THE ABDOMINAL SONOGRAPHIC FEATURES OF BURKITT'S LYMPHOMA IN PATIENTS SEEN AT UGANDA CANCER INSTITUTE, MULAGO HOSPITAL - KAMPALA.

BY

DR. PASCAL KWITONDA MBChB (Mak)

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF A MASTER OF MEDICINE IN RADIOLOGY OF MAKERERE UNIVERSITY.

OCTOBER-2009
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2009
DECLARATION

I Dr Pascal Kwitonda do hereby declare that this is an original work done by me. Contributions of other people in preparing and carrying out this study have been acknowledged and appreciated. The views expressed herein are mine unless otherwise stated, and where such has been the case acknowledgement or reference has been quoted. This dissertation, in full or otherwise, has not been submitted for an academic award in this or any other university or institution of higher learning.

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DEDICATION

This book is dedicated to my family.
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The development and completion of this study was made possible by support, contribution and encouragement from many people. I wish to extend my heartfelt appreciation to all of them.

Special gratitude goes to my supervisors: Dr. Byanyima K Rosemary, Dr. Orem Jackson and Dr. Muyinda Zeridah for their unparalleled input into this research right from the proposal development up to the draft of this dissertation. I will forever be grateful for all your sacrifice.

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OPERATIONAL DEFINITIONS

Ultrasound:  Is a diagnostic technique, which uses inaudible sound in the frequency of 1-20MHZ (mega hertz)

Echogenicity:  Intensity of echoes reflected by tissues or structures from inside the body.
Echogenicity of a structure is described relative to the surrounding or adjacent tissue.

Hyperechoic:  Refers to high intensity echoes

Hypoechoic:  Refers to low intensity echoes

Anechoic:  Refers to no internal echoes

Isoechoic:  Refers to two structures generating the same intensity echoes.

Echotexture:  Refers to the uniformity of echoes within a mass. It may be homogeneous or heterogeneous.
LIST OF ACRONYMMS

UCI - Uganda Cancer Institute
LTC - Lymphoma Treatment Centre
WHO - World Health Organization
EBV - Epstein Barr Virus
BL - Burkitt’s lymphoma
eBL - Endemic Burkitt’s Lymphoma
sBL - Sporadic Burkitt’s Lymphoma
CNS - Central Nervous System
CPM - Cyclophosphamide
VCR - Vincristine
MTX - Methotrexate
ARA-C - Cytosine Arabinoside
COMP - Cyclophosphamide + Vincristine(Oncovin)+ Methotrexate + Prednisolone
CHOP - Cyclophosphamide+ Vincristine(Oncovin)+Doxorubicine+ Predinisolone
TNF - Tumour Necrosis Factor
IL - Interluekin
IFN - Interferon
RES - Reticulo Endothelial System
LFT - Liver Fuction Test
RFT - Renal Function Test

CXR - Chest x-ray

CSF - Cerebral Spinal Fluid

HIV - Human Immune deficiency Virus

WBC - White Blood Cell

LDH - Lactate Dehydrogenase

IVP - Intravenous Pylorogram

CT Scan - Computed Tomography scan

TB - Tuberculosis.

C-myc - A strong proto-oncogene very often found to be up regulated in many types of cancer.

B-cells - B-lymphocytes that are produced and mature in the bone marrow.
# TABLE OF CONTENTS

Declaration........................................................................................................i

Dedication......................................................................................................ii

Acknowledgement........................................................................................iii

Operational definitions..................................................................................iv

List of acronyms............................................................................................v

Table of contents..........................................................................................vii

List of Tables................................................................................................x

List of Figures................................................................................................xi

Abstract..........................................................................................................xii

## CHAPTER ONE.........................................................................................1

1.0 Introduction............................................................................................1

1.1 Background.............................................................................................1

1.2 Statement of the problem.........................................................................2

1.3 Justification of the study.........................................................................3

1.4 Research Question..................................................................................4

1.5 Objectives of the study...........................................................................4

1.5.1 General objectives.............................................................................4

1.5.2 Specific objectives.............................................................................4

## CHAPTER TWO.........................................................................................5

2.0 Literature Review....................................................................................5

2.1 Burkitt’s Lymphoma clinical variants......................................................5

2.2 Clinical characteristics..........................................................................6
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3 Burden of Burkitt’s Lymphoma in Uganda</td>
<td>6</td>
</tr>
<tr>
<td>2.4 Risk factors for Burkitt’s Lymphoma</td>
<td>8</td>
</tr>
<tr>
<td>2.5 Diagnosis of Burkitt’s Lymphoma in Africa</td>
<td>9</td>
</tr>
<tr>
<td>2.6 Role of ultrasound in diagnosis</td>
<td>9</td>
</tr>
<tr>
<td>2.7 Role of surgery in Burkitt’s Lymphoma</td>
<td>11</td>
</tr>
<tr>
<td>2.8 Staging of Burkitt’s Lymphoma</td>
<td>11</td>
</tr>
<tr>
<td>2.9 Treatment of Burkitt’s Lymphoma</td>
<td>12</td>
</tr>
<tr>
<td>CHAPTER THREE</td>
<td>13</td>
</tr>
<tr>
<td>3.0 Methodology</td>
<td>13</td>
</tr>
<tr>
<td>3.1 Study design and duration</td>
<td>13</td>
</tr>
<tr>
<td>3.2 Study setting</td>
<td>13</td>
</tr>
<tr>
<td>3.3 Study population( participants)</td>
<td>13</td>
</tr>
<tr>
<td>3.4 Inclusion criteria</td>
<td>13</td>
</tr>
<tr>
<td>3.5 Exclusion criteria</td>
<td>13</td>
</tr>
<tr>
<td>3.6 Variables</td>
<td>14</td>
</tr>
<tr>
<td>3.7 Sampling criteria</td>
<td>14</td>
</tr>
<tr>
<td>3.8 Data Collection Procedure</td>
<td>15</td>
</tr>
<tr>
<td>3.9 Data Management and Analysis</td>
<td>16</td>
</tr>
<tr>
<td>3.10 Quality Control</td>
<td>16</td>
</tr>
<tr>
<td>3.11 Ethical issues</td>
<td>17</td>
</tr>
<tr>
<td>3.12 Study limitations</td>
<td>17</td>
</tr>
<tr>
<td>3.13 Dissemination of results</td>
<td>17</td>
</tr>
<tr>
<td>CHAPTER FOUR</td>
<td>18</td>
</tr>
<tr>
<td>4.0 Results</td>
<td>18</td>
</tr>
<tr>
<td>4.1 Socio-demographic characteristics</td>
<td>18</td>
</tr>
<tr>
<td>4.2 Clinical characteristics of the study patients</td>
<td>18</td>
</tr>
</tbody>
</table>
4.3 Abdominal ultrasound findings ............................................... 21
4.4 Other imaging findings ..................................................... 22
4.5 Laboratory findings at baseline ........................................... 22
4.6 Follow up results ............................................................ 25
4.7 Illustrations ................................................................. 27

CHAPTER FIVE ........................................................................... 31

4.0 Discussion ......................................................................... 31
5.1 Demographic variables .................................................... 31

5.2 Clinical characteristics .................................................... 32

5.3 Sonographic findings ....................................................... 32
5.4 Other imaging findings ................................................... 33
5.5 Laboratory findings ........................................................ 34
5.6 Follow up results ............................................................. 35
5.7 Conclusions ..................................................................... 36

5.8 Recommendations ........................................................ 36

REFERENCES ........................................................................... 37

APPENDICES ........................................................................... 41
Appendix 1- Time table of the research events ......................... 41
Appendix 2- Consent form (English) ........................................ 42
Appendix 3- Consent form (Luganda) ................................ ...... 45
Appendix 4- Assent form ....................................................... 47
Appendix 5- Questionnaire .................................................... 49
LIST OF TABLES

Table 1: Patients clinical characteristics .........................................................20

Table 2: Abdominal sonographic findings .......................................................23

Table 3: Laboratory findings: Full haemogram and LDH levels .......................23

Table 4: Distribution of residual masses in the abdominal organs .................26

Table 5: Laboratory findings at follow up: Full haemogram and LDH levels .......26
List of Figures

Figure 1: Classical microscopic appearance of Burkitt's lymphoma .............................................. 5

Figure 2: Typical jaw tumour of Burkitt's lymphoma ................................................................. 6

Figure 3: Age specific incidence rate of Burkitt's lymphoma in Kyadondo county, Uganda; 1993-1997 ................................................................. 7

Figure 4: Proportional contribution of different cancer sites among children aged 0-14 years in the Kyadondo County, Uganda for 1993-1997 ......................................................... 7

Figure 5: Age distribution of the study patients ........................................................................... 19

Figure 6: Clinical stage of patients at presentation ................................................................. 19

Figure 7: Presenting symptoms Vs Duration of symptoms ..................................................... 21

Figure 8: Variation of LDH levels with Tumour size at base line ........................................... 24

Figure 9: Variation of LDH levels with clinical stage of the disease ........................................ 24

Figure 10 and 11: Huge heterogeneous hypoechoic ovarian masses ........................................ 27

Figure 12: Bilateral pleural effusion and splenic masses ......................................................... 28

Figure 13: i. Unilateral hydronephrosis due to right renal pelvis calcific mass ..................... 28

Figure 13: ii. Mass compressing on the cystic duct ................................................................. 29

Figure 14: Huge lobulated intraperitoneal and retroperitoneal masses ................................ 29

Figure 15: Splenic hilum and para aortic nodular masses ....................................................... 30

Figure 16: Bilateral hypoechoic renal masses ........................................................................... 30
ABSTRACT

Introduction:

Burkitt lymphoma is a B-cell lymphoma presenting in three main clinical variants: the endemic, the sporadic and the immunodeficiency-associated variants.

