MAIN IMMUNOGENETIC, PATHOGENETIC, AND CLINICAL FEATURES OF EPSTEIN-BARR VIRUS INFECTION (literature review)

Chemych M., Saienko O., Svitailo V., Klymenko N., Chemych O.

Sumy State University, Sumy, Ukraine

https://doi.org/10.35339/ic.2025.12.2.css

ABSTRACT

Epstein-Barr Virus (EBV), or human herpesvirus type 4, is a common pathogen that infects [90–95]% of the adult population worldwide. Over the past 10 years, research has significantly expanded our understanding of the etiological characteristics of EBV infection, its role in the development of malignant and autoimmune diseases, and its mechanisms of interaction with the immune system. EBV is a complex herpesvirus that has the ability to infect B lymphocytes and epithelial cells, ensuring lifelong persistence in the human body. It has two phases in its life cycle – lytic and latent in which different genetic programs and immune mechanisms are activated. Depending on the functional state of the cell and the type of latency, the virus can change gene expression patterns to avoid immune surveillance. The immune response to EBV infection includes humoral and cellular components. Cytotoxic $CD8^+$ T lymphocytes play a decisive role, but the virus is able to effectively modulate or suppress their activity. To ensure long-term persistence, the virus employs a number of immune evasion strategies, including disruption of antigen presentation via major histocompatibility complex I and II molecules, induction of regulatory T cells, and suppression of proinflammatory responses. EBV infection can manifest in various clinical forms, from infectious mononucleosis to severe chronic diseases: chronic active EBV infection, post-transplant lymphoproliferative disorders, and EBV-associated neoplasms. There is a close relationship between EBV and the development of certain autoimmune diseases, including rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. The virus is capable of causing immune dysregulation through molecular mimicry, expression of viral proteins, activation of cytokine pathways, and loss of immune tolerance.

Keywords: *pathogenesis, clinical presentation, autoimmune processes, oncogenicity, robust health and well-being.*

Introduction

Epstein-Barr Virus (EBV) is one of the most common viruses in the world. It is estimated that over 90% of the adult population worldwide is infected with this virus [1; 2]. Seropositivity increases with age: [0–6] months – high seropositivity (~79%) due to the presence of maternal antibodies, [6–12] months – decrease to 14% due to the disappearance of maternal antibodies [3], in children [6–8] years old – approximately 54%, while in adolescents [18–19] years old – already 83%. The prevalence of EBV varies by region. Asia: in China, seropositivity among children reaches 81 %, and among people over 40 years of age, it is almost 95% [4]. Europe: in France, over the past 15 years, seropositivity among children has decreased to 60% [5]. North America: In the US, seropositivity among children and adolescents aged [6–19] years is 67% [4].

As mentioned above, EBV shows high seropositivity worldwide, especially among adults. In Ukraine, there has been an increase in the incidence of infectious mononucleosis among children, but detailed data on the overall seroprevalence of the population are lacking. Further epidemiological studies are needed in Ukraine to more accurately determine the prevalence of EBV and develop effective prevention and treatment strategies.

Corresponding Author:
Saienko Oleksandr – PhD, Associate Professor of the Department of Infectious Diseases with Epidemiology, Sumy State University, Ukraine.
✉ Ukraine, 40007, Sumy, Kharkivska st., 116.
E-mail: o.saienko@kinf.sumdu.edu.ua

The COVID-19 pandemic has affected the epidemiology of EBV: in 2020, the number of seropositive EBV cases decreased by 30% compared to 2019 [3]. Some studies indicate a possible reactivation of EBV after SARS-CoV-2 infection [6].

EBV belongs to the gammaherpesvirus subfamily of the Herpesviridae family, is a common oncogenic agent discovered during the study of biopsy material from a patient with Burkitt's lymphoma [7]. It is the first identified human lymphotropic herpesvirus that the World Health Organization (WHO) has officially recognized as carcinogenic. According to epidemiological studies, more than 95% of the population is infected with EBV [8]. The main route of transmission is through saliva, although infection is also possible through other biological fluids, breast milk, and organ transplants containing the virus [9].

Among the known subtypes of the virus are EBV-1 and EBV-2. The first is globally distributed and is characterized by a high ability to transform B-lymphocytes into immortalized lymphoblastoid cell lines in vitro. In contrast, EBV-2 is more common in Africa and shows tropism mainly to T cells in culture [10].

The EBV infection process goes through three stages: primary infection with lytic replication, latency, and lytic reactivation [11]. In most cases, the initial infection occurs in early childhood. For example, in northern China, the seroprevalence of EBV antibodies among children exceeds 80% [12]. In childhood, the infection is usually asymptomatic or manifests itself with symptoms of acute respiratory viral infection, but in adolescence or adulthood, it can lead to Infectious Mononucleosis (IM) [13].

After the initial infection, the virus enters a latent phase, remaining in memory B cells, the main reservoir for long-term persistence [14]. In most people, the latent form of EBV infection proceeds without clinically significant signs. However, in conditions of immunodeficiency, reactivation of the virus may occur, accompanied by the development of diseases.

