Original Article

Histopathologic Spectrum of Lymph Node Disease in a Lagos Facility

Olubanji Ajibola Oguntunde, Nzechukwu Zimudo Ikeri[1], Uche Igbokwe[2], Fatimah Biade Abdulkareem, Adekunbiola Fehintola Banjo

Department of Anatomic and Molecular Pathology, College of Medicine, University of Lagos, Lagos, Nigeria, [1]Department of Cellular Pathology, Betsi Cadwaladr University Health Board, Bodelwyddan, Wales, [2]Department of Cellular Pathology, Queen's Hospital, Romford, Essex, UK

Abstract

Background and Objective: Hematopathology is often a technical and challenging aspect of pathology, requiring robust ancillary testing and second specialist opinion, both of which are not readily available and affordable to the Nigerian population. The aim of this study, therefore, was to determine the histological spectrum of lymph node diseases and highlight the diagnostic challenges. **Methodology:** A retrospective review of lymph node biopsies submitted to The Specialist Laboratories, Lagos, Nigeria, over an 8-year period was carried out. A proportion of these had a specialist's second opinion and ancillary immunohistochemistry testing where necessary. **Results:** Two hundred and ten lymph node biopsies were studied. Majority of the cases were diagnosed as nonspecific reactive changes (31.0%). This was followed by metastases to the lymph nodes (22.9%) and lymphomas (18.6%). Non-Hodgkin's lymphoma accounted for 79.5% of lymphomas, of which small cell lymphoma (35.5%) and diffuse large B-cell lymphoma (29.0%) were the most predominant subtypes. There was a 62.1% concordance between the preliminary and final diagnoses. **Conclusion:** These morphologic findings are in keeping with those in published literature. A significant number of discordant cases highlight the need for specialist training in hematopathology as well as the establishment of well-equipped facilities for accurate and cost-effective diagnosis.

Keywords: Hematopathology, histopathologic, lymph node, lymphoma, spectrum

Received on: 24-02-19 **Review completed on:** 21-03-19 **Accepted on:** 26-04-19 **Published on:** 06-12-19

Introduction

Lymph nodes are involved by a very wide range of pathologic conditions and are, therefore, commonly biopsied for histologic analysis. When lymphoma features in the differential diagnoses, analyses are often very technical requiring second opinion by a specialist haematopathologist.[1] It is not surprising therefore that there is paucity of data on the specific lymphoma subtypes in our environment where ancillary testing and specialist's opinion are not readily available or affordable. Indeed, only a few Nigerian studies with the required corroboratory ancillary testing were found after an extensive search.[2-6] There has also been a change in the epidemiology of lymph node diseases over the years. Burkitt lymphoma, once the most common childhood malignancy in Lagos and other parts of Southwest Nigeria, now occurs less commonly than retinoblastoma.[7-9] This has been attributed to the better control of malaria, a cofactor for its occurrence. A reduced incidence has also been reported in other parts of Southwest Nigeria. It, however, remains the most common childhood malignancy in the northern regions of the country.[10,11] In adults, lymphomas remain a leading cause of cancer mortality, especially with the advent of HIV – AIDS, making studies on it important in our environment.[12]

The aim of this study was, therefore, to give an update of the morphologic spectrum of the various lymph node diseases seen in our facility as well as to highlight the challenges faced with lymphoma diagnosis.

Methodology

This study was carried out to review and categorize all lymph node specimens received at The Specialist Laboratories,

Access this article online

Quick Response Code:

Website: www.atpjournal.org

DOI: 10.4103/atp.atp_8_19

Address for correspondence: Dr. Olubanji Ajibola Oguntunde, Department of Anatomic and Molecular Pathology, College of Medicine, University of Lagos, PMB 12003, Lagos, Nigeria. E-mail: bjbanji@gmail.com

How to cite this article: Oguntunde OA, Ikeri NZ, Igbokwe U, Abdulkareem FB, Banjo AF. Histopathologic spectrum of lymph node disease in a lagos facility. Ann Trop Pathol 2019;10:114-8.

