



Non-Essential Intervention in the Management of Ovarian Burkitt Lymphoma: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author CEA, designed the study and wrote the first draft of the manuscript. Authors EAN, HI and AAS, managed the literature searches including laboratory investigations All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: Ovarian involvement by Non-Hodgkins Lymphoma (NHL) may manifest within the four subtypes of lymphoma: diffuse large B-cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, or anaplastic large cell lymphoma. Burkitt Lymphoma (BL) rarely manifests as a primary ovarian disease given the various epidemiological studies, putting the incidence at 0.5% of NHL and 1.5% of all ovarian neoplasm.

Objective: This study is intended to highlight necessary intervention in the event of an uncommon manifestation of Burkitt lymphoma in a milieu of diagnostic challenges.

Methods: A comprehensive review, and analysis of diagnosis, intervention and treatment of the index case was conducted by a team of health caregivers of the Federal Medical Centre, Bida, North Central Nigeria.

Results: This review identifies a 15-year old female, with features suggestive of abdominal malignancy. In view of the associated severe abdominal discomfort, and pressure effects arising from the huge abdominal mass, the patient underwent exploratory laparotomy partly as a palliative measure to debulk as well as determining the extent of the local disease spread, and obtain tissue

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for histology. Following a histological diagnosis of ovarian Burkitt lymphoma stage IIIB (St. Jude / Murphys staging), the patient was commenced on supportive therapy; a monthly course of intensive multi-agent (cyclophosphamide, Vincristine, Methotrexate) chemotherapy including intrathecal Methotrexate prophylaxis. Haematologic remission was achieved by the end of the fifth cycle of the scheduled six cycles. Patient is currently well, and on hormone replacement therapy while being followed up at both the haematology and gynaecology clinics.

Conclusion: Burkitt lymphoma (BL) as we have and seen in this case is highly responsive to standard high-dose chemotherapy, but it could be rapidly fatal if treatment is delayed. Although surgery is not considered as first line of treatment, but offers an opportunity for debulking and obtaining tissue biopsy for histological analysis. Standard multi-agent chemotherapeutic management remains the recommended first line choice in established case.

Keywords: Ovarian burkitt lymphoma; surgical intervention; diagnosis; Intensive multi-agent chemotherapy; haematologic remission; Limited diagnostic tools.

1. INTRODUCTION

Burkitt lymphoma (BL) is a form of non-Hodgkin lymphoma (NHL) in which the malignant cells originate in the B cells. [1,2] It is an aggressive tumour, classified as high-grade B-cell malignancy and has the fastest doubling time among human tumours and growth potential of 100% [3]. This B cell lymphoma is a result of the translocation of cMYC gene from the long arm of chromosome 8 to the immunoglobulin heavy chain gene locus on the long arm of chromosome 14 depicted as being t (8;14) (q24;q32). The other variants are the t(2;8) (p12;q24) and t(8;22) (q24;q11) involving cMYC and either the kappa(k) or lambda(λ) immunoglobulin light chain loci of chromosome 2 and 22 respectively [2,4,5].

Burkitt Lymphoma has a worldwide distribution and globally account for 1% to 2% of adult lymphoma. (1, 2) According to several epidemiological studies, BL is more common in children and seen more in males than females, with the average male: female ratio being 2-3:1 [2, 6, 4, 7-11]. The median age of presentation is 9 years while the age ranges between 2 to 45 years. (2) In the 2016 revision and classification of lymphoid neoplasm, the World Health Organization, highlighted three types of Burkitt lymphoma: the African type or endemic (eBL), non-African type or sporadic (sBL) and the immunodeficiency-associated BL. [1, 2, 12,13,6, 4] The endemic variant is mostly prevalent in endemic malaria regions of Africa and highly linked with Epstein-Barr virus infection (EBV), which account for about 98% of African cases. (1-4, 8) sBL subtype is diagnosed mostly in young adults in Western Europe and North America although its distribution is worldwide. It is also well documented that sBL frequently

