Significance of Bone Marrow Biopsy in Staging of Hodgkin's Lymphoma

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Introduction: Lymphomas are malignant neoplasms arising from the lymphoid tissue. They are divided into two groups, Hodgkin's Lymphoma and Non- Hodgkin's Lymphoma. Staging of Hodgkin's lymphoma is important for the management and treatment of the patient. Bone marrow biopsy is one of the investigations carried out for staging of the disease along with other investigations.

Objective: To determine the significance of bone marrow biopsy in clinical staging of patients diagnosed with Hodgkin's disease.

Study Design: Descriptive case series study.

Settings: Pathology Department King Edward Medical University Lahore, along with all the medical, surgical and oncology wards of Mayo hospital and affiliated hospitals.

Duration: 20th March 2009 to 19th September 2009.

Subjects: 50 patients diagnosed to have Hodgkin's lymphoma on lymph node biopsy.

Methods: Clinical history was taken and relevant physical findings were recorded in the proforma.. CBC was done on Sysmex KX 21. Bone marrow aspirate and trephine biopsies were performed from posterior iliac crest. Bone marrow aspirates were stained with Wright- Giemsa stain and trephine biopsies were stained with Hematoxylin and Eosin. Aspirates and trephine biopsies were evaluated and assessed for cytological features, marrow architecture, haemopoietic tissue and any lymphoprolifrative infiltration.

Results: Out of 50 patients bone marrow infiltration was seen in 15 (30%) cases. After bone marrow examination 5 patients in clinical stage II and 8 patients in stage III were placed in stage IV due to infiltration by Hodgkin's lymphoma.

Conclusions: Bone marrow infiltration is more common in our setup as patients present at later stages. Bone marrow biopsy should be performed during initial staging of Hodgkin's lymphoma.

Key Words: Hodgkin's lymphoma, Significance, Staging.

Introduction and Background

Hodgkin's lymphoma has always engendered much interest despite its relative rarity. This, perhaps is mainly due to the fact that Hodgkin's lymphoma was amongst the first treatable cancers that responded well to combination chemotherapy. It is described by the occurrence of pathognomonic Reed-Sternberg and Hodgkin's cells[1].

Regional lymphadenopathy is the most common clinical presentation of Hodgkin lymphoma. Usually there is involvement of a single group of peripheral lymph nodes and thereby spreads to the contiguous lymph nodes. Cervical and supra clavicular lymph nodes are the most common sites of involvement.

WHO classifies Hodgkin's lymphoma into Classical Hodgkin's lymphoma including Nodular Sclerosis, Lymphocyte Depletion, Lymphocyte Rich and Mixed Cellualrity Hodgkin's lymphoma and Lymphocyte Predominance as a separate entity.[2] Hodgkin's lymphoma is confirmed by the existence of Reed–Sternberg cells within a mixed cellular infiltrate. In the cases of nodular sclerosing type and nodular lymphocyte predominant Hodgkin's lymphoma, the presence of variant forms of Reed–Sternberg cells is adequate to ascertain the diagnosis.

The advent of radiotherapy and combination chemotherapy in treating Hodgkin's disease requires accurate clinical staging for the selection of the type of therapy. As bone marrow lacks lymphatics, its infiltration indicates vascular dissemination and puts patient in stage IV.[3] In adult population the incidence of bone marrow infiltration in Hodgkin's lymphoma is around 10% but in pediatric population the incidence is very low (1.8%). A primary extranodal involvement by Hodgkin's lymphoma (HL) is rare, occurring in <0.25% of patients with Hodgkin's lymphoma.[4]

Bone marrow biopsy is an indispensable investigation in the management of various lymphomas. It is not only an essential investigation in the staging of malignant lymphomas but is also of primary importance as the diagnostic investigation in patients where overt lymph node enlargement is not present or where lymph node biopsy is inadequate to classify lymphoma. Furthermore, the results of bone marrow biopsy may modify the initial treatment as well as affect the decision at the time of relapse (feasibility of autologous bone marrow transplant).

