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BURKITTS LYMPHOMA - 50 Years After Discovery - Review Article

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INTRODUCTION

Jaw tumours in African children were described since 1904. The unique Clinical features were however first described by Dr Denis Burkitts, a British surgeon in 1958 while working at Mulago hospital in Kampala Uganda. He described a rapidly growing childhood sarcoma of the jaw and abdomen that was surgically unresectable.

Dennis Wright, a Makerere University pathologist described simple method of diagnosis through direct examination of tumour imprints and gave the name Burkitts lymphoma. In 1961, Burkitts and his colleagues undertook the mapping of geographical spread of the tumour with a Grant of 25 Pounds from The Medical Research Council of Britain and they documented a spread corresponding to the Malaria belt[1]. Michael Epstein [2] suspected a viral aetiology after attending one of Burkitts lectures in London and requested for tumour tissue sample. Epstein and Yvonne M Barr isolated the virus Epstein - Barr virus (EBV) in 1964.

Definition and Classification

Burkitts lymphoma (BL) is an aggressive (fast-growing) B-cell Non Hodgkins Lymphoma. It is a neoplasm of childhood. Few adult cases occur. The three main types of BL are Endemic Burkitts Lymphoma (eBL) common in tropical belts, sporadic Burkitts Lymphoma which occurs world wide and immunodeficiency related Burkitts Lymphoma common in AIDS patients mostly in adults. Characteristically, BL is one of the fastest growing malignancies with high growth fraction and short tumour doubling time.

Epidemiology

Burkitts lymphoma is rare in the USA with about 100 new cases /year. Internationally, it is endemic in certain regions of equatorial Africa and other tropical locations between latitudes 10° south and 10° north. Incidence in these areas of endemic disease is 100 per million children.[3]

In Nigeria it forms 24.1% of all paediatric cancers in Enugu Eastern Nigeria (Ocheni et.al. 2005)[4], 39% in Northern Nigeria (Edington 1981)[5]. Two hundred and sixty patients with BL were seen from 1986 2003 at Obafemi Awolowo University Teaching Hospital Ile Ife Nigeria (OAUTH) (Adeoye etal 2007).[6] In Ibadan, it formed 51.5% of paediatric cancers between1960-1972 ,37.1% between 1973-1990 and 19% between 1991-1990 (Ojesina et al 2002)[7].The Male : Female ratio is 2-3 : 1. In Africa, the mean age is 7 years while outside Africa; the mean age is 11 years.

The aetiology of BL is linked with Ebstein Barr Virus (EBV). Almost all tissues of eBL have EBV DNA isolated and high titres of antibodies to EBV precede the development of the disease. Other possible cofactors include chronic malaria infection which lowers immunity against EBV and infection with AIDS virus especially in western countries. [8,9]

Pathology: BL is a solid soft tissue tumour. Microscopically the lymphoma consists of medium-sized malignant cells with basophilic cytoplasm. Numerous benign macrophages confer a histologic pattern referred to as starry sky. (figure 1)

Table 1: Differences between endemic and sporadic Burkitt's lymphoma

Feature	Endemic	Sporadic
Geographic location	Equatorial Africa & New Guinea	Europe & North America
Age	Children	Young adults
Site	Jaw	Abdomen
Marrow involvement	Late	Early
EB virus antibody	Invariably presents100%	Few 20%

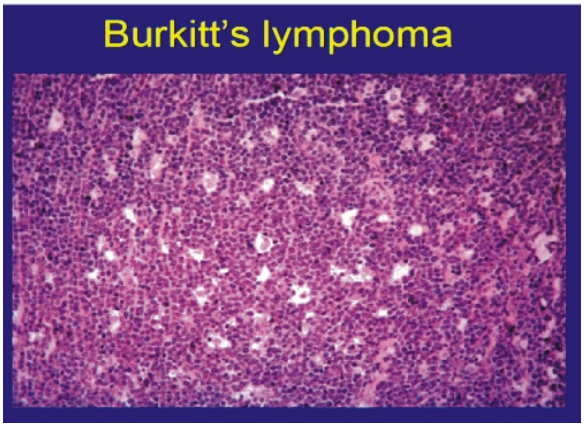

Figure1. **Microscopy**

Chromosomal Changes associated with BL include translocation of c-myc proto-oncogene from its normal position on chromosome 8 to chromosome 14. Immunoglobulin (Ig) heavy chain gene in 90% of cases i.e. t(8:14) while t(8:2) and t(8:22)occur in 10% both involving Ig light chain genes.

