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# IMMUNOLOGICAL FEATURES OF ACUTE RHINOSINUSITIS ASSOCIATED WITH EBV VIRUS (LITERATURE REVIEW)

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**Abstract**

Acute rhinosinusitis is one of the most common upper respiratory tract pathologies and is viral in 90–98% of cases. In recent years, interest has increased in the role of the Epstein-Barr virus (EBV) in the development of immune-inflammatory responses in the nasal mucosa and paranasal sinuses. Although direct evidence of the etiologic role of EBV in acute rhinosinusitis is limited, accumulated data indicate its possible involvement in the impairment of innate and adaptive immunity, increased cytokine response, damage to the epithelial barrier, and prolongation of the inflammatory process. This review analyzes current understanding of the immunopathogenesis of EBV-associated acute rhinosinusitis, the characteristics of the cellular and humoral immune response, and the diagnostic value of serological and molecular markers. Existing gaps in the evidence base and areas for further research are discussed.

**Key words**

acute rhinosinusitis; Epstein–Barr virus; EBV; immunity; cytokines; immunopathogenesis; mucous membrane; inflammation.

**Introduction.** Acute rhinosinusitis is a leading cause of inflammatory diseases of the ENT organs and is considered one of the most common conditions seen by primary care physicians and otolaryngologists. According to current clinical guidelines, the vast majority of cases of acute rhinosinusitis are viral in nature, with bacterial infections occurring in only a limited number of patients. This is why, in recent years, the emphasis in pathogenesis studies has shifted from a bacterial model to the analysis of virus-induced disturbances in immune homeostasis of the nasal mucosa and paranasal sinuses. EPOS 2020 indicates that acute rhinosinusitis is usually a consequence of a viral upper respiratory tract infection, and its annual prevalence in adults is approximately 6–15%.

The most studied viral agents in acute rhinosinusitis remain rhinoviruses, influenza viruses, parainfluenza viruses, adenoviruses, and respiratory syncytial virus. However, in recent years, interest in the role of herpesviruses, particularly the Epstein-Barr virus, has increased. This interest stems not so much from the proven frequency of EBV as a direct etiologic factor in acute rhinosinusitis, but rather from its unique ability to persist in the body, infect both B lymphocytes and epithelial cells, alter the immune response, and create conditions for protracted or atypical inflammation. More than 90% of the world's adult population has serological evidence of previous EBV infection, making the virus a virtually universal component of the human immune system.

From an immunological perspective, EBV is of particular interest because it combines several pathogenetically significant properties. First, the virus is capable of latent persistence in memory B cells, evading complete elimination by the immune system. Secondly, upon reactivation, it activates proinflammatory and antiapoptotic signaling pathways, including NF-κB and a number of interferon-dependent cascades. Thirdly, EBV possesses pronounced immune evasion mechanisms: it modulates antigen presentation, weakens the recognition of infected cells by T lymphocytes and NK cells, and influences the balance of proinflammatory

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and anti-inflammatory cytokines. These properties allow us to consider the virus not only as an infectious agent but also as a factor in chronic immune remodeling of the mucous membranes.

Of particular importance for the mucous membranes of the upper respiratory tract is the fact that EBV interacts with the epithelium of the oropharynx and nasopharynx, and modern studies further emphasize the importance of the epithelial component in the viral life cycle. In 2025, data on the receptor mechanisms of epithelial cell infection were presented, reinforcing the understanding of the key role of the epithelium as an active participant in EBV infection, and not merely as a barrier surface. For rhinosinusitis, this is of fundamental importance, since epithelial dysfunction, disruption of intercellular contacts, decreased mucociliary clearance and local production of cytokines are the early and determining events of the inflammatory process.

Current literature emphasizes that in virus-associated inflammation of the upper respiratory tract mucosa, not only the presence of the virus itself but also the nature of the host's immune response is crucial. Impaired innate antiviral defenses, excessive secretion of IL-6, TNF-α, IL-1β, chemokines, and interferon mediators can determine the severity of symptoms, the duration of swelling, the degree of obstruction of the natural sinus ostia, and the risk of secondary bacterial superinfection. In the case of EBV, this issue is particularly complex, as a direct causal link to acute rhinosinusitis has been proven limited, but the virus has a high potential to modulate local and systemic immunity.

