Review

Epstein–Barr Virus and Oral Health: Clinical Manifestations, Diagnostic Insights, and Implications for Dental Practice

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Epstein–Barr Virus and Oral Health: Clinical Manifestations, Diagnostic Insights, and Implications for Dental Practice

Shyamkumar Sriram [1], Mambakkam Jayakanth [2], Sajad Ahmad Buch [3], Tanveer Alam [4] and Shamimul Hasan [5,*]

[1] Department of Rehabilitation and Health Services, College of Health and Public Service, University of North Texas Denton, Texas, USA
[2] Department of Internal Medicine, Patiala Heart Institute, Patiala, India
[3] Clinical Oral Health Sciences, School of Dentistry, IMU University, 126 Jln Jalil Perkasa 19, Bukit Jalil, Federal Territory of Kuala Lumpur 57000, Malaysia
[4] Department of Biomedical Dental Sciences, College of Dentistry, Al Baha University, Alaqiq, Al Baha, Kingdom of Saudi Arabia
[5] Department of Oral Medicine and Radiology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India
* Correspondence: shasan1@jmi.ac.in; Tel.: +91-9953290676

Abstract: Epstein–Barr virus (EBV), a widespread human herpesvirus, establishes lifelong latency and is linked to a range of systemic and oral diseases. Although primarily associated with infectious mononucleosis and lymphoproliferative disorders, its oral health implications are often overlooked. The oral cavity serves as both a site of viral transmission and an early indicator of EBV infection, particularly in immunocompromised individuals. This narrative review examines current literature on EBV-related oral manifestations, diagnostic approaches, and clinical management. A systematic literature search using PubMed and Google Scholar identified studies focusing on EBV and its oral presentations, including keywords like ""Epstein–Barr Virus," "oral health," "oral manifestations," "oral hairy leukoplakia," "periodontal disease," and "oral squamous cell carcinoma." EBV-related oral lesions include palatal petechiae, pharyngeal erythema, oral hairy leukoplakia, and ulcers, with emerging links to periodontal diseases and oral cancer. Diagnosis relies on clinical assessment, histopathology, Polymerase chain reaction (PCR), in situ hybridization, and serology. Management is typically supportive, though antiviral therapy and multidisciplinary care may be necessary for immunocompromised patients. Early detection is crucial for effective treatment. Dentists play a key role in recognizing EBV manifestations and ensuring comprehensive care through infection control and collaboration with medical professionals.

Keywords: Epstein–Barr virus; infectious mononucleosis; Oral hairy leukoplakia; Oral health; Oral squamous cell carcinoma; Periodontal diseases

1. Introduction

Epstein–Barr virus (EBV), also known as Human Herpesvirus 4 (HHV-4), is a prevalent double-stranded DNA virus from the gamma herpesvirus family. Over 95% of people are infected with EBV by adulthood, with primary infections often occurring in childhood or adolescence [1]. While childhood infections are usually asymptomatic, adolescents and young adults commonly develop infectious mononucleosis, characterized by fever, pharyngitis, lymphadenopathy, and fatigue [2–4].

During primary infection and reactivation, EBV replicates in oropharyngeal epithelial cells, leading to its shedding in saliva—a major route of person-to-person transmission [4]. The usual route of spread is by close oral contact such as through deep kissing (hence also known as "the kissing disease") [2].

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After primary infection, EBV establishes lifelong latency in memory B lymphocytes and oral keratinocytes, particularly in the Waldeyer's tonsillar region and salivary glands. These cells act as reservoirs, enabling persistent presence of the virus in oral fluids. Reactivation can occur in either B cells or oral epithelial cells, leading to productive infection and further shedding of infectious virus [5–7].

The dual role of the oral cavity as a primary site of EBV infection and a pathway for viral transmission has important implications for oral health practitioners, who are frequently the first to recognize EBV-related mucosal changes during clinical assessments [8].

Although rare, EBV can also be transmitted via organ transplants, breast milk, and potentially through genital or orogenital contact, due to its presence in genital secretions [7].

EBV is associated with a spectrum of oral manifestations, ranging from benign self-limiting lesions to more serious mucosal conditions with oncogenic potential [9].

During acute infection, clinical signs may include palatal petechiae, enlarged tonsils, and inflamed gingiva [4]. In immunocompromised individuals, especially those with HIV/AIDS, EBV reactivation is closely linked with the emergence of oral hairy leukoplakia (OHL), a distinct white plaque lesion typically found on the lateral tongue borders [5].

