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FREQUENCY AND PATTERN OF BONE MARROW INFILTRATION IN HODGKIN'S LYMPHOMA

AYAZ LONE[1] AND SAMINA NAEEM[2]
[1]*Department of Haematology, Fatima Memorial Hospital College of Medicine and Dentistry,*
[2]*Department of Pathology, King Edward Medical University, Lahore – Pakistan*

ABSTRACT

Introduction: Lymphomas are malignant neoplasms arising from lymphoid tissue. They are divided into two groups i.e Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma. Staging of Hodgkin's Lymphoma is important for the management and treatment of the patient. This study was carried out to determine the frequency of bone marrow infiltration at the time of diagnosis as well as various patterns of bone marrow involvement.

Materials and Methods: Clinical history and physical findings were recorded in the proforma. Investigations were carried out. Bone marrow aspirate and trephine biopsies were performed from posterior iliac crest. Aspirates and trephine biopsies were evaluated and assessed for cytology, marrow architecture, haemopoietic tissue and any lymphomatous infiltration. In cases with infiltration, the infiltration pattern was studied.

Results: Fifty Hodgkin's lymphoma patients were studied. Bone marrow infiltration was found in 19 (38%) cases. Among these 19 patients with infiltration 17 (89.4%) patients were of Hodgkin's Lymphoma mixed cellularity and 2 (10.5%) had Hodgkin's Lymphoma Nodular Sclerosis. Pattern of infiltrate was interstitial in majority of cases followed by diffuse type of infiltration.

Conclusion: Bone marrow involvement in Hodgkin's Lymphoma is more common in our setup as patients present at a later stage. It is recommended that bone marrow examination should be performed as a part of staging investigations in patients with Hodgkin's Lymphoma.

Key Words: Hodgkin's Lymphoma (HL), bone marrow infiltration.

INTRODUCTION

Lymphomas are malignant neoplasms characterized by the proliferation of cells native to the lymphoid tissue. They are divided into two broad groups, Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). HL is characterised morphologically by the presence of neoplastic giant cells the Reed – Sternberg (RS) cells admixed with a variable inflammatory infiltrate.

RS cells express CD30 and CD15 antigens. Hodgkin's lymphoma was first described in 1832.[1] In adult population the incidence of bone marrow infiltration in Hodgkin's lymphoma is around 10% but in paediatric population the incidence is very low (1.8%).[2]

HL is classified according to the WHO Classification, which is the reviewed REAL classification into a) Classical Hodgkin's lymphoma, which includes Nodular Sclerosis, Lymphocyte Depletion, Lymphocyte Rich and Mixed Cellualrity HL and b) Lymphocyte Predominance as a separate entity.[3]

Staging of the lymphoma is important for the management and treatment of the patient. Bone marrow trephine biopsy is one of the first investigation, which is being carried out for staging[4,5] along with clinical findings and other investigations like CBC, CT scanning, Ultrasonography and MRI. In many centers flow cytometry of bone marrow aspirates is also being used in staging.[6-8]

This study was conducted to see how many patients presenting to us have bone marrow infiltration at the time of diagnosis. This places them in Stage IV disease, which is associated with poor prognosis. Patterns and extent of bone marrow involvement by different varieties of HL was also studied.

MATERIALS AND METHODS

This study was conducted at King Edward Medical University, department of Pathology, Lahore from January 2004 to January 2005and included all the cases from the affiliated and referring hospitals. The patients of Hodgkin's Lymphoma diagnosed on tissue biopsy (nodal and extra nodal) were included in the study. Patients already on treatment and relapsed cases were not included in this study.

A detailed clinical history was taken from the patients selected, thorough clinical examination was done. Relevant investigations which included blood complete examination, urine complete examination, urea and creatinine levels, liver function tests, LDH

levels, tissue biopsy, ultrasonography and CT scans were also recorded.

Bone marrow aspiration and trephine biopsy was performed from posterior Iliac crest, under local anaesthesia with minimal discomfort. Marrow aspirates were stained with Wright – Giemsa stain. Sections of trephine biopsy were stained with Haematoxylin and Eosin. Assessment was made of the cytological features of cells in marrow aspirate smears. Trephine biopsies were evaluated for architecture, vessels, stroma, haemopoietic tissue and pattern of lymphoid infiltrates (diffuse, interstitial, focal, nodular, focal patchy and paratrabecular).

