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ORIGINAL ARTICLE / RESEARCH

Histopathological Spectrum of Paediatric Hodgkin's Lymphoma

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ABSTRACT

Background: Hodgkin's lymphoma (HL) accounts for 5 per cent of the malignancies in the pediatric age group and is potentially curable. However, early diagnosis is essential for timely management. The diagnosis and classification of Hodgkin's lymphoma was considered to be relatively simple and straightforward earlier, but the characteristic Reed-Sternberg cells (R-S cell) that occur within an inflammatory milieu and are required for the diagnosis can also be seen in other reactive conditions, such as infectious mononucleosis and other malignant lesions, such as nonHodgkin's lymphomas. The advances in phenotyping, molecular characteristics, histogenesis and possible mechanisms of lymphoma genesis, have led to a change in the classification into the Revised European American Lymphoma (R.E.A.L) classification followed by the World Health Organization (WHO) scheme. This has been done with a view to reflect the differences in clinical presentation, prognosis, and management. In the process, while the borders between some histological types of lymphoma became sharper, others continue to remain ill defined.

Material and Methods: Paraffin sections and medical records of the diagnosed cases of HL were retrospectively studied during the period between Jan 1992 and Dec 2003. The sections were studied to assess the architecture, the presence of R-S cells and its variants, background infiltrate, and fibrosis.

Results: 29 cases of pediatric HL were encountered out of a total of 106 cases of Hodgkin's lymphoma. The age range was 3-14 years with an M: F ratio of 24:5. The most common clinical presentation was lymphadenopathy in 18 cases. Histologic sub typing of 29 cases revealed mixed cellularity to be the predominant subtype.

Conclusions: Pediatric HL accounts for 27.3 % of all cases of Hodgkin's Lymphoma in our study. The mean age at presentation was 8.5 years with a male predominance. Mixed cellularity was found to be the most common subtype.

Key words: Hodgkin's lymphoma, paediatrics

Introduction

Paediatric cases account for 10% of all cases of Hodgkin's lymphoma (HL) [1], with a higher incidence in developing countries. Male preponderance is observed in children less than 10 years of age. Most common presentation is cervical lymphadenopathy [2]. In Western literature, nodular sclerosis is the most common subtype followed by mixed cellularity and predominant nodular lymphocyte. Lymphocyte depletion is the rarest. 96 per cent cases of mixed cellularity are associated with EBV infections.

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In literature, especially in the Indian context, the references generally pertains to case studies of variants of Hodgkin's lymphoma, application of molecular markers, or treatment modalities in assessing the outcome. The literature available on the significance of different histological features in the diagnosis as well as on the prognosis of Hodgkin's lymphoma is inadequate. With the aim of facilitating a histologic diagnosis of Hodgkin's lymphoma, a comprehensive review has been undertaken on the various histologic parameters.

Materials and Methods

Source of data

The study included those cases of Hodgkin's lymphoma that were presented to the departments of pediatrics at St. John's Medical College Bangalore The study was both retrospective and prospective. The clinical features and other laboratory parameters were studied from the medical records of the hospital and archives of the department of Pathology retrospectively from January 1992 to December 2001 and prospectively from January 2002 to December 2003. A total of 29 cases were studied.

Paraffin sections were reviewed. Haematoxylin and Eosin stain was used to study the basic morphology.

A. The following *histologic parameters* were studied:

1. *The architecture of the lymph node*: It was marked as total diffuse or partial effacement of the architecture. Other than these two, nodular pattern was also observed.
2. *The composition of background infiltrate*: The presence of neutrophils, eosinophils, plasma cells, and lymphocytes was studied.
3. *Fibrosis*: It *was* graded according to the density as mild, moderate, and severe. Wherever possible, Reticulin stain was used to highlight the fibrosis.

Based on these features, each case was assigned to any one of the following histologic subtypes:

- Nodular lymphocyte predominant
- Mixed cellularity
- Lymphocyte rich
- Nodular sclerosis
- Lymphocyte depleted

If the case did not fit into any of the above subtypes, it was labelled as *unclassified* [Fig 1].

B. Demographic details

The age and sex of the patients were retrieved from the records and were tabulated to see the prevalence of the different histologic subtypes in this age group.

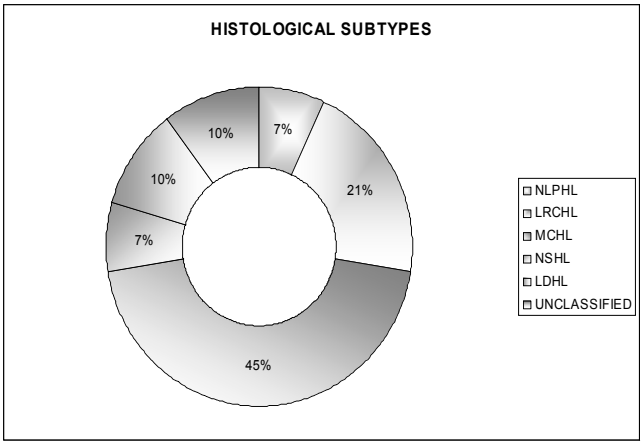

Fig.1 Fibrosis as detected by Reticulin stain was seen in nodular sclerosis and lymphocyte-depleted subtype and was semi-objectively graded as 3+. It was least in lymphocyte-rich and mixed cellularity subtype.