Mode of spread: BL is commonly multifocal. Direct spread also occurs to surrounding tissues. Other modes of spread include haematogenous especially in bone marrow disease, through CSF and lymphatics (especially in sporadic BL).

Clinical Presentation: eBL presents with jaw swelling in 70% of cases, abdominal swelling**:** 30%, CNS signs and symptoms in 30-40%, renal function derangement in 25% and bone marrow involvement in 10-30%.[10] Other modes of presentation include lymph node enlargement , skin nodules and malnutrition. Jaw tumours usually start in the region of the alveolar process leading to expansion of the alveolus resulting in loosening of the teeth with subsequent displacement and premature shedding commonly described as dental anarchy. In maxillary lesions, the tumour frequently invades and destroys the antrum and may extend into the orbit. (figures 2-4)

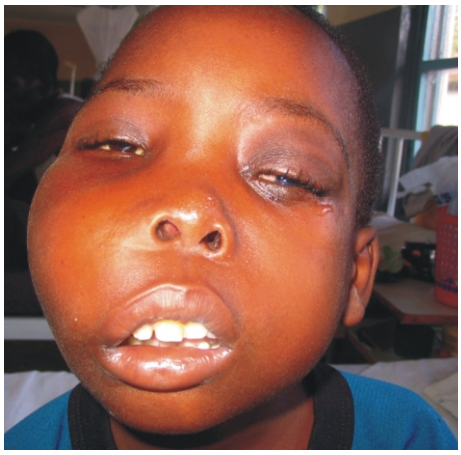

Figure 2. Jaw tumour before treatment

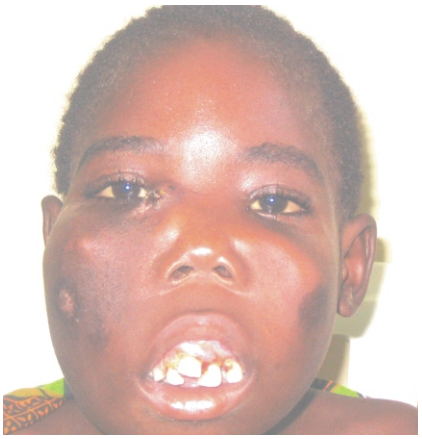

Figure 3. Jaw tumour after treatment

There is clinical evidence of involvement of the orbit in 16- 18% of the patients .Tumours can arise from the orbit or can be an upward extensions of maxillary tumour.

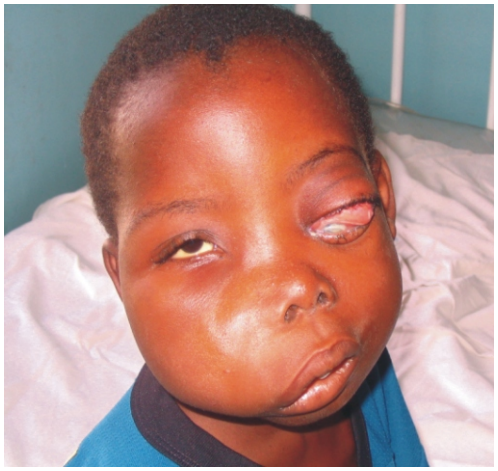

Figure 4. Tumour involving the orbit.