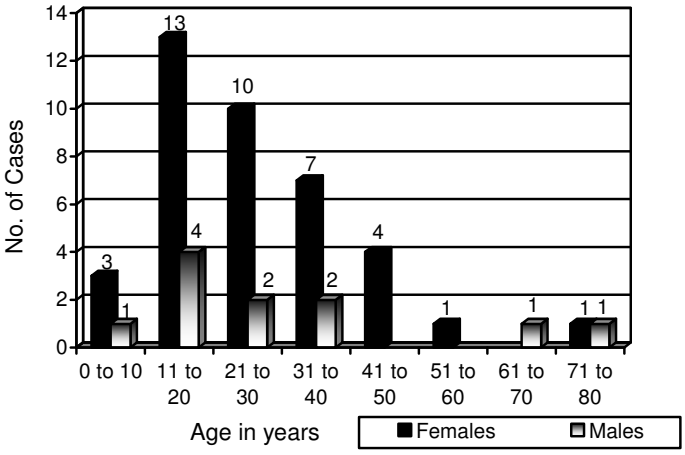

Fig 1: *Age distribution in Hodgkin's lymphoma in males and females (n = 50).*

RESULTS

Among the 50 HL patients 11 were females (22%) and 39 (78%) were males. The age of the patients ranged from 7 to 80 years with a mean age of 28.1 years S.D ± 17.11. Ten patients (20%) were in paediatric age group below 15 years (1 female and 9 males). Age distribution in male and female cases is shown in figure 1.

Majority of the cases presented with cervical lymphadenopathy (42%) followed by generalised lymphadenopathy (12%).

Thirty nine patients (78%) had Hodgkin's lymphoma Mixed Cellularity (8 females and 31 males), 7 patients (14%) had Hodgkin's lymphoma nodular sclerosis type (3 females and 4 males), 3 (6%) had Hodgkin's lymphoma Lymphocyte predominant (males) and only one (2%) case was of Hodgkin's lymphoma lymphocyte depletion (male) type.

Table 1: *Frequency of bone marrow involvement in different types of Hodgkin's Lymphoma in total cases, females and males.*

Types	*Total Cases*			*Females*			*Males*		
	Total	*Bone Marrow Involvement*		*Total*	*Bone Marrow Involvement*		*Total*	*Bone Marrow Involvement*	
		N	*%*		*N*	*%*		*N*	*%*
Mixed cellularity	39	17	43.5	8	4	50	31	13	41.9
Nodular Sclerosis	7	2	28.5	3	2	66.6	4	-	-
Lymphocyte predominance	3	-	-	-	-	-	3	-	-
Lymphocyte Depletion	1	-	-	-	-	-	1	-	-
Total	50	19	38	11	6	54.5	39	13	33.3

Table 2: *Pattern of bone marrow infiltration in different types of Hodgkin's Lymphoma.*

Type	Total Cases with Infiltration	Interstitial Infiltration	Diffuse Infiltration	Focal Infiltration
Mixed cellularity	17	10	5	2
Nodular Sclerosis	2	2	-	-
Total	19	12	5	2

According to clinical and diagnostic work up prior to bone marrow examination these patients presented in different stages of disease. Thirteen (26%) were in Stage I, 9 (18%) were in Stage II, majority of the patients, 18 (36%) were in Stage III and 10 (20%) patients were already in Stage IV disease with liver involvement. B symptoms were present in 11 (22%) cases. Bone

Table 3: *Role of bone marrow examination in staging of Hodgkin's Lymphoma.*

Type	Total No of Cases	Before Bone Marrow Examination								After Bone Marrow Examination							
		Stage I		Stage II		Stage III		Stage IV		Stage I		Stage II		Stage III		Stage IV	
		No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Mixed Cellularity	39	8	20.5	5	12.8	17	43.5	9	23	8	20.5	4	10.2	7	17.9	20	51.2
Nodular Sclerosis	7	3	42.8	4	57.1	-	-	-	-	2	28.5	3	42.8	-	-	2	28.5
Lymphocyte Predominance	3	2	66.6	-	-	1	33.3	-	-	2	66.6	-	-	1		-	-
Lymphocyte Depletion	1	-		-		-	-	1	100	-	-	-	-	-	-	1	100
Total	50	13	26	9	18	18	36	*10	20	12	24	7	14	8	16	~23	46

*Cases grouped in Stage IV because of Liver involvement
~ 4 cases didn't showed marrow infiltration. They were in Stage IV before marrow examination because of Liver involvement

marrow infiltration was found in 19 (38%) cases (6 females and 13 males).

