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Differential diagnosis of chronic allergic conjunctivitis in allergic rhinitis

Diagnóstico diferencial de conjuntivitis alérgica crónica en rinitis alérgica

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ABSTRACT

Introduction: At the optometry clinic of the Faculty of Higher Studies (FES) Iztacala, at the Universidad Nacional Autónoma de México, a clinical case of persistent, monocular, allergic rhinoconjunctivitis was presented in a 13-year-old patient, diagnosed and treated as bacterial conjunctivitis in several medical exams prior to our consultation. The case was analyzed considering the signs and symptoms, as well as the evolution of the pathology. *Objective*: To develop a differential diagnosis between chronic allergic conjunctivitis and persistent allergic rhinoconjunctivitis, starting from a process that was diagnosed as infectious. *Method*: Evaluation using biomicroscopy, as well as examination of nasal passages, throat and conjunctival exudate, as a diagnostic aid. *Results*: After clinical evaluation, chronic allergic rhinitis was diagnosed; thus, the patient was referred to a general practitioner for systemic treatment and antihistamine treatment was administered locally. *Conclusion*: Persistent rhinoconjunctivitis has a prevalence of approximately 88% in patients attending ophthalmological consultation. It is important that in clinical practice optometrists strengthen the diagnosis with special tests for allergy detection, while applying diagnostic questionnaires such as the one presented by the International Study of Asthma and Allergies in Childhood (ISAAC) and multidisciplinary work.

Keywords: allergic rhinitis, allergic conjunctivitis, bacterial conjunctivitis.

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RESUMEN

Introducción: en la clínica de optometría de la Facultad de Estudios Superiores (FES) Iztacala, de la Universidad Nacional Autónoma de México, se presentó un caso clínico de rinoconjuntivitis alérgica persistente monocular en un paciente de 13 años de edad, diagnosticado y tratado como conjuntivitis bacteriana por varias instancias médicas previas a nuestra consulta. Se analizó el caso al considerar los signos y síntomas, así como la evolución de la patología. *Objetivo*: desarrollar un diagnóstico diferencial entre conjuntivitis alérgica crónica y rinoconjuntivitis alérgica persistente, a partir de un proceso diagnosticado como infeccioso. *Método*: valoración a través de biomicroscopia, revisión de fosas nasales y garganta y, como apoyo al diagnóstico, exudado conjuntival. *Resultados*: después de efectuar la valoración clínica del paciente, se diagnosticó rinitis alérgica crónica; así, se remitió al médico general para tratamiento sistémico y se administró un tratamiento local con antihistamínicos. *Conclusión*: la rinoconjuntivitis persistente tiene una prevalencia de cerca del 88 % de los pacientes que asisten a consulta oftalmológica. Es importante que en la práctica clínica el optometrista fortalezca el diagnóstico con pruebas especiales para la detección de la alergia y con la aplicación de cuestionarios diagnósticos como el presentado por el estudio International Study of Asthma and Allergies in Childhood (ISAAC) y el trabajo multidisciplinario.

Palabras clave: rinitis alérgica, conjuntivitis alérgica, conjuntivitis bacteriana.

INTRODUCTION

The World Health Organization (WHO) reports that allergic rhinitis is a common chronic condition in the population. The 2014 International Study of Asthma and Allergies in Childhood (ISAAC) shows that, at ages 6 to 7, the worldwide prevalence of asthma is 11.6% and 8.5% for rhinitis; at ages 13 to 14, prevalence is 13.7% with asthma and 14.6% with rhinitis. In Latin America, the prevalence of allergic rhinitis is similar to that of industrialized countries. In Mexico it is higher (12.75%) than the global average (12.1%): asthma represents a prevalence of 8.4% in the group of children between the ages of 6 to 7 years, and rhinoconjunctivitis represents 11.6%. On the other hand, in the group of 13 to 14 years old, asthma has a prevalence of 15.6% while rhinitis has a prevalence of 15.4%. Thus, in Mexico, studies conducted by ISAAC in phase III to determine the prevalence of allergic symptoms and estimate the temporal trend after five years, report a total prevalence of allergic rhinitis of 4.6% (1).