Lagos, Nigeria, from January 2010 to August 2017. Only cases where the lymph nodes were being investigated as the primary clinical problem were studied. Lymph nodes received as part of resection specimen, for example, mastectomy and colectomy were, therefore, excluded from the study. Second-opinion cases from our institution are routinely sent to a referral center in the United Kingdom for second opinion and ancillary testing when a diagnosis of lymphoma is entertained. The antibody panels used for ancillary immunohistochemistry include CD3, CD5, CD10, CD15, CD20, CD23, CD30, CD34, CD38, CD45, CD56, CD79a, cyclin D1, Bcl2, Bcl6, Ki-67, TDT, EMA, S100, ALK1, MUM1, Pax 5, and Epstein–Barr virus (EBV) latent membrane protein 1 (LMP1). Immunohistochemical analysis for the cases was performed on 4-μ formalin-fixed paraffin-embedded sections, which were stained using an automated immunostaining system with monoclonal antibodies manufactured by DAKO against each of this protein. Every other process was carried out according to the manufacturer's instruction. The data extracted from the pathology reports included the patient's age, sex, anatomical site, preliminary diagnoses, final diagnoses and the immunohistochemistry profile where present. These data were analyzed using SPSS 23 (Statistical Package for Social Sciences for Windows 22.0 IBM, Armonk, NY, USA), and the results are represented in figures and tables.

Results

Two hundred and ten lymph node biopsies met the inclusion criteria for the study. Of these, 104 were female patients and 93 from males, giving a male-to-female ratio of 1:1.1. Gender was not indicated in 13 patients. The age was not specified in 21 of the patients. The peak age of involvement was 40 years, the median age was 44 years, and the age range was 2–87 years. Figure 1 shows the age distribution of patients. The anatomical site was specified in 141 cases. The cervical and axillary lymph nodes were the most common lymph node specimens submitted for histopathologic assessment [Figure 2].

The majority of lymph nodes had nonspecific reactive changes. These were followed by metastases and lymphoma [Table 1]. Of the 48 metastatic cases, 36 (75.0%) were adenocarcinomas, 5 (10.4%) were squamous cell carcinomas, 1 (2.1%) was a neuroendocrine carcinoma, and 6 (12.5%) were poorly differentiated carcinomas.

Thirty-five cases (16.7%) were tuberculous lymphadenitis. A definitive diagnosis was made in these cases with either a positive Ziehl–Neelsen (ZN) stain or clinical response to therapy when histologically ZN is negative. The mean age of occurrence of tuberculous lymphadenitis was 35.2 years with a male-to female-ratio of 1:1.3, and the vast majority of these cases (81%) were found in the cervical lymph nodes. Diagnoses in the miscellaneous categories included 2 (20%) cases of Castleman disease, a case each of Rosai–Dorfman disease (10%) and Kikuchi necrotizing lymphadenitis (10%), and 6 (60%) cases of dermatopathic lymphadenopathy.

Table 1: Histologic diagnosis of lymph node disease

Diagnosis	Frequency (%)	Mean age	Male:female
Nonspecific reactive changes	65 (31.0)	39.3	1.5:1
Metastases	48 (22.9)	44.9	1:2
Lymphoma	39 (18.6)	45.4	1:1.7
Non-Hodgkin's	31 (14.8)	45.6	1:1.5
SLL	11 (5.2)	56.0	1:1.2
DLBCL	9 (4.3)	51.4	1.2:1
MCL	2 (1.0)	42.0	1:1
ALCL	2 (1.0)	35.0	Both female
ALL	2 (1.0)	12.0	Both female
Burkitt	1 (0.5)	6.0	Male
Lymphoplasmacytic	1 (0.5)	46.0	Female
Follicular	1 (0.5)	44.0	Female
Unspecified	2 (1)	42.0	Female
Hodgkin's	8 (3.8)	43.8	1:1.6
Nodular sclerosis	6 (2.9)	37.6	1:1
Lymphocyte rich	2 (1.0)	65.0	Both female
Tuberculous lymphadenitis	35 (16.7)	35.2	1:1.3
Suspicious for lymphoma	13 (6.2)	44.8	1:1.2
Specific nontuberculous lymphadenitis	10 (4.8)	44.3	1:1.5

