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Research Article

Paediatric African Burkitt Lymphoma Clinical Updates

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Abstract: Bukitts Lymphoma is the most common childhood malignancy in Africa. The aetiological factors include early EBV infection, chronic malaria infestation, chromosomal translocations, other viral infections such as HIV and even exposure to some chemicals. Tumours often involve the jaw bones and abdominal organs, though no tissue or organ that is completely exempted. Non African BL (non endemic BL) and the HIV association BL commonly involve lymphoid organs. The hallmark of the diagnosis is histology or cytology. There are two morphological variants: classic and atypical. The classic BL morphology is characterized by medium sized cells with abundant basophilic cytoplasm containing vaculations. The nuclei are round with clumped chromatin and multiple nucleoli. The histological sections of this variant usually give a "starry sky" appearance of this because of the numerous closely packed hyperchromatic monomorphic lymphoid cells interspersed within sheets of lymphoblasts. The atypical variant has greater pleomorphism in nuclear size and shape with fewer nucleoli. The main stay of the treatment is chemotherapy which is adequate in early stages of the disease. Surgery and radiotherapy can be employed in advanced BL. Modern management of ATLS renders surgery unnecessary except for gastrointestinal tract tumour. Newer modalities of treatment include; fractionated radiotherapy, immunotherapy, bone marrow transplantation, and biotherapy. These may prove more useful as adjuvant to chemotherapy and surgery in relapse-prone advance Burkitts' lymphoma. Based on the new insight into BL pathogenesis clinical evaluation of drugs targeting other pathogenetic pathways such as Protein kinase inhibitor and blocking of tonic BCR signal in addition to the cyclin dependant kinase inhibitor will eventually in a combination therapy provide more effective and less toxic ways of treating BL worldwide.
Keywords: Burkitts lymphoma, Clinical, Updates, Jos, Nigeria

Introduction

Burkitt's lymphoma is the most common childhood cancer in Africa with an annual incidence of 6 per 100,000 children and peak incidence at 8 years of age [1]. In Nigeria the peak incidence of occurrence was found to vary from 5 to 10 years [2, 3, 4]. The prevalence of Burkitt's lymphoma in Africa is estimated to be fifty times that in the USA [5]. It is now six decades on since Denis Parsons Burkitt a British Surgeon who was working in Uganda first saw a case of Burkitt's lymphoma in a 5 year old in 1957 and gave a detailed description in the first definitive paper as a clinicopathological entity in 1958 [6]. This description was later ratified by a W.H.O committee of experts in Paris-France in 1969 [7].

The epidemiological survey by Denis Burkitt in 1962 led to the finding that BL is endemic in a geographical belt with distinct topographic and climatic distribution [8]. The so called "Lymphoma belt" incidentally coincided with an area of holoendemicity for malaria in tropical Africa, South America and New Guinea [9]. This discovery of the Lymphoma belt was soon followed by the observation of the tumour's dramatic response to chemotherapy [10, 11, 12]. The observation that some patients had spontaneous regressions and long term remissions, has led Burkitt and others to postulate a tumour-directed host immune response. The tumour is most commonly seen in male with male to female ratio on an average 2:1, thus some have reported abdominal Burkitt to be commoner in female [2, 14] it is extremely rare to see a case below the age of 2 years, implying that at least one significant aetiological event must have taken place after birth [9].

Aetiopathogenesis of Burkitt's Lymphoma

Currently the aetiologies of African Burkitt's Lymphoma are based on three hypotheses. The first one is early infection by Epstein Bar virus (EBV). Evidence supporting this hypothesis is the finding of African patient with Burkitt's lymphoma with significantly elevated antibody titre to a variety of EBV determined antigens [15]. Between 80 and 90 % of tumours contain multiple copies of the EBV DNA genome [16]. In Africa 80% of children less than 5 years are infected with EBV, but most of them were

asymptomatic [15, 17, 18]. Epstein Bar virus infected cells undergo continuous cell line transformations; EBV has also been implicated in causing human nasopharyngeal carcinoma [19, 20, 21]. The search for EBV in non endemic or sporadic cases of Burkitt's lymphoma has revealed an infrequent association in about 15-20% of cases [22, 23].

