

## PAEDIATRIC HAEMATOLOGICAL MALIGNANCIES: AN INCIDENCE AND CLINICOPATHOLOGICAL STUDY

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### ABSTRACT

Paediatric cancer is considered 1% to 3% of all cancer cases. This is the second most common cause of death in children. In case of the haematological malignancies acute lymphoblastic leukaemia is the most common neoplasm that affects the children.

### MATERIALS AND METHODS

Children presented with haematological and lymphoreticular malignancy referred during 2003-2005 were included in this study. The routine haematological evaluation reveals malignancies such as acute leukaemia, the slides were stained routinely with Leishman and Giemsa stains and further subjected to histochemical evaluation with special stain such as periodic Acid-Schiff and Sudan Black B. lymph node specimen with initially suspected lymphoma in the initial cytomorphological diagnosis were fixed in toto in buffered neutral formation and processed routinely; 3-5 micron sections were cut and stained with haematoxylin and eosin. Reticulin and CD makers were also applied in doubtful cases for final confirmation.

### OBSERVATION AND RESULTS

This study covered a total of 63 paediatric haematological malignancies. In 63 haematological cancers observed, 42 were males (66.67%) with age ranging from 2-15 yrs. (mean age 8.2 yrs.) and 21 were females (33.33%) with age ranging from 2-14 yrs. (mean age 8.6 yrs.). The average incidence observed is 44.49%; there was increased incidence of haematological malignancies in the age group of more than 10 yrs. The incidence of haematological/lymphoreticular malignancy is low at less than 2 yrs. and also the incidence is high in male children. In 45 haematological cancers, 32 cases were Acute Lymphoblastic Leukaemia [(ALL), (71.11%)] and [11 Cases, 24.44%]] were diagnosed as lymphoproliferative/lymphoma spill. Only 2 cases of Acute Myeloid Leukaemia (AML, 4.44%) was observed in this study. In the 18 cases of lymphoreticular malignancies 15 cases were NHL, in which large cell anaplastic and lymphoblastic type was commonly observed. Only 3 cases of Hodgkin's disease was observed in this study. Cases were diagnosed initially as lymphoma, further confirmation with CD Marker - CD 30 for RS cell was also done.

### CONCLUSION

In the present study of 63 cases of Paediatric haematological cancers evaluated with clinical light microscopy, histochemical and IHC, the acute lymphoblastic leukaemia is the commonest neoplasm in childhood. The histochemical stains shall have their value in differentiating acute leukaemias and in all cases of lymphoma final confirmation with CD marker for treatment and prognosis is the gold standard strategy/method.

### KEYWORDS

Children, Haematology, Malignancy.

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### INTRODUCTION

Paediatric cancer is considered 1% to 3% of all cancer cases. This is the second most common cause of death in children; 50% of the children with age group younger than 15 years suffer from leukaemia and lymphoma. The other 50% suffer from the solid tumours and CNS tumours, etc.

In case of the haematological malignancies, acute lymphoblastic leukaemia is the most common neoplasm that affects the children. Next one is the acute myeloid leukaemia and JMML. In case of lymphoma both HL and NHL can occur, but HL is most common.

A number of genetic conditions associated with elevated risk of Childhood Cancers such as Down's Syndrome, NF - I and II, Beckwith-Wiedemann Syndrome, Tuberous Sclerosis and Li-Fraumeni Syndrome. The risk factors for the major paediatric cancer includes ionizing radiation, non-ionizing power frequency electromagnetic field, pesticides, parental occupational chemical exposures, dietary factors and environmental cigarette smoke. The role of viruses such as Polyomaviruses, EBV and HTLV in aetiologic importance is unclear.

The treatment of paediatric cancers improve the patient's survival rates significantly; 75% of the children can be cured on treatment. In general, there is diversity in the occurrence of paediatric neoplasm all over the world.

In this study, the actual incidence and presentation of paediatric neoplasm in semi-urban area is evaluated. Molecular cytogenetics, Immunohistochemistry and histochemical stains play a major role in determining the exact underlying pathology of various paediatric haematological malignancies.

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## MATERIALS AND METHODS

Children presented with haematological and lymphoreticular malignancy referred during 2003-2005 were included in this study. A thorough clinical evaluation, routine haematological investigations, ultrasonogram and CT scan (In proportion of cases) were done in each case.

