Universidad Europea

TRABAJO DE FIN DE GRADO

Grado en Odontología

BURKITT LYMPHOMA IN ORAL CAVITY

Madrid, curso 2020/2021

Número identificativo **129**

Abstract:

Background:

Burkitt lymphoma is a rapidly proliferating B-Cell Non-Hodgkin lymphoma first described in 1958 by Dr. Denis Burkitt with some authors describe it as the fastest growing human tumour. There are three clinical forms; Sporadic, Endemic and Immunodeficiency related.

Objectives:

The main objective is to investigate the oral manifestations of Burkitt lymphoma with the secondary objectives looking into; the carcinogenic process of the Endemic variant, exploring oral diagnosis of BL, looking into the treatment of the malignancy in the oral cavity and comparing the rates of it over the last 20 years.

Methodology:

Using published data including books and websites by including the key words I used was; Oral Manifestations, Burkitt Lymphoma, Treatment, Malaria, Epstein Barr Virus, Pathophysiology, Evolution of, Case studies of, Reviews, Classification. The bibliographic review is focused on literature published within the last 10 years (from 2010 to 2020): 52 references were finally used.

Results:

Most common type of BL affecting oral cavity is endemic type: It appears in black kids as a rapidly enlarging exophytic lesion on the angle of the mandible. It is related to EBV and falciparum infection. There is a strong tie with the balanced translocation of the locus *MYC*/8q24 which result in the overexpression of oncogene C-MYC with histologically

presenting with the diagnostic starry sky appearance. It is a vary treatable and even in some cases curable malignancy through using chemotherapeutic protocols such as CODOX-M/IVAC, HyperCVAD and DA-REPOCH.

Conclusions:

The overall rate of BL worldwide is very low, however within the last 20 years as better diagnostic methods and unfortunately higher rates of malaria are being encountered the rate appears to be increasing in some areas. With XXI chemotherapy drugs, survival rates are higher than 90% of patients.

Resumen

Introduccion:

El linfoma de Burkitt es un linfoma no Hodgkin de células B de rápida proliferación descrito por primera vez en 1958 por el Dr. Denis Burkitt y algunos autores lo describen como el tumor humano de más rápido crecimiento. Hay tres formas clínicas; Esporádico, endémico y relacionado con inmunodeficiencias.

Objetivos:

El objetivo principal es investigar las manifestaciones orales del linfoma de Burkitt con los objetivos secundarios indagar; el proceso carcinogénico de la variante endémica, explorando el diagnóstico oral de LB, investigando el tratamiento de la neoplasia maligna en la cavidad oral y comparando las tasas de la misma durante los últimos 20 años.

Metodología:

Usar datos publicados, incluidos libros y sitios web, al incluir las palabras clave que utilicé fue; Manifestaciones orales, Linfoma de Burkitt, Tratamiento, Malaria, Virus de Epstein Barr, Fisiopatología, Evolución de, Estudios de caso de, Revisiones, Clasificación. La revisión bibliográfica se centra en la literatura publicada en los últimos 10 años (de 2010 a 2020): Se recogieron 52 referencias bibliográficas para este trabajo.

Resultados:

El tipo de LB que produce afectación oral con mayor frecuencia es la variedad endémica. Clínicamente suele aparece en niños de raza negra como una lesión exofítica de rápido crecimiento en el ángulo mandibular. Se relaciona con la infección por VEB y plasmodium

falciparum. Existe un fuerte vínculo con la translocación equilibrada del locus MYC / 8q24 que da como resultado la sobreexpresión del oncogén C-MYC con presentación histológica con la apariencia de cielo estrellado de diagnóstico. Es una un tumor maligno tratable e incluso en algunos casos curable mediante el uso de protocolos quimioterapéuticos como CODOX-M / IVAC, HyperCVAD y DA-REPOCH.

Conclusiones:

La tasa global de LB en todo el mundo es muy baja; sin embargo, en los últimos 20 años, a medida que se han encontrado mejores métodos de diagnóstico y, lamentablemente, tasas más altas de malaria, la tasa parece estar aumentando en algunas áreas. Sin embargo, con la quimioterapia del siglo XXI, las tasas de supervivencias son superiores al 90% de los casos.

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1.Introduction

1.1 What is Burkitt Lymphoma

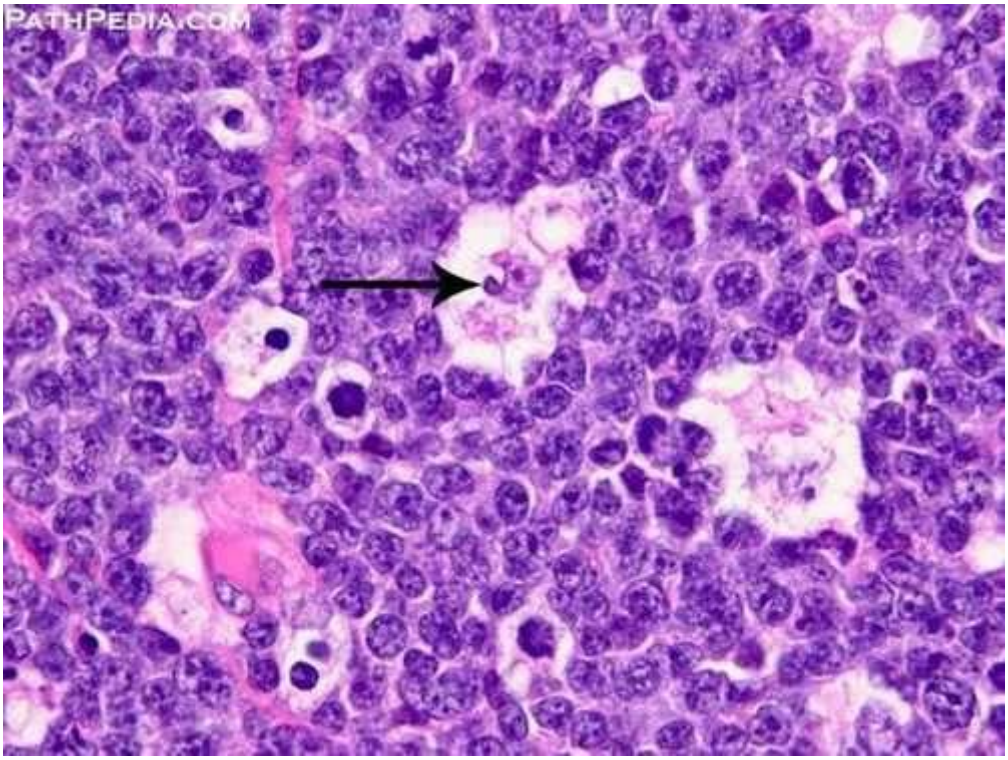
Burkitt lymphoma is a potentially very destructive and rapidly growing B-Cell Non-Hodgkin lymphoma in which some authors describe it as the fastest growing human tumour (1).

It was first described in 1958 by Dr. Denis Burkitt as "*A sarcoma involving the jaws of African children has recently been discovered"*, whilst working in Mulago Hospital in Uganda (2). With the neoplasm described by Burkitt being classified as a malignant lymphoma where it was previously described clinically as a syndrome was named in 1961 as Burkitt Lymphoma (BL) (3). BL is also intimately linked to infection by the Epstein Barr virus (EBV), but also related with the human immunodeficiency virus (HIV). It must also be noted that some authors strong ties with the translocation of chromosomes which result in the overexpression of oncogene C-MYC (1).

It presents in three main clinical forms;

- **Sporadic Burkitt lymphoma**
- **Immunodeficiency-related Burkitt lymphoma**
- **Endemic Burkitt lymphoma.**

From a cell histology point of view, Burkitt Lymphoma presents with cells of medium size, basophilic cytoplasm with round multiple nuclei and monomorphic consistency. Malignant neoplasia presents with a very high turnover rate of cells in both the proliferative and apoptotic states. With a *"Starry Sky"* (3) morphology being described due to the high presence of benign macrophages which have phagocytosed the apoptosed tumour cells (Fig 3: arrow).



<u>Figure 1:</u> Tissue biopsy; Showing the starry sky appearance typically seen in H&E staining of Burkitt Lymphoma samples (49).

The current consensus is that BL is of B-cell germinal centre origin, however some studies have presented with IgHV genes (immunoglobulin heavy chains) which could suggest possible B memory cell origin (3).

1.2 Types of Burkitt Lymphoma

1.2.1 Sporadic Burkitt lymphoma

The Sporadic variant of BL or referred to as Non-African type is the most common type encountered outside of Africa. Within North America and Europe, the sporadic form also tends to be more encountered within adults with an annual incidence of 2.5 per 1 million and an average age of diagnosis being 45 for this type. Interestingly, the average age of diagnosis in children is between 3 and 12 years old with an incidence of 4 per 1 million in patients under 16 (9).

Although the tumours in this form present with a similar clinical appearance to the endemic form in terms of histology and morphology, it is less associated with EBV infection, seen in 30% of cases (5,11).

The sporadic type tends to have clinical manifestations more within the abdominal area with very rare facial or jaw involvement (see figure 4). With its presentation prevalence generally following the trend of 56% lymphoid presentation characterized by lymphadenopathies in the mesenteric and retroperitoneal areas, 21% abdominal and very rarely, inly as much as 7% of sporadic cases present with jaw swelling (17, 26). As mentioned above, Sporadic BL presents in the lymphoid tissue of the gut and upper respiratory tract with frequent presentations within the Wanderers ring or terminal ilium with it not being uncommon to present with large abdominal involvement (11).

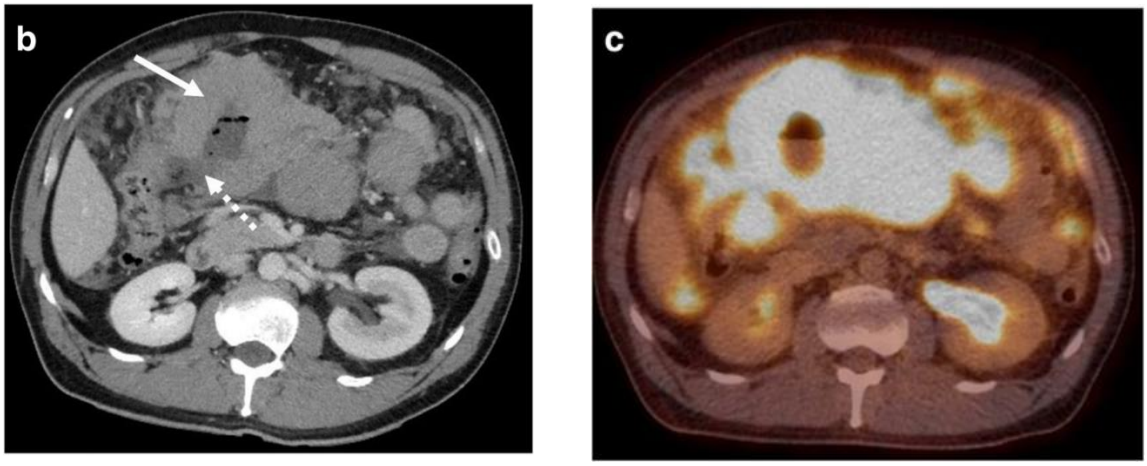


Figure 2: Picture b showing a bowl perforation on an Axial CT scan (dashed arrow) and the associated solid mass (solid arrow). Picture c is a follow-up of the same patient using a Fused Axial PET-CT demonstrating extensive abdominal involvement and hypermetabolic activity associated with BL. (16)

1.2.2 Immunodeficiency-related Burkitt lymphoma

The immunodeficiency variant of BL is frequently associated with patients who have HIV, taking immunosuppressants and have some underlying immunodeficiency (5). One feature of interest which appears to be counter intuitive is the fact that unlike other HIV related lymphomas BL tends to appear in patients with a CD4 count above 200 cells/pL (12). With one study concluding the median CD4 count at diagnosis of Immunodeficiency-related Burkitt lymphoma was 375 (range 140–760) cells/mL (27).

It has been noted that the presence of by BL might be an early indication of an underlying infection of HIV (5).

Of note, it has been demonstrated that Immunodeficiency-related BL often presents with the same extra-nodal clinical presentation as the sporadic type. Where it is typically encountered in the abdominal area or intra-abdominal lymphatic area. Another point to note is the involvement, especially in adults of the central nervous system of between 13 and 17% with higher manifestations present within the bone marrow (12)

1.2.3 Endemic Burkitt lymphoma

The Endemic variation of BL or often referred to as the African variant is known to present with manifestations on the jaws of children. It is seen to occur very frequently in known malaria endemic areas. The endemic variant also appears to have a very intimate relationship with the EBV and Malaria infections (5,8). Investigations have shown a measurable increase in this endemic version and its close link with infections by Plasmodium falciparum in areas of endemic Malaria in places such as equatorial Africa, Brazil and Papua New Guinea (13).

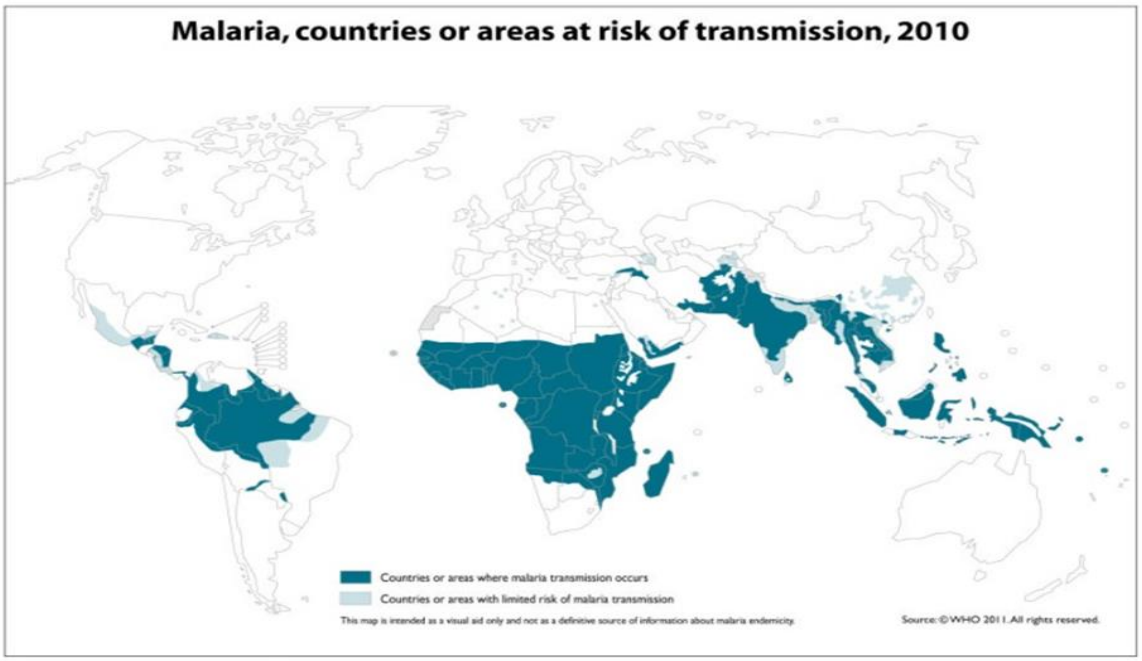


Figure 3: Map created by the WHO illustrating the regions of the world most associated with Plasmodium falciparum infections. (25)

Current research suggests that the endemic form of BL amounts to approximately 30-40% of childhood malignancies in endemic malaria areas such as in equatorial Africa. One interesting fact that appears to be happening is that the distribution of endemic BL closely follows the distribution of endemic malaria and is why this form is termed

as endemic Burkitt Lymphoma. The reason for this occurrence is hypothesized that chronic infection by Malaria reduces the resistance to infection by the Epstein-Barr virus (EBV), which is a widely known oncogenic virus and like malaria infection has a close relationship with BL.

The usual age presentation of endemic BL is usually around the ages of 4-7 and presents with a jaw mass in 58% of cases, however like the other two forms the endemic variant can also present with masses in the abdominal area, kidneys, ovaries, ilium or even have bone marrow or CNS involvement (3,5).

One factor to consider is there is some overlaps in the presentation of both Sporadic and Endemic BL is the presence of the translocation t(8;14) and the consequent c-myc rearrangement leading to overexpression of the oncogene (Fig 4).

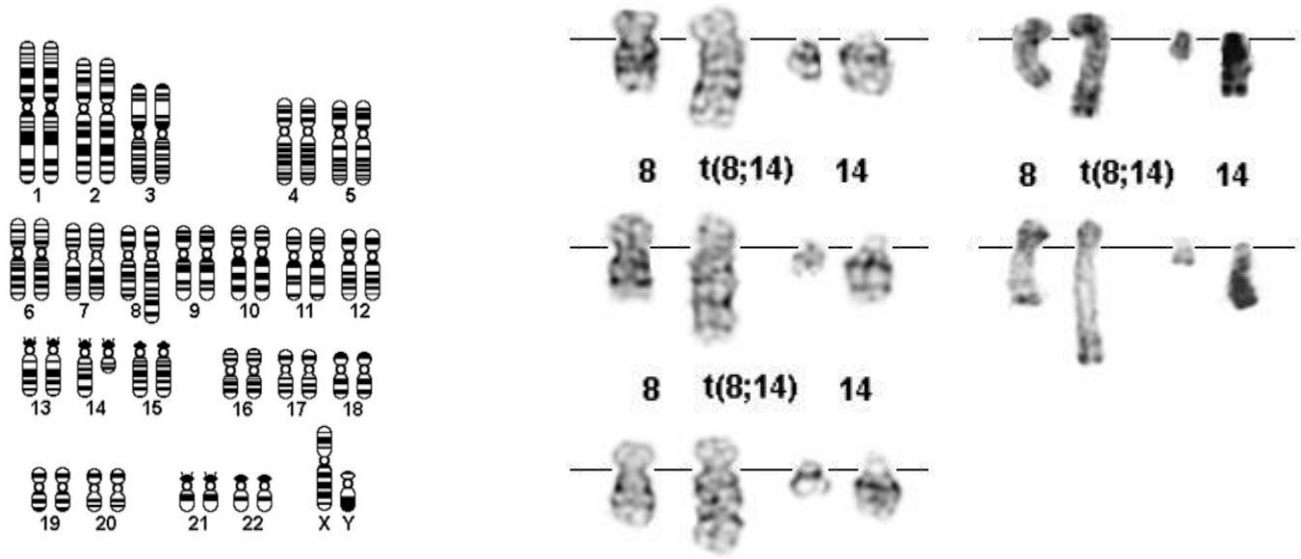


Figure 4 (Left): Translocation 8;14: Kariotype (50)

Figure 5 (Right): Translocation 8;14 (q24;q11) G-banding (left) and R-Banding (right) (51).

Conversely there have been some associations between JH and DH recombination which have been identified at 14q32, which presents with some distant 5‘ c-myc recombination in endemic cases of BL. However, in Sporadic BL, the fact that there is a Sμ and Sα recombination identified at 14q32, with near 5‘ or intronic c-myc recombination at 8q24. These similarities but also differences suggest that the differentiation between the various subtypes of BL is not always as clearly demarcated as we would like (3)

In following table (table 1), describes the main differences between the 3 forms of BL:

Characteristics	Endemic BL (eBL)	Sporadic BL (sBL)	HIV associated BL
Epidemiology	-Equatorial. -Median age 7 yrs. -Associated with malaria / climate.	-Median age 30yrs. -Children (30%). -Older adults (1%) -Low Socio Economical status.	-HIV risk groups. -Median age 10–19 yrs. -Children in Africa.
Clinical Presentation	-Facial skeleton (50%). -CNS (33%). -Other organs also affected.	-Abdominal, ileo-coecal (80%). -Bone marrow (20%). -Other organs also affected.	-Organ and nodal presentation.
Geographic regions	-Malaria belt.	-Worldwide	-In endemic HIV areas in Africa
Ig region involved	-Ig heavy chain joining region. (early B-cell)	-Ig switch region. (late stage B-cell)	-
EBV association	100%	30%	30-50%

Table 1: Differences between 3 main types of Burkitt Lymphoma.

1.3 Differential Diagnosis of Burkitt Lymphoma.

Currently the gold standard diagnostic criteria of BL being the over-expression of MYC due to the balanced translocation of the locus *MYC*/8q24 and an immunoglobulin (Ig) gene, most frequently encountered being *IGH* [*t*(8;14)(q24;q32) (15). Where this translocation ultimately leads to the expression and activation of the *MYC* oncogene (20).

These translocations interestingly enough are absent through fluorescence *in situ* hybridization (FISH) in up to about 10% of otherwise typical cases. It is hypothesized that in these cases there are a variety of other factors to consider such as the possible failure of the 'break-apart probes' used to detect all *MYC* translocations. What is also suggested is high level *MYC* expression is possible through mechanisms including *MYC* amplification and down-regulation of *MIR34B* (21).

An important factor considered by some authors the mere presence of *MYC* translocations is not a sufficient diagnostic for BL as they also appear within other malignancies such as B-cell lymphoma unclassifiable (BLU) and within a diffuse large B-cell lymphoma (DLBCL) in 5-15% of cases. This points to the fact that in absolute terms, *MYC* translocations are more commonly found in DLBCL than in BL (15).

This also points the fact that some authors hypothesize the idea that potentially, of the presence of a molecularly distinct subset of B-cell lymphomas reminiscent of BL, which is characterized by deregulation of genes in 11q. it is suggested this may be due to the minimal region of gain being defined by defined by the high-level amplifications in 11q23.3 and presenting an association with overexpression of genes including *PAFAH1B2* on a transcriptional and protein level. This showed within the

recurrent region of loss contained a focal homozygous deletion in 11q24.2-q24.3 including the *ETS1* gene present in a number of cases (21).

Due to the similarities and aggressive natures of Burkitt Lymphoma, B-cell lymphoma unclassifiable (BLU) and within a diffuse large B-cell lymphoma (DLBCL) it is of paramount to be able to differentiate between them. In DLBCL we encounter a more diffuse nodal architectural effacement or extra-nodal infiltration by sheets of large B-cells. It also presents with small T-lymphocytes/histiocytes. In contrast to this Burkitt lymphoma presents as being more homogeneous and uniform in histology (22).