Emerging evidence indicates that EBV may contribute to the pathogenesis of periodontitis, potentially through synergistic interactions with periodontal pathogens like Porphyromonas gingivalis and Fusobacterium nucleatum [10].

EBV has been identified in specimens of oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC), sparking continued investigation into its possible oncogenic involvement in the oral mucosa [11].

EBV was the first human oncogenic virus to be discovered and has been linked to numerous malignancies, including various epithelial (nasopharyngeal carcinoma and gastric cancer) and lymphoproliferative malignancies (Hodgkin’s lymphoma, Burkitt’s lymphoma, and Non-Hodgkin lymphoma) [12].

Dental professionals must recognize the broader implications of EBV, including its transmission through saliva and its varied oral manifestations. Effective infection control, early detection of lesions, and prompt referrals—particularly for high-risk or immunocompromised patients—are vital components of comprehensive care [13].

This narrative review aims to elucidate the multifaceted role of EBV in oral health, highlighting its epidemiology, virological characteristics, oral manifestations, diagnostic modalities, and implications for dental practice.

2. Materials and Methods

This narrative review was undertaken to evaluate the literature on the oral health implications of Epstein–Barr Virus (EBV). A narrative approach was selected for its effectiveness in exploring broad and complex topics like EBV-associated oral diseases, which may not fit narrowly focused research questions.

To establish the review framework, two independent authors conducted an initial literature scan using Medical Subject Headings (MeSH) terms including “Epstein–Barr Virus,” “oral health,” “oral manifestations,” “oral hairy leukoplakia,” “periodontal disease,” and “oral squamous cell carcinoma.” Boolean operators (AND/OR) were used to refine results. Insights from this preliminary review informed the development of a structured outline, which was refined through discussion and consensus among all co-authors.

A comprehensive literature search was subsequently performed using PubMed and Google Scholar to retrieve peer-reviewed, English-language articles published from January 2010 to March 2025. The search focused on studies pertaining to EBV epidemiology, virology, pathogenesis, clinical oral manifestations, diagnostic methodologies, and infection control practices in dental settings. Additional references were identified by manually screening the bibliographies of relevant publications.

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The inclusion criteria comprised original research articles, systematic reviews, meta-analyses, clinical guidelines, case reports, and expert commentaries relevant to EBV and its impact on oral health. Preference was given to recent publications, high-quality reviews, and studies from reputable sources. Articles published in languages other than English or lacking direct clinical relevance were excluded. A total of 82 references were used in this narrative review. These included 57 original research articles, which formed the primary evidence base. Additionally, the review incorporated 4 systematic reviews, 2 meta-analyses, and 4 case reports, reflecting both the breadth and clinical relevance of the topic. To support practice-oriented insights, 2 clinical guidelines and 11 expert commentaries were also included. Moreover, 2 references were categorized as book chapters or other academic sources (such as textbook chapters or institutional documents).

To maintain scientific rigor and quality, the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines were applied throughout the manuscript preparation.[14] These criteria informed the formulation of review objectives, the organization of content, the selection of references, and the strength of scientific argumentation. The final manuscript underwent review by two senior authors to ensure adherence to SANRA standards and overall academic integrity.

3. Results & Discussion

3.1. Virology and Pathogenesis of Epstein–Barr Virus

Epstein–Barr Virus (EBV) has a linear double-stranded DNA genome (~175 kb) that becomes circular inside host cells. The EBV genome comprises over 80 coding genes and approximately 40 non-coding RNAs. This genetic material is enclosed within an icosahedral capsid, which is itself surrounded by a lipid envelope, forming the complete virion. Between the capsid and the envelope is a protein-dense region known as the tegument [15].

EBV undergoes a biphasic life cycle comprising a lytic (productive) phase and a latent (non-productive) phase. Both phases are essential for the establishment of lifelong persistence within the host and contribute distinctly to EBV-associated pathogenesis, including immune evasion, cellular transformation, and oncogenesis [9,15].

3.1.1. Lytic Phase

During the lytic phase, Epstein–Barr Virus (EBV) infects epithelial cells of the oropharynx, especially those in the tonsillar and nasopharyngeal regions, through glycoprotein interactions with CD21 and other surface receptors. Upon entry, the virus undergoes active replication, synthesizes viral proteins, and releases new virions into the saliva, enabling person-to-person transmission. This stage often presents clinically with sore throat and mucosal ulcerations, particularly in acute conditions like infectious mononucleosis [1].

