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Histopathological Profile of Extranodal Lymphoma: A Retrospective Study for 5 Years in Tertiary Care Hospital

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ABSTRACT

Introduction
Extranodal lymphomas account for 30% of all lymphomas. The diverse location and various clinical manifestation of extranodal lymphoma lead to difficulty in diagnosis. The different types of extranodal lymphoma behave and respond differently to therapy. The information regarding the incidence of extranodal lymphoma is still limited, hence further study is needed.

Methods
Descriptive observational research design with a retrospective approach. This study used data from anatomical pathology examinations at the Dr. Soetomo General Academic Hospital, Surabaya, over a 5-year period, with the diagnosis of lymphoma originating from organs other than lymph nodes and no prior history of lymphoma in the lymph node.

Result
As many as 379 cases were diagnosed as lymphoma originating from the extranodal. The highest age group was 51–60 years old (27.70%), male patients were slightly higher (54.91%), and the highest location was in the head and neck region (48.11%). On anatomical pathology examination, the most common diagnosis was high grade B cell NHL (48.11%).

Conclusion
This study showed the incidence of extranodal lymphoma, with the majority of cases occurring in the fifth decade of life, with M:F ratio is 1.33:1 and the most common location was in the head and neck area. The most common histological diagnosis was high grade B cell NHL, with DLBCL being the most common subtype. This study provided initial information on the epidemiology of extranodal lymphoma at Dr. Soetomo General Academic Hospital in Surabaya. Further research is needed to determine the relationship between variables and patient survival.

Keywords: Extranodal lymphoma, Non-Hodgkin's lymphoma, Diffuse large B cell lymphoma, Plasmacytoma

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INTRODUCTION

Lymphoma is a lymphoid system cancer that comes in many forms. It is more prevalent in underdeveloped nations. The global incidence has increased by 3–4% over the previous four decades; the explanation of this increase is unknown, but it is thought to be related to the AIDS epidemic and an increase in unhealthy lifestyles.[1,2]

Lymphoma is a form of cancer that develops from the malignancy of B cell, T cell, and natural killer (NK) cells. It is characterized based on clinical, morphological, immuno-phenotypic, and cytogenetic characteristics. The International Lymphoma Study Group produced the Revised European-American Classification of Lymphoid Neoplasms (REAL) in 1994, which advocated the classification of lymphoma. The World Health Organization's (WHO) categorization of lymphoid neoplasms is then used.[3]

As much as 30-40% of lymphoma is extranodal origin. The incidence is various in every country. The number is directly proportional to the lymphoma of nodal origin.[3,4]

Lymphomas of nodal and extranodal origin are difficult to distinguish because both are morphologically and immunophenotypically similar. Should also rule out the possibility of extranodal lymphoma originating from metastatic nodal lymphoma.[3]

Furthermore, this retrospective study aimed to describe the histopathological profile of lymphomas of extranodal origin that were diagnosed at the Anatomical Pathology Laboratory of Dr. Soetomo Academic General Hospital Surabaya for five years.

METHODS

This research was an observational descriptive study with a retrospective approach. The population of this study were all patients who were diagnosed by histopathological examination as extranodal lymphoma in the Anatomical Pathology Unit of the Central Laboratory Installation of Dr. Soetomo General Academic Hospital from January 2016 to December 2020. Demographic data were retrieved including gender, age group, and organ location.

This retrospective study has obtained ethical approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital with number 2003/120/4/II/2023.

RESULTS

In a period of 5 years, a total of 1778 cases of lymphoma and suspected lymphoma were found, and 756 was extranodal origin. Among the 1778 cases, 397 (22.32%) cases had been confirmed as lymphoma of extranodal origin by histopathological examination. Extranodal lymphoma was slightly more common in males than females. There were 222 cases (95.91%) in males and 175 cases, (44.08%) in females. Male to female ratio of 1.33:1 (Table 1).

