

Atopy in Patients With Ocular Cicatricial Pemphigoid

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Purpose: To evaluate the presence of atopy in patients with ocular cicatricial pemphigoid (OCP).

Method: Patient encounters between August 2005 and November 2016 at the Massachusetts Eye Research and Surgery Institute (MERSI) were searched to identify those with biopsy-proven OCP who had concurrent evidence of atopy.

Results: There were 230 patients with biopsy-proven OCP. Thirty-three of them were found to have clinical symptoms of atopy (asthma, hay fever, and eczema) and of these, 23 had evidence of atopy in their conjunctival biopsy specimens. All patients were administered immunomodulatory therapy for treatment of their OCP with 20 patients requiring additional antiallergy treatment to control residual atopic ocular symptoms. Among patients who used antiallergy medications, 80% showed improvement in residual symptoms. Rituximab and/or intravenous immunoglobulin is a preferred OCP medication for patients with OCP with some evidence of atopy.

Conclusions: Clinicians should consider the coexistence of atopy in patients with OCP, especially in those with persistent symptoms after initiation of immunomodulatory therapy.

Key Words: atopy, ocular cicatricial pemphigoid, rituximab, IVIG, asthma, hay fever, eczema

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Mucous membrane pemphigoid (MMP) is a chronic progressive autoimmune disease, which presents with blisters of the skin and mucous membranes of the nasal cavity, oral cavity, genitalia, and eye. MMP is potentially lethal and requires immunosuppressive therapy (IMT). When limited to the eye, MMP is called ocular cicatricial pemphigoid (OCP). Blisters develop from subepithelial tissue through disruption of the adhesions between the conjunctival epithelium and the subepithelium. This results in scarring conjunctivitis that can progress to involve the cornea and lead to blindness.¹ Direct immunofluorescence showing continuous linear deposition of autoantibodies and complement components in the basement membrane zone of conjunctival specimens is required to make the diagnosis. The exact pathogenic mechanism of OCP remains unclear, but the $\beta 4$ subunit of $\alpha 6 \beta 4$ integrin of hemidesmosomes in the lamina lucida of the conjunctival basement membrane is believed to be the target autoantigen. Prompt treatment is important to prevent vision loss.²

Allergies are extremely common in the general population. Allergic conjunctivitis presents with bilateral itching, edema, lacrimation, irritation, chemosis, and vasodilation. Atopic keratoconjunctivitis (AKC) represents the extreme end of the spectrum of allergic conjunctivitis and is characterized by chronic inflammation of eyelids and conjunctiva, which can result in cicatricial conjunctivitis, ectropion of the lower lid, and corneal involvement. AKC is the result of type I and IV hypersensitivity with IgE-mediated mast cell activation and subsequent eosinophil recruitment.^{3,4} It is associated with systemic manifestations such as eczema, atopic dermatitis, and asthma.⁴

OCP and AKC have common ocular findings including conjunctival fibrosis and scarring as well as corneal epitheliopathy. In this study, the frequency and characteristics of atopy in patients with biopsy-proven OCP are explored.

METHODS

Institutional review board approval was obtained for a retrospective chart review at the Massachusetts Eye Research and Surgery Institute (MERSI). Patients with biopsy-proven OCP between August 2005 and November 2016 were identified. Direct immunofluorescence testing for autoantibodies and complement components revealed linear staining of the epithelial basement membrane zone of conjunctiva in these patients. Medical records were reviewed to identify those with clinical features of atopy such as a history of eczema, asthma, hay fever, or allergic rhinitis. Conjunctival pathology specimens were additionally reviewed to look for significant numbers of IgE-positive cells,

TABLE 1A: Information of the ocular cicatricial pemphigoid (OCP) patients with atopya: Histological, clinical and blood findings suggestive of atopy in biopsy-proven OCP patients.

