

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

Soorebettu R. Prabhu, MDS, MOMed, RCS(Edin), FFD RCS(Ire)(Oral Med); David F. Wilson, MDS (Hons)



Cite this as: *J Can Dent Assoc.* 2016;82:g2

## 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  $\gamma$ , 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>9</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.

## The Authors



**Dr. Prabhu** is senior lecturer, School of Dentistry and Health Sciences, Charles Sturt University, Orange NSW, Australia.



**Dr. Wilson** is professor, School of Dentistry and Health Sciences, Charles Sturt University, Orange NSW, Australia.

**Acknowledgements:** Authors wish to thank Jenna Hattersley for her secretarial assistance in the preparation of the manuscript.

**Correspondence to:** Dr. S.R. Prabhu, School of Dentistry and Health Sciences, Charles Sturt University, Leeds Parade, Orange, NSW 2800 Australia. Email: [sprabhu@csu.edu.au](mailto:sprabhu@csu.edu.au)

The authors have no declared financial interests.

This article has been peer reviewed.

## References

- Serraino D, Piselli P, Angeletti CI, Scuderi M, Ippolito G, Capobianchi MR. Infection with Epstein-Barr virus and cancer: an epidemiological review. *J Biol Regul Homeostat Agents*. 2005;19(1-2):63-70.
- Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118(12):3030-44.
- Gillison ML, Shah KV. Human papillomavirus-associated head and neck squamous cell carcinoma: mounting evidence for an etiologic role for human papillomavirus in a subset of head and neck cancers. *Curr Opin Oncol*. 2001;13(3):183-8.
- Prabhu SR, Wilson DF. Human papillomavirus and oral disease — emerging evidence: a review. *Aust Dent J*. 2013;58(1):2-10.
- Okano M. Epstein-Barr virus infection and its role in the expanding spectrum of human diseases. *Acta Paediatr*. 1998;87(1):11-8.
- Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet*. 1964;1(7335):702-3.
- Evans AS. The spectrum of infections with Epstein-Barr virus: a hypothesis. *J Infect Dis*. 1971;124(3):330-7.
- Williams H, Crawford DH. Epstein-Barr virus: the impact of scientific advances on clinical practice. *Blood*. 2006;107(3):862-9.
- Borza CM, Hutt-Fletcher LM. Alternate replication in B cells and epithelial cells switches tropism of Epstein-Barr virus. *Nat Med*. 2002;8(6):594-9.
- Carbone A, Gloghini A, Dotti G. EBV-associated lymphoproliferative disorders: classification and treatment. *Oncologist*. 2008;13(5):577-85.
- IARC (International Agency for Research on Cancer) Working Group on the Evaluation of Carcinogenic Risks to Humans. Epstein-Barr virus. In: *A review of human carcinogens. B. Biological agents*. IARC monograph on the evaluation of carcinogenic risks to humans 100(B). Lyon, France: IARC; 2012. p. 49-92.
- Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res*. 2004;10(3):803-21.
- Odumade OA, Hogquist KA, Balfour HH Jr. Progress and problems in understanding and managing primary Epstein-Barr virus infections. *Clin Microbiol Rev*. 2011;24(1):193-209.
- Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. *Nat Rev Cancer*. 2004;4(10):757-68.
- Fingerroth JD, Weis JJ, Tedder TF, Strominger JL, Biro PA, Fearon DT. Epstein-Barr virus receptor of human B lymphocytes is the C3d receptor CR2. *Proc Natl Acad Sci U S A*. 1984;81(14):4510-4.
- Li Q, Turk SM, Hutt-Fletcher LM. The Epstein-Barr virus (EBV) BZLF2 gene product associates with the gH and gL homologs of EBV and carries an epitope critical to infection of B cells but not of epithelial cells. *J Virol*. 1995;69(7):3987-94.
- Okano M. Haematological associations of Epstein-Barr virus infection. *Baillieres Best Pract Res Clin Haematol*. 2000;13(2):199-214.

