

# Oral medicine case book 69: Burkitt lymphoma of the oral cavity

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## CASE REPORT

A 25-year-old female was referred to the Haematology Unit at Tygerberg Hospital for further management of a rapidly expanding and large submandibular mass which on fine needle aspiration was suggestive of lymphoma (Figure 1). Five months earlier she had been diagnosed with pulmonary tuberculosis and was confirmed to be HIV positive with a CD4 count of 17. She was placed on anti-retroviral (ARV) and antituberculous therapy (the ARV therapy included efavirenz, emtricitabine and tenofivir). Her CD4 count, at the time of the current consultation, was 204 and the viral load was suppressed. Lumbar puncture was normal. Significant clinical findings were



**Figure 1:** The patient presented with a swelling in the right submandibular region. She also had trismus, which made intraoral examination very difficult but despite this, an intraoral exophytic soft tissue mass can be seen.

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## ACRONYMS

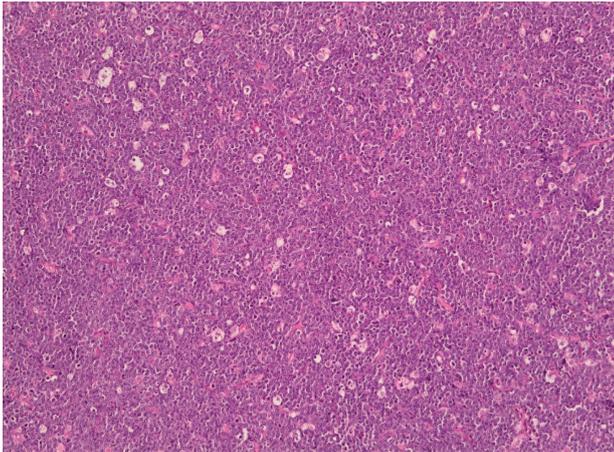
<b>ARV:</b>	Antiretroviral
<b>FISH:</b>	Fluorescent <i>in situ</i> hybridization
<b>HIV:</b>	Human immunodeficiency virus
<b>CNS:</b>	Central nervous system
<b>CT:</b>	Computerized tomography
<b>EBV:</b>	Epstein Barr Virus

a large right submandibular mass and right cervical and axillary lymphadenopathy. The submandibular mass was removed and submitted for histological examination.

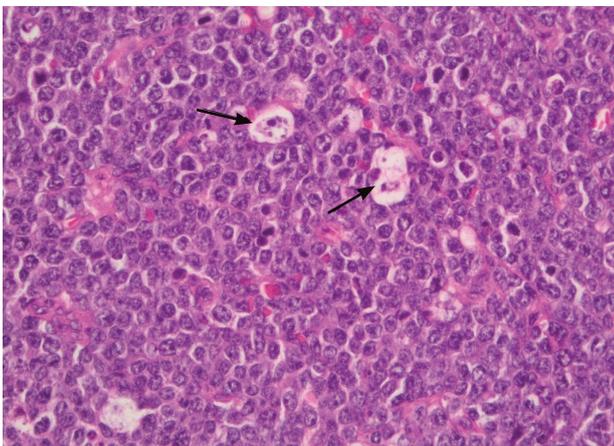


**Figure 2:** The tissue mass removed from the submandibular region showed a homogenous gelatinous consistency in cross section.

Macroscopic examination revealed a 62 gram, homogenous firm whitish-yellowish mass with areas of myxoid consistency. The size of the mass was 100 x 80 x 50 mm and, on cross section, neither necrosis nor haemorrhage was seen (Figure 2). Microscopic examination showed that the lesion was lymphoid in nature with relatively monomorphic cells with blue cytoplasm and nuclei that contained 3-5 nucleoli. High mitotic and apoptotic activity were seen as well as the presence of prominent scattered tingible body macrophages (ie. macrophages containing phagocytized, apoptotic cells in various states of degradation: "tingible" meaning stainable) (Figures 3 and 4). A panel of immunohistochemical markers was done to type the lymphoma (Figure 5 and 6). The cells were positive for the following markers: CD45 (leukocyte common antigen, confirming the lymphoid nature of the neoplasm); the B-cell antigen, CD20 (confirming that the lymphoma is of B-cell origin); and germinal centre B-cell



**Figure 3:** The tumour revealed the starry sky appearance, typical of Burkitt lymphoma, at low magnification (H and E stain, original magnification x 100).



