

# Evidence of Epstein–Barr Virus Association with Head and Neck Cancers: A Review

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## Abstract

Epstein–Barr virus (EBV) is ubiquitous: over 90% of the adult population is infected with this virus. EBV is capable of infecting both B lymphocytes and epithelial cells throughout the body including the head and neck region. Transmission occurs mainly by exchange of saliva. The infection is asymptomatic or mild in children but, in adolescents and young adults, it causes infectious mononucleosis, a self-limiting disease characterized by lethargy, sore throat, fever and lymphadenopathy. Once established, the virus often remains latent and people become lifelong carriers without experiencing disease. However, in some people, the latent virus is capable of causing malignant tumours, such as nasopharyngeal carcinoma and various B- and T-cell lymphomas, at sites including the head, neck and oropharyngeal region. As lymphoma is the second-most common malignant disease of the head, neck and oral region after squamous cell carcinoma, oral health care workers including dentists and specialists have a responsibility to carry out a thorough clinical examination of this anatomical region with a view to identifying and diagnosing lesions that may represent lymphomas. Early detection allows early treatment resulting in better prognosis. The focus of this review is on the morphology, transmission and carcinogenic properties of EBV and clinical and diagnostic aspects of a range of EBV-associated malignancies occurring in the head, neck and oral region.

As carcinogenic agents, viruses contribute to a significant proportion of the global cancer burden: approximately 15% of all human cancers, worldwide, are attributable to viruses.<sup>1,2</sup> Serologic and epidemiologic studies are providing mounting evidence of an etiologic association between viruses and head and neck malignancies.<sup>3</sup> To update oral and maxillofacial surgeons and oral medicine specialists and raise awareness of this association, we recently reviewed the evidence of the etiologic role of human papillomavirus in oral disease.<sup>4</sup> In this paper, we review the current state of knowledge of the association of Epstein–Barr virus (EBV) with malignant diseases in the head and neck region.

## Epstein-Barr Virus

EBV, also called human 4, belongs to the herpesvirus family.<sup>5</sup> EBV was first identified in 1964 by Epstein's group in a cell line derived from Burkitt's lymphoma.<sup>6</sup> Sero-epidemiologic studies indicate that more than 90% of adults worldwide are infected with EBV.<sup>7,8</sup> In developing countries, infection occurs early in life, and most early childhood infections are subclinical. In more affluent Western societies, when primary infection is delayed until later

childhood or adolescence, it manifests in approximately 25–75% of cases as infectious mononucleosis.<sup>7</sup> This is a self-limiting disease associated with the triad: fever, lymphadenopathy and pharyngitis.<sup>8</sup> Once infected, people become lifelong carriers of EBV, often without experiencing disease.<sup>8</sup> The virus persists in 2 main forms: in circulating latently infected immune cells and in epithelial cells of the oropharynx and possibly also of the urogenital tract and salivary glands.<sup>9</sup> The primary site of EBV infection is the oropharynx and the virus is capable of infecting both B cells and epithelial cells and switching between the two.<sup>9</sup>

## Structure and Life Cycle of EBV

EBV is an enveloped virus with a DNA core surrounded by a protein capsid. This capsid is surrounded by a protein tegument, which in turn is contained in a lipid envelope.<sup>10,11</sup> The EBV genome is a linear, double stranded DNA molecule that encodes more than 85 genes<sup>11</sup> and a series of products that interact with a wide variety of anti-apoptotic molecules, cytokines and signal transducers. These products and events promote EBV infection, immortalization and transformation.<sup>12</sup> EBV becomes latent in lymphocytes without active viral production,<sup>13</sup> but can induce proliferation of the latently infected cells.<sup>14</sup>

EBV infection of B lymphocytes is mediated through the interaction of the viral envelope glycoprotein gp350/220 with the cellular receptor for the C3d complement component CR2 (CD21).<sup>15</sup> After binding of the viral particle to the host cell and endocytosis, the viral envelope fuses with the host-cell membrane by a mechanism involving 3 other viral glycoproteins: gp85, gp25 and gp42.<sup>16</sup>

Recent studies have shown that in addition to B cells and epithelial cells, EBV can also infect T lymphocytes, natural killer cells, monocytes/macrophages, smooth muscle cells and endothelial cells.<sup>17</sup> This is evidenced by the presence of EBV in some T-cell lymphomas and other diseases, such as nasopharyngeal and gastric carcinomas and oral hairy leukoplakia in immunocompromised patients.<sup>18</sup>

EBV infection in healthy chronic virus carriers is largely restricted to B lymphocytes, although in certain situations the virus can be detected in epithelial cells. The most likely role of epithelial cells is as a site for replication and amplification of EBV rather than a site of persistent latent infection.<sup>19</sup>