ALCL: Anaplastic large-cell lymphoma, DLBCL: Diffuse large B-cell lymphoma, MCL: Mantle cell lymphoma, ALL: Acute lymphoblastic lymphoma

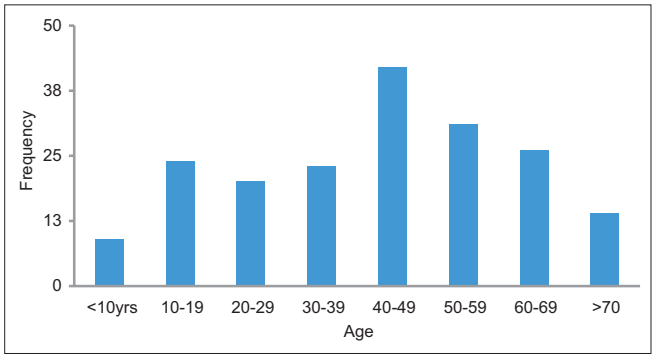

Figure 1: Age distribution of cases with lymph node disease

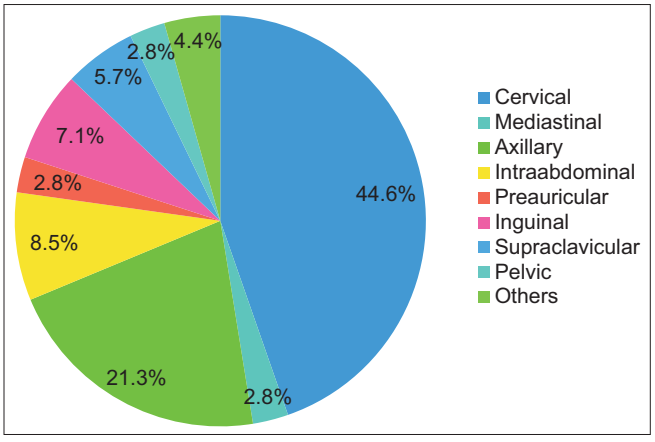

Figure 2: Distribution of lymph nodes sampled by location

Sixty-six cases were sent for second opinion and immunohistochemistry. In 41 (62.1%) of these cases, the final diagnosis was concordant with the preliminary histologic diagnosis. Sixteen (24.2%) cases had discordance between preliminary and final diagnoses [Table 2]. In the remaining 9 cases, no preliminary diagnosis was given.

Thirty-nine (59%) of the 66 cases sent for immunohistochemistry and second opinion were found to be lymphomas. Of the lymphoma cases, non-Hodgkin's lymphoma (NHL) accounted for 31 (79.5%), whereas the remaining 8 (20.5%) were Hodgkin lymphoma. Small lymphocytic lymphoma (SLL) and diffuse large B-cell lymphoma (DLBCL) were the most common NHLs, whereas nodular sclerosing type was the most common Hodgkin's lymphoma subtype [Table 1]. Details of immunohistochemical profile for SLL, DLBCL, follicular lymphoma (FL), and lymphoplasmacytic lymphoma are given in Table 3 and Figure 3. Only 2 (25%) of the Hodgkin's lymphoma showed positive staining for EBV LMP1. One of the two cases of anaplastic large-cell lymphoma (ALCL) was ALK-positive.

Discussion

The most common lymph node diagnosis seen in this study was nonspecific reactive changes. This is consistent with local and international reports. This is not surprising as a wide variety of conditions such as infection, drugs, chemicals, environmental pollutants, and even malignancy are associated with this histologic pattern.[13,14] These nonspecific changes could be in the follicular, paracortical, or sinusoidal compartments, or could have a mixed morphologic appearance.[15] Recognizing these patterns can sometimes suggest the underlying diagnosis. Reactive follicular hyperplasia is associated with rheumatoid arthritis, Sjögren syndrome, HIV-associated lymphadenopathy, or progressive transformation of lymphoid follicles.[15] Reactive paracortical hyperplasia is more often seen in the context of viral infections, immunization, or drug use. Reactive sinus hyperplasia is in relation with monocytoid B-cell hyperplasia, hemophagocytic syndromes, Whipple's disease, or lymph nodes draining sites of prostheses or malignancy.[15] Identifying the primary cause is, however, only possible in a minority of cases. As a group, reactive nonspecific lymphadenopathy is self-limiting and requires no further treatment.[15]