In Uganda, Burkitt’s lymphoma represents 50-70% of childhood cancers presenting mainly as facial tumour. Diagnosis depends on tissue examination. Imaging provides very useful diagnostic and staging information. Characteristically abdominal BL sonographically presents as well defined solid hypoechoic mass with mass effect; they lack calcifications and are avascular on colour doppler study. Ultrasound therefore plays an important auxiliary role in early detection and diagnosis of this potentially curable tumour and can be used to predict the prognosis.

Objectives:

The major objective of the study was to describe the sonographic features of BL and to relate them with the clinical features and laboratory findings in order to determine the prognostic benefit of abdominal ultrasound in patients with BL at the UCI-Mulago hospital.

Methodology

This case series study was conducted in UCI and Department of Radiology–Mulago Hospital from March 2009 to September 2009. Sixty (60) patients with confirmed BL had abdominal ultrasonography done before initiation of chemotherapy and at one month after initiation of chemotherapy.

Results

Sixty (60) patients participated in the study. The age range was 3-18 years with a mean of 7.2 and standard deviation of 2.98. The peak incidence was between 5-9 years. There were 43 (71.7%) males and 17(28.3%) females. Facial bone tumours remained the commonest clinical finding however, the commonest single presenting complaint was palpable abdominal mass with pain in 31(51.7%) patients. Abdominal ultrasound showed that 40(66.7%) of all patients had intra
abdominal masses. Forty-four (73.3%) patients had the tumours involving other parts of the body. Most patients presented with stage D disease and therefore had poor prognosis.

The commonest ultrasound findings were multiple lobulated heterogeneous hypoechoic abdominal masses in 40(66.7%) patients. Of these masses 20(33.3%) were in the kidneys. Follow-up abdominal ultrasound showed that 32(80%) patients had tumour regression after one month of induction.

5.4 Conclusions

- Abdominal ultrasound was able to demonstrate greater disease extent than clinical evaluation, thus highlighting the value of imaging in tumour staging and follow up of patients.
- This study showed more cases of abdominal BL involvement than previously seen in our patients, possibly due to better imaging facilities now.
- Burkitt’s lymphoma should be strongly suspected in a child presenting with large lobulated hypoechoic intra-abdominal mass and histological diagnosis must be established as soon as possible.
- Serum LDH levels were very high in patients with large and multiple tumour sites involvement but decreased as the tumour mass regressed.

5.5 Recommendations

- Follow up abdominal ultrasound should be done after one month of treatment in order to assess early response to chemotherapy.
- A bigger study should be done to comprehensively assess the role of ultrasound and serum LDH levels in follow up and determination of prognosis in BL patients.
CHAPTER ONE

INTRODUCTION

1.0 Background

Burkitt's lymphoma (BL) was described more than five decades ago by Dr. Denis Burkitt in Uganda.\(^1\) However Sir Albert Cook, a missionary doctor in Uganda in 1887, had reported seeing children with similar features earlier. Burkitt's lymphoma is a cancer of the lymphatic system in particular, the B-lymphocytes. BL is the fastest growing tumour known, with the tumour doubling in size within 24hrs. Burkitt lymphoma is a monoclonal proliferation of B-lymphocytes characterized by small noncleaved cells that are uniform in appearance and that produce a diffuse pattern of tissue involvement. Under the microscope, Burkitt lymphoma is characterized by the presence of a "starry sky" appearance, imparted by scattered macrophages with phagocytes cell debris. BL is genetically characterized by a chromosomal translocation that results in deregulation of the c-myc oncogene.\(^2,3\)

There are several forms of BL according to its geographic distribution, incidence magnitude, immunology and risk factors. Endemic BL (eBL) is the disease originally described by Burkitt and largely found in Africa, characteristically affecting the facial skeleton in children between two to nine years. 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. The third subtype of BL is association with HIV infection. The unifying characteristic in all patients with BL is the unique morphology and the chromosomal translocation involving the myc oncogene, irrespective of geographical location and immunodeficiency status.

In Uganda, Burkitt's lymphoma commonly occurred in low lands where malaria commonly occurs and is rare in mountainous areas.\(^1\) However with the current climatic changes the situation could be changing.

The male to female ratio is 2:1 in Uganda; it is most frequently seen in the 5-9 years age group and rarely occurs below the age of two years or in the adults. Burkitt's lymphoma represents 50-70% of childhood malignancies in Uganda. Seventy-two percent of patients clinically present with facial swellings involving the mandible or maxilla. The facial swelling is painless and
grows rapidly destroying the eye and displacing the teeth. The second common presentation is abdominal swelling due to enlarged glands or abnormal organs such as the kidneys, the ovaries or the liver.\textsuperscript{4,5} It may present with sudden flaccid paralysis of the lower limbs due to cord compression by the tumor. Superficial glands are rarely involved.

Ultrasound imaging is potentially a very useful investigative modality in diagnosis of Burkitt’s lymphoma since it is available in most institutions. It’s cost effective, noninvasive, capable of imaging multiple abdominal organs, may be used to guide biopsy, can be used to assess early response hence prognosis, and the results are immediately available. Ultrasound can demonstrate tumour size before and after initiation of chemotherapy, the location and relationship between tumour and normal organs and the presence of ascites. This information is important if either surgical debulking or a second line combination of chemotherapy is to be considered.

The characteristic findings in abdominal Burkitt’s lymphoma are of a well defined solid hypoechoic mass that causes tissue displacement rather than invasion; they lack calcifications and are avascular on colour doppler study.

Burkitt’s lymphoma is an important clinical entity, since it is curable provided that there is early diagnosis and prompt treatment with chemotherapy.

This study has provided the descriptive information on the abdominal sonographic findings in patients with BL as well as highlighting the early response to treatment. This is aimed at identifying patients who may be at risk of non-response or relapse in order to design appropriate therapy, hence improving the prognosis.

1.1 Problem Statement

The endemic Burkitt’s lymphoma is the commonest childhood cancer in sub-saharan Africa. Endemic Burkitt’s lymphoma represents 50-70\% of childhood malignancies in Uganda.

About 300 new cases of Burkitt’s lymphoma are seen at the UCI annually. Clinically, 72\% of the patients present with facial swellings involving the mandible or maxilla. Abdominal Burkitt’s lymphoma accounts for 56\% and the central nervous system involvement 30\%.\textsuperscript{4,5}
Aywak et al 2004 ⁹ showed that in BL the disease extent radiologically is more extensive compared to clinical evaluation alone.

By determining the tumour site and size, the clinicians can then select those patients who can benefit from surgical debulking before chemotherapy since it has been shown that abdominal tumour that has been resected up to 90% carries a good prognosis like that of a patient with stage A of the disease.¹⁰

Early diagnosis and prompt treatment with chemotherapy leads to good outcome; the majority of patients are cured hence good prognosis. Ultrasound imaging is a very useful auxiliary investigative modality in diagnosis of Burkitt’s lymphoma since it can demonstrate tumour location and size and the relationship between tumour and normal organs. There is no recent update on the role of abdominal ultrasound in the management of BL in Uganda. In addition to the descriptive features of the disease, ultrasound could provide staging and treatment- response information.

1.2 Justification of the study

Endemic Burkitt’s lymphoma is the commonest childhood cancer in Uganda. Burkitt’s lymphoma is highly chemo-sensitive especially to the current combined drug therapy. About three hundred (300) new patients with confirmed BL are seen annually at the UCI-Mulago hospital. Disease stage at presentation is a very important prognostic factor. Patients presenting with abdominal resectable BL can undergo resection for down staging of the tumour with dramatic improvement in prognosis similar to those in stage A of the disease. Abdominal sonography could be a very useful tool in detecting potentially resectable tumour. This study describes the abdominal sonographic findings in patients with BL and looks at early response to treatment with the aim of improving the prognosis. This is important because ultrasonography is the commonest imaging modality available in most health facilities and it is cost effective.
1.3 Research Question

What are the common abdominal sonographic features of Burkitt’s lymphoma in patients seen at the Uganda Cancer Institute - Mulago Hospital?

1.4 Objectives of the study

1.4.1 General objective:

To describe the abdominal sonographic features of Burkitt’s lymphoma in patients at the Uganda Cancer Institute at diagnosis and after one month of treatment.

1.4.2 Specific Objectives and aims of the study:

i. To describe the abdominal sonographic features of BL in patients seen at UCI-Mulago hospital.

ii. To describe the abdominal sonographic findings in relation to the clinical features in patients with BL at UCI.

iii. To describe the laboratory findings in patients with BL at UCI.

iv. To describe the changes in abdominal sonographic findings following initial treatment with chemotherapy.
CHAPTER TWO

LITERATURE REVIEW

In 1967, the World Health Organization (WHO) defined BL as recognizable histopathological entity with distinct pathological and clinical features. Microscopically, the tumor is composed of homogeneous immature B-lymphocytes. Within the nuclei, there are 3-5 distinct nucleoli and granular chromatin. There are microphages intervening in myriads of neoplastic cells resulting in the so called “starry sky” appearance.  