Characteristics	DLBCL	BL	BLU
Age at presentation	Usually older but can occur at any age.	Children, young adults.	Older adults.
Pathogenesis	May be related to the germinal center (GCB), activated B cell or other pathway.	GCB derived.	GCB derived.
Growth rate	Rapid.	Extremely rapid, Ki67 approaching 100%.	Extremely rapid but usually less than 100%
Stage	Even distribution, 50% stage 1 or 2.	Usually high stage.	Usually advanced III/IV
Bone marrow involvement	Uncommon, often terminal.	Common	Common
CNS involvement	Unusual	Leptomeningeal disease common at presentation in children and adults.	Common
EBV	Uncommon in the absence of immunodeficiency or age-related senescence.	>90% in endemic BL 40% in sporadic and HIV-related BL	Negative
MYC translocation	Uncommon, usually a secondary event associated with a complex karyotype	Almost always present as initiating event and single abnormality (MYC simple)	Often double hits with translocations involving MYC, plus BCL2 and/or sometimes BCL6

Table 2: Differences between Burkitt Lymphoma, B-cell lymphoma unclassifiable (BLU) and within a diffuse large B-cell lymphoma (DLBCL). (22)

1.4 Clinical Manifestations

The main clinical manifestation of Burkitt Lymphoma is swelling due to the rapidly growing mass with a short doubling time with some authors suggesting the peak growth occurs within the first 4 weeks of developing the malignancy (23). With patients suffering from the sporadic variant typically presenting swelling in the abdomen but it is not unknown for it to present in the head and neck region. In contrast, Endemic BL lesion in the majority of cases presents with enlargement of the jaw, periorbital swelling, or genitourinary involvement. In these cases, malnourishment is commonly presented as well as the fact that the majority of these cases involve children (9, 17, 23). Patients with Sporadic BL tend to present with abdominal pain secondary to ileocecal disease, abdominal distention, nausea, vomiting, and gastrointestinal bleeding. Adult patients tend to more frequently present with constitutional symptoms such as; fever, weight loss, night sweats (9). Rarely does BL present with bone marrow and central nervous system (CNS) involvement. However, it has been is reported in 30–38% and 13–17% of adults. Bone marrow involvement is more frequently encountered within the more progressive stages of BL (11). BL infrequently presents manifestations within the mediastinum, central nervous system, testes, skin, thyroid gland, or breast tissues (9).

Due to this high cell turnover rate patients also tend to present another clinical sign often presented by patients is elevated levels of lactate dehydrogenase (LDH), and increased uric acid levels (9,11). These elevated levels again give an insight into the fact that Burkitt Lymphoma is a very rapidly growing malignancy and a very high tumour turnover rate.

Another clinical sign which should be taken into account especially when it comes to treatment and prognosis is If the patient has bone marrow involvement and presents with a greater than 25% of cellularity, then the disease is classified as Burkitt leukaemia. Burkitt's leukaemia is considered a manifestation of an advanced stage of BL. This also includes patients with acute lymphoblastic leukaemia (1–2%), who have circulating blast cells which morphologically and histologically resemble the cells seen in Burkitt Lymphoma (9, 11).

What is also of interest from a diagnostic point of view is the apparent overlap in clinical presentation between the three variants. Where although in theory all 3 variants have distinctive patterns one of the clinical features is the similarity presented between the three (11).

1.5 Staging

The main aim of staging a disease is to allow for the description of its extent, spread and to determine its pathological course. When this idea is understood through the creation of a clear and easy to understand staging system it is possible to design a treatment plan. The staging also allows for the realization of the prognosis of the disease and allows the clinician to inform the patient on the progress or the outcome of the situation.

There are various staging systems used for Burkitt Lymphoma, the most common systems being used today is the Murphy/St Jude system most often used in children and the Ann Arbor system in adults. With staging being done as rapidly as possible and treatment to start within 48 hours of final diagnosis. One tool used in this staging

process is Positron emission tomography (PET) scanning which has demonstrated to have a high sensitivity for identification of Burkitt Lymphoma (15).

The Murphy staging system has a particular focus on the frequent extra-nodal manifestations present in BL. It also has a focus on the poorer prognosis of the intra-thoracic manifestations. What should be noted though is that this system and all other previously were devised full resection surgeries or more aggressive exploratory surgery was more common, meaning that Stage IIR (fully resected abdominal disease) manifestations is now rarely encountered. The Murphy system differs in the way that a single extra-nodal site is categorized and includes upgrading of non-resected intra-thoracic and intra-abdominal manifestations. The Murphy system also distinguishes central nervous disease (CNS) and bone marrow disease from other types of Stage IV disease as defined in the Ann Arbor system (15, 24).

In contract the Ann arbour system puts more focus on B-symptoms. In a clinical setting, the variable use of the different staging systems in adults only makes a difference to the prognostic stratification and treatment offered to a minority of patients. However, it does create difficulties in the comparison of different series (15).

The earliest staging system for Burkitt Lymphoma was created in 1974 by Ziegler and Magrath. This system used a grouping using letters based on the location of the various tumours. Group A is a single extra-abdominal tumour and AR is an intra-abdominal tumour for which >90% was surgically resected. Whereas groups B, C and D (multiple extra-abdominal sites, intra-abdominal tumour, and intra-abdominal tumour with involvement of greater than or equal to one extra-abdominal site,) this

means that groups B-D are more indicated for the staging of more disseminated cases of BL (24).

Staging systems used in Burkitt lymphoma		
	Murphy system	**Ann Arbor system**
Stage I	Single nodal or extra-nodal site *excluding mediastinum or abdomen*	Single nodal or extra-nodal site
Stage II	Two or more nodal areas on one side of diaphragm	Two or more nodal areas on one side of diaphragm or Localized involvement of an extra-lymphatic site and of one or more nodal sites on the same side of the diaphragm (IIE)
Stage IIR	*Completely resected intra-abdominal disease*	
Stage III	Two or more nodal areas on opposite sides of the diaphragm or *Primary intrathoracic tumour* *Paraspinal or epidural tumours* *Extensive intra-abdominal disease*	Two or more nodal areas on opposite sides of the diaphragm which may include/involvement of the spleen (IIIs) or localized involvement of an extranodal site (IIIE)
Stage IIIA	*Localized non resectable abdominal disease*	
Stage IIIB	*Widespread multiorgan intra-abdominal disease*	
Stage IV	*Central nervous system or bone marrow involvement*	Diffuse or disseminated involvement of one or more extra-lymphatic sites Two single extra-nodal tumours on opposite sides of diaphragm
Favourable	Stage I or IIR	*Also A + B depending on symptoms* Stage IA and IIA Stage I, II and III

Table 3: Comparison between the Murphy and Ann Arbour systems for grading BL.

However, as time went on and the technology improved from the 1960s where staging was based purely physical examinations and full blood-counts, chemistry screen, chest x-ray, intravenous pyelogram, gastro-intestinal contrast studies, bone marrow aspirations and cerebrospinal fluid examinations. During the 1970s bone marrow biopsies using bone-marrow aspirations were introduced but were largely ineffective. This was subsequently followed by nuclear imaging through the use of gallium or full bone scans. This was improved upon in the 1980s through the development and use of computerized axial tomography (CT scan). As diagnostic imaging methods have become more effective in the 2000s; positron emission tomography (PET) imaging methods are being used to replace bone scans and gallium scans. Currently being used is minimal residual disease (MRD) technology (flow cytometry and polymerase chain reaction [PCR] for immunoglobulin gene rearrangements) has also been studied and now introduced into current protocols of further investigation (24).

The main focus of this investigation will be on Endemic type as it is the form that most frequently presents with oral manifestations (4).

2.Objectives:

Primary objective: The main objective of this literature review was to analyse the most common oral manifestations of Burkitt Lymphoma.

Secondary Objectives:

- Describe carcinogenic process in endemic BL
- Review possible ways for oral BL diagnosis
- Update oral BL therapy in the XXI century
- Compare BL rates in last 20 years

3. Methodology:

The information gathered for this investigation was done through the use of books and scientific articles available. The majority of the research was conducted using online access through; Medline, PubMed, Google Scholar and the European University of Madrid library.

- -Inclusion criteria:
    - Key words: Oral Manifestations, Burkitt Lymphoma, Treatment, Malaria, Epstein Barr Virus, Pathophysiology, Evolution of, Case studies of, Reviews, Classification.
    - Time: Scientific literature published within the last 10 years (from 2010 to 2020).
    - All age groups were included
    - All papers with full text obtained through on-line access or through Dulce Chacon Library (UEM library)
    - Languages: papers in English and Spanish were included.
- Exclusion criteria
    - Those articles impossible to get from university interlibrary borrowing

The articles were then compiled and cited according to the Vancouver referencing system.

After bibliography review, there were 51 sources used: articles and chapters from books

Introduction: 27 References

- What is Burkitt Lymphoma
- Types of Burkitt Lymphoma
- Differential Diagnosis of Burkitt Lymphoma.
- Clinical Manifestations
- Staging

Discussion of results: 24 References

- Burkitt lymphoma inside oral cavity
- Clinical manifestations
- Differential diagnosis
- Therapy and prognosis

4.Discussion of results

4.1 Burkitt lymphoma inside oral cavity:

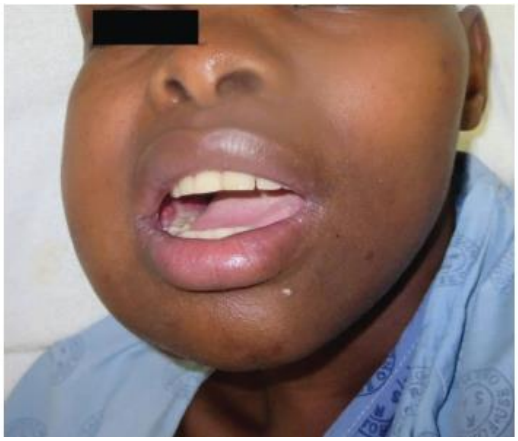
As mentioned in the introduction the main type of Burkitt lymphoma which presents with oral-facial manifestations in the Endemic type (more than 50% of all cases) however in some rare cases oral and head and neck presentations have been encountered in the Sporadic (around 7%) and Immunodeficiency variants.

An important factor to consider when looking at oral manifestations of Non-Hodgkin's lymphomas is the age of the patient, due to patients tending to be older, the exception being BL which tends to be more common in young patients. (28). A noteworthy factor to consider when looking at the oral manifestations of Burkitt lymphoma is the fact that it from a purely clinical manifestation it is very difficult to distinguish from other oral manifestations of other lymphomas. This makes it imperative that clinical manifestations are not sufficient to draw conclusions from and needs to be followed up by a diagnosis based on the radiological, histological and serological findings. Moreover, it has to be appreciated that the oral clinical manifestations of BL despite it being a very rapidly growing neoplasm is often mis-diagnosed as being a stomatological problem (29). Of note however, lymphomas present as the most frequently encountered non-epithelial malignant neoplasm encountered within the oral cavity and maxillofacial region. Moreover, it represents the third most common malignancy within the oral cavity being superseding squamous cell carcinomas and tumours of the salivary glands (30).

Due to this the presentation in the oral cavity is very similar to osteomyelitis, or advanced periodontal disease, with lymphomas within the oral cavity often being manifestations of more disseminated pathological process (30).

4.2 Clinical manifestation

Typically, BL presents in the in the oral cavity as an exophytic lesion on the jaw and is associated with swelling in the alveolar regions, gingival enlargement, jaw expansion and pain which can also be seen in the maxilla, but is more common in the mandible



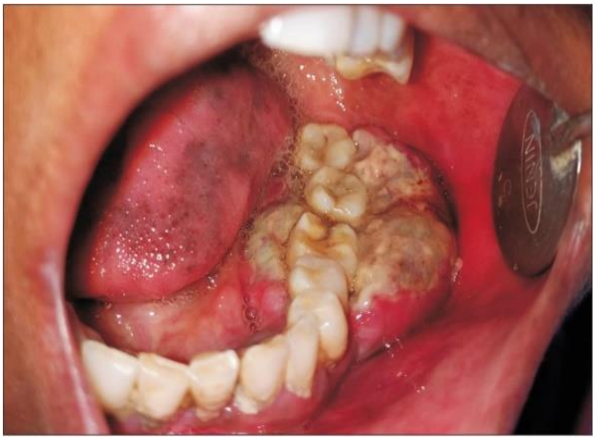


Figure 6 (Left image): patient presenting with a large submandibular swelling on the right-hand side, typical of BL. The patient in this case also presented with marked trismus and difficulty opening her mouth. However, a clear exophytic lesion is visible in the posterior region of the mandibular region on the buccal side. (5)

Figure 7 (Right image): Presents a large exophytic lesion in the posterior region of the mandibular region on the buccal side. Which is a very common sign of the oral manifestations present in BL. (6)

This is often followed with premature exfoliation of primary teeth and extrusion of the teeth involved. With it being noted that patients often present with teeth hypermobility which is often as a result of osteolytic destruction of the underlying cortical bone and destruction of the underlying lamina dura. This often appears radiographically as a radiolucent area around the affected structures. Of paramount importance is due to the location of lesion in the mouth the associated swelling and

expansion of the neoplasm can lead to the development of rapid and unexpected and life-threatening obstructions of the airway (28-32).

As mentioned previously, although these lesions are more typical of the endemic form of BL they can be found in the other variants as well and are not necessarily indicative of BL as they can be caused by a great variety of other pathologies.

4.3 Differential diagnosis

The differential diagnosis for Burkitt Lymphoma is very important, especially considering the oral lesions it presents has very similar clinical characteristics to many other exophytic oral lesions.

One important factor to look at when analysing oral manifestations of Burkitt Lymphoma is to investigate the occurrences of other more common oral tumours and lesions. The first look at these are the series of non-malignant tumours which are often present in infants as their appearance is much more common than malignant tumours.

With some studies suggesting that up to 87% of these tumours being non-malignant with most frequently encountered type being haemangiomas (33). Additionally, of note it was found that this series on non-malignant oral pathologies appeared to have a stronger female predication whereas BL has a stronger male predication. Within that study group it was concluded that the most common type of lesion encountered was reactive/ inflammatory type lesions which presented (75.8%), followed by tumour/tumour-like lesions (16.8%) and cystic (7.4%) lesions. With the most common location being the lower lip, which lies in contrast to BL which most commonly in the oral cavity presents on the mandible (34).

The most common non-malignant reactive/ inflammatory type lesions were; Pyogenic Granuloma, Peripheral ossifying fibroma and Peripheral giant cell granuloma. These lesions all appear to have a much more female predicated origin with almost exclusive presentation within the maxillary gingiva being often associated with trauma. These lesions also have a tendency for recurrence if the causal factor is not stopped (35). Moreover, another noteworthy factor to consider is the location of the lesion or malignancy within the oral cavity. With some research results concluding that the Maxilla was the most common location for benign lesions with the Mandible being the region which mostly presented with the development of malignant lesions (36). Although BL is a very rare malignancy by itself with oral manifestations being even more uncommon, one retrospective study conducted from 1990 to 2010 concluded that over the time-period there was a notable increase in the incidence in malignant paediatric oral tumours due to an increase in BL cases (37).

Another important avenue which has to be looked at when diagnosing oral pathologies, especially tumours, lies within the two groups which comprise of Odontogenic and Non-Odontogenic origin tumours. This becomes of paramount importance due to the locally destructive nature of these pathologies, especially from the point of view of destructive potential to the local surrounding tissues. The aggressive destructive potential of these pathologies should not be underestimated due to their long-term disfigurement potential. This potential damage can thus be mitigated by accurate and correct diagnosis of the tumour lineage and malignancy potential through histopathological diagnostic methods (38).

With the distinction between Odontogenic and Non-Odontogenic tumours being based upon their tissue of origin. Most common ones of both of them are shown at table 4 below.

Where Non-Odontogenic tumours tend to arise from either arise from mesenchymal tissues present at the site or from the osseous tissues present within the jaw. This is contrasted by Odontogenic tumours which arise from the tooth forming tissues. Within these tissues there are two main parts; *central odontogenic tumour* which arises from the bony tissue within the jaws or *peripheral odontogenic tumour* which arises from the peripheral tissues with various tissues being involved (39). The first tissue to be involved is the *Pre-functional dental lamina* which is an odontogenic epithelial tissue with the ability to produce dental structures with a high abundance distal to the mandibular molars. The following layer of tissue involved in the development of Odontogenic tumours is the *Post-functional dental lamina* which covers epithelial remnants such as Serre´s epithelial rests; which are located within the fibrous gingival tissue or Epithelial rests of Malassez which occur within the periodontal ligament and within the reduced enamel organ whose function is to cover the tooth's enamel until it has erupted. The subsequent layer of possible tumour development is the *Basal Cell Layer of the Gingival Epithelium*, which was responsible for the development of the dental lamina. Another possible site for development is the *Dental Papilla* which gives rise to the pulp, but also has the potential to initiate the development of odontoblasts and the subsequent synthesis of dentin and/or dentinoid tissues. Then final two sites of potential tumour development are the *Dental Follicle* and the *Periodontal ligament*; which has the potential to induce the synthesis of both fibrous and cemento-oesseous tissues (40).

NON-ODONTOGENIC TUMORS	ODONTOGENIC TUMORS
I. Benign mesenchymal tumors.	**I. Epithelial tumors.**
a) Giant Cell Lesions. **b) Fibro-osseous lesions.** **c) Myxoma**	**a) Ameloblastoma (Peripheral, Unicystic, Solid, Multicystic)** **b) Adenomatoid odontogenic tumor** **c) Calcifying epithelial odontogenic tumor**
II. Hematopoietic and reticuloendothelial tumors.	**II. Mesodermal tumors**
a) Langerhans cell histiocytosis **b) Burkitt's lymphoma** **c)Lymphoma**	**a)Cementoma** **b)Periapical cemental dysplasia** **c)Cementifying fibroma** **d)Cementoblastoma** **e)Odontogenic fibroma**
III. Neurogenic tumors.	**III. Mixed tumors**
a) Neurofibroma **b) Neurilemmoma** **c) Neuroma** **d) Ganglioneuroma** **e) Neuroblastoma** **f) Melanotic neuroectodermal tumor**	**a)Ameloblastic fibroma** **b) Odontoma**
IV. Vascular lesions.	
a) Vascular malformation (capillary, lymphatic, venous, arterial, combined)	

b) Hemangioma **c) Aneurysmal bone cyst**	
V. Malignant mesenchymal tumors.	
a) Osteogenic sarcoma **b) Chondrosarcoma** **c) Fibrosarcoma** **d) Ewing's sarcoma**	
VI. Malignant epithelial tumors.	
a) Squamous cell carcinoma **b) Mucoepidermoid carcinoma** **c) Adenoid cystic carcinoma** **d) Adenocarcinoma**	

Table 4: Jaw tumours in children: differential diagnosis (40).

Equally of importance to look at when looking at oral manifestations of various pathologies, it is important to look at the possibility of these presentations being caused by metastasis of more distant cancers. The most frequently encountered metastasis being found around the molar region of the mandible and these metastases are unfortunately often the primary metastatic sites for breast lung and kidney cancers. What makes diagnosis of these sites more difficult is the fact that often these lesions appear as simple non-aggressive dental infections (41).

4.4 Therapy and prognosis

Generally, the prognosis for patients suffering from BL is very good, especially within developed countries. With some 5-year survival rate of 78% with an estimated overall cure rate approaching 90% in paediatric patients (9, 31). However, it has to be noted that the survival rate drastically reduces in patients with systemic, CNS involvement or are suffering from HIV as does the relapse rate. A point of interest for this investigation was that patients that only presented with head and neck and facial bone manifestations had a significantly lower rate of recurrence than those who has abdominal or CNS involvement (31). From an historical point of view and from an overall societal view, BL is considered to be one of the earliest malignancies to be cured and with clinically significant results being present within two weeks of starting treatment and in the case of treatment in paediatric patients odontogenesis often continues once treatment has finished (31).

Another important factor to look at when analyzing the overall survival rate of BL is the stage of it, especially when using the Murphey system. With some authors seeing event free long-term survival rates of 85-100% in patients within stages i and ii and in more advanced stages of iii and iV of survival rates of 75-85% (31). Within this it has to be taken into account that the age of the patient does also play a significant role in the overall prognosis and survival of the patient (31, 42).

Ultimately, when looking at overall survival rates and long-term prognosis it is important to separate BL into three distinctive age groups; Children (<15 years of age), Adults (40–70 years of age) and Elderly (>70 years of age) (42). With these parameters being chosen due to some studies suggesting distinct peaks at ages; 10, 40 and 75 (43).

Moreover, when looking at these distinct age peaks it also has to mentioned that each age group has significantly different survival rates, with children having the highest overall survival rate of 90.3%, adults 46% and the elderly 21.7%. These figures thus demonstrate that age plays an important factor in the overall survival rate. However, it can also be seen that sex, site of primary tumour, but most significantly the staging of the disease appeared to be the clearest 5-year survival indicator across all 3 age groups (42)

	Children		Adults		Elderly	
	OS	**RS**	**OS**	**RS**	**OS**	**RS**
Overall	90.3	90.4	46	47.8	21.7	28.9
Sex						
Female	87.9	88	46.7	48.2	24.1	28.3
Male	90.9	90.9	45.8	47.7	19.7	26.7
Primary Site						
Lymph node	89.8	89.8	44.4	46.1	20.1	26.2
Head and neck	89.4	89.4	67.6	70.3	18.8	19.6
GI tract	95.2	95.2	55	57	25.5	34.9
Bone marrow	85.7	85.8	28.2	29.1	19.3	23.2
CNS	100	100	45.3	47.2	0	0
Others	92.2	92.2	57.2	59.3	29.1	36.1
Stage						
I	96.2	96.2	66.1	68.9	39.4	49.1
II	94.6	94.7	61.3	63.5	20.4	27.5
III	92	92	49.2	51.1	18.5	26.4
IV	84.7	84.8	38.2	39.7	16.1	20.7
Unknown	86.4	86.5	32.1	33.2	18.3	22.9

(**CNS:** central nervous system; **GI:** gastrointestinal; OS: observed survival; **RS:** relative survival.)

