

Giant papillary conjunctivitis

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Purpose of review

Despite shorter replacement intervals and new lens materials, giant papillary conjunctivitis still limits the ability of some patients to wear contact lenses.

Recent findings

Recent research has elucidated many new mediators of inflammation. The presence of chemokines and cytokines such as IL-8, IL-6, IL-11, macrophage inflammatory protein-1 α , tissue inhibitor of metalloproteinases-2, macrophage–colony stimulating factor and monokine-induced gamma interferon, eotaxin, pulmonary and activation-regulated CC chemokines have been shown to be elevated in patients with giant papillary conjunctivitis. In addition, M cells and B lymphocytes have been hypothesized to play a role in the pathogenesis of giant papillary conjunctivitis.

Summary

The pathophysiology of giant papillary conjunctivitis is complicated with both immune and mechanical mechanisms playing a role in the development of this condition; understanding these mechanisms is important in both treatment and prevention of giant papillary conjunctivitis.

Keywords

contact lens complications, contact lens papillary conjunctivitis, giant papillary conjunctivitis

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Introduction

Giant papillary conjunctivitis (GPC) is primarily associated with contact lenses and is also referred to as contact lens-induced papillary conjunctivitis (CLPC). This condition has also been reported in association with exposed sutures, filtering blebs, scleral buckles, ocular prostheses, corneal foreign bodies, limbal dermoids and tissue adhesives used on the ocular surface. A recent review covers this condition in detail [1•].

Signs and symptoms

The classic signs of GPC consist of decreased contact lens tolerance, excessive mucous and increased awareness of the contact lens associated with excessive movement, usually superior displacement with each blink. The mucous is usually noticed first in the morning, upon awakening, involving the inner canthus of the eye. Patients will typically complain of ocular irritation, redness and itching. Many patients will also complain of intermittent blurry vision, contact lens coating and difficulty keeping their contact lenses clean. Ocular examination will reveal hyperemia and injection of the upper tarsal conjunctival surface along with the presence of papules larger than 0.3 mm.

The superior tarsal conjunctiva is normally moist with a pink color and easily visible vascular arcades (Fig. 1). In the

early stages of GPC, the surface becomes hyperemic, and it becomes difficult to discern the vessels. The normal superior tarsal surface may be devoid of papules, displaying a smooth satin appearance, or papules may be present. However, if they are present, they are rarely larger than 0.3 mm [1•]. The degree of inflammation and the papillary reaction in GPC depends on the severity of the condition. In the initial stages, there is hyperemia of the surface and papules that approach a diameter of 0.3 mm. As the disease progresses, hyperemia increases, the tarsal conjunctiva becomes thickened, the vascular arcade becomes difficult to visualize and the papules become larger, often reaching 1 mm or larger in diameter (Fig. 2).

Examination of the upper tarsal conjunctiva is best accomplished in the following manner:

- (1) With the patient at the slit lamp, fluorescein dye is instilled into the lower cul-de-sac.
- (2) The patient is asked to blink 2–3 times.
- (3) The upper lid is inverted, and the surface is examined with both white and cobalt blue illumination.
- (4) The amount of inflammation and hyperemia is noted.
- (5) The ability to visualize the vascular arcade is determined.
- (6) The location and size of the papillary reaction is recorded.

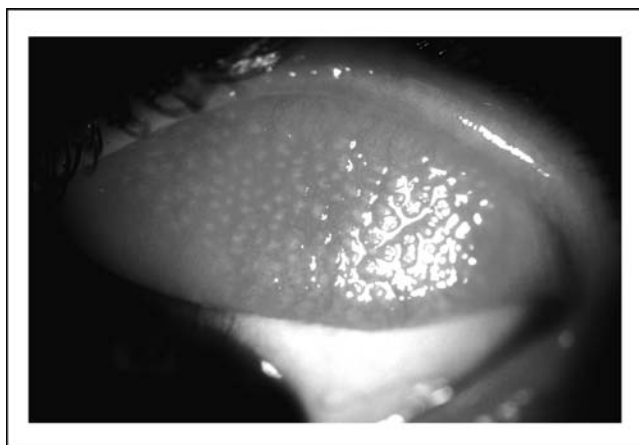
Figure 1 The normal conjunctiva is smooth and moist with the vascular arcade clearly visible



