement using IVCM, including reduced reflectivity of corneal epithelial cells (B_2 versus A_2) and decreased activation of stromal keratocytes (B_3 versus A_3). A_{1-3}: Before treatment; B_{1-3}: After treatment. Bar=50 μm.

keratocytes (Figure 5), even when only mild changes of the ocular surface was visible under slit-lamp examination (Figure 6).

Outcome After the immunosuppressive treatment described above, remission of ocular surface inflammation was achieved in all the patients. A total of 18 eyes (75%) remained stable, 6 eyes (25%) presented recurrent conjunctivitis, cicatrization was progressing in 2 eyes (8%). Two eyes underwent amniotic membrane transplant and 1 eye underwent oral mucosal graft transplant for the reconstruction of ocular surface due to severe symblepharon or ankyloblepharon.

DISCUSSION

There is a consensus that, for patients with OCP, early diagnosis is crucial for prompt treatment to prevent disease related complications, especially blinding sequelae [15]. DIF

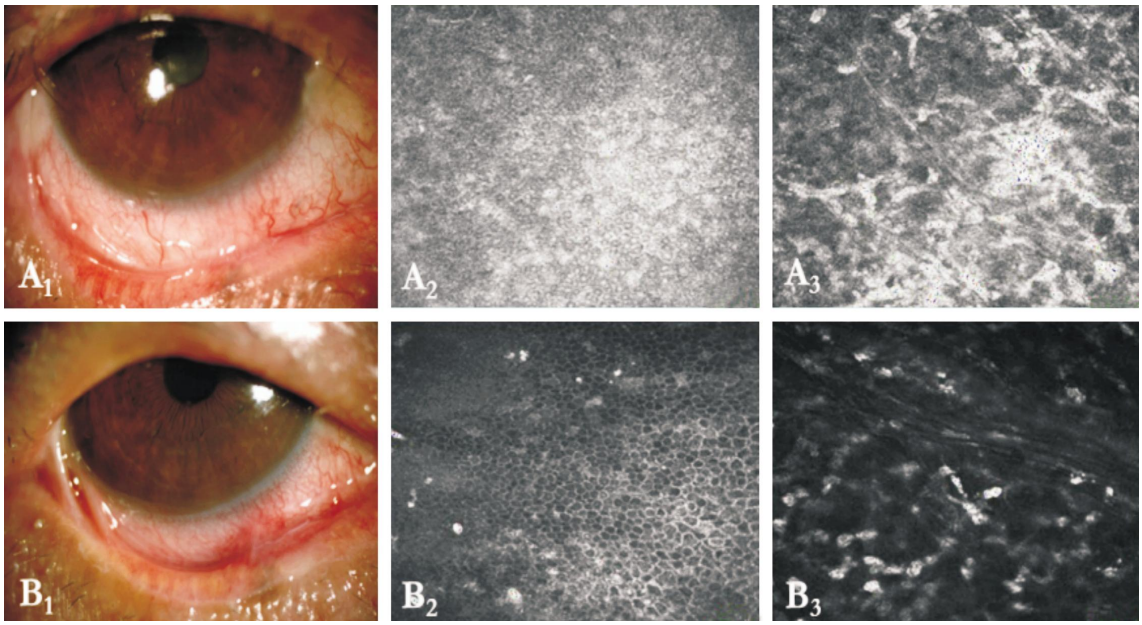

Figure 6 A comparison before and after immunosuppressive treatment on the right eye of case 5 Although no obvious change were noted at slit lamp examination, great improvements were detected by IVCM. A_{1-3}: Before treatment. Slit-lamp microscopy images (A_1). IVCM images note highly reflective cytoplasm and nuclei and obscure cell boundary in corneal basal cells (A_2) and heteromorphic activated stromal keratocytes (A_3). B_{1-3}: After treatment. Slit-lamp microscopy images (B_1). IVCM images showing reduced high reflectivity of basal cells (B_2) and quiet stromal keratocytes (B_3). Bar=50 μm.

and IIF results are considered to be highly reliable evidence for the diagnosis of OCP, however, the accuracy have not yet reached clinically satisfactory levels. The rate of positive DIF varied in the literature from 20% to 67%, and IIF is less sensitive for patients with OCP affecting the eyes alone[16-17]. In our study, the positive rates of DIF and IIF were 17% and 25% respectively. We made the diagnoses based on clinical manifestations, principally recurrent ocular surface inflammation and progressive conjunctival scarring instead of DIF and IIF results, this diagnostic criterion has also been used in multiple studies [6,15,18]. Since the initial symptoms of OCP are non-specific and easily misdiagnosed, the mean duration of symptoms prior to diagnosis of OCP in our study was 2.95 ±2.85y and the Foster classification for 18 eyes (75%) were within or greater than stage Ⅲ on presentation. So, we agree that the ophthalmologist should be aware of the possibility of underlying OCP in cases of chronic, recurrent conjunctivitis, especially when there is evidence of subepithelial scarring, and also in cases with entropion, including those without a cicatricial component [2,19-20].

