ORIGINAL ARTICLE

Hodgkin lymphoma: Clinicopathologic features in Benin City, Nigeria and update on its biology and classification

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Abstract

Objective: To review the age incidence, common pathohistologic subtypes, and anatomical nodal sites of lymph nodes involvement for histology.

Materials and Methods: A 25 (May 1985-June 2010) years retrospective study of all patients who had lymph node biopsy.

Setting: Department of Pathology and Haematology, University of Benin Teaching Hospital, Benin City, Nigeria.

Results: Of 821 lymph node biopsies encountered, 56 (6.8%) cases biopsied were for Hodgkin lymphoma (HL). There was a bimodal peak incidence of age interval of 1$\tilde{1}$15 years and 2$\tilde{1}$25 years and the relationship between the age and sex distribution was statistically significant (P = 0.03). The overall median age was 23 years with a mean age of 25.6 ± 2.0 (SEM). Pathological re-appraisal of these 56 cases in the study indicates that mixed cellularity HL constituting 36 cases (64.3%) was the predominant subtype. This was followed by lymphocyte depleted HL with a total of 11 cases (19.6%). The major site of lymph node involvement where biopsy was taken for histological diagnosis was the cervical group of lymph nodes constituting 78.6%. Staging classification of the disease indicates low frequency of early stage disease (I-II) with 19 cases (33.9%) and high frequency of late stage (III-IV) with 37 cases (66.1%).

Conclusion: Patients are predominantly males, children and young adults presenting with cervical lymphadenopathy at late stage of the disease, and a dominance of mixed cellularity and lymphocyte depleted histological subtypes were observed.

Key words: Age incidence, Hodgkin lymphoma, pathohistologic subtype, staging

Date of Acceptance: 14-Feb-2011

Introduction

Hodgkin lymphoma (HL) is a distinct primary solid tumor of the immune system that shows wide variation in incidence among different geographic regions and various races.[1] HL is an unusual cancer among human malignancies in that the epidemiology suggests an infectious etiology with Epstein Barr Virus (EBV) in up to 40% of cases and this association is believed to be causal.[2-4] Current insight on trends, causes, and mechanisms revealed that HL has a unique and distinct history, epidemiology, treatment, and biology.[5] The B-cell nature of the pathognomonic Hodgkin and Reed-Sternberg (HRS) cells has been documented along with several recurrent genetic lesions.[6,7] HRS cells in classical HL has several characteristics that are unusual for lymphoid tumor cells and the microenvironment is dominated by an extensive mixed potentially inflammatory cellular infiltrate.[7] Risk factors for HL that were reported with greater or lesser evidence include: genetic (variation in the HLA class II region); viral infections (EBV); childhood environment and socioeconomic status; congenital and acquired immunodeficiency; medical conditions; and occupational

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.91752

PMID: 22248946

exposure (the wood industry and its derivatives).[8] The current study aims at defining the demographic pattern and age incidence, common pathohistologic subtypes and presentation of lymph nodes involvement for histology in our environment.

Materials and Methods

Lymph node biopsy cases with histological diagnosis of HL from May 1985 to June 2010 were extracted by multiple information sources from the Departments of Histopathology and Haematology of University of Benin Teaching Hospital (UBTH), Benin City and referrals from recognized Pathology Laboratories in Nigeria. Clinicopathologic and demographic data regarding age, gender, anatomical site of nodal biopsy, and histological subtypes obtained from request cards and case files were reviewed.

The study pathologist (A.N.O) reviewed the slides to verify the diagnosis of HL while the study hematologist (C.E.O) reviewed the demographic pattern, clinical records including therapy used for the patients. Where necessary, new slides were made from formalin fixed, paraffin embedded blocks and stained with hematoxylin and eosin stains. Histopathologic classification of tumor into histological subtypes was based on the Revised European American Lymphoma Classification.[9]

Data analysis

Data was analyzed using Instat GraphPad™ version 2.05a statistical software. The statistical methods applied include frequency counts and cross tabulations using Yates correction whenever necessary and one-way analysis of variance (ANOVA) for significant association. The results are presented as mean±SEM, median and range. *P* value of <0.05 was considered significant.

Results

Of the 821 lymph node biopsies encountered in the department of Pathology during the 25 years study period (May 1985 to June 2010), a total of 56 cases (6.8%) of HL were reported. There were 43 males (76.8%) and 13 females (23.2%) with a male to female ratio of 3.3:1. The age and sex distribution is shown in Table 1. Pathology report-based diagnosis were made for 56 (93.3%) of 60 cases. A change in diagnosis was made for 4 cases. These 4 cases were classified as non-Hodgkin's lymphoma in 3 cases and sinus histiocytosis (Rosai Dorfman) in one case. Analysis of the data on these 56 cases on epidemiologic grounds showed 4 different types: childhood (0–15 years) were 20 cases (35.7%); young adult (16–35 years) were 28 cases (50.0%); older adult (36–55 years) were 6 cases (10.7%) while the elderly (>55 years) were only 2 cases (3.6%). There was a bimodal peak incidence of age interval of 11–15 years and 21–25 years. HL age incidence was low after 45 years in this study. The relationship between the age and sex distribution was statistically significant ($P = 0.03$). The overall median age was 23 years with a mean age of 25.6 ± 2.0. The male age range was 4–65 years with a mean age of 25.4 ± 15.0, while the female age range was 5–55 years with a mean of 26.1 ± 15.1.