## Transmission of EBV

Transmission of EBV occurs mainly via saliva, in which large numbers of infectious viruses can be detected.<sup>19</sup> Transmission commonly occurs during exchange of saliva among young children, directly or through handling of contaminated toys and utensils.<sup>13,20</sup> Among adolescents, transmission

occurs by kissing, which accounts for infectious mononucleosis and, hence, the name “kissing disease.”<sup>20</sup> EBV is shed in high concentrations in oral secretions consistently for more than 6 months following primary infection and intermittently at lower concentrations throughout life; thus, the risk of transmission is greater from individuals who have been recently infected. It has been reported that at any given time, as many as 20–30% of healthy adults who are previously infected with EBV shed the virus in low concentrations in oral secretions.<sup>20</sup> Immunosuppression facilitates reactivation of latent EBV, and the proportion of EBV-infected immunosuppressed people shedding virus increases to 60–90%.<sup>20</sup> EBV is also found in female and male genital secretions and can be transmitted by sexual contact.<sup>20</sup>

## EBV-Host Interactions

Like other viruses, EBV needs a host in which to replicate. Attachment to the host cell and penetration into it are important events in viral infection. Transmitted by saliva, EBV enters and replicates in the epithelial cells of Waldeyer's tonsillar ring, which is situated in the oropharynx, and then infects B lymphocytes in the underlying lymphoid tissues.<sup>11</sup> Attachment and penetration of the host cell occurs when glycoprotein gp350 in the EBV envelope binds to CD21 (a type 2 complement receptor) on the cell surface.<sup>21</sup> After primary infection, the virus persists in a latent form in memory B lymphocytes.<sup>21</sup> The virus occasionally reactivates, switching from a latent cycle to a lytic cycle during which transactivating proteins, structural proteins and envelope glycoproteins are produced.<sup>21</sup>

Cell-mediated immunity (CD8+ T-cell response) plays an important role in controlling both primary EBV infection and lifelong latent EBV infection.<sup>21</sup> Infection by EBV results in the production of antibodies to 4 distinct antigen complexes: EBV-induced nuclear antigen (EBNA), EBV-induced early antigen, viral capsid antigen and EBV-induced membrane antigen.<sup>22,23</sup> Antibodies to viral capsid antigen are detectable early in the course of the disease, peaking at 3–4 weeks then declining to become undetectable.<sup>24</sup> Antibodies to early and membrane antigens are also produced early on, and anti-membrane-antigen antibodies target the envelope glycoprotein gp350 and stop dissemination of the virus. Antibodies to EBNA develop later and persist throughout life.<sup>21</sup>

EBV exerts numerous immunomodulating effects, including inhibition of apoptosis; inhibition of the anti-EBV effect of interferon- $\gamma$  in B cells; and changes in the production of cytokines, such as interleukin-1 $\beta$ , tumour necrosis factor- $\alpha$  and interleukin-6.<sup>21</sup> A viral cytokine that shares the properties of interleukin-10 allows the virus to elude the host's antiviral response.<sup>21,22</sup>

Two strains of EBV, types 1 and 2, have been identified.<sup>25</sup>

These differ in distribution: EBV type 1 is more common in developed countries and type 2 is more common in Africa<sup>25</sup> and among homosexual men.<sup>26</sup> Current evidence suggests that the specific geographic distribution of EBV-associated malignancies, such as endemic Burkitt's lymphoma in Africa and Papua New Guinea and nasopharyngeal carcinoma in Southeast Asia, is probably not solely a result of differences in EBV infection, but rather the activation of viral replication caused by additional cofactors.<sup>27</sup>

## EBV as a Carcinogenic Agent

EBV is the first human virus to be directly implicated in carcinogenesis.<sup>11,27</sup> In an International Agency for Research on Cancer (IARC) review, EBV was classified as a group 1 carcinogen,<sup>11,28,29</sup> indicating that there is sufficient evidence to suggest that the virus plays an oncogenic role. In 2009, IARC reported that mechanistic data available to date strongly support an oncogenic role for EBV in human cancer. In summary, EBV immortalizes normal B cells in culture; 1 or several EBV gene products are expressed in all EBV-associated cancers; and, at the molecular level, these encoded gene products associated with latent viral infection induce cell proliferation, block apoptosis, induce genomic instability or modulate cell migration. These events occur before or during tumour initiation. Several of these gene products are also involved in mechanisms contributing to continued tumour maintenance, cell growth and progression.<sup>30</sup>

IARC has concluded that EBV is etiologically associated with the development of nasopharyngeal carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma and extranodal natural killer/T-cell lymphoma (nasal type).<sup>11,30</sup> The report also reports a positive association of EBV with lympho-epithelioma-like carcinoma. The same report points to an association of EBV with gastric adenocarcinoma and smooth muscle tumours in immunocompromised patients, but its etiologic role remains inconclusive.<sup>11</sup>

Because some of these EBV-associated malignant diseases are known to involve the head and neck region, it is important that dental practitioners have a clearer understanding of the clinical features and the association of EBV with this heterogeneous group of cancers. In this paper, we review malignancies of the head, neck and oropharyngeal region that have been shown to be associated with EBV.

## Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) represents the vast majority of cancers that arise from the epithelial cells of the nasopharynx. It commonly originates in the fossa of Rosenmüller, a region of the nasopharynx rich in lymphoreticular tissue, but it can

also arise from the roof of the nasopharynx.<sup>30</sup>

NPC has a remarkable geographic and racial distribution. Its incidence is high in China, particularly among Cantonese, but there is substantial variation among regions.<sup>30</sup> In southern China, people in the lower socioeconomic strata have a high rate of NPC.<sup>30</sup> Its rate of occurrence is also high among Chinese and Malays in Singapore and Malaysia.<sup>30</sup> High rates of NPC have also been reported in Chinese migrants in the United States<sup>31</sup> and New South Wales, Australia.<sup>32</sup> In New South Wales, migrants of high socioeconomic status born in Hong Kong and those of lower socioeconomic status born in Taiwan both show high rates of NPC.<sup>5,33</sup>

NPC is caused by an interplay of viral, environmental and genetic risk factors. Well-established risk factors include elevated antibody titres against EBV, consumption of salt-preserved fish and herbal medicine containing plant extracts and a family history of NPC.<sup>30,34</sup> Disease risk has also been linked with certain human leukocyte antigen class I genotypes.<sup>34</sup>

**Evidence of EBV association:** EBV is consistently detected in nasopharyngeal carcinomas.<sup>30,35</sup> Monoclonal EBV has also been found in pre-invasive dysplastic and carcinoma in situ lesions.<sup>36</sup> In pre-invasive lesions related to NPC, a single EBV-infected cell proliferates, indicating that EBV plays an important role in the development of the tumour.<sup>36</sup> The EBV DNA is clonal, indicating that the lesions represent a focal cellular growth that arose from a single EBV infected cell and that EBV infection is an early, possibly initiating event in the development of nasopharyngeal carcinoma.<sup>36</sup> Serological studies have consistently shown elevated titres of IgG and IgA antibodies against EBV viral capsid antigen, early antigen and nuclear antigens in nasopharyngeal carcinoma patients.<sup>30</sup>

**Nasopharyngeal involvement:** Most NPCs are exophytic, although a small percentage of lesions can be ulcerated.<sup>37</sup> Presenting symptoms may include blood-stained nasal discharge, nasal obstruction, blood-stained sputum, tinnitus and hearing loss.<sup>30</sup> Cranial nerve palsies, particularly involving cranial nerves III, IV, V, VI, IX and X are often seen.<sup>30</sup> Cervical lymph node enlargement is common, typically at the apex of the cervical triangle or in the superior jugular chain of nodes.<sup>38</sup>

Three microscopic subtypes of NPC have been recognized: well, moderately or poorly differentiated keratinizing squamous cell carcinomas; differentiated non-keratinizing carcinomas; and undifferentiated carcinomas.<sup>30</sup> The undifferentiated type is the most common.<sup>37,39</sup>

The diagnosis of NPC requires a detailed history, clinical examination and blood tests for routine hematology and elevated EBV DNA. Imaging modalities used in NPC diagnosis include computed tomography (CT) scans, magnetic resonance imaging (MRI) and positron emission tomography (PET). The extent of the

disease can be determined by PET scans. Endoscopic examination and biopsy are necessary to confirm the diagnosis. The primary treatment of NPC includes radiotherapy with or without chemotherapy.<sup>40</sup> The reported global 5-year survival rate ranges from 32% to 62%.<sup>41</sup>

## Hodgkin's Lymphoma

Hodgkin's lymphoma (HL), also known as Hodgkin's disease, is a malignant neoplasm that develops from B lymphocytes of the germinal centres in lymph nodes in over 98% of all cases; in rare instances, it develops from post-thymic T cells.<sup>42</sup> HL is distinguished morphologically by the presence of malignant cells, called Reed-Sternberg cells, amid a background of non-neoplastic cells.<sup>43</sup>