EBV is associated with several pathological conditions: IM, Chronic Active EBV Infection (CAEBV), EBV-related autoimmune disorders, and EBV-induced tumors. These pathologies can pose a serious threat to health, therefore scientists are actively researching the mechanisms of viral persistence and possible ways to eliminate it from the host's body.

Aim. To review scientific publications on the study of immunological features of EBV infection and pathophysiological mechanisms leading to multiple organ and autoimmune damage.

Materials & Methods

Scientific articles and studies published in the PubMed database, the Public Health Center of the Ministry of Health of Ukraine, Karger, Robert Koch Institute, Onlinelibrary, Centers for Disease Control and Prevention, and European Centre for Disease Prevention and Control were used. Particular attention was paid to studies on the immunological characteristics and pathophysiological mechanisms of EBV infection. Articles published between 2015 and 2025 were analyzed using systematic literature review methods and comparative analysis of clinical results to ensure the relevance and accuracy of the conclusions.

Results

EBV has a spherical morphology and consists of three main structural components: an outer envelope, a tegument, and a nucleocapsid [15]. The envelope contains several glycoproteins, eight of which play a key role in the process of virus penetration into the host cell. The tegument is represented by unevenly distributed proteins, a distribution pattern characteristic of herpesviruses. Inside is the nucleocapsid, an icosahedral structure consisting of capsid proteins that surround a double-stranded DNA genome approximately 172,000 base pairs in size [16]. The EBV genome has over 100 genes encoding approximately 85 proteins and up to 50 non-coding RNAs [15].

The virus is transmitted mainly through saliva. In the early stages of infection, the virus affects B-lymphocytes and epithelial cells of the oropharynx. Viral glycoproteins bind to the complement receptor type 2 (CD21, Cluster of Differentiation 21) on B cells, which mediates viral attachment. Subsequently, interaction with Major Histocompatibility Complex (MHC) type II molecules promotes the virus's approach to the cell membrane and triggers the fusion mechanism [17]. Since epithelial cells do not express CD21 and MHC-II, EBV uses alternative entry mechanisms to infect them, including lipid raft-dependent endocytosis and micropinocytosis.

After fusion of the viral envelope with the cell membrane, the tegument and nucleocapsid are released into the cytoplasm. Further release of genetic material and activation of viral DNA polymerase occur in the cell nucleus during the lytic phase. In this phase, the EBV genome expresses more than 80 gene products necessary for viral replication and synthesis of structural components [18].

EBV also activates cellular transformation mechanisms, stimulating the proliferation of infected B cells and their differentiation into memory cells within the germinal center reactions. During the immune response, antigen-presenting cells present viral antigens to T lymphocytes, in particular Cytotoxic T Cells (CTLs, Cytotoxic T-Lymphocytes), which destroy infected cells, controlling the viral load. Some of the infected memory B cells enter the peripheral blood, where they can remain in a latent state or undergo lytic replication. EBV actively replicates in both epithelial cells and B cells, contributing to the constant release of viral particles into the oral cavity. This process promotes the circulation of infected cells between the oropharynx and the general vascular system [19].

EBV is capable of remaining in a latent phase in the human body, which complicates its complete elimination and contributes to the long-term persistence of the virus. After primary infection, linear EBV DNA transitions to a circular form (episome) in the nucleus of the host cell [20]. These episomes attach to the chromatin of the cell with the help of the EBV Nuclear Antigen (EBNA-1), replicate synchronously with the cell cycle, and are transmitted to daughter cells [21].

In the latent phase, EBV expresses only a limited set of proteins and non-coding RNAs. The virus can implement different patterns of latent gene expression (latent types 0, I, II, III), depending on the type of infected cells and their functional state [19]. For example, in the latency phase I, the EBV genome is stored in memory B cells, during latency II their differentiation is stimulated, and latency III is associated with the proliferation of naive B cells. In latent state 0, the expression of viral genes is completely suppressed, allowing the virus to "hide" in the immune system [22].

Under certain conditions, infected B cells can be activated, transformed into plasma cells, and initiate lytic reactivation of EBV. In this phase, special proteins bind to the sites of DNA replication initiation, activating the transcription of viral genes and initiating the lytic cycle. After replication of the viral genome, the newly formed DNA is converted from a circular to a linear form by the terminase complex, packaged into a capsid, wrapped in tegument proteins, and then enveloped by the Golgi apparatus. The cycle ends with exocytosis, when mature viral particles are released from the cell into the extracellular space [9; 23].

Adaptive immunity plays a key role in the recognition and elimination of foreign antigens, including viral antigens, and involves the participation of both B and T cells in the response to EBV infection. B cells produce specific antibodies against viral antigens. In particular, IgM and IgA to the Virus Capsid Antigen (VCA) appear in the early stages of infection, while IgG to VCA peaks after [2–4] months and persists for a long time. Antibodies to gp350, gp42, and gHgL are also produced, which block EBV binding to B cells and inhibit virus fusion, limiting its spread [24; 25].