Allergic reactions require expression of acquired immune response, involving the existence of antibody (Ac) and B lymphocyte (LB) and/or T lymphocyte (LT), produced and stimulated in the sensitization phase. Type 1 hypersensitivity (immediate hypersensitivity) is mediated by immunoglobulin E (IgE) (2).

The IgE antibodies bind to Fc receptors present in mast cells and basophils; when a cross-linking between antigen and antibody occurs, these cells are activated to release various mediators, which cause increased vascular permeability, vasodilatation, contraction of the bronchial and visceral muscle, and local inflammation, generating immediate hypersensitivity and anaphylaxis, a contraction of the airway that can cause asphyxia, cardiovascular collapse, and death. Two to four hours later, a late phase reaction characterized by inflammatory infiltrate of eosinophils, basophils, neutrophils and lymphocytes occurs, which can cause tissue damage. There is a genetic predisposition to respond to the common antigens with IgE called *atopy*; this involves the interaction of LTh2 and LB in the sensitization phase or first exposure to the antigen; the immune system initiates the antibody response with IgM production. In allergic or atopic subjects, an imbalance occurs in the subpopulations of LTh antigen-specific, with predominance of LTh2, which secretes cytokines (IL-4 and IL-13) and promotes the change of IgM class to IgE (2,3).

Allergic rhinitis, which is also called *hay fever*, is a consequence of reactions of immediate hypersensitivity to common allergens such as pollen and mites, which enter the upper respiratory tract through inhalation. The clinical manifestations of the disease are: mucosal edema, leukocyte infiltration with abundant eosinophils, secretion of mucus, cough, sneezing, and difficulty breathing. In patients suffering from episodes of allergic rhinitis, they develop focal protuberances of the nasal mucosa called *polyps*, occupied by edematous fluid and eosinophils. Allergic rhinitis is an organ-specific manifestation of allergic disease; it coexists with other immunoallergic conditions such as asthma, sinusitis, conjunctivitis, otitis media with or without hearing loss, decreased smell and taste, lymphoid hypertrophy, and obstructive sleep apnea (3,4).

Rhinitis and conjunctivitis are related, due to the anatomical connection of the naso-lacrimal duct, tube or bony canal that connects the lacrimal sac to the inferior meatus of the nose. All ducts of the lacrimal drainage system are covered by stratified epithelial mucosa consisting of 4 to 5 cellular and goblet layers; the mucosa of the junctional canal of the sac and the nasal canal have a chorion below which extends a lymphatic submucosa network; the innervation of the canaliculi, sac and lacrimal canal are in charge of the external nasal nerve (5).

Exposure to a particular allergen triggers both a cellular (T-cell) and humoral (IgE) response; these two mechanisms culminate in the release of inflammatory mediators responsible for the characteristic symptomatology of allergic rhinitis and conjunctivitis.

The conjunctiva protects the eyeball and is the first barrier against chemical and infectious environmental aeroallergens. The anatomy of the conjunctiva allows interaction and weighting of the tear layer function, and lymphatic irrigation of the conjunctiva, limbus and eyelids drains into the preauricular and submandibular lymph nodes. The lymphatic vessels of the conjunctiva form two systems: a superficial network of the conjunctiva itself and a deep network in the fibrous layer. In limbus, the lymphatic vessels form the pericorneal plexus and the tarsal and postarsal plexus in the tarsus. These plexuses drain into the preauricular, parotid, and submandibular lymph nodes. The blood vessels supplying the conjunctiva and eyelids are branches of the ophthalmic artery. The presence of blood vessels, lymphatics, cells and immunological molecules in the conjunctiva make the latter have the capacity to generate a rapid inflammatory and immunological response (6).

The conjunctiva can have different types of inflammatory reactions (bacterial, viral, fungal, or parasitic), which may be classified according to type of secretion (serous, mucous, mucopurulent, and purulent), type of tissue reaction (papillary and follicular), or according to evolution (hyperacute, acute, and chronic), among others, such as duration and severity of the damage.

Hyperemia is the increase of local blood supply with vascular dilatation; it is produced by increasing the nutritional need of the area irrigated by obstruction or defense on exertion; there are four basic clinical forms of red eye: conjunctival injection, ciliary or periquertic injection, mixed injection, and ecchymosis or subconjunctival hemorrhage. The coloration of the bulbar and tarsal conjunctiva is important in order to classify the degree of hyperemia (grades 1, 2, and 3).

