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Abuse of vasoconstrictive eyedrops mimicking an ocular pemphigoid

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PURPOSE. *To describe conjunctival histopathologic alterations induced by excessive chronic astringent use.*
METHODS. *Report of a case with clinical picture, epicutane test results, histologic workup of conjunctival biopsy using conventional staining, and immunohistochemical markers.*
RESULTS. *A 45-year-old man using a phenylephrine preparation hourly for years presented with grotesque eye redness, fornix shortening, and scarring of puncta lacrimalia. Direct and indirect immunofluorescence were negative for ocular pemphigoid. Histology revealed signs of chronic inflammation and neovascularization in the conjunctiva. Symptoms resolved after cessation of therapy.*
CONCLUSIONS. *Chronic abuse of decongestant eyedrops can produce a clinical picture resembling an ocular pemphigoid. Histology suggests that late onset immunoreaction and chronic vasoconstriction cause chronic inflammation and neovascularization, respectively. (Eur J Ophthalmol 2009; 19: 129-32)*

KEY WORDS. *Vasoconstrictive eyedrops, Phenylephrine, Rexophthal, Ocular pemphigoid, Histology, Immunohistochemistry*

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INTRODUCTION

Vasoconstrictive eyedrops, advertised as wellness products, are frequently sold over the counter for treating ocular discomfort. Previous reports have shown that so-called ophthalmic decongestants may exacerbate dry eye symptoms or lead to allergic blepharoconjunctivitis (1, 2). We report a case of a patient with massive abuse of eyedrops containing phenylephrine. The resulting conjunctival alterations mimicked an ocular pemphigoid.

Case report

A 45-year-old man presented to our clinic complaining of itching and redness in both eyes. Symptoms persisted for several years despite treatment with a variety of eyedrops including artificial tears, antibiotics, and steroids. Medical history revealed an atopic predisposition to allergic rhinoconjunctivitis but was otherwise unremarkable. In the ophthalmologic examination we found thickened and red eyelids, massively injected conjunctivas, fornix shortening, and atresia of three out of four puncta lacrimalia (Fig. 1). The conjunctival smear did not show bacterial growth and a specific testing for *Chlamydia trachomatis* yielded negative results. To further evaluate the presumed diagnosis of an ocular pemphigoid, a conjunctival biopsy was performed. Histology showed swelling of the basal membrane, focal subepithelial fibrosis and keratinization, spongiosis of the epidermis with intercellular edema, epithelial atypia with increased mitotic activity, prominent nucleoli and nuclear polymorphism of basal cells, and inflammatory infiltrates containing eosinophilic granulocytes (Fig. 2). The histologic findings were typical for chronic inflammation and judged to be compatible with the diagnosis of an ocular pemphigoid. More specific testing with direct immunofluorescence on native tissue, however, failed

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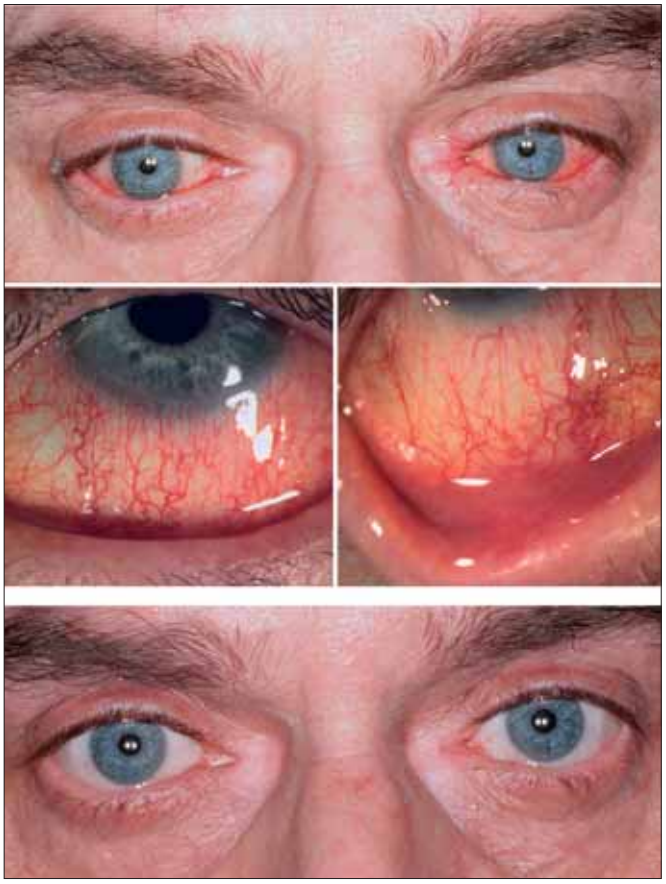

