RESEARCH ARTICLE

Frequency and Pattern of Bone Marrow Infiltration in Classical Hodgkin's Lymphoma: Experience from Southern Pakistan

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Abstract

   <u>Background</u>: **Hodgkin's lymphoma (formerly, Hodgkins disease) is a potentially curable malignancy with distinctive biological behavior and specific clinical characteristics. Limited information is available from developing countries for patients with classical Hodgkin's lymphoma (cHL). Therefore we reviewed the demographical and clinico-hematological profiles along with bone marrow infiltration patterns in adult patients presenting at Liaquat National Hospital and Medical College.** <u>Materials and Methods</u>: **In this cross sectional study, 62 adult (≥15 years) patients with cHL were enrolled from January 2010 to December 2014.** <u>Results</u>: **The mean age was 29.7±13.8 years with a median of 30 years. The male to female ratio was 2:1. B symptoms were present in 72.5% of patients and lymph node enlargement in 85.4%. The frequency of bone marrow infiltration in our cHL patients was found to be 27.4%, the pattern being predominantly focal followed by diffuse. The mean hemoglobin was 9.4±1.9g/dl with a mean MCV of 78.1±7.9 fl, a mean total leukocyte count of 10.9±20.6x10⁹/l and a mean platelet count of 241.6±150.1x10⁹/l.** <u>Conclusions</u>: **Our analysis shows that clinico-pathological features of cHL in Pakistan are comparable to published data. Peripheral lymphodenopathy associated with B symptoms is the commonest presentation. Bone marrow involvement is more common in our setup as patients usually presented at an advanced stage of disease.**

Keywords: Hodgkin's lymphoma - clinico-pathology - bone marrow infiltration -Pakistan

Introduction

   Classical Hodgkin lymphoma (cHL) encompasses a group of lymphoid neoplasms with a multifaceted etiology and epidemiology (Roshandel et al., 2011). As per WHO, cHL accounts for about 1% of all cancers and ~30% of the lymphoid malignancies worldwide (Swerdlow et al., 2008). Literature review demonstrates a remarkable diversity of the disease incidence according to age, gender, ethnic background, geographical location and socioeconomical status (Jarrett et al., 1996; Cartwright et al., 2004). The highest incidence was reported among Caucasians, followed by African Americans and Hispanics (Cartwright et al., 2004).

   Hodgkin lymphoma is an uncommon malignancy with an overall incidence of about 2.4-2.8/100,000 individuals yearly with the peak cases reported between 15-29 years of age (Sive and Linch., 2011; Smith et al., 2015; Sader-Ghorra et al., 2014). Recent advancement in diagnosis and treatment of Hodgkin's lymphoma has changed the perspective of disease.

   Though no clear cut etiological agent has been identified, but the association between Hodgkin's lymphoma and viral infections has been discussed, especially regarding Epstein Barr Virus infection and human immunodeficiency virus (Tang et al., 2013; Li et al., 2012).

   The clinical biology of cHL among patients is highly heterogeneous depending upon disease stage at presentation. These symptoms often include fever, drenching sweating, weight loss, fatigue or peripheral lymphodenopathy. Visceromegaly may occur in these patients, but it is typically mild and mostly asymptomatic.

   Hodgkin lymphoma (cHL) is characterized morphologically by the presence of distinctive pathognomonic cells called Reed Sternberg (RS) cells in the background of reactive lymphocytes, histiocytes (macrophages) and granulocytes. Bone marrow involvement by Hodgkin lymphoma is rather uncommon in western studies (Howell et al., 2002; Levis et al., 2004). The involvement of the marrow in a patient with classical Hodgkin lymphoma represents advanced stage IV disease.

   To date very little information is available from our country on this disorder. Research on epidemiological

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features of cHL is poorly reported from countries with limited resources. This report describes the demographical data, clinical features and laboratory findings in cHL patients. Secondly we also determined the frequency and pattern of bone marrow infiltration by cHL at the time of diagnosis.

Materials and Methods

This retrospective cross sectional study was conducted at hematology department of Liaquat National Hospital, extended over a period of 5 years from January 2010 to December 2014.

The cases were diagnosed by morphology on H & E sections and IHC profile according to WHO classification of lymphoid neoplasms. Immunohistochemical (IHC) stains using antibodies against CD 20, CD 3, CD 10, CD 5, CD 23, BCL2, cyclin D1, CD 79a, CD 30 and CD 15 were done in each case. Patients diagnosed as classical HL (CD 15 & 30 positivity) who were ≥15 years of age were included in the study. Patients with other lymphoid neoplasm were excluded. Patients with another associated malignancy or having relapsed/ refractory HL were also excluded. All post-chemotherapy and radiotherapy cases were not included in the study.

Based on this, a total of 62 subjects with newly diagnosed untreated classical HL were included in this analysis.

Complete blood counts were determined by Automated Cell Dyne counter. Bone marrow aspirate and trephine samples were taken from posterior superior iliac spine by the standard technique through Jamshidi needle after informed written consent. Trephine sections were stained with H& E, which was reviewed by expert hematologist.

An ethical approval to conduct this analysis was granted by the institutional ethical review committee.

Statistics analysis

Data was assembled and analyzed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc, Chicago, IL, USA). The results were expressed as mean (SD) for quantitative variables and are presented as frequency & percentages for qualitative variables.

