

Burkitt Lymphoma: A Review

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Abstract

Burkitt lymphoma being a highly aggressive lymphoma, frequently presenting in extranodal sites and having the shortest doubling time; creates special challenges for diagnosis and treatment. It is the first tumour to be associated with EBV and the first type of NHL to be associated with HIV infection. Three major types are recognized; the endemic, sporadic and immunodeficiency associated. It is a potentially curable malignancy using modern chemotherapeutic combinations and avoiding all factors that minimize good prognostic outcome.

Keywords: Burkitt; Aggressive; Endemic; HIV; Chemotherapy; NHL

Introduction

Burkitt Lymphoma (BL) is a high grade Non-Hodgkins Lymphoma (NHL) that is characterized histopathologically by a mass of diffuse small non-cleaved B cell lymphocytes [1,2]. It is a highly aggressive lymphoma that frequently presents in extranodal sites with a very high proliferation rate. It is the fastest growing tumour, characterized by explosive growth with a doubling time of 24 hours. BL is of greatest importance in sub-Saharan Africa where it is the most common childhood (2-16 years, mean 7 years) cancer, accounting for up to 36% of childhood cancers and 70% of childhood lymphomas [3] but, overall constitutes 5% of lymphomas for both adult and childhood populations.

Historical background

Denis Burkitt, a British surgeon, working in central Africa in Kampala, was the first to describe Burkitt lymphoma in 1956 [4]. He noted children with facial swellings involving one or both sides of the face and upper and lower jaws, sometimes accompanied by proptosis. He also observed that some of the children had huge abdominal masses sometimes with facial swelling. There was usually no lymph node involvement. This malignancy was thought to be a sarcoma [5,6] but later established to be a lymphoma and given the name Burkitt lymphoma which happens to be the most common in children in that area [5]. The lymphoma was found to occur throughout tropical Africa with higher occurrence in areas of greater rainfall and altitude greater than 1550 m. These geographic and climatic associations suggested an association with falciparum malaria.

In 1961, Burkitt shared samples of the lymphoma patients with Epstein who along with his colleagues, in 1964, identified a virus in culture cell lines of the tumor [6,7]. The virus come to be known as Epstein-Barr virus (EBV) and was proposed to be oncogenic [5].

Pathogenesis

Burkitt lymphoma belongs to the extended family of Non-Hodgkins lymphoma (NHL) which is solid tumour of lymphoid organs. NHLs are generally clonal malignancies of the multiple cellular components of the normal lymph node, spleen and thymus.

In line with other NHLs; Burkitt lymphoma arise as a clonal transformation occurring at specific stage of normal B cells differentiation during antigenic stimulation in accordance with Murphy's law which holds that for every cell type and stage of differentiation there will occur neoplastic counterparts. Figure 1 depicts the differentiation pattern of B cells. At the level of immature B cell, there occurs a clonal transformation and proliferation of the immature B cell.

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Aetiological factors

The aetiological factors of Burkitt lymphoma differ to a great extent with the clinical variants as described in the World Health Organization (WHO) classification. However, it appears that the major and common aetiological factors are closely and strongly linked with geographical location/climate, immunosuppression and chromosomal abnormalities.

The WHO recognizes the Classical (Endemic) Burkitt and two other variants

The african or endemic burkitt lymphoma

The African type (endemic) is commonly found in the malaria belt of

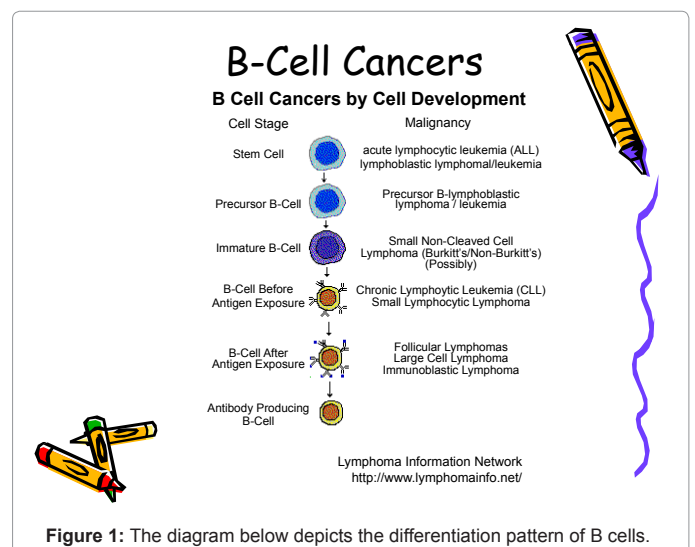


Figure 1: The diagram below depicts the differentiation pattern of B cells.

