Surgical Management of Corneal Plaques in Vernal Keratoconjunctivitis

A Clinicopathologic Study

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Purpose: To describe the surgical management and histopathologic and immunohistochemical findings in corneal plaques of shield ulcers in vernal keratoconjunctivitis.

Patients and Methods: Three children (ages 4, 7.5, and 9) presented with corneal plaques unresponsive to conservative systemic and topical medical treatment. Plaques were scraped under general anesthesia, and soft bandage contact lenses were placed. The excised tissue was evaluated by histopathology and immunohistochemistry.

Results: During surgery, plaques were found to extend beyond the ulcer margins. Histopathology revealed granular, deeply-eosinophilic, laminar material, firmly attached to the Bowman layer in all cases. Immunohistochemistry confirmed this to be eosinophil-derived major basic protein (MBP). After surgical removal, complete epithelization was evident within 1–4 weeks in all cases.

Conclusions: Corneal plaque is a rare complication of vernal keratoconjunctivitis. These plaques usually do not resolve with standard conservative measures. Failure to epithelialize may be a result of the plaque material extending below the edges of adjacent epithelium. We suggest that MBP plaques precipitate on the denuded stromal bed, thereby playing a pathogenic role in nonhealing shield ulcers.

Key Words: vernal keratoconjunctivitis, corneal plaques, major basic protein

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Shield ulcers pose a difficult management problem in patients with vernal keratoconjunctivitis (VKC). They are typically oval, superficial, and located superiorly.[1] They may be indolent and persist for months. When inflammatory debris accumulates at the base of an ulcer, an opaque plaque is formed. The composition of these plaques has not been resolved. However, Trocme et al have identified eosinophil major basic protein (MBP) in the plaques of 2 VKC patients[2] and suggested that MBP, a cytotoxic protein, may play a pathogenic role in the formation and/or persistence of shield ulcers.

Shield ulcer plaques may not respond to the conventional topical treatment and may be complicated by amblyopia, strabismus, microbial keratitis, and corneal perforation.[2] There is a paucity of literature on the management of nonhealing shield ulcers and plaques. Previous publications have described conservative medical treatment or surgical removal of such plaques with variable success.[1,3,4] In this report we present histopathologic and immunohistochemical evidence of eosinophil major basic protein in shield ulcer plaques in three patients, supporting the findings described by Trocme et al.[2] We also discuss the role of surgical debridement of these ulcers and the possible mechanical and toxic pathogenic roles of the plaque in chronic shield ulcers.

PATIENTS AND METHODS

Our patients were 9, 4, and 7.5 years old. Before their referral to us, their vernal keratoconjunctivitis was managed by topical corticosteroids alone or in combination with topical mast cell stabilizers. They were referred because of persistent corneal plaque despite the use of topical therapy. Surgical intervention was offered for corneal plaque persisting for at least 1 month, associated with decreased visual acuity or symptoms of ocular irritation.

Surgical Technique

All surgeries were performed under general anesthesia. Plaque material was meticulously scraped with a 3.2-mm crescent knife, trying to find a plane between the plaque and Bowman layer (Fig. 1B–D). An attempt was made to avoid lamellar dissection of the corneal stroma. The dissection was performed under dry field to help differentiate plaque material from the denuded stroma. When the surrounding corneal epithelium at the visible edges of the plaque was peeled, an additional 1 mm