CLINICAL CASE

The patient is a 13-year-old male high-school student who plays soccer and is a frequent computer user; he lives with his pet dog, which often sleeps in bed, and he does not have any systemic or ocular antecedents. He visited the FES Iztacala optometry clinic, reporting an 8-month-old irritation in his left eye (LE); he was treated in different medical facilities and by different specialists; he underwent monocular treatment with ciprofloxacin, dexamethasone, diclofenac and naphazoline for

a month, but he does not remember the dosages. During the examination, he mentioned having a foreign body sensation, pruritus and mucopurulent discharge throughout the day in the left eye.

During a slit-lamp examination of both eyes (BE), a whitish foamy secretion was observed; the photographic sequence of BE reveals grade 1 hyperemia in the upper and lower tarsal conjunctiva, grade 2 follicles in the inferior tarsal conjunctiva, obstructed meibomian glands (Figure 1), hyperemia, grade 1 and bulbar conjunctival vasodilation in the right eye (Figure 2), and staining shows inflammation of the conjunctiva bulbar and a BUT (1-sec break-up-time) in BE (Figure 3). The only difference in the clinical evaluation with biomicroscopy of RE and LE is that the latter showed grade 2 bulbar hyperemia (figures 4 and 5). Considering the chronicity of antecedents, and monocular symptoms, and signs, the prescription was as follows: 1 drop of tobramycin every 4 hours for 2 days, then decrease to 1 drop every 6 hours for 4 days, and end with 1 drop every 8 hours for 3 days; 1 drop of sodium

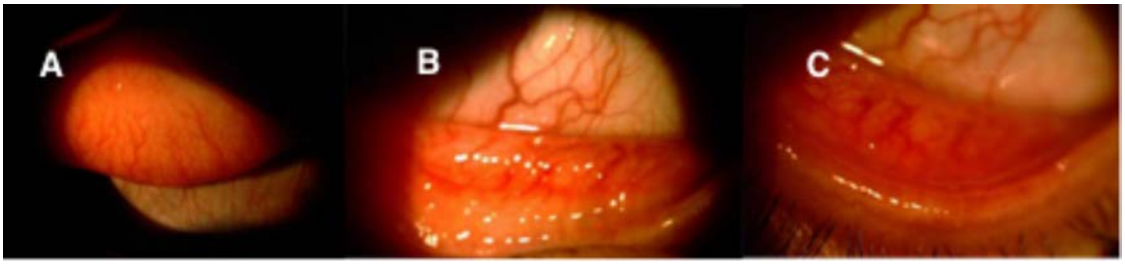

FIGURE 1. **Photographic sequence of the scan of the anterior segment of both eyes**
A) Conjunctive sample tarsal, grade 1 hyperemia in the right eye. B) Inferior tarsal conjunctiva, hyperemia grade 1, follicles grade 2 and vasodilation of bulbar conjunctiva in left eye. C) Inferior tarsus of right eye obstruction of meibomian glands.

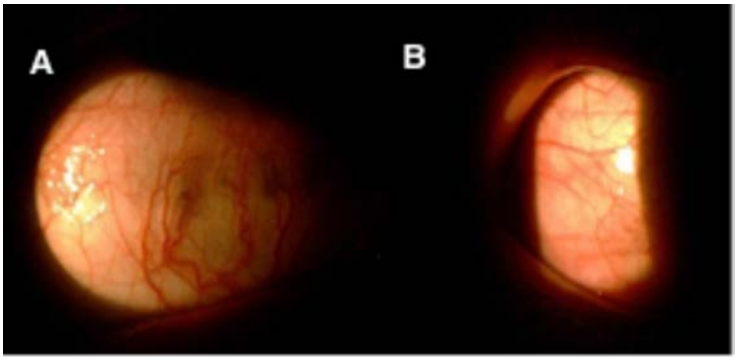

FIGURE 2. **Photographic sequence of the right eye bulbar conjunctiva**
A) Grade 1 lower conjunctival sample hyperemia and vasodilation of bulbar conjunctiva. B) Hyperemia and vasodilation.