On pathological re-appraisal of these 56 cases, the histological subtypes of HL encountered in the study are shown in Table 2. Histological analysis indicates that mixed cellularity (MC) HL constituted 36 cases (64.3%) and was the predominant subtype. This was followed by lymphocyte depleted (LD) HL with a total of 11 cases (19.6%). Lymphocyte predominant was the least histological subtype (5.4%). The age range for patients with MCHL was 12–45 years. Of the 56 anatomical nodal sites analysed, the major site of lymph node involvement where biopsy was taken for histological diagnosis of HL was the cervical group of lymph nodes. This constituted 44 cases (78.6%) of the total cases seen followed by axillary nodes with 6 cases (10.7%).

Table 1: The age and sex distribution of Hodgkin lymphoma cases during study period

Forms	Age (years)	M	F	T	(%)
Childhood	0- 5	1	0	1	(1.8)
	6-10	5	1	6	(10.7)
	11-15	10	3	13*	(23.2)
Young adults	16-20	6	1	7	(12.5)
	21-25	8	6	14*	(25.0)
	26-30	6	0	6	(10.7)
	31-35	4	0	4	(7.1)
Older adults	36-40	1	0	1	(1.8)
	41-45	1	0	1	(1.8)
	46-50	0	1	1	(1.8)
	51-55	0	0	0	(0.0)
Elderly	>55	1	1	2	(3.6)
Total		43	13	56	

P = 0.03

Table 2: Baseline characteristics of clinicopathologic variables during the study period

Variables	Frequency	(%)
Histological subtypes		
Lymphocyte predominant HL	3	5.4
Nodular sclerosis HL	6	10.7
Mixed cellularity HL	36	64.3
Lymphocyte depleted HL	11	19.6
Anatomical nodal site		
Cervical	44	78.6
Axillary	6	10.7
Inguinal	4	7.1
Not stated	2	3.6
Clinical staging		
Early stage (I-II)	19	33.9
Late stage (III-IV)	37	66.1

Review of the clinical records of the patients showed that Ann Arbor stage I-II in 19 cases (33.9%) and high frequency of late stage (III-IV) with 37 cases (66.1%). The patients were treated with chemotherapy, radiotherapy, or combined modality therapy (Standard chemotherapy and radiotherapy) according to the anatomic extent of the disease while a high-dose combination therapy was used for relapse. The commonly used chemotherapeutic agent was ABVD (iv Adriamycin 25mg/m^2 Days 1,15; iv Bleomycin 10U/m^2 Days 1,15; iv Vinblastine 6mg/m^2 Days 1,15 and iv Dacarbazine 375mg/m^2 Days 1,15). A total of 31 patients (55.4%) had chemotherapy; 9 patients (16.1%) had radiotherapy, while 16 patients (28.6%) had combined therapy. The response to treatment was good with a prognostic outcome of over 80% for 5 years survival.

Discussion

HL is reported as the third most common malignancy among children.[10] The occurrence of HL in previous studies has shown that its incidence is lower compared to non-Hodgkin's lymphoma (NHL) in Nigeria[11-13] and in the diaspora.[14,15] The variation in incidence according to age, sex, race, socioeconomic status and histologic subtypes suggests an etiologic heterogeneity of this tumor.[4] The male preponderance in the study has been reported in previous studies[16,17] and sex has been known to play a role in lymphomagenesis.[18] The sex of an individual confers one of the greatest known risk for contracting lymphomas and leukemias.[18] It has been reported that the preferential male involvement in lymphoid cancer is most marked in the youngest age group in NHL and HL.[18] A recent international consortium pooled patient data identified a male sex factor as one of the prognostic score for advanced HL.[19]