HL represents approximately 4% of all lymphomas of the head and neck.<sup>44</sup> Extranodal involvement of HL as the primary site is less common. In western populations, a bimodal age distribution has been noted, with HL cases accumulating in young adults and the elderly.<sup>45</sup> This feature may be considered one of the distinguishing characteristics of lymphomas. In developed countries, the incidence rate of HL increases with age.<sup>46</sup> In developing countries, HL occurs primarily in children of lower socioeconomic classes, perhaps because of early exposure to EBV.<sup>30</sup> Genetics and an association with environmental agents, such as occupational wood working, radiation therapy, chemotherapy, long-term use of phenytoin and EBV infection, have been reported to play a role in the development of HL.<sup>30,46</sup>

**Evidence of EBV association:** Epidemiologic, serologic and molecular studies have all suggested that EBV is involved in the development of a significant proportion of HLs. In Australia, Europe and North America, 30–50% of HL cases are associated with EBV.<sup>47</sup> Some epidemiologic evidence suggests an increased risk for HL following infectious mononucleosis.<sup>48</sup> Elevated EBV-related antibody titres have been well documented in patients with HL,<sup>49,50</sup> and the EBV genome is frequently detected in Reed-Sternberg cells.<sup>51,52</sup>

Based on clinical and biological criteria, 2 main types of HL are recognized: classical HLs and nodular lymphocyte predominant HLs.<sup>53,54</sup> The vast majority of HL patients present with lymph node involvement. HL usually arises as a unifocal lesion in cervical lymph nodes.<sup>55</sup> Contiguous spread of the tumour to adjacent lymph nodes gives rise to palpable enlarged nodes. The tumour spreads through lymphatic channels and involves other organs, such as the spleen and distant lymph nodes.<sup>54</sup> As the disease progresses, the liver and kidney may also be involved. Bone marrow involvement is indicative of tumour infiltration and is associated with systemic symptoms including leukopenia, anemia, thrombocytopenia and elevated levels of alkaline phosphatase.<sup>55</sup>

Clinical features of HL include painless lymphadenopathy in most cases. The predominant sites of lymph node involve-

ment include mediastinal and cervical lymph nodes.<sup>56</sup> For unknown reasons, HL patients may experience pain in the affected areas immediately after drinking alcoholic beverages, and this symptom may be an indication of the presence of HL.<sup>46</sup> Intense pruritus is also an early feature. Others include fever, night sweats and unintentional weight loss. Symptoms related to the involvement of internal nodes, liver, spleen and bone marrow become evident as the disease progresses. "Pel-Ebstein fever," characterized by a few days of high temperature regularly alternating with a few days of normal or below-normal body temperature, is often present.<sup>46</sup> Splenomegaly and hepatomegaly are frequently encountered in HL.<sup>46</sup>

**Oropharyngeal involvement:** Extranodal HL without nodal involvement is uncommon. The gastrointestinal tract has been reported to be the most frequent extranodal site.<sup>57</sup> Oropharyngeal involvement of HL is rare. As of 2006, fewer than 200 cases of HL involving Waldeyer's ring had been reported in the English literature.<sup>58</sup>

Locations of oropharyngeal involvement of HL include Waldeyer's ring, which encompasses the lymphoid tissues of the nasopharynx, tonsils, base of the tongue and wall of the oropharynx.<sup>58,59</sup> Presenting symptoms and signs may include neck mass, nasal stuffiness, nasopharyngeal mass, tonsil enlargement, throat pain, obstructed airway and an exophytic lesion at the base of the tongue or mouth ulcers.<sup>59</sup> Primary or relapsed HL of the oral soft tissues and jaw bones is extremely rare.<sup>58,60</sup> HL may present as a fast-growing soft tissue mass with or without surface ulceration and pain. Jaw involvement may be evidenced by pathological fracture with an abnormal trabecular pattern and irregular radiolucency.<sup>61</sup>

Diagnosis of HL is based on lymph node biopsy that reveals Reed-Sternberg cells in a heterogeneous cellular infiltrate consisting of histiocytes, lymphocytes, monocytes, plasma cells and eosinophils.<sup>46</sup> Imaging tests include CT and MRI. Other test results that may be abnormal but non-diagnostic include those for polymorphonuclear leukocytosis, lymphocytopenia, eosinophilia, thrombocytosis and microcytic anaemia. Elevated serum alkaline phosphatase level and erythrocyte sedimentation rate are reflective of active disease.<sup>46</sup> Once the diagnosis is established, staging is determined to guide therapy. Staging is based on symptoms, physical examination findings and results of all tests including CT and PET scans.