Table 2: List of discordant cases

Provisional diagnosis	Final diagnosis	Number of cases
CLL	Castleman disease	1
Hodgkin's lymphoma	Reactive	2
Non-Hodgkin's lymphoma	Reactive	9
Necrotizing lymphadenitis	Hodgkin's lymphoma	1
Non-Hodgkin's lymphoma	Suppurative lymphadenitis	1
Non-Hodgkin's lymphoma	Dermatopathic lymphadenopathy	1
Reactive	DLBCL	1
Total		16

DLBCL: Diffuse large B-cell lymphoma, CLL: Chronic lymphocytic leukemia

Table 3: Immunoprofile of the low-grade small cell lymphomas

Diagnosis	CD5+	CD23+	Cyclin D1+	Bcl6+	CD10+
SLL	11/11	11/11	0/9	0/3	0/7
MCL	1/2	0/2	2/2	0/2	0/2
FL	0/1	0/1	-	-	1/1
LPL	0/1	0/1	0/1	0/1	0/1

SLL: Small cell lymphoma, LPL: Lymphoplasmacytic lymphoma, FL: Follicular lymphoma, MCL: Mantle cell lymphoma

Tuberculous lymphadenitis, while accounting for a considerable proportion of cases, was seen in much lower frequencies compared to studies from other parts of Nigeria. In our study, they accounted for 16.7% of cases compared to 35% in Benin, 30% in Kano, and 38% in Ilorin.[16-20] This finding is consistent with other reports from Lagos, which have consistently shown a lower proportion of tuberculous lymphadenitis in lymph node specimen submitted to the study center.[13,19] A closer look at these institutional studies shows a detection rate of tuberculous lymphadenitis to be 8–9/year/institution in Lagos, 5/year/institution in Benin, 12/year/institution in Ilorin, and 15/year/institution in Kano. A detection rate in Kano being almost twice that in Lagos and thrice that in Benin suggests a higher incidence of tuberculous lymphadenitis in Northern Nigeria.[16-20] In Bradford UK, 15% of lymph node biopsies were tuberculous, amounting to a detection rate of 17/year.[14] This is most probably due to improved access to health-care facilities in the region. Tuberculosis, therefore, occurs less commonly in Lagos and other southern parts of the country. What is consistent in all geographic locations, however, is the cervical lymph node being the most common site of tuberculous lymphadenitis as was the case in this study.[14-19]

In this study, metastases from occult malignancies to the lymph nodes also occurred more commonly than tuberculous lymphadenitis, which is consistent with the previous reports from institutions in Lagos but at variance with those from other parts of the country.[13-19] Lagos appears to have a much higher rate of occult metastases to lymph nodes approaching a detection rate of 22 cases/year/institution. Reports from institutions in other parts of the country show a detection rate of 6/year in Benin, 8/year in Ilorin, and 9/year in Kano.[16-19] It could be that the reason for this is related to the higher levels of environmental pollutants from automobiles and factories, as well as the adoption of harmful lifestyles such as cigarette smoking, high-calorie diet, late age of first confinement, and poor breastfeeding history, all of which are risk factors for the development of cancer. This will need to be further explored by more studies. Specific nontuberculous lymphadenitis is the least common type of lesion seen in most studies worldwide.[13-19] It usually requires a higher index of suspicion