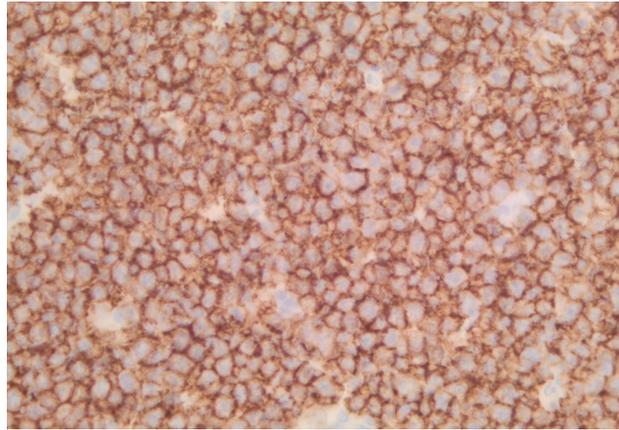
**Figure 4:** A higher power view of the H & E stained section highlights the morphology of the cells: the lymphocytes have a medium size and the scattered macrophages (indicated by the arrows) contain tissue debris, and are commonly referred to as tingible body macrophages (original magnification X400).

antigens, CD10 and Bcl6 (confirming that the B-cell lymphoma derives from the lymphocytes in the germinal centre of the lymphoid follicle). The cells showed a 100% proliferative activity as illustrated by the Ki67, which is an immunohistochemical antibody that targets the tumour cells that are dividing or in a mitotic stage.

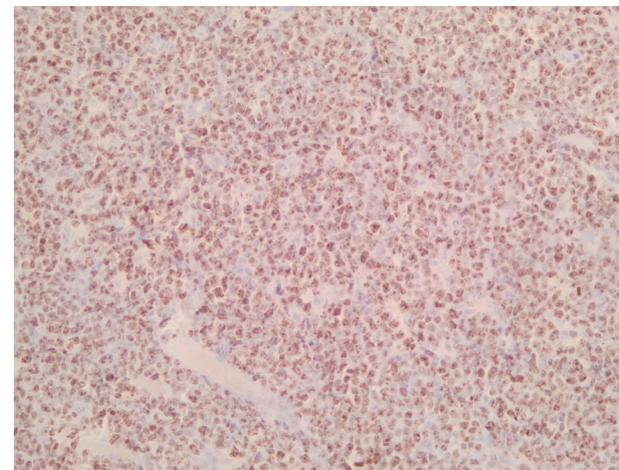
The morphology of this case is typical of Burkitt lymphoma and, in order to confirm this provisional diagnosis, molecular confirmation of translocation (8;14) involving c-myc gene was requested. The molecular investigations using fluorescent in situ hybridization (FISH) showed the presence of that translocation (8;14), thus confirming a diagnosis of Burkitt lymphoma. Staging CT scan revealed Ann Arbor stage IV disease with extensive lymphadenopathy involving the right submandibular, mediastinal, para-aortic, porta-hepatic and iliac nodes as well as splenic and hepatic involvement. There was no evidence of bony involvement. The patient received intensive combination chemotherapy together with continuation of ARV therapy. At the time of publication of this report, she had received four cycles of chemotherapy and showed an excellent interim response.

## DISCUSSION

Lymphomas are neoplasms that affect the lymphoid system. They are divided into two major categories;



**Figure 5:** The CD20 immunohistochemistry stain highlights the cell membrane of B-lymphocytes thus confirming that the neoplastic cells are of B-cell origin (original magnification X400).



**Figure 6:** Immunohistochemistry of the proliferation marker Ki67 is very high, with the brown staining indicating cell nuclei in mitosis (original magnification x 400).

Hodgkin and non-Hodgkin lymphoma. The non-Hodgkin lymphomas are further sub-classified into B-cell and T-cell lymphomas with B-cell lymphomas showing a high level of morbidity in HIV positive patients. Burkitt lymphoma is a very aggressive high grade non-Hodgkin B-cell lymphoma that is derived from germinal centre lymphoid B cells. This neoplasm is the third most common malignancy in African children, preceded only by Wilms' tumour (a rapidly developing malignant mixed tumour of the kidneys) and brain tumours. Burkitt lymphoma is named after Dennis Parsons Burkitt, a surgeon who first described the tumour in 1958 while working in equatorial Africa.<sup>1-3</sup>

Burkitt lymphoma is classified into three variants:<sup>4-10</sup>

- Endemic variant (also referred to as the African variant), most commonly occurring in the jaws of children living in malaria endemic regions of the world (eg. equatorial Africa, Brazil and Papua New Guinea). The endemic form of Burkitt lymphoma accounts for 30-40% of malignancies in children living in equatorial Africa.<sup>4</sup> Interestingly, the distribution of the neoplasm in these areas corresponds to the distribution of endemic malaria, hence the term endemic Burkitt lymphoma. It is thought that chronic malaria reduces resistance to infection with the Epstein-Barr virus (EBV), a known oncogenic virus associated with endemic Burkitt lymphoma.<sup>4</sup> The common age of presentation is 4 to 7 years and the most common clinical presentation

is as a jaw mass (58%), or abdominal mass including involvement of the ileum, kidneys and ovaries. The bone marrow and the central nervous system may also be involved.<sup>1,3,4,8</sup>