Table 5: Survival rates in BL (42).

When looking at the age differences it has to be taken into account that the majority of treatment protocols of BL involves very intensive chemotherapy programs. This has two features; first being BL being sensitive to chemotherapy and secondly younger patients

tend to respond better to the treatment related toxicities and generally have a lower rate of co-morbidities. This toxicity and comorbidities become a factor in reduced survival rates in elderly patients. In young patients however, they are less likely to suffer from acute toxicities they appear to be more susceptible to suffer long-term side effects such as secondary malignancies and infertility (42, 44).

Although BL is very sensitive to chemotherapy, it remains of paramount importance to firstly diagnose the pathology correctly. This is due to the fact that previous NHL treatments such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for DLBCL (Diffuse Large B-Cell Lymphoma) or other high-grade lymphomas with MYC translocations is inadequate. With Patients experiencing high rates of recurrence and lower overall survival rates than those on high intensity ALL regimes (16, 44, 46,47). With the known high sensitivity of BL to chemotherapy agents it is often the only method used, with surgery only being considered in cases where the disease is causing complications (16). With most chemotherapy regimens being cyclophosphamide-based (31).

An important factor to consider when looking at chemotherapy treatments is their possible side effects on the mouth, especially in terms of their effects on the developing tissues within the oral cavity of children. With the most severe side-effects being seen in children younger than 6 and younger than 12 often presenting altered

tooth development changes. These developmental alterations include anomalies such as enamel hypo-mineralization, altered root development, microdontia, aplasia or delayed development in permanent dentition. Despite this, dental carries and mucositides are the most commonly noted side effects of chemotherapy, thus good oral hygiene and care post treatment is of paramount importance (31, 45).

As previously stated, the treatment of BL has a significant history with using high dose chemotherapy agents based on other lymphoma treatments. Currently the National Comprehensive Cancer Network recommends multiagent regimens with CNS prophylaxis, these include; **CODOX-M/IVAC** (cyclosphosphamide, doxorubicin, vincristine, methotrexate, ifosfamide, cytarabine and etoposide) with or without Rituximab, **HyperCVAD** (hyperfractionated cyclophosphosphamide with doxorubicin, vincristine, and dexamethasone alternating with 4 cycles of metotrexate and high-dose cytarabine) + Rituximab and **DA-REPOCH** (Dose Adjusted etoposide, prednisone, vincristine, cyclophosphamide, adraimycin) (9, 47).

It was not until the late 1980s when and colleagues developed the specific BL protocol of CODOX-M/IVAC (cyclosphosphamide, doxorubicin, vincristine, methotrexate, ifosfamide, cytarabine and etoposide) (44, 46, 47). With the initial treatment regime putting the patients into 2 risk groups; High and Low. With patients in the low-risk group being classified with a single mass of <10 cm or completely resected abdominal disease with normal LDH (48). With these patients receiving three cycles of CODOX-M. The rest received two cycles of CODOX-M and IVAC with the overall survival rate of this schedule reaching 92%. This regime does however present with high toxicity and due to this is better tolerated by paediatric patients (47). With a modified version

for the CODOX-M or Magrath regime being available in adults which presents with less toxicity but with similar high survival rates (46, 48).

Another effective treatment protocol investigated in the 2000s was the HyperCVAD (hyperfractionated cyclophosphosphamide with doxorubicin, vincristine, and dexamethasone alternating with metotrexate and high-dose cytarabine) + Rituximab (44, 47, 48). The initial investigation only made use of the HyperCVAD without Rituximab, where patients received 4 cycles of it, this investigation was more focused on adults. The overall survival rate of this treatment plan was 49%, with patients under 60 having a 77% and over only having a 17% survival rate. However, the overall survival rate of this regime can be boosted to 89% with the addition of rituximab (48). One problem with the initial treatment was the high rate of treatment related complications as a result of prolonged myelosuppression. With 19% of patients of patients succumbing to death during treatment induction and 86% suffering neutropoenia related fever (44).

An alternative approach to the conventional high-dose and subsequently high toxicity associated is the DA-REPOCH / EPOCH-RR (Dose Adjusted etoposide, prednisone, vincristine, cyclophosphamide, adraimycin and rituximab) protocol. With the focus of this treatment being on exposure time vs maximal dosage as the two previously mentioned treatment protocols (44). One investigation protocol gave low-risk patients 3 cycles of the treatment and saw 100% progression free survival rate at 2 years. With the high-risk group seeing an 80% progression free survival rate at 2 years. The investigation also found that advanced age and HIV status didn't have a great

effect on the overall survival rate. The group which did suffer from a poorer outcome was those afflicted with CNS progression (44, 46, 47).

5. Conclusions

1. Endemic BL is the type that more frequently presents with oral involvement.
2. The most common oral manifestations seen in patients are large, destructive and rapidly growing exophytic lesions in the oral cavity.
3. These lesions often present with large radio lucid areas in the mandible of young children.
4. Its origin in Endemic BL is related with EBV and plasmodium falciparum infection.
5. The most effective way of diagnosing BL in the oral cavity is “the starry-sky appearance” in lymph node biopsy and through chromosomal phenotyping by looking for over-expression of MYC due to the balanced translocation of the locus *MYC*/8q24.
6. The most recent shift appears to be heading towards less aggressive and toxic chemotherapy treatment protocols such as DA-REPOCH, with the use of Rituximab being put forward in all treatment protocols to improve overall success.
7. Overall survival rate in BL affecting mouth is more than 90% of patients.
8. The overall rate of BL worldwide is very low, however within the last 20 years as better diagnostic methods and unfortunately higher rates of malaria are being encountered the rate appears to be increasing in some areas.

6. Social responsibility

6.1 Patient responsibility

It is the patients' responsibility to notify the dentist as soon as possible if they notice any possible lesion in the mouth. Moreover, it is their responsibility to wherever and whenever possible to seek treatment is soon as they notice any illness or suspect they may have it. It should also be seen to be their responsibility to go to the dentist for routine dental check-ups to ensure that the dentist can monitor their overall oral health and investigate any anomalies present and treat them as soon as possible to ensure the best possible outcome. It should also fall within their responsibility to perform all of the possible preventive measures to prevent the development of for Burkitt Lymphoma through following the advice on personal malaria prevention and to follow the preventative measures to prevent their infection with HIV. Although sometimes difficult, it is the patients' responsibility to adhere to the treatment schedules and to follow the directions set out by the dentist and subsequent medical professionals with regards to their treatment. Finally, it is down to the patient to be honest with all their medical professionals with regards to their medical history to ensure they provide the most accurate and appropriate information which will ultimately make a possible diagnosis easier and quicker and often allow for more prompt treatment.

6.2. Professional responsibility of the dentist

It is the responsibility of the dentist as a professional to have the adequate knowledge of oral health and pathologies to be able to recognise the early oral manifestations of for Burkitt Lymphoma. This not only allows for more effective treatment but ultimately allows for a better prognosis for the patient. Another important responsibility of the dentist as a professional is to educate their patients on oral health, care and risk factors and to encourage their patients to seek help and advice when they suspect any problems. The dentist should also wherever possible try and encourage as far as possible the patients to follow their treatment schedules and go to regular check-ups. Ultimately from a professional view it is the dentists' responsibility to provide the patient with the best possible care under the given circumstances.

6.3 Government social responsibility

It should fall within the responsibility of the government to provide the facilities and resources necessary to treat patients suffering from Burkitt Lymphoma. They should also be responsible for providing where-ever possible the healthcare facilities necessary to not only treat but also to diagnose BL. It is also their responsibility in countries within the malaria belt to do as much as possible to prevent the spread of malaria infections. They should also be responsible for education and prevention programs of preventable infections such as HIV through providing contraceptives and education related to the prevention of such infections.

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Annexes

Burkitt's lymphoma

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Burkitt's lymphoma is a highly aggressive B-cell non-Hodgkin lymphoma and is the fastest growing human tumour. The disease is associated with Epstein-Barr virus and was one of the first tumours shown to have a chromosomal translocation that activates an oncogene (*c-MYC*). Burkitt's lymphoma is the most common childhood cancer in areas where malaria is holoendemic. The incidence is very high in immunosuppressed patients in non-endemic areas, especially when associated with HIV infection. Outcome with intensive chemotherapy has improved and is now excellent in children, but the prognosis is poor in elderly adults. The success of intensive treatment relies on good supportive care. The therapy offered in oncology units in low-income countries is not as aggressive as in centres in high-income countries and outcomes are less successful. Adjuvant monoclonal antibody therapy with rituximab shows promise for improved outcomes and reduced toxic effects in the future.

Introduction and history

Burkitt's lymphoma has had an important role in the understanding of tumorigenesis. It was the first human tumour to be associated with a virus,[1] one of the first tumours shown to have a chromosomal translocation that activates an oncogene,[2,3] and the first lymphoma reported to be associated with HIV infection.[4] Burkitt's lymphoma is the fastest growing human tumour, with a cell doubling time of 24–48 h, and was the first childhood tumour to respond to chemotherapy alone.[5] It is the most common childhood cancer in areas where malaria is holoendemic—eg, equatorial Africa, Brazil, and Papua New Guinea.[6] The so-called Burkitt's lymphoma belt stretches across central Africa 15° either side of the equator where the climate is hot and wet (more than 50 cm annual rainfall). The epidemiological maps of malaria and Burkitt's lymphoma overlap.[5–7]

Early in the 20th century, Sir Albert Cook, a missionary doctor in Uganda, and other medical staff working in west, east, and central Africa noted the high frequency of jaw tumours and childhood lymphomas.[8–10] In 1958, Denis Burkitt, an Irish surgeon working in Uganda, reported cases of children presenting with rapidly growing jaw or abdominal tumours.[11] Burkitt suggested that these tumours were round-cell sarcoma. However, in 1960 George O'Connor, a pathologist, concluded that the cancer was of lymphoma lineage.[12] In 1964, three virologists, Michael Anthony Epstein, Yvonne Barr, and Bert Achong identified viral particles in the tumour tissue; this virus became known as Epstein-Barr virus (EBV).[1] Meanwhile, Burkitt travelled through eastern and central Africa to map the tumour spread and found records of affected children in all the malarial areas of the region.[13] These associations with malaria and EBV have inspired research throughout the world (figure 1).

Classification

The WHO classification of Burkitt's lymphoma describes three clinical variants: endemic, sporadic (the predominant type found in non-malarial areas), and immunodeficiency-related.[20] These types are similar in morphology, immunophenotype, and genetic features. The endemic variant is associated with malaria endemicity and EBV is found in almost all cases. The sporadic type occurs mainly throughout the rest of the world (predominantly North America and Europe), with no special climatic or geographical links, and is rarely associated with EBV infection. 1–2% of adult lymphomas and 30–40% of childhood non-Hodgkin lymphomas in Europe and North America are sporadic-type Burkitt's lymphoma.[21] The immunodeficiency-related type is seen most often in patients with HIV infection and less than 40% of US and European cases are associated with EBV. Before the advent of antiretroviral therapy in North America the disorder was 1000 times more common in HIV-positive people than in uninfected individuals.[22,23] Immunodeficiency-related Burkitt's lymphoma is more common when the CD4 T-cell count is greater than 200 per µL (early in the progression of HIV infection). The association of HIV with Burkitt's lymphoma is not as clear in the endemic form.[24] The risk of BL increases 4 to 5 years after organ transplantation, but this risk is much less than that associated with HIV infection.[25]

Epidemiology

The distribution of endemic Burkitt's lymphoma across Africa and Papua New Guinea corresponds to areas of holoendemic malaria and the early acquisition of EBV.[11,26–31] The annual incidence has been estimated at 40–50 per million children younger than 18 years.[32] In these high-risk areas endemic Burkitt's lymphoma comprises about half of all childhood cancer diagnoses and up to 90% of

Search strategy and selection criteria

We searched for articles in English on Medline and Embase with the search terms "Burkitt lymphoma" and "Burkitt's lymphoma", together with the terms "paediatric", "pediatric", "children", "adult", "sporadic", "epidemiology", "co factor", "HIV", "malaria", "EBV", "pathology", "immunology", "treatment", and "outcome". We also searched the reference lists of articles identified by this strategy. We did not limit ourselves by date so as to provide historical context.

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A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN

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MALIGNANT tumours of the jaws in children, primary or secondary, are generally regarded as rare. A sarcoma involving the jaws in African children has recently come to be recognized at Mulago Hospital as a distinctive clinical condition and certainly the commonest malignancy of childhood.

Thirty-eight patients with this sarcoma in the jaws have been seen during the past 7 years; 32 of them were seen at Mulago Hospital and 6 at district hospitals. The tumour was diagnosed clinically in a further 8 children, but these have not been included in this series owing to lack of histological confirmation.

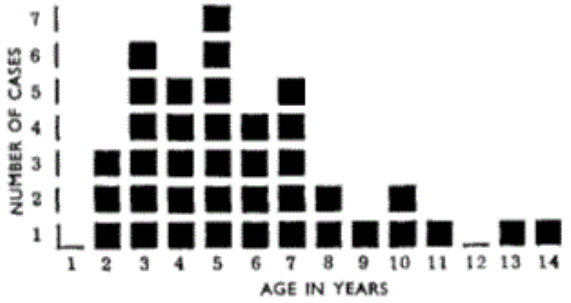

FIG. 246.—Showing age distribution in 38 cases.

Records of only 3 cases of this type of jaw sarcoma in children have been traced in the literature (Christiansen, 1938; Salmon and Darlington, 1944; Burford, Ackerman, and Robinson, 1944). Gelfand (1957) published an illustration of a sarcoma of the jaw in an African child without clinical details.

GEOGRAPHICAL DISTRIBUTION

Patients have not been limited to any particular area in Uganda, and have represented 11 different tribes. This sarcoma has also been observed in Kenya (Clifford, 1958), Tanganyika (Morris, 1958; Blackman, 1958), Nigeria (Thomas, 1958), the Belgian Congo (Thijs, 1958), and Southern Rhodesia (Gelfand, 1957). Patients with this syndrome have not yet been recognized in Johannesburg (Oettlé, 1958), Khartoum (Taylor, 1958), Lusaka (Buck, 1958), or Lourenço Marques (Prates, 1958).

CLINICAL FEATURES

These patients were from 2 to 14 years of age, 30 being between the ages of 2 and 7 years (*Fig.* 246).

In most cases the tumour started in the region of the alveolar process of a maxilla (*Fig.* 247) or the mandible (*Fig.* 249). Loosening of the deciduous molars was often the first symptom, the teeth in the involved area soon becoming embedded in tumour tissue only, and losing their insertion in bone. The next stage was irregular displacement of the teeth prior to their falling out. The tumour grew rapidly,

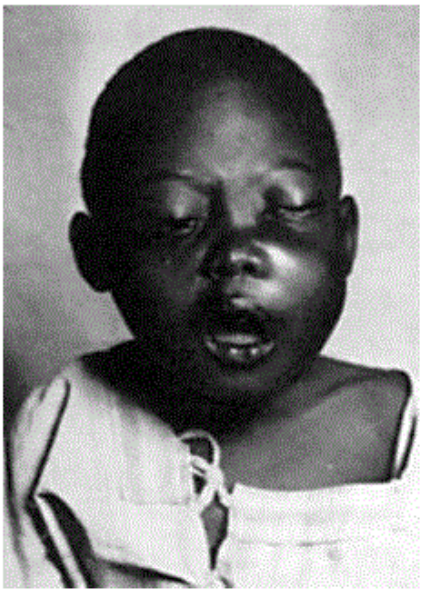

FIG. 247.—Sarcoma involving the left maxilla and arising in relation to the teeth. *Case* 1, taken 2 months after onset of symptoms.

grossly distorting the face. In only one patient (*Case* 20) did it ulcerate through the skin. Œdema of the eyelids and chemosis of the conjunctivæ indicated invasion of the orbit, and if the patient survived the eye became proptosed and finally destroyed. Less commonly the tumour presented as a swelling high in the maxilla with early invasion of the orbit (*Fig.* 248). Pain was not usually as severe as would have been expected from the appearance of the tumour. Within two or three months of onset of symptoms their relatives removed the majority of the children from hospital in a moribund condition.

Unless secondary infection occurred, which was not usual, the regional lymph-nodes were not

REVIEW

Burkitt's lymphoma: new insights into molecular pathogenesis

C Bellan, S Lazzi, G De Falco, A Nyongo, A Giordano, L Leoncini

J Clin Pathol 2003;**56**:188–193

The World Health Organisation classification reports three subcategories of Burkitt's lymphoma (BL)—endemic, non-endemic, and immunodeficiency associated—proposed to reflect the major clinical and genetic subtypes of this disease. These different types of BL have been reviewed and studied by immunohistochemistry and molecular methods. The results point out the heterogeneity of BL and suggest that AIDS related BL may have a different pathogenesis from that of classic BL.

In 1958, Dennis Burkitt first described a disorder associated with jaw tumours in African children.[1] In 1961, the neoplasm was identified as a form of malignant lymphoma, and what had initially emerged as a clinical syndrome became a pathological entity called Burkitt's lymphoma (BL).[2] Histologically, Burkitt's tumours are composed of monomorphic, medium sized cells with round nuclei, multiple nucleoli, and relatively abundant basophilic cytoplasm, which may give the cells a "cohesive appearance" (fig 1). These tumours have an extremely high rate of proliferation, in addition to a high rate of cell death (apoptosis). A "starry sky" pattern is usually present, imparted by numerous benign macrophages that have ingested apoptotic tumour cells. The cell of origin of BL is currently thought to be a germinal centre B cell,[3] although several studies of IgHV genes in BLs suggest that they may derive from memory B cells rather than germinal centre B cells.[4]

> "Most AIDS related Burkitt's lymphomas in Western countries are Epstein-Barr virus (EBV) negative, whereas in Africa they are strongly associated with EBV"

BL occurs as an Epstein-Barr virus (EBV) associated malignancy among children in the malaria belt of equatorial Africa (endemic BL),[5] and sporadically in other geographical areas, where it also occurs among adults (sporadic BL).[6 7] The most common site of involvement of endemic BL is the kidneys. Jaw tumours are age related with an overall incidence in Uganda of 50%.[5] In contrast, the terminal ileum and lymph nodes are the more commonly involved sites in sporadic BL.[8 9] A common translocation t(8;14) and the consequent c-myc rearrangement and overexpression have been identified in endemic and sporadic BL. However, some not very strict associations between JH and DH recombination have been identified at 14q32, with distant 5′ c-myc recombination in endemic cases of BL, whereas in sporadic cases Sμ and Sα recombination was identified[10] at 14q32, with near 5′ or intronic c-myc recombination at 8q24. These differences between endemic and sporadic BL do not mean that each of these subtypes of lymphoma represents a perfectly homogeneous entity.[8] Instead, it seems probable that BL is composed of a mixture of molecular types and that the incidence of each subtype might depend upon environmental factors.[7 11] Yet, the sporadic form of BL can also occur in endemic areas,[12] as reported in table 1, which summarises the distribution of BL collected from endemic areas of Kenya according to the age of patients, the clinical pathological characteristics, and the EBV and human immunodeficiency virus (HIV) status. These observations emphasise the importance of precise disease definition for biological and epidemiological studies. In particular, it is interesting that eight cases stand out from BL occurring in young adults as being HIV positive.

In fact, BL has frequently been reported as a common neoplasm in HIV infected patients,[13] although it is not known why BL is so common in HIV and not in other forms of immunodepression. These lymphomas, which are now better listed as "AIDS related BL",[14] usually display an activation of c-myc by chromosome translocations that show structural similarities to those found in patients with sporadic BL.[15] Nonetheless, most AIDS related BLs in Western countries are EBV negative,[16] whereas in Africa they are strongly associated with EBV.[17]

The term Burkitt-like (BL-like) lymphoma has been commonly applied to those tumours that have morphological features intermediate between large cell lymphoma with centroblastic or immunoblastic features and typical BL. The revised European–American lymphoma classification gives BL-like lymphoma provisional status, leaving the differential diagnosis between BL and diffuse large B cell lymphoma (DLBCL) unresolved.[18] The oncologists recommended that the category of BL-like lymphoma be reserved for tumours to be treated "like Burkitt lymphoma". A recent study by the southwest oncology group concluded that BL-like lymphoma can be recognised by its combined morphology and phenotypical features and that it represents a high

See end of article for authors' affiliations

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Abbreviations: BL, Burkitt's lymphoma; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; Rb, retinoblastoma; WHO, World Health Organisation

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CASE REPORT

Intra-oral HIV-associated Burkitt's lymphoma with mandible involvement

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KEYWORDS
Burkitt's lymphoma;
HIV;
Oral

Summary Although Burkitt's lymphoma (BL) of the oral cavity is very uncommon in human immunodeficiency virus (HIV)-infected patients, its occurrence is highlighted as one of the earliest clinical manifestations. This report deals with the first occurrence of intra-oral HIV-associated BL with plasmacytoid differentiation and mandibular involvement. It also serves to illustrate the importance of histological and immunohistochemical analyses of oral lesions to indicate the possibility of HIV-infection.

Introduction

In the most recent World Health Organization (WHO) classification, Burkitt's lymphoma (BL) is separated into three clinical variants: endemic BL, non-endemic BL, and human immunodeficiency virus (HIV)-associated BL.[1] Additionally, three subtypes of HIV-associated BL have been suggested by the WHO:[1] classic BL, BL with plasmacytoid differentiation and atypical BL. This report has documented an intra-oral case of HIV-associated BL with plasmacytoid differentiation and mandibular involvement. It also serves to illustrate the importance of histological and immunohistochemical analyses of oral lesions to indicate the possibility of HIV-infection.