The age of extranodal lymphoma patient was fairly wide, ranging from 1 to 82 years old, with an average age of 49.58 years old. The age of patients in this study were divided into eight groups. The majority of cases affected patient in in the age group of 51-60 years old (110 cases, 27.70%) (Table 1).

Tabel 1. Distribution of gender and age.

Patient characteristic	n	%
Gender		
Male	222	55.91
Female	175	44.08
Age		
<10 years old	9	2.26
10-20 years old	22	5.54
21-30 years old	30	7.55
31-40 years old	50	12.59
41-50 years old	68	17.12
51-60 years old	110	27.70
61-70 years old	73	18.38
>70 years old	35	8.81
Total	397	100

The distribution of cases of extranodal lymphoma based on location was very wide. The highest distribution was in the head and neck, with 196 (49.37%) cases, followed by the abdomen, with 73 (18.38%) cases. The number of cases in the regions of thorax/mediastinum, soft tissue and bone, urogenital and breast, brain and spine were 53 (13.35%), 40 (10.07%), 20 (5.03%), and 15 (3.77%) respectively (Figure 1). Details of the location of each region are described in Table 2.

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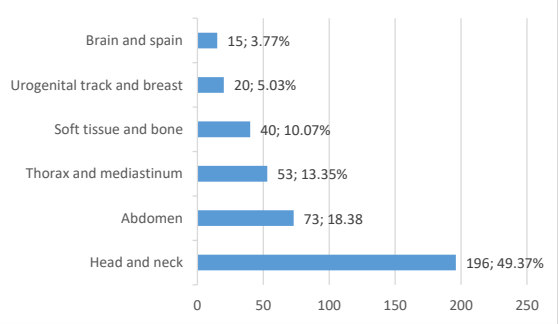

Figure 1. Tumor site distribution.

Table 2. Tumor site distribution base on the organ.

Tumor site	n	%
Head and neck		
Pharynx	58	14.60
Orbita	46	11.58
Cavum nasi	44	11.08
Cavum oris	16	4.03
Sinus maxilaris	9	2.26
Nasal sinus	7	1.76
Thyroid	5	1.25
Parotis	5	1.25
Larynx	4	1.00
Nasolabial	2	0.50
Abdomen		
Gastrointestinal	47	11.83
Cavum abdomen	23	5.79
Mesenterium	2	0.50
Spleen	1	0.25
Thorax and mediastinum		
Mediastinum	35	8.81
Lung	9	2.26
Thorax	8	2.01
Pericard	1	0.25
Soft tissue and bone		
Skin and soft tissue	29	7.30
Bone	11	2.77
Urogenital track and breast		
Breast	11	2.77
Female organ	4	1.00
Testis	3	0.75
Renal	1	0.25
Supra renal	1	0.25
Brain and spine	15	3.77
Total	397	100

Based on histopathology examination, there were 374 (94.20%) non-Hodgkin's lymphoma (NHL) cases, 15 (3.77%) Hodgkin's lymphoma (HL) cases and 8 (2.01%) cases of plasmacytoma (Figure 2).

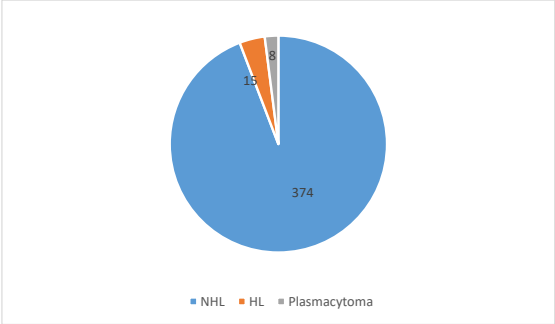

Figure 2. Distribution of lymphoma base on histopathologic group.

The majority of NHL cases were B cell origin (262 cases, 65.99%). There were 33 cases of T cell origin NHL (8.31%) and there were 87 cases (21.91%) with undetermined entity and only conclude as NHL (Figure 3).