A detailed clinical history, family history, particularly consanguinity, socio-economic status and nutrition, personal history, particularly about the parental occupation and also similar neoplasms in other family members were also recorded.

The routine haematological evaluation when reveals malignancies such as acute leukaemia, the slides were stained routinely with Leishman and Giemsa stains and further subjected to histochemical evaluation with special stain such as periodic Acid-Schiff and Sudan Black B.

Lymph node specimen with initially suspected lymphoma in the initial cytomorphological diagnosis were fixed in toto in buffered neutral formation and processed routinely; 3-5 micron sections were cut and stained with haematoxylin and eosin. Reticulin and CD makers were also applied in doubtful cases for final confirmation.

## OBSERVATION AND RESULTS

This study covered a total of 63 paediatric haematological malignancies. In 63 haematological cancers observed, 42 were males (66.67%) with age ranging from 2-15 yrs. (mean age 8.2 yrs.) and 21 were females (33.33%) with age ranging from 2-14 yrs. (mean age 8.6 yrs.).

In the total number of haematological malignancies observed during the period from Jan-2003 to December-2005, the average incidence observed is 44.49%.

When the children are divided into six groups (i.e. <2 yrs., 2-4 yrs., 5-6 yrs., 7-8 yrs., 9-10 yrs. and >10 yrs.) there was increased incidence of haematological malignancies in the age group of more than 10 yrs. followed by 3-4 yrs. and 5-6 yrs.

Table 2 shows the incidence of haematological/lymphoreticular malignancy is low at less than 2 yrs. and also it shows the incidence is high in male children (42 cases, 66.67%) when compared with females (21 cases, 33.33%).

Most of the children with haematological/lymphoreticular malignancies were from surrounding villages with low socioeconomic status, presented with the clinical symptoms as given in Table 3.

Most of the children presented with a triad of fever, anaemia and splenomegaly as common presenting symptoms and generalised lymphadenopathy is the commonest presenting symptom in children with lymphoreticular malignancies exhibiting firm, discrete, non-tender enlargement of the lymph nodes. Gum hypertrophy is also present in case of AML (Fig. 1).

When paediatric haematological/lymphoreticular malignancies were divided, haematological cancers were observed in 45 cases (71.43%) and lymphoid neoplasms in 18 cases (28.57%). In 45 haematological cancers, 32 cases were acute lymphoblastic leukaemia [(Fig. 2 and Fig. 3) (ALL), (71.11%)] and [11 Cases, (24.44%)] were diagnosed as Lymphoproliferative/lymphoma spill (Fig. 6). Only 2 cases of Acute Myeloid Leukaemia (AML, 4.44%) (Fig. 4 and Fig. 5) was observed in this study.

Similarly, the lymphoreticular malignancies were also divided as shown in Table 5.

In 18 cases 15 cases were NHL, (Fig. 6) in which large cell anaplastic and lymphoblastic type was commonly observed. Only 3 cases of Hodgkin's disease (Fig. 7) was observed in this study. Cases were diagnosed initially as lymphoma, further confirmation with CD Marker - CD 30 for RS cell was also done.

## Special Studies

In 2 cases of Acute Myeloid Leukaemia and 11 cases of lymphoproliferative lesions, histochemistry (Fig. 8 and Fig. 9), (PAS and Sudan Black B (Fig. 10 to Fig. 12)) was done and the results were given in Table 6.

## Immunohistochemistry

CD Makers - for NHL and Hodgkin Lymphomas was also undertaken and the results were given in the following Table 7 (Fig. 13 to Fig. 14).

Sl. No.	Period	Total Haematological Cancers	Paediatric Cancers	%
1	Jan 2003- June 2003	96	15	15.63%
2	July 2003-Dec 2003	120	13	10.83%
3	Jan 2004- June 2004	124	20	16.13%
4	July 2004-Dec 2004	152	21	13.82%
5	Jan 2005- June 2005	167	33	19.76%
6	July 2005-Dec 2005	2	30	12.82%

**Table 1: Shows Total Number of Haematological Malignancies Observed**

Sl. No.	Age	Male	Female	Total No. of Cases	%
1	< 2	4	-	4	6.6%
2	3-4	9	2	11	17.46%
3	5-6	7	4	11	17.46%
4	7-8	2	5	7	11.11%
5	9-10	5	4	9	14.29%
6	> 10	15	6	21	33.33%

