Hematologic Profile in Patients with Nasopharyngeal Carcinoma

Susilawati Susilawati[1,*], Hamsu Kadriyan[2], and Wayan Putu Sutirtayasa[3]

[1]*Department of ENT-HNS Praya Hospital, West Nusa Tenggara*
[2]*Department of ENT-HNS Medical Faculty Mataram University / Provinsi Hospital West Nusa Tenggara*
[3]*Medical Faculty Udayana University*
[*]*Corresponding author. Email: susilawatiketut88@gmail.com*

ABSTRACT
Nasopharyngeal carcinoma (NPC) patients who are undergoing chemoradiotherapy, it is important to have a hematological profile examination to see hemoglobin and erythrocyte levels, the incidence of infection that has an effect on leukocyte levels and the risk of bleeding arising from a decrease in platelet levels. hematopoietic system. This study is a descriptive study using data from medical records of nasopharyngeal cancer patients at the NTB Provincial Hospital for the period January 2019 to December 2020. The data collected included patient identity, diagnosis, hemoglobin levels, erythrocyte index, leukocytes and platelets. Nasopharyngeal cancer is established through anamnesis, physical examination, histopathology and radiological investigations. Routine hematological examination is important in NPC patients to determine the presence of hematological abnormalities. Generally, the higher the NPC stage, the more complete the haematological abnormality will be. The incidence of anemia is related to the continuation of therapy and the patient's quality of life. Leukocytosis is associated with the more progressive cancer; this leukocytosis will also increase platelet cells and cancer cells themselves. Thrombocytosis can be associated with advanced stage or metastases and a poor prognosis in NPC. Leukopenia can cause a decrease in the immune system so that patients are susceptible to infections, both bacterial and viral. Thrombocytopenia can increase the risk of bleeding.

Keywords: *Nasopharyngeal Carcinoma, Stage, Hematological Disorders.*

1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor that appears in the nasopharynx, especially in the Rosenmuller fossa and the roof of the nasopharynx [1]. Based on the epidemiological data, NPC can be found in all countries. However, the incidence between continental is different. The highest incidence found in Asia especially southern China. On the other hand, the incidence found very low in Europe and North America [2]. The incidence in Guangdong, China reaches 20-50 per 100,000 population per year [3]. In Cantonese tribes in Guangdong province and Guangxi region reached more than 50 per 100,000 population per year [4]. In Indonesia, there were 348,809 new cases and 207,210 deaths caused by nasopharyngeal cancer [5]. The data in Indonesia found that NPC is the fourth most common malignancy after breast cancer, cervical cancer and lung cancer. NPC is commonly found in men of reproductive age, with a male-to-female ratio of 2.18:1 [6].

Hematologic profile may affect the physical performance of the patients and may also correlated with the prognosis. The hematologic profile may different between NPC patients. Chemo-radiotherapy has been known to altered the hematopoietic system [7]. The large dose of radiotherapy may lead to irreversible bone marrow damage. If the bone marrow exposed by the radiotherapy, it will suppress the process of proliferation and differentiation of blood cells [8]. Chemotherapy has a similar effect on hematopoetic process due to the depression of bone marrow and influence the hematopoietic system [9].

The common hematological profiles examined were hemoglobin, erythrocytes, leukocytes and platelets. Hemoglobin levels during chemoradiotherapy usually

slightly decreased. This finding may be due to the good nutritional intake and food consumed by patients during the chemoradiotherapy process or blood transfusions before chemo-radiotherapy [10]. It is important to know the hematologic profile such as hemoglobin and erythrocyte levels, as well as leucocyte to knows the occurrence of secondary infection and the risk of bleeding arising from a decrease in platelet levels.

2. METHODS

The descriptive study with medical records data of nasopharyngeal cancer patients at the West Nusa Tenggara general hospital is conducted. The period of data collection is between January 2019 to December 2020. The subjects were patient with a diagnosis of nasopharyngeal carcinoma.