Contact lenses associated with giant papillary conjunctivitis

GPC can occur with hydrogel contact lenses of either hydroxyethyl methacrylate (HEMA) or silicone polymers as well as rigid contact lenses of either polymethyl methacrylate (PMMA) or the new gas-permeable polymers. The appearance and location of the papillary reaction can vary depending on the type of contact lenses worn. To describe the characteristics of GPC, the tarsal plate can be divided into three zones (Fig. 3). The papillary reaction associated with HEMA-based soft contact lenses usually begins in zones 1 and 2 and then progresses to involve all three zones or the entire central area of the tarsal conjunctiva. In patients wearing rigid lenses, especially the rigid gas-permeable (RGP) contact lenses, the papules usually form first in the zone along the lid margin (zone 3) and then progress to the middle area (zone 2). The reaction tends to be more localized than that associated with HEMA-based soft contact lenses. GPC associated with the high Dk silicone hydrogels can

Figure 2 This patient with moderate giant papillary conjunctivitis shows a papillary pattern with whitening of the apices of the papillae and obscuration of the vascular arcade

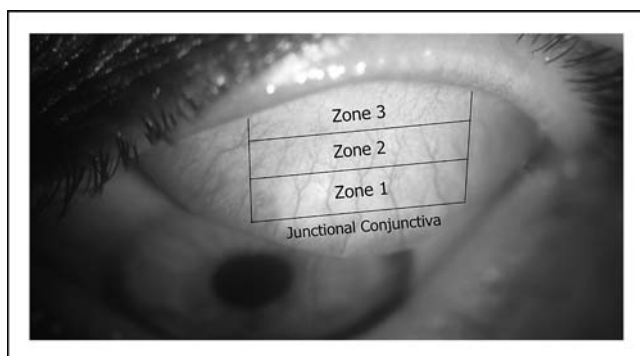


present in two forms; a generalized form similar to that seen with HEMA-based soft contact lenses and a more localized form. The localized form is described as a papillary reaction that is confined to zones 1 or 2 of the tarsal conjunctiva. The localized form is more common than the generalized form in wearers of high Dk silicone hydrogel contact lenses, and the symptoms associated with the localized form are typically milder than those associated with generalized GPC [2]. There is also a high recurrence rate of GPC in silicone hydrogel contact lens wearers [3]. The papillary reaction associated with ocular prostheses is usually generalized, with the tarsal surface becoming thickened and inflamed, and GPC associated with filtering blebs or exposed sutures is generally more localized, usually coinciding with the exposed suture or bleb [4]. The onset of GPC in wearers of soft hydrogel contact lenses tends to be earlier than in wearers of rigid contact lenses. Studies have reported an average interval of 10–19.9 months for GPC to develop in soft contact lens wearers, whereas individuals wearing RGP contact lenses required an average of 21.6 months for GPC to develop and those individuals wearing PMMA-based contact lenses took 90 months for the signs and symptoms of GPC to develop [5]. The time of development of localized or generalized forms of GPC in silicone hydrogel wearers was similar and slightly less than the time reported for development of GPC in soft hydrogel contact lens wearers [2].

Individuals with GPC universally have coated contact lenses, but the degree of coating is influenced by both the severity of the condition and the lens polymer. As the condition progresses, the coating becomes more severe, and patients find it increasingly difficult to keep their contact lenses clean [1**]. High-water-content contact lenses tend to coat more than low-water lenses, and Food and Drug Administration group IV contact lenses that have a high water content and ionic polymers tend to coat the most. Glyceryl methyl methacrylate (GMM) contact lenses coat less than HEMA-based contact lenses [6]. Silicone hydrogel contact lenses deposit less lysozyme and protein than HEMA hydrogels, but accumulate more lipid deposits [7,8].

Not all patients with coated contact lenses develop GPC. Studies have tried to determine whether there is any difference in the material or type of coating on lenses from patients with GPC compared with contact lens wearers who do not develop GPC [9–14]. The significance of lens coating was demonstrated when coated contact lens from patients with GPC induced a superior tarsal conjunctival reaction when placed on the eyes of Rhesus monkeys. This reaction appeared clinically similar to that seen in humans with GPC; when biopsied, the conjunctiva from these monkeys reveals a cellular infiltrate consisting of eosinophils and plasma cells,

Figure 3 The conjunctiva is divided into three zones, with zone 1 nearest the lid margin



The junctional conjunctiva near the border of the tarsal plate may show papillary changes in individuals without giant papillary conjunctivitis and is considered normal.

similar to that found in the biopsy of human conjunctiva from contact lens wearers with GPC [15]. However, virgin contact lenses or lens from non-GPC contact lens wearers did not produce a similar reaction. This animal model suggests that the coated contact lenses from patients with GPC have an antigenic component that can initiate a reaction that we see clinically as GPC.