It should be noted that most studies devoted to viruses in sinus pathology focus on chronic rhinosinusitis, nasal polyps, and refractory disease. Moreover, data on EBV are more often found in studies of chronic inflammation, where B-cell activation, tissue expression of EBV-associated proteins, and the virus's role in maintaining local immune imbalance are discussed. Nevertheless, these data are also important for understanding the immunological characteristics of the acute process, as they allow us to trace the mechanisms by which EBV can prolong the acute phase and contribute to the transition to protracted or chronic inflammation. Clinical cases of refractory sinusitis associated with chronically active EBV infection described in 2022 and 2025 further support the need for a more detailed immunological analysis of this problem.

Thus, the current view of EBV-associated acute rhinosinusitis is based on the concept of the virus as a potential immunomodulatory cofactor capable of altering innate and adaptive mucosal defense mechanisms, enhancing the inflammatory response, and disrupting local barrier restoration. This underscores the relevance of systematizing data on the cellular, humoral, and cytokine aspects of the disease and justifies the need for further research in this area.

**Materials and Methods.** This literature review was conducted based on a search of publications in the international scientific databases PubMed, Scopus, Web of Science, Elsevier, the Cochrane Library, and PMC for the period 2015–2026. The following keywords and their combinations were used: “acute rhinosinusitis”, “Epstein-Barr virus”, “EBV”, “immunity”, “cytokines”, “sinonasal inflammation”, “viral rhinosinusitis”, “immune response”, “nasal mucosa”, “B cells”, “epithelial barrier”. The review included systematic reviews, clinical guidelines, immunological reviews, molecular biological studies, clinical observations and case reports that examined viral rhinosinusitis, the immunopathogenesis of EBV infection and inflammatory processes of the upper respiratory tract mucosa. When selecting sources, priority was given to English-language publications from the last 10 years. Particular attention was paid to data on cytokines, the cellular composition of the inflammatory infiltrate, the characteristics of the humoral response, and the mechanisms of EBV immune evasion.

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**Results and discussion.** Analysis of the current literature demonstrates that the immunological characteristics of acute rhinosinusitis associated with the EBV virus should not be viewed as an isolated phenomenon of a classic acute viral upper respiratory tract infection, but rather as a complex model of interaction between persistent herpesvirus, respiratory epithelium, and multilayered innate and adaptive immune responses. The epidemiological context itself makes this problem particularly complex: over 90% of adults show signs of EBV infection, while acute rhinosinusitis is also viral in 90–98% of cases. This means that the detection of EBV serological markers or even viral DNA alone does not prove the virus's causal role in acute sinusitis. However, it does create the preconditions for studying EBV as a factor that can intensify, modify, or prolong the immune-mediated inflammatory process.

The most compelling data concerns EBV's ability to infect both B lymphocytes and epithelial cells. This fundamentally distinguishes it from many respiratory viruses, which are primarily restricted to the epithelial compartment. EBV establishes a latent infection in memory B cells, and upon reactivation, it initiates a cascade of immune events, accompanied by the activation of cytotoxic CD8+ T lymphocytes, NK cells, and the synthesis of interferons and a number of proinflammatory mediators. In terms of the nasal mucosa and paranasal sinuses, this means that even in the absence of a classic primary EBV infection, the virus is capable of maintaining immune activation in the presence of a different respiratory viral load, a compromised barrier, or local dysregulation. Current reviews of EBV immunology emphasize that it is the tension of T-cell surveillance that determines the clinical manifestations of viral reactivation and the severity of inflammatory changes.

One of the key links in immunopathogenesis is the epithelial barrier. Normal nasal mucosa is characterized by tight intercellular junctions, preserved mucociliary clearance, and adequate synthesis of antimicrobial molecules. Viral inflammation, including potentially EBV-associated inflammation, leads to decreased barrier stability, increased epithelial permeability, impaired ciliated cell function, and altered local cytokine profiles. Reviews of viral infections and chronic rhinosinusitis emphasize that loss of barrier function and innate defense failure are common mechanisms contributing to protracted illness and secondary microbial colonization. New data on EBV entry receptors on epithelial cells further strengthen the hypothesis that the epithelial compartment of the upper respiratory tract is an active participant in EBV-induced inflammatory responses.