3.1.2. Latent Phase

Following primary infection, EBV establishes latency in memory B cells, where its genome persists as a circular episome in the nucleus. During this phase, the virus expresses a restricted set of proteins—mainly Epstein–Barr nuclear antigens (EBNAs) and latent membrane proteins (LMPs), that help maintain latency, evade immune responses, and promote B cell survival and proliferation [1,15].

According to the specific pattern of latent viral gene expression, EBV latency is categorized into five distinct latency programs—Latency 0, I, IIa, IIb, and III.14 These latency types are associated with specific disease entities: Latency I is typically observed in Burkitt lymphoma, Latency II in nasopharyngeal carcinoma, and Latency III in immunodeficiency-related lymphoproliferative disorders. Latency 0, marked by minimal or absent viral gene expression, reflects a dormant state and has not been implicated in oncogenesis [16].

3.1.3. Immune Evasion

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During latent infection, EBV employs immune evasion mechanisms by downregulating the expression of its immunogenic proteins and major histocompatibility complex (MHC) class I and II molecules on host cells. This reduction in antigen presentation impairs recognition by cytotoxic T lymphocytes (CTLs), thereby facilitating long-term viral persistence within the host [17].

Furthermore, EBV employs both protein-coding genes, such as LMP1, BHRF1, and EBNA1 and non-coding RNAs like EBERs and BARTs to alter host cellular pathways. These viral factors inhibit apoptosis, impair antigen presentation, and suppress interferon signaling, facilitating immune evasion and lifelong latency [18].

Understanding the complex life cycle and immune modulation strategies of EBV is essential for recognizing its clinical implications in oral health. Ongoing research continues to explore how these virological mechanisms contribute to both transient and chronic disease processes in the oral environment.

3.2. Clinical Manifestations of Epstein–Barr Virus Infection

The oral cavity often serves as both the entry point and a reservoir for the virus, which explains its central role in EBV-related oral disease. Understanding these manifestations is critical for early recognition and appropriate management, particularly in immunocompromised populations. EBV is linked to a broad range of oral manifestations, from mild, self-limiting lesions such as oral hairy leukoplakia to more severe mucosal disorders with potential for malignant transformation including nasopharyngeal carcinoma and lymphomas [19].

3.2.1. Infectious Mononucleosis

Most primary EBV infections are subclinical and not apparent in young children. Therefore, less than 10% of these children develop clinical infections after exposure to EBV. On the other hand, primary EBV infection in adolescents and young adults results in infectious mononucleosis (IM) in approximately 75% of cases [2]. EBV causes approximately 90% of the cases of IM, with the remainder due largely to cytomegalovirus, human herpesvirus 6, toxoplasmosis, HIV, and adenovirus [4].

IM, (also known as glandular fever, or kissing's disease) is characterized by a triad of fever, fatigue, tonsillar pharyngitis, and cervical lymphadenopathy, where lymphocytosis and atypical lymphocytes (also called Downey cells) are typically present [2–4].

The primary mode of disease transmission is through close personal contact with a person who is infected, particularly their saliva, including sharing eating utensils or water bottles, kissing, or through sexual intercourse [3].

The incubation period between Epstein–Barr virus exposure and the onset of infectious mononucleosis typically ranges from 4 to 8 weeks, though it may be shorter in children. A preceding prodromal phase lasting 1 to 2 weeks may occur, marked by nonspecific symptoms such as malaise, loss of appetite, headache, low-grade fever, chills, muscle aches, and joint pain [20,21].

The patient's temperature is typically low-grade but may reach 38.9oC to 40oC. The acute symptomatic phase usually lasts for 2 to 4 weeks [2].

Pharynx is usually diffusely inflamed. There is often marked tonsillar enlargement with thick tonsillar exudates. The tonsillar exudate may appear white, yellow, or gray [2,4]. Tonsillar exudate is seen in 50% of people with infectious mononucleosis [3]. A "whitewash"' exudate on the tonsils may also help to distinguish infectious mononucleosis from the more speckled exudate of bacterial tonsillitis and the erythema of a viral pharyngitis that is void of exudate [4]. Tonsillar inflammation is nonspecific [3].

Palatal petechiae with streaky hemorrhages and uvular edema may be present [2]. Palatal petechiae are more suggestive of IM but are less common than tonsillar exudate and may also be seen in streptococcal pharyngitis. Diffuse erythema and gingival swelling, particularly in adolescents, has also been reported [20].