The cellular response includes the activation of specific $CD8^+$ and $CD4^+$ T cells. $CD8^+$ cytotoxic T lymphocytes recognize viral peptides presented through MHC-I and destroy infected cells. The proportion of lytic antigen-specific $CD8^+$ T cells can reach up to 2% of the total $CD8^+$ population, while latent responses account for about 1% [26]. These cells show the greatest activity towards the products of early lytic genes, with less activity towards Early (E) genes and low activity towards Late (L) genes. Among latent antigens, the immune response of $CD8^+$ T cells is most pronounced to proteins of the EBNA3 family, which limit the proliferation of transformed B cells [26; 27]. Weakening of T-cell immunity, for example after transplantation, can lead to the development of EBV-associated Post-Transplant Lymphoproliferative Disease (PTLD), which can be treated with adaptive transfer of EBV-specific T cells [8; 28].

$CD4^+$ T cells are activated through interaction with MHC-II on EBV-infected B cells. They promote antibody production, support $CD8^+$ T cell function, and can act as effector cells, destroying infected or transformed B cells. Their response to latent antigens is more stable than to lytic antigens, although the activity of $CD4^+$ T cells against IE-, E-, and L-products is relatively uniform [26; 29].

To achieve long-term survival in the host and establish persistent infection, EBV has also developed many strategies to evade immune surveillance. In particular, the virus can suppress the activation of certain receptors on myeloid cells (e.g., Toll-like receptors) and directly influence the expression of MHC-I and MHC-II molecules. Finally, EBV modulates the function of T lymphocytes, NK cells, and antigen-presenting cells, reducing the effectiveness of the immune response [30].

EBV also effectively evades adaptive immune surveillance using a number of mechanisms. In particular, it can disrupt antigen presentation via MHC-I molecules, which prevents infected cells

from being recognized by $CD8^+$ T lymphocytes. Normally, peptides formed by the proteasome are transported to the endoplasmic reticulum, where they bind to MHC-I and are presented on the cell surface to T cells [31].

In addition, EBV can also block antigen presentation via MHC-II. For example, lytic phase proteins can interfere with antigen recognition by $CD4^+$ T cells by binding to the MHC-II complex on the surface of B lymphocytes [32].

It has also been established that EBV can promote the growth of a population of specific regulatory T cells, which potentially suppresses the antitumor immune response and promotes the survival of tumor cells [33].

EBV can cause a wide range of clinical manifestations, from asymptomatic infection to the development of malignant neoplasms. One of the most common manifestations is IM, which develops in [35–50]% of adolescents during primary EBV infection [34]. Its main symptoms are sore throat, fever, lymphadenopathy, and atypical lymphocytosis, which occur as a result of the activation of $CD8^+$ T cells against viral antigens, in particular proteins of the EBNA3 family and products of lytic genes [1; 27].

The diagnosis of acute EBV infection is based on the detection of specific antibodies to EBV or heterophilic antibodies. The virus primarily infects B cells, and the disease usually regresses after the activation of $CD8^+$ T cells, which destroy infected cells [35]. Antiviral therapy, particularly with acyclovir, is effective only against the lytic phase and does not affect latent infection, therefore it does not shorten the course of the disease or reduce the frequency of complications [36]. In most cases, symptomatic treatment is prescribed, although sometimes the disease can progress.

CAEBV is a prolonged (>3 months) course of the disease with high levels of viral DNA in the absence of immunodeficiency [37]. The main symptoms are persistent or recurrent signs similar to IM, as well as liver damage, lymphadenopathy, hepatosplenomegaly, Hemocytic LymphoHistiocytosis (HLH), retinitis, interstitial pneumonia, mosquito bite allergy, etc. [38]. Such complications are associated with the infiltration of organs by EBV-infected lymphocytes. According to a prospective study, EBV mainly infects T cells (60%) and NK cells (40%), with $CD4^+$ cells dominating among the infiltrate. At the same time, the infection proceeds as a latent type II with expression of the EBV Nuclear Antigen (EBNA1), Latent Membrane Proteins (LMP1/2), and short RNA molecules encoded by EBV (EBER, Epstein-Barr Encoded RNA) [30].

The only effective treatment currently considered is hematopoietic stem cell transplantation, although antiviral agents, chemotherapy, and immunotherapy are also used [39].