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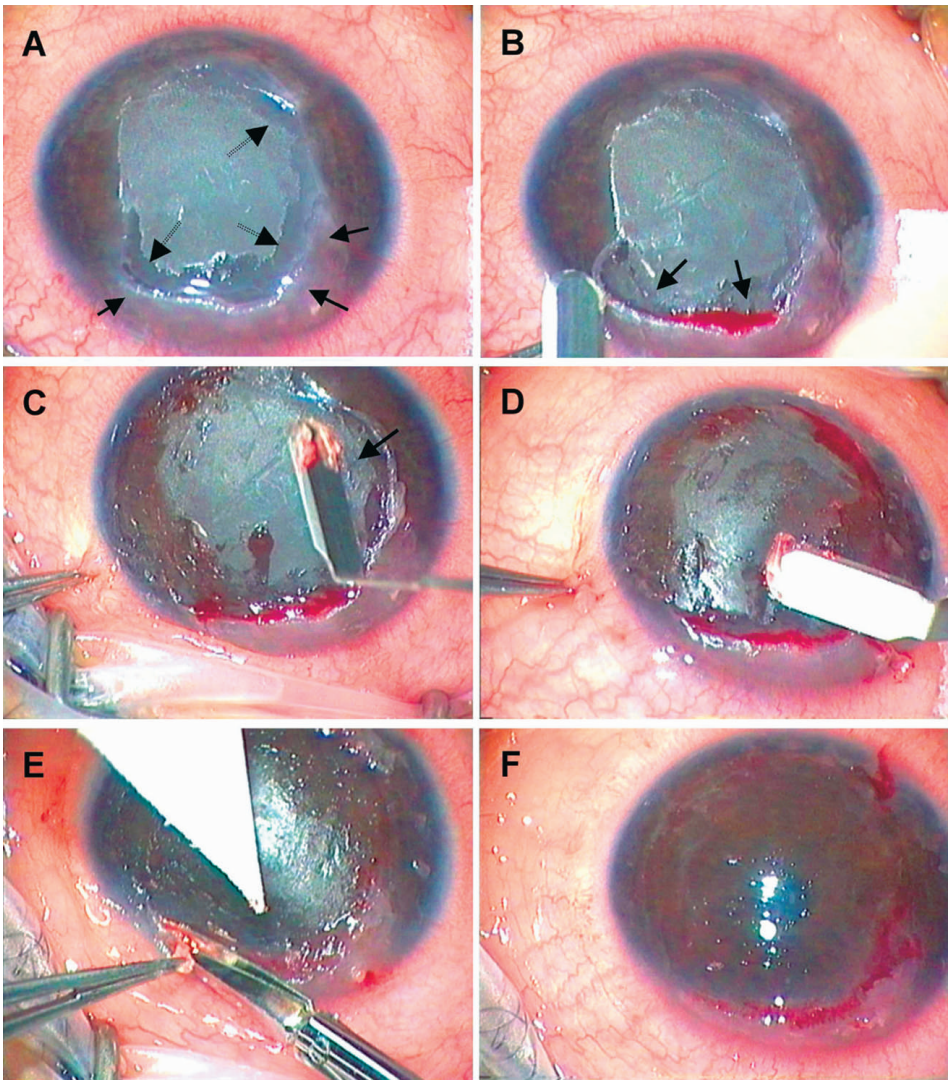

FIGURE 1. A, Preoperative appearance of a large corneal plaque (case 2, surgeon's view). An opaque dense material extends throughout the base of the ulcer, covered in its circumference by epithelium (dashed arrows). An area of bulging hypertrophic epithelium is covering the superior margins of the plaque (solid arrows). B, C, Scraping of the plaque with a sharp crescent knife, revealing the true edges of the plaque, which extend beyond the epithelial margins (arrows). D, Dissection of the plaque from the center of the cornea. Note that the procedure is performed under a dry field to enhance visualization of the remaining plaque material. E, Excision of the hypertrophic epithelium covering the superior portion of the plaque. F, Appearance of the clear cornea at the end of the procedure.

of plaque material was discovered in all cases, extending peripherally under the epithelium (Fig. 1D). Therefore, the entire circumference of the epithelium at the plaque edges was scraped to uncover all of the plaque material. Areas of thickened, heaped epithelium were excised (Fig. 1E). At the end of the procedure, a soft bandage contact lens was applied over the cornea. Topical fluorquinolone was administered 4 times a day until complete epithelialization of the cornea occurred, at which time the contact lens was removed and topical corticosteroids were resumed.

Immunohistochemistry of Plaque Samples

All plaque samples were taken for routine histopathology. Immunohistochemical analysis was carried out to confirm our impression of the presence of eosinophil-derived major basic protein (MBP) on hematoxylin-eosin sections: Sections were deparaffinized, washed three times in xylene, followed by three washes in absolute alcohol, distilled water, and PBS. Mouse anti-human monoclonal eosinophil-derived major basic protein (Chemicon International, Temecula, CA) was prepared at a final concentration of 1 μg/mL and incubated at room temperature for 45 minutes. After three washes in PBS, sections were incubated for 10 minutes with a peroxidase conjugated to anti-mouse second antibody (Universal Immunoperoxidase Polymer, N-Histofine, Nichirei Corp, Tokyo, Japan). Sections were washed and stained with aminoethyl carbazole (AEC) substrate for five minutes and counterstained with hematoxylin for two minutes.