Periorbital and/or palpebral edema, typically bilateral, occurs in one-third of patients with IM (Hoagland sign) early in the course of the disease and disappears in a few days. The Hoagland sign,

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when present, is useful to distinguish IM from streptococcal pharyngitis and other viral causes of pharyngitis [2].

In EBV-related IM, lymphadenopathy commonly appears as a bilateral, symmetrical enlargement of the posterior cervical lymph nodes, with less frequent involvement of posterior auricular and anterior cervical nodes. This bilateral, symmetrical distribution pattern helps differentiate it from other causes of pharyngitis, including streptococcal tonsillitis (where the lymphadenopathy is usually limited to the upper anterior cervical chain) and non-EBV viral infections [22,23]. Generalized lymphadenopathy may occassionally be seen, a distinguishing clinical feature that aids in differentiating it from other causes of pharyngitis [2].

However, the clinical presentation of IM is often variable and may encompass symptoms such as headache, fatigue, cutaneous rash, jaundice, and hepatosplenomegaly. Rarely, it may lead to complications including marked lymphocytosis, hepatic dysfunction, peritonsillar abscess, upper airway obstruction, and splenic rupture [21].

The concurrence of fever, sore throat, fatigue, and a morbilliform rash, along with distinct clinical signs like tonsillar exudates, palatine petechiae, periorbital edema, posterior cervical lymphadenopathy, and splenomegaly in adolescents or young adults is highly indicative of IM [24]. The absence of lymphadenopathy decreases the clinical likelihood of IM, while marked atypical lymphocytosis strengthens the diagnostic assessment [2,24,25].

The monospot test is a commonly used, cost-effective, and rapid screening tool for IM, detecting heterophile antibodies via latex agglutination using equine erythrocytes [26]. While a positive result indicates EBV infection, the test has notable limitations, including false negatives in up to 25% of adults during early illness, poor sensitivity in pediatric patients (<five years of age), and persistence of antibodies for up to a year post-infection [2]. Due to these limitations, the CDC does not recommend the monospot test as a definitive diagnostic method for IM [2,26].

In instances where the monospot test is positive without accompanying classical clinical features, further EBV-specific serological markers, such as viral capsid antigen (VCA-IgM, VCA-IgG), and Epstein-Barr nuclear antigen (EBNA-IgG) are recommended, with definitive diagnosis established through EBV DNA quantification using polymerase chain reaction (PCR) [27].

IM is usually self-limiting, but symptomatic cases may require supportive care such as rest, hydration, and Non-steroidal anti-inflammatory drugs (NSAIDs) for relief. While NSAIDs are generally safe, virus-related immune changes may increase the risk of unusual drug sensitivities, not limited to antibiotics [28].

Patients with IM should avoid exercise for at least three weeks to prevent splenic rupture and refrain from alcohol, acetaminophen, and other hepatotoxic substances to reduce liver injury risk [29]. Aspirin is contraindicated in children and adolescents due to the potential for Reye's syndrome and bleeding. Corticosteroids are not routinely advised except in severe cases or airway obstruction, and current evidence does not support routine use of antiviral therapy in uncomplicated cases [2–4].

3.2.2. Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is an opportunistic EBV infection of terminally differentiated epithelial cells of the oral mucosa. First reported in 1984 among homosexual HIV-positive patients, it was once considered a hallmark of HIV/AIDS, occurring in over 50% affected patients [5,30].

OHL has also been observed in immuno-suppressed patients, including those undergoing hematopoietic stem cell or organ transplantation, patients with leukemia, and those receiving systemic corticosteroids or immunosuppressive therapy. It has also been reported in immune-related conditions such as autoimmune or hypersensitivity disorders [6,30].

Recent case studies have reported the occurrence of OHL in immunocompetent individuals, particularly in older adults, indicating that OHL is no longer exclusive to those with HIV. Although the exact mechanism in such cases is not well understood, it is hypothesized that immunosenescence-an age-related decline in immune function may increase susceptibility to EBV-related manifestations like OHL [5,31].

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OHL commonly presents as asymptomatic, non-removable white, velvety plaques localized to the lateral borders of the tongue, appearing unilaterally in the majority of cases (96.3%) and bilaterally in fewer instances (3.7%) [32]. Occasionally, the lesions may spread to the dorsal surface of the tongue, and in rare cases, may involve the buccal mucosa, soft palate, pharynx, or esophagus [5,32]. The lateral tongue margins are thought to act as a site of latent EBV persistence in EBV-seropositive individuals. Additionally, the noticeable absence or significant reduction of Langerhans cells within the lesional epithelium indicates a localized mucosal immune defect, potentially facilitating EBV reactivation and OHL pathogenesis [5,6].

