Plasmablastic lymphoma: a case report

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ABSTRACT
A male patient presented at the University of Witwatersrand with a rapidly growing mass on the palate extending across to the buccal aspect. The growth had a history of three months and presented with symptoms of pain together with spontaneous bleeding. Examination revealed that the patient was a smoker and tested seropositive for HIV despite being unaware of the condition. Radiographic bone loss is evident on a panoramic radiograph and clinically correlated by grade three mobility of involved teeth. The biopsy revealed a definitive diagnosis of plasmablastic lymphoma which is linked to oncogenesis potential of Epstein Barr virus. Presented in this paper is a case study of an HIV positive male who developed plasmablastic lymphoma.

ACRONYMS AND ABBREVIATIONS
EBV – Epstein Barr Virus
PTLD - Post-transplant lymphoproliferative disease

KEYWORDS
Epstein Barr Virus
Lymphoma
Plasmablastic lymphoma
Virus oncogenic potential

INTRODUCTION
Until the middle of the 20th century, infectious agents such as viruses were not considered to play a role in oncogenesis.¹ The idea gained prominence when married couples contracted the same cancers and both mother and child had infections or certain cancers, suggesting transmission of the infectious agent from one person to the other. Viral infections are responsible for an estimated 15 to 20 % of all cancers in humans. The Epstein-Barr virus infects more than 90 % of the human population worldwide.² It has the ability to transform resting B cells into rapidly growing lymphoblastoid cell lines.³,⁴ According to Bu et al. (2022), the Epstein Barr virus is classified as a class 1 oncogenic virus by the WHO and is responsible for about 200,000 cancer cases and 1.8% of cancer-related deaths per year.⁵ Burkitt’s lymphoma, nasopharyngeal carcinoma, Hodgkin’s lymphomas, and other epithelial, B, T, and natural killer cell cancers are linked to EBV.⁶ Autoimmune conditions like multiple sclerosis and systemic lupus erythematosus have been linked to EBV.

CASE PRESENTATION
A 53-year-old male patient presented at the Wits Oral Health Center with the main complaint of “enlarging gums” that he started noticing for two months prior to seeking medical attention. He noticed progressive growth, constant pain and bleeding on the site especially when trying to brush his teeth. Upon conducting further clinical examination the patient revealed that he is hypertensive, has a history of malaria fever with which he was hospitalized for three months. At the time of initial consultation, the patient was not aware of his HIV status which was later found to be positive upon further investigations.

An intra-oral examination revealed an exophytic pedunculated mass on the palatal aspect of the first quadrant spanning from the 12 to the 16 area. (see figure 1) The same lesion extends to the buccal aspect also an exophytic mass with the same colour consistency as the surrounding mucosa. (see figure 2) The surfaces of the pathologic tissues were smooth with the palatal aspect showing some erythematous outlook.

Figure 1: Shows the exophytic pedunculated soft tissue mass on the palate

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Histology report
Sections show representation of a haematolymphoid neoplasm with overlying intact and ulcerated stratified squamous mucosa. The tumour comprises large cells arranged in a diffuse growth pattern with scanty intervening stromal connective tissue. The tumour cells have varying amounts of amphophilic cytoplasm. Tumour cell nuclei are pleomorphic, round to oval with course chromatin and prominent centrally located nucleoli. There is brisk mitotic and apoptotic activity.

Immunohistochemistry chart

<table>
<thead>
<tr>
<th>CD3</th>
<th>Positive in reactive T-cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20</td>
<td>Negative in the tumour cells</td>
</tr>
<tr>
<td>EMA</td>
<td>Positive in the tumour cells</td>
</tr>
<tr>
<td>CD30</td>
<td>Negative in the tumour cells</td>
</tr>
<tr>
<td>CD38</td>
<td>Negative in the tumour cells</td>
</tr>
<tr>
<td>CD138</td>
<td>Positive membranous staining of the tumour cells</td>
</tr>
<tr>
<td>MUM1</td>
<td>Diffuse nuclear staining of the tumour cells</td>
</tr>
<tr>
<td>Ki67</td>
<td>80% tumour proliferation index</td>
</tr>
</tbody>
</table>

Table 1

Radiographic examination showed loss of bone on the first quadrant involving 18, 17 and distal 16. This was confirmed clinically with the patient presenting with grade three mobility of the teeth 18, 17 and 16.

