

Allergic Conjunctivitis and Latent Infections

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Purpose: The purpose of this study was to evaluate in a large series the incidence of latent infection during chronic allergic conjunctivitis.

Methods: In a 5-year follow-up prospective, nonrandomized trial, we evaluated 236 patients (472 eyes) with a history of allergic conjunctivitis but without evidence of infection. Conjunctival scrapings were examined cytologically, and antibiograms and antimicrograms were assessed. The 472 eyes were divided into 5 subgroups based on the percent of eosinophilic cells in conjunctival specimens.

Results: Latent concurrent infection was identified in 176 of 472 eyes (37%): *Candida albicans* (55.2%), *Staphylococcus epidermidis* (50.9%), *Chlamydia trachomatis* (30.7%), and *Staphylococcus aureus* (23%). The incidence of concurrent infection (mainly bacterial infection) strongly correlated with the percent of eosinophilic cells. Concurrent bacterial infection was identified in 26 of 26 cases of the subgroup with the highest percent of eosinophilic cells.

Conclusion: Chronic allergic conjunctivitis may be associated with latent infection. Pathogens can stimulate activation of eosinophils with a consequent worsening and chronicity of allergic symptoms.

Key Words: allergic keratoconjunctivitis, eosinophils, chronicity

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INTRODUCTION

Allergic conjunctivitis is defined as conjunctival inflammation determined by an abnormal reaction to antigenic stimulation.^{1,2} It is caused by genetic and environmental factors (a higher incidence is associated with a hot climate). There are 6 main forms of this condition: seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis, and contact or drug-induced dermatconjunctivitis.³

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Allergic conjunctivitis may be the result of a type I hypersensitivity reaction (which is immediate and involves mainly IgE, ie, pollinosis conjunctivitis), a type IV hypersensitivity reaction (delayed-type, cell-mediated), or a combination of both. In 2006, the International Ocular Inflammation Society proposed a classification for conjunctivitis and blepharitis. Ocular allergy was classified as a “noninfectious, immunomediated” conjunctivitis. Seasonal allergic conjunctivitis and perennial allergic conjunctivitis were included in the “IgE-mediated” group, whereas vernal keratoconjunctivitis and atopic keratoconjunctivitis were included in the “non-IgE-mediated” group. T-cells, macrophages, neutrophils, and eosinophils play an important role in type IV allergic inflammation.⁴ In particular, the concentration of eosinophils is related to the degree of allergic inflammation.

The exact etiologic mechanisms of allergic conjunctivitis and their possible correlations with pathogens are still debated. IgE does not appear to be involved in contact lens conjunctivitis,⁵ whereas a correlation between vernal keratoconjunctivitis and *Chlamydia trachomatis* has been identified in atopic patients.⁶ In an attempt to shed light on this issue, we evaluated the incidence of latent infections during chronic allergic conjunctivitis in a large series of patients.

MATERIALS AND METHODS

In this prospective, nonrandomized trial, we evaluated 236 patients (472 eyes) seen in the Eye Department of the University of Naples Federico II from 2003 to 2008 with a diagnosis of chronic allergic conjunctivitis but without clinical evidence of conjunctival infection. An allergic etiology was diagnosed from a familial history of atopy, clinical examination, Prick test, and identification of specific IgE in tears and blood with the RAST technique.^{7,8} In 174 patients (73.7%), previous antiallergic topical and systemic treatment and topical steroid treatment had been unsuccessful. Topical or systemic anti-inflammatory or anti-infective treatment was not allowed during the 2 weeks preceding our study. Patients with any systemic or ocular disease were excluded from the study. Patients with a nonurban lifestyle were also excluded to reduce the risk of conjunctival contamination from a rural environment.

The superior and inferior tarsal conjunctiva of each eye was scraped with an Ayre spatula to collect samples for cytologic examination. Specimens were fixed and stained with May-Grunwald-Giemsa.⁹ Antibiograms and antimicrograms were obtained to identify possible infection. Cultures were confirmed positive based on neutrophil count to avoid false-positive results from contamination. Direct immunofluorescence

on conjunctival scrapings was used to identify *C. trachomatis*. The conjunctival specimens of the 472 eyes were divided into 5 groups based on percent of eosinophilic cells: class 1, 0% to 1% eosinophilic cells; class 2, 2% to 4% eosinophilic cells; class 3, 5% to 8% eosinophilic cells; class 4, 9% to 13% eosinophilic cells; and class 5, 14% to 20% eosinophilic cells. All procedures adhered to the tenets of the Declaration of Helsinki and the protocol was approved by the Institutional Review Board for Human Research of the University of Naples Federico II. Statistical analysis was performed with SPSS software (version 13.0; SPSS Inc., Chicago, IL). Correlations between the classes of eosinophilia and type of infection was evaluated with Pearson's chi square coefficient and Pearson's correlation coefficient *r*. *P* < 0.05 was defined as statistically significant.