18. Kief E. Epstein-Barr virus and its replication In: Fields BN, Knipe DM, Howley P, et al. editors. *Fields virology* (3rd ed.). Philadelphia; Lippincott-Raven; 1996. p. 2343-96.
19. Gerber P, Lucas S, Nonoyama M, Perlin E, Goldstein LI. Oral excretion of Epstein-Barr virus by healthy subjects and patients with infectious mononucleosis. *Lancet*. 1972;11(7785):988-9.
20. Jenson HB. Epstein-Barr virus. *Pediatrics Rev*. 2011;32(9):375-83.
21. Fox RI, Luppi M, Pisa P, Kang HI. Potential role of Epstein-Barr virus in Sjögren's syndrome and rheumatoid arthritis. *J Rheumatol Suppl*. 1992;32:18-24.
22. Evans AS. The history of infectious mononucleosis. *Am J Med Sci*. 1974;267(3):189-95.
23. Lenette ET. Herpesviridae: Epstein-Barr virus. In: Lenette EH, Halonen P, Murphy FA, Balows A, Hausler Jr WJ, editors. *Laboratory diagnosis of infectious diseases: principles and practice*. New York: Springer-Verlag; 1988. p. 230-246.
24. Higgins CD, Swerdlow AJ, Macsween KF, Harrison N, Williams H, McAuley K, et al. A study of the risk factors for acquisition of Epstein-Barr virus and its subtypes. *J Infect Dis*. 2007;195(4):474-82.
25. Young LS. Epstein-Barr virus: general features. In: Mahy BWJ, van Regenmortel MHV, editors in chief. *Encyclopaedia of virology* (3rd ed.). Oxford: Academic Press; 2008. p. 148-57.
26. van Baarle D, Hovenkamp E, Dukers NH, Renwick N, Kersten MJ, Goudsmit J, et al. High prevalence of Epstein-Barr virus type 2 among homosexual men is caused by sexual transmission. *J Infect Dis*. 2000;181(6):2045-9.
27. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogenesis — Part B: biological agents. *Lancet Oncol*. 2009;10(4):321-2.
28. Griffin BE. Epstein-Barr virus (EBV) and human disease: facts, opinions and problems. *Mutat Res*. 2000;462(2):395-405.
29. Parkin DM. Cancers attributable to infection in the UK in 2010. *Br J Cancer*. 2011;105(Suppl 2):S49-56.
30. IARC (International Agency for Research on Cancer) Working Group on the Evaluation of Carcinogenic Risks to Humans. Nasopharyngeal carcinoma. In: *Epstein-Barr virus and Kaposi's sarcoma herpes virus/Human herpesvirus 8*. IARC monograph on the evaluation of carcinogenic risks to humans 70. Lyon, France: IARC; 1997. p. 164-94.
31. King H, Locke FB. Cancer mortality among Chinese in the United States. *J Natl Cancer Inst*. 1980;65(5):1141-8.
32. Zhang YQ, MacLennan R, Berry O. Mortality of Chinese in New South Wales, 1969-1978. *Int J Epidemiol*. 1984;13(2):188-92.
33. Grulich AE, McCredie M, Coates M. Cancer incidence in Asian migrants to New South Wales, Australia. *Br J Cancer*. 1995;71(2):400-8.
34. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1765-77.
35. Maeda E, Akahane M, Kiryu S, Kato N, Yoshikawa T, Hayashi N, et al. Spectrum of Epstein-Barr virus-related diseases: a pictorial review. *Jpn J Radiol*. 2009;27(1):4-19.