Figure 2: Shows the posterior exophytic mass with the same colour consistency extending from the palatal aspect to the buccal aspect. The picture marked B shows both anterior and posterior lesion on the same quadrant.

Figure 3: Panoramic radiographic view showing advanced loss of alveolar bone on the first quadrant around teeth 18, 17 and 18.
EBV entry into B lymphocytes

Infection to B lymphocytes begin with viral attachment of the glycoprotein gp350/220 to the complement receptor CR2/CD21 on B cells.1,12 Entry is facilitated by additional glycoproteins gH, gL and gp42.2 The initial attachment results in endocytosis of the virion, followed by a trimeric complex that forms between with the gH and gL binding to HLAII thereby allowing fusion with the endocytic membrane by the Gb EBV glycoprotein.12 B lymphocytes are rich in areas such as the Waldeyer’s ring. The Waldeyer’s ring consists of the palatine, lingual tonsils, pharyngeal and tubular tonsils, memory B cells are primary reservoir of the virus for virus long persistence.5 After the virus enters the cell the naive B-cell become proliferating blasts.6 Infected Latent memory cells circulate in the Waldeyer’s ring and the blood without immune cells recognition.

EBV’s carcinogenic potential

EBV relies on B cell activation and differentiation to remain persistent in lymphoid tissue. EBV persistence has been linked to several lymphoid and epithelial cancers, most frequently in the mouth cavity, though reports have also included other anatomical locations.10 While LMP1 mimics CD40 signalling and LMP2 mimics B-cell receptor signalling, together these proteins play a role in transcriptional control and provide signals essential for B-cell activation, proliferation, and survival.8 EBV-infected B cells are immortalized and capable of endless proliferation, which is a typical feature in the development of tumours.

Even though EBV stays in latent phase, the virus in latency allows for expression of viral oncogenes while evading detection by the immune system. The increased number of viral proteins has been associated with tumour development, more so in individuals with previous infectious mononucleosis infection who carry a four-fold risk of developing Hodgkin’s lymphoma.9 EBV associated malignancies have since expanded to include Hodgkin’s lymphoma, natural killer/ T cell lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and oropharyngeal squamous cell carcinoma.2

EBV infected B cells that present with genetic alteration can interfere with cellular homeostasis, by promoting cell growth, immune evasion and apoptosis inhibition.10 The Virus DNA is methylated and undergoes histone modification to have similar structures as the host genome, facilitating in the host immune evasion.9 EBV can cause epigenetic changes in gene expression that do not result in DNA mutation. EBV can be reactivated in an immune suppressed host who was previously infected and this can contribute to neoplasia.9, 14

Most B cell that are infected have demonstrated in definitive proliferation in vitro. Apoptosis or programmed cell death is an active process resulting in cell death, it serves as an important cellular response to a damaged genome.15 p53 is an important mediator of cell cycle arrest by inducing G1 arrests (quiescence and senescence) and apoptosis in some instances. Most viral DNA interact with p53 directly by suppression its activity.15

On the other hand, micro-RNA, small noncoding RNA are able to regulate gene expression. They are regulatory molecules that play a role in differentiation, cell proliferation and apoptosis.14 Abnormal expression of micro-RNA indicates their role in cancer in malignant transformation. Expression of different profiles of micro-RNA can determine the cancer differentiation stages.

EBV encoded genes such as LMP1 acts as an oncogene by promoting B cell proliferation. LMP1 also uses the NF-κB and JAK/STAT pathways, both promote B cell proliferation and survival. The virus uses this pathway to increase the pool of infected cells.16

DISCUSSION

The EBV biology and life cycle

The 173 kb long EBV encodes more than 30 functional RNAs and roughly 85 protein-coding genes.2 EBV type 1/A and EBV type 2/B are the two genetically distinct types of the virus; they are identified by allele polymorphism in the gene that codes for the nuclear antigens. While type 1 strains are more common in western nations, type 2 strains are more suited to specific demographic locations.7 According to reports, type 2 EBV infection predominates in New Guinea and sub-Saharan Africa.8