CASE REPORTS

All three patients presented with a corneal plaque of 1 to 2 months duration and were conservatively managed with topi-

cal corticosteroids by their referring ophthalmologists (Table 1). The patients complained of photophobia and reduced best corrected visual acuity. The plaque was located at the superior cornea in one patient and was central in the other two patients. During surgery, extension of the plaque material for at least 1 mm under the surrounding epithelium was noted in all the patients (Fig. 1B,C). After surgical removal, complete epithelialization was evident within 2 to 4 days in two of the patients, whereas one patient required four weeks for the epithelium to completely heal. None of the plaques recurred during a follow-up period of 8 to 15 months, but residual signs of irregular epithelium or scarring were noted at the plaque area. In one patient, a new plaque appeared in the contralateral eye.

Histopathologic and Immunohistochemical Findings

Examination of hematoxylin-eosin–stained sections revealed the presence of densely eosinophilic, granular material in all 3 cases (Fig. 2A,D). This material was adhered to excised Bowman layer and had a laminar structure. A few inflammatory cells were evident below the Bowman layer and embedded within the inflammatory deposit (Fig. 1C). This eosinophilic material closely resembled the Splendore-Hoepply phenomenon, in which eosinophil-derived MBP is deposited around parasitic infectious elements.[5,6] This, as well as the previous two cases reported by Trocme et al,[2] prompted us to look for immunohistochemial evidence for the presence of MBP in the sections. Indeed, these deposits were positive for eosinophil-derived major basic protein antibodies, which stained large portions of the plaque's substance (Fig. 1B). Positive granular staining for MBP was also noted within the cytoplasm of some of the inflammatory cells infiltrating the plaque and under the Bowman layer, indicating that these were eosinophils and serving as an internal positive control.

DISCUSSION

Corneal shield ulcers and plaques are rare but severe manifestations of vernal keratoconjunctivitis. Their incidence is variable, ranging from 3% in a large series of 400 cases of VKC[7] to an estimate of 20% in a large referral clinic for VKC in Moorfields Eye Hospital.[3] The pathogenesis of these ulcers is believed to involve a combination of mechanical damage to the corneal epithelium from giant papillae[4] as well as toxic epitheliopathy from inflammatory mediators secreted by eosinophils and mast cells.[8] Once a plaque forms on the base of a shield ulcer, it may prevent epithelialization and pose a significant management problem. Because these plaques do not resolve spontaneously, prolonged medical treatment and delay in surgical intervention may result in complications such as microbial keratitis, amblyopia,[9] strabismus, corneal vascularization, scarring, or even perforation.[1,3] Cameron has graded corneal plaques by severity and concluded that grade 2 and 3 plaques must be removed by surgery as soon as possible to avoid these complications.

Our 3 patients presented with grade 2 corneal plaques, ie, ulcers that were covered by translucent material that was not elevated above the adjacent epithelium. Conventional topical and systemic treatment with corticosteroids had been ineffective, and visual acuity was decreased in all cases. Surgical removal was therefore attempted, resulting in reepithelization in two patients within a few days and in the third patient within a month.

In all three cases, plaque material was found to extend under the surrounding epithelium for at least 1 mm beyond the ulcer's circumference. This observation has been reported only once[3] and may explain the failure of these plaques to resolve spontaneously and to reepithelize under conservative medical therapy. Epithelial growth over the plaque may represent an abortive attempt of reepithelialization, failing because of the MBP plaque that separates the Bowman layer from the epithelium. The inability of the corneal epithelial cells to migrate between the plaque and Bowman layer may be explained by previous transmission electron microscopy studies, demonstrating collagen fibrils originating from the eroded Bowman layer, extending deeply into the plaque layers.[10] This also explains the difficulty of surgically separating the plaque from the cornea.