The data collection included patient characteristics, diagnosis, stage, type of histopathology, hemoglobin level, erythrocyte, leukocytes and platelets count. The results of the complete blood count were obtained from the results of the automatic hematology analyzer. Nasopharyngeal cancer was established by systematic anamnesis, physical examination, histopathology and radiological investigations by the attending physician. The stage of the disease is determined according to the American Joint Commition on Cancer (AJCC) 8th edition, 2017 [11].

According to the United State National Cancer Institute, anemia divided into 5 classifications. Normal if Hb> 12 g/dL and if Hb> 11 g/dL for male and female respectively. Mild, moderate, severe, and extremely severe anemia sequentially if Hb >10.0 g/dL to normal levels, between 8.0 – 10.0 g/dL, Hb 6.5-7.9 g/dL, and Hb < 6.5 g/dL [12,13].

Based on the morphology of red blood cells, anemia can be classified into microcytic, normocytic, and macrocyitic anemia marked by mean of corpuscular volume (MCV) consecutively <80 fl, 80-100 fl and >100 fl. According to mean corpuscular hemoglobin, anemia is divided into hypochromic indicated by mean corpuscular hemoglobin (MCH) <26 pg and normochromic marked by normal MCH 26-34 pg [14]. Another hematological examination was the leukocytes and platelets count where the normal value of leukocytes was 3.200-10.000/mm^3 (SI: 3.2-10.0x10^9/L) and the normal value for platelets was 170-380.10^3/mm^3 (SI: 170-380.10^9/L) [15].

3. RESULT AND DISCUSSION

3.1 Result

Based on the present study, there were 48 patients included on this research. The frequent NPC patients were male with a male to female ratio was 3:2. Majority of the patients were found in the elderly (>41-60 years), followed by young adults (21-<41 years). Regarding the stage, most subject were in an advanced stage. In addition, most of the patients were stage IVA followed by stage III and stage II (Table 1).

Table 1. Characteristics by age, sex and stage

Characteristics	Cases Number	%
Age		
< 21	4	8,3
21 – 41	11	22,9
41 – 60	30	62,5
> 60	3	6,3
Gender		
Male	29	60,4
Female	19	39,6
Stage		
I	0	0
II	3	6,3
III	17	35,4
IVA	27	56,3
IV B	1	2,1

According to Table 2, show that more than half of the patients were anemia. However, it mostly mild anemia. Based on the erythrocyte index, normochromic anemia is dominant, followed by microcytic hypochromic anemias.

Based on the leukocyte count, more than quarter patients found leukocytosis. On the other hand, only 4.2% found leukopenia. For the platelet count, thrombocytosis is predominated compared to thrombocytopenia.

According to hematological disorder, show that the most patients were mild anemia accompanied by leukocytosis and thrombocytosis were 5 patients, followed by thrombocytosis in 3 patients. In patients with moderate anemia accompanied by thrombocytosis as many as 4 patients. There were 3 patients with leukocytosis and thrombocytosis (Table 3). The result also indicated that the higher the stage followed by the more complicated hematological abnormality.

According to table 4, show that based on the NPC stage, the highest incidence of anemia was at stage IVA as many as 55.6%, the highest leukocytosis at stage IVA as 25.9% and the highest thrombocytosis at stage IVA as 63%. In stage IVB patients, 1 patient have anemia accompanied by leukocytosis and thrombocytosis.

Table 2. Characteristics based on anemia status, erythrocyte, leukocytes and platelets count

Characteristics	Case Number	%
Anemia Status		
Normal	23	47,9
Mild	16	33,3
Moderate	8	16,7
Severe	1	2,1
Extremely severe	0	0
Erythrocyte Index		
Normochromic normocytes	31	64,5
Normocytic hypochromic	6	12,5
Microcytic hypochromic	9	18,8
Microcytic normochromic	2	4,2
Leukocyte Status		
Normal	32	66,7
Leukopenia	2	4,2
Leukocytosis	14	29,1
Platelet Status		
Normal	24	50
Thrombocytopenia	3	6,2
Thrombocytosis	21	43,8

3.2 Discussion

NPC was mainly found in reproductive age male, the ratio of male to female is 2.18:1 and 60% of patient is between 25 and 60 years old [16]. The result of this study consistent to previous study [16,17]. Based on the stage in present study, patients in advanced stages were predominant and also similar with the other study [18].