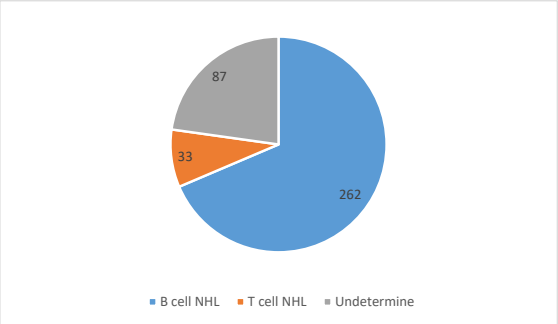

Figure 3. Distribution of NHL base on cell of origin.

Grading was determined by immunohistochemical examination using Ki67 antibody, with a cutoff of >30% for high grade and ≦ 30% for low grade. From the B cell NHL cases, 191 (48.11%) cases were high grade, 31 (7.80%) cases were low grade, and 32 (8.06%) cases were undetermined grade, concluded as B cell NHL without carried out Ki67 examination (Figure 4).

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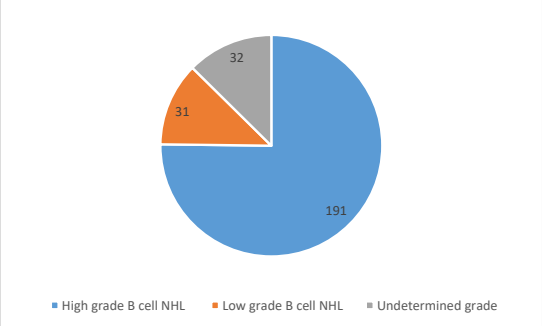

Figure 4. Distribution of NHL B cell type base on tumor grade.

The high-grade B cell type NHL consisted of 19 (4.78%) cases of diffuse large B cell lymphoma (DLBCL), 11 (2.77%) cases of lymphoblastic lymphoma, 1 (0.23%) case of primary mediastinal B cell lymphoma (PMBCL) and 1 (0.23%) case of Burkitt's lymphoma. There were 159 (40.05%) cases that only concluded as NHL B cell type high grade without followed by further subtyping (Figure 5). There were 2 cases of DLBCL were followed by IHC examination to determine the subtype, 1 case DLBCL activated B cell-like (ABC) subtype and 1 case DLBCL germinal center B cell-like (GCB) subtype.

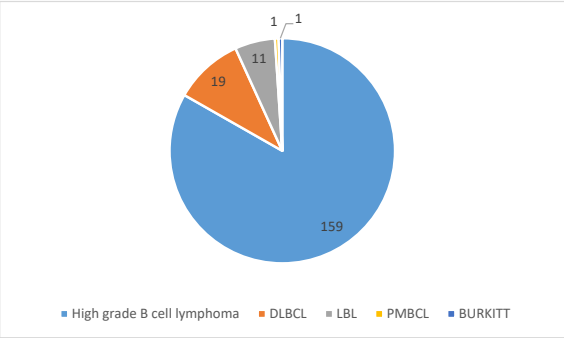

Figure 5. Distribution of high-grade B cell NHL base on tumor subtype.

The low-grade B cell NHL consisted of 7 (1.76%) cases of mucosa associated lymphoid tissue (MALT) lymphoma, 2 (0.50%) cases of Mantle cell lymphoma (MCL) and 22 (5.54%) cases of low-grade B cell NHL without further subtyping (Figure 6).

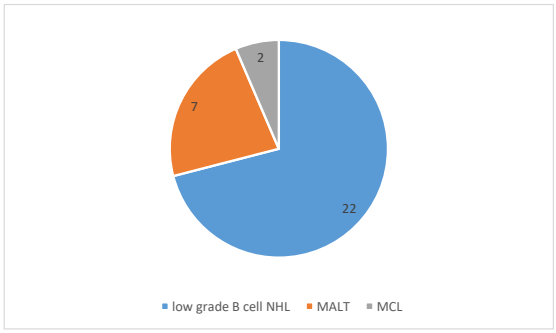

Figure 6. Distribution of low-grade B cell NHL base on tumor sutype.