An increased risk of HL in young adult population has been associated with higher childhood socioeconomic status and this is a major problem among the adolescence in some populations.[1,5,20] In keeping with the study, majority of the patients (71.4%) were adolescents and young adult male group. There was paucity of cases above the age of 45 years, which is in contrast to the incidence peak of over 60 years seen in developed world.[21, 22] This may be due to genetic and racial factors. Nevertheless, the sample size is too small to arrive at a definitive conclusion. A significant higher incidence has been reported among adolescents and young adults in some industrialized countries,[1,23,24] whereas less developed countries continue to show high rates in childhood.[25] These observations emphasize the need to identify risk factors for HL in the young. The bimodal incidence peak of 11–15 and 21–25 years age group in this study displays an intriguing variation compared with the striking bimodality of peaks in young adults and older adults seen in the Western World.[1] In a study carried out in South Africa on ethnicity and characteristics of HL in children, it was observed that Black patients presented at the youngest age (median, 103 months) whereas White patients were the oldest at presentation (median age,133 months, $P = 0.04$).[17] Evidence from 1 multiply affected families, a case-control study and population based registry studies implicate genetic factors such as the variation in the HLA Class II regions. [1,5,8,17,26]

Recent evidence on molecular biology of HL showed that it is not a single disease entity but is made up of two distinct types: the nodular lymphocyte predominant HL (NLPHL) with a peculiar nature and presence of "popcorn cells" and the Classical HL (CHL).[27,28] The CHL made up of 4 subtypes is characterized by the appearance of giant abnormal cells called HRS cells which arise from the germinal center B lymphocytes. In our study, the mixed cellularity (MC) HL (64.3%) and lymphocyte depleted (LD) HL (19.6%) histologic subtypes were the most common. The predominance of MCHL in this study has been reported in other studies in Nigeria[29] and other developing countries.[17] This however contrast with reports of NS subtype which has increased overtime and MCHL decline in industrialized nations .[30] Our finding is similar to the study carried out in Ile-Ife, South Western region of Nigeria in which 60% of cases were MC subtype. [29] Another study on co-existing HIV and HL cases in South Africa phenotypically showed predominance of MC and LD subtypes.[31] An unusual case of MCHL with prominent involvement of the base of the tongue at diagnosis has also been reported.[32] These two histologic subtypes, MC and LD define an aggressive clinical course, advanced stage disease, constitutional symptoms and immunodeficiency in comparison to other variants.[25] Although the MC and LD subtypes might be part of a biologic continuum, the nodular sclerosis (NS) subtype has a distinct epidemiology, clinical presentation, and histology.[28] An increase was said to have occurred primarily for NS subtype in incidence and specific trend study carried out in Nordic countries of Denmark, Sweden, Norway, and Finland from 1978-1997.[23] HL of NS subtype has increased over time, whereas HL of MC has declined in most Western countries.[33]

HL usually presents with typical lymphadenopathy detected either incidentally by the patient or by imaging procedures performed for assessment of other clinical conditions. Detection of an unusual mass or lymphadenopathy in these patients is usually located in the lymph nodes of the neck and mediastinum.[34] The major site of lymph node involvement for histology in our study was the cervical region (78.6%) followed by the axillary region (19.7%). This is similar to the study carried out in the US where neck was the commonest site of involvement.[30] The cervical lymphadenopathy has been documented worldwide as the most common type of peripheral lymphadenopathy.[35] Sixty to eighty percent of HL usually involve cervical nodes, 6–20% in the axillary nodes and 6–12% in the inguinal nodes.[25]

For prognostic and therapeutic considerations, HL patients are conveniently divided into those with early stage (Clinical Stage I and II) and those with advanced-stage (CS III and IV) disease at presentation.[36] Majority of our patients (66.1%) presented in advanced stage of the disease according to the Ann Arbor staging system, which is the usual norm for patients in our environment due to a number of factors .[11,37] These factors include ignorance and poverty, no access to hematologists at the primary healthcare level, less likely to be able to afford treatment due to the poor economy, absence of a functioning national health insurance scheme and at times lack of blood components support even in some tertiary health center.

The classification is not optimal for staging lymphomas and staging laparatomy was not indicated/justified in many cases. Hence, the modification of the Ann Arbor system known as Cotswold classification.[38] The disease is usually disseminated at presentation and therefore majority of our patients are treated with systemic chemotherapy. Specific criteria used for localized presentations of HL (CS I and II) has been reported to differ in different centers and have been divided into very favorable, favorable, and unfavorable subgroups.[39-41]

In conclusion, our study shows that the incidence of HL is low in our environment; patients are predominantly males, children, and young adults presenting with cervical lymphadenopathy at late stage of the disease; and mixed cellularity and lymphocyte depleted were the predominant histologic subtypes.

Acknowledgement

We wish to acknowledge the input of Dr. A. E. Omoti, Professor of Ophthalmology, for his analysis and review of the article and Dr Nworgu Ben, a Senior Registrar in the Department of Haematology for his valuable contribution to the write up of this article.

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How to cite this article: Olu-Eddo AN, Omoti CE. Hodgkin lymphoma: Clinicopathologic features in Benin City, Nigeria and update on its biology and classification. Niger J Clin Pract 2011;14:440-4.
Source of Support: Nil, **Conflict of Interest:** None declared.