The latent and lytic stages make up the biphasic life cycle of EBV. B cells have latent infection, while epithelial cells have lytic infection.5 When a host is immunocompetent, the virus will only replicate briefly at the infection site after the first infection.8 EBV infects cells in both latent and lytic forms, and, like all herpes viruses, it remains in the host for life.8 In B cells, the virus goes dormant, and the viral DNA is permanently preserved in the nucleus.9 After entering the nucleus, the virus delivers its linear genome there. After that, it recombines its terminal ends to form a circular genome. According to Bu et al. and Niedobitek et al., EBV replicates in epithelial cells and survives in the epithelial basal cell, where it produces progeny virions. Lytic genes that encode very early, early, and late proteinases are expressed during the early stages of the EBV primary infection.4,5 Lupo et al., showed that virions exhibiting a linear DNA presentation are indicative of a lytic or productive infection. BZLF1 and BRLF1 are the switch driving genes that propel the virus’s reactivation from the latent phase to the lytic phase.5,10

Transmission of EBV

Family members can contract EBV early in childhood and become infected themselves. This is typically dependent on the standard of cleanliness procedures. Asymptomatic or moderate EBV primary infections are the norm.4,10,11 Children typically contract an infection from contaminated saliva on their fingers, toys, or other objects, but close contact is necessary for the infection to take hold. Since EBV is present in saliva, young adults frequently spread it by kissing. Studies have also shown the virus in the vaginal fluids of both men and women, but there is little proof that this is the case.11

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**EBV and Lymphomas**

The most prevalent lymphomas originate from B cells that have moved into germinal centers subsequent to activation by antigens. B cells in the germinal center swap immunoglobulin classes, enabling them to express immunoglobulins other than IgM. Hypermutation may happen during this phase, which could result in B cell cancer. Since lymphoid neoplasms are clonal, they originate from a single altered cell.15

Porter et al., formulated that there are three main classifications for lymphomas in the Revised European American lymphoma (REAL) classification: B-cell lymphomas, T-cell lymphomas and presumed natural killer cell neoplasms, and Hodgkin’s disease.17 Unlike earlier morphologically based lymphoma classifications, the new classification is based on clinical, histologic, and immunohistochemical characteristics.17 Lymphomas in the oral cavity are uncommon and account for less EBV is associated with Hodgkin’s lymphomas in 50% of the cases but they rarely appear in the oral cavity, although that are reported cases that occur on the tongue, palate, and tonsils. Diffuse large B cell and Burkitt lymphoma are the most common EBV associated non-Hodgkin’s lymphoma that occur in the oral cavity.3, 17 The increased frequency of non-Hodgkin’s lymphoma has been reported in homosexual males and drug users who use injection methods.17

**Oral diffuse large B cell lymphoma**

Most common type of adult lymphoma representing 30% of all non-Hodgkin’s lymphomas.10 Can appear in any organ or tissue, but the most common extra nodal site is the gastrointestinal tract. Patients presents with asymptomatic masses at one or several sites. Associated with EBV in the elderly in Asia and to a lesser extent in Europe and North American.9 EBV associated diffuse large B cell lymphomas arise in the setting of HIV and immunosuppression in transplant patients and the elderly. Polyclonal B cell proliferation driven by EBV, may regress after restoration of immune function.

There are different clinicopathological subtypes namely, EBV associated diffuse large B cell lymphomas-(discussed above), Kaposi sarcoma herpesvirus (HHV8)- tumour arising within the pleural cavity, pericardium, and peritoneum and lastly the mediastinal large B cell lymphoma-in young women, tends to spread in the abdominal viscera. One third of diffuse large B cell lymphomas have a BCL2 gene rearrangement. EBER positive cells vary with a presentation of 20 to 50% being positive of EBER cells, this can serve as a marker for this tumour.2 EBV positive DLBCL carries lower frequency of PS3 mutation, however it has a poor prognosis, and has increased macrophages infiltration in relation to the EBV negative type.9

EBV positive DLBCL is aggressive and carries a poor prognosis in comparison the EBV negative DLBCL.10 Without treatment they are rapidly fatal. A combination therapy of chemotherapy and anti-CD20 immunotherapy can achieve complete remission in 60-80% of patients. Stem cell transplantation can be used in cases that do not respond to a combination therapy.