Infiltrate comprised of eosionphils, lymphocytes, plasma cells, Reed Sternberg cells, and Hodgkin's cells. Fibrotic and hypocellular marrow was also seen in some cases. Among the 19 patients with infiltration 17 (89.4%) were of Hodgkin's lymphoma mixed cellularity (4 females and 13 males) and 2 (10.5%) had Hodgkin's lymphoma nodular sclerosis type (both females) (Table 1). So bone marrow infiltration was present in 43.5% (17 of 39) cases with mixed cellularity Hodgkin's lymphoma and 28.5% (2 of 7) of those with nodular sclerosis. Twelve patients (63%) had interstitial infiltration with background fibrosis, 5 (26%) had diffuse pattern of infiltration with fibrosis and 2 (10%) patients had focal infiltration (Table 2). Bone marrow aspirates of 10 patients showed prominence of lymphocytes, plasma cells, eosinophils with occasional atypical mononuclear cells. Only 2 patients with these findings on aspirates had lymphoma cell infiltration in marrow on trephine biopsy.

DISCUSSION

The objective of present study was to determine the frequency of bone marrow involvement in different clinical stages and histological types of Hodgkin's Lymphoma. The present study reflects the growth and invasive potential of Hodgkin's lymphomas in our population. All the cases included in this study were already categorised and typed by immunohistochemistry either from Agha Khan Hospital, Karachi or Shaukat Khanum Memorial Cancer Hospital, Lahore.

A total of 50 cases of Hodgkin's lymphoma were investigated for frequency and pattern of bone marrow infiltration. Among these 19 (38%) had bone marrow infiltration at the time of diagnosis, which placed them in Stage IV disease. Mixed cellularity Hodgkin's lymphoma was the most common histological type and showed marrow involvement in 43.5% (17 of 39) cases. This was followed by nodular sclerosis 28.7% (2 of 7) cases. Study carried out at Agha Khan University Hospital Karachi showed that Mixed Cellularity Hodgkin's lymphoma is more prevalent in our population,[9] this is similar to our study. In adult population the incidence of bone marrow infiltration is estimated between 2 – 32%.[2] Bone marrow involvement represents Stage IV disease i-e disseminated involvement of an extra nodal organ.

The study carried out by Fauzia et al[1] showed bone marrow infiltration in 27.5%, the frequency was higher in females i.e 57% as compared to males showing 21.9%. Infiltration of bone marrow was seen most commonly with mixed cellularity Hodgkin's Lymphoma. Study carried out by Sharma[10]

showed a much higher incidence of bone marrow involvement. In his study bone marrow infiltration was present in 36.2% cases. Most of the cases were in Stage III and Hodgkin's Disease mixed cellularity showed highest incidence of marrow involvement. In our study the frequency of marrow infiltration is also high (38%) and majority of the cases are of mixed cellularity Hodgkin's lymphoma. Patients in Pakistan present late for treatment because of lack of resources or ignorance. Lei K et al[11] studied 6 cases and only one was in Stage IV, giving a percentage of 16.6%. In another local study carried out by Akram et al[12] bone marrow infiltration was seen in 21.3% cases. Ananthamurthy[13] in his study found infiltration of the marrow in 20% cases at the time of diagnosis with marrow suppression, fibrosis and lymphocytes aggregates.

In the present study after the bone marrow trephine biopsy 1 patient was in Stage I, 2 in Stage II, 10 patients III and 6 patients stage IV showed bone marrow infiltration. Four patients who were in Stage IV disease prior to bone marrow examination because of liver involvement didn't show bone marrow infiltration (Table 3). All the corresponding bone marrow aspirates were negative for infiltration and this showed that biopsies are superior to aspirates for the diagnosis of infiltrate in Hodgkin's lymphoma. In our study only two corresponding bone marrow aspirates were also positive for infiltration on trephine biopsy and eight were negative on bone biopsy. Another study showed infiltration in 17.1% cases.[14] Study reported at King Edward Medical University, Lahore showed bone marrow infiltration of Hodgkin's lymphoma in 30% of cases.[15]

In the present study females showed a much higher incidence 54.5% (6 of 11) of bone marrow infiltration despite less number of cases as compared to males. This is probably because we have a male dominated society and females are brought to hospital at a much later stage of disease. Higher incidence could be because most of the patients with infiltration were already in stage III.

In ***conclusion*** bone marrow involvement in Hodgkin's Lymphoma was seen in CS II and beyond, therefore it is recommended that bone marrow examination may be performed as a part of staging investigations in patients with Hodgkin's lymphoma when it is CS II or high. Due to poor economic conditions, lack of awareness and treatment facilities in rural areas these patients come at a late stage of disease.

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