The incidence of bone marrow involvement in Hodgkin's lymphoma varies with the histologic subtype: 10% in classical Hodgkin's mixed cellularity, approximately 1% in lymphocyte predominant Hodgkin's and lymphocyte rich classical Hodgkin's lymphoma, and 3% in Nodular Sclerosis subtype.[5] Although lymphocyte depleted Hodgkin's lymphoma is the rarest subtype it often shows selective extranodal presentation including involvement of bone marrow with relative sparing of peripheral lymph nodes. Diagnosis of Hodgkin's disease at extranodal sites requires the presence of Reed-Sternberg cell, it is not required in case of bone marrow infiltration as only 2/3rd of the cases show the presence of Reed-Sternberg cells. As the course of disease, choice of therapy, treatment, management and prognosis are all intimately related to the staging of disease, this study will be helpful in establishing the significance of bone marrow biopsy in staging and management of the disease in our population.

Objective

To determine the significance of bone marrow biopsy in clinical staging of patients diagnosed with Hodgkin's disease.

Materials and Method

It was a descriptive case series study, conducted in Pathology department of King Edward Medical University, Lahore and included all the cases from the medical, surgical and oncology wards of Mayo Hospital and affiliated referring hospitals. 50 Consecutive cases of Hodgkin's lymphoma, histologically diagnosed on lymph node biopsy were included. Treated or relapsed cases and patients with inconclusive histological findings were excluded from the study.

After selecting the subjects of study, their socio- demographic information was obtained. A detailed clinical history was taken. The patients included in the study were examined thoroughly and methodically. The history and clinical findings were supported by relevant investigations which included blood complete examination, urine complete examination, estimation of urea and creatinine levels, liver function tests, LDH levels, tissue biopsy, ultrasonography and CT scanning. Bone marrow aspiration and trephine biopsy were performed from posterior iliac crest, under local anesthesia with minimal discomfort after an informed consent. Marrow aspirates were stained with Wright-Giemsa stain. Imprints were made from biopsy and specimen was placed in formalin for fixation. After fixation it was decalcified in 10% nitric acid, embedded in Paraffin wax blocks, thin sections were cut and stained with Hematoxylin and Eosin. The slides obtained were evaluated by light microscopy. Data was entered on and processed using statistical program for social sciences (SPSS) version 10.

Results

Fifty consecutive patients diagnosed as Hodgkin's lymphoma were included in our study. Out of 50 patients 18 were females (36%) and32 (64%) were males. The age of the patients ranged from 7 to 70 years with a mean age of 31.8 years. Age distribution among males and females is shown in Figure 1.

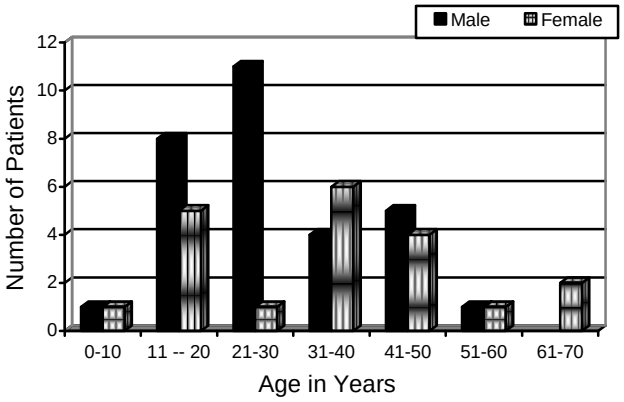

Fig. 1: *Age Distribution among Patients with Hodgkin's Lymphoma.*

Table 1: *Clinical Presentation of Patients with Hodgkin's Lymphoma.*

Sr. No.	Primary site	Number of patients	
		Total Cases 50	%
1.	Cervical Lymph nodes only	13	26
2.	Cervical and Sub-Mandibular lymph nodes	3	6
3.	Cervical and Supra-clavicular lymph nodes	1	2
4.	Cervical and Axillary lymph nodes	6	12
5.	Cervical and Mediastinal lymph nodes	2	4
6.	Supraclavicular lymph nodes	1	2
7.	Supraclavicular and Axillary lymph nodes	1	2
8.	Axillary lymph nodes	1	2
9.	Multiple sites above diaphragm	1	2
10.	Cervical and abdominal lymph nodes	4	8
11.	Cervical and Inguinal lymph nodes	4	8
12.	Inguinal lymph nodes	2	4
13.	Axillary and Inguinal lymph nodes	3	6
14.	Generalized Lymphadenopathy	8	16

In case of clinical presentation, majority of the patients presented with cervical lymphadenopathy alone (26%). Frequency of different clinical presentations is shown in Table 1.