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Africa and Papua New Guinea. It is associated with low socioeconomic status, undernourishment, malaria holoendemicity and Epstein Barr virus (EBV) infection. The actual age range of occurrence of endemic Burkitt is 2-16 years but the most common age of occurrence is 4-7 years with a male: female ratio of 2:1. The lesion usually involve bones of the jaw and other facial bones, as well as kidneys, gastrointestinal tract, ovaries, breast and other extranodal sites [8].

Non-African (sporadic)

This refers to other type of Burkitt lymphoma seen elsewhere in the world and which do not show the rearrangement of the C-myc proto-oncogene and immunoglobulin genes that typically characterize endemic Burkitt lymphoma. It accounts for 1-2% of lymphoma in adults and up to 40% of lymphoma in the children in the US and Western Europe [9]. The abdomen especially the ileocaecal area is the most common site of involvement. The ovaries, kidneys, omentum, Waldeyers ring and other sites may also be involved. Bilateral involvement of the breast may occur in association with onset of puberty or with lactation [10]. Lymph node involvement is more common among adults than amongst children [11]. Rarely, patient may also have malignant pleural effusion and ascites [10,11]. EBV positivity is 15-30% in some cases or fewer in other series [12].

Immunodeficiency associated Burkitt lymphoma

This occurs mainly in patients with HIV but also occurs in Allograft recipients [13,14] and individuals with congenital immunodeficiency. Several cases of Burkitt lymphoma had been described in homosexual women [15,16].

Epstein Barr Virus (EBV) and BL

EBV was identified in 1964 in African type Burkitt lymphoma [7]. It is present in over 95% of BL in Africa, 50% South Africa, 85% in North African Burkitt Lymphoma and 5-15% Western Countries. Previous studies have shown that endemic Burkitt lymphoma is highly associated with Epstein Barr virus whereas only one third of non-endemic cases carry the virus [17,18]. It is believed that EBV, analogous to malaria, leads to polyclonal B cell activation and permits poorly controlled proliferation of EBV positive B cells which further leads to a greater risk of c-myc rearrangement, and then to lymphoma.

Chromosomal abnormalities in BL

The characteristic chromosomal translocation involving chromosome 8 and 14 in Burkitt lymphoma was discovered in 1976 [19]. Majority of BL carry translocations between c-myc proto-oncogene and IgH gene t (8;14) (q24.1;q32.3) found in 80% of cases. The remaining 20% of Burkitt lymphoma have presence of translocations between c-myc and the gene for kappa light chain t (2;8) in 15% and lambda light chain t(8;22) in 5% [20]. However, specific lymphoma-associated translocations like IgH/bcl-2 and translocations bcl 6 are absent in Burkitt lymphoma. The Break point on long arm chr. 8q is up stream of myc in endemic whereas it is within in the sporadic.

Evidence linking the Risk of BL to malaria infection

The incidence of BL correlates within and between countries with the incidence of malaria and with parasitaemia rates. The age of peak levels of anti-malaria antibodies (5-8 yrs) is same as the peak incidence of BL. Individuals living in urban areas where malaria transmission rates are lower have a lower incidence of BL. In regions where death rate due to malaria had declined, BL incidence has also declined. The age of BL cases among immigrants from malaria free area to malarious

area is higher than that of the original inhabitants. There is an inverse relationship between the age of onset of BL and the intensity of infection with *P. falciparum*. There is reduced incidence of BL in individuals with sickle cell trait which also protects against malaria. There is evidence for seasonal variation and for time-space clustering of BL cases.

Incidence

The incidence of Burkitt lymphoma appears to vary widely with geographic locations and climate. The highest incidence of 36.1/10⁶ was found in Kampala, Uganda, followed in descending order by Blantyre, Malawi (35.8/10⁶) Ibadan, Nigeria (18.0/10⁶), Harare, Zimbabwe (2.4/10⁶), Bamako, Mali (1.7/10⁶) and in the United States (Whites) (2.5/10⁶).

Clinical presentation

The clinical presentation of BL varies with the type. The endemic BL afflicts children of age 2-16 years with a mean age of 7 years, usually in the jaw and in the retroperitoneum, and commonly with bilateral involvement of the kidneys and ovaries or a para spinal tumor [6,7].