Treatment of HL involves chemotherapy with or without radiotherapy. Disease-free survival after therapy is generally considered a cure because relapse is very rare after 5 years. Both chemotherapy and radiotherapy may increase the risk of malignant tumours of the breast, lungs and gastrointestinal tract.<sup>46</sup>

## Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas (NHLs) constitute a heterogeneous group of malignancies, 85–90% of which arise from B lymphocytes, the remainder from T lymphocytes or natural killer lymphocytes.<sup>62</sup> NHLs arise primarily within the lymph nodes, but can occur in almost any tissue. Approximately 24% of NHLs involve extranodal locations.<sup>63</sup>

NHL is the 8th most commonly diagnosed cancer in men and 11th in women. It accounts for about 5.1% of all cancer cases and 2.7% of all cancer deaths.<sup>64</sup> Areas with the highest incidence of NHL include North America, Europe, Oceania and several African countries.<sup>64</sup> In Australia, over 4600 new cases of lymphomas were diagnosed in 2009, of which over 4300 were NHL.<sup>65</sup> The incidence of lymphomas has more than doubled over the past 20 years and is continuing to rise. Men are at higher risk of developing NHL and the incidence rises steeply with age.<sup>64</sup> The risk of being diagnosed with NHL by age 85 is 1 in 42.<sup>65</sup> The most consistently observed risk factors include primary as well as acquired immune deficiencies, including HIV/AIDS; an estimated 3% of AIDS cases present with a lymphoma.<sup>2</sup> Other risk factors include familial aggregation,<sup>66,67</sup> autoimmune conditions,<sup>64,68</sup> such as rheumatoid arthritis, celiac disease, systemic lupus erythematosus, Sjögren's syndrome and exposure to certain hair dyes.<sup>69</sup> Medications for which an association with NHL has been reported include phenytoin, cimetidine, benzodiazepine, immunosuppressants, non-steroidal anti-inflammatory drugs and corticosteroids.<sup>64</sup> Microbial agents reported to be associated with NHL include EBV, hepatitis C virus, human T-cell lymphotropic virus and a Gram-negative bacterium, *Helicobacter pylori*.<sup>64</sup>

**Evidence of EBV association:** EBV infection is associated with a heterogeneous group of NHLs, including Burkitt's lymphoma, natural killer/T-cell lymphomas and lymphoproliferative disease.<sup>70,71</sup> EBV can cause lymphoproliferative diseases in those with immune dysfunction; most are polyclonal B-cell proliferations classified as diffuse lymphomas.<sup>72</sup> EBV is present in two-thirds of AIDS-related lymphomas, and it is believed to play an important part in lymphomagenesis.<sup>44</sup> EBV has also been linked to a small proportion of peripheral T-cell NHLs arising in patients without overt pre-existing immunodeficiency and to a smaller number of B-cell NHLs arising in such patients.<sup>73</sup> Post-transplant lymphoproliferative disorders are also associated with EBV infection, where the virus can be found in atypical lymphocytes or tumour cells.<sup>73</sup> The association of EBV with lymphomas in immunosuppressed patients and with sinonasal angiocentric T-cell lymphomas indicates a possible causal role of EBV in these forms of NHL.<sup>74</sup>

Nearly 85% of NHLs arise from B lymphocytes, with the remainder arising from T lymphocytes or natural killer cells.<sup>54,55</sup> In 2008, the World Health Organization (WHO) proposed a classification of lymphomas based on a combination of morphologic, immunotypic, and genetic

features and clinical syndromes.<sup>75,76</sup> This classification deals with several histologic types that are too complex from a clinical point of view. In clinical classification, it is useful to view various histologic features in terms of aggressiveness and prognosis. In this context, NHLs can be divided into 2 groups: indolent and aggressive types.

Indolent lymphomas are often insidious, presenting with slow-growing lymphadenopathy, hepatomegaly, splenomegaly or cytopenias. Indolent NHL types have a relatively good prognosis, with median survival as long as 10–20 years, but they are usually not curable when discovered at advanced clinical stages.<sup>46</sup> Early-stage indolent NHL types can be treated effectively with radiation therapy alone. Most indolent NHLs are follicular (nodular) in morphology.

Aggressive lymphomas are rapidly progressive, but often curable.<sup>46</sup> They commonly present acutely as a rapidly growing mass with systemic symptoms (called B symptoms), such as fever, night sweats and weight loss. Patients with aggressive lymphoma have elevated levels of serum lactate dehydrogenase and uric acid. The natural history of these tumours shows significant variability. Between 10% and 35% of patients have primary extranodal lymphoma at diagnosis, whereas approximately 50% of patients develop secondary extranodal lymphoma during the course of their disease.<sup>77</sup>