Recent studies indicate a close link between EBV infection and the development of autoimmune diseases, such as Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Sjögren's Syndrome (SS), and Systemic Lupus Erythematosus (SLE). EBV can activate and stimulate the immune system, thereby increasing the risk of autoimmune diseases. Defective EBV-specific T cells, increased viral load and expression of lytic phase proteins, as well as high levels of antibodies to EBV in patients with RA, SS, and SLE confirm the etiological role of EBV in the development of autoimmune diseases [29; 30; 40]. There are several mechanisms by which EBV causes autoimmune diseases. First, it can infect lymphocytes and express immune regulatory proteins involved in evading the immune response, which can affect the human immune system. Second, it can induce the production of many cytokines and inflammatory factors. The virus-encoded EBER can form complexes with the cellular EBER-binding protein La (SSB, Sjögren's Syndrome antigen B) and can release large amounts of pro-inflammatory factors, mediating the TLR3 signaling pathway, thereby enhancing the autoreactivity of nuclear ribonucleoprotein La in patients with SS and SLE [24; 41]. Finally, EBV can cause loss of immune tolerance and promote the progression of autoimmune diseases through molecular mimicry [42]. Most patients with RA produce characteristic autoantibodies, including Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA). Studies have shown that latent EBV transcripts and latent and lytic EBV proteins are found in ectopic lymphoid structures resembling germinal centers in the synovial membrane of RA, and antibodies against EBNA2 citrullinated peptides are found in patients with RA. Thus, EBV can induce an immune response in the body, which can then be redirected to self-antigens through cross-reactivity and epitope spreading [43].

EBV is an oncogenic virus associated with the development of various malignant neoplasms, capable of provoking the development of various types of lymphomas, including Burkitt's Lymphoma (BL) and Hodgkin's Lymphoma (HL) [2]. BL is one of the first EBV-associated lymphomas to be identified, predominantly in children, with

a high degree of malignancy and rapid progression [44]. According to the WHO classification, BL is divided into endemic, sporadic, and immunodeficiency-associated forms. Endemic LB (eLB), prevalent in equatorial Africa, is associated with EBV and is characterized by translocation of the proto-oncogene MYC, caused by overexpression of AID in B cells infected with latent EBV [45]. Malaria caused by Plasmodium falciparum also promotes AID-induced mutations by increasing the number of B cells and their sensitivity to EBV [46]. In addition, EBV induces the expression of a triad of proteins that promote the survival, proliferation, and immune mimicry of transformed B cells: EBNA1, BamHI Rightward Reading Frame 1 (BHRF1) protein, LMP1 (Latent Membrane Protein 1) (Inhibits Proapoptotic Protein (BIM), preventing apoptosis), and EBER. Clinically, LB may manifest as enlarged lymph nodes, abdominal masses, jaw lesions, and leukemia-like symptoms. The main treatment is intensive chemotherapy, as the standard Cyclophosphamide-Doxorubicin-Oncovin-Prednisone (CHOP, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone) regimen is ineffective. The addition of rituximab improves the prognosis, and in severe cases, allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is effective [2; 47].

Back in 1987, it was established that EBV DNA is detected in 20–50 % of cases in Hodgkin and Reed-Sternberg (HRS) cells [48]. The WHO distinguishes two types of HL: Classical (cHL), which is often associated with EBV, and Nodular Lymphocytic Variant (NLPHL). In cHL, EBV is in type II latency mode, with expression of EBNA1, LMP1/2A, and EBER [49]. LMP1 activates the NF-κB, JAK/STAT, and PI3K signaling pathways, mimicking CD40, which promotes the transformation of B cells into HRS cells. The expression of B-cell markers is also reduced, and LMP2A compensates for the loss of BCR in some HRS cells [50]. In 90% of cases, the first symptom is enlarged lymph nodes; later stages are accompanied by damage to the liver, spleen, and bone marrow. Some patients may experience general symptoms such as fever, weight loss, and itching. Treatment includes chemotherapy and radiation therapy, followed by HSCT or biological agents in cases of recurrence [51].

EBV is closely associated with the development of NasoPharyngeal Carcinoma (NPC), especially in endemic regions of southern China and Southeast Asia. The WHO classifies NPC into three histological types, of which undifferentiated (type III) is most closely associated with EBV. Due to its asymptomatic onset, the cancer is often diagnosed at a late stage [52]. The virus infects epithelial cells in a latent type II pattern, expressing EBNA1, LMP1/2, EBER, and viral microRNAs [53]. LMP1 promotes cell growth, prevents apoptosis, activates MMP9, mucin-1, ezrin, and the VEGF-C/VEGFR-3 axis, which facilitates metastasis. BART microRNAs also contribute to the evasion of T-cell immunity. The most common manifestation is metastasis to the cervical lymph nodes, sometimes accompanied by nasal discharge, nasal congestion, ear discomfort, and headache. The mainstay of treatment is radiation and chemotherapy [54].

The global prevalence of EBV in cases of gastric adenocarcinoma is 8 % [55]. In 2020, EBV-associated cancers caused between 239,700 and 357,900 new cases and between 137,900 and 208,700 deaths worldwide [56].

In 2014, the TCGA first classified gastric cancer into four molecular subtypes, one of which is associated with EBV (EBVaGC, (Epstein-Barr Virus-associated Gastric Carcinoma). EBVaGC is characterized by type I or II latency with expression of EBNA1, LMP1, and LMP2A. Such tumors often have PIK3CA mutations, DNA hypermethylation, and amplification of the JAK2 and PD-L1/2 genes [57; 58]. This type is more common in men and is associated with pronounced lymphoid infiltration and a relatively favorable prognosis [59]. The main approaches to treatment include surgical resection, supplemented by chemotherapy and radiation therapy.

