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Spectrum of Hodgkin’s Disease in Children and Adults: Impact of Combined Morphologic and Phenotypic approach for exclusion of “Look-alikes”

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Abstract

Objective: To determine the prevalence of Hodgkin’s disease (HD) and its various subtypes in children and adults and assess the use of immunohistochemical (IHC) studies in confirming HD cases and excluding its close mimics/look-alikes.

Material and Methods: All 265 Hodgkin’s disease cases diagnosed at The Aga Khan University Hospital, Karachi over the last 6 years (July 1991 - July 1997) were included. Of these 219 were diagnosed on routine H&E examination while in the remaining 46 cases, diagnosis was made after a thorough IHC workup. (This group initially included 161 cases labelled as lymphoproliferative disorder with HD as one of the differentials).

Results: Out of a total of 265 HD cases (206) 78% were males and (59) 22%were females in a ratio of 3.5:1. 26%(69) cases were <15 years while 74% (196) were >15 years old. In both age groups, the commonest subtype proved to be Mixed Cellularity (MC) (60% of <15 years old and 40% of >15 years old) followed by Nodular Sclerosing (NS) (20% of <15 years old and 27% of >15 years old). Lymphocyte Predominant (LP) and Lymphocyte Depleted (LD) were seen less frequently. With the help of IHC studies performed on 161 cases in which HD was part of the differential diagnosis, 46 were conclusively diagnosed as HD. In the rest of the cases the main differential was Non-Hodgkin’s Lymphoma (NHL) that accounted for 72 of the cases.

Conclusion: This study shows that the most common sub-type of HD in our series in MC followed by NS. This study also suggests reasons why the more aggressive sub-type MC is predominant in Third world countries like ours compared to the better prognostic NS seen more in developed countries and why LP and LD are less and less commonly diagnosed (JPMA 49:211, 1999).

Introduction

Hodgkin’s disease (HD) is an old disease that was described by Sir Thomas Hodgkin in 1832. According to the universally accepted Rye classification, there are four subtypes of HD-Mixed Cellularity (MC), Nodular Sclerosing (NS), Lymphocyte Predominant (LP), and Lymphocyte Depleted (LD). Recently, in the new Revised European-American Lymphoma (REAL) classification, a provisional entity by the name of ‘Lymphocyte Rich Classic HD’ has been added. The common diagnostic factor in all these subtypes is the classic! variant forms of the Reed Stemberg (RS) cells, but generally, the morphology of each subtype is quite distinct. This is due to the presence of not only classic and variants of Hodgkin’s cells, but also due to different background cytological environments. The classification of hematological malignancies, including HD, has undergone a significant reappraisal in recent years. These changes have resulted from insights gained through the application of immunological and molecular techniques as well as better understanding of the clinical aspects of HD through advances in diagnosis, staging and treatment.

In Southern Pakistan, the facility for IHC studies is only available at The Aga Khan University Hospital in Karachi. While morphology is still the starting point for the histologic diagnosis of HD, immunologic and molecular techniques are crucial in confirmation of various entities particularly in an
equivocal situation with a differential diagnosis. In this study, besides looking at the spectrum of HD and its various subtypes with comparison to other studies, the impact of combined morphologic and phenotypic approach was studied to distinguish it from morphologically similar cases.

**Materials and Method**

This study includes all 265 cases of HD that were recorded in the files of the Surgical Pathology Department at The Aga Khan University Hospital, Karachi, between July 1991 and July 1997 (6 years). Most of the patients belonged to the southern part of Pakistan, especially the province of Sindh. Paraffin blocks of formalin-fixed nodal biopsies were cut at 3-5 um. and stained with H&E. In 46 cases (out of the 265) diagnosis of HD could only be made after a thorough IHC workup. These 46 cases were initially part of 161 cases labeled as lymphoproliferative disorders and had HD as one of the differentials. IHC studies were performed on all these 161 cases, by PAP technique. The Monoclonal Antibodies (MAbs) used included Leucocyte Common Antigen (LCA), Pan-T marker (UCHLI), Pan-B marker (CD20, L26), Leu-M1 (CD15), and Ki-1 (CD30). All sections were examined by the histopathologic consultants in the Department of Pathology at AKUH and were classified according to Rye’s scheme.