The non-endemic cases show a broader age range (up to 35 years) and a higher mean age of 11 years. Male cases predominate in both endemic and non-endemic areas and other clinical features (apart from the ones stated above) and prognosis are similar [18].

The outline of the usual clinical presentation of BL includes the followings:-

- Swelling of the mandible or maxillae (1-4 quadrants), which is the commonest presentation in Africa.
- Earliest sign is the loosening of child's molar or premolar.
- Proptosis may be marked but not usually painful.
- Intra-abdominal tumors, especially retroperitoneal lymph nodes or ovaries.
- Extradural lesion causing spinal cord compression and paraplegia.
- Enlargement of the parotid glands, breasts (usually both), testis, thyroid and kidneys (all are uncommon).
- Lymph node enlargement is also uncommon except in the abdomen.
- However, the child's general condition is usually remarkably good.

Methods of Diagnosis

Burkitt lymphoma being an aggressive tumor requires a quick and prompt diagnosis and more often Fine Needle Aspiration Cytology (FNAC) of facial mass or Ultrasound (USS) guided abdominal mass. Excision Biopsy for histology may also be used in confirmation of diagnosis.

Cytologic appearance

Cells of BL are fairly uniform in size with rounded nuclei and granular nuclear chromatin. The cytoplasm of the cells form a thin rim round the nucleus, it is basophilic, non granular and usually contains some small vacuoles corresponding to lipid droplets. The nucleus is slightly indented and has 2-5 nucleoli, evenly distributed chromatin and occasionally mitosis.

Histological appearance

Starry Sky appearance indicating sheets of monomorphic small non cleaved cell with bluish cytoplasm interspersed by cellular debris-laden macrophages

Immunophenotyping

The Burkitt's cell is Tdt -ve, but CD10, CD19, CD20, CD22, CD24, CD 37, CD 38 and SIgM positive. In most African BL cases, the cells are CD21 positive but negative in American BL cases.

Endemic Vs Sporadic BL

Both look alike histologically, have similar B cell ancestry, share same explosive proliferative potential and exhibit t [8,14] type relocations all through the break points affecting c-myc. However, clinically and phenotypically both are dissimilar. Burkitt lymphoma endemic to Africa and New Guinea is a distinctive syndrome of large extra nodal tumors affecting the jaw bone and abdominal viscera, particularly kidneys, ovaries and retroperitoneal structures; less often it presents as isolated tumor of thyroid, distal long bones, mediastinum, liver or spleen. The vigorous growth rate of retroperitoneal or extradural tumor causes paraplegia, either by vascular compromise or by direct invasion of spinal cord or cranial neuropathy. It rarely involves bone marrow, lymph nodes, lungs, mediastinum, liver or spleen. CNS invasion is often heralded by meningeal involvement with shedding of tumor cells into spinal fluids. The mean age of African patient is 7 years [range 2-16 yrs].

In contrast, sporadic (non African BL) usually originate in payers patches or mesenteric nodes and often home in follicular B cell zone of abdominal and peripheral nodes. Because of the proliferate vigor; patients often present with obstruction of the intestine, airway or ureters. Jaw tumors characteristic of endemic tumors develop in only 15% of sporadic cases compared to 88% in African patients. Marrow involvement occurs earlier and much earlier in non endemic cases than in African Burkitt Lymphoma [20% vs 5%]. It has a broader age range of up to 35 yrs and a higher mean age of 11 yrs as against 7 yrs for endemic. The leukaemia associated with sporadic BL has L3 morphology and confers a dismal prognosis.

BL-staging

Staging of Burkitt lymphoma can be performed using Ann Arbor or, more often, the St Jude/Murphy staging system [8,10,21,22]. Approximately 30% of patients present with limited stage disease (I or II) while 70% present with wide spread disease (III or IV) [8]. The most commonly used staging system is that of Uganda cancer institute originally designed for African patients with BL.

- A Single Extra Abdominal Tumor
- AR Completely resected intra-abdominal tumor without Extra-abdominal tumor.
- B Multiple Extra abdominal tumor
- C Intra-abdominal tumor with or without a single jaw tumor
- D Intra abdominal tumor with extra abdominal sites other than a single jaw tumor

Investigations required for management

- Physical examinations
- Complete Blood Count

- Liver and Renal serum Serum Chemistries
- Serum LDH
- Serum Uric Acid
- Chest X-ray
- Chest CT scan if CXR are abnormal or suspiciously abnormal CXR
- Chest CT
- Abdominal Ultrasound Examination [including liver spleen kidneys and pelvis]
- Galium 67 scan
- Bone Marrow examination
- CSF cytology

Lab. Findings in BL

Major biochemical findings in Burkitt lymphoma include hyperuricaemia, lactic acidosis, high lactate dehydrogenase and high antibodies to early antigens of EBV.