![Image: Classical microscopic appearance of Burkitt's lymphoma. Haematoxylin- and eosin-stained section showing a diffuse population of intermediate-sized cells with scattered macrophages.]

2.0 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, immunology and risk factors. 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 cofactor has been described. A third subtype of BL has been proposed based on its association with HIV.  

2,3,6
2.1 Clinical characteristics:

The unifying characteristic in all patients with BL is the unique morphology and the chromosomal translocation involving the Myc oncogene, irrespective of geographical location and immunodeficiency status. In this region eBL is the predominant subtype of BL, presenting as jaw swelling in 72%, abdominal tumours in 56% and as central nervous system tumours as a primary presentation in 30% of cases. Children aged between two and nine years typically have the characteristic facial tumour shown in Figure 2.

![Figure 2: Five-year-old boy with the typical jaw tumour of BL. (Source: Ugandan Cancer Institute, Kampala, Uganda with permission from guardians)](image)

Despite the typical clinical features exhibited by the disease in Africa (Figure 2), accurate diagnosis still rests with tissue examination as standard for the diagnosis of non-Hodgkin’s lymphomas.

2.2 The burden of Burkitt’s lymphoma in Uganda:

BL which is endemic in Africa affects mainly children, and boys seem to be more susceptible than girls (Fig.3).
Data from Globocan 2002 has been used to estimate the proportional contribution of different cancer sites among children aged 0-14 years in the Kyadondo County, Uganda for 1993-1997 (Fig. 4). The most common malignancy was Kaposi sarcoma accounting for 29% of all cancers, followed by BL accounting for 20% of all pediatric cancers and in third position all other lymphomas accounting for 15% of all cancers.
2.3 Risk factors for Burkitt’s lymphoma:

EBV

Epstein Barr Virus (EBV) is a lymphotrophic gamma human herpes virus widely spread among humans, and was the first virus to be associated with a human tumour. In Uganda, children with higher baseline titers to EBV antigens are at a higher risk of developing BL.6

Malaria

Although P. falciparum is not considered as an oncogenic agent, its role in the development of BL has been suggested by the shared geographic distribution of eBL and holoendemic malaria. Both diseases show highest incidence rates in the lymphoma belt or malaria belt, an area around the equatorial Africa (+/-10°) where average temperature exceeds15.5°C and have yearly rainfall higher than 50 ml. Reduction of BL incidence was observed in areas where malaria was eradicated.

HIV

BL has been reported as a common neoplasm in HIV infected patients, but not in other forms of immune suppression. HIV associated BL display an activation of c-myc by chromosome translocations that show structural similarities to those found in patients with sporadic BL.6

Socioeconomic factors

The impact of socioeconomic factors in the distribution and clinical characteristics of BL is unclear: poverty lowers the age of initial EBV infection, and early exposure to EBV could be a trigger for BL development.11 Low socioeconomic factors may be associated with a poor defense response toward environmental exposures due to poor nutrition and/or poor hygienic conditions.

Herbal exposure

The sap of the milk bush (Euphorbia tirucalli spurge) and other Euphorbiaceae species are possible environmental risk factors for BL due to their ability to activate the viral replication cycle in the latent phase of EBV-infected cells.6
2.4 Diagnosis of BL in Africa:

BL is the fastest growing tumour known, with the tumour doubling in size within 24 hrs. Despite the typical clinical features exhibited by the disease in Africa (Figure 2), accurate diagnosis still rests with tissue examination as standard for the diagnosis of non-Hodgkin’s lymphomas.\textsuperscript{11,12} The methods commonly employed in obtaining tissue for diagnostic purposes include:

- Excisional biopsy
- Cytological methods such as touch preparation and fine needle aspiration (FNA)
- Cytocentrifuge of body cavity fluids.

Each of these procedures has its advantages and disadvantages depending on the circumstances which are often dictated by the clinical setting.

Excisional biopsy has the merit of providing sizeable tissue samples for histology and allowing for further advanced tests such as immunohistostaining. It also allows for the storage of pathological material which may be useful for later review.\textsuperscript{7} The disadvantage is that there is need for surgery, which is costly and which requires skills and theatre may not be readily available. Further, patients must present early and in very good general health. Cytological investigations, on the other hand, can lead to diagnosis using body cavity fluids or aspirate samples from an accessible tumour mass. In patients with a rapidly progressive disease, a cytological sample could be obtained by fine needle biopsy of an accessible mass for confirmatory diagnosis. This may be useful in HIV-associated BL, which can present as a systemic disease.

2.5 Role of ultrasound in diagnosis of African BL

Determination of the anatomical sites and extent of organ involvement with malignant lymphoma is particularly critical before therapy. The endemic BL (African type) characteristically involves the mandible or maxilla but other facial bones and the abdominal organs e.g. liver, spleen, distal ileum, cecum, ovaries, kidneys are affected.
Ultrasound imaging is potentially a very useful investigative modality in diagnosis of Burkitt’s lymphoma since it is available in most institutions. It’s cost effective, noninvasive, and capable of imaging multiple abdominal organs for clinically suggested lymphomatous involvement and the results are immediately available. Ultrasound can demonstrate tumour size and location and the relationship between tumour and surroundings as well as presence of ascites. This information is important if either surgical debulking or radiation therapy is to be considered and also for predicting the likely prognosis.\textsuperscript{7,8,9}

Within the abdomen, any viscera may be involved. The alimentary tract may be involved with intraluminal masses that may present with features of intestinal obstruction. Small lymphoma deposits may involve the liver where they appear as hypoechoic, avascular lesions radiologically. Retroperitoneal glands and suprarenals can be involved. The ovaries are commonly affected and may clinical present as abdominal mass.\textsuperscript{7}

Renal involvement of Burkitt’s lymphoma appears well defined solid hypoechoic lesions that causes tissue displacement rather than invasion; they lack calcifications, are solid and avascular on doppler. In this way renal cell carcinoma and angiomyolipoma can be excluded.\textsuperscript{8}

In a study done by Thomas H. Shawker, et al abdominal ultrasound findings were compared with clinical, surgical and other radiological findings. Ultrasound was able to distinguish between renal lymphoma and hydronephrosis. By locating and quantifying tumour mass and distinguishing between renal lymphoma and hydronephrosis, ultrasound proved to be clinically useful in the management of this disease.\textsuperscript{7}

A study done by Juri V et al demonstrated that ultrasonography is capable of imaging of multiple abdominal organs for clinically suggested lymphomatous involvement.\textsuperscript{8}

In a study done by A. Aywak et al; clinical and radiological findings were compared in 49 patients with BL in the age range 2 to 14 years. It was concluded that the disease extent on radiological examination was more extensive compared to clinical evaluation alone.\textsuperscript{9}

In a study by Magrath et al ultrasound was used to localize and determine the abdominal tumour sizes. Patients who had masses of widest diameter 10cm and above were randomly selected to undergo complete or partial resection or biopsy only before chemotherapy. A highly significant
difference in the proportion of patients achieving a sustainable durable remission and a significant difference in survival was seen in patients who had complete resection than in other groups.\textsuperscript{10}

2.6 Role of surgery in BL:

Surgical debulking is an accepted successful treatment modality for Burkitt's lymphoma. It also improved survival for patients with Burkitt's lymphoma by down staging the disease \textsuperscript{10,11,12}. Tumor burden is an important predictor of survival in patients with BL. Large tumour masses of more than 10cm in diameter at presentation are associated with high serum LDH levels.\textsuperscript{13,14,15} Surgical debulking is associated with subsequent decreased LDH levels, which gives better prognosis.

2.7 Staging of BL:

According to the Ziegler's clinical staging, endemic BL is staged as follows:

- A - Localised extra-abdominal mass
- B - Two or more extra-abdominal masses
- C - Intra-abdominal tumor, with or without facial bone involvement
- D - Intra-abdominal tumour with multiple extra-abdominal sites
- AR - Stage C, but with more than 90% of intra-abdominal tumor resected

The prognosis is better in stages A and AR. Those in stage D have the worst prognosis.\textsuperscript{16}

The basic evaluation of BL for staging includes clinical evaluation with medical history, physical examination supplemented by imaging studies (X-rays of the jaw, chest X-ray) and abdominal ultrasound. For staging purposes laboratory investigations should include complete blood counts, bone marrow aspirate with or without biopsy, cerebrospinal fluid analysis, blood chemistry (liver function tests, renal function tests), lactate dehydrogenase and uric acid and electrolytes. Routine stool and urine examinations should also be done. Routine counseling and testing for HIV is advisable for all patients.
2.8 Treatment of BL:

Burkitt lymphoma is a very fast growing tumor. Systemic chemotherapy is the treatment of choice for this aggressive disease in all its stages. The overall survival rate of Burkitt lymphoma depends upon the stage of the disease at initial diagnosis. Patients with localized disease respond well to chemotherapy and have an excellent survival rate. Patients with disseminated disease respond less well to chemotherapy and have a less favorable survival rate. Cyclophosphamide therapy alone has been curative for 80% of children from Africa with localized (early stage) disease. However, combination chemotherapy has markedly improved treatment results, particularly in patients with extensive disease.\(^\text{17}\)

For patients with limited disease, including localized extra-abdominal or completely resected abdominal disease, a long-term survival rate greater than 90% can be achieved with combination chemotherapy.\(^\text{10,11,12}\) Chemotherapy combinations include the following:

- COM - Cyclophosphamide + vincristine (Oncovin) + methotrexate.
- Adriamycin + Cytarabine Arabinosine
- CHOP - A similar regimen as (COM) using doxorubicin in place of methotrexate
CHAPTER THREE

METHODOLOGY

3.0 Study design and duration:

This was a series of cases collected in a period of six months. Permission was granted from the institutional review board. The consecutive patients who were histologically proven to have BL and met the selection criteria underwent abdominal ultrasound scanning before starting chemotherapy and after one month of treatment.