The cytokine response plays a significant role in the immunological picture. During viral infection of the nasal and sinus mucosa, the leading mediators are considered to be IL-6, IL-1β, TNF-α, type I interferons, and chemokines that recruit neutrophils, monocytes, and lymphocytes. EBV is characterized by a combination of proinflammatory activation and simultaneous immune evasion: the virus stimulates NF-κB pathways, induces cytokine expression, and simultaneously uses its own proteins and microRNAs to weaken effective antiviral control. The literature on EBV-induced diseases repeatedly emphasizes that elevated IL-6 and TNF-α correlate with disease activity and the severity of systemic inflammation. Although large quantitative studies specifically on acute EBV-associated rhinosinusitis are lacking, extrapolation from data on viral sinusitis and EBV reactivation suggests that elevated levels of these cytokines contribute to increased vascular permeability, mucosal edema, and blockage of the natural sinus ostia. Reviews of inflammation in rhinosinusitis also highlight the role of IL-6 as one of the key mediators of persistent mucosal inflammation.

Interestingly, in viral forms of rhinosinusitis, the inflammatory response is not always limited to innate immunity. In the case of EBV, the adaptive immune system plays a particularly significant role. The primary immune response to the virus is characterized by polyclonal activation of B cells and a powerful expansion of CD8+ T lymphocytes. Classic

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infectious mononucleosis, the best-known model of acute EBV infection, is accompanied by a pronounced T-cell response, atypical lymphocytosis, and elevated levels of antibodies to viral capsid antigens. This can have two consequences for local inflammation in the nose and sinuses. On the one hand, it generates a relatively effective cytotoxic response, limiting viral replication. On the other hand, excessive cellular infiltration and mediator activation can exacerbate damage to the mucosa, maintaining swelling and obstructing sinus drainage. Thus, in the case of EBV, immunopathology may be no less significant than the direct cytopathic effect of the virus.

The involvement of B cells deserves special attention. Studies on chronic rhinosinusitis with polyps have described signs of B cell inflammation and expression of EBV-induced protein 2, supporting the hypothesis that the virus is involved in local immune remodeling of the mucosa. Although these data pertain primarily to chronic inflammation, they are important for understanding possible mechanisms in acute inflammation, especially if it is protracted. B-cell activation can be accompanied by increased local immunoglobulin synthesis, immune complex formation, and maintenance of chronic cytokine levels. Recent reviews emphasize that B-cell skewing and disruption of local humoral balance are significant components of mucosal inflammation in nasal and sinus pathologies. Therefore, in the presence of EBV, a more pronounced dysregulation of humoral immunity can be expected compared to conventional acute viral rhinosinusitis.

Equally important is the question of the interferon response. Types I and III interferons are crucial for the effective control of respiratory viruses, but many viruses have developed mechanisms to suppress these pathways. EBV is particularly illustrative in this regard: it can weaken adequate antiviral signaling and alter antigen presentation, making the immune response incomplete and protracted. This situation could theoretically contribute to a longer persistence of acute rhinosinusitis symptoms, including nasal obstruction, hypersecretion, and facial pain. EPOS clinical guidelines define "protracted acute viral rhinosinusitis" as a condition lasting more than 7-10 days with slow improvement. It is in this category of patients that the role of modifying immune factors, including herpesvirus reactivation, may be most significant.

Based on the cellular composition of the inflammatory infiltrate, EBV-associated conditions are characterized by a complex combination of lymphocytic and mononuclear responses. In typical acute viral rhinosinusitis, innate mechanisms and neutrophilic responses predominate in the early stages; however, with EBV involvement, earlier and more pronounced lymphocytic involvement is possible. This is indirectly confirmed by clinical observations of chronically active EBV infection, in which refractory sinusitis was accompanied by systemic immune-inflammatory manifestations and severe T/NK cell pathology. Such cases are rare, but they demonstrate that in some patients, sinus inflammation may not only be a local infection but also a reflection of profound immune dysregulation secondary to EBV. This is especially important in situations where rhinosinusitis is associated with fever, generalized lymphadenopathy, hepatosplenomegaly, cytopenias, or an atypically prolonged course.

Immune evasion mechanisms play a significant role in the pathogenesis of EBV-associated inflammation. Recent reviews indicate that the virus reduces the effectiveness of its recognition of infected cells by interfering with antigen processing, modifying MHC-dependent presentation, and expressing viral molecules that suppress proper immune surveillance. For the sinus mucosa, this means the possibility of prolonged immune activation despite incomplete viral elimination. Clinically, this situation can manifest as a discrepancy between the severity of symptoms and the absence of a typical bacterial pattern, as well as a protracted course without a convincing response to standard therapy. This mechanism is consistent with data on refractory sinusitis in chronically active EBV infection, although direct evidence for typical acute rhinosinusitis is still limited.