As a systemic autoimmune disease with the possibility of blindness, the treatment strategy for OCP is currently based on systemic and local immunosuppressive therapy according to the clinical severity and disease progression [9,21]. Many different regimens, including corticosteroid, cyclophosphamide, anti-tumor necrosis factor therapy and intravenous immunoglobulin have been reported with varying efficacy[18,22-24]. Based upon the published literatures and our clinical experience, oral methylprednisolone and topical corticosteroids were administered as the initial treatment and this was reduced gradually according to clinical manifestations, with appropriate monitoring for side effects. Oral mycophenolate mofetil or cyclosporine eyedrops were added when poor responses were observed or side effects occurred. Generally, the immunosuppressive therapy was continued for approximately two years. The patients in our study achieved satisfactory clinical outcomes which showed the efficacy of immunosuppressive therapy for OCP.

The advantage of IVCM in our study consists of three aspects. First, it helps to provide supporting evidence for the diagnosis of OCP, such as subepithelial conjunctival fibrosis, which is considered to be a typical feature for OCP involved eyes in the absence of other diseases presenting conjunctival scarring, such as Stevens-Johnson syndrome (SJS), chemical burn, *etc* [2,13]. Besides conjunctival fibrosis, IVCM reveals clues about dry eye or limbal stem cell deficiency, including dendritic cell infiltration and abnormality of the Vogt palisades in the limbus, which have been addressed in other ocular surface diseases [25-26]. Second, IVCM provides microstructural abnormalities of the transparent cornea, including high reflectivity of corneal epithelial cells with inflammatory cells infiltration and remarkable keratocytes activation, which encouraged the administering of immunosuppressive treatment for OCP patients, particularly when the lesions are not visible under conventional slit-lamp examination. Third, IVCM allows disease course follow-up at a cellular level, again, the ocular surface changes were visible earlier on IVCM compared to slit-lamp examination.

In addition, as an important feature in cell-cell communication during inflammation [27-28], MBS on IVCM seems positively correlated to the severity of inflammation and the duration of the disease in our study, which also serves as an important clue in disease follow up.

The main limitations of our study are that, 1) the sample size was small due to the low incidence of OCP, although it reflected the features of the OCP-affected patients presenting to our clinical center for over 4y, it made unfeasible to quantify the IVCM images for evaluating the therapeutic effects with treatment. Further case-control study are strongly needed to statistically analyze the IVCM images and explore their correlations with clinical manifestations during follow-up, which can strengthen the above advantages of IVCM on the diagnosis and therapeutic follow-up monitoring; 2) the positive rates of DIF and IIF were relatively low in our study, considering repeat biopsy may increase disease activity [2,15], diagnosis was based on demonstrating typical progressive conjunctival cicatrization in the absence of other causes of conjunctival scarring. Although this clinical criteria is considered adequate in most cases, further efforts still need to be done to improve the positive yield of biopsies; 3) most of the cases in our study were in their late disease stages, since the early immunoinflammatory phase would be expected to respond to immunosuppression, while the late phase may not [29], therefore, in order to standardize the therapy effect and reduce the side effects of immunosuppression, we used systemic corticosteroids at a dosage of 0.5 mg/ (kg•d) as the initial treatment instead of 1-1.5 mg/ (kg •d) or other immunosuppressive drugs indicated by other studies[9,30]. The results manifested that low dose systemic steroids combined with local steroids achieved satisfactory outcomes, however, comparative studies still should be carried out to confirm our treatment strategy.

In conclusion, OCP is a systemic progressive cicatrising autoimmune disease which can cause blindness due to its non-specific nature and initial clinical manifestations, both local and systemic immunosuppressive treatments play important roles in preventing disease related complications. As a quick and non-invasive technique, IVCM is a valuable supplementation to slit-lamp examination for OCP eyes by providing microstructural changes of the ocular surface, further studies are needed to explore the potential value in the diagnosis and monitoring therapeutic effects for OCP patients.

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