TABLE 1. Clinical Presentation and Outcome of 3 Children With Vernal Plaques

Age/Gender/Eye	Previous History of VKC	Duration of Plaque at Presentation	BCVA at Presentation	Plaque Location and Size	Epithelialization Time After Surgery	BCVA at Last Follow-up	Follow-up Period	Status at Last Follow-up
9/M/RE	3 years	1 month	20/40	Superior, 2 × 2 mm	4 days	20/30	9 months	Irregular epithelium at superior cornea BE
4/M/RE	1 year	2 months	20/50	Central, 8 × 8 mm	2 days	20/20	15 months	Scarring in RE, new plaque in LE
7.5/F/LE	1 year	1 month	20/50	Central, 4 × 5 mm	4 weeks	20/40	8 months	Superficial central scarring

VKC, vernal keratoconjunctivitis; BCVA, best corrected visual acuity; RE, right eye; LE, left eye; BE, both eyes.

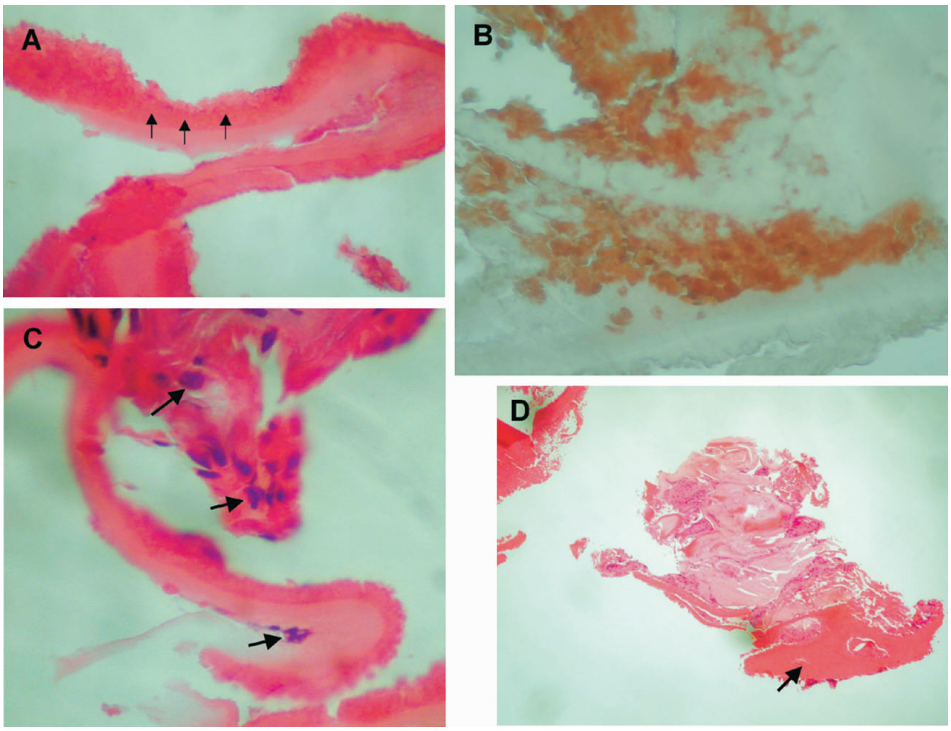

FIGURE 2. Histologic and immunohistochemical findings. A, Section of a plaque specimen, showing a dense eosinophilic material (arrows) closely attached to and covering the Bowman layer (hematoxylin and eosin, ×400). B, Immunostaining for major basic protein (brown stain) demonstrating the eosinophil-derived cationic protein in parts of the plaque material. C, Inflammatory cells (arrows) are observed below Bowman layer and inside the plaque material. The densly eosinophilic plaque material is firmly adherent to Bowman layer. D, A clump of folded epithelium and Bowman layer attached to a dense eosinophilic plaque material. This specimen was taken from the superior portion of the plaque, which was covered with epithelium (see Fig. 1E).

The surgical technique to remove corneal plaques associated with VKC may vary from simple scraping of the material to superficial keratectomy. Buckley advised to perform true superficial keratectomy because there is no surgical plane of cleavage between the plaque and Bowman layer.[3] Cameron, on the other hand, reported on 27 surgical procedures performed on vernal plaques. Twenty-three were simple scraping of the plaque, in 2 cases superficial keratectomy was performed, and 2 additional procedures were scraping followed by excimer laser phototherapeutic kertectomy.[1] Our surgical specimens showing eosinophilic material adhered to Bowman layers are evidence of the fact that truly superficial keratectomy was performed in some of the areas, whereas in others only plaque material is seen without corneal tissue. This may be a result of varying attachment forces that exist between the inflammatory debris accumulating on the denuded cornea and the collagen fibers.