Serological tests are the basis for the diagnosis of EBV infection, especially IM. They allow the stage of infection to be determined and differentiated from other diseases. Antibodies to VCA: VCA-IgM appear in the early stages of infection and disappear after 4–6 weeks; VCA-IgG are detected at the onset of infection, peak after 2–4 weeks, and remain for life. Antibodies to class G nuclear antigen (EBNA-IgG, Epstein-Barr Nuclear Antigen-Immunoglobulin G) appear [6–8] weeks after the onset of infection and indicate a past infection. Antibodies to early antigen (EA-IgG, Early Antigen-Immunoglobulin G) may be detected during acute infection or virus reactivation (*Table*).

Serological tests are used for most patients, but in some cases, especially in immunosuppressed individuals, the results can be difficult to interpret.

Molecular diagnostics, in particular Polymerase Chain Reaction (PCR), allows the detection

Table. Interpretation of serological test results to determine the stage of infection

Stage of infection	VCA-IgM	VCA-IgG	EBNA-IgG	EA-IgG
Acute infection	+	+	–	±
Previous infection	–	+	+	–
Reactivation	–	+	+	+
Not infected	–	–	–	–

Notes: "+" – antibodies are present, "–" – absent, "±" – may be present or absent.

and quantification of EBV DNA in various biological samples. It is used to monitor viral load, especially in immunosuppressed patients, such as transplant recipients. Cerebrospinal fluid PCR is used to diagnose EBV encephalitis and other neurological complications.

In Situ Hybridization (ISH) is used to diagnose EBV-associated tumors and CAEBV by detecting EBV-infected cells in tissue samples using an EBER probe.

Immunohistochemistry is the "gold standard" for confirming EBV infection in tissues by detecting LMP1 EBNA and other proteins.

The Monospot test allows for rapid detection of heterophile antibodies characteristic of IM, but it has low sensitivity in children under 4 years of age and may produce false-positive results in other diseases, so it is not recommended for general use, especially in pediatric practice [60].

Conclusions

The Epstein-Barr virus is a complex herpesvirus that can infect both B lymphocytes and epithelial cells, ensuring lifelong persistence in the human body. It has two phases in its life cycle – lytic and latent in which different genetic programs and immune mechanisms are activated. Depending on the functional state of the cell and the type of latency, the virus can change gene expression patterns to evade immune surveillance.

The immune response to the Epstein-Barr virus includes both humoral and cellular components. Cytotoxic $CD8^+$ T lymphocytes play a decisive role in controlling the infection, but the virus is able to effectively modulate or suppress their activity. To ensure its long-term presence in the body, the virus employs a number of immune evasion strategies, including disruption of antigen presentation via MHC I and II molecules, induction of regulatory T cells, and suppression of proinflammatory responses.

Epstein-Barr virus infection can manifest itself in a wide range of clinical forms: from infectious mononucleosis to severe chronic diseases such as chronic active Epstein-Barr virus infection, post-transplant lymphoproliferative disorders, and EBV-associated neoplasms.

There is a close relationship between EBV and the development of certain autoimmune diseases, including rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. The virus is capable of causing immune dysregulation through molecular mimicry, expression of viral proteins, activation of cytokine pathways, and loss of immune tolerance.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

Funding Sources

There are no external sources of funding.

Consent for publication

All authors give their consent to publication.

References

1. Infectious mononucleosis. Public Health Center of the Ministry of Health of Ukraine. [Internet]. Available at: https://phc.org.ua/kontrol-zakhvoryuvan/inshi-infekciyni-zakhvoryuvannya/krapelni-infekcii/infekciyniy-mononukleoz [in Ukrainian]. [Accessed 10 Jun 2025].

2. Damania B, Kenney SC, Raab-Traub N. Epstein-Barr virus: Biology and clinical disease. Cell. 2022; 185(20):3652-70. DOI: 10.1016/j.cell.2022.08.026. PMID: 36113467.

3. Cai F, Gao H, Ye Q. Seroprevalence of Epstein-Barr virus infection in children during the COVID-19 pandemic in Zhejiang, China. Front Pediatr. 2023;11:1064330. DOI: 10.3389/fped.2023.1064330. PMID: 36846160.

4. Hoover K, Higginbotham K. Epstein-Barr Virus. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. PMID: 32644711.

5. Aubry A, Francois C, Demey B, Louchet-Ducoroy M, Pannier C, Segard C, et al. Evolution of Epstein-Barr Virus Infection Seroprevalence in a French University Hospital over 11 Years, Including the COVID-19 Pandemic, 2013-2023. Microorganisms. 2025;13(4):733. DOI: 10.3390/microorganisms13040733. PMID: 40284570.

6. Amarillo ME, Lindl K, García Lombardi M, Preciado MV, De Matteo E, Chabay P. Pandemic-Driven Shifts in Epstein-Barr Virus (EBV) Epidemiology: Single Center Study. Viruses. 2025;17(3):375. DOI: 10.3390/v17030375. PMID: 40143303.

7. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet. 1964;1(7335):702-3. DOI: 10.1016/s0140-6736(64)91524-7. PMID: 14107961.