3.1 Study setting:

The study was conducted from the Uganda Cancer Institute and Department of Radiology of Mulago National Referral and Teaching Hospital. The Uganda Cancer Institute is the only centre with specialized cancer treatment facilities for both children and adults in the country. It receives referrals from other units of the Mulago hospital, all regional and district hospitals in the country.

3.2 Study population (Participants):

These were patients with histologically confirmed diagnosis of Burkitt’s lymphoma seen at the Uganda Cancer Institute – Mulago Hospital who fulfilled the study criteria and presented within the period of the study.

3.3 Inclusion criteria:

Patients with new histologically confirmed BL who were seen at UCI within the study period and consent to participate in the study.

3.4 Exclusion criteria:

Patients with relapsed BL

Patients with proven co-morbidities like TB or other intra-abdominal malignancies.
3.5 Study Variables:

Data was collected using a standardized formatted questionnaire on the following:

- Social demographics which included: Age at onset of symptoms of Burkitt's lymphoma, gender, Geographical location (County and District of origin), Tribe.

- The chief complaints of the patient as reported by the caretaker which included: presenting site of tumour, duration of symptoms, abdominal pain, distension and the physical findings on examination.

- Results of other radiological investigations done in some patients i.e CXR, IVP, CT Scan, Myelography and Barium studies.

- Laboratory results of serum lactate dehydrogenase (LDH), RFT's, LFT's, WBC counts, Haemoglobin levels, Platelet counts, cerebral spinal fluid (CSF) analysis, and HIV serology.

- The abdominal sonographic features assessed were: Location of the tumour masses, the size, whether focal or diffuse lesion, solitary or multiple, the echogenicity of the mass and echopattern of the abdominal organs; liver, spleen, kidneys, pancreas and ovaries.

On follow up visit after 4 weeks:

- The clinical, abdominal sonographic features and laboratory tests were re-assessed after one month of induction with chemotherapy.

3.6 Sampling criteria:

The populations under study were patients with histologically proven Burkitt's lymphoma. Consecutive sampling was used for all the patients who satisfied the inclusion criteria.
3.7 Data Collection Procedure:

3.7.1 Recruitment procedure:

All patients were recruited from the UCI basing on the inclusion criteria. Consent was obtained from the parent/guardians of the patient for enrollment in the study. The advantages and disadvantages of the abdominal ultrasound examination were explained to the patient, parent/guardian, and then a thorough physical examination was done.

3.7.2 Ultrasound scanning procedure:

The scanning was done in the department of radiology. Prior preparation was done which included both physical and psychological preparation; the patient was required to have a full urinary bladder whenever possible. This acts as an acoustic window for visualization of pelvic organs. Any previous radiological investigations were reviewed. The ultrasound machine Sonace (Medson) SA9900 with Doppler capacity was used. This machine has a 3.5-5MHz (low frequency) curvilinear probe for abdominal and pelvic scanning and 6.5-12 MHz (high frequency) linear probe for superficial structures and bowel.

The patient was positioned in the supine position. Coupling gel was then applied to the abdomen and scanning was done in both transverse and longitudinal planes starting from the midline to visualize the abdominal viscera. The cranio-caudal length of the liver was measured in the right mid clavicular line; 12cm was taken as the upper normal limit. The spleen size was determined by measuring the greatest distance between its superior and inferior poles, 12cm was taken as the upper limit for a normal spleen. The kidneys were scanned in both sagittal and coronal planes. The bowel loops were assessed and normal small bowel wall thickness was taken to be 3 mm. The patient was turned to the lateral oblique, decubitus, sitting or prone positions to improve on the visibility of the abdominal structures. Ultrasound images taken were saved as hard copy print on thermal paper after being reviewed by the supervisors and a back up copy was saved on the ultrasound machine memory. A written report was then prepared and forwarded to the clinicians. Follow up scans were done after one month of treatment using the same technique and ultrasound appearances i.e size of the masses, and echopattern noted. The information obtained was then filled into the data sheets.
The UCI laboratory within Mulago hospital was used to carry out the laboratory tests as part of pre-chemotherapy work up.

Other radiological investigations like CXR and CT Scan examinations were ordered by the attending clinicians to exclude co-morbidities.

3.8 Data management and Analysis:

Data was collected using a pre-coded questionnaire by the investigator; a data base was created in EPI-DATA V.3.0 software. The data was cleaned and double entered to make sure there were no errors. The data was then exported from EPI-DATA to STATA V.10 for analysis. The data was analysed with the help of a statistician. Numerical data was expressed as means, medians and categorical variables as frequencies and percentages.

The following data was analysed;

- The age and sex distribution of BL
- Geographical distribution of BL
- The clinical and abdominal sonographic findings of the disease
- The abdominal sonographic findings versus serum levels of lactate dehydrogenase before and after one month of treatment.
- The abdominal sonographic and laboratory findings before and after one month of treatment.

3.9 Quality control:

Data collection forms were pre-tested and standardized before commencement of the study.

Data collection forms were checked and edited for completeness at the end of each day.

All patients were clinically examined and abdominal ultrasound scanning was done. The ultrasound images were reviewed by the supervisors before the report would be forward to the clinicians.
3.10 **Ethical Issues:**

Approval was sought from the Department of Radiology, Mulago Hospital Research and Ethics Committee, Faculty of Medicine Research Committee and the National Council of Science and Technology.

An informed consent was obtained from the patients, parents/ guardians of the participants and for children above 8 years an assent was obtained. Failure to consent did not in any way affect patients’ management. To ensure confidentiality, code numbers were used.

3.11 **Study limitations:**

- Irregular supply of free anti cancer drugs leading to high rates of defaulters.

- Most cases were out patients because of limited ward space and they did not attend the scheduled visits for review probably due to lack of transport.

- BL is associated with high mortality rates and as such some patients died before follow up ultrasound scan was done.

- Some patients were too sick to be moved to the Department of Radiology for an ultrasound scan.

- Failure to ascertain the anatomical origin of the mass at ultrasound especially if huge.

- Unsuspected co-morbidities.

3.12 **Dissemination of results:**

The results will be disseminated to the Department of Radiology and the Faculty of Medicine Research committee, Mulago Hospital Research and Ethics Committee, Uganda Cancer Institute, Ministry of Health, Sir Albert Cook Library- Makerere University, School of Post graduate studies- Makerere University and selected journals for publication.
CHAPTER FOUR

RESULTS

In this study, sixty patients who had histologically confirmed Burkitt’s lymphoma were enrolled. The majority of the patients were children.

4.0 Baseline characteristics of the study participants:

4.1 Socio-demographic characteristics:

The study patients consisted of 43 (72%) males and 17 (28%) females with an age range of 3-18 years and median age of 6.5 years. The peak incidence was between 5-9 years as shown in graph 1 below. The male to female ratio was 2.5:1. The majority of the patients were from the eastern region 26 (43.3%) followed by the central region 21 (35%) and the least were from the northern region 2 (3.3%).

4.2. Clinical Characteristics and Physical Examination Findings of Participants:

All patients were staged according to the Ziegler’s clinical staging criteria for endemic BL. Of the 60 cases, 13 (21.7%) were in stage A, 2 (3.3%) were in stage AR, 6 (10%) were in stage B, 7 (11.7%) were in stage C and 32 (53.3%) were in stage D as shown in graph 2 below. Clinically 31 (51.7%) patients had features of abdominal tumour while 44 (73.3%) patients had evidence of BL elsewhere in the body. Of these patients with extra-abdominal symptoms the commonest sites involved were the facial bones- including the maxilla, mandible and orbits in 42 (70%) patients.

The most common single presenting symptom was abdominal masses with pain in 15 (25%) patients followed by unilateral mandibular swelling in 11 (18.3%) patients, 6 (10%) patients had maxillo-orbital tumours. The least complaints presented were abdominal pain alone, scalp mass, headache and peripheral lymph node enlargement which involved 1 case (1.6%) each.

The other common clinical findings at the time of presentation were hepatomegally, splenomegaly, ascites, proptosis and pallor as shown in table 1. The duration of symptoms at presentation ranged from 1-32 weeks with an average of 8 weeks.
Patients with facial tumours presented earlier than those with abdominal symptoms as shown in graph 3.

