



Original Research Article

## Hodgkin's Lymphoma in Children Aged 6 Years Or Below- Long Term Follow Up Results

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### ABSTRACT

**Introduction and scientific background:** Although pediatric Hodgkin's lymphoma (HL) is a curable malignancy, the natural history of HL in very young children (below the age of 6 years) is largely unknown due to rarity of HL in this age group.

**Aims and objectives:** The aim of this study is to analyze the clinical presentation, histology and treatment outcome in children diagnosed with HL at the age of 6 years or less.

**Material and methods:** This was a retrospective observational study.

**Results:** We evaluated 28 patients diagnosed with HL at the age of 6 years or less. There was a male preponderance with 25 (89%) boys and 3 (11%) girls. Most common clinical presentation was cervical lymphadenopathy. Of the 28 patients, 17(60.71%) presented with advanced disease (stage III and IV). Mixed Cellularity was the most common histologic subtype. Patients were given ABVD chemotherapy (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). One patient died before starting treatment. Six children received IFRT along with chemotherapy. Complete remission (CR) with first line chemotherapy and/or RT was 100%. Four patients were lost to follow up. Five year disease free survival was 87% and overall survival was 91%.

**Conclusion:** Hodgkin's lymphoma in children aged 6 years or below, commonly occurs in male with mixed cellularity histology type. Despite the advanced stage of presentation in this age group, it remains one of the most curable malignancies.

**Key words:** Hodgkin's, ABVD, Pediatric

### INTRODUCTION

Pediatric Hodgkin's lymphoma (HL) is one of the most curable childhood malignancies. Therapy is stratified based on disease stage and adverse prognostic factors. In Western countries, HL has a bimodal distribution, however in developing countries, particularly India, this bimodal

peak is not observed. Most data from developing countries report the median age of occurrence as 8-9 years compared to 12 years in industrialized countries. In western countries, only about 5% cases of HL are diagnosed at the age of 6 years or less. The natural history of HL in very young children (below the age of 6 years) remains largely

unknown due to its rarity. Published studies of the disease in this age population are few and in all published series, reported patient numbers have been small. [1-4] In fact, in most publications of childhood HL, there is no separate analysis of response to treatment and outcome for children in this age group. The aim of this study is to analyze the clinical presentation, histology and treatment outcome in children who were diagnosed with HL at the age of 6 years or less.

## **MATERIALS AND METHODS**

This was a retrospective observational study. With the concurrence of Institutional Ethics and Review Board we analysed all children with HL who were 6 years of age or less at the time of diagnosis. Diagnosis of HL was based on lymph node biopsy and immunohistochemistry studies. Lymph node biopsy tissue morphology was classified as per the WHO criteria, Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) & Classical type including nodular sclerosing (NS), mixed cellularity (MC), lymphocyte rich and lymphocyte depleted (LD). Disease was staged according to the Cotswold modification of Ann Arbor staging system. [4] Staging investigations included bone marrow biopsy and computed tomography (CT) scan of neck, chest, abdomen and pelvis. PET/CT scan was not available in our institute during the study period. Follow up information is available for twenty three patients. The median follow up duration for surviving patients is 5 years.

### **Statistical analysis**

All variables were entered on Microsoft excel/Statistical Package for Social Sciences 15 (SPSS 15). Calculation of mean, median and range was done using Microsoft excel, and median survival was calculated based on the time from lymphoma diagnosis to death due to any

cause. Disease free survival was based on the length of time that the patient survived without any signs or symptoms of lymphoma after completing the primary treatment.

### **Treatment strategy**

Our patients ABVD chemotherapy in standard doses. Number of cycles of chemotherapy was based on stage of disease. Patients with early stage disease (stage I & II) were given 4-6 cycles of chemotherapy while those with advanced stage disease (stage III & IV) received 6-8 cycles of chemotherapy. Children with bulky disease, extranodal involvement or localized residual disease were given additional radiotherapy (20 Gy) after the last course of chemotherapy. Six children received IFRT along with chemotherapy.

### **Definitions of response**

(International Working Group)(5): According to International Working Group, the definitions of response were as in the table 1.