Histologic analysis of the plaque samples showed dense laminated deposits of granular, eosinophilic extracellular material adherent to the Bowman layer, which was positive for eosinophil-derived major basic protein (MBP). MBP is one of several cationic proteins that are secreted from activated eosinophils, including eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO). MBP has been shown to possess cytotoxic properties.[11,12] In addition, MBP, ECP, and EPO were found to decrease the viability of corneal epithelial cells in vitro[13] and to adversely affect epithelial wound healing.[14] One previous report demonstrated deposition of major basic protein in plaques of patients with VKC.[2] Taken together, these findings may suggest the following pathologic model to explain the pathogenesis of corneal plaques in VKC: Activated eosinophils that infiltrate the tarsal conjunctiva secrete MBP, damaging the corneal epithelium. This is clinically evident as coarse punctate keratopathy. This chemical damage, augmented by the mechanical friction of the giant tarsal papillae, results in the formation of a corneal ulcer. MBP, whose concentration was found to be high in the tear fluid of VKC patients,[8] is deposited on the denuded Bowman layer, forming a dense plaque.

Additional studies on the nature of interaction between collagen fibers and MBP may help to better understand the pathogenesis of shield ulcers and vernal plaques and will aid in developing a pharmacologic therapy targeting the eosinophil-derived cationic proteins, which may play an important role in the corneal complications in VKC.

REFERENCES

1. Cameron JA. Shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. *Ophthalmology*. 1995;102:985–993.
2. Trocme SD, Kephart GM, Bourne WM, et al. Eosinophil granule major basic protein deposition in corneal ulcers associated with vernal keratoconjunctivitis. *Am J Ophthalmol*. 1993;115:640–643.
3. Buckley RJ. Vernal keratopathy and its management. *Trans Ophthalmol Soc UK*. 1981;101:234–238.
4. Jones BR. Vernal keratitis. *Trans Ophthalmol Soc UK*. 1961;81:215–228.
5. Kephart GM, Andrade ZA, Gleich GJ. Localization of eosinophil major basic protein onto eggs of *Schistosoma mansoni* in human pathologic tissue. *Am J Pathol*. 1988;133:389–396.

6. Rathinam S, Fritsche TR, Srinivasan M, et al. An outbreak of trematode-induced granulomas of the conjunctiva. *Ophthalmology*. 2001;108:1223–1229.
7. Neumann E, Gutmann M, Blumenkrantz N, et al. A review of four hundred cases of vernal conjunctivitis. *Am J Ophthalmol*. 1959;47:166–172.
8. Udell IJ, Gleich GJ, Allansmith MR, et al. Eosinophil granule major basic protein and Charcot-Leyden crystal protein in human tears. *Am J Ophthalmol*. 1981;92:824–828.
9. Cameron JA, Mullaney PB. Amblyopia resulting from shield ulcers and plaques of the cornea in vernal keratoconjunctivitis. *J Pediatr Ophthalmol Strabismus*. 1997;34:261–262.
10. Rahi AHS, Buckley R, Grierson I. Pathology of corneal plaques in vernal keratoconjunctivitis. In: O'Connor GR, Chandler JW, eds. *Advanced in Immunology and Immunopathology of the Eye.* New York: Masson; 1985: Ch 23.
11. Gleich GJ, Frigas E, Loegering DA, et al. Cytotoxic properties of the eosinophil major basic protein. *J Immunol*. 1979;123:2925–2927.
12. Frigas E, Loegering DA, Gleich GJ. Cytotoxic effects of the guinea pig eosinophil major basic protein on tracheal epithelium. *Lab Invest*. 1980; 42:35–43.
13. Trocme SD, Hallberg CK, Gill KS, et al. Effects of eosinophil granule proteins on human corneal epithelial cell viability and morphology. *Invest Ophthalmol Vis Sci*. 1997;38:593–599.
14. Trocme S, Gleich G, Kephart G, et al. Eosinophil granule major basic protein inhibition of corneal epithelial wound healing. *Invest Ophthalmol Vis Sci*. 1994;35:3051–3056.