*Figure 5: Age distribution of the study participants. The peak incidence was between 5-9 years.*

*Figure 6: Clinical stage of patients at presentation (Ziegler’s Classification)
Most of the patients presented with stage D disease and therefore had poor prognosis at presentation.*
<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain and swelling</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Unilateral mandibular tumour</td>
<td>11</td>
<td>18.3</td>
</tr>
<tr>
<td>Both maxilla and orbital tumour</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Unilateral maxilla tumour</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Bilateral maxilla tumour</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Abdominal swelling</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Maxilla and mandibular tumour</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Orbital tumour</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Abdominal and mandibular tumour</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Abdominal and maxillo-orbital tumour</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Bilateral mandibular tumour</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Bone pain</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Scalp tumour</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Peripheral lymph nodes</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The commonest presenting symptoms were palpable abdominal masses with pain followed by mandibular tumour and maxilla-orbital masses. Headache and peripheral lymph node enlargement were rare symptoms.
Figure 7: Presenting symptoms Versus the duration of symptoms for the study patients:

Most patients with facial tumours presented earlier than those with abdominal symptoms. Facial tumour in this study includes the maxilla, mandible and/or orbital tumours.

4.3 Abdominal ultrasound findings:

The most common sonographic findings were abdominal lymphadenopathy. These predominantly involved the para aortic areas. Other sites included the porta hepatis, splenic hilum and mesenteries. Only one patient had peripheral lymphadenopathy involving the inguinal region.

Diffuse hepatosplenomegally was also a common finding among the patients however, well defined solid hypoechoic masses were seen in the liver in 5 (8.3%) patients and also in the spleen in 13 (21.7%) patients. Sonographically 22 (36.6%) patients had renal involvement, twenty of these had discrete rounded hypoechoic renal masses and two had bilateral diffuse renal enlargement. One patient had unilateral hydronephrosis due to tumour compressing on the renal pelvis. Most of the abdominal masses were solid and heterogeneously hypoechoic. This study found 6 (15%) cases with ovarian masses at ultrasound. These masses were large solid heterogeneous hypoechoic and associated with massive ascites.

Most of the abdominal lymphnodes were along the para-aortic areas in 24 (75%) patients. Other sites involved were the porta hepatis, splenic hilum and mesenteries.
Most of the abdominal lymphnodes were along the para-aortic areas in 24 (75%) patients. Other sites involved were the porta hepatitis, splenic hilum and mesenteries. These nodes were mainly heterogeneous hypoechoic.

4.4 Other imaging findings:
Chest radiographs revealed abnormalities related to Burkitt’s lymphoma in 21(35%) patients. Pleural effusions and hilar adenopathy were the most common abnormalities; they were present in nine patients each. Pleural effusions were bilateral in nine patients while in one patient the effusion was limited to the right side. All the pleural effusions were associated with ascites apart from the one which was unilateral. Nine patients had bilateral hilar adenopathy and two patients had both bilateral pleural effusions with hilar adenopathy. In addition, soft-tissue neck and axillary masses were visible on chest radiograph in one patient. No lung parenchymal lesions were seen.

CT Scan was done for three patients who presented with maxilla-orbital tumours and it showed destructive osteolytic lesions involving the maxilla antrum and orbital walls, one patient had intracranial extension.

4.5 Laboratory findings at base line:
Positive HIV serology was found in only one patient (1.7%), 50 (83.3%) patients were negative and in 9 (15%) patients the status was unknown.
Fifty two (86.7%) patients had abnormal renal function tests and 51 (85%) patients had abnormal liver function tests.
Twelve (20%) patients had abnormal CSF results. The common laboratory findings were pleocytosis and tumour cell presence in CSF.
All patients had some degree of anaemia at presentation and the serum LDH levels were high. The LDH levels were highest in patients with large tumour size and disseminated disease as shown below.
Table 2: Abdominal sonographic findings (n=40)

<table>
<thead>
<tr>
<th>Sonographic findings</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy</td>
<td>32</td>
<td>80</td>
</tr>
<tr>
<td>Hepatomegally</td>
<td>26</td>
<td>65</td>
</tr>
<tr>
<td>Splenomegally</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Renal masses</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Ascites</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>Splenic masses</td>
<td>13</td>
<td>32.5</td>
</tr>
<tr>
<td>Mass involving bowel</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>Ovarian masses</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Hepatic masses</td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>Pancreatic masses</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>Diffuse renal enlargement</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Stomach lesion</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The most common sonographic findings were lymphadenopathy and diffuse hepatosplenomegaly, the least finding was a mass infiltrating the stomach wall.

Table 3: Laboratory findings: Full haemogram and LDH levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin level (normal range=12-17g/dl)</td>
<td>9.1</td>
<td>2.47</td>
</tr>
<tr>
<td>WBC count (normal range=4-11x10⁹/l)</td>
<td>7.7</td>
<td>4.06</td>
</tr>
<tr>
<td>Platelet count (normal range=150-400x10⁹/l)</td>
<td>316</td>
<td>133</td>
</tr>
<tr>
<td>Serum Lactate Dehydrogenase level (normal range=133-250IU/L)</td>
<td>975</td>
<td>822</td>
</tr>
</tbody>
</table>

All the patients had some degree of anaemia at presentation and LDH levels were high.
All the patients had some degree of anaemia at presentation and LDH levels were high.

Figure 8: Variation of LDH levels with Tumour size. LDH levels showed significant correlation with tumour size.

Figure 9: Variation of LDH levels with clinical stage of the disease.

Serum LDH levels were lowest in patients with localised disease and highest with disseminated disease.
4.6 Follow up results:

Of the 60 patients recruited 11(18.3%) patients died within the first one month before the follow up scan was done, 9 (15%) patients were lost to follow up and 40 (66.7%) patients had the follow up abdominal scan and were discharged from the study.

4.6.1 Abdominal ultrasound findings at follow up.

Of the 40 patients who had follow up abdominal ultrasound scan, 30 (75%) patients had tumour remission and 10 (25%) had residual tumour present after 1 month of treatment. The organs that were involved with residual masses are as shown below in table 4.

The other abdominal ultrasound findings were diffuse hepatomegally in 17 (44.7%) cases, splenomegally seen in 16 (42.1%) cases and ascites which was found in 2 (5%) of the patients.

4.6.2 Laboratory findings at follow up.

Most of the patients had leucopenia, thrombocytopenia and severe anaemia that required blood transfusion. The serum LDH levels were significantly low as shown below in table 5.

Other laboratory findings were renal function tests (RFT) which were abnormal in 39 (97.5%), and liver function tests (LFT) were abnormal in 40 (100%).
Table 4: Organs with residual masses (n=10)

<table>
<thead>
<tr>
<th>Organ involved</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Spleen</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Ovaries</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal lymph nodes</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Bowel loops</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

*Residual masses were mainly seen in the liver, spleen, ovaries and lymph nodes.*

Table 5: Laboratory findings at follow up; Full haemogram and LDH levels.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin level</td>
<td>8.2</td>
<td>1.86</td>
</tr>
<tr>
<td>Normal range (12-17g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td>4.1</td>
<td>1.26</td>
</tr>
<tr>
<td>Normal range (4-11x10⁹/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>208</td>
<td>80.2</td>
</tr>
<tr>
<td>Normal range (150-400x10⁹/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Lactate dehydrogenase</td>
<td>400</td>
<td>183</td>
</tr>
<tr>
<td>Normal range (133-250 I/U/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Most of the patients had leucopenia, thrombocytopenia and severe anaemia. The serum LDH levels were significantly low after one month of treatment.*
ILLUSTRATIONS

SALIENT FEATURES SEEN AT ABDOMINAL ULTRASOUND

Figure 10: Nine years old female who presents with gross abdominal distension for 12 weeks. Large heterogeneous hypoechoic masses were seen arising from the pelvis bilaterally most likely of ovarian origin with ascites.

Figure 11: Fourteen years old female who presented with large lower abdominal masses for 14 weeks. Had huge heterogeneous hypoechoic masses arising from the pelvis bilaterally with some ascites.
Figure 12: Nine years old female who presented with bilateral mandible swellings for 8 weeks.

Ultrasound showed multiple hypoechoic masses in the spleen with bilateral pleural effusions.

Figure 13: i. Five years old female who presented with maxillo-orbital tumour, jaundice and abdominal pain for 8 weeks. She had a heterogeneously hypoechoic mass compressing on the right renal pelvis causing unilateral hydronephrosis. The mass had some calcifications, an unusual finding.
Figure 13(ii). Same patient as above, a hypoechoic mass was seen at the neck of the gall bladder compressing on the cystic duct. The intrahepatic ducts were not dilated.

Figure 14: Six years old male patient who presented with right maxilla swelling and palpable abdominal masses. Abdominal ultrasound showed large intraperitoneal and retroperitoneal heterogenously hypoechoic masses.
Figure 15: Four years old male who presented with right maxillo-orbital tumour for 3 weeks. Abdominal ultrasound showed multiple hypoechoic masses at the splenic hilum and para aortic masses.

Figure 16: 6 years old patient who presented with bilateral mandibular swellings for 3 weeks. Abdominal ultrasound showed bilateral hypoechoic renal masses with some ascites.
CHAPTER FIVE

DISCUSSION

There is limited data on the role of abdominal ultrasound in the management of Burkitt’s lymphoma in Uganda. This study has highlighted the major clinical relevancy and role of abdominal ultrasound in the management of BL in Uganda. The study highlights the salient ultrasound imaging findings in patients with BL and also its role in follow up of these patients.