The second theory is that of chronic malaria infestation by Plasmodium falciparum which promotes B-Lymphocytes proliferation due to its T-cells suppressive activity [9]. These T-cells normally are needed to eliminate EBV infected B-cells [9]. Some have suggested that apart from activation caused by malaria, it is also possible that it can activate an endogenous oncogenic RNA virus. This was confirmed by finding of RNA-viral "footprint" in tumour derived cell lines [24, 25]. This may explain the HIV associated form of BL. Newer theories suggest synergy of multiple factors; apart from malaria and EBV co-infections, there is clear evidence of micronutrient deficiency and chronic malnutrition necessary to set the stage for endemic Burkitt's lymphoma tumourigenesis [9].

The third hypothesis, malignancy is very unlikely to result in the absence of chromosomal translocation, occurrence of which is universal in all cases of BL [9]. In 10 to 20 percent cases of lymphoma that apparently lack chromosomal abnormalities it is believed that these could be as a results of examination of an inadequate number of mitoses [26]. The translocation is from chromosome 8 to chromosome 2, 14 or 22 [9]. Chromosome 8 contains C-myc gene an oncogene which regulates cellular proliferation [9]. As a result of alteration in the function of VDJ-recombinase which is an enzyme responsible for gene re-arrangement, the C-myc gene is translocated from chromosome 8 in exchange for antibody coding genes on chromosome 2, 14 or 22. In this situation the capacity to regulate cellular proliferation by the C-myc oncogene is lost in its new location. Some have postulated that the dysfunction of C-myc gene is due to increased transcription of the gene by an enhancer gene on chromosome 2, 14 or 22 [9]. The function of the oncogene is only expressed in rapidly proliferating cells such as Lymphocytes [9]. Therefore the final results of all these are an unending excessive proliferation of the B lymphocytes.

After the C-Myc translocation recurrent mutations in ID3 and TCF3 have been found in all variants of BL as the most common genetic event. Unlike the C-Myc translocation which can be found in other germinal center B cell neoplasms such as diffuse large B- cell lymphoma (DLBCL) TCF3 and ID3 mutations occur only in BL cell clones which is a very important distinguishing factor.[27] Other less common mutations that play a role in the pathogenesis of BL include: CCND3,[27] p53,[28] methylation of DAP (death-associated protein)-Kinase,[29] Epstein-Barr virus(EBV)-induced FLICE (FADD [fas-associated dead domain protein]-like interleukin 1β –converting enzyme) inhibitory protein[30] have been described.

Clinical features

Burkitt's lymphoma is the fastest growing tumor characterized by explosive growth with a cell doubling time of 24hrs [15, 16]. There are three types of BL recognized; endemic, sporadic and immune-deficiency associated BL [16]. Burkitt's lymphoma commonly involves facial bones, abdominal organs and the central nervous system [2, 4, 6]. What is most striking is the frequency of facial bone involvement. The mandible, maxilla and orbital bones are affected in decreasing order of frequency [6]. The Burkitt's lymphoma of the jaw is more common in the younger age group peaking at 5 years in contrast to abdominal Burkitt peaking at 7 years of age [4]. However some reports have indicated higher incidence of facial bone tumours in relation to abdominal tumours [2, 4, 17]. Abdominal organ involvement is the commonest finding in autopsy reports [18]. Predilection of tumour for ovaries makes abdominal presentation commoner among females. [2, 4] However, any organ in the abdomen can be involved in which kidney is the commonest, [17] Liver, spleen and abdominal lymph nodes are rarely involved in African BL [14, 17].

The tables below shows a recent sex distribution of Burkitt's lymphoma in north-eastern Nigeria by Mava et al [2] featuring the age and sex distribution of BL among studied population and the anatomical location as well as clinical staging of BL. These findings were consistent with most findings by others [2, 4, 14, 17, 18].