Abdominal Tumours occur in 40% of the cases and are as presenting features in 20% of cases of eBL and 80% in sporadic cases.[11] They can present as one of the following: abdominal swelling , retroperitoneal mass, an enlarged liver, ovarian tumour or intestinal tumours. (figure 5)

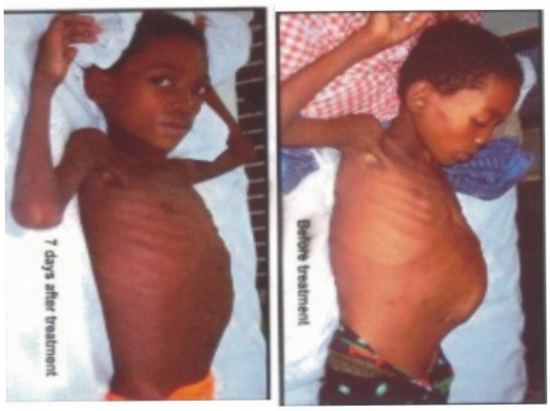

Figure 5: Intra abdominal tumour

CNS Involvement: 29% of the patients have CNS manifestations at presentation. 4.5% have paraplegia as the presenting feature. Other features include meningeal involvement and cranial neuropathies particularly third, fourth, sixth, even and tenth cranial nerves. Bone marrow involvements occur in 12.5% especially in those with abdominal disease.[12]

INVESTIGATIONS: Relevant investigations include full blood count + platelets (FBC) to access the haematological profile, electrolytes urea and creatinine (E&U + Cr), magnesium (Mg) and uric acid to ascertain renal function , liver function tests, cerebro-spinal fluid (CSF) analysis to reveal CNS involvement, tissue Biopsy/ fine needle aspiration cytology (FNAC) for histological diagnosis, bone marrow biopsy to exclude bone marrow involvement. Malarial parasite and HIV tests are needed to ascertain predisposing factors and to guide treatment. Radiological investigations like chest -X-ray, abdomino-pelvic ultrasound , computerized tomographic (CT) Scan, magnetic resonance imaging (MRI) and Positron emission tomography [PET] are needed to ascertain bony and soft tissue extent of the disease.

Staging

The National Cancer Institute (NCI) 1992 staging is widely used.

A - Single solitary extra-abdominal site
AR - Intra-abdominal, more than 90% of tumour resected
B - Multiple extra-abdominal tumours
C - Intra-abdominal tumor
D -Intra-abdominal plus one or more extra-abdominal sites

Prognostic Factors in BL include stage of disease as it reflects tumour burden, primary site (jaw better than abdomen,) bone marrow and CNS involvement which connote poor prognosis.

Treatment of BL is guided by its characteristics which include high growth fraction, highly aggressive, radiosensitive with high tumour doubling time and rapid tumour growth. It is also highly chemosensitive and potentially curable. Multiple sites are possible and the child is usually very ill while pressure effects on vital organs like the brain, could be life threatening. The child is treated as an emergency with hydration, blood transfusion if indicated, alkalination of urine with oral bicarbonate, and allopurinol to prevent hyperkalaemia and urate nephropathy. Staging should be done in hours. Acute renal failure can occur before and during treatment and haemodialysis may be required. Monitoring of electrolytes, urea, creatinine and uric acid should be done.

Chemotherapy is the main stay of treatment. It is indicated in early disease (Stages A, AR), extensive disease (B, C&D) and relapse disease. Chemotherapy regimens are as follows:

Early disease:
Cyclophosphamide 40mg/kg - 2-3weekly x 3-4 doses gives 80-90% response in new cases[13]

Extensive disease Combination chemotherapy

1. COMP cyclophosphamide 30mg/kg,vincristin 2mg/m^2- days 1 & 14 Methotrexate 15mg/m^2 days 1, 2 & 3, prednisolone 20mg tid x 2wks

2. CHOP Doxorubicin 50mg/m^2 replaces methotrexate in COMP. These give 40% response rate [14]

3. French LMB-89 - High-dose cyclophosphamide + high-dose methotrexate/ leucovorin + cytarabine + vincristin + prednisolone + doxorubicin

4. NHL-BFM90(GERMAN) - Prednisolone+ dexamethazone + vincristin+ doxorubicin + cyclophosphamide+ ifosfamide+ etoposide + cytarabine + methotrexate (3&4 give 80% response rates)[15]

Relapse disease: Usually occurs within 8-10 months of treatment. Treatment is with high dose chemotherapy +Bone Marrow Transplant (BMT). CNS Prophylaxis is indicated in extensive, relapse, testicular and ocular diseases. This is done with intra- thecal (IT) methotrexate +/- cytarabine and hydrocortisone. Surgery has some role in the management of BL. The indications include.[16]

a. Abdominal disease - Exploratory laparotomy in cases of doubtful diagnosis. Tumour debulking is attempted and sample for histological diagnosis is taken. Chemotherapy should be commenced within 48hrs of surgery.
b. Disease- related problems like intestinal obstruction, perforation, haemorrhage intususception (usually ileo caecal), airway obstruction (pharynx disease) and pleural effusion should receive appropriate surgical interventions.