	Conjunctival Biopsy Findings	Clinical Symptoms	Additional Lab Investigation
Case 1	IgE, mast cell degranulation	History of atopy and hay fever	—
Case 2	IgE	History of atopy, eczema	—
Case 3	IgE, mast cell in the epithelium	History of atopy	—
Case 4	IgE	History of atopy, eczema, and dry itchy skin	—
Case 5	IgE	History of atopy, hay fever, rhinitis	Increased level of IgE in the serum
Case 6	IgE	Allergic	—
Case 7	IgE	Hay fever	MMP
Case 8	IgE	History of atopy	Increased level of IgE in the serum
Case 9	IgE	Allergic conjunctivitis	
Case 10	IgE, eosinophil	Eczema, asthma	
Case 11	Mast cell in the epithelium	Atopy was suggested according to biopsy, allergic conjunctivitis	
Case 12	IgE, eosinophil	Asthma, seasonal/contact/environmental allergies, allergic conjunctivitis	Increased eosinophil in the serum
Case 13	IgE, eosinophil, mast cell	Atopy was suggested according to biopsy	Corneal ulcer and perforation in 1 eye
Case 14	IgE	Atopy, asthma	
Case 15	IgE	Multiple allergies, hay fever	Increased level of IgE in the serum
Case 16	IgE, eosinophil	Atopy suggested according to biopsy and laboratory tests	Increased level of IgE in the serum
Case 17	IgE	Atopy, asthma, severe seasonal allergy	
Case 18	IgE	Atopy, asthma, seasonal allergy	
Case 19		Atopy	
Case 20	—	Asthma, seasonal allergy	
Case 21		Perennial allergy	Increased level of serum eosinophil
Case 22	IgE	Eczema, asthma	
Case 23	IgE, mast cell in the epithelium	Atopy	
Case 24	IgE, eosinophil, mast cell in the epithelium	Atopy	MMP
Case 25	Mast cell in the epithelium	Chronic hay fever, severe allergy	Increased level of IgE in the serum
Case 26	IgE	Allergy proved by a skin test	
Case 27		Atopy	
Case 28		Severe eczema	Increased level of eosinophil in the serum
Case 29		Hay fever, multiple allergies	
Case 30		Allergic conjunctivitis	
Case 31		Multiple allergies including food allergy	
Case 32		Multiple allergies including seasonal and environmental allergies	
Case 33		Allergic conjunctivitis, seasonal allergy	

TABLE 1B: Residual symptoms despite OCP medication in addition to treatments delivered to target atopic disease, months of follow up and subsequent response.

	Residual Symptoms Despite Treatment With OCP Medications	Antiallergic Medication	Follow-up (mo)	Response to Antiallergic
Case 1	No data	—	Lost to follow-up	No data
Case 2	No data	—	Lost to follow-up	No data
Case 3	Chronic conjunctival redness and irritation, partial response to rituximab infusion	—	10	NA
Case 4	Irritation and itching while on MTX, mycophenolate mofetil, and rituximab	Topical antihistamine	32	Yes
Case 5	Redness, MTX was suggested	—	Lost to follow-up	No data
Case 6	Itching, tearing, redness, irritation, failed mycophenolate mofetil, MTX, azathioprine	Topical cyclosporine	26	No, residual symptoms continues
Case 7	Itching, failed dapsone, and mycophenolate mofetil, good response to IVIG, stopped IMT	Topical antihistamine	44	Yes
Case 8	Eye swollen	—	Lost to follow-up	No data
Case 9	Itching while on MTX	Topical antihistamine	40	Yes
Case 10	Redness, irritation, discharge, improved on rituximab and IVIG	Oral cyclosporine	44	Yes, although with significant vision loss in the left eye due to stromal scarring

TABLE 1B: (Continued) Residual symptoms despite OCP medication in addition to treatments delivered to target atopic disease, months of follow up and subsequent response.

Residual Symptoms Despite Treatment With OCP Medications		Antiallergic Medication	Follow-up (mo)	Response to Antiallergic
Case 11	Irritation while on MTX	Topical antihistamine	44	yes
Case 12	Irritation, partial response to rituximab and IVIG	Systemic and topical antihistamine	22	yes
Case 13	Irritation, still active on rituximab and IVIG, systemic and topical steroid	No	40	NA (progressed to corneal ulcer and perforation OS)
Case 14	Improved on MTX	No	16	NA
Case 15	Blurry vision, symptomatic on MTX	Systemic and topical antihistamine	31	Yes
Case 16	Irritation and redness while on MTX	Topical antihistamine	47	No, progressed to advanced disease and vision loss of both eyes
Case 17	Redness while on MTX	No	26	NA
Case 18	Itching, off IMT	No	10	NA
Case 19	Irritation while on mycophenolate mofetil and topical corticosteroid	Oral and topical antihistamine	82	yes
Case 20	Redness, chemosis while on MTX	Topical antihistamine	82	Yes
Case 21	Redness, partial response to IVIG	Topical antihistamine	96	Yes
Case 22	Redness, partial response to MTX	Oral cyclosporine, topical antihistamine	42	No, progressed to legal blindness OU
Case 23	Redness, pain, resistant to mycophenolate mofetil	—	Lost to follow-up	No data
Case 24	Dryness, redness, irritation, failed mycophenolate mofetil, rituximab, IVIG, cytarabine, corticosteroid	Oral cyclosporine, topical antihistamine	34	No, progressed to legal blindness OU
Case 25	Dryness, failed mycophenolate mofetil, partial response to rituximab and IVIG	Oral cyclosporine and topical antihistamine	27	yes
Case 26	No residual symptoms, improved on IVIG and prednisolone forte	No	19	NA
Case 27	Swelling and irritation while on MTX	Oral cyclosporine and switch to rituximab were suggested	Lost to follow-up	No data
Case 28	Redness, itchiness, irritation while on MTX	Tacrolimus ophthalmic ointment	6	Yes
Case 29	Irritation, redness, burning sensation while on MTX	Systemic antihistamine	16	Yes
Case 30	Itching while on MTX	Topical antihistamine	126	yes
Case 31	Redness, partial response to cyclophosphamide and IVIG	No	16	NA
Case 32	Lid edema, partial response to MTX	Allergy shots	9	Yes
Case 33	Itching, redness, mucous discharge, improved on mycophenolate mofetil, rituximab, IVIG, multiple flare-ups while on dapsone	Topical antihistamine	120	Yes