OHL presents with plaques that vary from faint white vertical striations to pronounced, corrugated folds with a shaggy, hair-like texture [5,6,33]. In longstanding cases, these lesions may mimic the appearance of idiopathic leukoplakia. While OHL is generally asymptomatic, secondary candida infection can lead to mild discomfort and taste disturbances [5,6,34].

The exact mechanism by which EBV induces OHL remains unclear; however, proposed pathways include infection through EBV present in saliva, reactivation of latent virus within the epithelial cells of the tongue, or transfer of the virus from lymphocytes to epithelial cells under immunosuppressive conditions [6,35].

EBV can be detected through various diagnostic techniques, including polymerase chain reaction (PCR), immunohistochemistry, electron microscopy, and in situ hybridization (ISH). ISH is considered the gold standard, as it not only confirms the presence of EBV but also effectively differentiates EBV-associated lesions from other white lesions, such as hyperkeratosis that exhibit similar clinical and histopathological features [36].

OHL is generally asymptomatic, poses no risk of malignant transformation, and usually does not necessitate treatment [37]. However, in certain cases, intervention may be considered to restore the tongue's normal appearance, eliminate potential microbial colonization sites, improve patient comfort, or address cosmetic concerns. Therapeutic approaches may involve systemic antiviral agents, topical retinoids or podophyllum resin, combination treatments (such as acyclovir with podophyllum), gentian violet, surgical excision, or cryotherapy [33].

3.2.3. Oral Potentially Malignant Disorders & Oral Squamous Cell Carcinoma

Emerging studies indicate a possible link between EBV and Oral Potentially Malignant Disorders (OPMDs), such as oral lichen planus, leukoplakia, and oral submucous fibrosis, with a potential role in Oral Squamous Cell Carcinoma (OSCC) pathogenesis. However, findings are inconsistent, and EBV's precise role in disease development remains unclear, highlighting the need for further research to determine its clinical significance and oncogenic potential [11].

Oral lichen planus (OLP), as defined by the World Health Organization, is a chronic inflammatory, autoimmune disorder affecting primarily the skin and oral mucosa, with infrequent occurrence in the genital mucosa, scalp and nails. It is considered the most common and clinically significant OPMD [38]. Unlike its cutaneous counterpart, OLP shows greater clinical variability, follows a more persistent course, rarely undergoes spontaneous remission, and carries a higher risk of malignant transformation [39,40].

The precise etiopathogenesis of oral OLP is not fully understood; however, it is thought to result from immune system dysregulation triggered by multiple contributing factors, such as microbial infections, certain medications, dental restorative materials, nutritional imbalances, psychological stress, and genetic susceptibility [41]. Among viral agents, hepatitis C virus (HCV) has been the most widely researched in association with OLP [38]. EBV has also been explored for its possible involvement with OLP, but the evidence remains inconclusive due to variability across studies [42].

Pedersen's early research indicated a dysregulated humoral immune response to EBV in OLP patients, suggesting a possible role of EBV in the disease's etiology [43]. Subsequent studies utilizing PCR methods showed notably increased EBV detection in OLP tissues compared to healthy controls [44,45], however, other research failed to demonstrate significant differences, contributing to inconclusive findings regarding this potential association [46,47].

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Recent studies demonstrate a statistically significant correlation between EBV infection and OLP, indicating a possible contributory role of EBV in the initiation or progression of the disease. A systematic review and meta-analysis revealed that OLP patients had over a fourfold increased likelihood of EBV positivity compared to healthy controls [48]. This association is further substantiated by findings from Kwon et al. (2022), who identified EBV in formalin-fixed OLP tissue samples using in a highly specific in situ hybridization technique [49].

EBV may play a role in OLP pathogenesis by infecting epithelial cells and altering immune responses. It can trigger chronic T-cell-mediated cytotoxicity against basal keratinocytes, evade immune detection through latent gene expression, and disrupt immune tolerance via molecular mimicry and cytokine upregulation. These mechanisms suggest that EBV may serve as an immunological trigger or amplifier in the inflammatory processes underlying OLP [42].

The association between EBV and OPMDs or OSCC remains unclear due to conflicting study results. While some research suggests increased EBV presence in OSCC tissues, others find no significant association.