Results

Clinical profile

In the present study, a total 29 cases of HL diagnosed in a period from January 1992 to December 2003 were included (<14 years of age). In this age group M:F ratio was 24:5.

The common clinical presentation was lymph-adenopathy in 18 cases and fever in 15 cases. The lymphadenopathy was cervical (17), axillary (5),or inguinal (2). Together with lymphadenopathy, heaptosplenomegaly was present only in 10 cases.

Histological features

The architecture was diffuse in 16 cases, nodular in nine cases, and partially preserved in four cases. Out of the 29 cases, one case had extra nodal involvement (liver).

Based on the histological features, the cases were subtyped and the distribution is as follows:

- Lymphocyte rich—6
- Mixed cellularity—13
- Lymphocyte depleted—3

Two each from nodular sclerosis and nodular lymphocyte were predominant. Three cases could not be classified including the one in the liver.

Discussion

Lymphoma history began in 1832, when Thomas Hodgkin published a remarkable paper entitled "*On Some Morbid Appearances of the Absorbent Glands & the Spleen*" [3]. A full description of the diagnostic cells came from Sternberg (1898) and, in particular, Dorothy Reed (1902).

Grey zones in classification and subtyping

The aims of lymphoma classification are to ensure the following[4]:-

- Provide an international language allowing communication
- Categorize into entities that must be reproducible and clinically relevant
- Sufficient flexibility to incorporate new data
- Base everything on histopathology

The previous lymphoma classification did not meet these criteria. In the last 10 years, much new information has been available about the lymphomas, resulting in recognition of new entities and refinement of previously recognised disease categories. Thus, the Revised European American Lymphoma (REAL) classification of lymphoid neoplasm was adopted [5] [tables 1 and 2].

Table 1. Comparison between REAL classifications of HL and Rye classification [6]

REAL classification	Rye classification
Nodular lymphocyte predominant	Lymphocyte predominant
Classical HL	
Lymphocyte-rich classical HL	Lymphocyte predominant, diffuse (most) Lymphocyte predominant, nodular (some)
Nodular sclerosis	Nodular sclerosis
Mixed cellularity	Mixed cellularity (most cases)
Lymphocyte depletion	Lymphocyte depletion
Unclassifiable classical HL	Mixed cellularity (some cases)

Table 2. Comparison of the features in classic and NLPHL

Features	Classic	NLPHL
Age distribution	Bimodal (NS)	Unimodal
Sites involved	Mediastinum and abdomen	Peripheral lymph node
Stage at diagnosis	Often II or III	Usually I
B-symptoms	40%	<20%
Course	Aggressive but curable	Indolent and late relapses
Risk of B-cell lymphoma	<1%	2–3%
Pattern	Diffuse, interfollicular, and nodular	Nodular at least in part
Tumour cells	R–S, mononuclear, or lacunar cells	L and H or popcorn cells
Background	Lymphocytes, histiocytes, eosinophils, and plasma cells	Lymphocytes and histiocytes
Fibrosis	Common	Rare
CD markers	CD 15+, CD 30+, CD45–, CD20±	CD15–, CD30–, CD45+, CD20+

Ten per cent of HL cases occur in paediatric age group in the USA [1]. In developing countries, the incidence is still higher. Average annual age standardised rate (ASR) during the period 1983–1987 was 0.4/100,000 for males and 0.2/100,000 for females in Asia [7]. This could be due to an infectious aetiology [8]. In India, ASR has been quoted as 1.9/100,000 and 1.3/100,000, respectively, for males and females [7]. The youngest patient in literature was a 5-month-old boy [9]. In our study, the youngest was a 3-year-old male child. In patients younger than 10 years of age, a male preponderance is noted, whereas in adults the incidence in both sexes is almost equal. The reason, other than infectious aetiology, could be a higher preponderance of mixed cellularity, which is known to have male preponderance.

The most common presentation is a symptomatic cervical or supraclavicular lymphadenopathy [2], which was also seen in our study. Axillary and inguinal node involvement is rare [10,11]. Two-thirds of the patients also have mediastinal disease. Systemic symptoms were seen in 25–30% of children, and these indicate a poor prognosis. Ninety-six per cent of cases of mixed cellularity in paediatric age group are associated with EBV infection [12]. EBV association in paediatric cases is associated with an improved prognosis [13].