Case report

A 28-year-old Chinese man presented with a 4-week history of a painful swelling on his right cheek (Fig. 1A). The patient did not have any known drug allergies, and had a history of cigarette smoking, alcohol consumption, and betel-quid chewing. No other significant previous medical history was noted apart from gastric disease and a recent

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

SADJ May 2015, Vol 70 no 4 p168 - p170

E Mosalleum[1], N Mohamed[2], FC Bassa[3], WP Dreyer[4]

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

ACRONYMS

ARV:	Antiretroviral
FISH:	Fluorescent *in situ* hybridization
HIV:	Human immunodeficiency virus
CNS:	Central nervous system
CT:	Computerized tomography
EBV:	Epstein Barr Virus

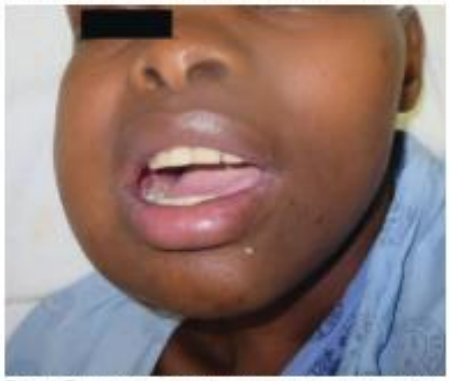

Figure 1: The patient presented with a swelling in the right submandibular region. She also had trismus, which made intraoral examination very difficult but despite this, an intraoral exophytic soft tissue mass can be seen.

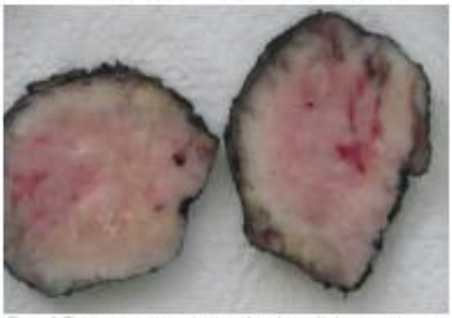

Figure 2: The tissue mass removed from the submandibular region showed a homogenous gelatinous consistency in cross section.

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

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Intraoral HIV-associated Burkitt's lymphoma: a rare case report with special emphasis on differential diagnosis

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Abstract (J Korean Assoc Oral Maxillofac Surg 2019;45:225-229)

Individuals with human immunodeficiency virus (HIV) infection present with unique intraoral manifestations of various neoplasms. Intraoral HIV-associated Burkitt's lymphoma is a rare presentation, especially in patients of Indian origin and may present as an initial sign of HIV. The objective of this paper is to report a rare case of Burkitt's lymphoma in an HIV-positive Indian patient along with a special emphasis on differential diagnosis. A 30-year-old Indian female presented with a solitary, well-defined, exophytic mass extending anteroposteriorly and buccolingually from the 35th to 38th regions with no evidence of intraosseous extension. An incisional biopsy was performed, and histopathology showed sheets of neoplastic lymphoid cells with numerous tingible body macrophages with clear cytoplasm, presenting a starry sky appearance, suggesting a diagnosis of BL. The tumor cells were positive for CD10, CD20, c-myc, and Epstein–Barr virus, with a nearly 100% Ki-67 proliferative index. The patient tested positive for HIV. This report indicates the importance of immunohistochemical analysis to differentiate Burkitt's lymphoma from other similar lesions like diffuse large B-cell lymphoma. Thorough knowledge of the clinical presentation, etiopathogenesis, histopathology, and immunoprofile of intraoral HIV-associated Burkitt's lymphoma is essential among clinicians and pathologists.

Key words: Aquired immunodeficiency syndrome, Burkitt lymphoma, Gingiva, HIV, Oral cavity

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I. Introduction

Non-Hodgkin's lymphoma (NHL) is one of the most common acquired immunodeficiency syndrome (AIDS)-defining neoplasms, accounting for one-third of AIDS-related malignancies[1,2]. Burkitt's lymphoma (BL) is an uncommon highly aggressive B-cell NHL, first described by Dr. Dennis Burkitt in 1958[3,4]. BL has the highest proliferation rate of any human neoplasm, with a possible doubling time of 24 hours[3]. Three forms of BL have been described by World Health Organization (WHO): 1) Endemic, 2) sporadic, and 3) immunodeficiency-associated[4]. BL exhibits an elevated incidence in immunocompromised patients, especially those with human immunodeficiency virus (HIV) infection, accounting for 2.4% to 20% of HIV-associated NHLs[2,3]. Extra nodal sites particularly in the abdomen and lymph node are the most common sites for HIV-associated BL, and intraoral lesions are very uncommon[5,6]. This subtype is considered one of the primary/initial conditions indicating an underlying HIV infection[6]. Therefore, we report a case of HIV-associated BL presenting as an intraoral mass in a female Indian patient.

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II. Case Report

A 30-year-old female reported to our institution with a chief complaint of an asymptomatic, gradually enlarging growth in the lower left back region of the jaw for 4 months. The patient did not reveal any significant medical history or drug allergies. Extraoral examination revealed facial asymmetry caused by a soft, painless swelling of the left cheek. An enlarged left submandibular lymph node was noted. Intraoral examination showed a solitary, well-defined, sessile, exo-

Gene expression analysis uncovers similarity and differences among Burkitt lymphoma subtypes

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Burkitt lymphoma (BL) is classified into 3 clinical subsets: endemic, sporadic, and immunodeficiency-associated BL. So far, possible differences in their gene expression profiles (GEPs) have not been investigated. We studied GEPs of BL subtypes, other B-cell lymphomas, and B lymphocytes; first, we found that BL is a unique molecular entity, distinct from other B-cell malignancies. Indeed, by unsupervised analysis all BLs clearly clustered apart of other lymphomas. Second, we found that BL subtypes presented slight differences in GEPs. Particularly, they differed for genes involved in cell cycle control, B-cell receptor signaling, and tumor necrosis factor/nuclear factor κB pathways. Notably, by reverse engineering, we found that endemic and sporadic BLs diverged for genes dependent on *RBL2* activity. Furthermore, we found that all BLs were intimately related to germinal center cells, differing from them for molecules involved in cell proliferation, immune response, and signal transduction. Finally, to validate GEP, we applied immunohistochemistry to a large panel of cases and showed that *RBL2* can cooperate with *MYC* in inducing a neoplastic phenotype in vitro and in vivo. In conclusion, our study provided substantial insights on the pathobiology of BLs, by offering novel evidences that may be relevant for its classification and possibly future treatment. (*Blood*. 2011;117(13): 3596-3608)

Introduction

Burkitt lymphoma (BL) is listed in the World Health Organization (WHO) classification of lymphoid tumors as a single genetic and morphologic entity with variable clinical presentation.[1] In particular, the WHO classification recognizes 3 clinical subsets of BL: endemic (eBL), sporadic (sBL), and immunodeficiency-associated (ID-BL). Each affects different populations and can present with different features.

The endemic form is overall the commonest type, being the most frequent childhood cancer in equatorial Africa.[1-4] eBL is almost invariably associated with Epstein-Barr virus (EBV) infection, although local environmental toxics (ie, *Euphorbia tirucalli*) and coinfection with arbovirus or, specially, malaria also appear to be important for its pathogenesis.[5-7]

sBL is the most commonly recorded form in the United States and Europe. As opposed to eBL, only ~20% of cases are associated with EBV.[8]

Immunodeficiency-associated BL occurs more commonly in patients infected with HIV (HIV-BL) and rarely in patients who have undergone organ transplantation.[9] Intriguingly, because HIV-BL can occur in patients with relatively high CD4 counts, immunnosuppression per se is not sufficient to explain the relatively high prevalence of BL in this setting.[10,11] On clinical ground, the link between EBV and HIV-BL is less clear than for eBL.[1,12,13]

On the basis of morphology, phenotype, and genetics, BL is currently regarded as a germinal center (GC)–derived neoplasm.[1] Nevertheless, according to the somatic hypermutation (SH) patterns and the expression of specific EBV-related molecules, in the WHO classification a different origin for the endemic and sporadic forms has been suggested.[1,14,15]

At genetics, BL molecular hallmark is the ectopic expression of the *MYC* oncogene, because of reciprocal chromosomal translocations, juxtaposing *MYC* to the immunoglobulin heavy chain (*IGH@*) locus [(t(8;14)(q24;q32)] or the κ or λ light chain loci [(t(2;8)(p12;q24) and t(8;22)(q24;q11), respectively]. Interestingly, differences in the break point on chromosome 14 for the translocation of *MYC* to the *IGH@* locus, as well as in the mutation pattern of the 5′-region of *MYC*, have been recorded between eBL and sBL.[16] In addition, although all BLs have similar phenotype and *MYC* translocation, it has been argued that the 3 subtypes may have different pathogenetic mechanisms. In particular, because of the peculiar association patterns, a role for EBV has been proposed.[15] However, there is still no satisfactory explanation of whether and how EBV participates in the pathogenesis of BLs, and it is probable that different (or multiple) environmental exposures may converge in a common pathogenetic mechanism.

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Getting the Facts

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Burkitt Lymphoma

Overview

Lymphoma is the most common blood cancer. The main forms of lymphoma are classified as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), which includes several B-cell lymphomas and T-cell lymphomas. Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor.

NHL is broadly categorized as B-cell lymphomas or T-cell lymphomas. B-cell lymphomas develop from abnormal B cells and account for 92 percent of all NHLs. T-cell lymphomas develop from abnormal T cells and account for about 7 percent of all NHLs. NHL may also be classified as *indolent* (slow-growing) or *aggressive* (fast-growing).

Burkitt lymphoma is a rare but highly aggressive B-cell NHL that is a form of mature B-cell lymphoma. In addition to commonly affecting the lymph nodes, this disease may affect the jaw, central nervous system, bowel, kidneys, ovaries, or other organs. There are three main types of Burkitt lymphoma: endemic, sporadic, and immunodeficiency-related. Endemic Burkitt lymphoma is the most common of the three forms, originating in Africa, where it is still the most common childhood cancer; endemic Burkitt lymphoma is rare outside of Africa. Sporadic Burkitt lymphoma occurs throughout the world. The immunodeficiency-related variety of Burkitt lymphoma is most common in people with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Immunodeficiency-related Burkitt lymphoma can also occur in patients who have inherited immune deficiencies or those who take immunosuppressive medications to prevent rejection after organ transplant. The Epstein-Barr virus (EBV) has been shown to be linked to the development of Burkitt lymphoma; the greatest association between EBV and Burkitt lymphoma is seen with the endemic form.

The sporadic form seen in the United States accounts for about one percent of B-cell NHLs. The most common site of endemic disease is the jaw; for sporadic and immunodeficiency-related Burkitt lymphoma, abdominal tumor is the most common site of disease occurrence. Burkitt lymphoma may spread to the central nervous system (CNS; i.e., brain and spinal cord). At diagnosis, a sample of cerebrospinal fluid may be taken to determine if the disease has spread to the CNS.

Translocation of the *MYC* gene is a hallmark of Burkitt lymphoma, making this an important finding for diagnosis of the disease; however, abnormalities in this gene are found in other aggressive mature B-cell lymphomas as well. In fact, in adults, Burkitt lymphoma is sometimes difficult to distinguish from diffuse large B-cell lymphoma (DLBCL)—another aggressive mature B-cell lymphoma that is a much more common form of NHL. Accurately diagnosing Burkitt lymphoma is critical because Burkitt lymphoma and DLBCL are treated differently.

Patients with Burkitt lymphoma may experience tumor lysis syndrome, a condition that occurs when tumor cells release their contents into the bloodstream. Symptoms of tumor lysis syndrome may include nausea and vomiting, shortness of breath, irregular heartbeat, clouding of the urine, lethargy, or joint discomfort. This condition can occur spontaneously or after patients have received chemotherapy, and it can be very serious. Tumor lysis syndrome can cause kidney damage, irregular heartbeat, seizures, loss of muscle control, and in some cases death. However, this condition can be managed with increased fluids and supportive medications like allopurinol (Aloprim, Lopurin, Zyloprim) or rasburicase (Elitek).

Treatment Options

Because Burkitt lymphoma is extremely aggressive, diagnosis of this disease is frequently a medical emergency, requiring urgent hospitalization and rapid institution of therapy. However, Burkitt lymphoma is often very responsive to the currently recommended intensive combination chemotherapy regimens, and cure rates for this disease remain high. Treatment options are determined based on low- versus high-risk status. CNS involvement at diagnosis is recognized as the strongest risk factor for *relapse* (disease returns after treatment); therefore, recommended treatment regimens for patients who are at a higher risk of recurrence include treatment to protect the CNS, which may be given *intrathecally* (injected into the spinal fluid).

The combination of agents used for low- versus high-risk disease is similar, but high-risk patients are given additional treatment. All of the treatments used are very intensive, using high doses of toxic drugs given very frequently; however, most of the treatments are of short duration. The monoclonal antibody rituximab (Rituxan) may be added to any of these regimens. Specific treatment options for adults include the regimens described below and on the next page.

- The *Dose-Adjusted EPOCH* regimen includes etoposide (Etopophos, Toposar, VePesid), prednisone, vincristine (Oncovin, Vincasar), cyclophosphamide, and doxorubicin plus rituximab (Rituxan) and intrathecal methotrexate for patients who are at low risk and without CNS involvement, or in high-risk patients who are not able to tolerate more aggressive treatments.
- The *HyperCVAD* regimen includes cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (Cytosar) plus rituximab. This regimen includes intrathecal therapy and may be given for a longer duration than the other regimens listed herein.

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Burkitt Lymphoma

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Burkitt lymphoma (BL) is an aggressive non-Hodgkin B-cell lymphoma. The disease is associated with Epstein Barr virus (EBV), human immunodeficiency virus (HIV), and chromosomal translocations that cause the overexpression of oncogene c-myc. The World Health Organization (WHO) classifies BL into three clinical groups: endemic, sporadic and immunodeficiency-related. The endemic form is linked to malaria and EBV. The immunodeficiency-related variant is associated with HIV and to a lesser extent, organ transplantation. With intense chemotherapy treatment disease prognosis is excellent in children but poor in adults. This activity illustrates the evaluation and management of Burkitt lymphoma and reviews the role of the interprofessional team in treating patients with this condition.

The 2016 revision of the World Health Organization classification of lymphoid neoplasms

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A revision of the nearly 8-year-old World Health Organization classification of the lymphoid neoplasms and the accompanying monograph is being published. It reflects a consensus among hematopathologists, geneticists, and clinicians regarding both updates to current entities as well as the addition of a limited number of new provisional entities. The revision clarifies the diagnosis and management of lesions at the very early stages of lymphomagenesis, refines the diagnostic criteria for some entities, details the expanding genetic/molecular landscape of numerous lymphoid neoplasms and their clinical correlates, and refers to investigations leading to more targeted therapeutic strategies. The major changes are reviewed with an emphasis on the most important advances in our understanding that impact our diagnostic approach, clinical expectations, and therapeutic strategies for the lymphoid neoplasms. (*Blood*. 2016;127(20):2375-2390)

Introduction

The 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors and the associated monograph represent the established guidelines for the diagnosis of malignant lymphomas; however, subsequently there have been major advances with significant clinical and biologic implications.[1] A major revision is therefore being published that will be an update of the current fourth edition and not a truly new fifth edition as there are still other volumes pending in the fourth edition of the WHO tumor monograph series. Because it is considered a part of the fourth edition, while some provisional entities will be promoted to definite entities and a small number of new provisional entities added, there will be no new definite entities.

As with the 2001 and 2008 classifications, an all-important Clinical Advisory Committee meeting was held in 2014 to obtain the advice and consent of clinical hematologists/oncologists and other physicians critical to the revision (supplemental Appendix, available on the *Blood* Web site). Additional editorial meetings and consultations followed leading to the updated classification (Table 1).[2] Although there are only limited alterations in the classification compared with 2008, the revised monograph will incorporate a large body of information published over the last 8 years relating to existing entities with some important diagnostic, prognostic, and therapeutic implications. The classification maintains the goals of helping to identify homogeneous groups of well-defined entities and facilitating the recognition of uncommon diseases that require further clarification.[3] This manuscript will review the major areas in lymphoid, histiocytic, and dendritic neoplasms where changes from the prior edition are foreseen as well as emphasize conceptual themes (Table 2).

Mature B-cell lymphoid neoplasms

An important element that pervades many parts of the new monograph derives from an explosion of new clinical, pathological, and genetic/molecular data concerning the "small B-cell" lymphomas. The concept that there are lymphoid proliferations that we used to diagnose as overt lymphoid neoplasms but which are not considered as such in 2016 will be further emphasized. Among the aggressive B-cell lymphomas, there are major changes that impact how these cases should be evaluated and diagnosed that have important therapeutic implications as well as being of biologic interest.

Chronic lymphocytic leukemia/small lymphocytic lymphoma and monoclonal B-cell lymphocytosis

The 2008 monograph recognized **monoclonal B-cell lymphocytosis** (MBL) as the presence of monoclonal B-cell populations in the peripheral blood (PB) of up to 5×10^9/L either with the phenotype of chronic lymphocytic leukemia (CLL), atypical CLL, or non-CLL ($CD5^-$) B cells in the absence of other lymphomatous features. Found in up to 12% of healthy individuals, in some it may be an extremely

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Review Article

Clinical Aspects and Therapy of Sporadic Burkitt Lymphoma

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Abstract: Burkitt's lymphoma is a highly aggressive mature B-cell neoplasm consisting of endemic, sporadic, and immunodeficiency-associated variants, sharing many morphologic and immunophenotypic features. It is characterized by a high proliferation rate and propensity for extranodal sites such as gastrointestinal tract and reproductive organs . Brief-duration, high-intensity chemotherapy regimens including aggressive central nervous system prophylaxis have had remarkable success in the treatment of this disease in the sporadic form, with very high complete remission rate and overall survival in adults. Although Burkitt's lymphoma is extremely chemosensitive, biologically targeted therapies should be developed, because current treatment options are suboptimal for patients with poor prognostic features or with relapsed disease.

Introduction: Burkitt's lymphoma (BL) is a small non-cleaved cell lymphoma with a high proliferation rate and characteristic molecular changes involving the *c-MYC* oncogene. It is a clinically distinct and aggressive disease, that frequently involves extranodal sites, such as the gastrointestinal tract and the central nervous system (CNS), so that it requires urgent treatment.

In the WHO classification three clinical variants are recognized: endemic, sporadic and immunodeficiency-associated [1]. The three subtypes are identical according to histological pattern, and they all possess chromosomal rearrangements of the *c-MYC* oncogene, that contributes to lymphomagenesis altering the mechanisms of cell cycle regulation, cellular differentiation, apoptosis, cellular adhesion, and metabolism. BL is common in children, accounting for 40-50% of childhood non-Hodgkin's lymphomas (NHL) in non-endemic areas [2,3].

These data have been recently update by a study about sporadic childhood BL incidence in United States during 1992-2005, reporting over this period 296 cases of children 0–14 years-old, accounting for approximately 30% of childhood NHL . The distribution of the cases indicated an early age onset (3–5 years) and a predominance in boys (79%) and in non-Hispanic Whites (81%), suggesting that male sex and factors correlated with race may be risk factors for sporadic BL [4].

These results were confirmed in another analysis conducted by the same Authors about age-specific incidence pattern for BL in US over the years 1973-2005. In this study a novel tri/bimodal incidence patterns for BL emerged, which showed disparities by gender but not race. In fact a notable finding was

Adult Burkitt leukemia and lymphoma

Kristie A. Blum, Gerard Lozanski, and John C. Byrd

The World Health Organization Classification of Lymphoid Neoplasms identifies Burkitt lymphoma/leukemia as a highly aggressive mature B-cell neoplasm consisting of endemic, sporadic, and immunodeficiency-associated variants. These subtypes share many morphologic and immunophenotypic features, but differences exist in their clinical and geographic presentations. All of these subtypes possess chromosomal rearrangements of the *c-myc* oncogene, the genetic hallmark of Burkitt lymphoma that contributes to lymphomagenesis through alterations in cell cycle regulation, cellular differentiation, apoptosis, cellular adhesion, and metabolism. Brief-duration, high-intensity chemotherapy regimens containing aggressive central nervous system prophylaxis have had remarkable success in the treatment of this disease, with complete remission rates of 75% to 90% and overall survivals reaching 50% to 70% in adults. Although Burkitt lymphoma cells are extremely chemosensitive, biologically targeted therapies should be developed because current treatment options are suboptimal for patients with poor prognostic features or in the setting of relapsed disease. (Blood. 2004;104:3009-3020)

Introduction

First described by Dennis Burkitt in 1958,[1] Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin lymphoma (NHL) often presenting in extranodal sites or as an acute leukemia. Originally thought to represent 2 different lymphoproliferative disorders, BL was historically classified as a small noncleaved cell lymphoma[2,3] in patients with a solid tumor or nodal mass and as L3 acute lymphoblastic leukemia (FAB [French-American-British] L3 ALL)[4] in patients with greater than 25% bone marrow involvement. However, on the basis of shared molecular and genetic features, the World Health Organization (WHO) Classification of Lymphoid Diseases[5] recognizes the lymphoma and leukemic phases of BL as a single entity; a mature B-cell neoplasm, subtype Burkitt lymphoma/Burkitt cell leukemia. The hallmark of this disease is the overexpression of c-Myc, most commonly resulting from t(8;14), although variant translocations have been described.[6]

Clinical presentation of BL

Three different clinical variants of BL have been described: endemic, sporadic, and immunodeficiency BL. Although there is considerable overlap, unique clinical and genetic features have been described among these variants. The endemic form is most commonly observed in equatorial Africa, in children aged 4 to 7 years, with frequent involvement of the jaw and kidneys, although ileal, cecal, ovarian, and breast involvement have also been reported. The particularly high incidence of BL in equatorial Africa (50-fold higher than in the United States) and the geographic distribution of this tumor, corresponding to the distribution of endemic malaria, have led to its designation as endemic BL. In contrast, in other geographic areas, most patients present with abdominal tumors with no specific geographic or climatic distribution. This clinical variant, designated sporadic BL, accounts for 1% to 2% of all adult lymphomas in Western Europe and the United States.[7] The immunodeficiency subtype is frequently observed in the setting of human immunodeficiency virus (HIV) infection and, unlike other HIV-related lymphomas, is frequently noted in patients with CD4 counts exceeding 200 cells/μL.[8] Adult patients with sporadic or immunodeficiency-associated BL typically present with extranodal disease, with the abdomen being the most frequent site of involvement. Symptoms can include abdominal pain, nausea, vomiting, bowel obstruction, gastrointestinal bleeding, or syndromes mimicking acute appendicitis or intussusception. Intra-abdominal presentations usually affect the bowel or intra-abdominal lymph nodes, although kidney, pancreas, liver, spleen, breast, or ovarian involvement can occur. At diagnosis, patients usually have bulky disease and elevated lactate dehydrogenase and uric acid levels. Bone marrow and central nervous system (CNS) involvement is reported in 30% to 38% and 13% to 17% of adults, respectively.[9-11]

Because of the frequency of extranodal disease, several different staging systems have been used for BL. Adult trials frequently reference the Ann Arbor system, although some researchers find this system inadequate because of its inability to fully describe the extent of extranodal involvement. Therefore, some trials report stage according to the St Jude or Murphy staging schema (Table 1). It is important to note that this staging system recognizes Burkitt leukemia as a separate entity, unlike the current WHO classification.[5] Also, this staging system was developed when surgery was often used for both diagnostic and therapeutic purposes, with the goal of surgery often being complete resection of intra-abdominal disease. Current therapy of BL does not routinely incorporate

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Relationship between *Plasmodium falciparum* malaria prevalence, genetic diversity and endemic Burkitt lymphoma in Malawi

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Endemic Burkitt lymphoma (eBL) has been linked to *Plasmodium falciparum* (*Pf*) malaria infection, but the contribution of infection with multiple *Pf* genotypes is uncertain. We studied 303 eBL (cases) and 274 non eBL-related cancers (controls) in Malawi using a sensitive and specific molecular-barcode array of 24 independently segregating *Pf* single nucleotide polymorphisms. Cases had a higher *Pf* malaria prevalence than controls (64.7% versus 45.3%; odds ratio [OR] 2.1, 95% confidence interval (CI): 1.5 to 3.1). Cases and controls were similar in terms of *Pf* density (4.9 versus 4.5 log copies, p = 0.28) and having ≥3 non-clonal calls (OR 2.7, 95% CI: 0.7-9.9, P = 0.14). However, cases were more likely to have a higher *Pf* genetic diversity score (153.9 versus 133.1, p = 0.036), which measures a combination of clonal and non-clonal calls, than controls. Further work is needed to evaluate the possible role of *Pf* genetic diversity in the pathogenesis of endemic BL.