In less developed countries where CT Scan and MRI are not available and even when available are not affordable, abdominal ultrasound remains an important tool available for staging and follow up of BL patients. Ultrasound imaging has the advantage of being available in most institutions, cost effective, noninvasive, capable of imaging multiple abdominal organs, guiding biopsy, assessing early response hence prognosis, and the results are immediately available.

5.1 Demographic characteristics:

The peak incidence was between 5-9 years with a male to female ratio of 2.5:1. Similar findings were noted in previous work done here in Uganda.\textsuperscript{4,5} However a study done in Kenya showed a peak incidence of 5-7 years and M:F ratio of 2.3:1.\textsuperscript{9} This difference in peak incidence could possibly be due to the fact that their study patients were younger with age range 2-14years. There is no logical explanation that can be given for the difference in sex distribution but other studies in Uganda, Kenya, Nigeria and India also showed a male preponderance.\textsuperscript{4,5,9,18,20}

The majority of the patients were from the eastern and central regions. This could be explained by a number of factors; the proximity of these regions to Mulago Hospital where the treatment centre is found, these regions lie within the equatorial belt where malaria is holoendemic, but also according to the Uganda national demographic and health survey 2006 there were high poverty levels in some parts of Buganda and Busoga regions.\textsuperscript{21}

The majority of the patients 32 (53.3%) presented in stage D of the disease, this meant that the prognosis in most of the patients was poor even before starting chemotherapy. Similar findings were noted by the studies in Nigeria and India.\textsuperscript{18,20} This could possibly be due to lack of awareness and the high poverty levels in the communities.
5.2 Clinical findings:

The present study revealed that endemic BL still presented commonly with facial bone tumours involving the mandible, maxilla and orbital bones in 42 (70%) patients. However, the single commonest presenting symptom was palpable abdominal masses with abdominal pain in 15 (25%) cases. Unilateral mandible tumour was the commonest facial lesion accounting for 11 (18.3%) cases followed by maxilla-orbital and unilateral maxillary tumour in 6 (10) cases. The study done by Aywak et al in Kenya found palpable abdominal lymphoma in 30.6% of the patients and the commonest facial involvement as unilateral maxilla at 8.2% followed by unilateral mandible at 4.1%. Bosco Jie et al in India studied 19 patients and found 14 (73.7%) with palpable abdominal masses, 9 (47.4%) with peripheral lymphadenopathy and 6 (31.6%) with maxillo- mandibular swelling. These findings were consistent with our findings apart from the peripheral adenopathy which we found in one patient who was HIV seropositive.

Clinically twelve cases presented with hepatomegally, 10 patients had splenomegally, 2 patients had palpable renal masses and 6 patients had palpable abdominal masses which one could not clinically determine the anatomical site of origin.

CNS involvement is a well known feature of BL. Involvement of the brain and meninges is rare and was reported in few cases. Aywak found 5 (8.2%) cases with CNS involvement. In our study orbital and brain CT scan were done in 3 cases who had clinically presented with facial tumours, 3rd and 7th cranial nerve palsies and they showed destruction of maxillary bone and orbital walls and one patient had intracranial extension as well.

5.3 Sonographic findings:

Abdominal ultrasound was able to show evidence of lymphomatous involvement in 40 (66.7%) patients. The kidneys were the commonest affected abdominal organs accounting for 22 (36.7%) cases with enlarged kidneys and 20 (33.3%) with kidney masses. These masses were hypoechoic and avascular on Doppler interrogation. Twenty six (43.3%) cases were found to have hepatomegally and 5 (8.3%) cases had multiple nodular hypoechoic masses. Splenomegally was seen in 24 (40%) cases and 13 (21.7%) cases had focal nodular hypoechoic masses, 6 (10%) had ovarian masses. Previous studies have documented similar findings.
Renal involvement of BL is known and has been previously demonstrated at necropsy in African children. In a comparative study between American and African BL, discrete renal masses were reported in African cases as opposed to diffuse involvement in the American cases. In the present study, 22 (36.7%) cases had discrete renal masses sonographically. Diffuse renal enlargement was seen in two cases, one of them had also ureteric obstruction with hydrenephrosis. Tumour infiltration into the urinary bladder was not seen.

Bilateral hyperechoic ovarian masses were seen in 6 (10%) cases, this is comparable with the findings of Arseneau et al in the American patients with BL. Aywak found one patient with a pelvic mass arising from the ovary. No cases of testicular tumour was seen in the male participants in this study though other studies have reported them.

Retroperitoneal adenopathy has been reported in BL, indeed in the present study it was the commonest abdominal lesion seen on ultrasound. The enlarged lymph nodes were homogeneously hypoechoic. Peripheral adenopathy is extremely rare in African cases but common in the non endemic American cases. The present study found one case (1.7%) with peripheral adenopathy involving the cervical, axillary and inguinal areas.

Gastrointestinal system BL deposits were seen in 10 (16.7%) patients, however none of the cases presented with intestinal obstruction as reported in other studies.

5.4 Other imaging findings:

Our study found bilateral pleural effusion in 9 (43%) cases, one case had right sided pleural effusion these patients had normal sized hearts on chest x-rays. Nine (43%) cases had bilateral hilar adenopathy and one case had mediastinal adenopathy. No case was seen with parenchymal lung lesion. Involvement of thoracic viscera is known in BL, parenchymal lung lesions, pleural effusion and mediastinal adenopathy have been documented in American BL cases. In African cases no parenchymal lung lesion has been seen both radiologically and at necropsy.

CT Scan was done for three patients who first presented in the eye clinic with maxilla-orbital tumours, third and seventh cranial nerve palsies. The scans showed destructive osteolytic lesions involving the maxillary antrum and orbital walls with one patient having intracranial extension. These findings were similar to those of Aywak et al.
5.5 Laboratory findings:

HIV was not a major factor in the epidemiology of BL in the present study as was found in other studies. In our study 93% of the patients were HIV negative. The association between BL and HIV has been detected at lower rates in Africa as compared to that observed in the western world. Poor survival of children infected with HIV perinatally (only 34% survive to the age of 3 years) has been suggested as one of the explanations for the lack of association found in some studies.

Examination of the cerebrospinal fluid showed pleocytosis and tumour cells in 3 patients.

All the clinical stages of BL showed some degree of anaemia (mild for stages A, B, and moderate for stages AR, C and D). However the haemoglobin levels of some BL children in Northern Nigeria were reported to be within the normal reference range, and so were not clinically anaemic. The presence of anaemia in our patients could be related to their late presentation and therefore it is due to chronic inflammatory response. This can be attributed to the mediators of inflammatory response such as tumour necrotic factors (TNF), interleukin-1 (IL-1) and interferon (IFN) as mediators of anaemia in BL. It has been proposed that three processes are involved in the production of the anaemia of chronic disease; (1) a modest shortening in red cell survival creating a demand for increased cell production by the bone marrow (2) inability of the marrow to respond completely to this increased demand because of impaired erythropoietin production or impaired ability of the erythroid progenitors to respond to erythropoietin or both; and (3) impaired mobilization of iron release from the reticulo endothelial system (RES). Tumour necrosis factor, Interleukin-1 and the interferons have all been reported to inhibit erythropoiesis.

In our study, higher serum LDH levels were associated with higher leukocytes counts and lower platelet count. Patients with high LDH level (greater than 1000 U/l) presented with stage C and D of the disease and responded to treatment slowly, whereas those with lowest level (less than 500 IU/l) had early remission, similar findings were noted by Arseneau et al 1975. High serum LDH levels are associated with high total tumor burden. There is also good relationship between serum LDH level and the degree of dissemination of the neoplastic process. Following induction of chemotherapy serum LDH level decreases significantly. Estimation of serum LDH
may be helpful in evaluating the response to therapy. These associations need to be studied using a large sample size.

Since the liver has a large functional reserve which requires the destruction of about 75% of the liver mass before being overwhelmed, it is not surprising that only one patient presented with jaundice but no other features of hepatic insufficiency, though the liver function tests were mild-moderately deranged.

Renal decompensation commences only when more than 50% of nephron mass is lost. However, acute tumour lysis syndrome is a known severe complication of Burkitt's lymphoma before and during treatment and could have been responsible for most of the death that occurred.

5.6 Follow Up:

Of the 60 patients recruited 11 (18.3%) cases died within the first one month before the follow up scan, 9 (15%) patients were lost to follow up and 40 (66.7%) patients had the follow up abdominal scan and were discharged from the study. These findings could be explained by the various factors; late presentation, multiple tumour sites, and high tumour burden at presentation. Thirty two (53.3%) patients presented clinically with stage D disease. Most of our patients were from the low socioeconomic group living in rural areas, associated with a combination of factors such as poor nutrition, poor hygienic living conditions and abject poverty in the communities. The fact that most of the patients were treated as out-patients despite their clinical state due to limited bed space on the LTC ward and the inadequate supply of anti-cancer drugs whereby patients had to buy their own drugs from private pharmacies resulted in the high mortality and default rates. Other factors include the pattern of presentation which appears to be changing. Initially most cases of endemic BL presented with facial tumours but current studies in Kenya, Nigeria and India have shown predominant abdominal presentations in Burkitt's lymphoma. This has implications both in tumour detection, management, and outcome. The high incidence of abdominal tumours in the recent studies could be due to improved modern investigative modalities using ultrasound scanning and CT Scan. From this study it was noted that those who had facial tumours presented early to hospital as compared to those with abdominal masses possibly because the facial tumours are striking and disfiguring. Similar findings were noted in both the Nigeria and India studies.
On follow-up abdominal scan, 32 (80%) of the patients had their masses regressed within the first month of chemotherapy while in 8 (20%) patients residual masses were seen but had significantly reduced in size. Follow up renal sonography showed disappearance of the hypoechoic masses and hydronephrosis.