8. Lupo J, Truffot A, Andreani J, Habib M, Epaulard O, Morand P, Germi R. Virological Markers in Epstein-Barr Virus-Associated Diseases. Viruses. 2023;15(3):656. DOI: 10.3390/v15030656. PMID: 36992365.

9. Nowalk A, Green M. Epstein-Barr Virus. Microbiol Spectr. 2016;4(3). DOI: 10.1128/microbiolspec.DMIH2-0011-2015. PMID: 27337443.

10. Choi SJ, Jung SW, Huh S, Cho H, Kang H. Phylogenetic comparison of Epstein-Barr virus genomes. J Microbiol. 2018;56(8):525-33. DOI: 10.1007/s12275-018-8039-x. PMID: 29948828.

11. Murata T, Sugimoto A, Inagaki T, Yanagi Y, Watanabe T, Sato Y, Kimura H. Molecular Basis of Epstein-Barr Virus Latency Establishment and Lytic Reactivation. Viruses. 2021;13(12):2344. DOI: 10.3390/v13122344. PMID: 34960613.

12. Wong KCW, Hui EP, Lo KW, Lam WKJ, Johnson D, Li L, et al. Nasopharyngeal carcinoma: an evolving paradigm. Nat Rev Clin Oncol. 2021;18(11):679-95. DOI: 10.1038/s41571-021-00524-x. PMID: 34194007.

13. Vedham V, Verma M, Mahabir S. Early-life exposures to infectious agents and later cancer development. Cancer Med. 2015;4(12):1908-22. DOI: 10.1002/cam4.538. PMID: 26377256.

14. Dugan JP, Coleman CB, Haverkos B. Opportunities to Target the Life Cycle of Epstein-Barr Virus (EBV) in EBV-Associated Lymphoproliferative Disorders. Front Oncol. 2019;9:127. DOI: 10.3389/fonc.2019.00127. PMID: 30931253.

15. Caruso LB, Maestri D, Tempera I. Three-Dimensional Chromatin Structure of the EBV Genome: A Crucial Factor in Viral Infection. Viruses. 2023;15(5):1088. DOI: 10.3390/v15051088. PMID: 37243174.

16. Machon C, Fabrega-Ferrer M, Zhou D, Cuervo A, Carrascosa JL, Stuart DI, Coll M. Atomic structure of the Epstein-Barr virus portal. Nat Commun. 2019;10(1):3891. DOI: 10.1038/s41467-019-11706-8. PMID: 31467275.

17. Connolly SA, Jardetzky TS, Longnecker R. The structural basis of herpesvirus entry. Nat Rev Microbiol. 2021;19(2):110-21. DOI: 10.1038/s41579-020-00448-w. PMID: 33087881.

18. Cui X, Snapper CM. Epstein Barr Virus: Development of Vaccines and Immune Cell Therapy for EBV-Associated Diseases. Front Immunol. 2021;12:734471. DOI: 10.3389/fimmu.2021.734471. PMID: 34691042.

19. Long HM, Meckiff BJ, Taylor GS. The T-cell Response to Epstein-Barr Virus-New Tricks from an Old Dog. Front Immunol. 2019;10:2193. DOI: 10.3389/fimmu.2019.02193. PMID: 31620125.

20. Umakanthan S, Bukelo MM. Molecular Genetics in Epstein-Barr Virus-Associated Malignancies. Life (Basel). 2021;11(7):593. DOI: 10.3390/life11070593. PMID: 34206255.

21. Alsaadawe M, Radman BA, Long J, Alsaadawi M, Fang W, Lyu X. Epstein Barr virus: A cellular hijacker in cancer. Biochim Biophys Acta Rev Cancer. 2024;1879(6):189218. DOI: 10.1016/j.bbcan.2024.189218. PMID: 39549877.

22. De Leo A, Calderon A, Lieberman PM. Control of Viral Latency by Episome Maintenance Proteins. Trends Microbiol. 2020;28(2):150-62. DOI: 10.1016/j.tim.2019.09.002. PMID: 31624007.

23. Longnecker RM, Kieff E, Cohen JI. Epstein-barr virus. In Fields Virology: Sixth Edition. Vol. 1. Wolters Kluwer Health Adis (ESP). 2013. p. 324-89.

24. Coghill AE, McGuire A, Sinha S, Homad L, Sinha I, Sholukh A, et al. Epstein-Barr Virus Glycoprotein Antibody Titers and Risk of Nasopharyngeal Carcinoma. Open Forum Infect Dis. 2022;9(12):ofac635. DOI: 10.1093/ofid/ofac635. PMID: 36519117.

25. Bu W, Joyce MG, Nguyen H, Banh DV, Aguilar F, Tariq Z, et al. Immunization with Components of the Viral Fusion Apparatus Elicits Antibodies That Neutralize Epstein-Barr Virus in B Cells and Epithelial Cells. Immunity. 2019;50(5):1305-16.e6. DOI: 10.1016/j.immuni.2019.03.010. PMID: 30979688.