Endemic Burkitt lymphoma (eBL) is a monoclonal B-cell non-Hodgkin lymphoma that is common in equatorial Africa and Papua New Guinea, which has been linked to childhood infection with *Plasmodium falciparum* (*Pf*)[1–4], a Class 2A carcinogen for eBL[5]. Evidence for associations between eBL and *Pf* is unclear with, for example, the risk of eBL being increased in children with antibody markers of recent *Pf* infection while decreased in those with antibody markers of long-term exposure to *Pf* infection[6,7]. An alternative approach is to assess *Pf* prevalence, density, or genetic diversity as risk factors for eBL. Early studies of the association between eBL and *Pf* prevalence yielded null[8,9] or inverse associations[10], but they were limited by small sample sizes and reliance on microscopy that has variable sensitivity to detect *Pf* infection and that cannot distinguish infection with multiple *Pf* genotypes.

A recent ecological study using published data from Ghana, Uganda, and Tanzania[11], countries where *Pf* transmission intensity is moderate to high (mesoendemic)[12–14], showed that the age-specific risk of eBL and the average number of distinct malaria genotypes per positive blood sample both peaked between ages 5–9 years. The peaks for age-specific asymptomatic parasitaemia and parasite density, in contrast to those of eBL, both peaked at age about 2 years[12–14]. Infection with multiple *Pf* genotypes is relatively common in children in areas with holoendemic malaria[15], but its association with eBL has yet to be fully studied.

Here, we report our investigation to test the hypothesis that *Pf* prevalence, parasite density in peripheral blood, and genetic diversity are associated with eBL among 303 children with eBL (cases) compared to 274 children with non eBL-related cancers or non-malignant conditions (controls) in Malawi. *Pf* genetic diversity was measured using a sensitive and specific *Pf* molecular-barcode array[16] of 24 independently segregating *Pf* single nucleotide polymorphisms (SNPs) representative of the 3D7 *Pf* genome.

Results

Pf malaria prevalence potentially associated with eBL. Cases were similar to the controls with respect to gender, but they were slightly older than the controls (7.7 [SD 0.2] years versus 6.5 [0.3] years) (Table 1). The distribution

Burkitt's lymphoma in Africa, a review of the epidemiology and etiology

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Abstract

Burkitt's lymphoma (BL) was first described in Eastern Africa, initially thought to be a sarcoma of the jaw. Shortly it became well known that this was a distinct form of Non Hodgkin's lymphoma. The disease has given insight in all aspects of cancer research and care. Its peculiar epidemiology has led to the discovery of Epstein Barr virus (EBV) and its importance in the cause of several viral illnesses and malignancies. The highest incidence and mortality rates of BL are seen in Eastern Africa. BL affects mainly children, and boys are more susceptible than girls.

Evidence for a causal relationship between EBV and BL in the endemic form is fairly strong. Frequency of association between EBV and BL varies between different patient groups and different parts of the world. EBV may play a role in the pathogenesis of BL by deregulation of the oncogene c-MYC by chromosomal translocation. Although several studies suggest an association between malaria and BL, there has never been a conclusive population study in support of a direct role of malaria in causation of BL. The emergence of HIV and a distinct subtype of BL in HIV infected have brought a new dimension to the disease particularly in areas where both HIV and BL are endemic. BL has been reported as a common neoplasm in HIV infected patients, but not in other forms of immuno-depression, and the occurrence of BL seems to be higher amongst HIV positive adults, while the evidence of an association amongst children is still disputed. The role of other possible risk factors such as low socio-economical status, exposure to a plant species common in Africa called *Euphorbiaceae,* exposure to pesticies and to other infections such as schistosomiasis and arbovirus (an RNA virus transmitted by insect vectors) remain to be elucidated.

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Introduction

Burkitt lymphoma's (BL) was described more than five decades ago by Dr Denis Burkitt in Uganda. However Sir Albert Cook, a missionary doctor in Uganda in 1887, had reported seeing children with similar features earlier. Despite all the initial work, BL still remains an elusive disease, which has provided many lessons on viral carcinogenesis and molecular oncology.[1-3] Over recent years the incidence of BL has increased in the endemic areas in Africa, overlapping with the epidemic of HIV and malaria in the region. This review aims at providing the current status of understanding of epidemiology and etiology of Burkitt's lymphoma.

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Burkitt lymphoma clinical variants:

BL is a B-cell lymphoma genetically characterized by a chromosomal translocation that results in deregulation of the c-MYC oncogene.

There are several forms of BL according to its geographic distribution, incidence magnitude and risk factors (Table 1). Endemic BL (eBL) is the disease originally described by Burkitt and largely found in Africa, characteristically affecting the facial skeleton in children between ages two to nine. Sporadic Burkitt's lymphoma (sBL) is the form subsequently described outside the African region, but morphologically similar to eBL and affecting mainly abdominal viscera; it can be detected at any age and no specific co-factor has been described. A third subtype of BL has been proposed based on its association with HIV infection. Though well described in the developed world and known among HIV positive adults in Africa, the childhood form of the disease among HIV positive children has not been well characterized. HIV associated BL can be identified in any geographical area and at all ages and is of great importance especially in sub-Saharan Africa.[4,5]

Burkitt lymphoma in adults

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Summary

The diagnosis of Burkitt Lymphoma (BL) and B-cell lymphomas unclassifiable with features intermediate between Diffuse Large B-cell Lymphoma and BL (BLU) in adults remains problematic even with immunophenotyping and *MYC* gene analysis. Gene expression profiling may improve categorization but is not routinely available. BL and its variants should be treated with specific regimens incorporating intensive courses of chemotherapy with fractionated alkylating agents and cell cycle phase-specific agents that readily cross the blood brain barrier. Subsequent courses should be given as soon as haematological recovery occurs, with the whole course completed within a few months. A number of regimens have been developed that encompass these principles but there have been no comparative randomized trials. The results from several studies suggest that the addition of rituximab is highly efficacious and this may be particularly valuable in older patients. It is usual to employ 'risk-adapted' strategies in the treatment of BL but these must be continually re-evaluated, and 'response-adapted' approaches should be explored. The role of transplantation is limited and largely confined to autologous transplants in patients who only achieve a partial response on front-line therapy or who have a chemosensitive relapse. Further advances will be greatly facilitated by randomized trials, which will require international collaboration.

Keywords: Burkitt lymphoma, adults, pathology, prognostic factors, treatment, outcome.

Burkitt Lymphoma (BL) can be endemic, sporadic or associated with immunodeficiency and this review focuses on the latter two forms of the disease in adults. A number of broad conclusions can be drawn about the incidence, clinical and pathological features of BL as well as the results of various therapeutic regimens, but it is more difficult to provide evidence-based recommendations than in the childhood form of the disease and many other types of adult lymphoma. Several reasons account for this uncertainty, including the relative rarity of this type of lymphoma in adults, the small size of many of the published series and the variable pathological inclusion criteria used in these studies. Most importantly, there are no randomized trials in adults.

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Incidence in adults

BL is estimated to account for only 1–5% of all Non Hodgkin Lymphoma (NHL) in adults, but it is not less common than in children; in fact the converse is true. As NHL overall is so much more common in adults than children, the absolute number of BL cases in adults exceeds that in children. Data from the Netherlands Cancer Registry (Boerma *et al*, 2004) indicates that the distribution of BL is bimodal with an early peak between 0 and 15 years and a later peak over 60 years of age. For children under the age of 16 years the incidence was just over four cases per million per year. For adults the incidence was approximately 2·5 cases per million per annum, and overall, because of the greater age-span of the adult population, this means that over half of all cases are adults. Analysis of the US Surveillance, Epidemiology and End Results database is in accord with this, with the median age of BL being 45 years and with about 30% of patients being over 60 years of age (Kelly *et al*, 2009). The limited size of the adult data-sets is not therefore due to fewer cases of BL in adults, but is due to the fact that there are far more centres treating adult lymphomas with consequently fewer cases of BL seen at each individual centre. Added to this is the weaker tradition of trial entry in adult practice, which is exacerbated by the fact that many adult patients are elderly, with this age-group being under-represented in most cancer trials.

Definition of Burkitt lymphoma

The robust definition of BL has undoubtedly been challenging. Initially, the diagnosis of BL was based on a clinical description of endemic forms of the disease associated with morphological features classified as 'undifferentiated lymphoma' in the Rappaport classification. The cells of BL are medium-sized with round nuclei, without cleaves or folds, with multiple basophilic, medium-sized nucleoli and deeply basophilic cytoplasm often containing vacuoles, which are best seen on tissue-imprints or blood or marrow smears. The growth pattern is diffuse and monotonous with a 'starry-sky' appearance due to numerous macrophages that have ingested the

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Insights into Imaging

EDUCATIONAL REVIEW Open Access

An update on Burkitt lymphoma: a review of pathogenesis and multimodality imaging assessment of disease presentation, treatment response, and recurrence

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Abstract

Burkitt lymphoma (BL) is a highly aggressive, rapidly growing B cell non-Hodgkin lymphoma, which manifests in several subtypes including sporadic, endemic, and immunodeficiency-associated forms. Pathologically, BL is classically characterized by translocations of chromosomes 8 and 14 resulting in upregulation of the c-myc protein transcription factor with upregulation of cell proliferation. BL affects nearly every organ system, most commonly the abdomen and pelvis in the sporadic form. Imaging using a multimodality approach plays a crucial role in the management of BL from diagnosis, staging, and evaluation of treatment response to therapy-related complications with ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography playing roles. In this article, we review the pathobiology and classification of BL, illustrate a multimodality imaging approach in evaluating common and uncommon sites of involvement within the trunk and head and neck, and review common therapies and treatment-related complications.

Keywords: Burkitt lymphoma, Lymphoma, B cell, Diagnostic imaging, Computed tomography, Drug therapy

Key points

- Burkitt lymphoma can be differentiated from other forms of diffuse large B cell lymphoma based on underlying pathobiology, which is reflected in the updated WHO classification.
- Radiologists should recognize common and uncommon presentations and sites of disease to appropriately guide clinicians given the urgency of potential of treatment.
- Multiple imaging modalities play a key role in Burkitt lymphoma evaluation throughout the entire disease course, each with advantages and disadvantages.

Introduction

Burkitt lymphoma (BL) is a highly aggressive B cell non-Hodgkin lymphoma (NHL) characterized by the translocation and deregulation of the *MYC* gene on chromosome 8 with the potential to involve multiple organ systems. Three subtypes of BL (sporadic, endemic, and immunodeficiency-associated) are recognized with different epidemiology, risk factors, and clinical presentations.

The sporadic subtype of BL is generally observed in the USA and Western Europe with an overall incidence of three cases per million persons per year in the general population. Sporadic BL is relatively more common in the pediatric population, accounting for 30% of pediatric lymphomas with a peak incidence around the age of 10 years old, while only representing less than 1% of NHL in adults [1, 2]. Sporadic cases are associated with Epstein-Barr virus (EBV), and the most common site of involvement is within the abdomen, particularly the

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Sporadic Burkitt lymphoma of the jaw: Case report and review of the literature

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Alison Yeung, DDS, MD[3]/Anitha Potluri, DMD[1]/Bobby Collins, DDS, MS[4]

Sporadic Burkitt lymphoma of the jaw is a rare neoplasm with an exceedingly fast doubling rate. This article presents a case of sporadic Burkitt lymphoma initially managed as an odontogenic infection. The early radiographic features and histologic criteria are discussed. Burkitt lymphoma should be considered in the differential diagnosis of any rapidly expanding or swelling jaw masses in young patients. *(Quintessence Int 2012;43:333–336)*

Key words: Burkitt lymphoma, Epstein-Barr, jaw, sporadic

Burkitt lymphoma is an aggressive lymphoma that manifests in three forms: endemic, sporadic, and immunodeficiency-associated. However, all forms are histologically identical, harboring the characteristic, but not entirely specific, chromosomal translocation t(8;14)(q24;q32) that results in a c-myc mutation.[1] The endemic form is the most common childhood malignancy in equatorial Africa. However, Burkitt lymphoma is a rare neoplasm in the United States with an incidence of 2.5 cases per million children.[2] Endemic Burkitt lymphoma presents in extranodal locations such as the jaw in about 50% of cases. Sporadic Burkitt lymphoma often presents in the lymph nodes (56%) or abdomen (21%), with only 9% presenting with jaw swelling.[2] Sporadic Burkitt lymphoma represents only 1% to 2% of all lymphomas. A male predilection is seen, and Burkitt lymphoma more commonly affects children and young adults.[3]

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Central nervous system involvement is seen in all three forms. High serum lactate dehydrogenase (an intracellular enzyme that is a serologic marker of cell death and tissue breakdown) and central nervous system and bone marrow involvement portend a poor prognosis.[4]

The mainstay of therapy for Burkitt lymphoma is intense combination chemotherapy, including intrathecal chemotherapy or systemic chemotherapy that crosses the blood-brain barrier, either therapeutically or prophylactically, due to the high risk of central nervous system involvement.[5–7] Survival rates of 90% are now seen with chemotherapy, but toxicities (sepsis, stomatitis/mucositis, peripheral neuropathy, and late cardiac toxicity) are not uncommon.[8] The role of bone marrow transplantation is limited. It is utilized as a salvage in patients with poor prognoses for whom initial chemotherapy does not work.[8,9]

While the Epstein-Barr virus genome is present in the majority of the neoplastic cells of patients with endemic Burkitt lymphoma, the Epstein-Barr virus is detected in 10% to 15% of sporadic cases. The endemic form is seen in areas with high rates of malaria and is associated with *Plasmodium falciparum* infection.[10] Thus, Burkitt lymphoma is most likely multifactorial. Epstein-Barr virus infection is often seen in other neoplasms such as nasopharyngeal carcinoma or other lymphomas, while present in lower rates in sporadic Burkitt lymphoma.[11–14]

Approach to the Diagnosis and Treatment of Adult Burkitt's Lymphoma

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ASSOCIATED CONTENT

See accompanying commentaries on pages 676 and 679

Abstract

Burkitt's lymphoma is a rarely encountered, aggressive B-cell lymphoma that is highly curable in children and young adults. In middle-aged and older adults, however, administering curative therapy may be challenging because standard Burkitt's lymphoma platforms are associated with high treatment-related toxicity in these age groups. Because of its high curability, the testing of alternative, less toxic approaches in Burkitt's lymphoma has been challenging. Although the critical role of *MYC* in Burkitt's lymphoma has been well described, recent biologic insights have identified several new mutations that cooperate with *MYC* in driving lymphomagenesis, paving the way for novel drug testing in this disease. Recently, intermediate-intensity approaches have been tested in Burkitt's lymphoma. Early multicenter results demonstrate good tolerability while maintaining high cure rates in all patient and age groups.

INTRODUCTION

Burkitt's lymphoma was originally described more than 50 years ago in Ugandan children with unusual jaw tumors in association with other specific anatomic sites.[1] This endemic variant occurs in specific geographic areas and typically affects boys between the ages of 4 and 7 years (Table 1). Sporadic Burkitt's lymphoma, in contrast, affects children and young adults in all regions of the world, and immunodeficiency-associated Burkitt's lymphoma is associated with HIV infection. Recently, with genomic technology advances, several novel mutations that cooperate with *MYC* and have key roles in Burkitt's lymphoma pathogenesis have been identified in all Burkitt's lymphoma subtypes. Although traditional treatment platforms for this disease are highly toxic, less toxic strategies that maintain the high cure rates of intensive standard treatments have recently been developed. Currently, the optimal treatment of adults with Burkitt's lymphoma is controversial.

PATHOLOGY AND BIOLOGY

Burkitt's lymphoma has a proliferation rate approaching 100%, and this accounts for its classic starry-sky appearance under the microscope (resulting from apoptotic tumor cells ingested by macrophages). Tumor cells are typically intermediate in size and nonpleomorphic with basophilic cytoplasm containing small vacuoles and round nuclei. The nuclear chromatin is granular with small nucleoli and frequent mitoses. Burkitt's lymphoma is of germinal center B-cell origin with tumor cells expressing CD10, BCL6, CD20, CD79a, and CD45; Epstein-Barr virus expression is detected in approximately 25% to 40% of sporadic and HIV-associated cases. The *MYC* translocation that is pathognomonic of the disease is typically at 8q24

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Burkitt Lymphoma and Atypical Burkitt or Burkitt-like Lymphoma: Should These be Treated as Different Diseases?

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A recurrent 11q aberration pattern characterizes a subset of *MYC*-negative high-grade B-cell lymphomas resembling Burkitt lymphoma

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Key Points

- A subset of lymphomas with gene expression and pathological characteristics of Burkitt lymphomas but absence of *MYC* translocation does exist.
- These lymphomas carry chr 11q proximal gains and telomeric losses, suggesting co-deregulation of oncogenes and tumor suppressor genes.

The genetic hallmark of Burkitt lymphoma (BL) is the t(8;14)(q24;q32) and its variants leading to activation of the *MYC* oncogene. It is a matter of debate whether true BL without *MYC* translocation exists. Here, we identified 59 lymphomas concordantly called BL by 2 gene expression classifiers among 753 B-cell lymphomas. Only 2 (3%) of these 59 molecular BL lacked a *MYC* translocation, which both shared a peculiar pattern of chromosome 11q aberration characterized by interstitial gains including 11q23.2-q23.3 and telomeric losses of 11q24.1-qter. We extended our analysis to 17 *MYC*-negative high-grade B-cell lymphomas with a similar 11q aberration and showed this aberration to be recurrently associated with morphologic and clinical features of BL. The minimal region of gain was defined by high-level amplifications in 11q23.3 and associated with overexpression of genes including *PAFAH1B2* on a transcriptional and protein level. The recurrent region of loss contained a focal homozygous deletion in 11q24.2-q24.3 including the *ETS1* gene, which was shown to be mutated in 4 of 16 investigated cases. These findings indicate the existence of a molecularly distinct subset of B-cell lymphomas reminiscent of BL, which is characterized by deregulation of genes in 11q. (*Blood*. 2014;123(8):1187-1198)

Introduction

Burkitt lymphoma (BL) is an aggressive B-cell lymphoma characterized by typical morphological, immunophenotypic, and molecular features.[1] The t(8;14)(q24;q32) hallmark translocation or its variants, which juxtapose the *MYC* oncogene to one of the 3 immunoglobulin (*IG*) loci, is detectable by cytogenetic or, currently, molecular cytogenetic techniques in almost all cases of BL.[2-4]

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Original Paper

MYC translocation-negative classical Burkitt lymphoma cases: an alternative pathogenetic mechanism involving miRNA deregulation†

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† No conflicts of interest were declared.

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Abstract

The molecular feature of Burkitt lymphoma (BL) is the translocation that places c-Myc under the control of immunoglobulin gene regulatory elements. However, there is accumulating evidence that some cases may lack an identifiable *MYC* translocation. In addition, during the EUROFISH project, aiming at the standardization of FISH procedures in lymphoma diagnosis, we found that five cases out of 35 classic endemic BLs were negative for *MYC* translocations by using a split-signal as well as a dual-fusion probe.

Related Information

Metrics

Citations: 147

Keywords

Burkitt lymphoma | microRNAs | c-Myc | hsa-mir-34b | Let7c | translocation negative

Modern Pathology (2013) 26, S42–S56

Aggressive B-cell lymphomas: how many categories do we need?