**Results**

During the period July 1991-July 1997 (6 years), a total of 265 HD cases were diagnosed in the Histopathology Department at AKUH, Karachi. These included 78% males (206 cases) and 22% females (59 cases) with a male to female ratio of 3.5:1. In the pediatric age group (~15 years), there were only 26% (69) cases, whereas the adult age group (>15 years) accounted for 74% (196) of the total number of cases. As shown in Figure 1, the age distribution pattern of 264 cases (one adult patient’s age was unknown) suggested that 78% of
the patients were <45 years old. The majority of these fell in the 15-29 years age group. The remaining 22% cases were >45 years old. The average age at diagnosis was 30.2 years. The youngest patient was a 2 years and 9 months old male while the oldest one was an 80 year old female. The male to female ratio among the children (<15 years old) was 4.3:1, while in the adult age group (>15 years old), it was 3.3:1.

In accordance with the pattern seen in third world countries, Mixed Cellularity (MC) was the most common subtype accounting for 45% (119) of all cases. Nodular Sclerosing (NS) was next, accounting for 25% (67) of all cases. Lymphocyte Predominant (LP) accounted for 14% (37) of the cases as did those cases that could not be sub-classified (Not Otherwise Specified/NOS). There were only 5 (2%) Lymphocyte Depleted (LD) cases.

Figure 2 illustrates the prevalence of the different subtypes in this study.

Out of the 69 cases in the <15 years age group, 60% (41) were of MC, 20% (14) of NS, 13% (9) of LP, and none of LD, while 7% (5) were unclassifiable (NOS). In the >15 years age group, out of 196 cases, 40% (78) were of MC, 27% (53) of NS, 14% (28) of LP and 3% (5) of LD, while 16% (32) were not classified further (NOS).

A comparison of the prevalence of different subtypes in the various Western and Third World countries is shown in Table 4-7.
It was noticed that in Western countries, NS is the most common subtype whereas in Third World countries like ours, MC is more common.

Out of the total 265 cases, 219 (83%) had been diagnosed on routine H&E examination, while the remaining 46 (17%) had been diagnosed after a thorough IHC workup. These 46 cases had initially been part of a group labeled as lymphoproliferative disorders (161 cases) in which HD was one of the differentials.

IHC studies had been performed on all these 161 cases and their results had helped in diagnosing the 46 HD cases (28.6% of the 161 cases). The other close mimics were reclassified as 44.7% (72) Non-Hodgkin’s Lymphomas (NHL), 5% (8) non-lymphoid disorders including sarcomas, carcinomas, etc., and a single case of angioimmunoblastic lymphadenopathy. In 21.1% (34) of these cases, the results proved inconclusive. The NHLs that made the majority of the cases, had been further classified as B-cell NHLs (23 cases), T-cell MHLs (22 cases), and T-cell rich B-cell NHLs (11 cases). The remaining 16 cases of NHLs included anaplastic large cell lymphoma, diffuse large cell lymphoma (NOS), immunoblastic NHL, lymphocytic lymphoma, or just lymphoma (NOS) (Figure 3).
Discussion

In this study, three glaring observations are made. The first is that there is an overwhelming majority of male cases in both age groups (<15 years and >15 years). In our society, it would not seem incorrect to attribute this biased sex statistic to the preference of seeking treatment for males over females. However, this trend of preponderance of Hodgkin’s disease (HD) among males is also seen in well-developed countries like USA. The most obvious illustration is Kerala (India), where it is a well-established fact that women have an equal position in the community; yet the sex ratio for HD in males and females over there is 3.1:16.

The second observation made in this study is that unlike Western studies which show a typically bimodal pattern of age distribution, with one peak at 15-40 years and another smaller peak in the 7th decade of life, there is a unimodal distribution pattern in Pakistan with 78% of the cases falling in the <45 years age group. Of these, majority of cases were between 15 and 29 years. Such a pattern has been seen in developing countries, suggesting significant geographical, racial, socioeconomic and personal (for instance, nutrition and immunological status) differences that lead to a higher incidence of HD in young adults here compared to the developed world. The reason for the lack of the second peak later in life could be the shorter life expectancies at birth in the developing countries. However, in African countries like Sudan and Kenya, an inexplicable bimodal pattern of age distribution has been observed.