36. Pathmanathan R, Prasad U, Sadler R, Flynn K, Raab-Traub N. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. *N Engl J Med*. 1995;333(11):693-8.
37. Thomson LD. Update on nasopharyngeal carcinoma. *Head Neck Pathol*. 2007;1(1):81-6.
38. Jain N, Bhatia V, Lattoo S. Epstein-Barr virus and associated head and neck manifestations. *Ann Nigerian Med*. 2011;5(2):38-41.
39. Chan AT. Nasopharyngeal carcinoma. *Ann Oncol*. 2010;21(Suppl 7):308-12.
40. Wei WI, Kwong DL. Current management strategy of nasopharyngeal carcinoma. *Clin Exp Otorhinolaryngol*. 2010;3(1):1-12.
41. Farias TP, Dias FL, Lima RA, Kligerman J, de Sá GM, Barbosa MM, et al. Prognostic factors and outcome for nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg*. 2003;129(7):794-9.
42. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011;117(19):5019-32.
43. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*. 1994;84(5):1361-92.
44. Urquhart A, Berg R. Hodgkin's and non-Hodgkin's lymphoma of the head and neck. *Laryngoscope*. 2001;111(9):1565-9.
45. MacMahon B. Epidemiology of Hodgkin's disease. *Cancer Res*. 1996;26(6):1189-201.
46. Portlock CS. Lymphomas. In: Beers MR, et al, editors. *The Merck Manual of Diagnosis and Therapy* (18th ed.). New Jersey: Merck Research Laboratories; 2006. p. 1117-24.
47. Smith C, Khanna R. Epstein-Barr virus-associated malignancies: pathobiology and emerging therapeutic options. *Microbiology Australia*. 2013; 34(3):120-4.
48. Hjalgrim H, Askling J, Rostgaard K, Hamilton-Dutoit S, Frisch M, Zhang JS, et al. Characteristics of Hodgkin's lymphoma after infectious mononucleosis. *N Engl J Med*. 2003;349(14):1324-32.
49. Herling M, Rassidakis GZ, Medeiros LJ, Vassilikopoulos TP, Liche KO, Nadali G, et al. Expression of Epstein-Barr virus latent membrane protein-1 in Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma: associations with presenting features, serum interleukin 10 levels, and clinical outcome. *Clin Cancer Res*. 2003;9(6):2114-20.
50. Levine PH, Ablashi DV, Berard CW, Carbone PP, Waggoner DE, Malan L. Elevated antibody titers to Epstein-Barr virus in Hodgkin's disease. *Cancer*. 1971;27(2):416-21.
51. Weiss LM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. *N Engl J Med*. 1989;320(8):502-6.
52. Wu TC, Mann RB, Charache P, Hayward SD, Staal S, Lambe BC, et al. Detection of EBV gene expression in Reed-Sternberg cells of Hodgkin's disease. *Int J Cancer*. 1990;46(5):801-4.
53. Kutok JL, Wang F. Spectrum of Epstein-Barr virus-associated diseases. *Annu Rev Pathol*. 2006;1:375-404.
54. Glaser SL, Jarret RF. The epidemiology of Hodgkin's disease. *Baillieres Clin Haematol*. 1996;9(3):401-16.
55. IARC (International Agency for Research on Cancer) Working Group on the Evaluation of Carcinogenic Risks to Humans. Hodgkin's disease. In: *Epstein-Barr virus and Kaposi's sarcoma herpes virus/Human herpesvirus 8*. IARC monograph on the evaluation of carcinogenic risks to humans 70. Lyon, France: IARC; 1997. p. 144-63.