shows extranodal manifestation, usually in the abdominal cavity. In the majority of cases, the gut, mesenteric and para-aortic lymph nodes are affected. Ovarian involvement of non-Hodgkin lymphoma could be in form of one of the four subtypes of lymphoma: diffuse large B-cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma or anaplastic large cell lymphoma. (9) In most cases ovarian involvement of Burkitt lymphoma is a result of disseminated disease, secondary manifestation of BL. [7-10] Burkitt Lymphoma rarely manifests as primary ovarian disease given the various epidemiological studies and this incidence is said to account for 0.5% of NHL and 1.5% of all ovarian neoplasm. [12, 5,7-11).

The case report is intended to highlight necessary intervention in the event of an uncommon manifestation of Burkitt lymphoma in a milieu of diagnostic challenges.

2. PRESENTATION OF CASE

We present a 15-year old female, Para 0⁺⁰, who achieved menarche at 13 years, with a regular monthly flow of 5 days in a 28 days cycle. Her last menstrual period was a few days before her visits to the gynaecology emergency unit of the Federal Medical Centre Bida, Nigeria. At first presentation, she gave a four (4) month history of progressive abdominal swelling and discomfort and five (5) weeks history of weight loss, drenching night sweat, generalised body weakness, low-grade pyrexia, cough and dyspnoea. Further enquiry revealed no positive associated findings.

On physical examination, she was chronically ill-looking, conscious with moderately pale conjunctival but not cyanotic. There was no

jaundice or dehydration. She had no significant lymphadenopathy or pedal oedema. The Cardiovascular, Respiratory, Central nervous system and other clinical parameters were essentially normal except for a moderately elevated pulse rate of 132 bpm (60-100bpm) and respiratory rate of 32cpm (12-16cpm) however, her SP_{O_2} was 97%. The abdomen was extensively distended with massive ascites which interfered with palpation of abdominal organs and or masses.

The initial laboratory investigations that were conducted including renal function test, liver function test and complete blood count demonstrated values within reference ranges except for the Aspartate transaminase enzyme (AST) of 119IU (0-46), haemoglobin concentration [Hb] of 8.4 g/dl (11.5-13.5) and haematocrit (HCT) of 27.1% (34-40). Table 1. The Peripheral blood film shows no abnormalities likewise, the Serological screening for HBsAg, antibody to HCV, HIV I and II.

Computed tomography (CT) scan could not be carried out due to financial constraints. However, she had an abdominal ultrasound scan done that revealed two heterogeneous intra-abdominal masses arising from the adnexa, measuring 17cm x 11cm and 13cm x 11cm in size on the right and left respectively. Based on this report, and admitting diagnosis of ovarian malignancy, coupled with severe abdominal discomfort and other pressure effects, the patient underwent an exploratory laparotomy. The following findings were noted intra-operatively: bilateral solid ovarian tumour measuring 20cm x 20cm, with oedematous bilateral fallopian tubes, blood-stained ascitic fluid, multiple (fourteen spots) lesions to the caecum, appendix, small and large intestines, with each measuring 6cm x 6cm in diameter. Additionally, multiple lesions to the anterior abdominal wall were also found. Consequently, bilateral salpingo-oophorectomy was carried out as well as tissue biopsy for histological analysis. She had 5 units of whole blood transfusion (3 units pre-operative, 2 units intra-operatively). The patient was then counselled along with her parents and discharged home on the 9th-day post-op on account of satisfactory postoperative recovery. She was to be followed-up a week later with a histology report but defaulted. She represented 12 days later and was readmitted with complaints of early morning facial puffiness, leg swelling, abdominal pain, and dizziness. Physical examination revealed pale conjunctival, bilateral

pedal oedema, healed exploratory laparotomy scar, abdominal swelling, and ascites (abdominal girth was 82.5cm).