Management

There is no time for leisurely workup; treatment must be commenced within 24-48 hours

Supportive: In order to prevent/correct tumor lysis syndrome, generous hydration is mandatory and Allopurinol must be given at a dose of 10-20 mg/kg daily

Definitive: Resection of large intra-abdominal mass is no longer favored since the tumor is highly chemo sensitive.

The mainstay of treatment is Chemotherapy [23]. All reported successful protocols include cyclophosphamide in doses of at least 1 g/m² and either high or intermediate dose methotrexate. Most also include anthracycline. Short duration, high intensity chemotherapy, often combined with CNS prophylaxis yields excellent survival in children. In localized disease >90%, 5 year survival rate is achievable.

Modified zeigler regimen

IV CPM 1000 mg/m² Day 1

IV VCR 1.5 mg/m² Day 1

SC Cytosar 50 mg/m² 12 hourly × 6 doses OR IV/PO Methotrexate 37.5 mg/m² Day 1

PO Prednisolone 40 mg/m² daily × 5days

Give every 14 days

A more recent, very intensive, highly effective, alternating non-cross resistant regimen developed by Magrath et al. [24] is CODOX-M/IVAC regimen

CODX-M →C=cyclophosphamide, O=oncovin/vincristine, Dox=Doxorubicin and M for High dose methotrexate while IVAC → Ifosfomide, Etoposide, Cytosar (high Dose) + IT therapy.

The combination chemotherapy is said to give a high cure rate [25,26]. However associated toxicities include frequent myelosuppression, severe mucositis, nausea and vomiting, neuropathy and treatment related deaths.

Complications

- Tumor Lysis Syndrome, especially with large tumor burden, is usually characterized by lactic acidosis, hyperuricaemia, hyperkalaemia, hypocalcemia, hyperphosphatemia.
- Haemorrhagic Cystitis which is preventable by maintaining high urine output during the first 24hrs and alkalinize urine with sodium bicarbonate until urinary pH exceeds 7.

CNS involvement and Intra- Theca [IT] therapy

The Cranial Nerve palsies in BL are often multiple and paraplegia may occur. Therefore prophylactic IT therapy is mandatory in all cases of BL while CNS IT therapy is required for all patients with CNS disease.

IT drugs being given either as single therapy or in combinations include.

- IT cytosar 30 mg/m² ± IT Methotrexate 12.5 mg/m² ± IT Hydracortizone 24 mg/m²

IT prophylaxis is given on Days 1 and 5 only per cycle of chemotherapy.

Triple IT therapy is preferred for CNS BL although obvious added advantage is still controversial.

Prognosis

With modern combination chemotherapy 85-100% of those with early stage disease and 75-85% of those with advanced disease will survive for at least 3 years without the need for treatment [23]. It is a curable malignancy and if there is no relapse a year after combination chemotherapy, patient has a 90% chance of surviving indefinitely. Prognosis with CPM alone is less favorable.

Factors responsible for poor treatment outcome in Nigeria for example include poverty, circulating fake drugs and poor treatment compliance [27,28]. Recently, complete remission rate was observed to be as low as 22.8% [29].

Relapse

Relapse in BL may be early or late.

In early relapse, tumor regrowth is usually in the same site and occurs at less than 3months post treatment.

Late relapse usually arise from a previously uninvolved site and likely to respond to the same agents. It occurs at greater than 3 months post treatment.