56. Mauch PM, Kalish LA, Kadin M, Coleman CN, Osteen R, Hellman S. Patterns of presentation of Hodgkin disease. Implications for etiology and pathogenesis. *Cancer*. 1993;71(6):2062-71.
57. Vadmal MS, LaValle GP, DeYoung BR, Frankel WL, Marsh WL. Primary localized extranodal Hodgkin disease of the transverse colon. *Arch Pathol Lab Med*. 2000;124(12):1824-7.
58. Treaba DO, Eklund JW, Wayne J, Nelson BP, Winter JN. Classical Hodgkin's lymphoma presenting with tongue involvement: a case report and review of the literature. *Clin Lymphoma Myeloma*. 2006;6(5):410-3.
59. Quinones-Avila Mdel P, Gonzalez-Longoria AA, Admirand JH, Medeiros LJ. Hodgkin lymphoma involving Waldeyer ring: a clinicopathologic study of 22 cases. *Am J Clin Pathol*. 2005;123(5):651-6.
60. Darling MR, Cuddy KK, Rizkalla K. Hodgkin lymphoma of the oral mucosa. *Head Neck Pathol*. 2012;6(4):507-10.
61. Cohen MA, Bender S, Struthers PJ. Hodgkin's disease of the jaws. Review of the literature and report of a case. *Oral Surg Oral Med Oral Pathol*. 1984;57(4):413-7.
62. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet*. 2012;380(9844):848-57.
63. Clark RM, Fitzpatrick PJ, Gospodarowicz MK. Extranodal malignant lymphomas of the head and neck. *J Otolaryngol*. 1983;12(4):239-45.
64. Boffeta P. I. Epidemiology of adult non-Hodgkin lymphoma. *Ann Oncol*. 2011;22(suppl 4):iv27-31.
65. Australian Institute of Health and Welfare. Australian cancer incidence and mortality books: non-Hodgkin lymphoma. Canberra, Australia: AIHW; 2015. Available: <http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129546403>.
66. Chang ET, Smedby KE, Hjalgrim H, Porwit-MacDonald A, Roos G, Glimelius, et al. Family history of hematopoietic malignancy and risk of lymphoma. *J Natl Cancer Inst*. 2005;97(19):1466-74.
67. Altieri A, Bermejo JL, Hemminki K. Familial risk for non-Hodgkin lymphoma and other lymphoproliferative malignancies by histopathologic subtype: the Swedish Family-Cancer Database. *Blood*. 2005;106(2):668-72.
68. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005;165(20):2337-44.
69. Takkouche B, Etmnan M, Montes-Martinez A. Personal use of hair dyes and risk of cancer: a meta-analysis. *JAMA*. 2005;293(20):2516-25.
70. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. *Nat Rev Cancer*. 2004;4(10):757-68.
71. Heslop HE. Biology and treatment of Epstein-Barr virus-associated non-Hodgkin lymphomas. *Hematology Am Soc Hematol Educ Program*. 2005;2005:260-6.
72. Niedobitek G, Meru N, Delecluse HJ. Epstein-Barr virus infection and human malignancies. *Int J Exp Pathol*. 2001;82(3):149-70.
73. Baumforth KR, Young LS, Flavell KJ, Constandinou C, Murray PG. The Epstein-Barr virus and its association with human cancers. *Mol Pathol*. 1999;52(6):307-22.
74. IARC (International Agency for Research on Cancer) Working Group on the Evaluation of Carcinogenic Risks to Humans. Summary of data reported and evaluation. In: *Epstein-Barr virus and Kaposi's sarcoma herpes virus/Human herpesvirus 8*. IARC monograph on the evaluation of carcinogenic risks to humans 70. Lyon, France: IARC; 1997. p. 255-62.