The histopathology analysis demonstrated homogenous sheets of lymphoblast with a round to oval nuclei slightly coarse chromatin, multiple nucleoli and basophilic cytoplasm. The homogenous appearance was interspersed with scattered tangible body macrophages imparting a starry sky appearance. (Fig. 1) These features / findings are in keeping with the diagnosis of ovarian Burkitt lymphoma.

The result of immunohistochemistry analysis shows CD10 +VE, CD20 +VE, BCL2 –VE (Figs. 2, 3, & 4). Other laboratory results including serial complete blood count are shown in Table 1.

Bone Marrow aspiration and chest x-ray did not reveal any involvement while Cerebrospinal Fluid (CSF) cytology was negative for malignant cells. On account of these findings, the final diagnosis of Ovarian Burkitt Lymphoma, stage III B (St. Jude / Murphys staging system) complicated by Anaemia and Sepsis was made.

Following this, the patient was conservatively treated for sepsis with empirical oral antibiotics; augmentin (625mg 12hourly for 7 days) and azithromycin (500mg daily for 3 days). In addition, one (1) unit of fresh whole was blood transfused. With the much desired clinical improvement (resolved sepsis, stable vital signs, improved complete blood count parameters), the Patient was subsequently counselled on the diagnosis, treatment and prognosis. She was then offered supportive treatment as well as definitive intensive treatment involving monthly courses of multi-agent chemotherapy comprising intravenous cyclophosphamide ($1.2g/m^2$) day 1, intravenous vincristine ($1.4mg/m^2$) day 1 and intravenous methotrexate ($75mg/m^2$) day 1 for six (6) cycles. In addition, Patient had intrathecal methotrexate at a dose of $12mg/m^2$ ($12.5mg$) day 1 along with chemotherapy for the systemic disease and intravenous Leucovorine at 50mg start and then 25mg 12 hourly for 48 hours in double dilutions as a rescue agent and parenteral antiemetic ondansetron. Xanthine oxidase inhibitor; allopurinol, and aggressive hydration were administered as a preventive measure against tumour lysis syndrome (TLS). Oral Broad spectrum antibiotics administration were extended for prophylaxis against neutropenic sepsis.

The patient had consistent and relatively normal level of serum electrolytes, urea as well as complete blood count. Also, the initially deranged aspartate transaminase enzyme assumed a normal value during the course of treatment. She maintains adequate vital signs, and had good tolerance to all administered medications all through, from the first (1st) cycle to the sixth (6th) cycle. At the end of the 5th cycle, her

performance status had improved significantly and with complete clinical remission. An initial abdominal girth of 80.5cm had regressed to 63cm. The complete blood count results at the end of the 6th cycle shows WBC: - $7.8 \times 10^9/L$, [Hb]:- 13.2g/dl, HCT: - 40.9%, Abs Neutrophils count: - $2.0 \times 10^9/L$, Abs Lymphocytes count: - $5.5 \times 10^9/L$ Platelets count: - $213 \times 10^9/L$ and other results are as shown in Table 1.

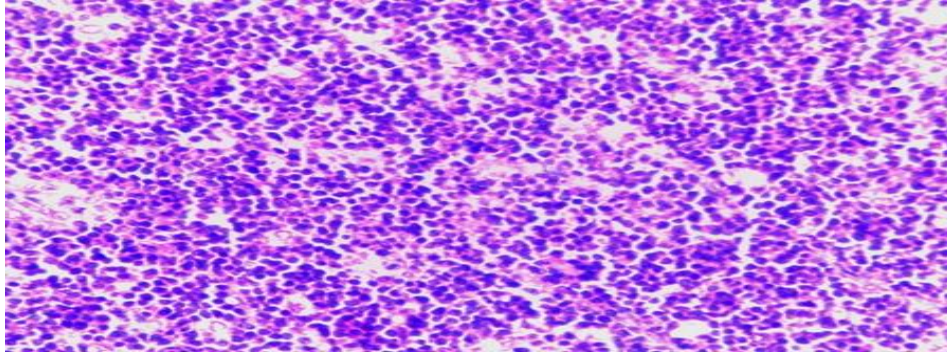


Fig. 1. Histology H&E x 40. Demonstrating homogenous sheets of lymphoblast with a round to oval nuclei slightly coarse chromatin, multiple nucleoli and basophilic cytoplasm. The homogenous appearance was interspersed with scattered tangible body macrophages imparting a starry sky appearance

