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Normal Immunity of Eye Ball Tissue and Its Features in Adenoviral Eye Infection (Review)

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Abstract Adenovirus infection is considered the most common type of viral pathology of the eye. Adenovirus conjunctivitis (AVC) is highly contagious and often takes the form of epidemic outbreaks, leading to forced closure of the eye compartments. In recent years, complicated, as well as chronic and recurrent forms of AVC, characterized by a chronic course, have begun to occur in ophthalmic clinical practice. Their appearance is associated with a number of factors, in particular, with the strain characteristics of the pathogen, associations of adenovirus with the herpes simplex virus, a decrease in the general immune background in the population (an increase in the number of patients with various immunodeficiency conditions, after organ transplantation, who take steroids for a long time, etc.), as well as with the consequences of irrational therapy.

Keywords Adenoviral conjunctivitis, Cytokines, Immunity, Eyeball

1. Introduction

Inflammatory eye diseases remain one of the serious problems of modern ophthalmology. Patients with this pathology occupy more than 40% of outpatient appointments with an ophthalmologist and up to 50% of inpatients. Inflammatory diseases are associated with up to 80% of temporary disability and 10 to 30% of blindness [2]. And in the autumn-winter period, the vast majority of children also suffer from colds caused by various adenoviruses. When infected with an adenovirus, a child develops the classic triad - conjunctivitis, pharyngitis and high fever. Currently, more than 50 serotypes of adenoviruses are known to cause diseases in humans. Symptoms of adenovirus infection such as runny nose, sore throat, cough and fever are often combined with conjunctivitis. Depending on the clinical course, there are 2 forms of eye damage due to adenoviral infection: adenoviral conjunctivitis (AVK) and epidemic keratoconjunctivitis (EKC). The diagnosis of EKC is usually based on clinical findings and can be confirmed by laboratory antigen tests, polymerase chain reaction (PCR), electron microscopy, and viral isolation in cell culture. Accurate, timely diagnosis and strict adherence to measures to prevent the spread of adenoviral keratoconjunctivitis are the most reliable methods of controlling the spread of infection. is based on the clinical picture and can be confirmed using laboratory antigen tests, polymerase chain reaction (PCR), electron microscopy and viral isolation in cell culture. Accurate, timely diagnosis and strict adherence to measures to prevent the spread of adenoviral keratoconjunctivitis are the most reliable methods of controlling the spread of infection. is based on the clinical picture and can be confirmed using laboratory antigen tests, polymerase chain reaction (PCR), electron microscopy and viral isolation in cell culture. Accurate, timely diagnosis and strict adherence to measures to prevent the spread of adenoviral keratoconjunctivitis are the most reliable methods of controlling the spread of infection.

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Despite the obvious fact that inflammation is the body's protective reaction to the introduction of pathogens, any inflammatory process in the tissues of the eye can result in decreased or even loss of vision. The eye is a zone of a special immune state, and in this zone there are laws to control inflammatory processes. Firstly, the blood-ophthalmic barrier (iris vessels and ciliary body epithelium, pigment epithelium and retinal vessels) largely prevents the access of various molecules and cells, in particular effector T cells and antibodies, to the eye. However, if the blood-ophthalmic barrier is disrupted (due to inflammation, trauma and other reasons), normally immunologically inactive intraocular tissues can be activated due to an increase in the production of lymphokines and interferons. Such "rapid response" areas include the center and periphery of the cornea, its endothelium, iris, ciliary body, trabecula, and retinal pigment epithelium [18]. Secondly, factors inhibiting intraocular inflammation also include the absence of lymphatic vessels in the eye, as well as reduced expression and presentation of major histocompatibility complex antigens of classes I and II. In addition, it is known from literature sources that cells with the phenotype of multipotent mesenchymal stromal cells with a suppressive effect are localized in the limbal zone of