75. Swedllow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours of hematopoietic and lymphoid tissues (4th ed.). Lyon: International Agency for Research on Cancer; 2008.
76. Zapater E, Bagán JV, Carbonell F, Basterra J. Malignant lymphoma of the head and neck. *Oral Dis*. 2010;16(2):119-28.
77. Anderson T, Chabner BA, Young RC, Berard CW, Garvin AJ, Simon RM, et al. Malignant lymphoma. 1. The histology and staging of 473 patients at National Cancer Institute. *Cancer*. 1982;50(12):2699-707.
78. Pazdur R, Coia LR, Hoskins WJ, Wagman LD, editors. Cancer management: a multidisciplinary approach (10th ed.). Lawrence, KS: CMP Media LLC; 2007.
79. Cheson BD. Staging and evaluation of the patient with lymphoma. *Hematol Oncol Clin North Am*. 2008;22(5):825-37.
80. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997;89(11):3909-18.
81. Burke JS. Waldeyer ring, sinonasal region, salivary gland, thyroid gland, central nervous system, and other extranodal lymphomas and lymphoid hyperplasias. In: Knowles DM, editor. Neoplastic hematopathology (2nd ed.). Philadelphia: Lippincott Williams & Wilkins; 2001. p. 1351-90.
82. Shenkier TN, Connors JM. Primary non-Hodgkin's lymphomas. In: Canellos GP, Lister TA, Young BD, editors. The lymphomas (2nd ed.). Philadelphia: Saunders Elsevier; 2006. p. 325-47.
83. Gleeson MJ, Bennett MH, Cawson RA. Lymphomas of the salivary glands. *Cancer*. 1986;58(3):699-704.
84. Barnes L, Myers EN, Prokopakis EP. Primary malignant lymphoma of the parotid gland. *Arch Otolaryngol Head Neck Surg*. 1998;124(5):573-7.
85. Ellis GL, Auclair PL. Malignant lymphomas of the major salivary glands. In: Ellis GL, Auclair PL, editors. Tumors of the salivary glands: AFIP atlas of tumor pathology series 4. Washington DC: Armed Forces Institute of Pathology; 1996. p. 387-402.
86. Wen S, Mizugaki Y, Shinozaki F, Takada K. Epstein-Barr virus (EBV) infection in salivary gland tumours: lytic EBV infection in nonmalignant epithelial cells surrounded by EBV-positive T-lymphoma cells. *Virology*. 1997;227(2):484-7.
87. Hew WS, Carey FA, Kernohan NM, Heppleston AD, Jackson R, Jarret RF. Primary T cell lymphoma of salivary gland: a report of a case and review of the literature. *J Clin Pathol*. 2002;55(1):61-3.
88. Stafford ND, Wilde A. Parotid cancer. *Surg Oncol*. 1997;6(4):209-13.
89. Hyjek E, Smith WJ, Isaacson PG. Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialadenitis. *Hum Pathol*. 1988;19(7):766-76.
90. Schmid U, Lennert K, Gloor F. Immunosaladenitis (Sjögren's syndrome) and lymphoproliferation. *Clin Exp Rheumatol*. 1989;7(2):175-80.
91. Aloulou S, Farhat H, Bosq J, Vanel D, Ribraq V, Turhan AG, et al. Hodgkin's disease primarily involving the oropharynx: case report and review of the literature. *Hematol J*. 2002;3(3):164-7.
92. Jordan RC, Speight PM. Extranodal non-Hodgkin's lymphomas of the oral cavity. *Curr Top Pathol*. 1996;90:125-46.