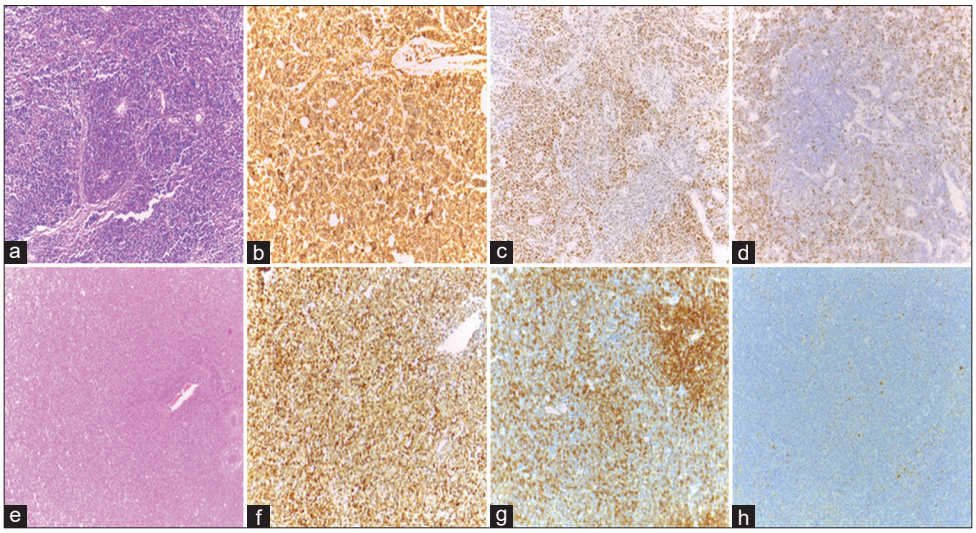

Figure 3: Photomicrograph of diffuse large B-cell lymphoma and small cell lymphoma (SLL) with their immunohistochemistry panel at × 100 a. H and E (DLBCL) b. CD20 (DLBCL) c. MUM1 (DLBCL) d. KI-67 (DLBCL) e. H and E (SLL) f. CD5 (SLL) g. CD23 (SLL) h. CYCLIN D1 (SLL)

and often a second opinion by a specialist in hematopathology. Due to a paucity of such specialists in Nigeria, these diagnoses are rarely ever made and often limited to a diagnosis of sarcoidosis or cat-scratch disease.[16]

Due to availability of specialist's second opinion in this study, diagnoses of dermatopathic lymphadenopathy, Castleman disease, Kikuchi necrotizing lymphadenitis, and Rosai–Dorfman disease were made. This shows that rare and exotic lymph node lesions also occur in the Nigerian population. There is, therefore, a need for specialist in hematopathology and more robust ancillary testing in this country as such diagnosis can often be confused with lymphoma.

Lymphomas were seen in 18.6% of all lymph node samples received. There was slight female predominance in this study for both Hodgkin's lymphoma and NHL. Consistent with findings in the literature, Burkitt lymphoma and acute lymphoblastic lymphoma had the youngest mean age of occurrence (6 and 12 years, respectively).[13] Nodular sclerosis variant of Hodgkin's lymphoma and ALCL also had mean ages of occurrence slightly lower than other lymphoma types.[13] The cervical lymph node was the most common involved site in both the Hodgkin's lymphoma and NHL subtypes.[14] Comparison with other local studies is difficult as there are very few studies with confirmatory ancillary testing. As is the case worldwide, NHL is by far the most common histologic subtype.[21] In our study, they accounted for 79.5% of lymphomas. Comparatively, they account for 84.5% in the study by Akinde *et al*. in Lagos, 80% in a study from Zaria, 79.5% in Ile-Ife, 91.9% in a study from the US, and 85.6% in the UK.[2-5,20,21] The incidence of lymphoma as a whole has been shown to be almost equal in all races, with a slightly lower rate in blacks. There is a greater variability, however, with regard to the specific lymphoma subtypes. Hodgkin's lymphoma has an almost equal incidence in blacks and whites. FL, and to a lesser extent, DLBCL and small lymphocytic lymphoma occur more frequently in whites, whereas plasma cell neoplasms, and to a lesser extent, T-cell lymphomas are seen more commonly in blacks.[20] With respect to geographical location, Burkitt lymphoma occurs far more commonly in Africa than in western populations.[22]