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The humoral response in EBV-associated conditions also has diagnostic and pathogenetic significance. In clinical practice, VCA-IgM, VCA-IgG, EBNA-IgG, and, when necessary, early antigens are most often assessed. However, the high seropositivity rate in the adult population significantly limits the interpretation of these tests in acute rhinosinusitis. The presence of VCA-IgG or EBNA-IgG often reflects a past infection rather than the virus's current causative role. Combining serological data with PCR detection of viral DNA in blood, saliva, nasopharyngeal fluid, or tissue may be more informative, but even here, the challenge of distinguishing between latent carriage, reactivation, and clinically significant infection remains. Therefore, immunological diagnosis of EBV-associated rhinosinusitis requires a comprehensive approach with a mandatory assessment of the clinical context.

A significant consequence of a disrupted immune response is the impact on the mucosal barrier and susceptibility to secondary bacterial superinfection. General data on viral rhinosinusitis indicate that epithelial damage, decreased mucociliary clearance, and impaired local defenses facilitate bacterial adhesion and invasion. With the involvement of EBV, these processes could theoretically be amplified by a more prolonged immune imbalance, lymphoid infiltration, and proinflammatory activation. Therefore, it makes sense to consider EBV not only as a possible trigger but also as a factor in the unfavorable immunological background, contributing to a protracted or complicated course of the disease. In this context, further research on local markers—secretory IgA, interferons, IL-6, IL-8, TNF-α, mucosal lymphocyte profiles, and tight junction molecule expression—is particularly important.

Thus, the totality of available data allows us to draw several fundamental conclusions. First, direct evidence that EBV is a frequent independent cause of acute rhinosinusitis is currently lacking; the evidence base here is limited primarily to immunological reviews, indirect pathogenetic models, and rare clinical observations. Secondly, the immunobiology of EBV—its ability to persist, infect B cells and epithelium, modulate the interferon response, and produce proinflammatory cytokines—makes it a plausible cofactor in protracted or atypical inflammation of the nasal and sinus mucosa. Thirdly, key immunological features of this process appear to include epithelial barrier dysfunction, mixed innate-adaptive inflammation, enhanced T-cell and B-cell activation, cytokine imbalance, and signs of incomplete but persistent antiviral immune stimulation. These mechanisms appear to be the most promising areas for further clinical and laboratory research.

**Conclusion.** The immunological characteristics of acute rhinosinusitis associated with the Epstein-Barr virus should currently be considered within the framework of the broader concept of virus-induced dysregulation of mucosal immunity in the upper respiratory tract. Despite the extremely high prevalence of viral forms of acute rhinosinusitis and the widespread prevalence of EBV infection in the population, the direct etiologic role of EBV in the development of typical acute rhinosinusitis remains insufficiently proven. However, a combination of immunological, molecular, and clinical data suggests that EBV is an important modifying factor capable of enhancing the inflammatory response, altering the nature of the local and systemic immune response, and contributing to the protracted course of the disease.

The main immunopathogenetic mechanisms associated with EBV include viral persistence in B lymphocytes, interaction with epithelial cells, activation of proinflammatory cytokine cascades, disruption of the interferon response, and the use of immune evasion mechanisms. These processes create the preconditions for epithelial barrier dysfunction, decreased mucociliary clearance, and the development of prolonged inflammation of the nasal mucosa and paranasal sinuses. Of particular importance is the mixed nature of the immune response, which combines activation of innate immunity, cell-mediated reactions and changes in the humoral link.

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Of practical importance, in patients with atypical, prolonged, or refractory rhinosinusitis, especially when accompanied by lymphadenopathy, severe asthenia, pharyngotonsillar manifestations, or laboratory evidence of systemic immune activation, the possible involvement of EBV should be considered. However, routine use of serological tests alone is insufficient, as the high seropositivity of the adult population limits their specificity. A comprehensive approach, including clinical assessment, PCR diagnostics, cytokine profiling, and examination of local immune markers of the mucosa, appears promising.

The scientific significance of this problem lies in the fact that existing data do not yet allow a definitive distinction to be made between latent carriage, reactivation, and pathogenetically significant EBV association in acute rhinosinusitis. Therefore, prospective multicenter studies with standardized patient selection criteria, quantitative assessment of viral load, examination of the local immune response, and comparison of clinical, endoscopic, and molecular data are needed. This approach will allow us to clarify the true role of EBV in the immunopathogenesis of acute rhinosinusitis and determine its place in modern diagnostic and therapeutic strategies.

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