93. Menárquez J, Mollejo M, Carrión R, Oliva H, Bellas C, Forteza J, et al. Waldeyer ring lymphomas. A clinicopathological study of 79 cases. *Histopathology*. 1994;24(1):13-22.
94. Longo F, De Maria G, Esposito P, Califano L. Primary non-Hodgkin's lymphoma of the mandible. Report of a case. *Int J Oral Maxillofac Surg*. 2004;33(8):801-3.
95. Sarda AK, Kannan R, Gupta A, Mahajan V, Jain PK, Prasad S, Uma K. Isolated involvement of the mandible by non-Hodgkin's lymphoma. *J Postgrad Med*. 1995;41:90.
96. Wolvius EB, Schulten EA, van der Waal I. Non-Hodgkin's lymphoma of the oral cavity as the first manifestation of AIDS. *Brit Dent J*. 1997;182(3):107-8.
97. Kolokotronis A, Konstantinou N, Christakis I, Papadimitriou P, Mafiakis A, Zaraboukas T, et al. Localized B-cell non-Hodgkin's lymphoma of oral cavity and maxillofacial region: a clinical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;99(3):303-10.
98. Angiero F, Stefani M, Crippa R. Primary non-Hodgkin's lymphoma of the mandibular gingiva with maxillary gingival recurrence. *Oral Oncol Extra*. 2006;42(3):123-8.
99. Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood*. 1997;89(4):1413-20.
100. Carbone A, Cesarman E, Spina M, Gloghini A, Schultz TF. HIV-associated lymphomas and gamma-herpesviruses. *Blood*. 2009;113(6):1213-24.
101. Brown RS, Campbell C, Lishman SC, Spittle MF, Miller RF. Plasmablastic lymphoma: a new subcategory of human immunodeficiency virus-related non-Hodgkin's lymphoma. *Clin Oncol (R Coll Radiol)*. 1998;10(5):327-9.
102. Saraceni C, Agostino N, Cornfield DB, Gupta R. Plasmablastic lymphoma of the maxillary sinus in an HIV-negative patient: a case report and literature review. *SpringerPlus* 2013;2:142. Available: <http://www.springerplus.com/content/2/1/142>.
103. Burkitt DP. A sarcoma involving the jaws in African children. *Br J Surg*. 1958;46(197):218-23.
104. Gong JZ, Stenzel TT, Bennet ER, Lagoo AS, Dunphy CH, Moore JO, et al. Burkitt lymphoma arising in organ transplant recipients: a clinicopathologic study of five cases. *Am J Surg Pathol*. 2003;27(6):818-27.
105. Magrath I. The pathogenesis of Burkitt's lymphoma. *Adv Cancer Res*. 1990;55:133-270.
106. Hecht JL, Aster JC. Molecular biology of Burkitt's lymphoma. *J Clin Oncol*. 2000;18(21):3707-21.
107. Rickinson A, Kieff E. Epstein Barr virus. In: Fields BN, Knipe DM, Howley PM, editors. *Fields virology*. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2511-73.
108. Adatia AK. Burkitt's lymphoma. In: Prabhu SR, Wilson DF, Daffary DK, Johnson NW, editors. *Oral diseases in the tropics*. Oxford: Oxford University Press; 1992. p. 449-56.
109. Burkitt D. A children's cancer dependent on climatic factors. *Nature*. 1962;194:232-4.
110. Cohen JL. Epstein-Barr virus infection. *New Engl J Med*. 2000;343(7):481-92.
111. Adatia AK. Burkitt's tumour in the jaws. *Br Dent J*. 1966;120(7):315-26.
112. Olweny CL, Katangole-Mbidde E, Otim D, Lwanga SK, Magrath IT, Ziegler JL. Long-term experience with Burkitt's lymphoma in Uganda. *Int J Cancer*. 1980;26(3):261-6.
113. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. *Blood*. 2004;104(10):3009-20.
114. Levine PH, Kamaraju LS, Connelly RR, Berard CW, Dorfman RF, Magrath I, et al. The American Burkitt's Lymphoma Registry: eight years' experience. *Cancer*. 1982;49(5):1016-22.
115. Philip T. Burkitt's lymphoma in Europe. In: Lenoir GM, O'Connor GT, Olweny CLM, editors. *Burkitt's lymphoma: a human cancer model*. Lyon: International Agency for Research on Cancer; 1985. p. 107-18.
116. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. *Oncologist*. 2006;11(4):375-83.
117. Jaffe ES, Chan JK, Su IJ, Frizzera G, Mori S, Feller AC, et al. Report of the workshop on nasal and related extranodal angiocentric T/natural killer cell lymphomas. Definitions, differential diagnosis, and epidemiology. *Am J Surg Pathol*. 1996;20(1):103-11.
118. Liess BD, Templer JW. NK-cell lymphomas of the head and neck. New York: Medscape; 2014. Available: <http://emedicine.medscape.com/article/871609-overview>.
119. Yamaguchi M, Ogawa S, Nomoto Y, Oka K, Taniguchi M, Nakase K, et al. Treatment outcome of nasal NK-cell lymphoma: A report of 12 consecutively diagnosed cases and a review of literature. *J Clin Exp Hematop*. 2001;41(2):93-9.
120. Cohen JL, Fauci AS, Varmus H, Nabel GJ. Epstein-Barr virus: an important vaccine target for cancer prevention. *Sci Transl Med*. 2011;3(107):107fs7.
121. Epstein MA, Achong BG. The EB virus. *Annu Rev Microbiol*. 1973;27:413-36.
122. D'Costa J, Saranath D, Sanghvi V, Mehta AR. Epstein-Barr virus in tobacco-induced oral cancers and oral lesions in patients from India. *J Oral Pathol Med*. 1998;27(2):78-82.
123. Higa M, Kinjo T, Kamiyama K, Iwamasa T, Hamada T, Iyama K. Epstein-Barr virus (EBV) subtype in EBV related oral squamous cell carcinoma in Okinawa, a subtropical island in southern Japan, compared with Kitakyushu and Kumamoto in mainland Japan. *J Clin Pathol*. 2002;55(6):414-23.
124. Higa M, Kinjo T, Kamiyama K, Chinen K, Iwamasa T, Arasaki A, et al. Epstein-Barr virus (EBV)-related oral squamous cell carcinoma in Okinawa, a subtropical island in southern Japan — simultaneously infected with human papillomavirus (HPV). *Oral Oncol*. 2003;39(4):405-14.