On the basis of clinical diagnosis, patients were investigated before bone marrow examination. Various investigations for clinical staging included abdominal ultrasonography, C T scanning and MRI (in selective cases). Majority of the patients 20 (40%) were in clinical stage III. Detailed distribution of patients among various stages is shown in Table 2.

Table 2: *Clinical Staging Before Bone Marrow Examination.*

Type	Total No. of Cases	Stage I	Stage II	Stage III	Stage IV
Mixed Cellularity	35	9 (25.7%)	12 (34.2%)	13 (37.1%)	
Nodular Sclerosis	10	1 (10%)	3 (30%)	5 (50%)	
Lymphocyte Predominance	4	2 (50%)	-	2 (50%)	
Lymphocyte Depletion	1	1 (100%)	-	-	
Total	50	13 (26%)	15 (30%)	20 (40%)	

Bone marrow infiltration was seen in 15(30%) of patients.

On bone marrow examination 5 patients from Stage II, 8 patients from stage III and both the patients from stage IV showed bone marrow infiltration.

B symptoms (Fever greater than 38°C, drenching night sweats, and weight loss exceeding 10 percent of baseline body weight during the 6 months preceding diagnosis are designated as B symptoms) were seen in 8 (16%) of patients. Frequency of various symptoms is shown in Figure 2.

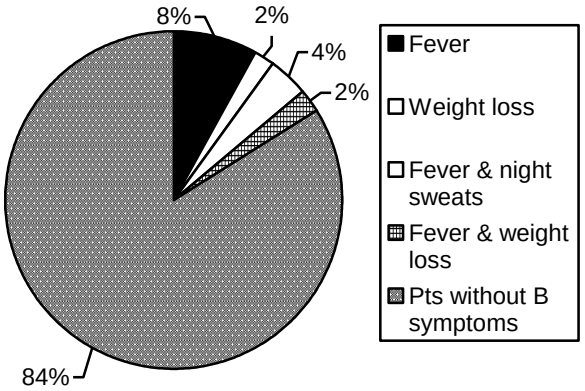

Fig. 2: *B Symptoms in Patients with Hodgkin's Lymphoma.*

Since B symptoms were seen more frequently in advanced disease, 6 out of 8 (75%) of our patients showed bone marrow infiltration. Details of relationship of B symptoms with clinical staging is showm in Table 3.

Discussion

Hodgkin's lymphoma is relatively rare and its incidence varies with geographical location. Amongst the malignant lymphomas it has an incidence of 20-40% in western countries, whereas it constitutes 4.4-18% of malignant lymphomas in Asian countries.

In this study the mainstay is bone marrow examination. For bone marrow examination trephine biopsy is necessary in Hodgkin's disease, because the neoplastic cells may not be present in the aspirate even when the marrow is involved. It is important to have a high index of suspicion and pick up the histopathological changes of Hodgkin's lesions in the bone marrow as the marrow may be the initial or sometimes the only site of involvement.

Humayun et al[6] observed a 10: 1 male to female ratio. In studies by Cheema et al[7] and Neelam Siddiqui et al[8] economic status, taboo for treatment of a female child and more care for male child has been attributed to a male dominated society. Hasanbegavic[9] in his study conducted at Sarajevo showed a slight male preponderance (1:1.4). In our study there were 32 males and 18 females which correlates with majority of above mentioned studies. It is difficult to state whether the male preponderance is due to limited care for females in a male dominated society or due to females having more resistance to the causative factors and initiating process of Hodgkin's lymphoma. A more scientific approach is required to study the epidemiology of Hodgkin's lymphoma.

Correa and Conner[10] did their land mark study of epidemiological pattern of the disease in relation to socioeconomic status, age and sex distribution. They observed a bimodal peak regarding age at presentation. However in a Pakistani study by Neelam et al[8] a unimodal peak pattern was seen with most of patients presenting at 18-30 years. In our study average age is 31.8 with 13 females and 24 males below the age of forty years. We had only 13 patients above the age of 40 years. A unimodal peak may logically be attributed to a lower life expectancy in our population.