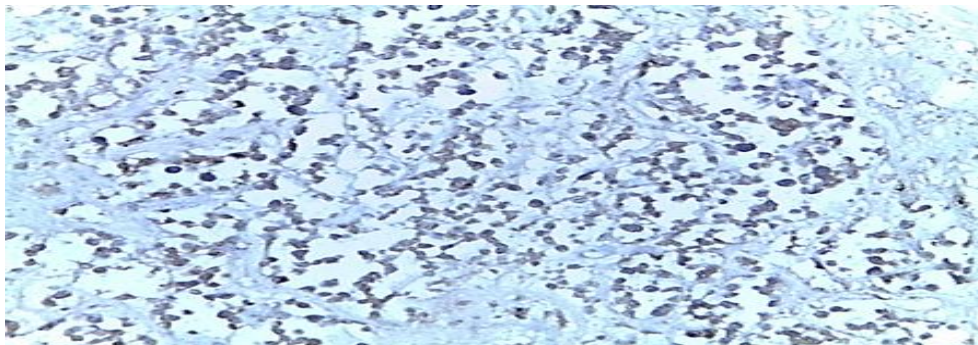


Fig. 2. Immunohistochemistry CD10 +VE x40. Tissue showing diffuse and intense membrane staining (expression of CD10)



Fig. 3. Immunohistochemistry CD20 +VE x40. Tissue showing diffuse and intense membrane staining (expression of CD20)

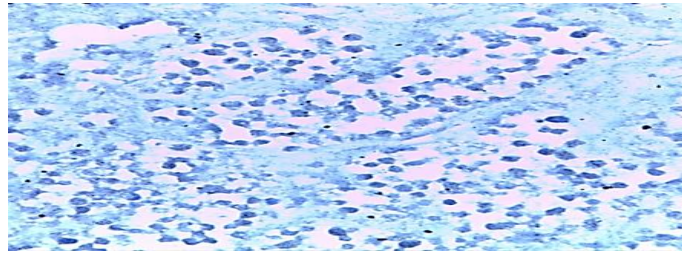


Fig. 4. Immunohistochemistry BCL2 –VE x40. Tissue showing lack of expression of BCL 2

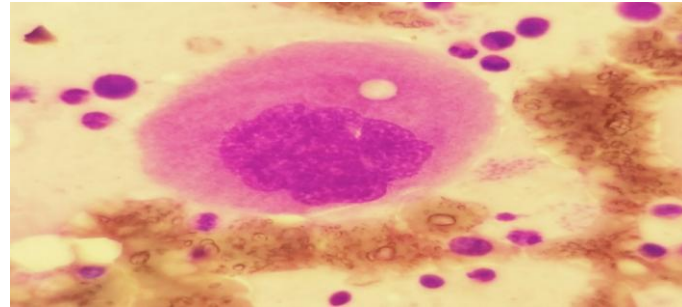


Fig. 5. Bone marrow aspiration x100. Marrow showing Megakaryocyte and absence of Burkitt cells