Jalouli et al. [50], and Reddy et al. [51], both reported low or statistically insignificant detection of EBV in cases of oral submucous fibrosis (OSMF), OPMDs, and OSCC, suggesting an inconclusive or limited role of EBV in oral carcinogenesis.

Recent evidence increasingly implicates EBV in the pathogenesis of oral cancer. Gopalakrishnan et al. [52], identified significantly elevated EBV viral loads in exfoliated oral cells from individuals with OPMDs and OSCC, indicating a potential role in the early stages of tumorigenesis. Pankam et al. [53] further reported a statistically significant association between EBV infection and OPMDs localized to the tongue, suggesting anatomical predilection and site-specific progression. Additionally, Heawchaiyaphum et al. [54] demonstrated that EBV may promote OSCC progression by inducing mitochondrial stress, reducing mitochondrial DNA, and reprogramming cellular metabolism, thereby enhancing cancer stem cell characteristics and tumor growth through increased expression of glycolytic enzymes and stem cell markers.

EBV infection significantly promotes OSCC progression by inducing proliferation, migration, invasion, and suppression of apoptosis of the cells. However, the underlying molecular mechanisms by which EBV drives OSCC carcinogenesis and tumorigenesis remain largely unknown [54].

3.2.4. Gingivitis and Periodontal Diseases

Emerging evidence implicates EBV in the pathogenesis of advanced periodontal diseases. EBV DNA has been identified in approximately 60–80% of cases of aggressive periodontitis and in 15–20% of gingivitis cases [55]. Co-infection with cytomegalovirus (CMV) is frequently observed in both marginal and apical periodontitis, suggesting a synergistic role in disease progression. Importantly, EBV has been shown to contribute directly to the development of gingival and periodontal inflammation in immunocompromised hosts, including organ transplant recipients [56].

The current etiopathogenic model of periodontitis highlights a complex interaction between herpesviruses, pathogenic bacteria, and the host immune system. Initial bacterial colonization induces gingival inflammation, which may trigger reactivation of latent herpesviruses in periodontal tissues. Active viral infection weakens local immunity, promoting bacterial overgrowth. In turn, bacterial virulence factors can further reactivate herpesviruses, creating a bidirectional cycle that disrupts immune regulation and drives periodontal tissue destruction and disease progression [57].

3.2.5. Epithelial and Mesenchymal Malignancies

EBV first identified in 1964, is the earliest recognized human oncogenic virus and is implicated in approximately 1.5% of global cancer cases. It plays a pathogenic role in a range of malignancies, including lymphoproliferative disorders—such as Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), extranodal NK/T-cell lymphoma, plasmablastic lymphoma (PBL), and primary effusion lymphoma (PEL)—as well as epithelial cancers like nasopharyngeal carcinoma and gastric carcinoma [58].

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Burkitt's Lymphoma

Burkitt lymphoma (BL) is a fast-growing non-Hodgkin B-cell lymphoma linked to EBV, human immunodeficiency virus (HIV) infection, and translocations of the MYC oncogene [59]. It primarily affects males in early life and commonly involves the maxilla, where it may manifest as a rapidly expanding facial swelling or an exophytic oral mass [60].

Burkitt lymphoma is categorized by the World Health Organization (WHO) into three clinical subtypes: endemic, sporadic, and HIV-related forms.

Endemic BL (eBL): Predominantly affects young children in equatorial Africa and Papua New Guinea, commonly presenting as jaw tumors. Nearly all cases are EBV-positive and strongly associated with regions where Plasmodium falciparum malaria is holoendemic and early EBV exposure is common.

Sporadic BL (sBL): Occurs worldwide, affecting older children and adolescents. It has a lower association with EBV in developed countries, though some regions like northeastern Brazil report high EBV positivity (over 80%) in sBL cases.

HIV-associated BL: Found in HIV-positive individuals, with an incidence over 100 times greater than sporadic BL. Approximately 30–40% of cases are EBV-positive. It typically presents early in HIV infection, often with generalized lymphadenopathy, and is considered an AIDS-defining illness [61–63].