the eye [15]. Thirdly, it is known that the induction of peripheral tolerance ("insensitivity") to eye antigens occurs in the spleen [27]. This process is ensured by the migration of macrophages from the eye through the blood vessels to the spleen. In the spleen, in turn, under the influence of these macrophages, young antigen-specific T cells turn into T-21 regulatory cells, which have the ability to suppress the immune response along both the Th1 and Th2 pathways. And finally, the fourth group of factors determines the local immunosuppressive and anti-inflammatory microenvironment through the secretion of cytokines, growth factors, neuropeptides and special molecules in intraocular fluids. Transforming growth factor, α-melanostimulating hormone, vasoactive intestinal polypeptide, calcitonin-related peptide, free cortisol, and interleukin 1 (IL-1) receptor antagonist were detected in the anterior chamber fluid. Apparently, the listed substances and many others, still unknown, determine the ability of the intraocular fluid to prevent or suppress severe intraocular immune inflammation. Under pathological conditions, there is a disruption in the production of the above immunosuppressive factors, which contributes to the development of immune-mediated inflammation [1,30,11]. Thus, it becomes obvious that the "immune privilege" of the eye is formed due to the coordinated work of many structural and functional, mainly suppressive mechanisms, including those that are unique only to the eye. In addition, the so-called mucosa-associated lymphoid tissue (MALT - from the English mucosa-associated lymphoid tissue), which is found in the mucous membranes of the gastrointestinal, respiratory and urogenital tracts, is found in the mucous membrane of the eye. It is a lymphoid formation in which all types of T and B lymphocytes are found, especially IgA-synthesizing ones, as well as macrophages, mast cells and immunoglobulin-secreting plasma cells. Mucosa-associated tissue appears to be a cooperative immune defense system for all mucous membranes in which it is present, even if contact with the antigen occurs only in one conjunctiva [19,16,27]. Cytokines are mediators (protein signaling molecules) of intercellular and intersystem interactions, participating in almost all vital processes occurring in the body [2,12]. Cytokines are divided into several groups (interleukins, interferons, tumor necrosis factors, growth factors), and their main biological effects (pro- and anti-inflammatory, chemotactic, angiogenic, etc.) are also taken into account. This division is very arbitrary, since almost all cytokines are multifunctional and act according to a network, cascade principle: increased secretion of one of the mediators leads to stimulation (or suppression) of the production of another, etc. When cytokines interact, their biological effects can change. It is generally accepted that normally cytokines are not produced in tissues or are secreted in low (picogram) concentrations (hematopoiesis, repair) [2]. With the development of pathology, immune response, inflammation, etc., their production can increase significantly. In the eye, cytokines are produced by keratocytes, cells of the lacrimal gland, iris and ciliary body, retinal pigment epithelium, lens epithelium, and vascular endothelium. Information about the importance of cytokines in adenoviral infection of the conjunctiva and cornea is scarce in the scientific literature [1,27,17]. For example, Japanese scientists A. Matsuda and Y. Tagawa investigated changes in the level of transforming growth factor TGF-β (TGF-β) in the setting of adenoviral keratoconjunctivitis. The interest of ophthalmologists in this type of cytokines is explained by the fact that this is a fairly large family of multifunctional active proteins with a wide spectrum of action, including an effect on the formation of stromal opacities. Researchers noted an increase in the level of TGF-β2, a significant content of which was noted in the superficial layers and less pronounced in the suprabasal regions, with which the authors associate the appearance of corneal opacities [27]. According to SK Mondal, in viral conjunctivitis, the secretion of cytokines is not as pronounced as in viral keratitis, which the author explains by the presence of MALT tissue in the conjunctiva of the human eye, which forms a full-fledged humoral response [28]. Research by N.E. Shevchuk revealed the leading role of IL-6 in the development of the inflammatory process during adenoviral eye infection, the content of which in the blood serum and tear fluid increases more than 3 times, with a slight increase in the levels of IL-1 and TNF. As the adenovirus is eliminated from the body and the inflammatory process subsides, a decrease in the level of IL-6 in the blood serum and tear fluid is observed, with an almost unchanged content of IL-1 and TNF. Studies have shown that changes in the amount of cytokines in the blood serum are a reflection of the body's reactivity to adenovirus infection of the eye membranes and complement our understanding of the mechanism of their interaction with the macroorganism [1]. As stated above, it is believed that cytokines are normally not synthesized in tissues at all, or are synthesized in minimal quantities. The specified position Apparently, this is true for the quantitative content of cytokines in the tear fluid, where they enter when the membranes of the cells of the conjunctiva and cornea are destroyed. We hypothesized that the content of cytokines in tear fluid may not correspond to their intracellular accumulation due to several reasons - the short half-life of the substance (several hours) and the peak of cytokine release may not coincide with the moment of tear fluid collection. All of the above served as a rationale for our study of the intracellular quantitative content of cytokines in the conjunctiva. It was revealed that 1/3 of the subjects had IFN-γ mRNA (30.0%), 2/3 had IFN-α, IL-1β, IL-6, IL8, IL-12, TNF-α mRNA. The determination of IL-4 and IL-10 mRNA was almost 100%. Regarding the quantitative content of cytokines in "healthy" conjunctival cells, according to our data, they are capable of expressing cytokine genes and producing the substances themselves (cytokines) in a wide range of values. Range of values for the quantitative content of cytokines in conjunctival cells in pkg/ml and in average ranks in healthy volunteers (n=60) [23] Cytokine Min/Max values (pkg/ml) IFN-γ 0 / 28.82 IL-5 0 / 1.96 IL-2 0 / 3.38 25 IL-4 0 / 36.37 IL-10 0.95 / 9.64 IL-12 0 / 7.47 IL-13 0 / 2.24 TNF-α 0 / 28.10 GM-CSF 0 / 16.88.

Previously, it was hypothesized that the formation of subepithelial infiltrates in viral keratoconjunctivitis in the stroma occurs by type of hypersensitivity reaction [16,22]. Later studies showed that during the formation of subepithelial infiltrates in the stroma a delayed antigen-antibody reaction occurs. In recent Studies have paid close attention to keratocytes, which play a leading role in the immune response of the corneal stroma [29].

In the available literature there are practically no studies devoted to the relationship of immune reactions with the normal microflora of the conjunctiva. In addition, the current data is not enough to make an unambiguous conclusion about what species composition of the microflora and what state of the local immune status (possibly depending on the flora colonizing the mucous membrane) can be considered the "norm".

2. Conclusions

As a result of in-depth analysis, it can be concluded that the presence or absence of cytokine mRNA (gene) reflects the potential (i.e. possible) cytokine response, while the actual synthesis of cytokines in conjunctival cells (quantity) corresponds to the actual (real) local response. Potential (gene) and actual cytokine responses do not coincide in half of the cases, which is probably due to the complex relationships in the "cytokines-virus-immunity" system, as well as the directed viral fight against the synthesis of "useful" cytokines.

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