Table 1. Laboratory data

Variables	Reference range ^{17, 18}	Months					
		1	2	3	4	5	6
WBC (x10 ⁹ /L)	2.5 – 7.5	-	3.7	6.3	4.9	5.8	7.8
Haemoglobin (g/dl)	11.5 – 13.5	8.7	8.4	10.6	11.3	12.6	13.2
Haematocrit (%)	34 - 40	26	27.1	32.7	35.1	38	40.9
Platelets (x10 ⁹ /L)	100 - 350	-	382	292	220	120	213
Neutrophils (x10 ⁹ /L)	1.5 – 7.5	-	1.4	2.4	1.9	2.5	2.0
Lymphocytes (x10 ⁹ /L)	1.5 – 3.0	-	1.9	2.0	2.1	3.0	5.5
Sodium (mmol /L)	135 – 145	136.5	140				
Potassium (mmol/L)	3.5 – 5.5	3.9	4.3				
Bicarbonate (mmol/L)	21 – 31	19	19				
Urea (μmol/L)	1.7 – 9.1	2.4	6.0				
Creatinine μmol/L	60 – 124	62	80				
Chloride (mmol/L)	96 – 106	100.5	100				
Alanine Transaminase (IU)	0 – 49	13	11				
Aspartate Transaminase (IU)	0 – 46	119	35				
Alkaline Phosphatase (IU)	64 – 306	95	90				
Total Protein (g/l)	60 – 80	68	64				
Albumin (IU)	35 – 50	39	34				
Total Bilirubin (μmol/L)	0 – 205	11.3	10				
Cong. Bilirubin (μmol/L)	0 – 68	74	75				
HBsAg		NEGATIVE					
HCV		NEGATIVE					
HIV I		NON-REACTIVE					
HIV II		NON-REACTIVE					

^aHBsAg = Hepatitis B surface antigen; ^bHCV = Hepatitis C Virus; ^cHIV = Human immunodeficiency virus

3. DISCUSSION

Ovarian Burkitt lymphoma is a rare type of sporadic Burkitt Lymphoma (sBL) and accounts for 0.5% of NHL and 1.5% of ovarian related tumour. [14, 5,7-11] Although, the projections for the diagnosis of BL especially the eBL type might be straightforward, this cannot be extended to ovarian BL in some cases, given the fact that the ovaries are not regarded as a primary lymphoid tissue and are therefore also prone to some other types of malignancies. Notwithstanding the aforementioned, the diagnosis of ovarian Burkitt lymphoma could be made less cumbersome given the availability of resources and necessary diagnostic tools such as ultrasound-guided biopsy and fine needle aspiration cytology, contrast enhanced computed tomography scan (CECT), Magnetic resonance imaging (MRI), flow cytometry, fluorescent in-situ hybridization (FISH) and polymerase chain reaction (PCR). [5,7,8,11] Unfortunately, some of these diagnostic tools are widely unavailable and cost-ineffective in developing countries, such as ours limiting diagnostic efforts. These limitations are frequently encountered by the oncologists / gynaecologists; who are constantly mitigating these shortcomings while providing treatment best suited for patients. In this case report, the diagnosis was established by the basic histology using haematoxylin and eosin stains as well as immuno-histochemical methods. The histology displays a classical starry sky characteristics which is the expected histological findings in Burkitt lymphoma. The scattered tangible body macrophages with the engulfed dead lymphoid cells impact this characteristics as seen in the figure. Furthermore, to strengthen the degree of confidence in the diagnosis, immunohistochemistry is usually advised. There are specific Burkitt cells signature such as CD10, CD20, BCL6 and Ki67. In this case, only two of these specific markers (CD20 & CD10) besides BCL2, were analysed because the immuno-stains for the others particularly Ki67 – a proliferation index (PI) marker, are scarcely unavailable in our setting. The tissue was strongly positive for CD10 and CD20, and negative for BCL2; a markers seen more frequently in other lymphoid malignant disease variants such as diffuse large B cell lymphoma [16].

However, with an established diagnosis and in providing treatment for Burkitt lymphoma cases, and given the various modalities involved, surgery is considered not to be the first line of

treatment especially in the case of sBL and in particular ovarian Burkitt lymphoma. [5] It is important to note also that these BL tumours are highly chemo-sensitive which therefore makes chemotherapy a first line treatment choice. However, some clinical conditions and accompanying exigencies as exhibited in the index case, may warrant the use of surgery as a form of palliative measure. Exploratory laparotomy was embarked upon in view of the severe abdominal pain, discomfort and pressure effect resulting from the huge ovarian tumour mass, and also for the purpose of debulking and elucidating the extent of the disease. The procedure also offers an opportunity for tissue biopsy required for histological diagnosis as depicted above [15, 5, 8, 9].