Cervical lymph node enlargement is a common presentation in Hodgkin's lymphoma. Nuzhat Yasmin et al observed in their study that a considerable proportion of patients

TABLE 3: *Relationship of B Symptoms with Clinical Staging after Bone Marrow Examination.*

		Before Bone Marrow Biopsy				After Bone Marrow Biopsy			
B Symptoms	**Total No. of Patients**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Fever	4	-	1 (25%)	2 (50%)	1 (25%)	-	1 (25%)	-	3 (75%)
Fever and Night Sweats	2	-	-	2 (100%)	-	-	-	-	2 (100%)
Fever and Weight Loss	1	-	1 (100%)	-	-	-	-	-	1 (100%)
Weight Loss	1	-	1 (100%)	-	-	-	1 (100%)	-	-
Total	8	-	3 (37.5	4 (50%)	1 (12.5)	-	2 (25%)	-	6 (75%)

with cervical lymph node enlargement (78%) were having antituberculous treatment.[11] In our study 26% patients were having cervical lymphadenopathy, out of which 65% had taken antituberculous treatment. This is due to the fact that tuberculosis has widespread occurance in our society and general practitioners are impulsive in writing antiuberculous drugs before meeting certain bio-chemical criteria of diagnosis.[11] In the study by Neelam Siddique et al[8] majority of the patients presented with lymphadepathy, fever, and weight loss.

Bone marrow infiltration was seen in 53.4% of patients.[8] Neelam et al. concluded high percentage of bone marrow infiltration by Hodgkin's lymphoma in Pakistan. This may be explained on the basis that more than 50% patient present at late stage (III and IV). There is delay in seeking medical advice and poor health care coverage in remote areas of Pakistan. In comparison, majority of western authors state that there is early presentation in stage I and II.[12] Our study showed 28 patients (56%) in stage I and II and 22 (44%) in stage III and IV. This shows some deviation from Neelam et al's results. We should have a more elaborate coverage of population to make this evident for comparison with local authors.

The significance of bone marrow biopsy is matchless in staging Hodgkin's lymphoma as bone marrow lacks lymphatics, its infiltration indicates vascular dissemination and categorizes patient in stage IV. A single bone marrow biopsy should be adequate in diagnosis in most cases. Subramanian et al did simultaneously bone marrow aspirate and bone marrow trephine biopsy in 66 cases of proven Hodgkin's lymphoma.[13] Bone marrow infiltration was seen in 14 (18%) cases. Only one aspirate was suspicious of metastasis. Rest were either diluted (28%) or normal 64%. Of all the diagnosed cases 18% were diagnosed on bone marrow trephine. Eleven patients were upstaged from stage I to stage III and from stage III stage IV based on bone marrow involvement. In our study bone marrow trephine biopsy was done on all the diagnosed patients. The role of bone marrow trephine has been considered as non-mandatory by some authors, especially in stage IA and B and in some patients with stage II. A decision for biopsy may be taken by considering individual clinical scenarios. This may be considered so that the concept of not performing bone marrow trephine in early stage Hodgkin's lymphoma could be revised. I wish to highlight the importance of bone marrow trephine over aspiration in staging even in clinically early stage of Hodgkin's lymphoma. It can be concluded easily that definitive epidemiological studies are required to evaluate causative factors, more preponderance for male sex and unimodal presentation. More stress should be emphasized for bone marrow trephine in early stage disease.

B-symptoms were observed in 56.82% of patients studied by Humayun et al[6] as compared to 30% in western countries. Humayun et al in their study failed to demonstrate relationship between B-symptoms and patients presenting in stage III and IV. In our study we can clearly see that eight (16%) patients had B-symptoms. Six (75%) patients had bone marrow infiltration thus indicating advanced disease in patients having B symptoms Bone marrow biopsy is an economical and a reliable investigation to identify marrow involvement in patients with B symptoms even at early stages as 3 (37.5%) patients were placed in stage II before bone marrow examination.

It can be easily concluded that definitive epidemiological studies are required to study causative factors regarding male preponderance, unimodal clinical presentation and relationship of B symptoms with bone marrow involvement. More stress should be made for bone marrow trephine in early stage disease.

Conclusion

We strongly recommend bone marrow biopsy in every case of Hodgkin's lymphoma. This is especially important in an under resourced country like Pakistan where most cases present late in their disease course and where more recent

staging investigations like PET scan are unaffordable to most patients.

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