**Oral lymphomas in the immunocompromised host**

Immune suppression due Acquired immune deficiency syndrome poses an increased risk of lymphomas.9 Recent studies have shown the synergistic role of EBV and HIV in lymphomagenesis, where HIV induces immune dysregulation that increases the EBV infected cells pool.10 HIV infection present with high level of B cells activation, if those cells are already infected by EBV the load will increase exponentially.10, 11 Before the introduction of antiretroviral therapy patients with AIDS presenting with a 60-200 fold increase in development of lymphomas compared to HIV negative individuals.10

A study done in HIV-positive persons in South Africa demonstrated a marked increased risk of Plasmablastic lymphoma development.18 EBV has been isolated in about 70% of those lymphomas.5, 18

**PLASMABLASTIC LYMPHOMA**

Plasmablastic lymphoma is a variant of Diffuse B cell lymphoma with immunoblastic morphology associated with latent EBV infection. Plasmablastic lymphoma present as an aggressive oral lymphoma that occurs in the oral mucosa and jaws of patients with AIDS causing local soft tissue and hard tissue destruction.5, 17 Less commonly affected extracoral sites are gastrointestinal tract, skin and lymph nodes.18 There are variants that have been described in immunocompetent individuals.18

Histopathological features include a diffuse immunoblasts like large cells with notable plasmacytic differentiation. The presence of EBV encoded RNA confirms plasmablastic lymphoma. VS38c marker is expressed in all Plasmablastic lymphomas.16, 17 Plasmablastic lymphoma carries a poor prognosis although some patients can still experience better clinical outcomes with introduction of highly active anti-retroviral therapy containing protease inhibitors. Overall survival rate of less than 1 year.17, 19

Post-transplant lymphoproliferative disease (PTLD) In patients who undergo organ transplant, a life-threatening complication can be post-transplant lymphoproliferative disease (PTLD). PTLD comprises of spectrum of disorders ranging from benign polyclonal lymphoid proliferation to malignant/clonal lymphomas.3 WHO classifies the PTLD according to their histopathological appearances and clonal characteristics namely, Non-destructive PTLD- non clonal, Polymorphic PTLD-clonal, Monomorphic PTLD- clonal and classified according to the lymphoma they correspond to Classic Hodgkin lymphoma PTLD- clonal. PTLD occurs mainly in gastrointestinal tract and a few cases have been observed on the gingiva, hard palate, and tongue.2 Latent EBV associated with 80% of PTLD.

PTLD risk is associated with the EBV status of the patient, age, duration and type of immune suppression, and type of organ transplanted.8 The decreased cytotoxic T-cell surveillance caused by immunosuppression in patients with PTLD also facilitates the actions of EBV.9 Symptoms of PTLD may include infectious mononucleosis(tonsillitis, pharyngitis, fever, fatigue), hepatic and haematological disorder, and organ specific disease.10 Investigations such as in situ hybridisation show EBV micro-RNA and EBNA. EBV viral load can be used as a screening tool for early detection of PTLDs. Monitoring patients who received transplants from EBV seropositive donors is essential as this could be the
1st encounter to the virus leading to symptomatic disease. European guidelines recommend weekly follow-up from the first week to the fourth month after transplantation followed by monthly or bimonthly monitoring for 1 year. Sudden increase in EBV DNA can be indicative of PTLDs.

CONCLUSION
Because EBV-related entities can resemble many well-known clinical entities, it’s critical to have a high index of suspicion and to be aware of the broad range of diseases and/or cancers that can be associated with EBV. It is impossible to overstate the significance of understanding the many serology markers and how to interpret them. Since EBV has a global infection rate of over 90% and no clinically licensed prophylactic vaccination exists as of yet, new approaches to prevent infection and related disorders are required. The variability of viral glycoproteins across individuals poses a challenge to the precise mechanisms behind viral entrance processes. One of the most commonly spread viruses in the world, EBV is linked to several new approaches to prevent infection and related disorders are required. The variability of viral glycoproteins across individuals poses a challenge to the precise mechanisms behind viral entrance processes. One of the most commonly spread viruses in the world, EBV is linked to several autoimmune conditions as well as cancer and continues to be a major health concern.

REFERENCES

CPD questionnaire on page 224

The Continuing Professional Development (CPD) section provides for twenty general questions and five ethics questions. The section provides members with a valuable source of CPD points whilst also achieving the objective of CPD, to assure continuing education. The importance of continuing professional development should not be underestimated, it is a career-long obligation for practicing professionals.