The T cell NHL consisted of 24 (5.79%) cases NK/T cell lymphoma, 4 (1.00%) cases T cell NHL, and 3 (0.75%) cases T cell lymphoblastic lymphoma (Figure 7).

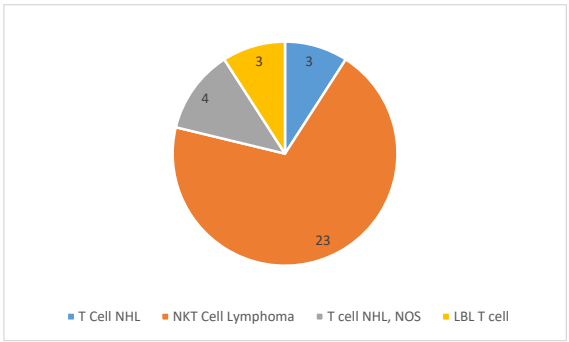

Figure 7. Distribution of NHL T cell base on tumor subtype.

All 15 Hodgkin lymphoma cases were Classical Hodgkin lymphoma, and no nodular lymphocyte predominant B cell lymphoma (NLPHL) cases were found.

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Tabel 2. Distribution of diagnosis.

Diagnosis				n	%
NHL	B cell NHL	B cell high grade NHL	DLBCL	19	4.78
			LBL B cell	11	2.77
			PMBCL	1	0.23
			Burkitt's lymphoma	1	0.23
			B cell high grade NHL	159	40.05
		B cell low grade NHL	MCL	2	0.50
			MALT	7	1.76
			NHL B cell type low grade	22	5.54
		B cell NHL ungraded		32	8.31
	T cell NHL	NK/T cell lymphoma		23	5.79
		LBL T cell		3	0.75
		NHL T cell NOS		4	1.00
		NHL T cell ungraded		3	0.75
	NHL indetermined			87	21.91
HL	CHL			15	3.77
Plasmacytoma				8	2.01
Total				397	100

DISCUSSION

Age

This study showed 397 cases of extranodal lymphoma, with a fairly wide age range, ranging from 1 to 82 years old, with an average age of 47.94 years old. Other study by Babu et al., showed similar result, with an average of 47.2 years old, yet another study by Shen et al, showed an average age of 56 years old.[5,6] This study showed most cases belong to the age group 51-60 years old patients with a total of 220 (25.25%) cases. Similar study conducted by Yoo et al, showed highest incidence of lymphoid neoplasms was observed in the group aged 50–79 years old. Another study conducted by Sardar et al also gave similar result in age group of 51–60 years old. This similarity may be due to all the study conducted in asian country.[3,7]

The high incidence of lymphoma is high in older age. The etiology of this phenomenon may be caused by several factors, including the accumulation of mutations with age, a weakened immune system, cellular aging lead a decrease in DNA replication as well as an increase in pro-inflammatory substances, reduced organ function, elderly lymphoma specific entities, such as EBV related DLBCL.[8,9]

Gender

This study obtained an M:F ratio of 1.33:1, similar results were obtained by Shen et al, with a M:F ratio of 1.24:1,and by Misra et al., with a M:F ratio of 1.5:1. A research by Jain et al. showed males was more common than female, with M:F ratio was 2.25:1 (6, 10, 11). The incidence of lymphoma in men is higher due to male-specific risk factors for lymphoma, such as work-related chemical exposure, lifestyle, and smoking habits, though the M:F ratio varies between NHL subtypes.[12,13]

Location

In contrast to several similar studies that found the gastrointestinal tract as the most common location for extranodal lymphoma,[5-7,10] a study from Jain et al. found the head and neck region as the most common location.[11] Lymphoma is the third most prevalent malignancy in the head and neck region, following carcinoma and sarcoma. However, determining the diagnosis of lymphoma in the head and neck region is difficult, which may be the reason for referring patients to Dr. Soetomo to hospital as tertiary hospital, for further pathology examination. This may lead to higher cases of extranodal lymphoma in the head and neck region recorded in Dr. Soetomo hospital. Lymphoma in the head and neck region is caused by a variety of factors, including a high risk of infection in the oral cavity and upper respiratory tract, which is a precursor to lymphoma.[14-16]

