A STUDY OF PATHOLOGICAL CHARACTERISTICS OF PEDIATRIC NON-HODGKIN LYMPHOMA BASED ON 2008 VERSION OF THE WORLD HEALTH ORGANIZATION CLASSIFICATION OF LYMPHOID NEOPLASMS AT CHILDREN'S HOSPITAL 1

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ABSTRACT

Introduction: *Among many classifications of lymphoid neoplasm, the 2008 version of World Health Organization (WHO) classification has been proved to be practical in clinical diagnosis and prognosis.*

Objective: *To evaluate the characteristics of children with non-Hodgkin lymphomas at Children's Hospital 1.*

Methods and Materials: *Descriptive study the pathological characteristics of 107 cases of pediatric non- Hodgkin lymphoma diagnosed at Children's Hospital 1 from 2013 to 2017 based on the 2008 WHO classification of lymphoid neoplasm.*

Results: *Pediatric non-Hodgkin lymphoma induced children from new born to 15 years old, most commonly children over 5 years old (60.7%). Male is predominant than female; male- female ratio is about 1.9:1. Based on the 2008 WHO classification of lymphoid neoplasm, most of pediatric non-Hodgkin lymphomas are aggressive. The most common type was diffuse large B cell lymphoma 29%, following lymphoblastic lymphoma 18.7%, anaplastic large cell lymphoma 17.8%. Peripheral lymph nodes were involved 52.3%, following the gastrointestinal tracts (GI) 11.2%, skin-soft tissues were involved 8.4%, bone 7.5%, mediastinum 7.5%, genital tracts 6.5%, pharyngeal tissues 6,5%. Non-Hodgkin lymphomas of GI tracts were Diffuse Large B cell lymphoma (50%) and Burkitt lymphoma (41.7%).*

Key words: *Non-Hodgkin lymphoma, Burkitt Lymphoma, Anaplastic large cell lymphoma, lymphoblastic Lymphoma, Diffuse large B cell lymphoma.*

I. INTRODUCTION

Non-Hodgkin lymphoma is a malignant disease of lymphoid tissue (lymph nodes, lymphoid organs such as nasopharynx, tonsils, digestive tract, spleen, thymus, bone marrow, etc) which originates from many types of lymphocytes such as progenitor B cell, progenitor T cell, mature B cell or mature T cell. Pediatric lymphoma is very specialized and differs from adult lymphoma in epidemiology, common morphology, clinical presentation, stages, and prognosis as well as treatment. In adults, low-grade lymphoma is predominant with indolent clinical manifestations, in contrary, most pediatric lymphoma is often aggressive and rapidly progressing; which

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is the major difference between pediatric and adult lymphoma [19]. Pediatric lymphoma ranks third in pediatric cancer after acute leukemia and brain tumors, accounting for about 7%. About 800 pediatric non-Hodgkin lymphoma cases are diagnosed each year in the United States [8,36,26]. According to statistics from 2001-2004, non-Hodgkin lymphoma accounts for 11.3% of pediatric cancer worldwide and 13.9% of pediatric cancers in Vietnam. Pediatric lymphoma can occur at any age from newborn to adolescent, and incidence increases with age [12].

In histopathology, non-Hodgkin lymphomas are classified based on cell morphology (small or large size), cell arrangement (diffuse or follicle), phenotype (B cell or T cell) and genetic mutations. In the United States and in developed countries, the most common types of pediatric lymphoma are Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma [26]; the other types are uncommon such as follicular lymphoma, Mantle cell lymphoma, accounting for only 7% of pediatric non-Hodgkin lymphomas.

There are many histologic classifications used for non-Hodgkin lymphomas in adult and children. Today, in many cancer centers around the world, the World Health Organization 2008 lymphoid tissue classification has been commonly applied in lymphoma diagnosis and the latest classification was the World Health Organization 2016 modified version. This revised edition was based on the 2008 classification including morphology, immune phenotype, genetic modifications [37]. With practical significance, this is a detailed classification system which is applied only in some high-tech hospitals of hematology; but not yet widely applied in Vietnam due to high cost. Furthermore, only a few studies of lymphomas using this classification with small numbers of patients were conducted on children. Therefore, this study aimed to evaluate the characteristics of children with non-Hodgkin lymphoma at Children's Hospital 1 from 2013 to 2017 based on the World Health Organization's Lymphoma Classification 2008, and also determine the relationship between histopathology and some clinical features.

II. MATERIALS AND METHODS

The study involved 107 children with non-Hodgkin lymphomas which were diagnosed at the Pathology department of Children's Hospital 1 from 2013 to 2017. The samples were lymph nodes and other tumors diagnosed with lymphoma based on the morphology and immunohistochemistry. We performed a cross-sectional descriptive study for the five-year period from 2013 to 2017, reevaluating morphology of cases diagnosed with lymphoma and classifying according to the criteria of the World Health Organization (WHO) 2008 lymphoma classification. Cellular morphology was determined by cell size (small or large), cell arrangement (diffuse or follicle), and other factors such as mitosis, phagocytosis, specific cellular characteristics of Burkitt lymphoma or anaplastic large cell lymphoma.

