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CORRELATION OF T-CELL LYMPHOMA SUBTYPES WITH ANEMIA AT DR MOHAMMAD HOESIN HOSPITAL PALEMBANG 2018-2022

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ABSTRAK

Penelitian ini bertujuan untuk mengetahui hubungan antara subtipe limfoma sel T dengan status anemia. Penelitian analitik observasional dengan desain potong lintang dengan sampel penelitian ini adalah semua pasien yang didiagnosis secara histopatologi dan imunohistokimia sebagai limfoma sel T di RSMH Palembang yang terdaftar pada tahun 2018 hingga 2022. Sampel yang diikutsertakan memiliki data rekam medis yang lengkap dan memiliki data laboratorium (kadar Hb) sebelum operasi atau terapi dilakukan. Sampel yang diambil sebanyak 38 kasus dengan data karakteristik klinikohistopatologi (usia, jenis kelamin, lokasi tumor, dan subtipe limfoma sel T) yang lengkap dan data laboratorium yang lengkap. Sampel diambil dengan menggunakan metode total sampling. Data dianalisis dengan uji Fisher (SPSS v27). Subjek penelitian didominasi oleh kelompok usia <55 tahun (73,7%), laki-laki (73,7%), lokasi ekstranodal (73,7%), dan ENKTCL subtipe nasal (55,3%). Anemia terjadi pada 60,5% kasus dan sebagian besar merupakan anemia ringan (60,9%). Tidak terdapat hubungan yang signifikan antara subtipe limfoma sel T dengan status anemia (*p = 0,178) dan subtipe limfoma sel T dengan derajat anemia (*p = 0,342). Dapat disimpulkan bahwa tidak ada korelasi yang signifikan antara subtipe limfoma sel T dan anemia.

ABSTRACT

Correlation Of T-Cell Lymphoma Subtypes With Anemia At Dr Mohammad Hoesin Hospital Palembang 2018-2022. This study aims to determine the relationship between T-cell lymphoma subtypes and anemia status. This observational analytic study utilized a cross-sectional design conducted at samples of this study were all patients who were diagnosed histopathologically and immunohistochemically as T cell lymphoma at RSMH Palembang registered from 2018 to 2022. The included samples have complete medical record data and have laboratory data (Hb levels) before surgery or therapy were performed. The samples were 38 cases with complete clinicohistopathology characteristics (age, gender, tumor location, and T-cell lymphoma subtypes) data, and a complete laboratory data. The sample was taken using total sampling method. The data was analyzed with Fisher exact test (SPSS v27). The subjects were dominated in the age group <55 years (73,7%), males (73,7%), extranodal location (73,7%), and ENKTCL, nasal subtype (55,3%). Anemia occurred in 60,5% cases and mostly a mild anemia (60,9%). There was no significant correlation between T-cell lymphoma subtype and anemia status (*p = 0.178) and T-cell lymphoma subtype and anemia degree (*p = 0.342). It can be concluded that there is no significant correlation between the T-cell lymphoma subtype and anemia.

INTRODUCTION

Lymphoma is a group of malignancies originated from lymphoid cells which classified by WHO into several types and subtypes. These malignancies can be grouped based on morphology, histology, immunohistochemical, cell of origin and specific genetic lesions. Lymphoma is classified into hodgkin lymphoma (HL) and non-hodgkin lymphoma (NHL). The NHL is classified into B-cells type, T cells and Natural Killer cells (NK).1 The most common lymphoma cases were NHL and only HL cases were found 10% of lymphoma cases.[2]

T-cell lymphoma came from uncommon, aggressive and indolent disease and account for 12 % all all lymphomas. Many biological, clinical, and epidemiological factors associated with T-cell lymphoma subtypes have been identified, but their clinical significance is still quite uncertained.[3] Anemia is more found in patients with higher stages of lymphomas particularly in patients with bone marrow involvement.[4] However, more specific information for T-cell lymphoma and its relationship with anemia status is still undefined.[5]