RESULTS

The mean age of the 236 patients (83 females, 153 males) was 22 years (range, 7–32 years). One hundred forty-five patients were affected by seasonal allergic conjunctivitis, 49 by perennial allergic conjunctivitis, 20 by atopic conjunctivitis, and 22 by giant papillary conjunctivitis. Concurrent infection was identified in 176 of the 472 eyes (37%), and the pathogens are listed in Table 1. We detected bacteria in 161 of the 176 eyes (91.4%) (Table 2), mycosis in 29 eyes (16.5%) (Table 3), and *C. trachomatis* in 54 eyes (30.7%). Concurrent infection associated with a high neutrophil count was present in 58 of the 176 eyes (33%). There was a strong correlation between the incidence of infections and percent of eosinophilic cells (Pearson's chi square test 14.05, *P* = 0.003) (Table 4). As shown in Table 5, infection was identified in 44.8% and 60.5% of cases in eosinophilia classes 4 and 5, respectively. Interestingly, eosinophilia class was correlated with risk of bacterial infection (Pearson's correlation coefficient *r* = 0.712, *P* = 0.003) (Table 6). In fact, bacterial infections occurred in 96.5% of cases in class 3, in 91.4% of cases in class 4, and in 100% of cases in class 5.

DISCUSSION

In our series of 472 eyes, concurrent infection was present in 176 eyes (37%), and in 161 cases (91.4%), it was the result of bacteria. Bacterial infections were most often the result of *Staphylococcus epidermidis* (82 of 161 cases [50.9%]) and *Staphylococcus aureus* (37 of 161 cases

TABLE 2. Subgroups of Bacteria Detected in 161 Eyes With Bacterial Infection During Allergic Conjunctivitis

No. Eyes (%)	Bacteria
82 (50.9)	<i>Staphylococcus epidermidis</i>
37 (22.9)	<i>Staphylococcus aureus</i>
8 (4.9)	<i>Staphylococcus albus</i>
5 (3.1)	<i>Escherichia coli</i>
4 (2.5)	<i>Staphylococcus haemolyticus</i>
4 (2.5)	<i>Staphylococcus capitis</i>
4 (2.5)	<i>Micrococcus luteus</i>
3 (1.8)	<i>Staphylococcus saprophyticus</i>
3 (1.8)	<i>Streptococcus viridans</i>
2 (1.2)	<i>Enterobacter agglomerans</i>
2 (1.2)	<i>Pseudomonas maltophilia</i>
2 (1.2)	<i>Klebsiella pneumoniae</i>
1 (0.6)	<i>Streptococcus haemolyticus</i>
1 (0.6)	<i>Micrococcus spp</i>
1 (0.6)	<i>Pseudomonas fluorescens</i>
1 (0.6)	<i>Serratia marcescens</i>
1 (0.6)	<i>Klebsiella oxytoca</i>

[23%]), mycotic infections were most often the result of *Candida albicans* (16 of 29 cases [55.2%]), and there was a high frequency of *C. trachomatis* infections (54 of 176 [30.7%]).

Severe corneal ulcers and keratitis secondary to fungal and bacterial infection have been reported in cases of vernal and atopic keratoconjunctivitis.^{10–13} The presence of a latent infection could be the first step in the development of these severe corneal complications.

S. aureus can be isolated from the lid margins of most patients with atopic keratoconjunctivitis.¹⁴ *S. epidermidis* normally inhabits the skin of humans and animals and mucous membranes and is usually nonpathogenic.¹⁵ In our study, the presence of *S. epidermidis* was considered an active infection because of the high neutrophil count in the inflammatory component of the conjunctival mucosa.¹⁶ *C. trachomatis*, an obligate intracellular parasite, infects moist mucosal surfaces where it produces covert damage principally by triggering a localized cell-mediated immune response that is magnified by repeated exposure to infection. *C. trachomatis* infection during atopic conjunctivitis has already been reported.^{6,17} It could be the result of the downregulation of the expression of a wide spectrum of epithelial cell adhesion proteins and

TABLE 1. Number and Type of Pathogens Detected in 176 Eyes With Concurrent Infection During Chronic Allergic Conjunctivitis

No. Eyes (%)	Pathogen
97 (55.1)	Bacteria
5 (2.8)	<i>Mycetae</i>
16 (9)	<i>Chlamydia trachomatis</i>
20 (11.4)	Bacteria + <i>Mycetae</i>
34 (19)	Bacteria + <i>C. trachomatis</i>
4 (2.3)	Bacteria + <i>C. trachomatis</i> + <i>Mycetae</i>

TABLE 3. Subgroups of *Mycetae* Detected in 29 Eyes Presenting Mycotic Infection During Allergic Conjunctivitis

No. Eyes (%)	<i>Mycetae</i>
16 (55.1)	<i>Candida albicans</i>
3 (10.3)	<i>Rhodotorula rubra</i>
3 (10.3)	<i>Pityrosporum ovale</i>
2 (6.9)	<i>Cryptococcus albidens</i>
2 (6.9)	<i>Tricosporon</i>
2 (6.9)	<i>Cladosporium werneckii</i>
1 (3.4)	<i>Candida kruzei</i>

TABLE 4. Number of Eyes in the 5 Eosinophilic Classes

Class	Eosinophilic Cells	Eyes
1	0–1%	52
2	2–4%	146
3	5–8%	153
4	9–13%	78
5	14–20%	43

cytoskeletal elements in the conjunctiva of patients with seasonal allergic conjunctivitis.¹⁸