DLBCL and small lymphocytic lymphoma (SLL) are the most common lymphomas in most literature with DLBCL occurring more frequently than SLL.[20,21] This was also the finding reported by Akinde *et al*. and Onwubuya *et al*. in Lagos and Ile-Ife, respectively.[2,3,5] In our study, the two tumors were the most common NHL subtypes, with SLL occurring slightly more frequently than DLBCL. This may likely be due to the smaller sample size of our study. It, therefore, appears that the frequency of the various subcategories of NHL follows the trends in the literature. In Zaria, however, Iliyasu *et al*. reported Burkitt lymphoma to be the most predominant NHL, which might suggest poorer malaria control in Northern Nigeria.[4] Peripheral T-cell lymphoma not otherwise specified (PTCL NOS) is the most common T-cell lymphoma reported in the literature.[20,21] This was also reported by Akinde *et al*. in their study.[2] Our study and an Ile-ife study however reported anaplastic large cell lymphoma as the commonest T-cell lymphoma. There was no record of PTCL in both studies.

As is reported worldwide, a nodular sclerosing variant of Hodgkin's lymphoma is the most prevalent subtype of Hodgkin's lymphoma.[20-22] In our study, it accounted for 75.0% of cases. Akinde *et al*. and Adelusola *et al*. reported mixed cellularity subtype to be the more common variant in their respective studies.[2,6] Only 25.0% of Hodgkin's lymphoma were associated with EBV LMP 1 in this study, whereas 60% was reported in Ile-Ife by Adelusola *et al*. It has been reported that EBV-positive Hodgkin's lymphoma is more common in developing countries where it accounts for up to 100% of cases as was reported in Kenya.[23,24] The gold standard of EBV detection is *in situ* hybridization, and this will need to be

performed to determine the true incidence of EBV in Hodgkin's lymphoma cases in our environment.

Lymphoma diagnosis evidently is very challenging, especially in low-to-medium income countries where the required ancillary tests and specialist in hematopathology are often in short supply. This is evidenced by a discordant rate of 24.2% in preliminary and final diagnoses shown in this study. In the majority of discrepant cases, reactive expansion of the interfollicular compartment was confused with NHL. Detailed attention to the lymph node architecture often helps to make the right diagnosis as reactive lymph nodes show the preserved architecture, do not form any discrete expansile mass, do not erode the mantles of the scattered follicles, and exhibit a mixture of lymphoid cell types which lack cellular atypia. Another lesson learnt from these discrepancies is that florid immunoblastic proliferation can be seen in viral lymphadenitis, and this must be interpreted in the context of the features of reactive changes listed above to avert misdiagnosis as lymphoma. Immunohistochemistry is useful when morphologic features are equivocal. Minimum markers that would help improve lymphoma diagnosis in our center would include CD20, CD3, and Bcl2 to differentiate a reactive process from a lymphoma, CD5, and CD23 to identify SLL seen in this study, CD15, and CD30 to confirm diagnosis of Hodgkin's lymphoma and Ki-67 to determine tumor grade which is useful for treatment planning.