Results

Baseline characteristics

Out of 62 patients, 42 were males (67.7%) and 20 were females (32.2%) with male to female ratio of 2:1. Age ranged between 15 and 76 years with the mean age was 29.7±13.8 years and the median age of 30 years. Majority of patients (74.1%) were under 30 years of age (table-1).

Clinical findings

B symptoms were present in 45 (72.5%) patients, out of which fever was commonest, seen in 40 (64.5%); drenching night sweats in 36 (55%) patients, while 23 (37%) patients had history of weight loss. Lymph node enlargement was present in 53 (85.4%) cases. The most common lymph node palpable was cervical and axillary nodes. The splenomegaly and hepatomegaly were noted

Table 1. Age Stratification in Adult Patients with Hodgkin's lymphoma

Age groups	Male	Female	Total	Percentage
	n=42	n=20	n=62	%
15-30	31	15	46	74.1
31-50	5	3	8	12.9
51-65	4	2	6	9.6
65-76	2	0	2	3.2

in 16 (25.8%) and 11 (17.7%) patients respectively.

Laboratory features

The frequency of bone marrow infiltration in our cHL patients was found to be 27.4% (n=17). Pattern of infiltrate was focal in 9 (14.5%) patients followed by diffuse in 7 (11.2%) patients. The least encountered type was nodular in 1 (1.7%) of patient.

The mean hemoglobin was 9.4±1.9g/dl (6.8-15.8g/dl) with the mean MCV of 78.1±7.9 fl. The mean total leukocyte count of 10.9±20.6x10^9/l (1.5-22.9x10^9/l); mean absolute neutrophils count of 3.8±3.0 x10^9/l and the mean platelets count were 241.6±150.1x10^9/l (16-651x10^9/l). Anemia (Hb<10gm/dl) was noted in 15 (24.1%) patients. Thrombocytopenia (platelets count <100x10^9/l) was detected in 5 (8.0%) patients.

Discussion

Classical Hodgkin's lymphoma is an uncommon B-cell lymphoid neoplasm which affect around 9000 new patients per annum (Ansell., 2015). The prognosis of patients with classical Hodgkin lymphoma has been tremendously improved during the last 4 decades. cHL is an uncommon entity and very limited studies are available from Pakistan. Herein we have described a series of 62 adults cHL patients followed at our institution during the five year period.

The principal cHL epidemiological features so far described show age predilection in more studies, with the median age around ~30 years. In Pakistani population disease is also identified in younger age group, as majority (3/4) of our patients were under 30 years. This is consistent with previous reports published from Pakistan on cHL by Siddiqui and Fatima et al (Siddiqui et al., 2006; Fatima et al., 2011). This is also similar to earlier studies from India and Egypt where average age were 30 and 31.4 years respectively (Ganesan et al., 2011; Gad Allah et al., 2014). However, we did not observe a second peak of age as have been noted in earlier studies from developed countries (Hasenclever et al., 1998).

It is consistently noted that cHL is frequently seen in male patients. Higher male to female ratio has also been established in earlier studies from Pakistan and other countries include Korea and Brazil (Cheong et al., 2006; Vassallo et al., 2005).

In general, Hodgkin lymphoma is characterized by the customary spread of disease from one lymph node group to another and by the development of B-systemic symptoms usually associated with advanced disease.

In the present study majority patients presented with intermittent fever, followed by night sweats and significant weight loss. It was noted that the prevalence of B-symptoms in our patients from southern Pakistan was comparable with that reported in the previous local study (fever; 59.6% , weight loss; 33.6%) from Pakistan (Siddiqui et al., 2006). Majority (85.4%) of our patients presented with lymph node enlargement. This is consistent with previous reports published from India and turkey on classical HL (Ganesan et al., 2011; Kılıçkap et al., 2013).

Staging of the cHL is foremost important for the therapeutic decisions in the management of these patients. Bone trephine biopsy is one of the important investigation, which is being carried out for staging workup along with other investigations like CBC, Computed tomography and PET scanning. Bone marrow infiltration in cHL has been observed from various racial backgrounds ranging from 2% to as high as 38% (Lone et al., 2011).

Previous studies reported from Pakistan revealed relatively higher prevalence of lymphomatous infiltration compared with western studies. Our findings are comparable with those of Butt (27.5%), Lone (38%) and Hamid (30%) reported from different areas from Pakistan (Butt et al., 2002; Lone et al., 2011; Hamid et al., 2010).

In contrast, studies from Italy and United Kingdom revealed fewer prevalence of infiltration accountable in 10% and 2.2% respectively (Franco et al., 2004; Howell et al., 2002). Distinctly in economically developed countries where majority of patients present with early stage (stage I and II), 27.4% of patients at our center presented with advanced stage (Shankar et al., 1997). A higher percentage of bone marrow infiltration in Pakistan may be explained on the basis that ~1/3 patients present at late stages of disease in contrast to developed countries. The delay in seeking medical treatment is attributed to financial constraints and lack of diagnostic and referral facilities.

Lastly limitations of our study need to be mentioned, related to its retrospective nature and relatively small sample study. A larger sample size study would be a better indicator of clinical and laboratory attributes in our patients population. The results are from a single tertiary care centre and consequently, there may be a referral bias.

In conclusion, the present study reflects the invasive potential of classical Hodgkin's lymphomas in our population. Important observations in the present study include young age at diagnosis, higher male to female ratio, higher incidence of B symptoms and higher proportion of patients with advanced cHL having marrow infiltration at disease manifestation.

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