Initial evaluation of the patient with newly diagnosed NHL must establish the precise histologic subtype, the extent and sites of involvement (localized or advanced; nodal or extranodal) and the general health of the patient. This information is useful in determining the appropriate therapy and the patient's prognosis. Clinical staging of NHL becomes useful in this context, and the Ann Arbor staging system is most commonly used.<sup>78</sup> It is primarily based on the distribution of lymphatic involvement with respect to the diaphragm and the presence of extralymphatic organ involvement.<sup>78</sup> It focuses on the number of sites (nodal and extranodal), location and the presence or absence of systemic symptoms, such as fever, night sweats or unexplained weight loss.<sup>76,79,80</sup>

Patients with NHL may present asymptomatic (A symptoms) peripheral lymphadenopathy with a predisposition to supraclavicular or cervical regions. Lymph nodes are enlarged, rubbery and discrete and may become matted at a later stage of the disease. Multiple areas of involvement are common. Weight loss, fever, night sweats and lack of strength (B symptoms) indicate disseminated disease.<sup>46</sup> Congestion and edema of the face and neck because of pressure on the superior vena cava may occur in NHL. Patients may also have splenomegaly and hepatomegaly.<sup>46</sup>

**Head and neck involvement:** Typical extranodal locations of NHL include the stomach, bowel, lung, orbital tissues, sinuses, thyroid gland, tonsils, salivary glands, testes and kidneys. However, Waldeyer's ring is second only to the gastrointestinal tract in terms of incidence of extranodal NHL.<sup>76,81,82</sup> NHL

of the salivary glands is an uncommon form of malignancy accounting for up to 5% of cases of extranodal lymphomas and 3–10% of malignant diseases of the salivary glands.<sup>83–87</sup> In the salivary glands, the parotid glands are the most common site of NHL involvement. In descending order of frequency, the submandibular glands, minor salivary glands and sublingual glands may also be involved.<sup>83,84,87</sup> NHL of the parotid glands presents as a painless mass indistinguishable from other non-malignant or other more commonly occurring epithelial tumours. In most cases, the facial nerve is not affected.<sup>88</sup> Most NHLs of the salivary glands are thought to develop as a result of antigenic stimulation from Sjögren's syndrome or a benign lympho-epithelial lesion.<sup>89,90</sup>

**Oropharyngeal involvement:** Approximately 90% of all lymphomas involving Waldeyer's ring are types of NHL.<sup>91</sup> Primary oral NHL is uncommon.<sup>92</sup> A considerable number of these are extranodal, diffuse large B-cell lymphomas and natural killer/T-cell lymphomas of the nasal type.<sup>93</sup> Primary NHL involvement in the jaw bones is rare, accounting for 0.6% of NHL cases.<sup>94</sup> Jaw lesions are usually mistaken for infections, such as osteomyelitis or dento-alveolar abscess.<sup>95</sup> NHL has been designated as an AIDS-defining condition and may be the first manifestation of AIDS.<sup>96</sup> In HIV-positive patients, NHL may occur in extranodal intraoral sites, such as the gingiva or the palate, and present as a painless local mass that may gradually increase in size and show signs of ulceration. In patients with tonsillar involvement, dysphagia and a lump-in-the-throat sensation are common symptoms.<sup>97</sup> Often, the signs and symptoms of NHL in the oropharyngeal region are similar to those of squamous cell carcinoma.

Current procedures for diagnosing extranodal oropharyngeal NHL include a panoramic radiograph, chest radiography, abdominal, chest and pelvic CT scans, PET scans, routine laboratory blood tests, including a hemogram, urinalysis, complete blood cell counts, lactate dehydrogenase level, erythrocyte sedimentation rate and bone marrow aspiration biopsy.<sup>46,98</sup> Definitive diagnosis is made by histologic examination of the lesion using immunohistochemical techniques on fresh-frozen tissue sections. In nodal disease, fine-needle aspiration is a useful tool for diagnosis.

Management of NHL involves a combination of chemotherapy and radiation. Biological therapy or immunotherapy using monoclonal antibodies is becoming increasingly popular. Indolent NHL B lymphomas are managed with immunochemotherapy, which includes rituximab plus cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) and consolidation field irradiation.<sup>76</sup> The standard therapy for aggressive B lymphoma is the combination therapy R-CHOP.<sup>76</sup> Currently, post-treatment immunotherapy with rituximab, vaccination or intralukin-2 is being studied. Steroids are also used in conjunction with chemotherapy to reduce adverse effects. Following chemotherapy, stem-cell treatment is also sometimes used. This involves transplant of a patient's own or donated stem

cells to help restore normal blood cells. Chemotherapy combined with radiation increases the risk of leukemia.

## Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) is a newly discovered aggressive NHL that occurs predominantly in HIV seropositive<sup>99</sup> and post-transplant or immunocompromised patients. A minority of PBL cases also occur in immunocompetent patients.<sup>99</sup> In HIV patients, PBL occurs in the jaws and oral cavity<sup>100</sup> and has a special affinity for the gingival mucosa, hard palate and soft palate. PBL infiltrates the bone as it progresses. Clinical manifestations of PBL are similar to those of Kaposi's sarcoma with lesions appearing as purple masses.<sup>101</sup>

**Evidence of EBV association:** PBL has been found to be frequently associated with EBV.<sup>99</sup> The prognosis for those with PBL is poor, with death occurring 1–24 months after diagnosis.<sup>101</sup> Standardized treatment guidelines for PBL have not yet been established. Chemotherapy with occasional use of radiotherapy has been the mainstay of treatment.<sup>102</sup>

## Burkitt's Lymphoma

In 1958, a British surgeon, Denis Burkitt, described a specific childhood lymphoma of the jaws occurring in equatorial Africa,<sup>103</sup> a tumour that subsequently became known as Burkitt's lymphoma. Although Burkitt's lymphoma is endemic in many parts of Africa, it occurs sporadically all over the world. Two forms have been recognized: the endemic or African form commonly found in Africa and Papua New Guinea and the sporadic form found in North America, northern and eastern Europe and the Far East.<sup>55</sup> A third form of Burkitt's lymphoma, called immunodeficiency-associated Burkitt's lymphoma, has also been reported particularly in HIV patients and allograft recipients with primary immunodeficiency.<sup>104</sup>

**Evidence of EBV association:** In 1964, Epstein et al.<sup>6</sup> demonstrated virus particles in cells cultured from Burkitt's lymphoma biopsies from Africa. This DNA virus of the herpes group, which came to be known as EBV, has been implicated as the etiologic agent for Burkitt's lymphoma. Early case-control studies indicated that patients with endemic Burkitt's lymphoma had a much higher titre of antibodies to EBV capsid antigen and early antigen than healthy people. EBV has been detected in virtually all cases of endemic Burkitt's lymphoma, 15–20% of sporadic Burkitt's lymphoma cases and 30–40% of the immunodeficiency-related variant of Burkitt's lymphoma.<sup>14</sup> In sub-Saharan Africa, the EBV genome can be demonstrated in the tumour cells of over 95% of Burkitt's lymphoma patients.<sup>2,105–107</sup> Evidence suggests that EBV is an important pathogenic factor in the development of Burkitt's lymphoma.<sup>74</sup> Other factors, such as the climatic

conditions in Africa and Papua New Guinea, suggest that the development of Burkitt's lymphoma depends on malaria as a co-factor,<sup>108</sup> and associated tumours have been found in patients with *arum* malaria.<sup>109</sup> Infection with malaria is thought to diminish T-cell control of proliferating EBV-infected B cells and, thus, enhance their proliferation.<sup>110</sup>

**Jaw involvement in Burkitt's lymphoma:** In endemic regions, Burkitt's lymphoma is common in children 4–7 years of age. The male to female ratio ranges from 2:1 to 3:1 in endemic regions. In these regions, the jaw bones are involved in 40–70% of cases.<sup>111,112</sup> In very young children, the tumour may not present in the jaw, but orbital involvement may be seen. However, in some of these cases involving the orbit, tumours may arise in the maxilla.<sup>55</sup> When the jaw bones are involved, it is often in all 4 quadrants. Tumours tend to occur near developing molar teeth. Other sites of involvement of endemic Burkitt's lymphoma include abdominal structures and the central nervous system.

In non-endemic regions, such as North America and Europe, the peak age of occurrence of Burkitt's lymphoma is older, but it accounts for 1–2% of lymphomas in adults and up to 40% of lymphomas in children.<sup>113</sup> The male to female ratio in non-endemic regions is 2.65:1 among those under 13 years of age and 1.35:1 in those  $\geq 13$ .<sup>114</sup> The clinical presentation of the tumour in non-endemic regions differs from that seen in endemic regions. In non-endemic regions abdominal involvement is common and jaw lesions occur in up to 18% of cases.<sup>111,114,115</sup>

Burkitt's lymphoma lesions can locally infiltrate surrounding tissues and may spread via the lymphatic system or blood vessels.<sup>55</sup> Radiographically, Burkitt's lymphoma lesions of the jaw bone are seen to be osteolytic. Initial involvement is evidenced by loss of lamina dura followed by the appearance of focal areas of radiolucency and enlargement of the crypts of developing teeth. In the maxilla, blurring of the shadow of the maxillary antrum may be seen.<sup>108</sup> Often dental sepsis, osteomyelitis, ameloblastoma and dentigerous cyst are confused with Burkitt's lymphoma lesions in the jaws.<sup>108</sup>