## **RESULTS**

We evaluated 28 patients diagnosed with HL at the age of 6 years or less. There was a male preponderance with 25 (89%) boys and 3 (11%) girls. The median age at diagnosis was 4 years. The youngest patient was two and a half years old. At presentation 78% had cervical lymphadenopathy and 28% had splenomegaly. Five children had mediastinal disease and five had bulky disease at diagnosis. Eleven (39.29%) children presented with early stage (stage I or II) disease and 17(60.71%) presented with advanced disease (stage III and IV).[ Table 2 shows disease stage of patients in present study]. Mixed Cellularity was the most common histologic subtype followed by nodular sclerosis subtype. [Table 3 shows histologic subtypes]

## Treatment Outcome

Out of 28 patients, one patient died before starting treatment. All remaining patients achieved CR with first line chemotherapy and/or RT. Follow up information is available for twenty three patients as four patients had lost to follow-up. Three patients had relapse and could not be offered salvage chemotherapy due to non affordability. One of these three patients is still alive and is on supportive care while the

other two relapsed patients succumbed to their disease. Five year disease free survival was 87% and overall survival was 91%.

## Treatment Toxicity

There was no treatment related mortality. Most common long term toxicity was hypothyroidism seen in three patients. One patient developed muscle wasting of neck. Till date none of the patients had any form of cardiac, pulmonary toxicity or therapy induced secondary malignancy.

**Table 1. Definitions of response (International Working Group)**

Response	Definition	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	Not palpable, nodules Disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD		
PD or relapsed disease	Any new lesion or increase by ≥50% of previously involved sites from nadir	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

**Table. 2 Disease stages of patients in present study (As per Cotswold modification of Ann Arbor staging system)**

Stage	A	B	Total (%)
I	1	1	2 (7.14)
II	6	3	9 (32.14)
III	4	12	16 (57.15)
IV	0	1	1 (3.57)

A - No symptoms

B- Unexplained fever (>38°C), drenching night sweats, unexplained loss of >10% body weight within the preceding 6 months.

X- Bulky disease: tumor ≥ 10cm or mediastinal widening >1/3

**Table.3 Histologic subtypes**

Subtypes	No of patients
NLPHL	2
Mixed cellularity	14
Nodular sclerosis	11
Lymphocyte depleted	0
Lymphocyte rich	1

## DISCUSSION

HL at or below the age of 6 years are rare, accounting for only about 5% cases of HL in Western countries. [4] Pediatric HL shows a slight male predominance in Western countries, with a male to female

(M: F) ratio of about 1.5:1. However, this male preponderance is much higher in developing countries, M: F ratios being 2.5:1 to 8:1. [4] In our study male:female ratio is 8:1, similar to other studies from India. In our study the common subtype is mixed cellularity followed by nodular sclerosis, similar to other studies in India, but in western literature nodular sclerosis is the commonest subtype in children under age of 6 years. [4,6,7] HL in this population has been attributed to Epstein Bar Virus (EBV) infection, Infectious mononucleosis and poor nutrition status. [8,9] In our study, 17.85% patients presented with bulky disease, >50% presented with advanced disease and 68% presented with B symptoms. In Western countries, three fourth of newly diagnosed children have early disease at presentation (stage I-II) and only one fourth of the patients have

advanced (stage III-IV) disease and <50% present with B symptoms. [7] The cause for such differences remains unknown. It might be related to a delay in reporting to the hospital, or to a more aggressive nature of the disease, or an altered host immune response resulting in more aggressive clinical features. All our patients received combination chemotherapy (ABVD) and all treated patients achieved CR with first line chemotherapy and/or RT. Five year disease free survival was 87% and overall survival was 91% which is comparable to other studies. [7,10] There was no treatment related death in our study. In our study during follow up 3 patients developed hypothyroidism and one had muscle wasting, in patients who received IFRT. Similar findings were reported in other studies. [6,10,11] To date no patients developed secondary malignancies. Because of only 5 years short follow up in our study, secondary malignancy outcome could not be predicted. Many studies have shown development of secondary malignancies even in third decade. [12-14] Hence long term follow up is required.

## CONCLUSION

Hodgkin's lymphoma in children aged 6 years or below, commonly occurs in male with mixed cellularity histology type. As in the other age group, response to treatment is excellent. Despite the advanced stage of presentation in this age group, it remains one of the most curable malignancies and needs a long term follow up.

*Conflicts of interest:* None.

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