26. Hislop AD, Taylor GS. T-Cell Responses to EBV. Curr Top Microbiol Immunol. 2015;391:325-53. DOI: 10.1007/978-3-319-22834-1_11. PMID: 26428380.

27. Lv M, Ding Y, Zhang Y, Liu S. Targeting EBV-encoded products: Implications for drug development in EBV-associated diseases. Rev Med Virol. 2024;34(1):e2487. DOI: 10.1002/rmv.2487. PMID: 37905912.

28. El-Mallawany NK, Rouce RH. EBV and post-transplant lymphoproliferative disorder: a complex relationship. Hematology Am Soc Hematol Educ Program. 2024;2024(1):728-35. DOI: 10.1182/hematology.2024000583. PMID: 39644052.

29. Ruiz-Pablos M. CD4+ Cytotoxic T Cells Involved in the Development of EBV-Associated Diseases. Pathogens. 2022;11(8):831. DOI: 10.3390/pathogens11080831. PMID: 35894054.

30. Silva JM, Alves CEC, Pontes GS. Epstein-Barr virus: the mastermind of immune chaos. Front Immunol. 2024;15:1297994. DOI: 10.3389/fimmu.2024.1297994. PMID: 38384471.

31. Ghasemi F, Tessier TM, Gameiro SF, Maciver AH, Cecchini MJ, Mymryk JS. High MHC-II expression in Epstein-Barr virus-associated gastric cancers suggests that tumor cells serve an important role in antigen presentation. Sci Rep. 2020;10(1):14786. DOI: 10.1038/s41598-020-71775-4. PMID: 32901107.

32. Quinn LL, Williams LR, White C, Forrest C, Zuo J, Rowe M. The Missing Link in Epstein-Barr Virus Immune Evasion: the BDLF3 Gene Induces Ubiquitination and Downregulation of Major Histocompatibility Complex Class I (MHC-I) and MHC-II. J Virol. 2015;90(1):356-67. DOI: 10.1128/JVI.02183-15. PMID: 26468525.

33. Hu Z, Usherwood EJ. Immune escape of γ-herpesviruses from adaptive immunity. Rev Med Virol. 2014;24(6):365-78. DOI: 10.1002/rmv.1791. PMID: 24733560.

34. Andrei G, Trompet E, Snoeck R. Novel Therapeutics for Epstein–Barr Virus. Molecules. 2019;24(5): 997. DOI: 10.3390/molecules24050997. PMID: 30871092.

35. Xie C, Zhong LY, Bu GL, Zhao GX, Yuan BY, Liu YT, et al. Anti-EBV antibodies: Roles in diagnosis, pathogenesis, and antiviral therapy. J Med Virol. 2023;95(5):e28793. DOI: 10.1002/jmv.28793. PMID: 37212266.

36. Pagano JS, Whitehurst CB, Andrei G. Antiviral Drugs for EBV. Cancers (Basel). 2018;10(6):197. DOI: 10.3390/cancers10060197. PMID: 29899236.

37. Kimura H, Cohen JI. Chronic Active Epstein-Barr Virus Disease. Front Immunol. 2017;8:1867. DOI: 10.3389/fimmu.2017.01867. PMID: 29375552.

38. Kawada JI, Ito Y, Ohshima K, Yamada M, Kataoka S, Muramatsu H, et al.; Committee for Guidelines for the Management of Chronic Active EBV Disease, Related Disorders (the MHLW Research Team in Japan). Updated guidelines for chronic active Epstein-Barr virus disease. Int J Hematol. 2023;118(5):568-76. DOI: 10.1007/s12185-023-03660-5. PMID: 37728704.

39. Bollard CM, Cohen JI. How I treat T-cell chronic active Epstein-Barr virus disease. Blood. 2018; 131(26): 2899-905. DOI: 10.1182/blood-2018-03-785931. PMID: 29712633.

40. Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296-301. DOI: 10.1126/science.abj8222. PMID: 35025605.

41. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. Front Immunol. 2021;11: 587380. DOI: 10.3389/fimmu.2020.587380. PMID: 33488588.

42. Sakkas LI, Daoussis D, Liossis SN, Bogdanos DP. The Infectious Basis of ACPA-Positive Rheumatoid Arthritis. Front Microbiol. 2017;8:1853. DOI: 10.3389/fmicb.2017.01853. PMID: 29033912.

43. Johansson L, Pratesi F, Brink M, Arlestig L, D'Amato C, Bartaloni D, et al. Antibodies directed against endogenous and exogenous citrullinated antigens pre-date the onset of rheumatoid arthritis. Arthritis Res Ther. 2016;18(1):127. DOI: 10.1186/s13075-016-1031-0. PMID: 27255888.

44. Kalisz K, Alessandrino F, Beck R, Smith D, Kikano E, Ramaiya NH, Tirumani SH. An update on Burkitt lymphoma: a review of pathogenesis and multimodality imaging assessment of disease presentation, treatment response, and recurrence. Insights Imaging. 2019;10(1):56. DOI: 10.1186/s13244-019-0733-7. PMID: 31115699.