Table 1: Age and Sex distribution of Burkitt's lymphoma in north-eastern Nigeria

Age (years)	Sex		Total n (%)	P value[a]
	Male n (%)	Female n (%)		
1-5	9 (18.4)	3 (6.1)	12 (24.5)	-
6-10	19 (38.8)	12 (24.5)	31 (63.3)	-
11-15	4 (8.2)	2 (4.1)	6 (12.2)	-
Total	32(65.3)	17(34.7)	49 (100)	-
Mean (SE)	10.7 (4.4)	5.5 (3.2)	-	0.021*

SE = Standard error, p value[a] = Student t test, *P value < 0.05 (significant)

Table-2: Anatomical location and the clinical staging of BL

Diagnosis	Stage A	Stage B	Stage C	Stage D	Stage AR	Total	% of total
Maxilla	13	9	11	5	-	38	77.6
Mandible	1	1	-	-	-	2	4.1
Orbit	1	-	3	-	-	4	8.2
CNS	1	-	-	1	-	2	4.1
Skin	-	-	-	1	-	1	2.0
Ovary	-	-	5	-	-	5	10.2
Abdominal/Para-aortic LN	-	-	7	-	-	7	14.3
Kidneys	-	-	-	2	-	2	4.1
Cervical LN	1	-	1	-	-	2	4.1
Total	17	10	27	9	-	63	

($\chi 2$ by William's criterion = 47.943, p = 0.003), LN=lymph node

The male excess in most studies is almost universal [2, 19, 20, 21]. Two explanations proposed for the male preponderance in BL as well as in other lymphoid malignancies is one the likelihood for male to have genetic susceptibility that does not withstand genetic injuries as the female may do [23]. Another reason for male preponderance is directed towards milk bush (Euphorbia tirucalli), a plant native to a region of Africa with particularly high rate of endemic BL. This plant is used for both medicinal and recreational purposes and the saps are known to have tumour promoting properties [24]. There is tendency for males to have higher exposure to this plant which may explain the high male preponderance in endemic BL. This hypothesis needs further research.

Neurological involvement in BL is usually a late presentation or may occur as relapse, [4, 14, 15, 17]. when patients present with single or multiple cranial nerve palsy or paraplegia [4, 14 17]. It is to be noted that no organ or tissue is exempted from tumour involvement [4 17]. However some organs or tissues are rarely involved in BL such as the lungs, subcutaneous tissues, long bones, skin and breast [4, 17] Ambe *et al.;* [22] have reported recently a case of unusual relapse presentation in the subcutaneous gluteal region in Maiduguri north eastern Nigeria

The involvement of the reticular endothelial system including peripheral lymph nodes and bone marrow are common in the non-Africa or non endemic BL [18, 25]. There are three modes of bone marrow involvement in BL; Reactive lymphopoiesis with peripheral lymphocytosis, this may be due to host immune response, [18, 25] Atypical lymphocytosis [18] and diffuse bone marrow replacement with Burkitt cells which are seen mostly in terminal cases. [5, 18, 26] It is rare to find Burkitt cells in peripheral circulation, if it happens it may not exceed 50 X 103 cells/mm^3[18].

Investigative modalities useful in BL

Histology:

At present the hallmark of diagnosis of BL is histology [7] immediate fixation of fresh tissue specimen is essential for accurate diagnosis. If cytotoxics have been instituted before biopsy it may alter the diagnostic histological features [18]. Histologically this appears as closely packed hyper chromatic monomorphic lymphoid cells that are round or oval shaped interspersed with phagocytic histiocytes [7, 18]. This gives a visual effect of starry sky appearance or water pot appearance at low power. [7, 18] Starry sky appearances can also be seen in Hodgkin's para granuloma, stem cell and Lymphocytic lymphomas. Starry sky appearance may not be seen uniformly in tumour tissues and may therefore be absent in the histological specimen. The malignant lymphoid cells seen may be difficult to differentiate from round cell sarcoma, meuroblastoma or retinoblastoma [17].