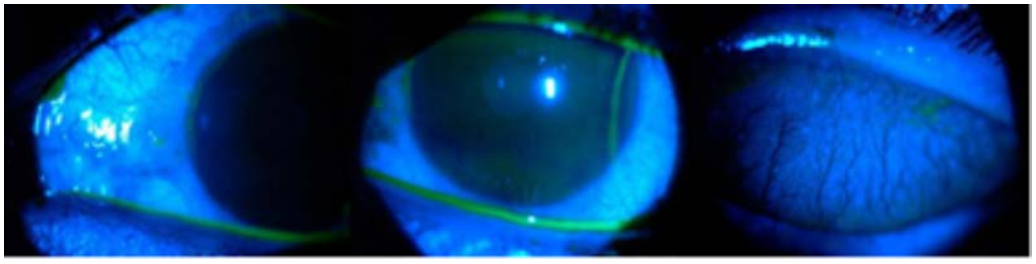

FIGURE 3. **Photographic sequence of bulbar conjunctiva**
A) Staining with fluorescein and inflammation of nasal bulbar conjunctiva in right eye. B) BUT and secretion. C) Upper tarsal papillae of the left eye.

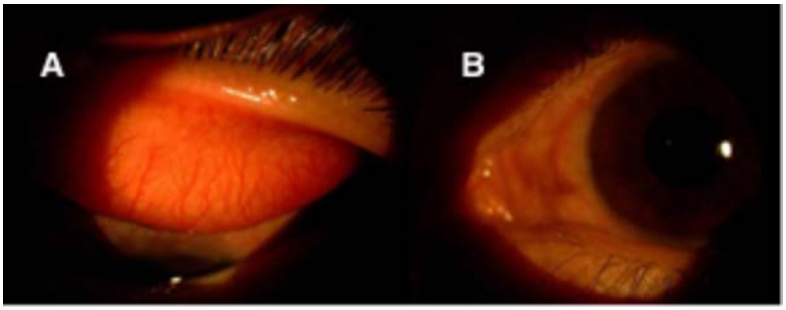

FIGURE 4. **Photographic sequence of left eye bulbar conjunctiva**
A and B) Grade 2 hyperemia in tarsal and bulbar conjunctiva.

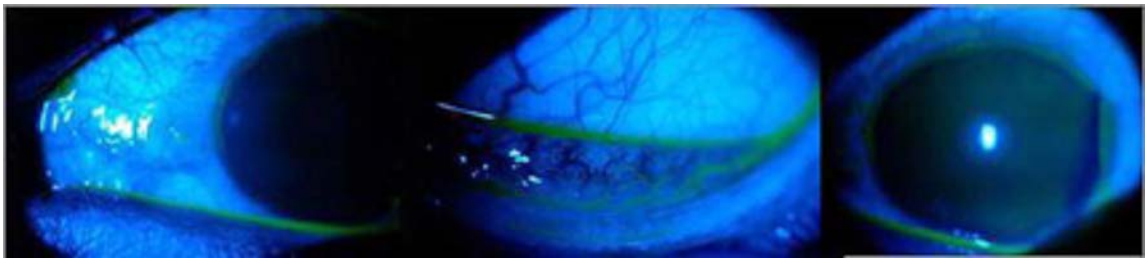

FIGURE 5. **Photographic sequence of left eye bulbar conjunctiva**
A) Conjunctival inflammation bulbar nasal. B) Lower tarsal follicles. C) Tear integrity.

hyaluronate every 2 hours for 7 days; applying compresses was also recommended.

At the end of the treatment, the patient came back for a check-up and reported that he still had mucopurulent discharge in the mornings, itching in BE after bathing, and a foreign body sensation at night; the tearing seems to have subsided. Oily tears were observed in BE, as well as BUT of 3 seconds in both eyes, grade 2 hyperemia in the upper tarsus, puncture in zone 6 of the cornea. The right eye (RE) also showed mucopurulent secretion with tissue adherence and corneal edema, which, due to etiopathogenic classification, is attributed to the epithelial lesion. Secretion was observed in the LE from the base to the tip of the eyelashes; the corneal inflammation registered in the previous review increased.