**Table 2: Incidence in Age**

Sl. No.	Clinical Features	No. of Cases	%
1	Fever	48	76.19%
2	Anaemia	52	82.54%
3	Upper Respiratory Tract Infection	32	50.79%
4	Joint pain (Lower extremity)	15	23.79%
5	Bony tenderness	2	3.17%
6	Gum Hypertrophy (Fig.1)	41	1.59%

7	Chloromas	-	-
8	Generalised Lymphadenopathy	58	92.06%
9	Splenomegaly	55	87.30%
10	Hepatomegaly	38	60.32%
11	Bleeding manifestation	25	39.68%

**Table 3: Clinical Features**

Sl. No.	Haematological Malignancy	No. of Cases	%
1	ALL	32	71.11%
2	AML	2	4.44%
3	JCMML	-	-
4	CML	-	-
5	Lymphoproliferative/ Lymphoma Spill	11	24.44%

**Table 4: Shows the Number of Various Haematological Malignancies**

Sl. No.	Lymphoreticular Malignancy	No. of Cases	%
1	HL	3	16.67%
2	NHL		
3	Large cell lymphoma	10	55.56%
4	Burkitt's lymphoma	2	11.11%
5	Lymphoblastic lymphoma	1	5.56%
6	Others	2	11.11%

**Table 5: Shows the Number of Various Lymphoreticular Malignancies**

Sl. No.	Peripheral Smear Number	Sudan Black B	PAS	Results
1	PS 1501/05	Positive	Negative	AML
2	PS 1404/05	Negative	Positive	ALL
3	PS 1395/05	Negative	Positive	ALL
4	PS 2096/05	Negative	Positive	ALL
5	PS 1494/05	Positive	Negative	AML

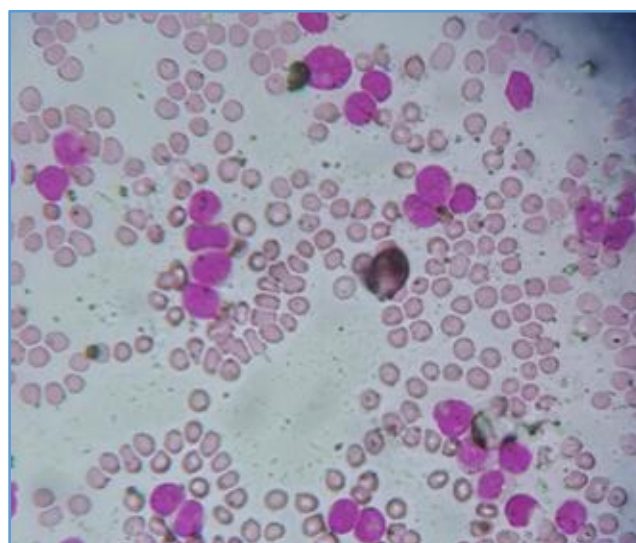
**Table 6: Shows the Results of PAS and Sudan Black B**

Sl. No.	IHC	Marker	Result	Impression
1	Hodgkin Lymphoma	CD-30	Negative	Non-Hodgkin Lymphoma
2	Non-Hodgkin Lymphoma	Pan-B Marker CD-20	Positive	Diffuse Large B-Cell Lymphoma
	1. Large Cell Lymphoma			
	2. Large Cell Lymphoma	Pan-T Marker CD-3	Positive	Diffuse Large T-Cell Lymphoma
	3. Large Cell Lymphoma			
4. Large Cell Lymphoma	Pan-B Marker CD-3	Positive	Diffuse Large B-Cell Lymphoma	

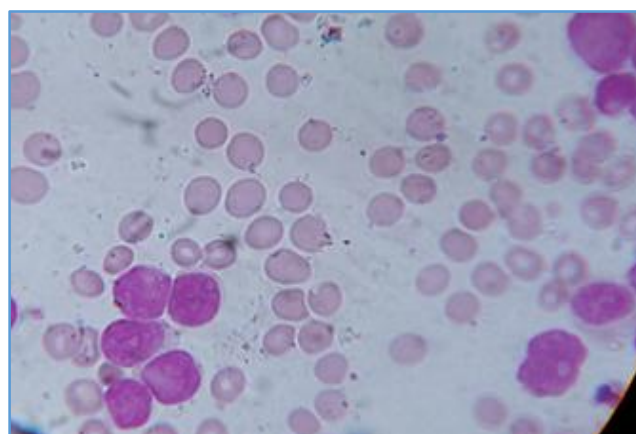
**Table 7: Shows the IHC Results of Lymphoma**