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Aggressive B-cell lymphomas are diverse group of neoplasms that arise at different stages of B-cell development and by various mechanisms of neoplastic transformation. The aggressive B-cell lymphomas include many types, subtypes and variants of diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), mantle cell lymphoma and its blastoid variant, and B lymphoblastic lymphoma. Differences in histology, cytogenetic and molecular abnormalities, as well as the relationship with the tumor microenvironment, help define characteristic signatures for these neoplasms, and in turn dictate potential therapeutic targets. Rather than survey the entire spectrum of aggressive B-cell lymphomas, this report aims to identify and characterize important clinically aggressive subtypes of DLBCL, and explore the relationship of DLBCL to BL and the gray zone between them (B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL).
Modern Pathology (2013) **26,** S42–S56; doi:10.1038/modpathol.2012.178

Keywords: aggressive B-cell lymphoma; Burkitt; double hit; high grade; unclassifiable

Introduction

Aggressive B-cell lymphomas (BCL) include both precursor lymphoid neoplasms (B lymphoblastic leukemia/lymphoma NOS and B lymphoblastic leukemia lymphoma with recurrent genetic abnormalities) and numerous mature B-cell neoplasms, including mantle cell lymphoma (MCL), primary effusion lymphoma (PEL), Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL) and its many types, subtypes and variants, and B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma. DLBCL includes a large number of disparate entities with marked differences in morphology, phenotype, molecular pathogenesis and clinical behavior (Table 1). There is an ongoing effort to tailor therapy based on specific subtypes of DLBCL, and prognostic markers are becoming increasingly important. Rather than a discussion of all types of aggressive BCL, this report attempts to identify those entities within the spectrum DLBCL that have distinctive pathologic and clinical significance, and the differential with Burkitt lymphoma, and high-grade unclassifiable B-cell lymphoma.

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Diffuse large B-cell lymphoma

DLBCL is characterized by diffuse nodal architectural effacement or extranodal infiltration by sheets of large cells of B-cell phenotype. Small T-lymphocytes/histiocytes are usually present unlike Burkitt lymphomas that are more homogeneous and uniform. In some subtypes, such as T cell/histiocyte rich large B-cell lymphoma, the background small lymphocytes and histiocytes may outnumber the large B cells. Sclerosis is variable but may be prominent, and mitotic figures are easily identified. Of clinical importance is classification of diffuse large cell lymphoma in patients with grade 3 follicular lymphoma. If there are diffuse areas containing greater than 15 centroblasts per high power field, a separate diagnosis of DLBCL should be rendered, and this should precede the diagnosis of follicular lymphoma. Staining for follicular dendritic cells with antibodies to CD21 or CD23 may be helpful in highlighting areas of follicular proliferation in a partially diffuse infiltrate (and vice versa).

The concept of separating the lymphomas into 'clinical grades' dates back to the mid-1970s and the working formulation, and was based on actuarial survival curves from patients in an international study group. The working formulation divided the DLBCL into large cell and immunoblastic, with the immunoblastic in the high-grade category often requiring central nervous system (CNS) prophylaxis. Since then DLBCL has become increasingly complex

Clinical characteristics of Burkitt's lymphoma seen in Kenyan patients

O W Mwanda [1]

Affiliations + expand

PMID: 15622606 DOI: 10.4314/eamj.v81i8.9211

Abstract

Objective: To document the clinical features of Burkitt's lymphoma (BL) in the study population.

Design: Retrospective and prospective documentation of clinical details using a standard clinical assessment model.

Setting: Kenyatta National Hospital and all the seven provincial hospitals in Kenya.

Subjects: The study involved all cases with tissue proven diagnosis of Burkitt's lymphoma during the study period of ten years.

Main outcome measures: For each BL case, the following were documented age, sex, geographical (province) area, complaints, physical examination, investigation result findings.

Results: This study documented 961 children and 44 adults with Burkitt's lymphoma. Male to female ratio was 1.5:1 in children and 1:1 in adults. All the eight provinces in Kenya had cases of BL and of the 44 tribes 22 were represented. The study showed that BL is a rapidly growing tumour with peak duration of 4 weeks and main complaint was swelling. The major sites involved were Jaw 51.6%, abdomen 25%, combined jaw and abdomen 13.8% and other sites 9.6%. In adults, involved sites were jaw 4.5%, abdomen 43.2%, combined jaw and abdomen 25% and other sites 27.3%. CNS disease

bjh review

Burkitt lymphoma: staging and response evaluation

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Summary

The refinements in both the staging and response evaluation of children with Burkitt lymphoma (BL) have contributed to the improvements in treatment outcome observed over the past 40 years. Ziegler and Magrath designed a staging system in the 1970s for children with BL in equatorial Africa. Currently, the most widely used staging system around the world is that described by Murphy in 1980, which was developed for children with non-Hodgkin lymphoma (NHL) of any histology. There are opportunities for refinement in this system, particularly with respect to certain extra-nodal sites, such as skin and bone. The findings obtained at diagnosis with novel technologies (functional imaging [e.g., positron emission tomography (PET)] and minimal residual disease (MRD) technology), which are more sensitive with respect to disease detection than historic modalities, also need to be considered. Technological advances have also had impact on the assessment of response evaluation. Standard x-rays were routinely used in the 1960s; nuclear imaging became widely used in the 1970s; computerized axial tomography was incorporated in the 1980s; PET imaging was incorporated and, in many cases, has replaced gallium/bone scans since 2000; and MRD technology has been explored in some of the most recent clinical trials. There is clearly a need for more clinical data on the use of PET and MRD technology in the determination of response evaluation of children with BL as well as other histological subtypes of NHL. An international working group is currently addressing the refinement of both disease staging and response evaluation in children with NHL.

Keywords: Burkitt lymphoma, staging, response evaluation.

Accurate staging and response evaluation for children with Burkitt lymphoma (BL) have provided a critical foundation for optimal treatment planning over the past 4 decades (Murphy, 1980). The refinements in both diagnostic imaging technology and pathological tools for disease detection have significantly influenced the ability to identify sites of disease and to determine response to therapy. This article will review the history of both staging and response evaluation for BL, and highlight some of the opportunities and challenges for the future.

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Presented at the Burkitt Lymphoma Symposium, School of Medicine, Trinity College Dublin.

Staging

The purpose of disease staging is to determine and describe the extent of disease spread and to permit a uniform treatment approach based on this information. A clearly defined staging system also permits comparisons among treatment approaches with respect to stage and to determine the prognostic significance of specific disease locations and stage.

The earliest staging system for BL was described by Ziegler and Magrath (1974). In this system, Group A comprised a single solitary extra-abdominal site and Group AR indicated an intra-abdominal tumour for which >90% was surgically resected. Groups B, C and D (multiple extra-abdominal sites, intra-abdominal tumour, and intra-abdominal tumour with involvement of greater than or equal to one extra-abdominal site, respectively) indicated more disseminated disease. Wollner *et al* (1976) described a system for non-Hodgkin lymphoma (NHL) of all histologies comprising limited stage (stage I and II: one single site, two or more sites on the same side of the diaphragm, respectively) and advanced stage (stage III and IV: disseminated disease without bone marrow or central nervous system involvement, and bone marrow and/or central nervous system involvement, respectively). The St. Jude staging system, which was intended for all histological subtypes and also included stages I to IV (stages I and II, limited stage; stages III and IV, advanced stage), was described by Murphy (1980). In this system, primary intrathoracic and primary intra-abdominal sites were defined as criteria for stage III, and usually corresponded to lymphoblastic lymphoma and BL respectively. As in the Zeigler system, those with BL who had completely resected intra-abdominal disease, were classified as a lower disease stage (i.e., II – associated with a better prognosis), whereas more disseminated disease was associated with a poorer outcome.

The modalities available for staging have changed significantly over the decades. (Murphy *et al*, 1989) During the 1960s, staging was largely based on physical examination,

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Review Articles

Epidemiology of Malaria in Endemic Areas

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Abstract. Malaria infection is still to be considered a major public health problem in those 106 countries where the risk of contracting the infection with one or more of the Plasmodium species exists. According to estimates from the World Health Organization, over 200 million cases and about 655.000 deaths have occurred in 2010. Estimating the real health and social burden of the disease is a difficult task, because many of the malaria endemic countries have limited diagnostic resources, especially in rural settings where conditions with similar clinical picture may coexist in the same geographical areas. Moreover, asymptomatic parasitaemia may occur in high transmission areas after childhood, when anti-malaria semi-immunity occurs. Malaria endemicity and control activities are very complex issues, that are influenced by factors related to the host, to the parasite, to the vector, to the environment and to the health system capacity to fully implement available anti-malaria weapons such as rapid diagnostic tests, artemisinin-based combination treatment, impregnated bed-nets and insecticide residual spraying while waiting for an effective vaccine to be made available.

Introduction. Malaria is one of the most important public health problem in term of morbidity and mortality, causing more than 200 million cases and 655.000 deaths every year.[1]

According to the World Health Organization (WHO) Malaria Report 2011, a total of 106 countries in the world are at risk of transmission of malaria infection (**Figure 1**).

A total of 216 million estimated malaria cases occurred in 2010, 81% of which were reported in the African Region, followed by South East Asia (13%) and Eastern Mediterranean Region (5%). The total number of malaria deaths was estimated to be 655.000 in 2010; 91% of whom occurred in the African Region, 6% in South-East Asia and 3% in Eastern Mediterranean Region (**Table 1**).

Although the proportion of people exposed to malaria parasites has decreased during the last century, the absolute number of people at risk for malaria infection increased from 0.8 billion in 1900 to 3.3 billion in 2010, as a consequence of the absolute increase of the population living in malaria-endemic

Hindawi
Case Reports in Oncological Medicine
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Case Report

Adult Sporadic Burkitt's Lymphoma Presenting with Rapid Development of Peritoneal Lymphomatosis

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Sporadic Burkitt's Lymphoma (BL) is a highly aggressive form of non-Hodgkin's lymphoma which requires prompt diagnosis and treatment. Though usual presentation involves abdominal lymphadenopathy with possible solid organ involvement, sporadic BL can rarely present with peritoneal lymphomatosis. We present a unique case with rapid evolution of BL presenting as peritoneal and omental lymphomatosis with hepatic lesions and pelvic and pericardial adenopathy.

1. Background

Burkitt's lymphoma (BL) is a highly aggressive subtype of B cell non-Hodgkin's lymphoma with a doubling time of 24 hours [1]. Sporadic BL is a clinical variant which comprises <1 percent of adult non-Hodgkin's lymphomas in the US [2]. Typical presentation includes abdominal symptoms of pain and distension secondary to ascites. Mesenteric and retroperitoneal lymph node enlargement is common. Extranodal involvement most commonly involves the GI tract and secondarily includes CNS, liver, spleen, kidneys, testis, and ovaries [1]. Peritoneal lymphomatosis is a rare presentation of extranodal lymphoma, usually associated with diffuse B cell lymphoma [3–5].

2. Case Report

An 18-year-old female, without significant medical history, presented with complaints of progressive abdominal pain and fullness. Additional symptoms included intermittent non-bloody vomiting, shortness of breath, fatigue, and low grade fevers. On physical examination, there was mild abdominal distension with tenderness to palpation in all 4 quadrants. No palpable masses were noted. No extremity edema was noted, and no cervical, axillary, or inguinal lymphadenopathy was present.

On laboratory evaluation, lactate dehydrogenase was markedly elevated (847 U/L) (nL 140–250 U/L) with uric acid (16.3 mg/dL) (nL 3–5.8 mg/dL). CA 125 level was found to be 637 U/mL (nL < 35). Additional labs were within normal limits including CBC/diff, BMP, and LFTs.

CT abdomen and US of abdomen performed one month priorly for similar complaints were without abnormalities. On repeat imaging during admission, computed tomography (CT) of the chest, abdomen, and pelvis was significant for extensive thickening, nodularity, and enhancement of the peritoneum and omentum, read as consistent with carcinomatosis (Figures 1–3). Additional findings included multiple bilobar attenuation hepatic lesions, pelvic and pericardial adenopathy, and moderate size bilateral pleural effusions. PET/CT was significant for hypermetabolic activity throughout peritoneal cavity with omental caking (Figures 4-5). Hypermetabolic liver lesions were noted with retrosternal and bilateral iliac chain nodes also suspicious for malignancy.

Peritoneal fluid cytology was consistent with CD10+ B cell population. Biopsy of omental and peritoneal implants was consistent with Burkitt's Lymphoma. Flow cytometry identified a CD10 positive, kappa-restricted B cell population. Immunohistochemistry found CD20 positive B cells without significant expression of *BCL-2*. Ki-67 was 100%. FISH was positive for *MYC/IGH*. EBV was found to be positive. Final

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Clinical Study

HIV-Associated Burkitt Lymphoma: Good Efficacy and Tolerance of Intensive Chemotherapy Including CODOX-M/IVAC with or without Rituximab in the HAART Era

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Background. The outcome of HIV-associated non-Hodgkin lymphoma (NHL) has improved substantially in the highly active antiretroviral therapy (HAART) era. However, HIV-Burkitt lymphoma (BL), which accounts for up to 20% of HIV-NHL, has poor outcome with standard chemotherapy. *Patients and Methods*. We retrospectively reviewed HIV-BL treated in the HAART era with the Magrath regimen (CODOX-M/IVAC±R) at four Canadian centres. *Results*. Fourteen patients with HIV-BL received at least one CODOX-M/IVAC±R treatment. Median age at BL diagnosis was 45.5 years, CD4 count 375 cells/mL and HIV viral load (VL) <50 copies/mL. Patients received PCP prophylaxis and G-CSF, 13 received HAART with chemotherapy and 10 rituximab. There were 63 episodes of toxicity, none fatal, including: bacterial infection, $n = 20$; grade 3-4 hematologic toxicity, $n = 14$; febrile neutropenia, $n = 7$; oral thrush; and ifosfamide neurological toxicity, $n = 1$ each. At a median followup of 11.7 months, 12 (86%) patients are alive and in remission. All 10 patients who received HAART, chemotherapy, and rituximab are alive. CD4 counts and HIV VL 6 months following BL therapy completion ($n = 5$ patients) were >250 cells/mL and undetectable, respectively, in 4. *Conclusion*. Intensive chemotherapy with CODOX-M/IVAC±R yielded acceptable toxicity and good survival rates in patients with HIV-associated Burkitt lymphoma receiving HAART.

1. Introduction

Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin Lymphoma (NHL) associated with chromosomal translocations resulting in upregulation of the proto-oncogene C-MYC, which drives progression through the cell cycle [1]. It has an estimated incidence of 1200 patients per year in the United States [2]. Immunodeficiency associated BL is more commonly seen with human immunodeficiency virus (HIV) infection than other forms of immunodeficiency [3] though its incidence is lowest in patients with a CD4 count <50 cells/mL [4]. NHL accounts for approximately one third of AIDS-related malignancies and the frequency of BL is 2.4–20% of HIV-associated NHL [5].

Several trials comparing the outcomes of patients with HIV-NHL have demonstrated improved outcomes in the HAART era [6–12]. Since the availability of rituximab (R), a monoclonal antibody directed against the B cell antigen CD20, outcomes have improved in HIV-negative B-cell lymphoma [13, 14]. In patients with BL or B-cell ALL treated with the intensive hyper-CVAD regimen; the addition of rituximab was identified in multivariate analysis as a favourable prognostic factor [15]. However, trials assessing the impact

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CASE REPORT

Burkitt's lymphoma of maxillary gingiva: A case report

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Author contributions: All the authors contributed to the acquisition of data, writing and revising the manuscript; Kane S helped with the immunohistochemical staining and diagnosis.

Conflict-of-interest statement: All the authors have no conflict of interest to declare.

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Abstract

Burkitt's lymphoma (BL) is an aggressive form of non-Hodgkin's B-cell lymphoma with three variants namely endemic, sporadic, and immunodeficiency-associated types. It is endemic in Africa and sporadic in other parts of the world. While the endemic form is widely reported to occur in early childhood and commonly involves the jaw bones, the sporadic form typically presents as an abdominal mass. This presentation reports a rare case of sporadic form of BL clinically manifesting as a generalized gingival enlargement in an immunocompetent adult male which demonstrated an aggressive behavior. The patient reported with a prominent anterior gingival swelling of 6 mo duration which slowly enlarged in size and associated with multiple lymph node involvement. Microscopic examination of the lesion using H, E and immunohistochemical diagnosis confirmed the diagnosis as BL. The patient succumbed to the disease before any therapy could be instituted. Since a wide array of causes can be attributed to gingival enlargements, it is necessary to consider malignancies as one of the important differential diagnosis so as to facilitate the need for appropriate diagnosis and prompt treatment.

Key words: Lymphoma; Diagnosis; Differential; Non-Hodgkin's; Gingival overgrowth; Prognosis; Pathology; Oral; Immunohistochemistry

Core tip: Burkitt's lymphoma (BL) is an aggressive form of non-Hodgkin's B-cell lymphoma with three variants namely endemic, sporadic, and immunodeficiency-associated types. It is endemic in Africa and sporadic in other parts of the world. We report a rare case of sporadic BL presenting as generalized gingival enlargement. The purpose of this case report is to illustrate the fact that gingival enlargements may be caused by any benign non-neoplastic lesions or aggressive malignancies like BL and bespeaks the need for prompt recognition and life-saving referral by the dental practitioner.

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Short communication

Widely disseminated sporadic Burkitt lymphoma initially presented as oral manifestations in a 6-year-old boy

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ABSTRACT

Burkitt lymphoma, a subtype of non-Hodgkin's lymphoma, is an aggressive neoplasm with three variants that are endemic, sporadic, and immunodeficiency associated. We present an unusual case of sporadic Burkitt lymphoma in a 6-year-old boy who initially presented with hypermobile teeth and no other specific signs or symptoms. On dental radiography, the patient was found to have alveolar bone resorption adjacent to the maxillary first molars, with the appearance of floating teeth. In addition, magnetic resonance imaging (MRI) showed extensive soft tissue masses involving four quadrants of the jaws. A definitive diagnosis of Burkitt lymphoma was made based on tissue and bone marrow biopsy. Subsequent images, including abdominal computed tomography (CT) and bone scan, revealed wide dissemination of the lymphoma into the abdominal cavity, pancreas, and numerous bones. This case suggests the possibility of dental complaints as an initial clinical manifestation of sporadic Burkitt lymphoma and emphasizes the role of dentists in early detection of the disease to improve prognosis.

1. Introduction

Burkitt lymphoma should be diagnosed as quickly as possible and requires prompt intervention because it is a rapidly growing high-grade malignant neoplasm.[1,2] However, the clinical features of oral lymphoma, especially of lesions involving alveolar bones are not specific, dentists often misdiagnose them as tooth-related diseases or any other problem and attempt to solve the problem with dental treatment. For example, dentists usually evaluate hypermobile teeth with a history of jaw pain or floating teeth with resorption of the adjacent alveolar bone as dental abscess or Langerhans cell histiocytosis, respectively. This might delay diagnosis and treatment, thereby worsening the prognosis. We observed a case of stage IV sporadic Burkitt lymphoma in a 6-year-old boy that initially presented as hypermobile teeth and jaw expansion, with no other specific signs or symptoms. This case highlights the dentist's role in the early detection of Burkitt lymphoma involving the jaw because the prognosis of the patient can be improved if the diagnosis is made as quickly as possible.

2. Case report

A 6-year-old boy visited for an evaluation of hypermobility of the maxillary right first molar. The boy's past medical history was non-specific, and he had no history of progressive systemic symptoms such as fatigue, weakness, or fever.

Intraoral examination revealed painless gingival and mucosal swelling in both posterior maxillas and mandibles. Furthermore, the right mandibular first molar was tilted lingually. A periapical radiograph (Fig. 1A) showed severe alveolar bone resorption around the maxillary right first molar, with uncompleted root development. A panoramic (Fig. 1B) view showed loss of the lamina dura around all four first molars. Enlarged follicular spaces were also observed in both mandibular second premolars. Cone-beam computed tomography (CT) images (Fig. 1C and D) showed large tumorous lesions occupying both maxillary sinuses, causing partial resorption of the sinus wall.

Histopathologic findings of the buccal mucosa of the upper right first molar showed sheets of monomorphic lymphoid cells and intervening phagocytic cells, imparting a "starry-sky appearance". Immunohistochemical staining was positive for CD10, CD20, and MUM1, which are specific to B-cell lymphocytes and late stages of B-cell differentiation. Ki-67 staining was positive in more than 95% of the cells, revealing high proliferative activity. Overall, histopathology results supported the diagnosis of Burkitt lymphoma. The patient was immediately referred to the Hematology-Oncology Department for

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Original Article

Clinical manifestations of oral lymphomas — Retrospective study of 15 cases in a Taiwanese population and a review of 592 cases from the literature

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KEYWORDS
Clinical manifestation;
Lymphoma;
Oral;
Review;
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Background/Purpose: Due to the rarity of oral lymphoma (OL), we aimed to evaluate the clinical features of OL and discuss these findings in light of the literature.
Methods: English language literature (1980–2019) related to OL was searched in two electronic databases. Patients (2000–2019) diagnosed with OL were also selected from the database of the Oral Pathology Department in our institution. The clinical features, radiographic appearance, and histopathological diagnosis in these selected cases from publications and our institution were then analyzed.
Results: 607 cases of OL (15 in our institution and 592 from literature) in patients aged between 0 and 92 years (average, 51.8 years) with a male to female ratio of 1.6:1 were included. The most common diagnosis was diffuse large B-cell lymphoma (n = 205), followed by Burkitt lymphoma (n = 72) and T-cell lymphoma (n = 37). The most frequent site was the gingiva, followed by palate, maxilla, mandible, tongue and buccal mucosa. The most frequent symptoms were swelling, ulceration, paresthesia, mobile tooth and pain. Radiographic findings included ill-defined osteolytic lesion, thickening of the periodontal ligament, loss of lamina dura and tooth displacement.
Conclusion: Despite the rarity of extranodal lymphomas in oral cavity, their occurrence may be part of disseminated disease. Detailed history-taking, clinical and imaging examination and awareness of the patient's signs and symptoms are important for early diagnosis and an

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Early Diagnosis of Burkitt Lymphoma on the Mandible: A Case Report

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Abstract

Burkitt lymphoma (BL) is an aggressive form of non-Hodgkin's B-cell lymphoma found primarily in the pediatric population. In the oral cavity, this tumor can grow rapidly and often brings about facial swelling or development of an exophytic mass involving the jaws.