The extensive nature of the disease are as highlighted in the intraoperative findings and consequently, prompt commencement of chemotherapy in line with the diagnosis of ovarian Burkitt lymphoma, stage IIIB was initiated. Multi-agent chemotherapy was commenced but again due to the reason of unavailability of some of the component in the recommended regimens and financial constraints, the standard and widely used Magrath chemotherapy regimens CODOX-M / IVAC (cyclophosphamide, doxorubicin, high dose methotrexate, ifosfamide, etoposide and high dose cytosine arabinoside) [4,11] had to be substituted with the use of COM (cyclophosphamide, vincristine and methotrexate). (2) Patient had intensive monthly courses of these combinations for six (6) cycles along with prophylactic intrathecal methotrexate, and Leucovorine. In order to prevent TLS, administration of xanthine oxidase inhibitor along with aggressive hydration therapy was ensured. While the combination chemotherapy (COM) used in this patient cannot be deemed optimal considering the combinations in the recommended protocols such as the Magrath regimen, or Hyper CVD, nevertheless, the patients response was quite encouraging as adjudged by her remarkably improved performance status and haematologic /clinical remission remission which was achieved by the end of the fifth cycle. The patient is currently well, and on hormone replacement therapy while being followed up at both the haematology and gynaecology clinics.

It is important to state that Burkitt lymphoma is highly fatal if left untreated, but if treatment is initiated promptly, especially in children, this

often leads to cure. However, it is pertinent to note also that the 5-year long-term disease-free survival rate in childhood with early stage disease (stage I & II) is over 90% while those with the advanced-stage disease (stage III & IV) is between 80-90% [1, 4, 17] and therefore timely intervention, may pave the way for a favourable outcome.

4. CONCLUSION

Burkitt lymphoma (BL) is highly responsive to standard high-dose chemotherapy, but it could be rapidly fatal if treatment is delayed. Although, surgery is not considered as the first line of treatment, as documented in many studies. Nevertheless, it may be required as a palliative measure and offers an opportunity for debulking and obtaining a biopsy for histological analysis. Otherwise, Standard multi-agent chemotherapeutic management remains the recommended first line treatment choice in established cases.

5. LIMITATIONS

This case study is limited by a number of unavailable investigations that could have aided prompt diagnosis, treatment and prognostic classification. Some of the inaccessible investigations are BCL 6, Ki67, CD3, MUM1, lactate dehydrogenase (LDH), flow cytometry, contrast enhanced computed tomography (CECT), and magnetic resonance imaging (MRI), fluorescent in-situ hybridization (FISH), and polymerase chain reaction (PCR). It is worthy of note that some of these investigations are pivotal to making objective determination of tumour load.

6. RECOMMENDATIONS

1. Financial constraint on the part of the patients, continues to be a concern amongst the oncologists and health care givers. The high cost of treatment and investigations is an added burden to patients with malignant disease and on their management. Therefore health institutions and government should focus on these lingering concerns and prioritize subsidies on the cost of treatment and investigations.
2. Availability of diagnostic tools – Hospitals should make a deliberate effort by ensuring procurement of basic diagnostic tools to enhance services while the government should strategize on establishing diagnostic referral centers with state of the art

equipment in the six geological regions of the country.

3. Availability of Anti- Cancer drugs – The pharmaceutical industry should endeavour to make anti-cancer agents widely available and affordable.
4. A High index of suspicion remains cardinal in establishing a diagnosis particularly in diagnosing rare cases of disease conditions. This should ultimately trigger prompt consultation and collaboration amongst physicians leading to prompt treatment.

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CONSENT

All authors declared that written informed consent was obtained from the patient and parents for publication of this case report. A copy of the written consent is available for review by the editorial office/editorial board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that this case report has been examined and approved by the hospital ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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