**Fig. 1: Massive Gum Hypertrophy in Acute Myeloid Leukaemia in Six Year Old Female Child**

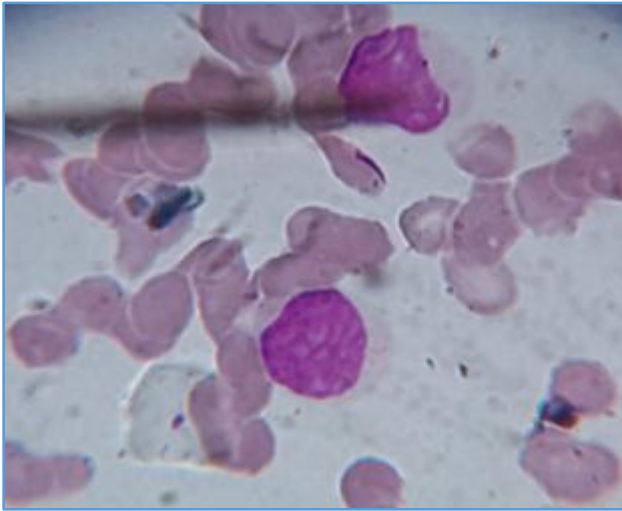


**Fig. 2: Acute Lymphoblastic Leukaemia. Peripheral Smear shows Several Lymphoblasts with Condensed Chromatin and Scant Cytoplasm (Leishman's Stain X1000)**

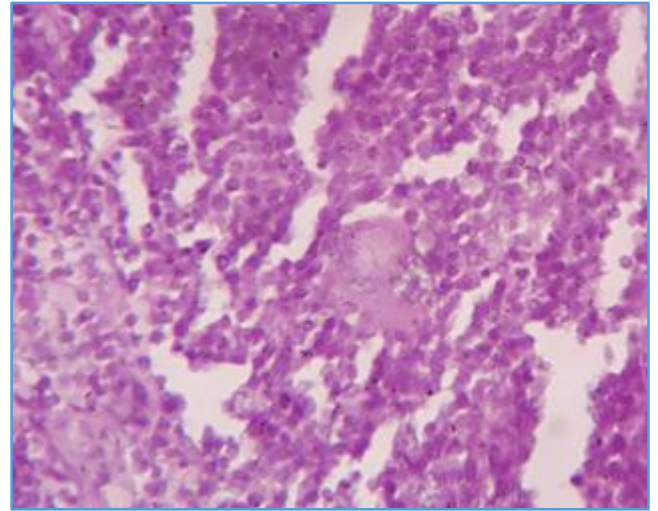


**Fig. 3: Acute Lymphoblastic Leukaemia. Peripheral Smear shows Several Lymphoblasts with One or Two Nucleoli. (Leishman's Stain X1000)**