Immunohistochemical findings in giant papillary conjunctivitis

In normal conjunctival tissue, neutrophils and lymphocytes are present in the epithelium and substantia propria; although mast cell and plasma cells are present in the substantia propria, they are not found in the epithelium. Basophils and eosinophils are not present in either the epithelium or the substantia propria. In patients with GPC, the total number of inflammatory cells is significantly greater than are seen in individuals without GPC. The location of inflammatory cells also differs. In patients with GPC, mast cells, eosinophils and basophils are present in the epithelium as well as in the substantia propria [16].

Two types of mast cells have been reported to be present. Tryptase-positive (MCt) mast cells contain tryptase, whereas tryptase-positive, chymase-positive (MCtc) mast cells contain both tryptase and chymase. The former are dependent on the presence of functional T lymphocytes, whereas the latter are not dependent on T lymphocytes for normal growth. MCt mast cells have been reported to be present in the conjunctiva of patients with vernal keratoconjunctivitis (VKC) but not in patients with GPC. MCtc mast cells are present in both patients with GPC and those with VKC, but in patients with GPC, the number of MCtc cells is elevated. In addition, CD4+ lymphocytes and CD8+ lymphocytes are present, and eosinophil numbers are elevated [17].

Elevation of cytokines and chemokines has been reported in the tears of patients with GPC. IL-6, monocyte chemoattractant protein-1 and monokine-induced gamma interferon values are increased four-fold in patients with GPC compared with control values, whereas eotaxin-2, IL-6 soluble receptor (IL-6sR), IL-11 macrophage inflammatory protein-1 delta, and tissue inhibitor of metalloproteinases-2 values are increased eight-fold compared with controls. The increase in IL-6sR was hypothesized to be an important mediator in the formation of papillary proliferation [18]. Eotaxin is an important mediator in attracting eosinophils, and eotaxin levels have been reported to be correlated with the severity of the papillary reaction, and thus may be involved in the formation of papules [19]. In addition, statistically significant elevations of IL-8 (which promotes neutrophilic invasion) and pulmonary and activation-regulated CC chemokines (PARC) (which promotes lymphocyte invasion) have been found in the tears of patients with GPC [20]. Leukotriene C4 (LTC4) level is elevated in the tears of patients with GPC. This mediator is felt to be responsible for conjunctival redness and edema, as well as the increase in mucoid secretion, and may also play a role in papillary formation [21]. LTC4 may be an early marker for the development of GPC. Increased levels were found in patients with mild symptoms and signs of conjunctival abnormalities in patients wearing contact lenses. Twenty percent of the mildly symptomatic patients went on to develop GPC during the study [22]. Elevated levels of locally produced tear immunoglobulins (IgE and IgG), and in severe cases, IgM, are present in the tears of patients with GPC [1^{••},23]. Elevated levels are related to the severity of the symptoms. In patients with contact lens-induced GPC, when these patients discontinue wearing lenses and the inflammation with associated signs and symptoms resolves, the levels of elevated tear immunoglobulins return to normal [1^{••}].

The complement system also appears to be involved. Levels of C3, factor B and C3 anaphylatoxin are elevated in the tears of patients with GPC [24]. Decay-accelerating factor, a regulatory protein of the complement system that inhibits C3 amplification convertase, is decreased in patients with GPC. This may enhance the complement activation [25]. Elevated levels of IgE have also been reported in patients with generalized and localized GPC who were wearing silicone hydrogel contact lenses. There was no difference in the levels between the two groups, which may suggest that they may share similar pathophysiology [23].

Neutrophil chemotactic factor (NCF) is released from injured conjunctival tissue, and NCF has been reported to be statistically elevated in the tears of patients with GPC. It is interesting to note that asymptomatic contact lens wearers also have elevated tear levels of NCF, but

their level is only three times more than that found in controls, whereas patients with GPC have levels that are 15 times more than that of controls [26]. In animal experiments, when NCF is injected into the tarsal conjunctiva of rabbits, a reaction occurs that is similar to that seen in human GPC. The tarsal inflammation and papillary reaction that occurs is composed of an infiltration of neutrophils, eosinophils and plasma cells [27].