Immunohistochemistry

The classification of the B cell and T cell origins was based on immunohistochemical expression as follows: B cell lymphomas were diagnosed when tumor cells were strongly positive for CD20, T cell lymphomas were diagnosed when tumor cells were positive for CD3, anaplastic lymphoma expressed CD30 and ALK 1 and lymphoblastic lymphoma was positive for TdT.

Data analysis: Data collected were statistically analyzed by Chi-square test using SPSS 16. We also analyzed the relationship between histopathology and tumor site, stage, age and gender.

III. RESULTS

Characteristics of children with non-Hodgkin lymphomas

A total of 107 children with non-Hodgkin lymphomas were enrolled into the study with

clinical characteristics as followed: Non-Hodgkin lymphomas could occur at any age from newborn babies to 15-year-old children; most common in children over 5 years old (60.7 %). Boys are more commonly affected than girls with male-female ratio was 1.9: 1. Peripheral lymph nodes were involved 52.3%, followed by gastrointestinal tract 11.2%, skin-soft tissues 8.4%, bones 7.5%, mediastinum 7.5%, genital tract 6.5 %, nasopharynx 6.5%.

Based on WHO 2008 lymphoma classification, most cases of non-Hodgkin lymphomas showed highly aggressive morphology. The most common type was diffuse large B cell lymphoma 29%, following lymphoblastic lymphoma 18.7%, anaplastic large cell lymphoma 17.8% and Burkitt lymphoma 10.3%. In our study, there were 7 cases (6.5%) of unclassified lymphomas with highly malignant morphology, lymphoma phenotypic accordance (LCA – strong expression), without expression of B-cell and T-cell markers.

Table 1: Percentage of histopathologic types of pediatric non-Hodgkin lymphoma based on WHO 2008 classification

Grade	Histopathologic types	n	%
Low grade		0	0
High grade	Mature B cell lymphomas: - Diffuse large B cell lymphoma - Burkitt lymphoma	 31 11	 29 10.3
	Mature T cell lymphomas: - Anaplastic large cell - Peripheral T cell lymphoma - Primary cutaneous T cell lymphoma - Nasal type T cell lymphoma	 19 16 2 1	 17.8 15 1.8 0.9
	Lymphoblastic lymphoma + B cell + T cell + Non B cell – T cell	20 1 16 3	18.7 0.9 15 2.8
	Unclassified lymphomas	7	6.5
Total		107	100

Table 2: Relationship between morphology and tumor site

Histopathological types	Mediastinum	Peripheral lymph nodes	Gastrointestinal tract
Burkitt lymphoma	0 (0%)	4 (3.7%)	5 (4.7%)
Diffuse large B cell lymphoma and Anaplastic large cell lymphoma	2 (1.8%)	28 (26.2%)	6 (5.6%)
Lymphoblastic lymphoma	3 (2.8%)	15 (14%)	0 (0%)
Comparing to 107 patients	8 (7.5%)	56 (52.3%)	12 (11.2%)

Histopathological types	Skin – Soft Tissues	Nasopharynx	Genital tract	Bones
Burkitt lymphoma	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)
Diffuse large B cell lymphoma and Anaplastic large cell lymphoma	1 (0.9%)	5 (4.7%)	3 (2.8%)	5 (4.7%)
Lymphoblastic lymphoma	1 (0.9%)	0 (0%)	1 (0.9%)	0 (0%)
Comparing to 107 patients	9 (8.4%)	7 (6.5%)	7 (6.5%)	8 (7.5%)

Eight patients with lymphoma in the mediastinum (accounting for 7.5%), in which the highest types was lymphoblastic lymphoma (37.5%). The lymphomas of peripheral lymph nodes were 56 cases (52.3%), in which the highest number was diffuse large B cell lymphoma and anaplastic lymphoma (50%), followed by lymphoblastic lymphoma (26.8%). Gastrointestinal tract lymphoma were 12 cases (11.2%), with the highest number of diffuse large B cell lymphoma and anaplastic lymphoma (50%), followed by Burkitt lymphoma (41.7%). Non-Hodgkin lymphomas also involved other organs such as skin, soft tissue, nasopharynx, genitourinary tract and bone, and the most common type was also diffuse large B-cell lymphoma. In addition, histopathological features of each type of lymphoma were not related to age and gender.

IV. DISCUSSION

Our study of 107 non-Hodgkin lymphoma cases at Children's Hospital 1 in five years showed that all cases of pediatric lymphoma were highly aggressive lymphoma, with common histopathological types as follows: diffuse large B cell lymphoma were the most common, followed by lymphoblastic lymphoma, anaplastic large cell lymphoma and Burkitt lymphoma. The results of our study were similar to other studies showing that most pediatric non-Hodgkin lymphoma had highly malignant histopathology > 90% [4].