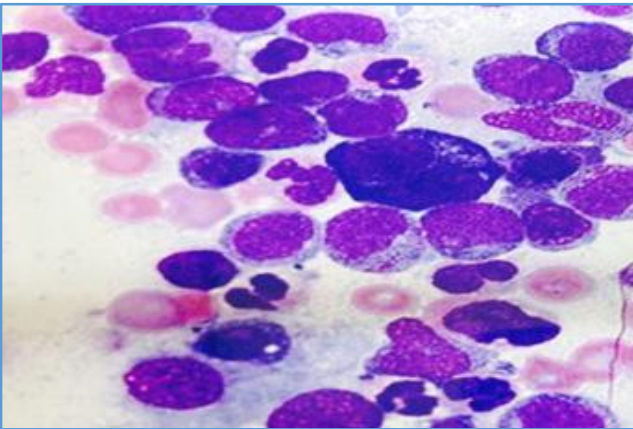




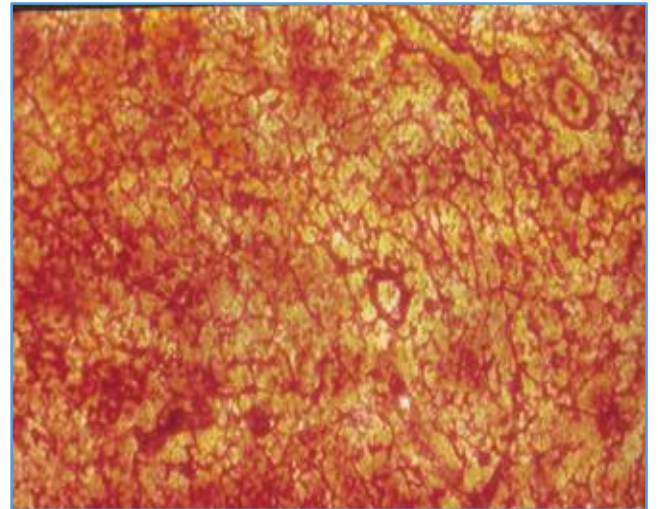
**Fig. 4: Acute Myeloid Leukaemia. Peripheral Smear shows One Myelocyte and Metamyelocyte. (Leishman's Stain X1000)**



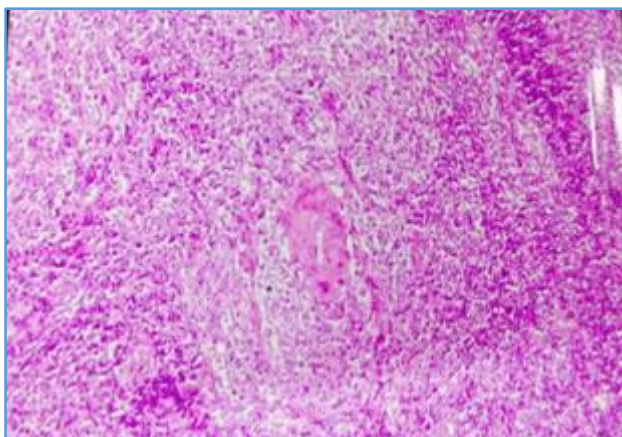
**Fig. 7: Hodgkin Lymphoma. High Power View shows the Diffuse Effacement of the Lymph Node Architecture. (H&E X400)**



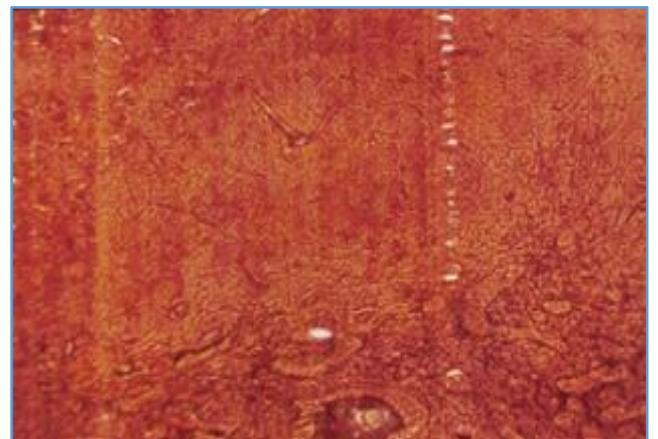
**Fig. 5: Acute Myeloid Leukaemia. Bone Marrow Aspirate shows Several Myeloblasts with Multiple Nucleoli. (Leishman's Stain X1000)**



**Fig. 8: Reactive Lymphadenitis Reticulin Stain**

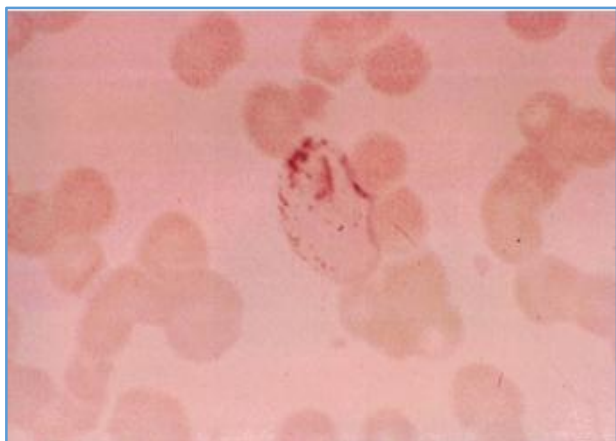


**Fig. 6: Non-Hodgkin Lymphoma. Low Power View shows the Diffuse Effacement of the Lymph Node Architecture by Monotonous Populations of Neoplastic Lymphocytes. (H&E X100)**