References

- Kearns DB, Smith RJ, Pitcock JK (1986) Burkitt's lymphoma. *Int J Pediatr Otorhinolaryngol* 12: 73-84.
- Ziegler JL (1977) Treatment results of 54 American patients with Burkitt's lymphoma are similar to the African experience. *N Engl J Med* 297: 75-80.
- Parkin DM, Kramarova E, Draper GJ, Masuyer E, Michaelis J, et al. (1998) International incidence of childhood cancer. Vol II Lyon IARC.
- Burkitt D (1958) A sarcoma involving the jaws in African children. *Br J Surg* 46: 218-223.
- Burkitt DP (1983) The discovery of Burkitt's lymphoma. *Cancer* 51: 1777-1786.
- Burkitt D, Wright D (1970) Burkitt's lymphoma. (1stedn), Edinburg and London: E and S Livingstone.
- Khanna R, Burrows SR, Moss DJ (1995) Immune regulation in Epstein-Barr virus-associated diseases. *Microbiol Rev* 59: 387-405.
- Diebold J (2001) Burkitt's lymphoma. In: Jaffe E, Harris N, Stein H et al., (Eds.), *Pathology and Genetics of Tumors of haematopoietic and Lymphoid tissues*. Washington, DC: IARC Press 181-184.
- Boerma EG, van Imhoff GW, Appel IM, Veeger NJ, Kluin PM, et al. (2004) Gender and age-related differences in Burkitt lymphoma—epidemiological and clinical data from the Netherlands. *Eur J Cancer* 40: 2781-2787.
- Blum KA, Losanski G, Byrd JC (2004) Adult Burkitt leukemia and lymphoma. *Blood* 104: 3009-3020.
- Burmeister T, Schwartz S, Horst HA, Rieder H, Gokbuget N, et al. (2005) Molecular heterogeneity of sporadic adult Burkitt-type leukemia/lymphoma as revealed by PCR and cytogenetics: correlation with morphology, immunology and clinical features. *Leukemia* 19: 1391-1398.
- Burkitt D, O'Connor GT (1961) Malignant lymphoma in African Children. I.A clinical syndrome. *Cancer* 14: 258-269.
- Gong JZ, Stenzel TT, Bennett ER, Lagoo AS, Dunphy CH, et al. (2003) Burkitt lymphoma arising in organ transplant recipients: a clinicopathologic study of five cases. *Am J Surg Pathol* 27: 818-827.
- Xicoy B, Ribera JM, Esteve J, Brunet S, Sanz MA, et al. (2003) Post-transplant Burkitt's leukemia or lymphoma. Study of five cases treated with specific intensive therapy (PETHEMA ALL-3/97 trial). *Leuk Lymphoma* 44: 1541-1543.
- Doll DC, List AF (1982) Burkitt's lymphoma in a homosexual. *Lancet* 1: 1026-1027.
- Ziegler JL, Drew WL, Miner RC, Mintz L, Rosenbaum E, et al. (1982) Outbreak of Burkitt's-like lymphoma in homosexual men. *Lancet* 2: 631-633.
- Ziegler JL (1981) Burkitt's lymphoma. *N Engl J Med* 305: 735-745.
- Naik KG, Bhagwande SB (1977) Pattern of lymphomas in Zambia. *East Afr Med J* 54: 491-496.
- Zech L, Haglund U, Nilsson K, Klein G (1976) Characteristic chromosomal abnormalities in biopsies and lymphoid-cell lines from patients with Burkitt and non-Burkitt lymphomas. *Int J cancer* 17: 47-56.
- Potter M, Mushinski JF (1984) Oncogenes in B-cell neoplasia. *Cancer Invest* 2: 285-300.
- Kasamon YL, Swinnen LJ (2004) Treatment advances in adult Burkitt lymphoma and leukemia. *Curr Opin Oncol* 16: 429-435.
- Murphy SB, Hustus HO (1980) A randomized trial of combined modality therapy of childhood non-Hodgkin's lymphoma. *Cancer* 45: 630-637.
- Sandlund JT, Downing JR, Crist WM (1996) Non-Hodgkin's lymphoma in childhood. *N Engl J Med* 334: 1238-1248.
- Magrath I, Adde M, Shade A (1996) Children of Non-Hodgkins lymphoma treatment progress. *J Clin Oncol* 14: 925-934.
- Mead GM, Sydes MR, Walewski J, Grigg A, Hatton CS, et al. (2002) An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adults Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. *Ann Oncol* 13: 1264-1274.
- Ferry JA (2006) Burkitt's lymphoma: clinicopathologic features and differential diagnosis. *Oncologist* 11: 375-383.
- Williams CK, Folami AO, Seriki O (1983) Patterns of treatment failure in Burkitt's lymphoma. *Eur J Cancer Clin Oncol* 19: 741-746.
- Aderere WI, Antia AU (1979) Burkitt's lymphoma in children in Ibadan: A review of 133 cases. *Nigeria J Paediatrics* 1-14.
- Fasola FA, Shokunbi WA, Falade AG (2002) Factors determining the outcome of management of patients with Burkitt's lymphoma at the University College Hospital Ibadan, Nigeria—an eleven year review. *Niger Postgrad Med J* 9: 108-112.