This paper discus about few subtypes of T-cell lymphoma because the availability of cases in the Department of Anatomic Pathology Faculty of Medicine Sriwijaya University for instance extranodal NK/T cell lymphoma, nasal type (ENKTCL, nasal type), cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma (PTCL), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL).[5]

Lymphoma patients often experience anemia even before starting chemotherapy and without bone marrow involvement. Anemia is a condition where the hemoglobin (Hb) level is <11,5 g/dl and it is grouped into mild anemia (Hb 11-11,5 g/dl), moderate (Hb 8-10,9 g/dl), severe (Hb <8 g/dl). According to NCBI, research conducted by Tahira Yasmeen et al. a total of 408 patients (272 men and 136 women) anemia was found in 184 patients (45%).[6] Anemia can caused by many conditions, such as NHL-related bleeding with or without iron deficiency anemia, anemia of chronic diseases, anemia autoimmune hemolytic, infiltration of NHL cells into bone marrow anemia caused by chemotherapy.[7]

Anemia is an important indicator for lymphoma patients. A study revealed that anemia occurred in about 48,5% patients. This proves that the presence of anemia is correlated with prognostic factors that involve bone marrow damage, albumin, performance status, and tumors.[8] Correlation between anemia and lymphoma can be caused by tumor cells and chemotherapy and is also caused by bone marrow infiltration which is one of them causes anemia where cytokines will encourage a decrease in hemopoiesis then inhibits the response of erythroid progenitor cells to erythropoietin. One of the important substances for regulating iron homeostasis is hepcidin whose activation is induced by IL-6 and lipopolysaccharide, this shows that anemia in chronic disease patients has a close relationship with ion homeostasis in vivo.[9]

Research on T-cell lymphoma with anemia remains limited and requires further investigation. This study was conducted to ascertain the occurrence of anemia in T-cell lymphoma patients and to explore the potential relationship between these conditions at Dr. Mohammad Hoesin Hospital Palembang (RSMH).

METHOD

An observational analytical study with a cross-sectional design conducted at the Department of Anatomic Pathology Faculty of Medicine, Sriwijaya University/Dr. Mohammad Hoesin Palembang Hospital (RSMH) and Central Laboratory RSMH, from June to December 2023. The population of this study comprises all patients histopathologically and immunohistochemically diagnosed as T-cell lymphoma with certain types at RSMH Palembang. Patients who were diagnosed outside RSMH Palembang were excluded from this research. The included samples must have complete data in the medical record and have laboratory data (Haemoglobin levels) before surgery and therapy were performed. The research samples consisted of 38 cases with complete data of clinicohistopathology characteristics (age, gender, tumor location, and T-cell lymphoma subtypes), and complete laboratory data of Haemoglobin level. The subtypes of T-cell lymphoma were previously determined by immunohistochemistry study. T-cell lymphoma subtypes data were collected as secondary data for this study. The sample was taken using total sampling method. The data was analyzed with SPSS v27 and presented in tabular form and descriptive explanation.

RESULT

From 38 patients, T-cell lymphomas were predominated in ages under 55 years (73,7%), males (73,7%), extranodal location (73,7%), ENKTCL, nasal type (55,3%). Anemia status was higher among T-cell lymphoma subtypes (Table 1).

Table 1. distribution clinicohistopathology characteristics of T-cell lymphoma patients

Variables		n	%
Age	<55	28	73,7
	>55	10	26,3
Gender	Male	28	73,7
	Female	10	26,3
Tumor Location	Nodal	10	26,3
	Extranodal	28	73,7
T-cell Lymphoma Subtypes	T-LBL, NOS	2	5,3
	MF	1	2,6
	SPTCL	1	2,6
	pcPTCL, NOS	0	0
	AITL	3	7,9
	PTCL, NOS	7	18,4
	ENKTCL, nasal type	21	55,3
	ALCL	3	7,9
Anemia Status	Anemia	23	60,5
	Not Anemia	15	39,5

Our data showed (Table 2) no significant correlation between T-cell lymphoma subtypes and anemia status (p value = 0,178) upon statistical analysis using Fisher exact test.