Fig. 1 - Top: *Overview of both eyes at initial presentation shows thickened and red upper and lower eyelids and injected conjunctivas.* Middle: *Detail views photographed at initial presentation show massively injected conjunctivas with tortuous vessels and fornix shortening.* Bottom: *Weeks after cessation of local vasoconstrictor use situation is markedly improved.*

to confirm the presumed diagnosis of an ocular pemphigoid: a granular low to moderate reaction with antiserum against complement C3, moderate to severe reaction with antiserum against IgA at the vessel walls, and no local accumulation of IgG and IgM were observed (data not shown). Blood analysis with indirect immunofluorescence for antibodies against stratum spinosum, urothelium and basal membranes, and ELISA for antibodies against desmoglein-1 and 3, BP180, and 230 were all negative. As the ocular symptoms did not resolve, the patient's history was re-elicited. At this point, the patient disclosed his use of Rexophthal® (containing 1.2 mg/mL phenylephrine and methylthionine) eyedrops hourly for several years. Rexophthal was initially prescribed by a resident ophthalmologist and the patient continued to buy it at the local pharmacy without a medical prescription. As the vasoconstringent phenylephrine was now suspected to have caused the conjunctival alterations, we performed post hoc stainings for several markers on previously collected histologic samples (Fig. 2). Staining with the endothelium-specific antibody against CD31 revealed a dense capillary network in the conjunctival stroma. Staining for MIB1, a mitosis marker, revealed a high cell turnover in conjunctival epithelium (more than 50% of epithelial cells were mitotic), while mitosis rate was within the normal range in the conjunctival stroma. Pan-CK staining showed irregular thickness of the epithelium. The subepithelial inflammatory infiltrates were composed of macrophages (CD68) and there were more T- (CD3) than B-cells (CD20). The number of CD68 positive macrophages was increased.

Furthermore, epicutane testing was performed, revealing a severe late onset allergic reaction to Rexophthal®. As a consequence we asked the patient to immediately stop Rexophthal® use and to instead use artificial tears hourly and topical steroids (fluorometholone 0.1%) three times a day and to taper them off within weeks. It took several appointments and several months to convince the patient to stop Rexophthal treatment. Three weeks after cessation of Rexophthal® conjunctival injections had nearly completely resolved and after another 4 weeks the only remaining symptom was epiphora because of the persisting atresia of puncta lacrimalia.

DISCUSSION

Conjunctival changes as described in our case may have a variety of etiologies including ocular pemphigoid, chronic allergic, or toxic blepharoconjunctivitis. The negative results of specific markers such as linear deposits of IgG, IgA, IgM, or complement C3 components at the basal membrane make the diagnosis of an ocular pemphigoid unlikely.

The chronic inflammatory response which is associated with a predominance of T-cells suggests that the described alterations may have been caused by a late onset immunoreaction to phenylephrine or another component of the galenic formulation. Previous reports have described such a delayed cell-mediated hypersensitivity to phenylephrine, which could be confirmed by epicutane patch testing (3).