Our study showed that 18.7% of patients were lymphoblastic lymphoma, lower than percentage found in the study of Neth O, Seidemann K (30%) [20], P T Viet Huong [27]. Lymphoblastic lymphoma (LBL) is a rare type and is classified in the same group of acute lymphoblastic leukemia (ALL) according to the World Health Organization classification 2008. However, unlike ALL, which express only 20-25% of T-cell progenitor, lymphoblastic lymphoma are almost exclusively T-cell progenitor, but very few B-cell progenitor with ratio 9:1. In the study of 607 T-ALL / LBL cases in Germany, the T-LBL rate was 16.6% [10] and the lymphoblastic lymphoma's rate was also low; the rate of B cell lymphoblastic lymphoma was extremely rare [7.33]. Our study also found that only 0.9% of B-cell LBL cases and 15% of T-cell LBL cases occurred in a total of 107 childhood lymphoma cases. Most studies have reported that LBL is more common in the mediastinum [13,32]. In our study, though lymphoma in the mediastinum was not high (8 cases), of them, three cases were the LBL. One study found that treatment with LSA-L2 in LBL, 5-year overall survival (OS) and disease-free survival rates were 79% and 75% [18].

In our study, Burkitt lymphoma rate was 10.3%. In the studies of T C Khương and N T M Huong did not show any Burkitt lymphoma, but the non-cleaved small cell lymphomas were 9.6% and 15.79% [22,38]. The study by P T Viet Huong [27] showed that Burkitt lymphoma was 31.8%. However, some studies in the world have also reported a very low incidence of Burkitt lymphoma (8-10%), especially in the past 10 years [1,17], which may be due to the diagnostic criteria of Burkitt lymphoma based on WHO classification, which is more complex than previous lymphoma classifications. The WHO lymphoma Classification 2008 has been added criteria of genetic abnormalities. In addition, Burkitt lymphomas are divided into two groups with different epidemiologic characteristics; that are epidemic Burkitt lymphoma and sporadic Burkitt lymphoma; in which epidemic Burkitt lymphoma is more common in Africa and scattered in other countries. Vietnam is not the epidemic area of Burkitt lymphoma, therefore the rate is low.

Our study also found that the highest rate of childhood lymphoma was diffuse large B cell lymphoma (29%), which was also a common lymphoma variant in adult. Our study showed similar percentage of this kind of lymphoma to many other studies [2, 27,29]. According to the

literature, diffuse large B cell lymphoma in children is about 10-20% of pediatric NHL [29,2] and has distinct characteristics from adult large B-cell lymphoma; in which *c-myc* translocation rate is higher [28] while t (14; 18) is less common [6,24]. In addition, the disease commonly involves the other site than lymph nodes; often morphologically expresses immunoblast or centroblast [24,30]; and has a survival rate of more than 85-95% [30.3,25] comparing to survival rate of 50% in adult [11] after chemotherapy. This difference may be related to the clinical, phenotypic or biological features of the tumor cells. In the 2008 WHO lymphoma classification, the diffuse large B cell lymphoma (DLBCL) is subdivided into germinal center B-cell (GC) and non-germinal center B-cell or activated B-cell (ABC) subtypes based on immunohistochemical expression of CD10, Bcl6 and MUM1 markers for germ center group [9]. Expression of CD10 and Bcl6 in diffuse large B-cell lymphoma show good prognostic significance [9,14,23]. MUM1 expression is associated with poor prognosis [9,5]. Germinal center B-cell phenotype has better prognosis [9].

Our study showed a result of 17.8% as anaplastic large cell lymphoma. This proportion is also consistent with other studies in the world and in Vietnam [15,22,27,38]. According to the literature, anaplastic large-cell lymphoma accounts for 2-8% of non-Hodgkin lymphoma in adult and 10-15% of pediatric lymphoma. About 60% of anaplastic the large cell lymphoma shows expression of ALK marker, a protein produced by the translocation t (2; 5)(p23; q35), which causes the fusion gene of ALK and NPM gene. The prognosis for this type of lymphoma is related to the presence of ALK marker [37].

Other types of lymphoma are very rare in children. No cases of follicular lymphoma have been reported in our study and other studies in the world also showed that pediatric follicular lymphoma was extremely rare.

According to our study, 53.2% of lymph nodes were involved, with the highest incidence of B-cell lymphoma and anaplastic large cell lymphoma. In the study of N T M Huong, lymphoma of abdominal lymph nodes accounted for 55.26% [22], and 22% in the study of T C Khuong [38]. Our study only showed data of involved peripheral lymph nodes such as head and neck lymph nodes, inguinal lymph nodes, but no abdominal lymph nodes due to challenges in biopsy procedure which may easily causes bleeding. Our study showed a small rate of mediatinal lymphoma (7.5%), in which the highest type was lymphoblastic lymphoma. The study of N T M Huong found that mediastinal lymphoma was 23.68% [22]. Our study also showed low number of lymphoma in Waldayer ring and in ear-nose-throat area, most of which are diffuse large cell lymphoma and anaplastic lymphoma. Other involved sites such as orbits, bones, skin, testis and ovary accounted for a very low rate of lymphoma. Other studies also showed that lymphomas in the skin, bone, testis and ovary are less common than in the mediastinum and lymph nodes.

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