45. Fang H, Wang W, Medeiros LJ. Burkitt lymphoma. Hum Pathol. 2025;156:105703. DOI: 10.1016/j.humpath.2024.105703. PMID: 39662784.

46. Redmond LS, Ogwang MD, Kerchan P, Reynolds SJ, Tenge CN, Were PA, et al. Endemic Burkitt lymphoma: a complication of asymptomatic malaria in sub-Saharan Africa based on published literature and primary data from Uganda, Tanzania, and Kenya. Malar J. 2020;19(1):239. DOI: 10.1186/s12936-020-03312-7. PMID: 32718346.

47. Fitzsimmons L, Kelly GL. EBV and Apoptosis: The Viral Master Regulator of Cell Fate? Viruses. 2017;9(11):339. DOI: 10.3390/v9110339. PMID: 29137176.

48. Weiss LM, Strickler JG, Warnke RA, Purtilo DT, Sklar J. Epstein-Barr viral DNA in tissues of Hodgkin's disease. Am J Pathol. 1987;129(1):86-91. PMID: 2821817.

49. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90. DOI: 10.1182/blood-2016-01-643569. PMID: 26980727.

50. Weniger MA, Küppers R. Molecular biology of Hodgkin lymphoma. Leukemia. 2021;35(4):968-81. DOI: 10.1038/s41375-021-01204-6. PMID: 33686198.

51. Tsotridou E, Hatzipantelis E. Epstein-Barr Infection, Hodgkin's Lymphoma, and the Immune System: Insights into the Molecular Mechanisms Facilitating Immune Evasion. Cancers (Basel). 2025;17(9):1481. DOI: 10.3390/cancers17091481. PMID: 40361408.

52. Li W, Duan X, Chen X, Zhan M, Peng H, Meng Y, et al. Immunotherapeutic approaches in EBV-associated nasopharyngeal carcinoma. Front Immunol. 2023 Jan 11;13:1079515. DOI: 10.3389/fimmu.2022.1079515. PMID: 36713430.

53. Nakanishi Y, Wakisaka N, Kondo S, Endo K, Sugimoto H, Hatano M, et al. Progression of understanding for the role of Epstein-Barr virus and management of nasopharyngeal carcinoma. Cancer Metastasis Rev. 2017;36(3):435-47. DOI: 10.1007/s10555-017-9693-x. PMID: 28819752.

54. Murer A, Ruhl J, Zbinden A, Capaul R, Hammerschmidt W, Chijioke O, Munz C. MicroRNAs of Epstein-Barr Virus Attenuate T-Cell-Mediated Immune Control In Vivo. mBio. 2019;10(1):e01941-18. DOI: 10.1128/mBio.01941-18. PMID: 30647153.

55. Hirabayashi M, Georges D, Clifford GM, de Martel C. Estimating the Global Burden of Epstein-Barr Virus-Associated Gastric Cancer: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2023;21(4):922-30.e21. DOI: 10.1016/j.cgh.2022.07.042. PMID: 35963539.

56. Wong Y, Meehan MT, Burrows SR, Doolan DL, Miles JJ. Estimating the global burden of Epstein-Barr virus-related cancers. J Cancer Res Clin Oncol. 2022;148(1):31-46. DOI: 10.1007/s00432-021-03824-y. PMID: 34705104.

57. Abe H, Kaneda A, Fukayama M. Epstein-Barr Virus-Associated Gastric Carcinoma: Use of Host Cell Machineries and Somatic Gene Mutations. Pathobiology. 2015;82(5):212-23. DOI: 10.1159/000434683. PMID: 26337667.

58. Saito R, Abe H, Kunita A, Yamashita H, Seto Y, Fukayama M. Overexpression and gene amplification of PD-L1 in cancer cells and PD-L1+ immune cells in Epstein-Barr virus-associated gastric cancer: the prognostic implications. Mod Pathol. 2017;30(3):427-39. DOI: 10.1038/modpathol.2016.202. PMID: 27934877.

59. Li Z, Lai Y, Sun L, Zhang X, Liu R, Feng G, et al. PD-L1 expression is associated with massive lymphocyte infiltration and histology in gastric cancer. Hum Pathol. 2016;55:182-9. DOI: 10.1016/j.humpath.2016.05.012. PMID: 27260946.

60. Epstein-Barr Virus and Infectious Mononucleosis. Laboratory Testing for Epstein-Barr Virus (EBV), 10 Apr 2024 [Internet]. Available at: https://www.cdc.gov/epstein-barr/php/laboratories/ [accessed 10 Jun 2025].

Received: 04 Mar 2025
Accepted: 28 June 2025
Published: 30 Jun 2025

Cite in Vancouver style as: Chemych M, Saienko O, Svitailo V, Klymenko N, Chemych O. Main immunogenetic, pathogenetic, and clinical features of Epstein-Barr virus infection (literature review). Inter Collegas. 2025;12(2):10p. In press. https://doi.org/10.35339/ic.2025.12.2.css

Archived: https://doi.org/10.5281/zenodo.