The third, important observation is that Mixed Cellularity (MC) is the most common subtype. The preponderance of HD in males could be due to the lack of sufficient Nodular Sclerosis (NS) cases since this type, unlike the other subtypes shows a female preponderance in most series. However, in the
present study there are more males with the NS subtype too. International data shows that NS is the most common subtype (—.60%)\textsuperscript{10,11}. The fact, however, remains that in third world countries like ours MC is the most common subtype and the most likely reason for this could be the high incidence of infectious diseases, like EBV and infectious mononucleosis\textsuperscript{12}, as well as malaria, AIDS, TB\textsuperscript{7}, etc. It is known that MC is found significantly more often to contain the EBV genome material than is any other histologic subtype of HD\textsuperscript{13}. The EBV halts the apoptotic destruction of the host B cells, thus rendering them immortal. This is what leads to neoplastic changes in these cells, giving rise to the disease. MC is also the predominant subtype found in AIDS patients who have HD\textsuperscript{14}. The poorer socioeconomic and environmental conditions in countries like Sudan, India, and Pakistan have, therefore, a stage set for a higher prevalence of the more aggressive subtypes (MC and LD) as compared to the less aggressive and better prognostic ones (LP and NS)\textsuperscript{15}. It appears reasonable to hypothesize that a slow chronic process of lymphoid system stimulation leads to continuous B-cell proliferation in which there is a high risk of mutations and neoplastic growths. Some authors believe that HD is usually initiated as LP, and then progresses to the NS stage, even later to MC and finally to the most aggressive subtype, LD. So, it may be deduced that in third world countries, diagnosis is being made more at the MC stage of the disease, when lymphadenopathy is very prominent.

NS is the next most common subtype in this series, unlike data from a study carried out in Northern Pakistan in which LD is the second most common subtype, after MC\textsuperscript{8}. This places Southern Pakistanii, with MC and NS as the most common subtypes, intermediate between developed and developing regions, whereas Northern Pakistan remains relatively underdeveloped. Better health status, with better control of communicable diseases, universal immunization in childhood, and a better standard of living would cause a changing pattern of HD towards the better prognostic subtypes in more urbanized populations. An excellent example of this is Iran where socioeconomic and environmental improvements over the past 25 years have lead to the histologic pattern of HD in Iranian children to now be intermediate between that in underdeveloped and affluent societies\textsuperscript{16}. Immunohistochemically, HD is subdivided into Lymphocyte Predominant (LP) and non-LP (Classic) groups, the latter including NS, MC, and NS subtypes\textsuperscript{17}. LP can be further divided into nodular and diffuse types, and its neoplastic cells are of B-cell phenotype. In the Classic group, the neoplastic cells are the Hodgkin’s cells, which are Pan-B and LCA (CD45) negative\textsuperscript{12} and classically CD\textsuperscript{15} and CD30 positive\textsuperscript{16}. Although classic cases of HD, i.e. MC, NS, and LD, do not express B-cell markers or immunoglobulins on their surface, current theory is that this is due to non-coding sequences in their genome so that it is possible to confirm their B-cell origin by in situ hybridization but not by IHC. In contrast to classic HD, NHLs rarely show non-coding sequences.

In world literature, as well as in this study, it is observed that 2 groups of HD are now shrinking, i.e. Lymphocyte Predominant and Lymphocyte Depleted.

Diffuse LP has a very close differential, T-cell rich B-cell lymphoma, so much so that high grade B-cell NHLs occasionally evolve from LP. Thus, this subtype may be considered as a B-cell NHL\textsuperscript{1}. Clinical history, besides IHC, may give important clues to the nature of the lesion as LP HD usually present in a young adult with a single lymph node enlargement, the resection of which is usually curable. T-cell rich B-cell NHL, on the other hand, is seen more in older people. T-cell NHLs usually contain scattered Hodgkin-like or immunoblastic cells. This problem may often be resolved with good IHC workup. Recently, in the new REAL classification of lymphomas, a new provisional entity by the name of Lymphocyte Rich Classic HD is added\textsuperscript{2}. This is defined as a diffuse tumour with relatively infrequent Reed-Sternberg cells, which are of classic type rather than the variants seen in LP HD. Another rather vanishing HD subtype is LD, as on IHC this subtype may now be classified as all sorts of entities ranging from anaplastic large cell NHLs to carcinomas and melanomas, etc. The extent of the problem faced by histopathologists in diagnosing LD HD cases can be evaluated from a study
conducted in France in 1994. Thirty-five LD cases were reviewed and the diagnoses of 31 had to be rectified to NHLs, of which 5 were anaplastic Ki1+ and 14 to another HD subtype (6 NS and 8 MC). In summary, all this data proves that IHC is becoming increasingly important, not only to diagnose and subclassify HD cases, but more importantly to be able to exclude close differentials that seem to mimic HD morphologically. The development of monoclonal antibodies and molecular genetic analyses has greatly improved understanding of the various characteristics of HD. The exclusion of NHLs and other "look-alikes" of HD with the help of these techniques is extremely important as far as prognosis and treatment are concerned. The exact explanation of the varying histologic pattern of HD among the different parts of the world has yet to be confirmed. Further studies are also required to determine the precise cause and origin of HD.

References