Cytology:

This procedure is easier, quick and sometimes more reliable. There are two basic methods employed; [17] the phase contrast microscopy (PCM) or Air-dried smears. The PCM involves the examination of tumour cells in their living state; they appear as two coherent, spherical cells of 8 – 12µ in diameter. [17] The presence of retractile superficial lipid granules in their cytoplasm is the most characteristic feature. The air-dried smear is by the use of Romanowsky staining. The tumour imprints in this stain displays the characteristic cytologic features of well defined and moderately abundant basophilic cytoplasm containing fat vacuoles. The nuclear has chromatin and 2-5 well defined nucleoli. The tumour imprint show considerable varieties of cell size and shape. [14, 17] With these the tumour cells can be differentiated from other malignant cells except multiple myeloma by their characteristic uniform staining with methyl green pyronin. [9, 17, 18]. The lipid cytoplasmic vacuoles in Burkitt cells can also be stained brightly red with oil-red-o (ORO). [7, 17, 18] Pyronin and ORO are rarely used in routine cytology to confirm presence of Burkitt cells.

Immunohistochemistry:

The diagnosis of BL is confirmed by demonstrating BCL2-negative, BCL6-positive, CD20+, CD10+, Ki67+(99-100%), CD3+ and TdT-negative

cells using monoclonal antibodies and special cytochemical stainings [5, 31].

Cytogenetic analysis:

Using florescence in situ hybridization (FISH), t(8;14)(q24;q32) or t(2;8)(p12;q24) or t(8;22)(q24;q11.2) associated with BL can be demonstrated [31].

Radiology:

Early bony involvement can be seen as minute osteolytic lesions of the trabecula bones as evident by the loss of lamina dura of molar teeth (in the jawbone) [25, 28]. This early changes can be seen in plain X-ray (obligue view) of the jaw for mandibular molars and frontal projection view for maxillary molars. These changes can be seen even in the absence of clinically obvious Jaw mass [5] loss of lamina dura can be seen in both erupted and unerupted teeth in Paediatric age group [32]. When long bones are involved; tibia is the most frequent, femur is more frequent than humerus [32]. The X-ray of these long bones will show multiple small osteolytic areas with or without periosteal elevation. The diaphyseal area of the bone is more frequently involved than metaphysic in younger children [32]. This may be related to regression of red marrow towards extremities of long bones with increasing age.

Scanning's:

Abdominal ultrasound, computerized axial tomography scanning and Gallium 67 scintigraphy can be used in defining area of abdominal tumours before surgical removal or debulking is done [14].

Biochemical investigations:

Elevated level of lactate dehydrogenase (LDH) is useful as a marker for tumour burden and can be used in monitoring of response to therapy [14, 18, 25]. Renal function test, levels of serum uric acid, phosphorus, potassium, calcium and bicarbonate are necessary for supportive therapy to prevent or to diagnose development of acute tumour lysis syndrome (ATLS) [14, 25].

Treatment modalities

Treatment strategies in BL especially endemic BL is chemotherapy and surgery [14, 33, 34]. Radiotherapy, immunotherapy, bone marrow transplantation and administering of agents that targets Myc oncogence such as those that inhibit its transcription are good candidates for clinical trials. [27, 35, 36, 37] Treatment of BL cell line with cyclin dependant Kinase inhibitor (CDK4/6 inhibitor) causes cell cycle arrest and induce apoptosis and regression of established BL [27] Based on the new insight into BL pathogenesis 27 clinical evaluation of drugs targeting other pathogenetic pathways such as Protein kinase inhibitor and blocking of tonic BCR signal [27] in addition to the cyclin dependant kinase inhibitor in a combination therapy may provide more effective and less toxic ways of treatment of BL worldwide. [27].