Burkitt's lymphoma invariably originates in B cells.<sup>55,108</sup> Microscopically, it is characterized by the presence of undifferentiated lymphoreticular cells,<sup>108</sup> which are highly proliferative and frequently show mitotic figures. Macrophages with abundant clear cytoplasm containing Burkitt's lymphoma cells or cell debris are scattered among the tumour cells, giving the characteristic "starry sky" appearance to histologic preparations.<sup>55,108</sup> Precise diagnosis is based on histologic, immunophenotypic and genetic features, and these remain considerations in planning appropriate therapy.<sup>116</sup>

Burkitt's lymphoma is highly sensitive to systemic chemotherapy. Surgery is limited to biopsy.<sup>108</sup> Cyclophosphamide (40 mg/kg) in a single dose intravenously and repeated about 2 weeks later gives good results.<sup>108</sup>

Combinations of cyclophosphamide, vincristine and methotrexate are reported to give better results.<sup>108</sup>

## Natural Killer-Cell Lymphoma (Nasal Type)

Natural killer-cell lymphoma, formerly known as angiocentric lymphoma, is a type of NHL.<sup>117</sup> Whether this lymphoma includes true natural killer cells or merely T cells with abnormal markers is debated, and many investigators prefer to use the term natural killer/T-cell lymphoma when classifying this condition.<sup>118</sup> Nasal natural killer-cell lymphoma is a rare clinical disease characterized by progressive ulceration and necrosis of the nasal cavity and midline facial tissues.

**Evidence of EBV association:** Most natural killer-cell lymphomas exhibit the presence of EBV-DNA and EBV oncogenic proteins. This malignancy has a poor prognosis even when discovered in the early stages because of its rapid progression. Treatment includes chemotherapy combined with radiotherapy.

**Nasal and oral involvement:** Extranodal sites of this tumour, other than the nose, are rare but may include the nasopharynx, palate, skin, orbit and gastrointestinal tract. Patients present with facial pain and swelling, nasal obstruction, purulent nasal discharge, palatal ulceration, epistaxis, trismus, halitosis, diplopia and systemic symptoms such as fever, weight loss and night sweats (B symptoms).<sup>118</sup> The origin of this lymphoma is thought to be the natural killer-cell lineage.<sup>119</sup>

Diagnosis of natural killer-cell lymphoma requires nasopharyngoscopy, laryngoscopy, imaging studies, blood tests and histologic, immunohistochemical and genetic studies of the tumour tissue.<sup>118</sup> CT scan of the head, neck, pelvis and abdomen and MRI of the head are necessary to determine the extent of the tumour. Histologic and immunohistochemical tests are essential in diagnosing the pattern of the tumour. Laboratory studies include complete blood count and liver and renal function tests. *In situ* hybridization of EBV RNA in the neoplastic cells are positive in natural killer-cell lymphomas.<sup>118</sup> Natural killer-cell lymphomas are known to be resistant to conventional chemotherapy. Currently, the recommended treatment includes both chemotherapy and radiotherapy.<sup>120,121</sup> This combined therapy has yielded 5-year survival rates ranging from 20% to 80%. Despite treatment, disease progression is common.

## Evidence of EBV Association with Oral Squamous Cell Carcinoma

Histopathologically, carcinogenesis in the oral epithelium is evidenced by a sequential process of mild to severe

epithelial dysplasia to carcinoma in situ and invasive carcinoma. Among those who do not use tobacco or alcohol, there is emerging evidence of an association between human papillomavirus and oral squamous cell carcinomas.<sup>4</sup> Other researchers have recently demonstrated the presence of EBV in epithelial squamous cell carcinoma.<sup>122-124</sup> However, an etiologic association between EBV and oral carcinogenesis has not yet been established.

## Conclusion

To date, evidence clearly shows that EBV is one of the most important viruses implicated in the development of lymphoid and epithelial tumours of the head and neck region, including various B- and T-cell lymphomas and nasopharyngeal carcinoma. Although these tumours are rare, because of such clinical features as cervical lymph node enlargement and salivary gland, nasopharyngeal and oral involvement, dental practitioners including specialists are often faced with the challenge of identifying the possibility of EBV-associated malignant tumours. Clinically, these lesions and conditions do not have specific characteristics to identify them as EBV-related pathologies. Nevertheless, general dental practitioners must have an understanding of EBV-related diseases of the head and neck region, not least because of their professional responsibility to maintain their knowledge of pathologies in and around the oral region. Furthermore, with the increase in "disease knowledgeable" patients presenting for care, it is evident that dental practitioners should be prepared to answer questions in an appropriate way based on current evidence.

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