Considering the signs and symptoms mentioned above, it was decided to suspend the antibiotic and continue the treatment with 1 drop of sodium hyaluronate every 2 hours for 7 days, doing compresses 3 times a day or using a gel mask, and washing the eyelid and eyelashes with neutral soap 3 times a day; it was also recommended to avoid cohabitation with his pet, to wash his hands constantly, to change the sheets and pillowcases every three days, to suspend sports activities, sun exposure and computer use during treatment; he was also asked to come back for a check-up three days later.

After three days of treatment, BE showed grade 2 bulbar and upper and lower tarsal hyperemia, obstructed meibomian glands, inflamed eyelids and partial eyelid closure; cell corneal detachment could be observed in zone 6 of the LE (figures 6, 7, 8 and 9). It was continued with 1 drop of sodium hyaluronate every 4 hours for 7 days, 1 drop of carbomer gel every 12 hours for 8 days, and 1 drop of loteprednol every 12 hours for 4 days, as well as the same recommendations prescribed before. On the other hand, the RE did not show any significant alterations.

After one week of treatment, we observed and assessed a decrease of the corneal edema in BE,

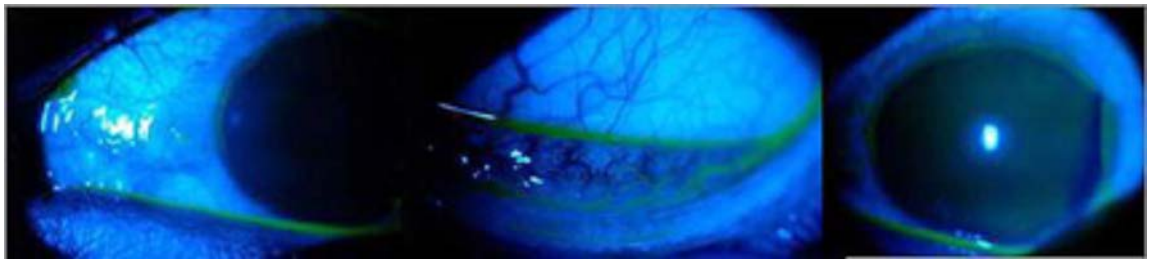

FIGURE 6. **Photographic sequence of left eye bulbar conjunctiva**
A) Secretion in lower eyelid. B) Appearance of conjunctival fibrous tissue. C) Oily tear.

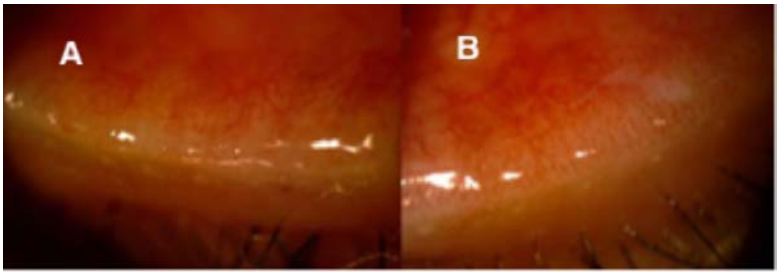

FIGURE 7. **Photographic sequence of lower tarsus of the left eye**
A and B) Inferior tarsal conjunctiva hyperemia grade 2, obstruction of glands of meibomium with vasodilation at free edge of the eyelashes.

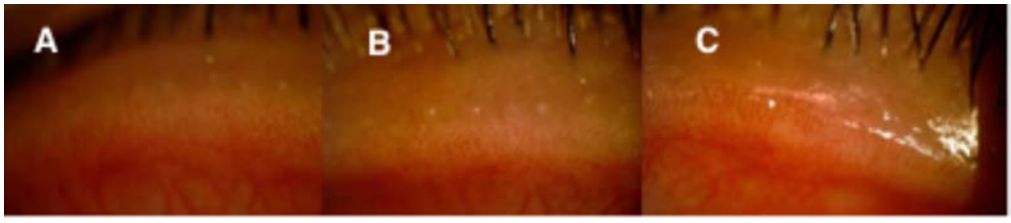

FIGURE 8. **Photographic sequence of upper tarsus in right eye**
A) Vasodilation at the free border of the eyelashes. B) Obstruction of meibomian glands. C) Grade 2 hyperemia.