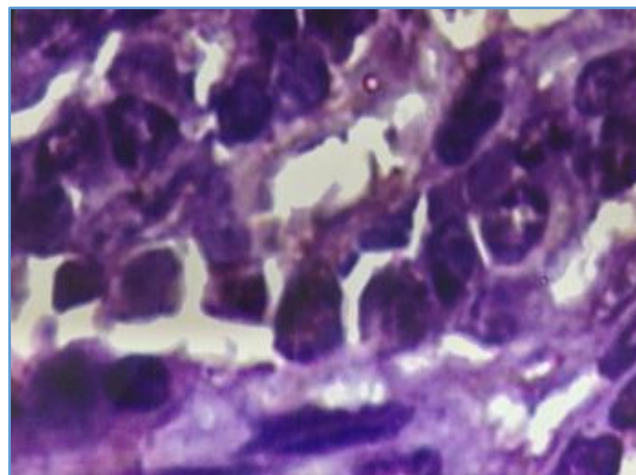


**Fig. 9: Non-Hodgkin Lymphoma - Reticulin Stain**

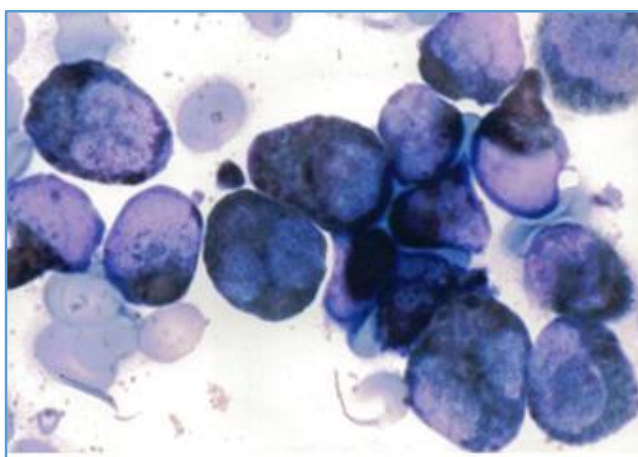




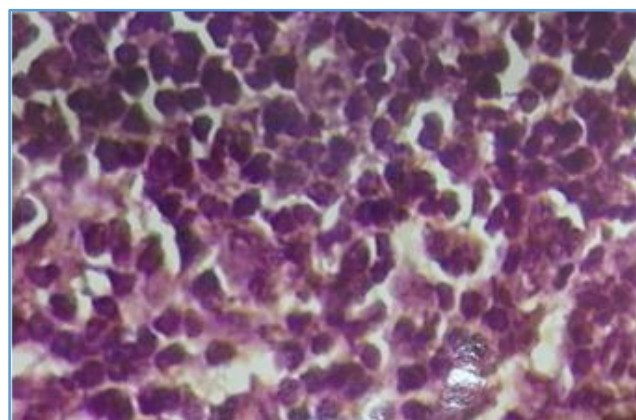
**Fig. 10: Acute Myeloid Leukaemia Sudan  
Black B Positive Cells**



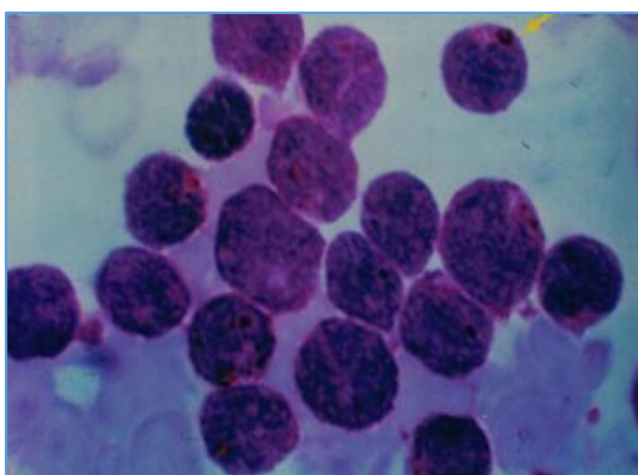
**Fig. 13: NHL - Diffuse Large B Cell Lymphoma  
CD-20 Positive B Cells**



**Fig. 11: Acute Myeloid Leukaemia Sudan  
Black B Positive - Auer Rods**



**Fig. 14: NHL - Diffuse Large B Cell Lymphoma  
CD 3 Positive T Cells**



**Fig. 12: Acute Lymphoblastic Leukaemia -  
PAS Block Positive Cells**

**DISCUSSION**

Although cancer among children is relatively uncommon, it remains a significant cause of mortality in this population and is second only to accidents as a cause of death in the age group of 5-14 years.<sup>1,2,3</sup>

The incidence of Paediatric cancer is increasing in comparison with studies conducted by various research workers and literature. In our study the incidence of Paediatric haematological malignancies is 44.49%, which is in correlation with studies conducted by Elizabeth Rosen, MD, Resident Physician. The average incidence of haematological Paediatric malignancy is 1 in 630, and the relative rate of haematological cancer below 5 yrs. is 40%.