All the patients who had facial tumours at presentation had their masses significantly reduced after one month of chemotherapy but facial asymmetry was still evident.

Most of the patients had leucopenia, thrombocytopenia and severe anaemia requiring blood transfusion. The serum LDH levels were significantly low after one month of chemotherapy. Renal function tests (RFT) were abnormal in 39 (97.5%), and liver function tests (LFT) were abnormal in 40 (100%). This could be explained by the tumour lysis syndrome due to chemotherapy.

5.7 Conclusions:

- Abdominal ultrasound was able to demonstrate greater disease extent than clinical evaluation, thus highlighting the value of imaging in tumour staging and follow up of patients.
- This study showed more cases of abdominal BL involvement than previously seen in our patients, possibly due to better imaging facilities now.
- Burkitt’s lymphoma should be strongly suspected in a child presenting with large lobulated hypoechoic intra-abdominal mass and histological diagnosis must be established as soon as possible.
- Serum LDH levels were very high in patients with large and multiple tumour sites involvement but decreased as the tumour mass regressed.

5.8 Recommendations:

- Follow up abdominal ultrasound should be done after one month of treatment in order to assess early response to chemotherapy.
- A bigger study should be done to comprehensively assess the role of ultrasound and serum LDH levels in follow up and determination of prognosis in BL patients.
REFERENCES:


37


APPENDICES

Appendix 1 - Time table of the research events

The study was carried out over a period of six (6) months from March 2009 to September 2009.

<table>
<thead>
<tr>
<th>ITEM</th>
<th>ACTIVITY</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Submission of research proposal to the ethical bodies</td>
<td>2 weeks</td>
</tr>
<tr>
<td>2</td>
<td>Pre-testing the questionnaire</td>
<td>2 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Data Collection</td>
<td>3 months</td>
</tr>
<tr>
<td>4</td>
<td>Data Analysis</td>
<td>1 month</td>
</tr>
<tr>
<td>5</td>
<td>Report writing</td>
<td>3 weeks</td>
</tr>
<tr>
<td>6</td>
<td>Dissemination of results</td>
<td>1 week</td>
</tr>
</tbody>
</table>
Appendix 2- Consent form (English)

RESEARCH TITLE: THE ABDOMINAL SONOGRAPHIC FEATURES OF ENDEMIC BURKITT’S LYMPHOMA IN PATIENTS SEEN AT UGANDA CANCER INSTITUTE, MULAGO HOSPITAL- KAMPALA.

Principal investigator: DR. PASCAL KWITONDA MBchB (Mak)

RE: INFORMED CONSENT

Purpose of the study

My name is Dr. Pascal Kwitonda, a final year M. Med Radiology student. I am carrying out a study to evaluate the role of abdominal ultrasound in the management of endemic Burkitt’s lymphoma in patients admitted to the Uganda Cancer Institute- Mulago hospital. I request you to participate in this study by allowing enrollment of yourself/your patient into the study. If you accept to participate, you/your child will undergo the usual clinical examination, laboratory work up and the necessary radiological examinations including an abdominal ultrasound scan. The findings of these investigations will be used to contribute information to the research study and treatment of yourself/your patient.

Procedure

As part of routine care an abdominal ultrasound will be done on all patients with clinical or histologically confirmed Burkitt’s lymphoma before initiating chemotherapy and after one month of treatment.

Patient Preparation

No premedication will be required. The participant will be examined preferably after having nil by mouth for 4-6 hours and with a full bladder.

The participant will lie on the couch in supine position.
A little coupling gel will be put on the abdomen and different transverse, longitudinal and oblique scans will be done. The sono images captured will be printed on thermal paper and also stored in the machine for review.

A report will be issued out to the patient after reviewing the images with a senior radiologist and a carbon copy kept for my records.

Discomforts

Abdominal ultrasound is free of any side effects to the participant apart from mild discomfort. This discomfort is almost similar to what would be experienced during an abdominal palpation and also the participant may be asked to hold his/her breathe for a few seconds during the scanning procedure.

Benefits

The ultrasound examination will be free for all participants in the study; however for non participants and other patients the examination costs 10,000shs in the department of Radiology.

The study will benefit the participant in that it will guide the management of his/her condition. This study will in future be used by healthy policy makers to develop management guidelines for Burkitt’s lymphoma to be used by sonographers, sonologists and oncologists.

Compensation

The study subjects will not be paid any incentives for participating in the study nor will they be required to pay for the ultrasound scans.

Confidentiality

The questionnaire will only have a number, not the patient’s name and it will be stored in a secure and safe place. The information obtained will only be used for this research and communicated to the managing team and no one else without the patient, parent/guardian’s permission.
Patient's rights

The study participant is free to withdraw from the study at any point when inconveniences arise. Upon withdrawal, the study participant will not in any way be denied access to routine healthcare at the hospital.

Any further information I may need will be provided by Dr. Pascal Kwitonda, the principal investigator (Tel:0774007777) or the study supervisors namely;

Dr. Banyima R.K Tel:0772500680 (Dept of Radiology- Mulago Hospital)

Dr. Orem Jackson Tel:0782320543 (Uganda Cancer Institute-Mulago Hospital)

Dr. Ibingira C Tel: 0414530020 (Chairman-Faculty of Medicine Research Committee)

STATEMENT OF CONSENT

The purpose and nature of this study has been explained to me. I understand that all the information obtained from me / my patient will be treated confidentially. I am free to withdraw from the study any time without jeopardizing my routine healthcare and I have the right to know the results of scans done.

I understand that by signing this sheet I have given my informed consent that information derived from myself / my child be used in this study.

Signature/Thumbprint of the participant / parent / guardian..........................Date...............
Appendix 3 - Luganda Consent Form

FOOMU Y'OKUKKIRIZA KW'ANNEETABA MU KUNOONYEREZA

Nze ..................................................ntegezeddwa nti nsabibwa okwetaba /okukkiriza omwana wange okwetaba mu kunoonyereza okugenda okweyongera okumanya omugaso gwa scan eeyo lubuto (aka TV) mu kujjanjaba obulwadde bwa Burkitt’s Lymphoma mu balwadde abawereddwa ebitanda mu Uganda Cancer Institute-mu dwaaliro lye Mulago.

Singa nzikkiriza okwetaba /omwana wange okweetaba mu kunoonyereza kuno, omusawo ajja kumwekebejja nga bulijjo, omusaayi gujja kumuggybawko, era n’ebifananyi ebyectagisa bikubibwe nga kotadde ne scan eeyo lubuto( aka TV).

Ebirungi ebiri mukunonyereza kuno:

Ebinazuulibwa biggya kweyongera kuyamba n’okutaangazza okunoonyereza kuno, n’okujjanjaba abalwadde ba Burkitt’s lymphoma mu Uganda cancer institute. Essiringi omutwalo gummu zewaliwasulidde sikaani eno zigenda kusasulwa nze Dokita Pascal Kwitonda okusobola okuyamba omulwadde.

Obuzibu mukunonyereza kuno:
Sikaani terina ngeri yonna gyekosa bulamu bwo/ bwamwanawo.

Ebikwata ku ddembe lyo ngomulwadde

Nnyinyonyoddwa era nkakkasiddwa nti sijjakufuna /omwana wange taggya kufuna obukosefu oba obulabe oluvanyuuma lwokumukuba scan eeyo lubuto(aka TV) era ajja kufuna obujjanjabi bwe bumu nga obwabo abateetabye mu kunoonyereza kuno naye nga balina obulwadde bwe bumu.
Ntegezeddwa nti ndi wa ddembe okuva / okujja omwana wange mu kunoonyereza kuno esaawa y’onna bwemba njjagadde ewataali okunyigirizzibwa eri obujjanijabi bwange / bwo’omwana wange.

Ebirala byonna bye nmetaaga okumanya biweebwa Dr.Pascal Kwitonda,(0774007777) omunoonyereza omukulu oba bakalabalaba bo’okunoonyereza kuno bano wamanga;
Dr. Byanyima R.K Tel: 0772500680 (Dept of Radiology-Mulago Hospital)

Dr. Orem Jackson Tel: 0782320543 (Uganda Cancer Institute –Mulago Hospital)

Dr. Muyinda Z Tel: 0772432796 (Dept of Radiology-Mulago Hospital)

Dr. Ibingira C Tel: 0414530020 (Chairman w’akakiiko akakulira okunonyereza mu Ttendekeko ly’abasawo mu Makerere University)

**Okukkiriza**

Ntegedde nti byonna ebikwaata ku mulwadde wange bijjakukuumibwa nga bya kyama.