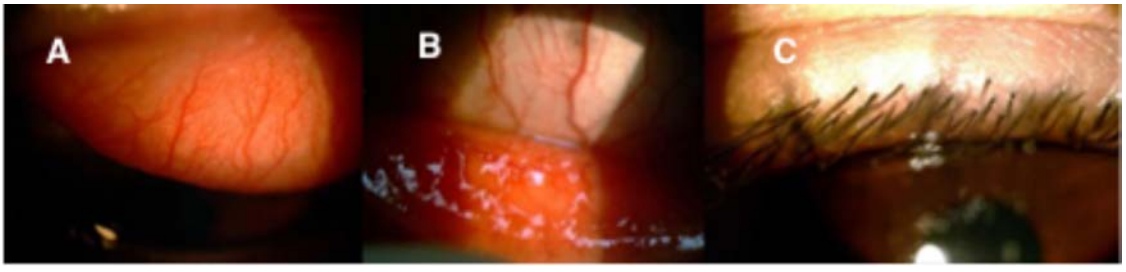

FIGURE 9. **The photographic sequence shows in upper tarsal conjunctiva**
A) Superior tarsal conjunctiva. B) Generalized grade 2 hyperemia in lower conjunctiva bulbar. C) Upper eyelid inflammation.

bulbar hyperemia and vasodilation at the free border of the eyelashes, as well as decreased inflammation of the follicles and papillae (Figure 10). The patient reported pruritus in LE.

The application of conjunctival exudate was considered important. Taking into count the corneal edema that still persisted, we prescribed: 1 drop of polyvinyl alcohol every 4 hours for 1

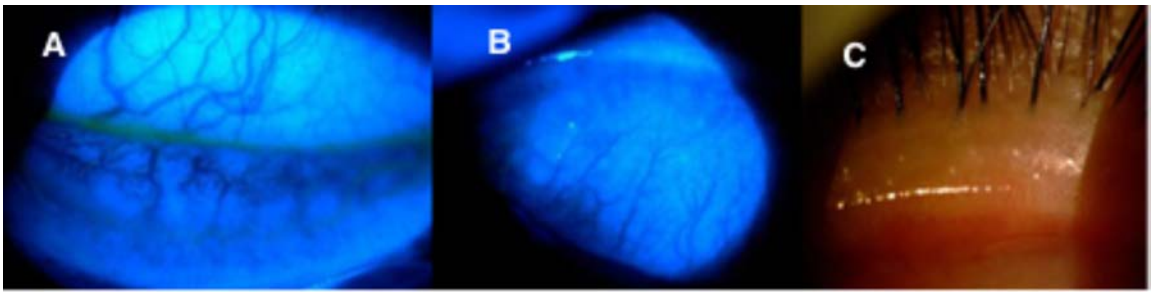

FIGURE 10. **Photographic sequence of bulbar and tarsal conjunctiva**
A and B) Decrease in inflammation of the follicles and papilla of the left eye. C) Decrease in the vasodilation in the free border of the eyelashes, meibomian glands of the right eye.

week, 1 drop of carbomer gel every 12 hours and continuing with the previous recommendations. The patient is referred for revision check-up as soon as he receives the results of the conjunctival exudate.

The patient came in 7 days later, showing the conjunctival exudate results, which indicated that, in both conjunctives, Gram-positive *Staphylococcus epidermidis* was isolated with resistance to all antibiotics except for levofloxacin (LEV); although the signs and symptoms had decreased significantly, we highlight the persistence of pruritus and hyperemia of the conjunctivae of BE. The patient's mother reported that they resided in a wooded area, and therefore an examination of the patient's nostrils and throat was performed, during which hyperemia and dryness in both structures were observed.