Alternatively, a direct sympathomimetic effect may have

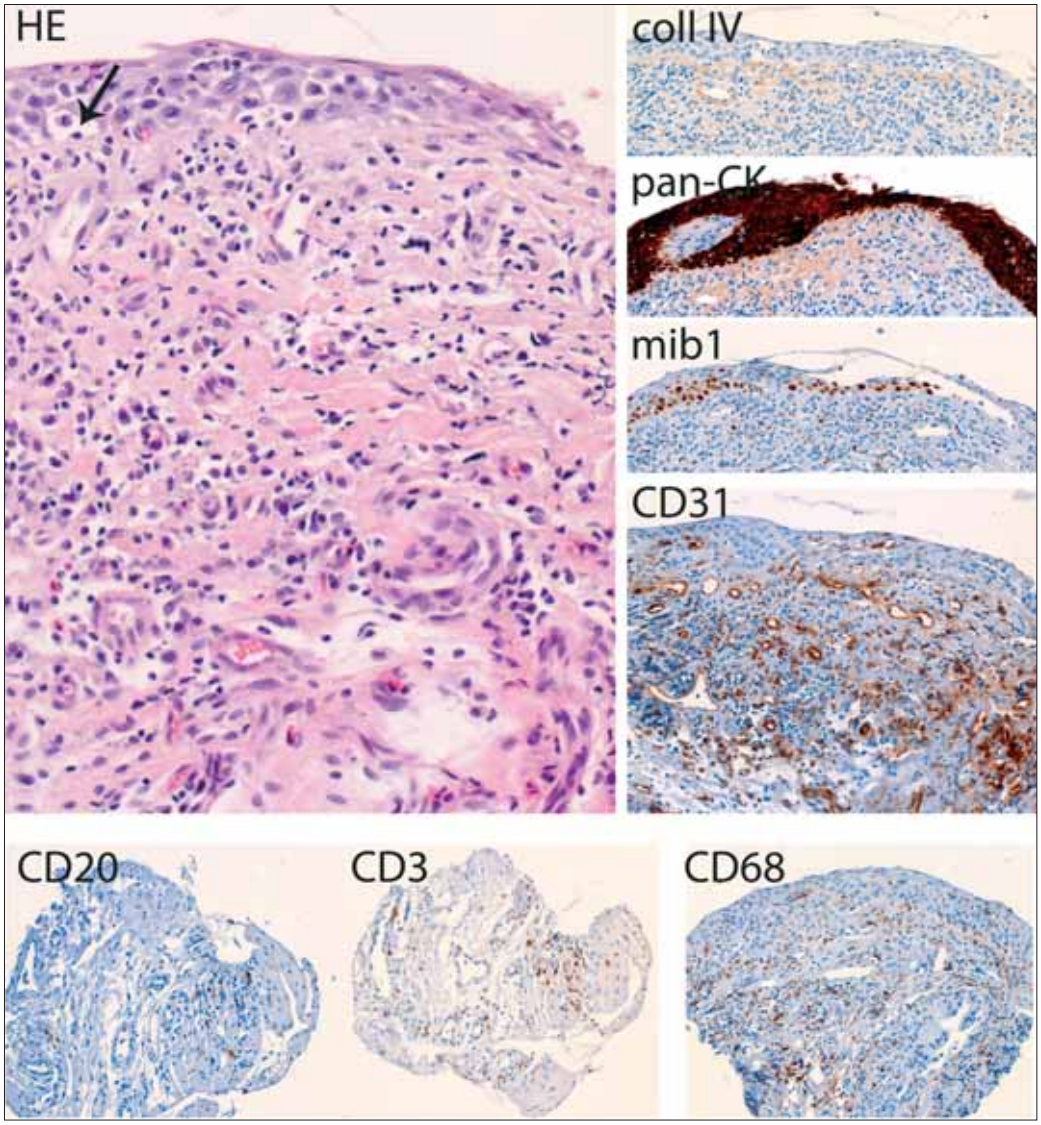

Fig. 2 - Top left: *Overview of histology sample collected from conjunctiva stained with hematoxylin-eosin (HE). Epithelial cells show atypia with nuclear polymorphism and intercellular edema (spongiosis; arrow). Conjunctival stroma is diffusely infiltrated by inflammatory cells and blood vessels thereby altering normal conjunctival architecture.*
Right and bottom: *Immunohistochemical staining with specific antibodies (brown dye). Collagen type IV (coll IV) staining unveils a basal membrane fragmented by a diffuse infiltration with inflammatory cells. Pancytokeratin staining (pan-CK) shows irregular thickness of conjunctival epithelium. About half of basal epithelial cells stain with a mitosis marker (MIB1) suggesting an increased epithelial turnover rate. Staining with an endothelial cell marker (CD31) reveals a dense capillary network in the submucosa. The inflammatory infiltrates are composed of macrophages (CD68), T-cells (CD3), and B-cells (CD20). The predominance of T over B lymphocytes suggests a T-cell mediated inflammatory response.*

been causally involved. The chronic vasoconstriction may have led to a relative ischemia in the conjunctiva which in turn might have triggered the formation of new vessels in the conjunctival stroma. This neovascularization may explain the increased presence of the endothelial cell marker in our biopsy sample (Fig. 2, CD31 staining). Previously, Isenberg and Green showed that phenylephrine-induced vasoconstriction can indeed lead to a significantly reduced conjunctival oxygen pressure (4). The clinical signs found on slit lamp examination pointing toward an ocular pemphigoid are fornix shortening, scarring, formation of symblepharon, and chronic inflammation. These signs are nonspecific and may be found in other chronic inflammatory diseases. In our case, symblepharon, which is a hallmark of an ocular pemphigoid, was absent, thereby seeding doubts on the presumed diagnosis of an ocular pemphigoid. Moreover, our patient did not match the population group primarily associated with ocular pemphigoid, i.e., older women.