- Sporadic variant (also referred to as the non-African variant), a variant not restricted to areas of endemic malaria and, although the tumour cells have a similar appearance to the endemic form, this tumour is rarely associated with EBV infection and is less commonly found in the jaws. It mainly involves the abdomen (88%), with rare involvement of the head and neck. There is no specific geographic association with this variant of Burkitt lymphoma, however, it is usually seen in European populations.<sup>1,3,4,6</sup>
- Immunodeficiency associated subtype of Burkitt lymphoma is frequently seen in Aids patients with a CD4 count below 200 cells/ $\mu$ L and can also be found in patients on immunosuppressive drugs following organ transplantation. It is considered to be one of the conditions signalling an underlying HIV infection.<sup>4-6</sup> Similar to the sporadic form, the immunodeficiency associated Burkitt lymphoma can be found in extra-nodal sites such as this case presented above. The abdomen is also commonly involved and abdominal pain, vomiting, bowel obstruction and gastrointestinal bleeding constitutes the usual clinical presentation. In 13-17% of patients the brain is involved.<sup>6</sup>

All forms of Burkitt lymphoma share the same morphology and it is almost impossible to differentiate these three variants on microscopic features alone. The chromosomal rearrangement associated with c-myc oncogene expression is the hallmark of the molecular alterations in Burkitt lymphoma and this leads to the disturbance in germinal centre B-cell proliferation and differentiation. As could be expected, most of the cases seen in South Africa fall in the sporadic or HIV-associated variants.<sup>1</sup>

### Histopathology, genetic features and pathogenesis

The morphology and the immunohistochemistry of Burkitt lymphoma support an origin from the follicular centre B-lymphocytes. The tumour forms sheets of small to intermediate monomorphic lymphocytes with basophilic cytoplasm and central nuclei containing 3-5 nucleoli. High proliferative activity is reflected by the tumour cells and the scattered associated tingible body macrophages give rise to the characteristic picture of a starry sky appearance.<sup>4,7</sup> The immunodeficiency phenotype of Burkitt lymphoma is consistent with a B-cell lineage. The cells are reactive for CD20, CD19, CD22, and CD79a, which are antibodies that detect surface antigens of B lymphocytes. They also express germinal centre antibodies, such as can be demonstrated by immuno-staining for Bcl6 and CD10.<sup>5</sup>

The ability of EBV to transform the B-lymphocytes in Burkitt lymphoma is said to be amplified by malarial parasitaemia.<sup>4</sup> This is why the endemic form of this lymphoma is common in the so-called lymphoma belt; an area between 10° south and 10° north of the equator, roughly corresponding to the area of endemic malaria.<sup>1</sup> However, additional mutations are required for the development of this lymphoma beside the involvement of EBV. These mutations generally involve chromosome 8 and 14 and, at times, chromosome 2 and 8.<sup>4, 6, 7</sup>

### Treatment and prognosis

Chemotherapy is the primary treatment modality for patients with Burkitt lymphoma. The neoplastic cells are very sensitive to cytotoxic therapy and intensive multi-agent chemotherapy regimens are recommended in Burkitt lymphoma patients who are HIV negative. In HIV positive patients, these protocols are modified in order to reduce toxicity particularly in patients who are ARV therapy naïve.<sup>4,7,11</sup> Involvement of the central nervous system (CNS), bone marrow and HIV infection indicate a less favourable outcome and therefore CNS chemoprophylaxis is advocated.<sup>4,7</sup> A recent study in a Korean population showed that the two-year survival rates are lower in patients with bone marrow and CNS involvement, however, involvement of other extra-nodal sites had no effect on the prognosis.<sup>8</sup> Therefore, a good understanding of the pathogenesis associated with the different subtypes is essential for the development of new chemotherapeutic therapeutic strategies.<sup>7</sup>

### CONCLUSION

Burkitt lymphoma is a very aggressive fast growing non-Hodgkin lymphoma. The importance of early diagnosis and treatment cannot be overemphasized as treatment success is dependent on the extent of disease. Burkitt lymphoma is one of the human cancers that highlight the role of viruses in the carcinogenic process and, as a consequence, it is one of the lymphomas that develop in persons who are immunodeficient, either as a result of HIV infection or subsequent to organ transplantation. Knowledge about the clinical presentation, usual extra-nodal involvement and the subtypes of this lymphoma is essential for making an early diagnosis and therefore can make a significant difference in the prognosis of the afflicted patient.

**Declaration:** No conflict of interest declared

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