Table 2. Correlation of T-cell lymphoma to anemia status

Subtipe TCL	Status Anemia		Total	*p
	Anemia n (%)	Tidak n (%)		
T-LBL, NOS	0 (0)	2 (13,3)	2 (5,3)	0,178
MF	1 (4,3)	0 (0)	1 (2,6)	
SPTCL	1 (4,3)	0 (0)	1 (2,6)	
pcPTCL, NOS	0 (0)	0 (0)	0 (0)	
AITL	3 (13)	0 (0)	3 (7,9)	
PTCL, NOS	3 (13)	4 (26,7)	7 (18,4)	
ENKTCL, nasal type	14 (60,9)	7 (46,7)	21 (55,3)	
ALCL	1 (4,3)	2 (13,3)	3 (7,9)	
Total n (%)	23 (100)	15 (100)	38 (100)	

*Fisher exact test

Anemia among patiens of our samples (Table 3) dominated by mild anemia in 14 patients (60,9%), moderate anemia in 7 patients (30,4%), and severe anemia in two patients (8,7%).

Table 3. Distribution of anemia levels associated with T-cell lymphoma.

Derajat Anemia	N	%
Mild	14	60,9
Moderate	7	30,4
Severe	2	8,7
Total	23	100

There is no significant correlation between T-cell lymphoma subtypes and anemia levels with p value = 0,352 by using Fisher exact test (Table 4).

Table 4. Correlation of T-cell lymphoma to anemia levels

Subtipe TCL	Status Anemia				
	Mild n (%)	**Moderate n (%)**	**Severe n (%)**	**Total**	***p**
T-LBL, NOS	0 (0)	0 (0)	0 (0)	0 (0)	
MF	1 (7,1)	0 (0)	0 (0)	1 (4,3)	
SPTCL	0 (0)	1 (14,3)	0 (0)	1 (4,3)	
pcPTCL, NOS	0 (0)	0 (0)	0 (0)	0 (0)	
AITL	1 (7,1)	2 (28,6)	0 (0)	3 (13)	0,352
PTCL, NOS	1 (7,1)	2 (28,6)	0 (0)	3 (13)	
ENKTCL	10 (71,4)	2 (28,6)	2 (100)	14 (60,9)	
ALCL	1 (7,1)	0 (0)	0 (0)	1 (4,3)	
Total n (%)	14 (100)	7 (100)	2 (100)	23 (100)	

*Fisher exact test

DISCUSSION

This study found that patients under 55 years age group was predominant (73,7%), which was higher compared to the patients over 55 years age group (26,3%). These findings align with a study conducted by Sharma et al. in 2019, 17 patients were found within the age range of 0-49 years and 13 patients aged over 50 years.10 One factor that can cause these findings is environmental factors, especially air pollution that could be gained by people who living in big and pollutant cities since their early age.[11] Air pollution contains several mutagens and carcinogens, including PAHs (e.g., benzo(a)pyrene, and polar compounds), dioxins, sulfur-containing compounds (SO3, H2SO4), and 3-nitrobenzanthrone. Polycyclic aromatic hydrocarbons (PAHs) are a class of compounds associated with human cancer risk due to their ability to generate DNA adducts. However, an individual's repair capacity may determine if DNA adducts are eliminated by the repair machinery, potentially inducing DNA mutations.[12]

The subject of this study were dominated by males. The same goes to study by Radkiewicz et al. in 2023, it was found 61,8% male T-cell lymphoma patients and 38,2% female patients. the higher number of male patients is associated with an increased risk of cancer due to exposure to cigarettes and alcohol. Immunologycally, males are more vulnerable to proto-oncogenic mutations, but also chronic potentially carcinogenic infections have been suggested. Men are generally bigger and taller than women in association with elevated cancer risk assumingly by increased mutational load through a higher number of stem cell divisions and/or growth hormone exposure since in childhood.[13]