eosinophils, or mast cell degranulation in the conjunctival epithelium. Some patients underwent testing for peripheral blood eosinophilia and quantitative IgE serum levels to further investigate the possibility of atopy in equivocal cases. All biopsies were performed and reported in our center. Patients having clinical and/or pathologic features of atopy were included for further analysis.

All patients with biopsy-proven OCP who showed signs of disease activity or progression during follow-up were administered IMT based on a stepwise approach. Patients were prescribed methotrexate as the first agent. In cases of side effects or nonresponsiveness, the next medication used was mycophenolate mofetil or rituximab [$\pm$ intravenous immunoglobulin (IVIG)]. Historically, dapsone has a role in the treatment of OCP, and intravenous pulse therapy with cyclophosphamide was an option considered in our patients in recalcitrant cases.

Patients with concurrent atopic features who had partial or no response to IMT were sometimes started on

an antiallergy regimen. The medications used included low-dose topical steroids, topical, or oral antihistamines, and/or cyclosporine in addition to desensitization immunotherapy depending on the severity of allergic signs and symptoms. Ophthalmic tacrolimus ointment was used in 1 patient. Patients were typically administered olopatadine and a low potency topical steroid such as loteprednol etabonate. Depending on the severity of symptoms and availability of the medication (insurance approval), switching to rituximab and/or IVIG infusions was considered as well. Oral and topical corticosteroids were not considered as antiallergy medications because they are nonspecific and can treat the symptoms of both OCP and AKC.

RESULTS

A total of 230 patient charts with biopsy-proven OCP were reviewed. All patients were placed on IMT. Fourteen percent (33/230) had clinical evidence of atopy. Twenty three

of these had evidence of atopy on pathologic specimens. Although OCP was considered the dominant disease process in these patients, atopy seemed to play a significant role in their symptoms.

Mean age of patients with atopy was 63 years (range 32–86), and 70% ($n = 23$) were women. Two patients had MMP as well. Four patients were tested for quantitative serum IgE and were found to have elevated levels [404, 1375, 135, and 236 kU/L (normal ≤ 114 kU/L)]. Another 3 patients were tested for blood eosinophil levels and were found to have elevated values (15, 7.4, and 6.4, normal 0%–5%). A summary of the atopic features in these OCP patients in addition to treatments delivered to the target atopic disease and the subsequent response is included in Table 1.

Six of 33 patients with both OCP and atopy were lost to follow-up shortly after presentation. The mean follow-up duration among the 27 patients who had at least 6 months of follow-up was 41 months (range: 6–126). Of the 27 patients with follow-up, 20 (74%) were prescribed antiallergy medications including antihistamines (topical in 8 and systemic in 4), cyclosporine (topical in 1 and oral in 5), allergy shots (1), and topical tacrolimus (1) to address residual atopic symptoms while receiving IMT for OCP; 80% ($n = 16$) responded to these interventions. Recalcitrant disease and vision loss occurred in 5 patients, 1 of whom was not administered antiallergy medications.

Twelve of 27 patients received rituximab and/or IVIG as their OCP medication, with 9 (75%) showing signs of improvement (in 3 without adding antiallergic medications); however, 3 (1 of which did not receive antiallergic medications) progressed to blindness, despite switching to this more aggressive regimen (Fig. 1).