This raised the suspicion of allergic rhinitis, and so it was decided to refer the patient to medical consultation at the Clínica Universitaria de Salud Integral (CUSI) of the Facultad de Estudios

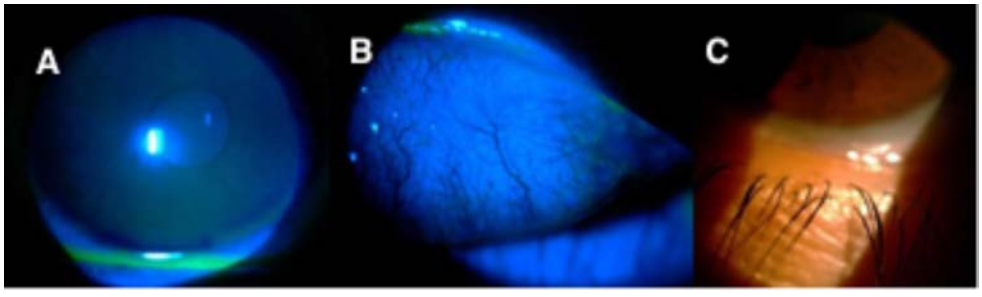

FIGURE 11. **Photographic sequence of bulbar and tarsal conjunctiva of right eye**
A) Decreased bulbar hyperemia, no secretion, and decreased dotting. B) Papillae. C) Decreased inflammation in eyelids and free border of eyelashes.

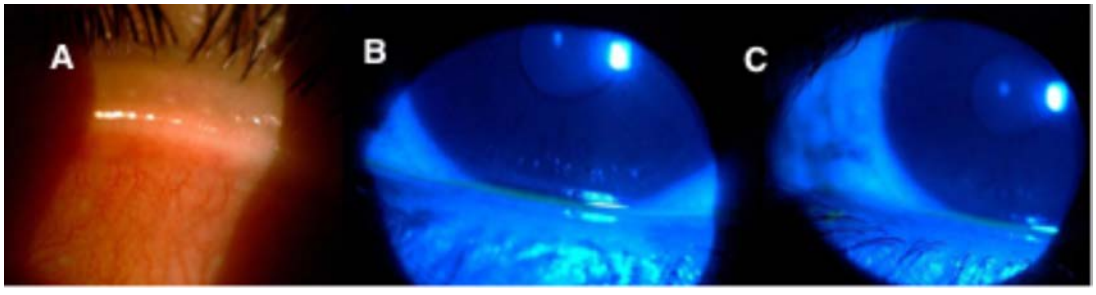

FIGURE 12. **Photographic sequence of the conjunctiva and tarsal in left eye**
A) Glands without obstruction. B and C) Homogeneous tear.

Superiores Iztacala (FES Iztacala) for diagnosis and treatment; he was instructed to continue with the previous treatment. After one week, the patient came back for a check-up, and he reported that he was under systemic treatment with antihistamines. A remarkable improvement was observed in the exploration of BE, although the follicles and papillae persisted on a lower grade (figures 11 and 12). An open appointment was made to continue the case and he was discharged with a definitive diagnosis of persistent allergic rhinoconjunctivitis (7).

DISCUSSION

According to Wagner (8), making a definitive diagnosis of patients with conjunctivitis can be complicated because the signs and symptoms of conjunctivitis produced by bacteria, viruses and fungi may be similar, especially in pediatric patients and in those where nasolacrimal duct obstruction may occur, resulting in the diagnosis and treatment being a combination of available literature about the subject and clinical experience (9). In addition, increased medication and misuse of the drugs may promote the presence of toxic alterations of the subjects. Kansky (9) defines *toxic keratoconjunctivitis* as a pathology that is generated after a physiological alteration by chemical irritation in the ocular tissue and annexes, produced by a drug and/or preservative that is applied topically as measured by the cellular response. It is caused by errors in the drug administration therapy plan where dose selection and treatment time is not based on the physical characteristics of the administered molecule.

Toxic keratoconjunctivitis is the third most frequent disease in ophthalmologic centers (13.9%), and 50% of the diagnoses go unnoticed because there is no in-depth investigation of previous treatments. It is characterized by an average use of between two and five drugs, where there is also corneal affection in 88% of the cases, and it has been reported that in 38% of the cases they have long-term effects on the epithelium. It seems that the case is solved between 2 and 49 days, according to Dart (10).