Nodular sclerosis is the most common histologic type in European countries, accounting for 40–70% of cases in this age group. NLPHL accounts for 10–15% of cases and mixed cellularity for about 30%. The low-power appearance of NLPHL shares morphologic overlap with *progressive transformation of germinal centres* (PTGC). PTGC is a peculiar form of follicular hyperplasia, which occurs in children and young adults in contrast to NLPHL, which occurs in the fourth decade. PTGCs can precede, occur with, or follow NLPHL. PTGCs are 2–3 times larger than reactive follicles and predominantly consists of small lymphocytes, and are round, well circumscribed, and widely spaced. In contrast, NLPHL nodules are back to back arranged with angulated borders and effaced architecture with no residual normal follicle [14]. In PTGC, the follicles predominantly consist of small lymphocytes, mantle cells, intermingled with some centroblasts, and follicular dendritic cells. They lack popcorn cells and are composed of a mixture of B- and T-cells, histiocytes, and follicular dendritic cells, which produce a ***"moth-eaten"*** appearance [15]. In difficult cases immunohistochemistry is helpful. In NLPHL, bcl-6-positive large cells rimmed by CD57+ cells were highly specific and were not seen in PTGC[35]. The nodularity seen in NLPHL is due to loose aggregates of follicular dendritic cells, which if break give rise to diffuse areas.

LRCHL can be confused with NLPHL. But in contrast to NLPHL, they show classic Reed–Sternberg cells (R–S cells) and immunohistochemistry aids in distinction. It is important to differentiate them, as relapses are more frequent in NLPHL compared to LRCHL. Survival after relapse was better in NLPHL.

Lymphocyte-depleted type is rarely seen in children and presents with widespread disease and has bad prognosis. MCHL is more common in children <10 years of age and those with HIV infection [16]. The epithelioid-cell-rich variant should be differentiated from the so-called *Lennert's lymphoma* (*LL*). It is a T-cell lymphoma with high content of epithelioid cells and occasional blasts resembling R–S cells. In LL, there is marked irregularity of the nuclear profile of the lymphoid component, whereas, in MCHL, the reactive lymphocytes have a regular nuclear outline. The cells in LL have peripheral T-cell phenotype and CD45 reactivity in contrast to R–S cells in HL, which are T-antigen and CD45 negative. Also, LL cases have a high mitotic activity. This distinction is important as LL cases have a rapid downhill course [Fig 2].

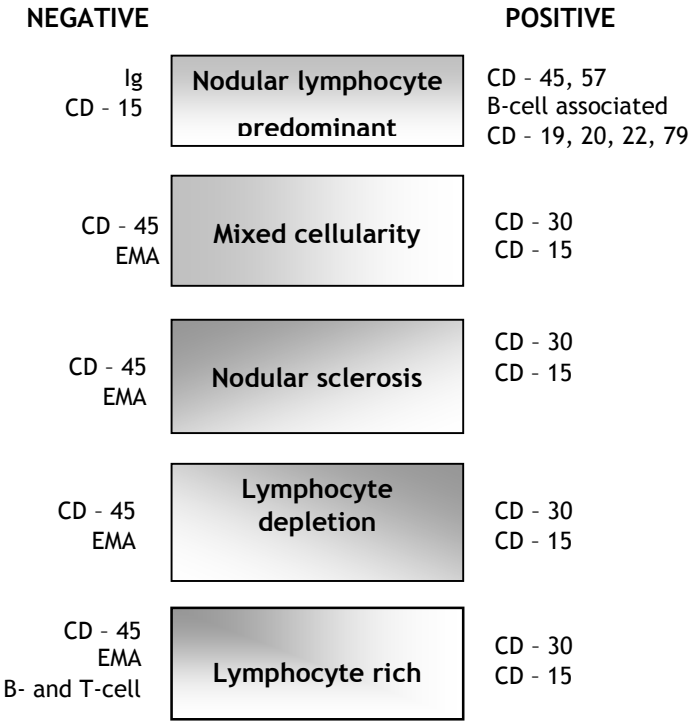

Fig. 2. EMA—epithelial membrane antigen.

In Indian context, MCHL is the most common subtype, with NS being extremely rare. The difference in frequency and peak age of occurrence between European and Asian/African countries could be due to different aetiologic factors. EBV has been implicated in pathogenesis of HL. Children <10 years of age usually show a higher rate of positivity, and the association is 100% in mixed cellularity subtype. Thus, EBV association could be the cause for difference in histologic subtypes and age incidence observed in developing and industrialised countries [17].

HL in children is curable in over 90% of cases; thus, the prompt and proper diagnosis is imperative. The childhood treatment regimens are based on the principle of avoidance of laparotomy staging, risk-adjusted therapy, combined modality of treatment in all stages of disease, and avoidance of procarbazine in boys to protect future fertility [18]. In a child, however, treatment of HL may be tricky, owing to the long-term complications, which may restrict therapy [19].

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