A 5-year-old boy was referred for swelling and pain in the left mandibular area. The patient showed diffuse swelling on the left side of the mandible and firm-moderate tenderness upon palpation. An intraoral examination showed moderate mobility and sensitivity to percussion on the left primary first and second molars, without severe caries. A radiographic examination revealed complete loss of the lamina dura on the left primary second molar and permanent first molar. There was a radiolucent osteolytic lesion and destruction of the cortical bone of the left mandibular body. Based on the clinical, radiographic, and immunohistochemical findings, the patient was diagnosed with BL, and was referred to a pediatrician for systemic evaluation and intensive chemotherapy. Even before the completion of chemotherapy, the swelling resolved and the displaced teeth were relocated to a normal position.

This patient showed a good prognosis due to prompt diagnosis and intensive chemotherapy. Early diagnosis and referral for treatment can prevent the development of BL.

Key words : Burkitt lymphoma, Signs and symptoms, Diagnosis, Chemotherapy, Adjuvant

Ⅰ. Introduction

In 1958, Denis Burkitt[1] published the first report of Burkitt lymphoma (BL) - derived from facial and abdominal lesions in young African children. BL is an aggressive form of non-Hodgkin's lymphoma (NHL), consisting of high-grade, diffuse, small, non-cleaved B-lymphocytes. The affected age group for BL is children and young adults[2].

BL may present as one of several types: endemic, sporadic, or immunodeficiency-associated. The endemic (African) type almost always occurs in children and involves the jaws in 50-70% of cases. Jaw lesions in the endemic type form at the age of 3 years in close to 100% of known cases. In contrast, jaw lesions are less frequent in the sporadic (American) type and presentation of this type is almost always associated with abdominal complications[2]. Children diagnosed with sporadic BL are typically older than children suffering from the endemic type. Furthermore, the incidence of BL also increases among patients with various immunodeficiencies, such as HIV infection[3].

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Retratação: *Linfoma de Burkitt: evolução clínica e prognóstico. Relato de dois casos diferentes em pacientes jovens* [Rev. odonto ciênc. 2010;25(4):417-421]

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Oral tumors and tumor-like lesions in infants and children

Ralf-Bodo Tröbs, Elinor Mader, Thomas Friedrich & Joachim Bennek

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Abstract

The aim of this retrospective study was to survey the spectrum of oral tumors and tumor-like lesions treated in a pediatric surgical unit. The clinical features and treatment outcome are presented, and guidelines for management discussed. Long-term follow-up was carried out both by re-examination and by means of a questionnaire. A total of 95 patients were encountered over a 30-year period. The age at presentation ranged from 1 day to 16 years, and the male to female ratio was 0.7:1. The lesions were located predominantly on the lips (22%), tongue (21%), and cheek (19%). Patients were divided into five groups based on histological diagnosis. Benign lesions accounted for 83 (87%) of the cases. Of these, 41 (43%) were benign tumors, the most common of which were the hemangiomas (17 cases). Hamartomas accounted for a further 22 benign lesions (23%), among which 12 were lymphangiomas. Furthermore, we

INTERNATIONAL JOURNAL OF PAEDIATRIC DENTISTRY

Paediatric oral pathology in a Chilean population: a 15-year review

MANUEL DONOSO ZUÑIGA, CRISTIAN ROSAS MÉNDEZ, RAFAEL RUBÍ KAUTERICH, DANIEL CARPIO PANIAGUA

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Abstract

Background. There is only limited information available in Chile regarding the frequency of biopsied oral lesions in paediatric patients.

Aim. To determine the frequency of histologically diagnosed lesions in oral pathology specimens from paediatric patients in a Chilean population over a 15-year period.

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Review Article

Peripheral Exophytic Oral Lesions: A Clinical Decision Tree

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Diagnosis of peripheral oral exophytic lesions might be quite challenging. This review article aimed to introduce a decision tree for oral exophytic lesions according to their clinical features. General search engines and specialized databases including PubMed, PubMed Central, Medline Plus, EBSCO, Science Direct, Scopus, Embase, and authenticated textbooks were used to find relevant topics by means of keywords such as "oral soft tissue lesion," "oral tumor like lesion," "oral mucosal enlargement," and "oral exophytic lesion." Related English-language articles published since 1988 to 2016 in both medical and dental journals were appraised. Upon compilation of data, peripheral oral exophytic lesions were categorized into two major groups according to their surface texture: smooth (mesenchymal or nonsquamous epithelium-originated) and rough (squamous epithelium-originated). Lesions with smooth surface were also categorized into three subgroups according to their general frequency: reactive hyperplastic lesions/inflammatory hyperplasia, salivary gland lesions (nonneoplastic and neoplastic), and mesenchymal lesions (benign and malignant neoplasms). In addition, lesions with rough surface were summarized in six more common lesions. In total, 29 entities were organized in the form of a decision tree in order to help clinicians establish a logical diagnosis by a stepwise progression method.

1. Introduction

Lesions in the oral cavity generally present as ulcerations, red-white lesions, pigmentations, and exophytic lesions. Clinical classification of oral lesions is of great importance in the diagnostic process [1, 2]. The term oral exophytic lesions is described as pathologic growths projecting above the normal contours of the oral mucosa [2]. There are several underlying mechanisms responsible for oral exophytic lesions such as hypertrophy, hyperplasia, neoplasia, and pooling of the fluid [1], which makes it difficult to approach such lesions clinically [3, 4]. According to a national epidemiologic study by Zain et al., exophytic lesions account for 26% of all oral lesions [3]. Therefore, attempts should be done to arrive at a timely diagnosis via more logical routes like decision trees rather than test-and-error methods [3, 4]. Exophytic lesions can be classified according to their surface texture (smooth and rough), type of base (pedunculated, sessile, nodular, and dome shape), and consistency (soft, cheesy, rubbery, firm, and bony hard) [1, 4]. This narrative review paper, however, focuses on the surface shapes of the lesions as the main clinical feature in order to build a diagnostic decision tree. In this regard, oral peripheral exophytic lesions are classified as lesions with rough surface and those with smoothly contoured shape [1, 5, 6].

2. Methodology

General search engines and specialized databases including PubMed, PubMed Central, Medline Plus, EBSCO, Science Direct, Scopus, Embase, and authenticated textbooks were used by the first author and the corresponding author to find relevant topics by means of MeSH keywords such as "oral soft tissue lesion," "oral tumor like lesion," "oral mucosal enlargement," and "oral exophytic lesion." Related English-language articles published since 1988 to 2016 in both medical and dental journals including reviews, meta-analyses, original papers (randomized or nonrandomized

Orofacial tumours and tumour-like lesions in children treated at Muhimbili National Hospital, Tanzania

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Introduction: Orofacial tumours and tumour-like lesions occur at any age. An increasing occurrence has made these tumours a significant cause of morbidity and mortality in children.

Objective: To determine the clinicopathological characteristics and treatment modalities of orofacial tumours and tumour-like lesions in children at Muhimbili National Hospital.

Methods: Children aged below 18 years with orofacial tumours and tumour-like lesions were interviewed using a structured questionnaire and clinically examined. The data were analysed using statistical package for social sciences (SPSS) version 20.0. Statistical significance was considered at a p-value of < 0.05.

Results: 121 children aged 4 days to 17 years (mean= 8.56 years ±5.5 SD), 52.1 % being male, participated in the study. The age groups 0-5 years (38%) and 11-15 years (28.1%) were most affected- p-value 0.38. The majority (86%) of the lesions were benign; haemangioma was the most (16.4%) common benign tumour. Dentigerous cyst was the most (7.8%) frequent tumour-like lesion observed, while Burkitt's lymphoma and squamous cell carcinoma were the most common malignant lesions. Swelling was the most common clinical feature in all tumours and tumour-like lesions and surgery was the most common treatment.

Conclusion: Benign orofacial tumours and tumour-like lesions were the types most commonly seen among children in Tanzania.

Key words: orofacial, tumours, tumour-like lesions, children, Tanzania.

INTRODUCTION

Orofacial tumours and tumour-like lesions occur at any age. An increasing occurrence has made these tumours a significant cause of morbidity and mortality in children. [1] The spectrum of diseases differs from that in adults as does the behaviour of certain lesions. [2] Some lesions change with development of the body and therefore their management changes as well. [3] Various reports have discussed the frequency, clinical presentation, histopathological characteristics and management of orofacial tumours and tumour-like lesions in children. Making comparisons between published series is difficult because of the differing descriptive criteria. [3, 4] In East Africa, and in Tanzania particularly, [5] reports are limited so this study aimed at addressing this shortfall in our knowledge.

The objective of the study is to determine the clinicopathological characteristics and treatment modalities of orofacial tumours and tumour-like lesions in Tanzanian children.

METHOD

The study was conducted at the Departments of Oral and Maxillofacial Surgery and Otorhinolaryngology (ORL) of Muhimbili National Hospital (MNH) Dar es Salaam, which receives patients from all over Tanzania.

Patients less than 18 years old with orofacial tumours and tumour-like lesions who attended MNH from September 2016 to March 2017 were studied. Clinical diagnoses were confirmed histologically. The lesions were classified as benign tumours, malignant tumours or tumour-like lesions. Those with no histological diagnosis or with

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PAEDIATRIC OROFACIAL TUMOURS: NEW ORAL HEALTH CONCERN IN PAEDIATRIC PATIENTS

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SUMMARY

Objective: This study aims to determine the incidence, age, gender, orofacial sites and histological pattern of paediatric orofacial tumours in a Nigerian population. The yearly findings will be analysed to identify the interval for increase in the incidence of paediatric orofacial tumours.

Patients and Methods: A 21-year (1990 to 2010) retrospective analysis of paediatric orofacial tumours in children younger than 16 years was carried out in the Department of Oral Pathology/Oral Medicine, University of Benin Teaching Hospital, Benin City, Nigeria.

Results: Of the 1013 diagnosed lesions within the study period, there were 137 (13.5%) paediatric orofacial tumours, among which 71 (51.8%) cases occurred within the last 6 years (2005 to 2010). There was male predilection for the lesions (78 males to 59 females, ratio = 1.3:1). The mean age was 9 + 4.3 years, with peak age group of 11 to 15 years (n=60, 43.8%). The mandible (n=44, 32.1%), followed by the maxilla (n=42, 30.7%) and orofacial soft tissue (n=19, 13.9%) were the most common sites. The benign tumours (n=72, 52.6%) were slightly more than the malignant tumours (n=65, 47.4%). There were more malignant tumours (n=23, 16.8%) than benign tumours (n=20, 14.6%) within the last 3 years (2008 to 2010) under review. Burkitt's lymphoma (n=38, 27.7%) was the commonest malignant lesion.

Conclusion: This study showed a recent increase in the incidence of paediatric orofacial tumours, particularly due to a higher incidence of Burkitt's lymphoma.

Keywords: Paediatrics, Orofacial tumour, Benign, Malignant, Oral Health

INTRODUCTION

Previous reports show that the incidence of paediatric orofacial tumours was relatively low, (9.1% to 10.7%). It consists predominantly of benign tumours (91% to 97.1%), while malignant tumours constitute 2.9% to 9%.[1-3] However, recent reports from Nigerian studies show an increasing incidence of paediatric orofacial tumours (24% to 28%) [4,5] in our environment.

A higher incidence of malignant orofacial tumours among paediatric patients is also reported among Nigerians by Ajayi et al4 in Lagos (13.3%) and Omoregie et al [6] in Benin (22.5%). Furthermore, Aregbesola et al[5] reported a higher incidence of malignant paediatric orofacial tumour (51%) than the benign tumours (49%).

Malignant lesions are a cause of oral health concern in children even with the current effort to control communicable diseases in the third world countries.[7] In our environment they rank fourth as a cause of mortality.[8] Orofacial malignancies are of great concern because of the associated high mortality due to late presentation for treatment,[9,10] a low 5-year survival rate (55%),[11] poverty, lack of awareness and local beliefs.[12] Moreover, paediatric orofacial tumours whether benign or malignant may be associated with facial disfigurement with associated psychosocial problems.[13-15]

So far, no study in our environment has evaluated the incidence of paediatric tumours with a view to determine if there is an increase incidence of these lesions over a given period. Also, the specific clinicodemographic factors and histological pattern of the lesions within a surge period is yet to be determined. This study aims to determine the incidence, age, gender, orofacial sites and histological pattern of paediatric orofacial tumours in a Nigerian population. It also aims to analyse the yearly findings in order to establish the incidence of the lesions during the study period.

METHODS

Ethical approval was obtained from the Hospital Ethical Committee to carry out a 21-year (1990 to 2010) retrospective analysis of all paediatric orofacial tumours seen in children younger than 16 years, in the Department of Oral Pathology/Oral Medicine, University of Benin Teaching Hospital, Benin City, Nigeria.

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CASE REPORT

Agressive mandibular tumors in pediatric patients. Report of 4 cases

Tumores mandibulares de conducta agresiva en pacientes pediátricos. Reporte de 4 casos

Francisco Mercado Montañez*

ABSTRACT

Children rarely experience tumors in the face. Nevertheless, tissue damage caused by these tumors can modify facial growth and development causing physical, esthetic and psychological alterations. The histopathological origin of these lesions is variable, but their local behavior is frequently aggressive, oftentimes not matching their "benign" histological appearance. In order to reach accurate diagnosis it is important to be familiar with radiographic and clinical characteristics exhibited by all lesions, adequately take a biopsy, as well as count with histopathological operators with experience in the recognition of these tumors, since they ultimately are responsible for the treatment to be prescribed. Lesion resection is the treatment's objective, to restore facial esthetics and function, and, whenever possible, favor growth of any affected anatomical structures. This is not easy to achieve in government hospitals with limited resources. There is yet a lot to be achieved in the field of favoring bone growth and later rehabilitate patient's occlusal conditions. In the present article we present four cases of tumors in pediatric patients. Tumors were of different histopathological lineage and low frequency, but all were locally aggressive. These tumors were treated at the Hospital de Alta Especialidad 134, Mexican Institute of Social Security, Torreon, Coahuila, Mexico.

Key words: Facial tumors, histopathology, clinical behavior.

RESUMEN

Los tumores de la región facial en niños son poco frecuentes pero el daño que ocasionan en los tejidos modifica el desarrollo y crecimiento de la cara, ocasionando alteraciones físicas, estéticas y psicológicas. El origen histopatológico de las lesiones es variable, pero la conducta local de las mismas suele ser agresiva, no correspondiendo en muchas ocasiones a su «benigna» apariencia histológica. Para llegar a un diagnóstico correcto es importante conocer características clínicas y de imagen que presenta cada lesión, realizar una adecuada toma de biopsia, además de contar con histopatólogos de experiencia en el reconocimiento de estos tumores, ya que de ello depende el correcto tratamiento a realizar. El objetivo del tratamiento es la resección de la lesión, restaurando función y estética facial y, de ser posible, favorecer el crecimiento de las estructuras anatómicas afectadas, siendo esto último difícil de llevar a cabo en hospitales del sector salud de presupuesto limitado, habiendo mucho por hacer en lo que se refiere a los tratamientos encaminados a favorecer el crecimiento óseo y posterior rehabilitación de las condiciones oclusales de los pacientes. En este artículo reportamos cuatro casos de tumores en pacientes pediátricos, de diferente estirpe histopatológica y de poca frecuencia, pero con la misma agresividad local, tratados en el Hospital de Alta Especialidad 134, del Instituto Mexicano del Seguro Social, Torreón, Coahuila, México.

Palabras clave: Tumores faciales, histopatología, conducta clínica.

INTRODUCTION

Primary maxillofacial tumors in pediatric patients are very rare when compared to tumors present in adults. Nevertheless, tissue damage caused by these lesions is of greater impact, since , in children, they directly alter facial growth and development as well as psycho-social evolution.[1] Generally, tumor lesions in children exhibit aggressive local behavior; initial diagnosis and ensuing treatment plan are difficult, since tumor malignity degree and histological lineage must be established. Treatment must be geared to lesion resection and immediate tissue reconstruction, in all possible cases restoring function and esthetics in one single procedure as well as favoring growth of affected structures.[2] All the aforementioned procedures are possible when lesions are benign but

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Original Investigation

Tumors of the Pediatric Maxillofacial Skeleton
A 20-Year Clinical Study

Katherine S. Perry, MD; Andrew T. Tkaczuk, MD; John F. Caccamese Jr, DMD, MD; Robert A. Ord, DDS, MD; Kevin D. Pereira, MD, MS

IMPORTANCE Pediatric jaw tumors are a rare clinical entity and are not well addressed in the otolaryngology literature. It is important that otolaryngologists be familiar with the clinical features, management, and outcomes associated with these lesions.

OBJECTIVE To review the clinical presentation, management, and outcomes of jaw tumors in children treated at a tertiary care academic center.

DESIGN, SETTING, AND PARTICIPANTS Retrospective medical record review of children 16 years or younger who presented to the departments of Oral-Maxillofacial Surgery and Otorhinolaryngology at the University of Maryland Medical Center between 1992 and 2012 and were diagnosed as having a jaw tumor. A PubMed review of literature from 1992 to 2013 on jaw tumors in children was also conducted.

MAIN OUTCOMES AND MEASURES Medical records were reviewed for data on symptoms, physical findings, pathologic diagnosis, intervention, and outcomes.

RESULTS The medical records of 76 patients evaluated for a jaw mass were reviewed, and 20 were found to have a diagnosis of a jaw tumor. The 2 most common pathologic diagnoses were ameloblastoma (n = 5) and juvenile ossifying fibroma (n = 4). Two tumors were malignant, a rhabdomyosarcoma and a teratoma. Thirteen patients presented with evidence of a mass or swelling, 5 patients were asymptomatic with a lesion found on surveillance panoramic radiography, and 1 patient presented with epistaxis and 1 with facial weakness and pain. All tumors excluding a lymphangioma and a rhabdomyosarcoma were managed surgically. Eight patients underwent more than 1 procedure including secondary reconstruction prior to a satisfactory outcome.

CONCLUSIONS AND RELEVANCE Pediatric jaw tumors are rare lesions most commonly presenting with a swelling or mass. Patients can be asymptomatic with the lesion identified on routine imaging. Certain clinical features such as age, location of tumor, and presence or absence of bone and soft tissue can narrow the differential diagnosis and identify tumors that may be malignant. Incisional biopsy is an important first step. A majority of jaw tumors are benign but require surgical intervention for eradication of disease. Multiple procedures, including reconstruction, may be required for certain lesions prior to cure.

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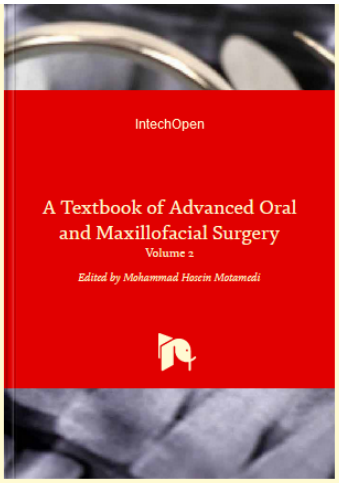
A Textbook of Advanced Oral and Maxillofacial Surgery

Volume 2

Edited by Mohammad Hosein Motamedi
BMSU and AUMS

The scope of OMF surgery has expanded; encompassing treatment of diseases, disorders, defects and injuries of the head, face, jaws and oral cavity. This internationally-recognized specialty is evolving with advancements in technology and instrumentation. Specialists of this discipline treat patients with impacted teeth, facial pain, misaligned jaws, facial trauma, oral cancer, cysts and tumors; they also perform facial cosmetic surgery and place dental implants. The contents of this volume essentially complements the volume 1; with chapters that cover both basic and advanced concepts on complex topics in oral and maxillofacial surgery.



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Metastatic tumors to the jaws and oral cavity

GS Kumar and BS Manjunatha[1]

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ABSTRACT

Go to:

Cancer is a disease involving complex multiple sequential irreversible dysregulated processes showing metastasis that results in morbidity and mortality. Metastasis is a complex biological course that begins with detachment of tumor cells from the primary tumor, spreading into the distant tissues and/or organs, invading through the lymphovascular structures followed by their survival in the circulation. Metastatic tumors to the oro-facial region are uncommon and may occur in the oral soft tissues or jawbones. The clinical presentation of metastatic tumors can be variable, which may lead to erroneous diagnosis or may create diagnostic dilemma. Therefore, they should be considered in the differential diagnosis of inflammatory and reactive lesions that are common to the oral region. Most of the literature on oral metastases involves either single case reports or reviews of these reported cases from scattered geographical areas. Hence this present article is an attempt to provide a detailed review of pathogenesis, epidemiological details including clinical and radiographic presentations, microscopic features and treatment of metastatic tumors to the jaws and oral cavity.

J Oral Maxillof

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Survival predictors of Burkitt's lymphoma in children, adults and elderly in the United States during 2000–2013

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Cancer Epidemiology

Burkitt's Lymphoma (BL) has three peaks of occurrence, in children, adults and elderly, at 10, 40 and 70 years respectively. To the best of our knowledge, no study has been conducted to assess predictors of survival in the three age groups. We hypothesized that survival predictors may differ by age group. We, therefore, sought to determine survival predictors for BL in these three groups: children (<15 years of age), adults (40–70 years of age) and elderly (>70 years of age). Using the Surveillance, Epidemiology, and End Results (SEER) database covering the years 2000-2013, we identified 797 children, 1,994 adults and 757 elderly patients newly diagnosed with BL. We used adjusted Cox proportional hazards regression models to determine prognostic factors for survival for each age group. Five-year relative survival in BL for children, adults and elderly were 90.4, 47.8 and 28.9%, respectively. Having at least Stage II disease and multiple primaries were associated with higher mortality in the elderly group. In adults, multiple primaries, Stage III or IV disease, African American race and bone marrow primary were associated with increased mortality whereas Stage IV disease and multiple primaries were associated with worse outcome in children. These findings demonstrate commonalities and differences in predictors of survival that may have implications for management of BL patients.