Chemotherapy:

Systemic chemotherapy is the treatment of choice in Burkitt's lymphoma. Burkitt originally used cyclophosphamide given in single high dose of 40mg. This resulted in dramatic tumour regression in the ensuring days with majority of patient achieving complete remission after one or two doses [10]. For the past three decades, treatment of Burkitt's lymphoma has concentrated on improving survival by several strategies such as combination chemotherapy combined modality therapy, prevention of central nervous system involvement and salvage therapy of patient who relapses.

Multiple doses of chemotherapeutic agents are usually given at two weeks interval for 3 to 6 courses. One of the common combinations is cyclophosphamide, vincristine, methotrexate and intrathecal methotrexate or cytosine arabinocide. This combination can reduce rate of relapses by preventing development of tumour resistance to drugs. [14, 38] A more aggressive combined systematic chemotherapy and central nervous system prophylaxis employs the use of cyclophosphamide, vincristine, doxorubicin, prednisolone, high dose of methotrexate augmented by intrathecal methotrexate and cytokine arabinocide is believed to increase the overall survival in excess of 70% [39].

Surgery:

This treatment option is logical in advanced disease where prognosis is directly proportional to the volume of the tumour [33]. Clinical experiences both in Africa and USA has established the prognostic value of resection of at least 80-90% of the tumor before chemotherapy. [33, 34] Even in bilateral huge ovarian tumours, significant reduction in mortality occurs only with bilateral oophorectomy [34].

Radiotherapy:

Radiotherapy is not indicated as the sole method of treatment in BL, and its role as an adjuvant is not certain. One of the major reason why radiotherapy is not successful in BL as opposed to other Lymphomas is that the conventional fraction of 100 to 150 rads are not appropriate in rapidly growing tumour like BL. Giving several large doses the so called supper fractionated radiotherapy is still being investigated with some success [40]. This act in a similar manner to alkalating agents. The major limitation of this modality is its toxicity with consequent bone marrow aplasia and need for bone marrow transplantation [41] In order to circumvent the toxicity from external beam irradiation techniques, conjugation of radioactive materials with tumour targeted monoclonal antibody has been employed with success [42].

Immunotherapy:

The observed cases of spontaneous regression of BL and even the prompt response to chemotherapy are direct evidence that immunosurveillance may play a significant role in curability of BL. This was further corroborated by transient response of the tumour to serotherapy and development of delayed hypersensitivity reaction to tumour antigen. [14] The use of BCG (Bacillus-Calmatte-Guerin) and tumour vaccine to evoke non-specific antibody response have been employed in BL [43]. However no significant impact on clinical outcome has been observed. [43] Another trial was conducted involved intravenous infusion of tumour directed monoclonal antibody with or without diphtheria toxin conjugates to enhance direct tumour cytotoxicity [42]. This approach has not been successful reasons are: There is rapid removal of both endogenous and exogenous antibodies by an overwhelming antigen released into peripheral circulation by the Burkitts tumour [14, 42]. or there is poor dilution of antibodies into the deeper layers of massive tumour bulk. [42] Because of these, monoclonal antibodies are best employed as adjuvant to chemotherapy in the management of BL. With improved scientific development this may become an additional tool especially in treatment of relapse cases or advanced BL [42].

Biotherapy:

The discovery of powerful modulator of cell differentiation such as retinoid analogues and of cell proliferation e.g. T-cell growth factors, open new ways to the biological control of cell proliferation. Many Lymphoid malignancies retain the functional characteristics of their progenitor cells and can be induced to differentiate and therefore it's possible that biotherapy of lymphoma can be a reality [44].

Bone marrow transplant:

This modality of treatment is useful in two clinical setting: Advanced BL with high risk of relapse and following the development of drug resistance tumour relapse. The use of granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte-colony stimulating factor (G-CSF) may allow increased dose of chemotherapy and avoid the need for bone marrow transplant in many patient [42].