DISCUSSION

Both OCP and AKC are characterized by chronic cicatricial conjunctivitis and subconjunctival fibrosis, which result in fornix foreshortening, trichiasis, distichiasis, meibomian gland dysfunction, and ocular surface dryness. Patients complain of dry eye symptoms such as foreign body sensation, photophobia, lacrimation, pruritis, mucous discharge, and hyperemia. With progression, ocular findings evolve to include conjunctival fibrosis, entropion, trichiasis, and symblepharon.³ Pruritus, papillary hypertrophy, abundant mucoid discharge, cataract, keratoconus, and ectropion are more common in atopy.

Biopsy can help differentiate between the 2 entities. Deposition of autoantibodies and complement in the basement membrane zone is the hallmark of OCP. Infiltration of eosinophils and increases in mast cells, IgE, and goblet cells in the conjunctiva are more common in atopy, although they can be seen in both conditions. Eosinophils can also be seen in OCP, especially in the active phase of the disease.⁵ Mast cells play a role in chronic inflammation and are involved in the pathogenesis of both AKC and OCP.⁶

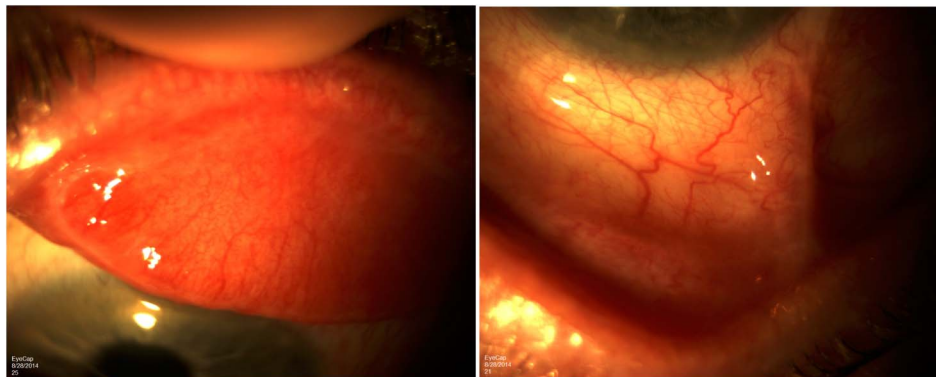
Histopathologically, mast cells are normally located in connective tissues such as the conjunctival stroma.⁷ Intense eye rubbing may lead to mast cell degranulation. Conjunctival eosinophilia can be seen in 7% to 15% of patients with external eye symptoms other than atopy. Blepharoconjunctivitis or conjunctivitis can cause up to a 4-fold chance of conjunctival eosinophilia.⁸ As a result, biopsy results alone may be misleading when considering the diagnosis of AKC and should be corresponded to clinical symptoms.

Therefore, in this study, the diagnosis of atopy was predominantly based on clinical features including severe

FIGURE 1. Case 28: a 60-year-old man presented with severe eczema and mild symblepharon, inferior tarsal conjunctival scar and foreshortening, subepithelial fibrosis, superficial punctate keratitis, inferior lower lid ectropion, and chemosis in the right eye. Eczema, blisters, and pale and featureless conjunctival edema were present in addition to eyelid thickening and tightening with trichiasis and madarosis. Despite severe atopic features, biopsy findings were compatible with OCP. Methotrexate was started. Tacrolimus ointment was added because of residual symptoms.



FIGURE 2. Case 25: a 72-year-old woman with biopsy-proven OCP and atopy. Giant papillary reaction of the upper tarsal conjunctiva suggestive of atopy as well as entropion, fornix foreshortening, subepithelial scarring and fibrosis, symblepharon, linear superior tarsus scarring, and later trichiasis. The patient achieved complete remission when oral cyclosporine and a topical antihistamine were added to rituximab and IVIG infusion.



chronic keratoconjunctivitis associated with the history of atopic features including atopic dermatitis and occasionally rhinitis and asthma³; however, increased eosinophils and mast cell infiltration of the conjunctival epithelium and substantia propria support a possible atopic component in the appropriate clinical context. Detection of a possible allergic component to OCP on conjunctival biopsy should be performed when clinical symptoms of allergy are present. This is especially important because allergy may not be present year-round, and if a biopsy is taken in the absence of active allergy, then a patient's poorly controlled symptoms may be misattributed to OCP flare or unremitting OCP.