In Western population, the increased incidence of haematological malignancies is observed below the age of 5 years. In our study, the Peak incidence of haematological malignancies is seen after 10 yrs. followed by 3-4 yrs., which is in contrast with the studies conducted by Western Research Workers. Probably related to low socio-economic status, poor education and lack of knowledge regarding the initial alarming symptoms of haematological malignancies.

The most common haematological neoplasm in children is leukaemia and it also stands as most common malignancy. In our study, acute lymphoblastic leukaemia is the commonest haematological neoplasm followed by lymphoma/lymphoproliferative disorders, which is well in correlation with literature.<sup>4,5,6</sup>

In doubtful cases, use of histochemistry with Sudan-Black B and PAS allows an initial, standard cost effective method, helpful in arriving at diagnosis.

One case of Hodgkin lymphoma<sup>7,8</sup> with total effacement of architecture and polymorphous population of lymphocytes with few RS-like cells when subjected to IHC<sup>9</sup> with CD marker CD-30, a classical RS cell marker revealed total negative staining for RS cells and positive for B cell markers of NHL.

Lymphomas comprise approximately 24.44% of all paediatric malignancies, making them the third most common cancer. Approximately, 60% of paediatric lymphomas are Non-Hodgkin's Lymphoma (NHL). Boys are affected more often than girls with a 3:1 ratio and the peak incidence of NHL is between the ages of 7 and 11 years.

Histologic varieties of NHL are divided into low-, intermediate- or high-grade categories based upon their clinical behaviour and over 90% of children have high-grade disease at presentation. High-grade lesions include large cell lymphomas,<sup>10,11,12</sup> constitute about 27% of paediatric NHL. Lymphoblastic lymphoma occurs in 29% of paediatric cases. The small cell non-cleaved lymphomas are found in 34% of paediatric NHL and Burkitt's Lymphoma (BL) is the most common of this subtype.

The evaluation of the child suspected to have a lymphoma begins of course with a complete history and physical. Examination definitive diagnosis requires tissue for pathologic evaluation, which may be obtained by a tonsillectomy or open biopsy of an involved lymph node. Because most paediatric patients with NHL present with disseminated diseases, a complete staging work-up must be undertaken. This would include laboratory studies (to include LDH, LFTs and HIV), LP with CSF analysis, bilateral iliac crest bone marrow biopsy, CT of the chest, abdomen and pelvis and bone scan. The reasoning for such an extensive workup is that accurate clinical staging is of utmost importance in assigning patients to an appropriate treatment protocol.<sup>13,14</sup>

Hodgkin's Disease (HD) is less common in the paediatric population than NHL. This occurring in children under the age of 10 years. Boys are affected more frequently than girls (3:1), although this ratio narrows after puberty (1.4:1).

There are four histologic subtypes of HD-nodular sclerosing, mixed cellularity, lymphocyte predominance and lymphocyte depletion. Overall, nodular sclerosing and mixed cellularity are the most common subtypes of HD, but in the paediatric population the lymphocyte predominance and nodular sclerosing are seen most frequently.

HD will present with asymmetric lymph node enlargement in about 90% of cases. The lymphadenopathy is described as firm, rubbery and non-tender and in the neck most often involves the supraclavicular fossa. The most common extralymphatic site of HD is the spleen followed by the liver. Nearly one-third of patients will have associated constitutional symptoms at presentation including fever, night sweats, anorexia, weakness or loss of 10% or more of body weight.

## CONCLUSION

In the present study of 63 cases of Paediatric haematological cancers evaluated with clinical light microscopy, Histochemical and IHC, following conclusions are made and presented.

1. In Haematological malignancy, acute lymphoblastic leukaemia is the commonest neoplasm in childhood.
2. Histochemical stains shall have their value in differentiating acute leukaemias.
3. In all cases of lymphoma, final confirmation with CD marker for treatment and prognosis is the gold standard strategy/method.

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