Pathophysiology

The previous discussion demonstrates that the immunology of the conjunctiva and the tear film is complex, and although the complete pathogenesis of GPC is still unknown, evidence supports an immune-mediated mechanism, with mechanical irritation also playing a part. The presence of locally produced immunoglobulins in the tears of patients with active GPC, the presence of a variety of cytokines in the tears of patients with GPC and the animal model all suggest that there is an antigen on the coated contact lens that initiates the immune reaction. The presence of NCF, which is released from injured conjunctival cells, with its ability to produce an inflammatory reaction and increased number of immune-associated cells, suggests that a mechanical cause may also be involved. This can help explain the occurrence of GPC secondary to exposed sutures, filtering blebs, corneal foreign bodies and extruded sclera buckles. A recent study by Xingwu *et al.* [28**] showed that membranous epithelial cells (M cells) play a key role in the pathogenesis of GPC, and the immune response is mediated predominantly by B cells. M cells are important in the binding, uptake and translocation of soluble and particulate antigens, as well as pathogens. M cells are located on top of the mucosa-associated lymphoid tissue (MALT) and enable antigens and other pathogens to be transported to macrophages, lymphocytes and dendritic cells. A cell similar to the M cell has been found in the conjunctiva that can bind and translocate macromolecular material, bacteria and lectin into the underlying lymphocytes, thus providing an entry route for antigens into the conjunctiva [29–31]. Xingwu *et al.* [28**] postulate that the antigenic substance on the coated contact lenses is transported to the B lymphocytes by a cell similar to the M cell. B cells are stimulated, proliferated in the conjunctival-associated lymphoid tissue (CALT) and are then transported to the lymph nodes and an immune response occurs. They were able to show that CALT was present in the papules of patients with GPC and that the anatomy and histology was similar to MALT. B cells were found to be present in the central follicular area and the intraepithelial pockets of the papules. Thus, the large papules and thickened tarsal conjunctiva that characterize the superior tarsal conjunctiva of patients with GPC result from an overproduction of M cells and the accumulation of lymphocytes.

Treatment

Treatment of GPC can be directed at either decreasing or eliminating the antigenic and mechanical stimulation from contact lenses or modulating the immune response. The strategies for decreasing contact lens coating involve improving contact lens cleaning, decreasing the wearing time, shortening the replacement interval or changing the contact lens material or design [1**]. The medications available for modulating the immune reaction consist of topical corticosteroids, topical nonsteroidal anti-inflammatory agents and mast cell stabilizers.

The goal in managing patients with GPC is to allow the patient to continue wearing contact lenses. The first step is to discontinue contact lens wear for 2–4 weeks, allowing the inflammatory reaction to subside. The papillary reaction will not resolve, but inflammatory markers will decrease. The clinician may then choose to change the polymer of the lens or the replacement schedule. Studies have shown that simply changing to a different contact lens polymer allows more than 80% of patients with GPC to continue lens wear. In particular, switching to frequent replacement or disposable contact lenses has a success rate of over 90% [32].

Although frequent replacement contact lenses have been shown to be very helpful in the management of GPC, it is important to note that the replacement schedule is an important factor in the development of GPC. There is a much lower incidence of GPC in patients wearing contact lenses that are replaced in 3 weeks or less compared with those replacing their contact lenses in 4 weeks or more [33].

The use of topical steroids has not been widely advocated because of the potential side effects of glaucoma, cataracts and secondary infections. However, loteprednol etabonate has been reported to be efficacious in treating the signs and symptoms associated with GPC [34,35]. Mast cell stabilizers have been shown to be effective. Kruger *et al.* [36] reported a 70% success rate in patients with moderate-to-severe GPC who had experienced a return of GPC symptoms after changing the contact lens polymer or design.

Our regimen for managing patients with GPC is as follows:

- (1) Discontinue contact lenses for 2–4 weeks.
- (2) Refit with daily disposable contact lens or frequent replacement contact lenses that are replaced at 1–2-week intervals.
- (3) If there is a return of symptoms, then discontinue contact lenses for 2–4 weeks, refit with daily disposable contact lens and add a mast cell stabilizer or combination antihistamine–mast cell stabilizer.

Conclusion

GPC has been a recognized complication of contact lens wear since 1974 and is still a potential problem for contact lens wearers. Recent research has helped elucidate the various inflammatory mediators that play a role in the pathogenesis of the condition and helped in understanding the pathogenesis of this syndrome. As a result, we now have a better understanding of the mechanisms that are responsible for this entity and have a rationale for managing this condition.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 495–496).

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