Our data showed that most tumour locations involved was extranodal sites (73,7%), while nodal sites was only 26,3%. This finding is different from the research conducted by Sharma et al. in

2019, that showed only 20,5% their tumors were extranodal sites.10 Nodal sites are more often seen in Caucasians, extranodal and leukemic counterparts are more often seen in Asia. In the region of Asia ENKTCL is predominant TCL subtype as a result of the endemic EBV infection in this area.[14] EBV contributes to the pathogenesis of NK/T-cell lymphoma through the actions of LMP1. LMP1 upregulates PCG1β, which results in the upregulation in the base excision repair enzyme OGG1. Alterations in this signaling pathway led to mitochondrial dysfunction and subsequent ROS activation. In addition, LMP1 plays roles in migration, invasion, cell survival, and cell cycle progression. It also plays a role in manipulating the tumour microenvironment (TME).[15] The increased involvement of extranodal sites in this study could also associated with the changes in the diagnostic criteria for T-cell lymphoma compared to the WHO classifications in 2001. Consequently, the immunohistochemical markers could allow for better classification of T-cell lymphoma subtypes.[16]

This study demonstrates that the ENKTCL subtype accounted for the highest frequency at 55,3%, followed by PTCL, NOS at 18,4%, AITL at 7,9%, ALCL at 7,9%, T-LBL, NOS at 5,3%, MF at 2,6%, and SPTCL at 2,6%. The study by Miyoshi et al. in 2018, Japan exhibited the highest frequency of ATLL subtype, whereas the ENKTCL subtype was most prevalent in China. The westernization of dietary habits might serve as potential explanation for these observed outcomes.[17] The differences in subtypes across Asian countries may be associated with environmental factors as well as racial factors associated with disease for instance the prevalence of EBV is linked to NK/T-cell lymphoma.[16] The exact causes for these subtypes' differences are still not conclusively known, therefore further research is needed to investigate this disparity.

The prevalence of anemia among our patients amounted to 23 patients (60,5%), while those without anemia accounted for 15 patients (39,5%). These findings are contrast with the study by Arkananda et al which showed anemia was observed in 38.5% of patients and 80% were generally considered moderate. However, they found similar fact that the subject of T cell NHL patients was dominated by male, aged under 60 years old, and the most common subtype was PTCL NOS, which differed from our findings. Besides, they observed that incidence of anemia in patients of T cell lymphoma can be predicted by nutritional status of underweight and obese subgroup and age of equal to or less than 33 years old.[18] The exact cause of anemia in our study is not known. The pathogenesis of anemia in lymphoma is unclear but several mechanisms might be involved. A possible hypothesis was lymphoma cells produce abundance inflammatory cytokine which cause anemia. Other possibility may be correlated to likely auto-immune hemolysis and the involvement of bone marrow. Chronic disease can cause anemia which characterized by bone marrow erythroid hypoplasia, a shortened red cells survival, and production erythropoietin can be deficiency resulting in reducing the hemoglobin level.[4]

The patients with mild anemia in this study accounted for 14 patients (60,9%), moderate anemia comprised 7 patients (30,4%), and severe anemia encompassed two patients (8,7%). The study conducted by Hardianti et al. in 2021 found anemia in 296 T-cell lymphoma patients (48,5%). Among them, 142 patients (48%) experienced mild anemia, and 139 patients (46,9%) experienced moderate anemia. The most possible pathogenesis of anemia was due to inflammation. Inflammatory mediators such as IL-6, TNF-α, IL-1, and gamma interferon inhibits erythropoietin which later contributes to the development of anemia. IL-6 is still believed to be the key player for anemia both in HL and NHL. Contribution of IL-6 for the changes in iron metabolism as remarked by an elevated ferritin, lower iron, reduced total iron-binding capacity and higher serum fibrinogen level.[8]

CONCLUSION

This research shows that T-cell lymphoma patients were commonly found at the ages under 55 years old, male gender, extranodal sites, and ENKTCL subtype. However, there is no significant correlation between T-cell lymphoma subtypes with both anemia status and level.

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