Various factors have been implicated in the development of a bacterial infection in allergic patients, although a direct relationship between allergy and infections has not been shown. Prolonged steroid treatment has been reported to increase bacterial and mycotic infections^{19,20} and was present in the history of many patients (73.7%) enrolled in our study. Furthermore, antihistamine therapy and sicca syndrome may reduce tear secretion²¹ with a consequent weakening of defense against pathogens. The antimicrobial effect of the tear film may be impaired in allergic conjunctivitis because of possible alterations of the immunoglobulin composition and reduced levels of lactoferrin, an iron-complexing protein with bacteriostatic properties. Conjunctival chemosis at the limbus may affect the stability of the tear film. Finally, the corneal

TABLE 5. Number and Type of Infections in Allergic Eyes in the 5 Eosinophilic Classes*

Infections/Allergic Eyes (%)	No. Eyes	Pathogen
Eosinophilic class 1 17/52 (32.7)	7	Bacteria
	5	<i>Chlamydia trachomatis</i>
	4	<i>C. trachomatis</i> + bacteria
	1	<i>Mycetae</i>
Eosinophilic class 2 42/146 (28.8)	23	Bacteria
	7	<i>C. trachomatis</i>
	5	<i>C. trachomatis</i> + bacteria
	4	Bacteria + <i>Mycetae</i>
Eosinophilic class 3 57/153 (37.2)	3	<i>Mycetae</i>
	32	Bacteria
	8	Bacteria + <i>Mycetae</i>
	11	<i>C. trachomatis</i> + bacteria
	3	<i>C. trachomatis</i> + bacteria + <i>Mycetae</i>
Eosinophilic class 4 35/78 (44.8)	3	<i>C. trachomatis</i>
	20	Bacteria
	8	<i>C. trachomatis</i> + bacteria
	5	Bacteria + <i>Mycetae</i>
Eosinophilic class 5 26/43 (60.5)	1	<i>C. trachomatis</i>
	1	<i>Mycetae</i>
	16	Bacteria
	7	<i>C. trachomatis</i> + bacteria
	2	Bacteria + <i>Mycetae</i>
	1	<i>C. trachomatis</i> + bacteria + <i>Mycetae</i>

*Pearson's chi square test = 14.05, $P = 0.003$.**TABLE 6.** One Hundred Seventy-six Eyes Affected by Allergic Conjunctivitis and Bacterial Infection According to Eosinophilic Class*

Eosinophilic Class	Cases of Bacterial Infection (%)
1	11/17 (64.7)
2	32/42 (76.2)
3	55/57 (96.5)
4	32/35 (91.4)
5	26/26 (100)

*Pearson's $r = 0.712$, $P = 0.003$.

epithelium may be damaged by the mechanical abrasion exerted by giant papillae or punctate superficial keratitis during allergic conjunctivitis²² with an increased risk of infection.²³

In our series, the incidence of concurrent infections was related to the number of eosinophilic cells. In fact, the number of eosinophils was greater in cases of bacterial infection (bacteria were present in all cases with class 5 eosinophilia). The phagocytic action of human eosinophils toward bacteria has been shown by in vitro studies.²⁴ Eosinophils can inactivate such bacterial species as *Escherichia coli*, *S. aureus* and *Mycoplasma*, and fungi,^{24–26} although it is not clear if they are comparable to neutrophils in phagocytic and bactericidal action^{24,27} or whether they are more efficiently triggered by high or low numbers of bacteria.^{24,28} The bactericidal potential of eosinophils arises from their ability to mount an oxidative burst^{29,30} and to produce cytotoxic proteins from specific granules located in the cytoplasm, namely, major basic protein, eosinophil peroxidase, and eosinophil cationic protein.^{31,32} Eosinophils can produce powerful oxidants thanks to their rich supply of NADPH oxidase molecules that generate superoxide and H₂O₂,^{33,34} and these oxidants may act synergistically with released granule proteins.³⁵ It is possible that when eosinophils come into contact with bacteria that have passed across leaky mucosal membranes or damaged skin, eosinophilic activation may perpetuate allergic inflammatory reactions. Bacterial species that are among the most potent activators of eosinophils (ie, *E. coli*, *S. aureus*, and *Clostridium perfringens*) have been implicated in the development of allergy because their numbers are relatively increased in the intestinal flora of infants destined to become allergic.³⁶ A high rate of *Chlamydia* infection associated with the presence of eosinophils has been reported during atopic conjunctivitis.^{6,37} It is likely that in our series, activation of conjunctival eosinophils by bacterial and mycotic pathogens may have elicited an abnormal and prolonged allergic response.

In conclusion, in a patient presenting with chronic allergic conjunctivitis, a latent infection may be present with consequent worsening and chronicity of symptoms. Increased levels of eosinophils are a consequence of infections and could promote chronic allergic conjunctivitis. In these cases, a high level of eosinophils could serve as a marker of concurrent infection. Detection of latent infections seems advisable so as to start prompt, targeted antibiotic therapy.

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