Sporadic Burkitt's Lymphoma (BL) is the most common non-Hodgkin's B-cell lymphoma in children.[1,2] In adults, sporadic BL accounts for 1–2% of the non-Hodgkin's Lymphomas (NHL).[2,3] Burkitt's Lymphoma is an aggressive tumor that arises in various parts of the lymphatic system.[3] It is one of the fastest growing tumors, with a doubling time, (*i.e.*, the time for a tumor to grow to twice its original size) of just 24 hrs.[3]

Burkitt's Lymphoma has three clinical types, each of which has distinct characteristics. The endemic type of BL is found mainly in tropical climates where malaria is endemic[3] and has a strong link to Epstein–Barr virus (EBV) infection.[3] It is thought that *Falciparum malaria* promotes the infectivity of EBV through reactivating latent EBV, suppressing T-cell immunity against EBV and produces the *myc* translocation that is common in BL.[3–5] The endemic type normally involves the jaws and has a favorable prognosis with appropriate treatment. The sporadic type of BL is more common in non-malaria endemic regions such as North America, East Asia and Eastern Europe[3] and is less likely to be associated with EBV than the endemic type.[6] The sporadic type is more widespread in the body, with most cases occurring in the abdomen, reproductive system and lymph nodes.[2] The last type of BL is immunosuppression related BL, mainly found in those with immunosuppression from HIV/AIDS, post-transplant recipients and congenital immunodeficiency.[3,7,8] All three forms of BL are responsive to treatment in children

Key words: Burkitt's Lymphoma, prognosis, survival, SEER
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Trimodal age-specific incidence patterns for Burkitt lymphoma in the United States, 1973–2005

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Burkitt lymphoma (BL) is a unique B-cell non-Hodgkin lymphoma with 3 established clinical-epidemiological variants: endemic, sporadic and AIDS-related BL. BL variants show characteristic dysregulation of *MYC* gene, but the causes of *MYC* dysregulation or BL arising at different ages are poorly understood. Therefore, we examined population-based BL incidence patterns in the United States to determine age-related risk. BL case and population data were obtained from the NCI's Surveillance, Epidemiology and End Results Databases (1973–2005). Standard cross-sectional age-standardized and age-specific incidence rates were stratified by sex and race and supplemented with age–period–cohort models. We analyzed 3,058 BL cases diagnosed during 1,160,300,297 person-years of observation. Age-standardized incidence rates rose 6.8% per year (95% CI 4.5–9.1) for males and 7.1% (95% CI 3.2–11.1) for females during the study period. The rate among males was 3.2 times that among females, and among Whites 1.3 times that among Blacks. Male-to-female incidence rate ratios did not differ by race, but were 4.2 for pediatric (0–19 years), 4.1 for adult (20–59 years) and 2.0 for geriatric (≥60 years) BL. Cross-sectional age-specific rates showed 2 separate peaks among males and females, near ages 10 and 75 years, and a 3rd peak near age 40 years among males. The tri/bimodal incidence pattern was present in sensitivity analyses excluding registries with many HIV/AIDS cases and in period-specific, cohort-specific analyses. To our knowledge, tri/bimodal incidence patterns have not previously been reported for BL. Trimodal/bimodal BL suggests heterogeneity in etiology or biology of BL diagnosed at different ages in males and females.

Epidemiology

Burkitt lymphoma (BL) is a rare aggressive B-cell non-Hodgkin lymphoma (NHL), first reported in African children 50 years ago.[1] Description of BL histopathology[2] and subsequent diagnosis of cases throughout the world revealed notable differences in incidence in different populations[3] and also a morphological spectrum of BL.[4] Today, 3 clinical-epidemiological variants are recognized, *i.e.*, endemic, sporadic and AIDS-associated BL. These three variants are indistinguishable by conventional diagnostic evaluation of morphology and immunostaining,[5–7] but subtle morphological variation broadly classified as typical and atypical BL are recognized among each of them.[7] All BL show characteristic dysregulation of the *MYC* gene,[8] mostly because of chromosomal translocation involving *MYC* and immunoglobulin (Ig) genes,[9] but also mutations in *MYC* or associated genes.[10]

The risk factors for sporadic BL are poorly understood and incompletely understood for endemic and AIDS-related BL.[11] For endemic BL, Epstein-Barr virus (EBV), whose genome is detected in nearly 100% of cases, and *Plasmodium falciparum* malaria, which has overlapping geographic distribution, are considered risk factors. For sporadic and AIDS-related BL, malaria is not relevant and EBV, although ubiquitous, is detected in a minority of cases.[11] BL is characterized by a very short doubling time (1–2 days),[12] and the interval from initiating or promoting events to diagnosis may be comparatively short. Thus, study of age-incidence patterns may provide clues about etiology. Therefore, we conducted a population-based analysis of age-standardized and age-specific incidence patterns for BL by gender using data collected in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program for cases diagnosed during the years 1973–2005.

Key words: non-Hodgkin lymphoma, epidemiology, multistage cancer models, tri/bimodal cancer, Epstein-Barr virus
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Material and Methods

Study population

Incident BL case and population data were obtained from the SEER 9 (1973–1991), 13 (1992–1999) and 17 (2000–2005) Registries Databases (November 2007 submission, http://

Intensive Chemotherapy with Cyclophosphamide, Doxorubicin, High-Dose Methotrexate/Ifosfamide, Etoposide, and High-Dose Cytarabine (CODOX-M/IVAC) for Human Immunodeficiency Virus–Associated Burkitt Lymphoma

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BACKGROUND. In the era of highly active antiretroviral therapy (HAART), standard-dose chemotherapy for human immunodeficiency virus (HIV)-associated diffuse large B-cell lymphoma is becoming the standard of care. In contrast, the safety and efficacy of intensive regimens have not been established for Burkitt lymphoma (BL), a highly aggressive lymphoma for which moderate-dose chemotherapy is substandard in the HIV-negative population.

METHODS. To evaluate the feasibility of intensive chemotherapy in HIV-associated BL, the authors retrospectively reviewed 14 HIV-positive adults with BL treated at their center between 1988 and 2000. Eight patients were treated between 1996 and 2000 with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC), one of the currently preferred intensive-dose chemotherapy regimens for BL. Six received other chemotherapy. Outcomes were compared with those of 24 HIV-negative adult patients with BL who had similar patient characteristics and were treated concomitantly (13 with CODOX-M/IVAC; 11 with other regimens).

RESULTS. Of the 14 HIV-positive patients, 63% had a complete response after CODOX-M/IVAC treatment, compared with 67% of patients receiving other chemotherapy. The 2-year event-free survival (EFS) rates were 60% and 60% after CODOX-M/IVAC or other regimens, respectively. Similar outcomes were seen despite the fact that 88% of CODOX-M/IVAC-treated HIV-positive patients had Stage IV disease, compared with one-third of HIV-positive patients treated with other chemotherapy. HIV status did not adversely affect long-term EFS independent of the treatment regimen ($P = 0.88$). When EFS was evaluated according to chemotherapy regimen independent of HIV status, CODOX-M/IVAC was found to be associated with improved EFS ($P = 0.05$) in all patients, and particularly those at high risk. HIV-positive patients treated with CODOX-M/IVAC tolerated chemotherapy well with similar rates of myelosuppression and infectious complications as HIV-negative patients.

CONCLUSIONS. The current nonrandomized retrospective study suggested that intensive chemotherapy with CODOX-M/IVAC is feasible and well tolerated in HIV-positive adults with BL. In the post-HAART era, intensive chemotherapy such as CODOX-M/IVAC may be appropriate in all adult patients with BL, and especially those with poor prognostic factors, regardless of HIV status. *Cancer* 2003;98:1196–205. © *2003 American Cancer Society.*

KEYWORDS: human immunodeficiency virus, Burkitt lymphoma, intensive chemotherapy, non-Hodgkin lymphoma.

Blood and Lymphatic Cancer: Targets and Therapy

Dovepress

REVIEW

Optimal management of endemic Burkitt lymphoma: a holistic approach mindful of limited resources

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Abstract: Endemic Burkitt lymphoma (BL) was publically described in 1958 and remains the most prevalent pediatric cancer in equatorial Africa with an annual incidence between two and five cases per 100,000 children. Several risk factors have been identified, including early-age infection with Epstein–Barr virus, a geographic association with high *Plasmodium falciparum* malaria transmission, and poor nutrition. However, other modifiable factors play a role in the survival of these children. Treatment regimens for BL have evolved over a time period that spans nearly 50 years. This review will compare survival between different combination chemotherapeutic regimens and discuss other key determinants of outcomes among children diagnosed with BL in resource-limited settings. A discussion of obstacles to diagnosis will be presented, including low community awareness of pediatric cancer, limited access to health facilities, inaccurate or delayed diagnosis often beginning at lower level health rural facilities that are typically staffed by those with limited training in oncology, and insufficient pathology support to confirm diagnosis. Other challenges examined here include those related to treatment adherence, specifically the social and economic stressors that can lead to abandonment of care, and treatment-related toxicity, a challenge compounded not only by the scarcity of medications for supportive care, but also the paucity of clinically trained medical professionals available to manage integrated care for these children. Future directions for enhancing BL survival will be discussed including molecular approaches for rational drug discovery as well as the benefits of forming a unified, global BL research network.

Keywords: pediatric cancer, treatment regimen, Africa, social and economic predictors, biomarkers

Introduction

Burkitt lymphoma (BL) is a mature B-cell neoplasm of the lymphatic system that was publically described in 1958 by a surgeon named Denis Burkitt who was working in equatorial Africa at the time.[1] He documented a clinical entity that characteristically affects the jaw or other facial bones of young children.[1] It is now known that BL also affects other sites, including the abdomen (lymph nodes, spleen, kidneys, liver, ovaries), extradural space of the spinal canal (often presenting as paraplegia), bone marrow, and central nervous system. One of the key clinical characteristics of BL is that it rapidly progresses and can double in size within 48 hours, and therefore requires urgent evaluation and treatment.[2] However, the rapid doubling time of these tumor cells make them exquisitely responsive to chemotherapy without the need for radiotherapy or surgery. This also makes this cancer imminently curable in resource-limited settings where it is most prevalent.

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Approach to the Diagnosis and Treatment of Adult Burkitt's Lymphoma

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ASSOCIATED CONTENT

See accompanying commentaries on pages 676 and 679

Abstract

Burkitt's lymphoma is a rarely encountered, aggressive B-cell lymphoma that is highly curable in children and young adults. In middle-aged and older adults, however, administering curative therapy may be challenging because standard Burkitt's lymphoma platforms are associated with high treatment-related toxicity in these age groups. Because of its high curability, the testing of alternative, less toxic approaches in Burkitt's lymphoma has been challenging. Although the critical role of *MYC* in Burkitt's lymphoma has been well described, recent biologic insights have identified several new mutations that cooperate with *MYC* in driving lymphomagenesis, paving the way for novel drug testing in this disease. Recently, intermediate-intensity approaches have been tested in Burkitt's lymphoma. Early multicenter results demonstrate good tolerability while maintaining high cure rates in all patient and age groups.

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INTRODUCTION

Burkitt's lymphoma was originally described more than 50 years ago in Ugandan children with unusual jaw tumors in association with other specific anatomic sites.[1] This endemic variant occurs in specific geographic areas and typically affects boys between the ages of 4 and 7 years (Table 1). Sporadic Burkitt's lymphoma, in contrast, affects children and young adults in all regions of the world, and immunodeficiency-associated Burkitt's lymphoma is associated with HIV infection. Recently, with genomic technology advances, several novel mutations that cooperate with *MYC* and have key roles in Burkitt's lymphoma pathogenesis have been identified in all Burkitt's lymphoma subtypes. Although traditional treatment platforms for this disease are highly toxic, less toxic strategies that maintain the high cure rates of intensive standard treatments have recently been developed. Currently, the optimal treatment of adults with Burkitt's lymphoma is controversial.

PATHOLOGY AND BIOLOGY

Burkitt's lymphoma has a proliferation rate approaching 100%, and this accounts for its classic starry-sky appearance under the microscope (resulting from apoptotic tumor cells ingested by macrophages). Tumor cells are typically intermediate in size and nonpleomorphic with basophilic cytoplasm containing small vacuoles and round nuclei. The nuclear chromatin is granular with small nucleoli and frequent mitoses. Burkitt's lymphoma is of germinal center B-cell origin with tumor cells expressing CD10, BCL6, CD20, CD79a, and CD45; Epstein-Barr virus expression is detected in approximately 25% to 40% of sporadic and HIV-associated cases. The *MYC* translocation that is pathognomonic of the disease is typically at 8q24

How I treat Burkitt lymphoma in adults

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Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma that is almost uniformly associated with translocations involving the gene for MYC on chromosome 8. The 3 subtypes of BL, endemic, sporadic, and immunodeficiency-associated, differ from epidemiologic and clinical perspectives but may be genetically similar. Prompt administration of multiagent immunochemotherapy regimens is associated with favorable outcomes for the majority of patients. Survival is inferior in older patients, likely reflecting increased therapy-related toxicity, possibly resulting in decreased treatment intensity. Central nervous system prophylaxis, tumor lysis prevention and treatment, and management of infectious complications from myelosuppressive regimens are critical. Prognosis of refractory or relapsed disease is poor and patients are best treated on clinical trials when available. (*Blood*. 2014;124(19):2913-2920)

Case

BG is a 40-year-old man with past medical history significant for type 2 diabetes, obesity, and hypertension who presented with hemoptysis. After receiving antibiotics for presumed sinusitis, he was started on prednisone with worsening bleeding. Subsequent laryngoscopic evaluation revealed a nasopharyngeal mass (4.8 × 2.2 cm on magnetic resonance imaging). On biopsy, the histologic appearance and immunophenotype (CD20 and CD10 positive, bcl-2 negative) were consistent with Burkitt lymphoma (BL). Fluorescence in situ hybridization confirmed t(8;14). Positron emission tomography (PET)/computed tomography (CT) revealed additional sites of disease in the liver and bone. Bone marrow biopsy showed 25% involvement. He had no fevers but complained of nondrenching sweats and 10-pound weight loss. Laboratory studies were notable for normal creatinine and complete blood count. Uric acid and lactate dehydrogenase (LDH) were elevated at 9.1 mg/dL and 538 U/L, respectively.

Introduction

BL is a highly aggressive B-cell non-Hodgkin lymphoma (NHL) with a doubling time of 25 hours. It is characterized by deregulation of the gene encoding MYC as a result of a chromosomal translocation most commonly involving the MYC gene locus on chromosome 8 and the immunoglobulin heavy chain (IgH) locus on chromosome 14 (t(8;14)). The first description of this disease was by Sir Albert Cook in 1887, although the disease was later described and defined by Dr Denis Burkitt in the 1950s.[1,2] Today, we recognize 3 distinct subtypes of BL: endemic (African) BL, sporadic BL, and immunodeficiency-associated BL.

Epidemiology

Endemic BL is highly prevalent, with ~3 to 6 cases per 100 000 children per year in equatorial Africa.[3] The incidence of endemic BL, which is uniformly Epstein-Barr virus (EBV) positive, has increased, coincident with an increase in HIV infection and malaria.[4] Although *Plasmodium falciparum* is not felt to be oncogenic, the geographic colocalization of endemic BL and malaria has led to speculation that coinfection with *P falciparum* relates to the oncogenic potential of EBV.[5] Although HIV infection is associated with an increased risk of immunodeficiency-associated BL, these lymphomas are often EBV negative. Sporadic BL is rare, accounting for 30% of pediatric lymphomas, and <1% of adult NHLs in the United States and Europe, or 2 to 3 cases per million persons per year.[6,7] It is more common in younger individuals, with a peak incidence at 11 years of age in pediatric patients, and at 30 years of age in adults.[8] Whites have a higher incidence of the disease, and men are more commonly affected at 3 to 4:1.[6,9,10] These lymphomas are EBV-associated only 10% to 20% of the time.

Finally, immunodeficiency-associated BL is prevalent among patients with HIV infection, as opposed to patients with other causes of immunodeficiency. Because BL can develop regardless of a patient's CD4 count, the incidence of immunodeficiency-associated BL has not declined in the era of antiretroviral therapy.[11]

Pathobiology

Genetics and pathogenesis

The discovery of the hallmark translocation t(8;14)in BL led to an appreciation of the role of MYC in human cancers.[12-14] This translocation brings MYC under the control of IgH enhancer elements, resulting in its constitutive expression. BL typically has a simple karyotype.[15] However, this translocation alone is not sufficient for malignant transformation and additional synergistic mutations are required.[16-18] Many of these mutations, although common in BL, are uniformly absent in diffuse large B-cell lymphoma (DLBCL) and are therefore felt to be pathogenic. Thirty-eight percent of sporadic BL harbor mutations in the CCND3 gene encoding cyclin D3, which regulates the G_1 to S transition during the cell cycle.[18] Additional

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Clinical Trial > Leuk Lymphoma. 2004 Apr;45(4):761-7. doi: 10.1080/1042819031000141301.

Modified magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity

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Affiliations + expand

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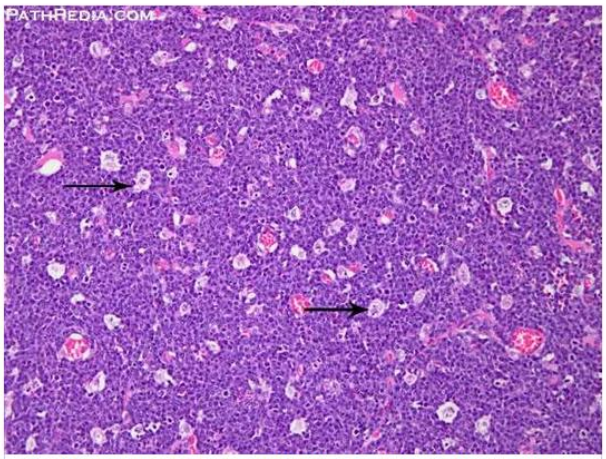
Abstract

Burkitt and Burkitt-like lymphomas are rapidly growing tumors which require specialized therapy. Although intensive, multi-agent regimens have been effective in children, results are more variable in adults. Magrath et al. previously described a regimen that was highly effective in children and young adults. This phase II study of a modified Magrath regimen was designed to assess its efficacy in older adults and reduce treatment-related toxicity. Fourteen patients with Burkitt/Burkitt-like lymphoma and median age of 47 years were stratified into two categories: low-risk (normal LDH and a single focus of disease measuring less than 10 cm, 3 patients) and high risk (all other, 11 patients). Low-risk patients received three cycles of modified CODOX-M (cyclophosphamide, doxorubicin, adriamycin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate, regimen A). High-risk patients received four alternating cycles of regimens A and B (A-B-A-B). Regimen B consisted of ifosfamide, cytarabine, etoposide and intrathecal methotrexate (IVAC). The modified treatment regimen was associated with no grade 3/4 neuropathy and only one episode of grade 3/4 mucositis. All patients completed protocol therapy and there were no treatment-related deaths. Twelve patients (86%, 90% CI: 61 97%) achieved a complete response; 1 patient achieved a PR and 1 patient died of progressive disease. Nine patients (64%) are alive and disease free at a median follow-up of 29 months. This modified Magrath regimen is effective and well-tolerated in a representative group of older adult patients.

Burkitt lymphoma



[BURKITT LYMPHOMA]. Burkitt lymphoma is a high-grade B-cell non-Hodgkin lymphoma with a predilection among children and young adults in immunocompetent patients. It is seen in three clinical settings: endemic, sporadic, and in immunocompromised patients. Morphologically, all cases share the same histologic features including a diffuse architecture, medium-sized lymphocytes with scant cytoplasm, and presence of numerous tangible-body macrophages representing histiocytes phagocytizing apoptotic cell debris (arrows).

Image ID: LN071.1

Slide 1/7

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SPECIAL THANKS to DR. NABEEL AKHTAR (N-57) for contibuting this Presentation.
May Allah Bless him. Ameen!

You can also contribute any help stuff by contacting me directly or by mailing me at aeymon[at]live[dot]com.

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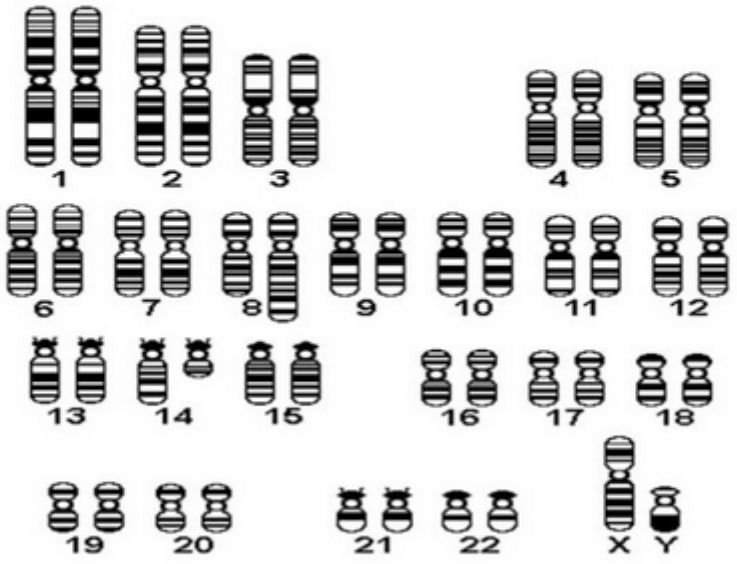

This karyotype of 46, XY, t(8;14) demonstrates the translocation typical for a Burkitt type (small non-cleaved) lymphoma

t(8;14)(q24;q11) TRA/MYC

Written 2001-04 Jacques Boyer
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Identity

ICD-Topo C420,C421,C424 BLOOD, BONE MARROW, & HEMATOPOIETIC SYS
ICD-Morpho 9811/3 B lymphoblastic leukaemia/lymphoma, NOS
ICD-Morpho 9837/3 T lymphoblastic leukaemia/lymphoma
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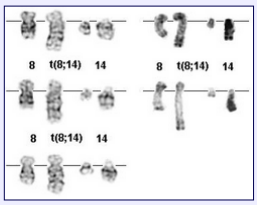

t(8;14)(q24;q11) G-banding - courtesy Charles Bangs and Leena Borkar, and R-banding (right) - courtesy Jacques Boyer.

Clinics and Pathology