In addition to clinical examination, histology is required to confirm the diagnosis. Whereas the general histologic picture may be nonspecific, detection of linear deposits of IgG, IgA, and complement C3 at the basal membrane is more specific. Finally and most importantly a complete medical history might be helpful to reveal a chronic toxic agent. In our case cessation of the causal drug was the

most effective way to demonstrate the etiology of the chronic conjunctival inflammation.

Vasoconstrictive eyedrops are known to be an inappropriate therapy for dry eye syndrome and are well known for side effects when applied for longer periods (5). Pseudopemphigoid conjunctival alterations are known to occur after topical application of different drugs (6, 7). Our report shows an extreme and probably rare form of conjunctival alterations induced by excessive use of vasoconstrictive eyedrops.

We conclude that vasoconstrictive eyedrops must be used cautiously. Patients, pharmacists, and general and specialized physicians should be aware of and warned about potential side effects. Long-term use should especially be avoided.

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REFERENCES

1. Resano A, Esteve C, Fernandez Benitez M. Allergic contact blepharoconjunctivitis due to phenylephrine eye drops. J Invest Allergol Clin Immunol 1999; 9: 55-7.
2. Soparkar CN, Wilhelmus KR, Koch DD, Wallace GW, Jones DB. Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. Arch Ophthalmol 1997; 115: 34-8.
3. Almeida L, Ortega N, Dumpierrez AG, et al. Conjunctival allergic contact hypersensitivity. Allergy 2001; 56: 785.
4. Isenberg SJ, Green BF. Effect of phenylephrine hydrochloride on conjunctival PO2. Arch Ophthalmol 1984; 102: 1185-6.
5. Lisch K. [Conjunctival alterations by sympathomimetic drugs (author's transl).] Klin Monatsbl Augenheilkd 1978; 173: 404-6.
6. Pouliquen Y, Patey A, Foster CS, Goichot L, Savoldelli M. Drug-induced cicatricial pemphigoid affecting the conjunctiva. Light and electron microscopic features. Ophthalmology 1986; 93: 775-83.
7. Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. Ophthalmology 2004; 111: 45-52.