Relapse in Burkitt's lymphoma

Burkitts lymphoma has an unusual relapse pattern. In Africa, two distinct patterns were recognized: early and late relapses. Early relapse occur within 3 months of chemotherapy and is characterized by tumour re-growth in original site, which is usually resistant to the initial treatment. There is a high incidence of central nervous system involvement and the prognosis was usually poor [45, 46]. Late relapse occur beyond 3 months of treatment and is characterized by tumour occurring in new previously unaffected sites with infrequent central nervous system involvement [22, 47]. These patients response readily to re-induction chemotherapy and often have prolong second remission. Very small subset of this second group will continue to have multiple late relapses often over period of years with satisfactory remission on treatment. Some late relapse occurs at interval of 10 years from the initial diagnosis [47].

The pathogenesis of late relapse may be related to variation in immunologic control of the original tumour allowing expression of escape clones in immunologically privileged sites such as orbit, thyroid glands and testis (tumor sanctuary sites) [47]. Some late relapses have been shown to represent a tumour re-induction phenomenon because the phenotypic cell markers were derived from a different cell clone and not from the original tumour as compared with concordant phenotypes in early relapse tumour.

Acute tumor lysis syndrome in BL

Since the earliest attempt at therapy for cancer, it has been recognized that in certain cases metabolic abnormalities arise during the course of treatment [48]. An acute tumor lysis syndrome (ATLS) can now be defined: It is characterized by biochemical disturbances consequent upon rapid destruction of tumour cells with consequent synchronized massive release of cellular breakdown products that is sufficient to overwhelm excretory mechanisms and the body's normal capacity to reutilize such products [48]. The cardinal features of ATLS are as follows:

1. Hyperkalemia
2. Hyperuricemia
3. Hyperphosphataemia
4. Hypocalcaemia

Burkitts lymphoma is a paradigm for ATLS because there is usually bulky, highly chemo sensitive tumour at presentation. Many of the strategies developed for the management of ATLS have been based on BL [49]. Acute tumour lysis syndrome has also occurred in patient treated by non-chemotherapy regimen such as steroids, hormonal and cytokines [50, 51, 52]. But the time course for ATLS in these cases may be extended. Chasty and Liu-Yin [51] proposed a risk scoring system as shown in Table III below, which can be used to assess the chances of a patient developing ATLS and help to select appropriate treatment strategies [48].

Tale-3: Risk score for the assessment of patient's like hood to develop ATLS

Clinical Parameter	Score
Bulk of tumour	2
Marked sensitivity of tumour to treatment modality	2
Renal impairment	1
Raised lactate dehydrogenase	1
Raised serum uric acid	1
Score 4-7=high risk. Score 3=medium. < 3 = low risk	

The management of ATLS is now anticipatory. Patients are grouped according to scoring system above (table-3). All patients irrespective of risk category are given pre-chemotherapy alluprinol; a xanthine oxidase inhibitor, while high and medium risk patients are given hyper hydration at 3L/M2/24hours of dextrose saline and maintenance hydration at 1.5L/M2/24hours [48] For high and medium risk patients, the serum sodium, potassium, urea, creatinine, calcium and phosphate should be monitored every 12 hours[49]. Urinary alkalinizaton (pH 7.0 -8.0), diuretic therapy, insulin with glucose infusion, calcium administration as well as hemodialysis may be needed to treat the tumour lysis syndrome and or to ensure metabolic stability before and after commencement of cytotoxics. Where there is persistent elevation of uric acid despite alluprinol therapy, uricase 500-1000 IU daily may be employed [48].

Other approaches to treatment of ATLS

Despite the apparent ideal preventive management renal failure still occurred in 25% of cases of BL studied. [53] Some have advocated the use of dopamine to reduce the need for dialysis in such patients. Surgery in form of large debulking operation can no longer be justified because of the improvement in the medical management of tumor lysis in this chemo sensitive disease [54]. However, the complete removal of a localized tumour involving the gastrointestinal tract does still have a place, because intestinal perforation and haemorrhage following chemotherapy can be lethal in these patients [48].

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