BL often mimics common dental conditions like odontogenic infections, periodontal disease, or other osteolytic lesions often resulting in misdiagnosis and delayed intervention [62]. A key clinical sign is swelling of the gingiva, adjacent soft tissues, or facial bones, which can lead to marked facial asymmetry. Patients may develop pain, tooth mobility, and displacement from tumor invasion into pulp and alveolar bone, with advanced cases showing ulcerative lesions that resemble common oral ulcers, making diagnosis more challenging [64,65]. Cervical lymphadenopathy, potentially spreading to the oral cavity and nasopharynx, can resemble dental infections and contribute to diagnostic delays, emphasizing the need for early biopsy in unusual presentations. Mental nerve neuropathy, manifesting as numbness in the lower facial region(numb chin syndrome), is an uncommon but significant sign suggestive of advanced disease and neural involvement [66].

Radiographic features include periodontal ligament (PDL) thickening, loss of lamina dura, irregular bone destruction, and absence of a tooth follicle in developing teeth [60,62].

Intensive chemotherapy is the mainstay of treatment for Burkitt's lymphoma, with 5-year survival rates ranging from 75% to 95%, depending on the stage at which the disease is diagnosed [61,65,66].

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a malignancy of the nasopharyngeal epithelium, most prevalent in Southeast Asia and southern China. It is associated with a multifactorial pathogenesis that includes environmental factors like tobacco use and intake of nitrosamine-rich foods, a genetic predisposition (particularly among Chinese populations), and EBV infection [67]. EBV plays a central role by infecting both B lymphocytes and epithelial cells, establishing latent infection, and driving tumorigenesis through mechanisms including NF-κB pathway activation, immune system evasion, and inhibition of apoptosis [68].

The clinical presentation of nasopharyngeal carcinoma (NPC) varies with the tumor's stage and extent of spread. Nasal symptoms—including unilateral obstruction, epistaxis, and altered olfaction—are reported in approximately 80% of patients. Ear-related manifestations, such as hearing loss, recurrent otitis media, and tinnitus, often result from Eustachian tube dysfunction. As the disease advances, cranial nerve involvement may lead to neurological deficits, and cervical lymphadenopathy frequently occurs. General systemic signs like headaches, anemia, and unintentional weight loss typically emerge in later stages [69].

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Diagnosing nasopharyngeal carcinoma (NPC) requires a multidisciplinary approach that combines clinical evaluation with imaging studies, histopathological analysis, and molecular diagnostics [70].

Treatment options for nasopharyngeal carcinoma include radiotherapy, chemotherapy, surgery, immunotherapy, targeted therapy, or a combination of these, depending on the case [69]. The primary goal is effective local and regional tumor control, as recurrence increases the risk of distant metastasis. Radiotherapy is the cornerstone of treatment, particularly for non-keratinizing tumors due to their radiosensitivity. Surgery is typically reserved for recurrent cases, while chemotherapy is often used alongside radiotherapy in advanced stages [71].

3.2.6. Miscellaneous Lesions

Sjogren's Syndrome

Sjogren's syndrome (SS) is a chronic autoimmune disease whose characteristic hallmark is lympho-plasmocytic infiltration of the salivary and lacrimal glands. Serological and genetic evidence increasingly implicates EBV in the pathogenesis of SS. EBV can directly trigger salivary gland epithelial cells to release chemokines, which recruit lymphocytes and lead to immune infiltration of exocrine tissues. In Sjögren's syndrome, EBV has been shown to infect labial salivary gland epithelial cells, and its chronic presence may drive polyclonal B-cell activation and the production of autoantibodies, thereby fostering the development of autoimmune responses [72].

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disorder of the central nervous system, caused by a complex interplay of inflammatory and neurodegenerative mechanisms [73]. Major risk factors include EBV infection, adolescent obesity, tobacco use, and vitamin D deficiency [74]. Pivotal research by Bjornevik et al. established a strong causal relationship between EBV and MS, demonstrating that EBV infection precedes the disease onset [75]. Proposed mechanisms involve molecular mimicry, which trigger immune responses against myelin, and EBV reactivation within the CNS, potentially intensifying neuroinflammation [76]. The identification of EBV-derived microRNAs and antigens in MS lesions further supports its direct involvement in MS pathogenesis [77].

Oral Ulcerations in Immunocompromised Patients:

EBV can cause chronic oral ulcerations in immunocompromised individuals, such as transplant recipients. These EBV-positive mucocutaneous ulcers (EBVMCU) may resemble malignancies but are often self-limiting. Early identification is crucial, as they may signal the onset of post-transplant lymphoproliferative disorder (PTLD) [78].

Table 1. summarizes the clinical features, diagnostic aids and treatment of EBV-associated lesions.