Ntegedde nti makuteekaako omukono ku kiwaandiko kino mpaddeyo okukkiriza kwange nti ebinazuulibwa kunze/ ku mwana wange bijja kukozesembwa mu kunoonyereza kuno.

Nsobola okufuna ko foomu eyange bwembanga njisabye.

Omukono/ekinkumu ky’omulwadde /muzadde..........................Ennaku z’omwezi...................

Omukono gw’omunoonyereza gweckikwatako............... Ennaku z’omwezi......................
Appendix 4 - ASSENT FORM

TITLE: THE ABDOMINAL SONOGRAHIC FEATURES OF ENDEMIC BURKITT'S LYMPHOMA IN PATIENTS SEEN AT UGANDA CANCER INSTITUTE, MULAGO HOSPITAL- KAMPALA.

INVESTIGATOR: DR. PASCAL KWITONDA MBChB (Mak)

SUPERVISORS:

1. DR. BYANYIMA. K. ROSEMARY MBChB, M.Med RADIOLOGY (Mak)

2. DR. OREM JACKSON MBChB, M.Med INTERNAL MEDICINE(Mak)

The investigator named above is carrying out a research study on patients with Burkitt’s lymphoma admitted at the UCI- Mulago Hospital.

What is this study about?

It is a study on all patients with Burkitt’s lymphoma admitted to UCI- Mulago Hospital to find out how their abdominal organs have been affected by the disease and which organs are involved.

Why is this study being done?

The study findings will guide the doctors who will be attending to the patient to plan his/ her management. This study will in future be used by healthy policy makers to develop management guidelines for Burkitt’s lymphoma to be used by sonographers, sonologists and oncologists.

What will happen to me?

If I accept to be in the study, the following things will be done:

1. The doctor will ask me some questions about my sickness.

2. The doctor will also carry out a physical examination on my body.

3. The doctor will use an ultrasound machine to look at my abdominal organs.
Will it hurt?

No. The examination will not hurt. The ultrasound will be placed on your abdomen and will remain outside your body.

Will I get any benefits from this study?

Yes. You will not be charged or paid to participate in this study. Information obtained will guide the doctors in the management of your disease. Information obtained from this study will in future help health policy makers to design management guidelines for patients with similar disease in Uganda.

What if I have questions?

You can ask your questions now or later. You can ask the other doctors who are treating you. You can also talk to your parent/ guardian or other patients in the study.

If you have further queries, you can contact my supervisors: Dr. Byanyima R.K Tel:0772500680 (Dept of Radiology- Mulago Hospital) and Dr. Orem Jackson Tel:0782320543 (Uganda cancer institute- Mulago hospital).

Do I have to be in the study?

You do not have to be in the study if you do not wish to. This will not in any way affect the health care patients with my condition are supposed to get. You are free to change your mind later. It is up to you.

Signature/ thumb print of child..........................Age..............Date.................................

Signature of witness..............................................Date.................................

Signature of person obtaining assent......................Date.................................
Appendix 5- Questionnaire

TITLE: THE ABDOMINAL SONOGRAPHIC MANIFESTATIONS OF BURKITT'S LYMPHOMA IN PATIENTS SEEN AT UGANDA CANCER INSTITUTE, MULAGO HOSPITAL- KAMPALA.

SECTION A: Demographic Data of Patient

1. Name..............................

2. Serial No..............

3. Age.........................

4. Sex.........................

5. Tribe.........................

6. Home address ..............

7. District.......................

8. Telephone Contact of parent /guardian..............

SECTION B: Clinical Presentation

1. Does the patient have abdominal tumour?
   
   1. Yes
   2. No

(If no go to question 2)

2. Evidence of BL elsewhere in the body
   
   1. Yes (If yes go to question 3)
   2. No
3. Which part of the body is involved?
   1. Facial mass
   2. Chest mass
   3. Others (specify)

4. Abdominal pain
   1. Present
   2. Absent

5. Abdominal distension
   1. Present
   2. Absent

6. Ascites
   1. Present
   2. Absent

7. Duration of symptoms (weeks)

SECTION C: Sonographic Findings

1. Is there abdominal mass?
   1. Yes
   2. No

2. If yes, which organ / organs are involved?
   1. Liver
   2. Spleen
3. Kidneys
4. Ovaries
5. Gut
6. Others (specify)

3. If yes,
   1. Solitary
   2. Multiple

   What is the size of the largest mass? (Largest measures ........... cm)

4. What is the echogenicity?
   1. Hypoechoic
   2. Hyperechoic
   3. Isoechoic
   4. Anechoic
   5. Echocomplex

5. Liver size
   1. Normal
   2. Enlarged (mild >145, moderate > 160, gross >170mm)

6. Liver echotexture
   1. Normal
   2. Increased
   3. Decreased
7. Spleen: Size
   1. Normal
   2. Enlarged (mild, moderate, gross)

8. Spleen echotexture
   1. Normal
   2. Increased
   3. Decreased

9. Kidneys
   1. Normal size
      | RT | LT |
      | [] | [ ] |
   2. Abnormal
      | RT | LT |
      | [ ] | [ ] |

10. Kidney echogenicity
    1. Normal
       | RT | LT |
       | [] | [ ] |
    2. Increased
       | RT | LT |
       | [ ] | [ ] |
    3. Decreased
       | RT | LT |
       | [ ] | [ ] |

11. Ovaries
    1. Normal size
       | RT | LT |
       | [ ] | [ ] |
    2. Abnormal size
       | RT | LT |
       | [ ] | [ ] |

12. Abdominal Lymphnodes
    1. Present
    2. Absent

52
13. Sites of Abdominal lymphadenopathy

1. Para Aortic
2. Mesenteric
3. Mesenteric+ Para Aortic
4. Other sites (specify)

14. Echogenicity of the lymph nodes

1. Hypoechoic
2. Iso echoic
3. Hyperechoic

15. Size of gut wall

1. Normal
2. Abnormal (specify which part of the gut)

16. Other organs involved (Specify size and echogenicity)

17. Ascites

1. Present (mild, moderate, gross)
2. Absent

SECTION C: Radiological Tests

1. CXR

1. Normal
2. Abnormal (If abnormal specify ..............................................................

..............................................................
Other radiological tests:

2. CT Scan
3. MRI
4. IVP
5. Myelography
6. Barium studies

What is the clinical stage of the disease? (ANC1 classification)

SECTION D: Histological Report

1. Nature of specimen
2. Site
3. Findings

SECTION E: Laboratory Results

5. HIV serology results
6. WBC count
7. Platelet count
8. RFT's, LFT's, and Lactate Dehydrogenase levels
9. CSF analysis

SECTION F: Follow up scan

Change in scan findings after one month of treatment.

1A. Is there abdominal mass now? [YES] [NO]
1B. was the mass present before starting chemotherapy?

1. Yes
2. No

(If yes go to question 2)

2. Evidence of BL elsewhere in the body

1. Yes (If yes go to question 3)
2. No

3. Which part of the body is involved?

1. Facial mass
2. Chest mass
3. Others (specify)

4. Abdominal pain

1. Present
2. Absent

5. Abdominal distension

1. Present
2. Absent

6. Ascites

1. Present
2. Absent
SECTION C: Sonographic Findings

1. Is there abdominal mass?
   1. Yes
   2. No

2. If yes, which organ/organs are involved?
   1. Liver
   2. Spleen
   3. Kidneys
   4. Ovaries
   5. Gut
   6. Others (specify)

3. If yes:
   1. Solitary
   2. Multiple

What is the size of the largest mass? (Largest measures.............cm)

4. What is the echogenicity?
   1. Hypoechoic
   2. Hyperechoic
   3. Isoechoic
   4. Anechoic
   5. Echocomplex
5. Liver size
   1. Normal
   2. Enlarged (mild >145, moderate > 160, gross >170mm)

6. Liver echotexture
   1. Normal
   2. Increased
   3. Decreased

7. Spleen: Size
   1. Normal
   2. Enlarged (mild, moderate, gross)

8. Spleen echotexture
   1. Normal
   2. Increased
   3. Decreased

9. Kidneys
   1. Normal size
      [ ]  [ ]
   2. Abnormal
      [ ]  [ ]

10. Kidney echogenicity
    1. Normal
       [ ]  [ ]
    2. Increased
       [ ]  [ ]
    3. Decreased
       [ ]  [ ]
11. Ovaries

<table>
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<tr>
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<th>LT</th>
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<tbody>
<tr>
<td>1.</td>
<td>Normal size</td>
<td>[ ]</td>
</tr>
<tr>
<td>2.</td>
<td>Abnormal size</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

12. Abdominal Lymphnodes

1. Present
2. Absent

13. Sites of Abdominal lymphadenopathy

1. Para Aortic
2. Mesenteric
3. Mesenteric+ Para Aortic
4. Other sites  (specify)

14. Echogenicity of the lymph nodes

1. Hypoechoic
2. Iso echoic
3. Hyperechoic

15. Size of gut wall

1. Normal
2. Abnormal (specify which part of the gut)

16. Other organs involved (Specify size and echogenicity)
17. Ascites

1. Present (mild, moderate, gross)
2. Absent

Laboratory Results

1. WBC count (Total and differential) and Platelet count
2. RFT’s, LFT’s, and Lactate Dehydrogenase levels