Diagnosis

According to this study, NHL is the most common type of extranodal lymphoma (94.20%). Similar results were shown by Fall et al.[15] NHL cases were dominated by B cell NHL (65.99%); comparable findings were found by Jain et al. and Misra et al.[8,10]

The Majority of the B cell NHL are high-grade (48.11%). According to a study by Perry et al, developing countries are dominated

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by high-grade B cell NHL. Genetic, environmental, and lifestyle variations can all contribute to this. Perry et al. discovered that Asians born and raised in developed countries had a higher incidence of low-grade B cell NHL, demonstrating the impact of environment and lifestyle.[12]

In this study, 19 extranodal DLBCL cases were found in the age of 41-78 years old, where the largest age group was 61-70 years old (6 cases). There were almost the same number of male (10 cases) and female (9 cases) patients. The location of the organs were quite diverse, the head and neck area as the most common location (8 cases). Figure 8 showed a case of DLBCL in the oral cavity in 78 years old female. DLBCL is increasing with age. This is associated to a decrease in immunity with increasing age, that will lead to the vulnerability for infection, particularly EBV, which is considered to have a role in DLBCL. Another theory is that when people become older, genetic and cellular changes occur, and in this case, BCL2 levels rise.[17,18]

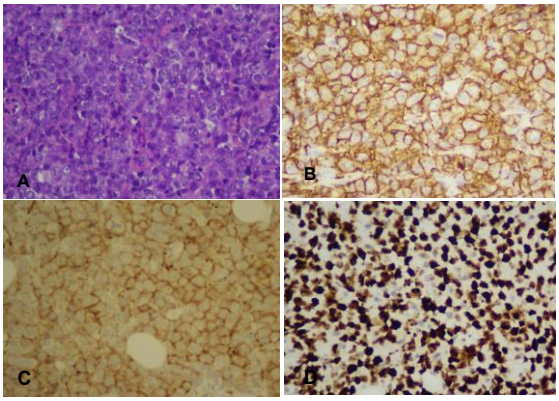

Figure 8. DLBCL in oral cavity. A. H&E section showed monotonous population of lymphoid cells displaying rounded and large sized nuclei, coarse chromatin, scanty cytoplasm (H&E, 400 times). B. CD20 was positive in diffuse and compact pattern (400 times). C) CD10 showed positive in tumor cells (400 times) D) Ki-67 showed high proliferation index (400 times).

Plasmacytoma is more common in the 4-5 decades, particularly in men. Plasmacytoma is classified into two types: bone plasmacytoma and extra-osseous plasmacytoma. The incidence of bone plasmacytoma is slightly higher compared to the extraosseous. Solitary plasmacytoma in bones can affect any bone in the body, though the spine is the most commonly affected. Extraosseous plasmacytoma, on the other hand, is commonly found in the aerodigestive tract.[19-22] In this study, 2 patients were female and 6 were male. There were six cases of bone origin and two cases of extraskeletal origin. The latter were originated from the palpebra and mediastinum. Except for one patient who was 20 years old, all patients were above the age of 45 years. The incidence of plasmacytoma in young patients is very rare, some cases occur with a history of previous bone fractures, but the exact cause cannot be ascertained yet.[23-25]

CONCLUSION

This study showed the incidence of extranodal lymphoma in Soetomo Hospital over a 5 years period. The most cases came from 51-60 years old age group, with a total of 110 cases (27.07%), and the least cases came from the <10 years old age group, with only 9 (2.26%) cases. Male to female ratio was 1.33:1. The largest distribution was in the head and neck, with 196 (49.37%) cases. The most frequent histological diagnosis was high grade B cell NHL, which accounted for 159 (40.05%) of the patients, while the most common subtype diagnostic was DLBCL, which accounted for 19 (4.78%) cases.

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CONFLICT OF INTEREST

The authors declare that there are no conflict of interests.

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