Radiotherapy: Although the disease is highly radiosensitive, its multifocal nature restricts radiotherapy. Indications include symptomatic space-occupying lesion e.g. superior vena cava obstruction (SVCO), central nervous system (brain/spinal cord) compression, poor response to chemotherapy, palliation of pain and mass effect on organs, as well as residual disease after chemotherapy in recurrent disease.

Treatment is usually as an emergency. Radiotherapy principle is that of hyperfractionation and accelerated fractionation to cope with the high rate of tumour growth. In CNS disease, the treatment volume is the whole brain with megavoltage equipment. A typical dose range is 1.2 - 1.5 Gy per fraction twice daily to a total of 6 - 7.5Gy. Deaxamethazone is given during the treatment.[17]

Adequate nursing care is important in the management of patients with BL. Close attention should be given to feeding, adequate urine flow rate which should be kept at 3.7 ± 0.3mls/kg/hr. Mucositis and febrile neutropaenia should be recognized early during treatment.

Side effects of treatment include possible specific side effects of the chemotherapy agents. Cyclophosphamide can cause myelosupression and haemorrhagic cystitis. Vincristin can cause peripheral neuropathy. Doxorubicin can cause cardiotoxicity while methotrexate is myelosuppressive and can also cause renal toxicity. Prednisolone may cause gastritis, hyperglycaemia and fluid retention. Early post operative chemotherapy may lead to wound infection and wound dehiscence

Survival

Fifty Percent 10 year survival was reported by Zeigler et al 1979[18] for stages A-C. Sixty three percent of these were head and neck lesions while 33% were abdominal diseases. Problems of follow up for longer periods due to inadequate addresses and poor communication facilities were also identified by Zeigler et al. especially in African countries.

Progress evaluation: A lot has been achieved in the understanding of the tumour biology and management of BL. However, after about 50 years of the study of this disease, mortality from it is still high especially in extensive disease in Africa. Problems include the facts that treatment is still haphazard with improper staging in most cases. Poor bone

marrow and CSF evaluation in most treatments, low doses of chemotherapy due to lack of facilities for bone marrow transplant in most centers, contribute to poor evaluation and inadequate treatment of most patients.

Follow up is inadequate in most treatment reviews.[19] High cost of treatment prevents most patients from accessing treatment. This fact was brought out in a recent interim report of UICC-Sanofi Aventis grants project for BL in Tanzania[20] in which new cases increased from 145 to 364 per year, follow up rate increased from 20%-85% and improved clinical skill in diagnosis and treatment were observed.

In Nigeria, a study of 41 cases of Burkitts lymphoma in Calabar, South Eastern Nigeria showed that 50% of the patients presented late. In 20 % of the patients, the parents could not afford the treatment and left against medical advice while 31 % abandoned the treatment half way for lack of funds[21].

To build on the success story of eBL, there should be increase in the funding of treatment of this disease and free treatment should be introduced. Public awareness campaign should be intensified and sustained and facilities for the management of the disease should be strengthened including functional National Cancer Registries.

EBV is human herpes virus and is oncogenic for eBL in susceptible populations. It is widespread in humans and transmission occurs early in life through saliva[22]. Efforts to prevent transmission of this virus to children and better control possibly through vaccine development to protect children against the virus can help in reducing the incidence of eBL. Malaria possibly disrupts immune response against EBV.[23]

Prevention of malarial infection especially between the first five years of life can help to control eBL. This can be done through provision of accessible facilities for prompt diagnosis and adequate treatment of infected patients. The use of treated mosquito nets and other prophylaxis can prevent infection with malaria. The control of malaria and HIV infections should therefore be pursued vigorously. If these measures are adopted, it is hoped that the next 50 years of the eBL story will change for better.

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