Allergic symptoms may sometimes be incorrectly attributed to undertreated OCP. Commonly used immunosuppressives such as methotrexate, azathioprine, and mycophenolate mofetil are known to be effective for OCP but may not alleviate atopic symptoms. Holland et al noted the lack of a therapeutic response to topical cyclosporine in a small series of patients with OCP.⁹

Most patients with atopy required the addition of antiallergy medications to the IMT that was started for their OCP to help address their symptoms. Residual symptoms of itching, tearing, and redness were frequent in these patients after initiation of IMT. Trichiasis was unlikely to be a major factor in these persistent cases of ocular surface irritation because it was aggressively managed with frequent epilation or surgical correction.

Adding an antihistamine, and in severe cases oral cyclosporine, was helpful in making the eyes relatively symptom-free with improvement in the ocular surface in

most patients; however, antihistamines also run the risk of worsening ocular surface dryness. As such, addition of lubricating eye drops should be strongly considered to avoid deleterious secondary effects of dry eye. Mast cell stabilizing agents have weak antiinflammatory properties but are better options in this regard and safe for long-term use. Topical tacrolimus has potent antiinflammatory effects and is a preferred substitution for anti histamines.

Ten (30%) patients with a history of atopy and clinical signs of allergy in the absence of significant evidence of allergic changes on conjunctival pathologic specimens benefited from the antiallergic medication; 1 required oral cyclosporine in addition to IMT to control residual symptoms. Of note, 3 patients in this series had allergic conjunctivitis without clear confirmation of atopy. Five patients (of the 27 patients who had at least 6 months of follow-up) showed disease progression, despite all receiving IMT and 4 receiving antiallergy medications. The presence of atopic traits may pose patients at heightened risk of progression to advanced stages of OCP (especially if atopy goes untreated) and therapy resistance (Figs. 2, 3).

In cases of concurrent OCP and atopy, intravenous rituximab and/or IVIG may address both conditions. OCP can be a challenge to diagnosis and the coexistence of atopy, although infrequent, can further complicate management. This study found that 19% of patients with biopsy-proven OCP had atopic features. Although IMT is the mainstay of OCP treatment, dedicated treatment of atopy is important to help control ocular symptoms in a significant portion of patients with OCP. Treatment strategies for atopic eye disease are

FIGURE 3. Case 24: a 69-year-old woman with severe atopy and refractory biopsy-proven OCP. A, Presentation. B, Advanced disease. Patient trials of dapson, mycophenolate mofetil, IVIG, rituximab, cyclosporine, intravenous corticosteroid, local antihistamine, and intravenous cytarabine arabinoside have failed.



varied, with topical (or rarely systemic) steroids, mast cell stabilizers, and/or topical/systemic cyclosporine or tacrolimus. The patients presented in this study typically responded well to a simple and well-tolerated regimen of olopatadine and a low potency steroid. Clinicians should remain mindful of the possible concurrent existence of atopy in patients with OCP, especially in those who did not respond well to therapy and have residual symptoms or flare-ups. Such patients may benefit from the addition of antiallergy medications to their regimen before escalation of IMT.

REFERENCES

1. Queisi MM, Zein M, Lamba N, et al. Update on ocular cicatricial pemphigoid and emerging treatments. *Surv Ophthalmol*. 2016;61:314–317.
2. Kirzhner M, Jakobiec FA. Ocular cicatricial pemphigoid: a review of clinical features, immunopathology, differential diagnosis, and current management. *Semin Ophthalmol*. 2011;26:270–277.
3. Faraj HG, Hoang-Xuan T: Chronic cicatrizing conjunctivitis. *Curr Opin Ophthalmol*. 2001;12:250–257.
4. Ackerman S, Smith LM, Gomes PJ. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. *Ther Adv Chronic Dis*. 2016;7:52–67.
5. Letko E, Bhol K, Colon J, et al. Biology of interleukin-5 in ocular cicatricial pemphigoid. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:565–569.
6. Yao L, Baltatzis S, Zafirakis P, et al.: Human mast cell subtypes in conjunctiva of patients with atopic keratoconjunctivitis, ocular cicatricial pemphigoid and Stevens-Johnson syndrome. *Ocul Immunol Inflamm*. 2003;11:211–222.
7. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol*. 2010;125(suppl 2):S73–S80.
8. Kari O, Haahtela T. Conjunctival eosinophilia in atopic and non-atopic external eye symptoms. *Acta Ophthalmol*. 1992;70:335–340.
9. Holland EJ, Olsen TW, Ketcham JM, et al. Topical cyclosporin A in the treatment of anterior segment inflammatory disease. *Cornea*. 1993;12:413–419.