Conclusion

The majority of lymph nodes biopsied showed features of reactive lymphadenopathy, with the majority being nonspecific etiology. Among the lymphomas, NHL was seen more frequently with small lymphocytic lymphoma and DLBCL variants accounting for the majority. These findings are consistent with those of published literature. Due to the highly technical and challenging nature of lymph node pathology diagnosis, there is a need for specialist training in hematopathology as well as the establishment of well-equipped facilities for accurate and cost-effective diagnosis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Teruya-Feldstein J. Getting the diagnosis right in NHL: Role of immunohistochemistry and molecular diagnostic testing. J Natl Compr Canc Netw 2008;6:422-7.
2. Akinde OR, Osunkalu VO, Anunobi CC, Oguntunde OA, Afolayan MO, Akanmu AS. Immunophenotypic patterns of lymphomas in a tertiary hospital, Lagos, Nigeria. Niger Postgrad Med J 2015;22:61-9.
3. Akinde OR, Anunobi CC, Osunkalu VO, Phillips AA, Afolayan OM. The challenges of lymphoma diagnosis in a tertiary hospital in Lagos, Nigeria. J Clin Sci 2016;13:58-71.
4. Iliyasu Y, Ayers LW, Liman AA, Waziri GD, Shehu SM. Epstein -barr virus association with malignant lymphoma subgroups in Zaria, Nigeria. Niger J Surg Sci 2014;23:6-8.
5. Onwubuya IM, Adelusola KA, Durosinmi MA, Sabageh D, Ezike KN. Lymphomas in ile-ife, Nigeria: Immunohistochemical characterization and detection of epstein-barr virus encoded RNA. J Clin Diagn Res 2015;9:EC14-9.
6. Adelusola KA, Titiloye NA, Rotimi O, Durosinmi M. Epstein barr virus latent membrane protein-1 in Hodgkin's lymphoma in Nigerians. Afr Health Sci 2009;9:174-8.
7. Tijani SO, Elesha SO, Banjo AA. Morphological patterns of paediatric solid cancer in Lagos, Nigeria. West Afr J Med 1995;14:174-80.
8. Akinde OR, Abdukareem FB, Daramola AO, Anunobi CC, Banjo AA. Morphological pattern of childhood solid tumours in Lagos university teaching hospital. Nig Q J Hosp Med 2009;19:169-74.
9. Akang EE. Tumors of childhood in Ibadan, Nigeria (1973-1990). Pediatr Pathol Lab Med 1996;16:791-800.
10. Mohammed A, Aliyu HO. Childhood cancers in a referral hospital in Northern Nigeria. Indian J Med Paediatr Oncol 2009;30:95-8.
11. Ochicha O, Gwarzo AK, Gwarzo D. Pediatric malignancies in Kano, Northern Nigeria. World J Pediatr 2012;8:235-9.
12. Giulia de F, Rogena EA, Naresh K, Rapheal M, Magrath I, Lorenzo L. Managing lymphomas in African setting: Improving diagnostic accuracy and carrying out research projects. Cancer Control 2013.p.75-82.
13. Anunobi CC, Banjo AA, Abdulkareem FB, Daramola AO, Abudu EK. Review of the histopathologic patterns of superficial lymph node diseases, in Lagos (1991-2004). Niger Postgrad Med J 2008;15:243-6.
14. Moor JW, Murray P, Inwood J, Gouldesbrough D, Bem C. Diagnostic biopsy of lymph nodes of the neck, axilla and groin: Rhyme, reason or chance? Ann R Coll Surg Engl 2008;90:221-5.
15. Mohseni S, Shojaiefard A, Khorgami Z, Alinejad S, Ghorbani A, Ghafouri A. Peripheral lymphadenopathy: Approach and diagnostic tools. Iran J Med Sci 2014;39:158-70.
16. Olu-Eddo AN, Ohanaka CE. Peripheral lymphadenopathy in Nigerian adults. J Pak Med Assoc 2006;56:405-8.
17. Ochicha O, Edino ST, Mohammed AZ, Umar AB, Atanda AT. Pathology of peripheral lymph node biopsies in Kane, Northern Nigeria. Ann Afr Med 2007;6:104-8.
18. Ojo BA, Buhari MO, Malami SA, Abdulrahaman MB. Surgical lymph node biopsies in university of ilorin teaching hospital, Ilorin, Nigeria. Niger Postgrad Med J 2005;12:299-304.
19. Akinde OR, Anunobi CC, Abudu EK, Daramola AO, Banjo AA, Abdulkareem FB, *et al.* Pattern of lymph node pathology in Lagos. Nig Q J Hosp Med 2011;21:154-8.
20. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR, *et al.* 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66:443-59.
21. Smith A, Crouch S, Lax S, Li J, Painter D, Howell D, *et al.* Lymphoma incidence, survival and prevalence 2004-2014: Sub-type analyses from the UK's haematological malignancy research network. Br J Cancer 2015;112:1575-84.
22. Orem J, Mbidde EK, Lambert B, de Sanjose S, Weiderpass E. Burkitt's lymphoma in Africa, a review of the epidemiology and etiology. Afr Health Sci 2007;7:166-75.
23. Flavell KJ, Murray PG. Hodgkin's disease and the epstein-barr virus. Mol Pathol 2000;53:262-9.
24. Weinreb M, Day PJ, Niggli F, Powell JE, Raafat F, Hesseling PB, *et al.* The role of epstein-barr virus in Hodgkin's disease from different geographical areas. Arch Dis Child 1996;74:27-31.