In the present clinical case, the signs and symptoms of the ocular disease process appeared mainly in the left eye, thus supporting an initial diagnosis of a toxic alteration, because prior to the check-up at the Fes Iztacala optometry clinic, there was a history of application of at least four different drugs, including dexamethasone and diclofenac, two potent anti-inflammatory drugs with an acid pH, which would allow the presence of obligate keratitis (11).

Since there was no corneal lesion despite a month of treatment, the possibility of toxic keratoconjunctivitis was ruled out. This led to thinking that this was a case of bacterial keratoconjunctivitis, mainly because of the laterality of the lesion, since, according to Matzke et al. (12), the clinical presentation of the types of ocular allergy is mainly binocular, with the sole exception of acute allergic conjunctivitis, which is a consequence of contact with an allergen in a sensitive patient. However, this condition is self-limiting, so it was resolved in hours and no treatment was required. This allowed us to support the idea that the alteration was bacterial, which is why we decided to prescribe tobramycin, a broad-spectrum aminoglycoside with preference to Gram-negative bacteria, because previous use of quinolones (cyproflaxin) promotes cross-resistance to antibiotics such as tetracyclines and chloramphenicol (the only drugs available without a combination in Mexico). Moreover, because of their high toxicity, quinolones are not recommended for children under 18 years old.

According to Sacre Hazouri (4) in his article "Allergic Rhinitis. Coexisting Diseases and Complications," adult allergic rhinitis is easily recognized; however, in children, the clinical manifestation varies depending on the duration of exposure to allergens, the age of the child, and the degree of affectation. Symptoms such as nasal itching, rhinorrhea and sneezing are characteristic of the

early phase, mainly produced by the concentration of histamine. These symptoms may be less obvious in children, who are constantly exposed to allergens; children rarely complain of congestion or nasal obstruction, which makes their diagnosis difficult, so treatment may be ineffective, since it is regularly suspected to be an infectious process, and it is therefore treated with multiple antibiotics.

When no results were obtained with the previous treatment, we considered applying the "washout period" technique (13), which recommends only eye wash and lubrication in order to assist the tissue in removing any reservoir of medication and detoxifying the ocular tissue. An exudate of both conjunctivae was also requested, which determined the presence of Gram-positive *Staphylococcus epidermidis* and resistance to all antibiotics except for levofloxacin, quinolone of the same generation as the antibiotic prescribed to the patient before coming to the clinic of the FES Iztacala. It is important to mention that *Staphylococcus epidermidis* is part of the microbiota of the healthy eye (14). This allowed us to think about a chronic allergic process, despite the monocular presence of the clinical profile.

Acceptance of a monocular diagnosis of allergic rhinoconjunctivitis remains a phenomenon that is not understood, because the nasolacrimal apparatus is the only physical connection between the nose and the ocular surface of both eyes, the nasal and ocular innervation originates or passes through a single ganglion, the pterygopalatine; and the venous system of the ocular surface of the nose is connected by the pterygoid plexus and the cavernous sinus, as reported by Hom and Bielory (5).

Sacre Hazouri (4) mentions that 42% of patients with rhinitis have an important ocular component, which should be taken in consideration during diagnosis and treatment. The prevalence of allergic rhinitis and allergic conjunctivitis is not easily defined and conjunctivitis symptoms are often considered unimportant and are not likely to be reported spontaneously by patients with rhinitis or asthma, both in clinical history and in evaluation and diagnostic questionnaires, such as ISAAC (4).

CONCLUSION

The presence of persistent rhinoconjunctivitis is an important case for the professional practice of the optometrist because it has a prevalence of about 88% of patients attending ophthalmological consultation, according to Hom and Bielory (5). The diagnosis of this type of alterations should be strengthened not only with the clinical profile and the experience, but also with a good anamnesis, the implementation of special tests for the detection of allergy and the application of diagnostic questionnaires as the one presented by the ISAAC study.

The importance of this particular case is due to the fact that the clinical condition manifested in a monocular way as compared to the information found in the reviewed bibliographical references, and because the clinical condition went beyond the experience of the evaluators (a monocular presence of the lesion and persistence of mucopurulent secretion), the time of correct treatment for the patient was prolonged. It is for this reason that it is important for the optometrist to develop a multidisciplinary clinical practice supported by laboratory studies for the benefit of the patient.

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