Sno	Clinical Features	Diagnostic Aid	Management
1.	Infectious Mononucleosis • Palatal petechiae • Pharyngitis and tonsillitis • Gingival inflammation	• Clinical examination • CBC with atypical lymphocytes • Monospot test / EBV-specific serology	• Supportive care (hydration, analgesics) • Symptomatic treatment • Avoid antibiotics unless secondary infection suspected
2.	Oral Hairy Leukoplakia (OHL) • White, non-removable plaques on lateral tongue • Corrugated, striated pattern	• Clinical appearance • In situ hybridization / PCR for EBV DNA • Histopathology	• No treatment if asymptomatic • Antiretroviral therapy if associated with HIV • Antivirals (e.g., acyclovir) in some cases

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Sno	Clinical Features	Diagnostic Aid	Management
3.	EBV and Periodontal Disease • Association with aggressive periodontitis • Gingival inflammation	• PCR detection of EBV DNA in periodontal pockets	• Conventional periodontal therapy •Consider adjunctive antimicrobials or antivirals
4.	EBV and Oral Potentially Malignant Disorders (OPMDs) • Detected in OLP, OSMF, leukoplakia, and possibly OSCC	• PCR / In situ hybridization for EBV DNA • Immunohistochemistry for LMP1	• Surveillance and biopsy of suspicious lesions • Treatment as per dysplasia or malignancy protocol
5.	Other Rare Manifestations • Sjogren's syndrome • Multiple sclerosis • Chronic oral ulcerations in immunocompromised patients	• Clinical exam • EBV viral load (blood/tissue) • Imaging, biopsy if needed	• Treat underlying cause • Immunosuppression modulation • Antivirals or chemotherapy (for PTLD)

3.3. Infection Control in Dental Settings

Infection control in dental settings is paramount, especially when managing patients with EBV-related oral conditions. EBV is primarily transmitted through saliva and can persist in the oral cavity, posing potential risks during dental procedures. While standard precautions are generally effective, certain measures can further minimize transmission risks [79].

3.3.1. Standard Precautions

Effective infection control in oral healthcare relies on rigorous hand hygiene, the use of personal protective equipment (PPE) such as gloves, masks, eyewear, and gowns, and proper instrument sterilization. Hands must be washed or disinfected before and after patient contact, especially when visibly soiled. PPE is essential for protection against exposure to saliva, blood, and aerosols. Reusable instruments must be thoroughly cleaned and disinfected using standardized sterilization protocols to prevent cross-contamination and ensure patient safety [80].

3.3.2. Environmental and Aerosol Control:

To minimize EBV transmission, clinical surfaces should be cleaned and disinfected with EPA-registered agents effective against herpesviruses, including EBV. Aerosol management involves using high-volume evacuation systems during procedures and pre-procedural antimicrobial mouth rinses to reduce airborne and salivary microbial loads [81].

3.3.3. Patient Screening and Treatment Planning:

Clinicians should screen for signs of active EBV infection, such as oral hairy leukoplakia or unexplained ulcers, as these may guide clinical decisions. For patients with active EBV lesions—particularly those who are immunocompromised—it is advisable to postpone non-urgent dental treatments to minimize risk and ensure appropriate care [82].

3.3.4. Staff Education and Training

Dental staff should undergo regular training in infection control, emphasizing standard precautions against EBV. Patient education is also vital, focusing on not sharing personal items like toothbrushes and maintaining good oral hygiene to reduce transmission risk [83].

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3.4. Limitations

This narrative review has several methodological limitations. As a non-systematic review, it lacks formal quality appraisal of the included studies, which may introduce selection bias. The literature search was confined to English-language articles available on PubMed and Google Scholar, possibly excluding relevant research from other databases or non-English sources. Although efforts were made to prioritize recent and high-quality evidence, findings-particularly those concerning EBV's role in the pathogenesis of oral potentially malignant disorders and its oncogenic potential remain inconclusive due to heterogeneity in study designs and diagnostic criteria. Furthermore, the absence of a meta-analytic approach limits the ability to derive quantitative insights into causality or disease prevalence.

4. Conclusions

EBV significantly impacts oral health, presenting with lesions that range from benign to potentially serious, especially in immunocompromised patients. The oral cavity functions as both a site of viral activity and a diagnostic window into systemic health. Dentists play a vital role in early detection, referral, and interdisciplinary management of EBV-associated conditions. Strict infection control is essential to prevent transmission. Ongoing research and emerging diagnostics will continue to shape comprehensive strategies for managing EBV within both dental and medical practice.

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