The determination of anemia was based on hemoglobin values that differ individually due to various body adaptations such as altitude, lung disease and exercise. In general, a hemoglobin count of less than 12 gm/dL indicates anemia. In determining the status of anemia, the total amount of hemoglobin was more important than the number of erythrocytes [15].

The causes of anemia in cancer patients are complex and multifactorial. The hormone serotonin and bombesin secreted by tumor cells can suppress appetite and trigger anorexia. Nasopharyngeal cancer can also cause inflammation of the oral mucosa and mucous membranes of the digestive tract, pain, decreased salivary gland secretion, psychological disorders and dental disorders. The decreased of intake can lead to the immunity impairment, infection susceptibility, and weight loss. Tumors in NPC are fragile and neovascularization is increased, prone to bleeding. Continues bleeding from NPC may induced the anemia. Cancer therapy also giving an effect on hematology properties [19].

Table 3. Characteristics of hematological abnormalities in patients with nasopharyngeal carcinoma accompanying anemia

Hematological Disorders	Anemia Status				
	N	Mild	Moderate	Severe	Extremely Severe
Normal	12	5	1	0	1
Leukopenia	0	1	0	0	0
Leukocytosis	4	0	0	0	0
Thrombocytopenia	1	2	0	0	0
Thrombocytosis	4	3	4	0	0
Leukocytosis, Thrombocytosis	1	5	3	0	0
Leukopenia, Thrombocytosis	0	1	0	0	0

Chemotherapy was the main treatments modality for advanced nasopharyngeal cancer. This agent work by several mechanisms such as destroying, suppressing and preventing the spread of rapidly growing cancer cells. However, chemotherapeutic agents have several side effects on the oral and gastrointestinal mucosa, hair follicles, reproductive system and hemopoietic system [20]. One of the effects of chemotherapy was the formation of free radicals due to cisplatin administration. The excessive amount of free radicals could damage the important normal cells such as bone marrow. Furthermore, suppression of blood cell formation can lead to anemia, leukopenia and thrombocytopenia [21].

Table 4. Characteristics of hematological disorders based on the stage of nasopharyngeal cancer

Hemato-logical disorders	**Stadium**				
	I N(%)	**II N(%)**	**III N(%)**	**IVA N(%)**	**IVB N(%)**
Hb					
Normal	0(0)	2(66)	8(47)	12(44)	0(0)
Anemia	0(0)	1(34)	9(53)	15(56)	1(100)
Leukocytes					

Normal	0(0)	3(100)	11(65)	18(67)	0(0)
Leukocytosis	0(0)	0(0)	6(35)	7(26)	1(100)
Leukopenia	0(0)	0(0)	0(0)	2(7)	0(0)
Platelets					
Normal	0(0)	2(67)	13(76)	9(33)	0(0)
Thrombocytosis	0(0)	1(33)	2(12)	17(63)	1(100)
Thrombocytopenia	0(0)	0(0)	2(12)	1(4)	0(0)
Total	0(0)	3(100)	17(100)	27(100)	1(100)

In patient treated by chemotherapy, 67-81% of them were anemia. The occurrence of anemia in the administration of chemotherapy and/or radiotherapy can cause the reduction of treatment effectiveness [20]. Kadriyan et al found that 82.5% NPC patient had anemia, most of them were mild 57.5% [17]. In the study of haemogblobin levels among NPC patients who undergoing chemotherapy, found that Hb levels decreased significantly after six courses chemotherapy [22].

The other factors which can induced the anemia were the low iron intake or the low iron absorption or the presence of inhibitors in iron absorption. This will lead to the level of iron was lower than the body's needs [4].

Anemia was rarely accompanied by symptoms of bone marrow infiltration or blood loss, hemolysis, renal, hepatic or endocrine disorders, or signs of nutritional deficiency. Anemia caused by cancer, can occur as a direct effect of malignancy, can be as a result of the production of certain substances produced by cancer, or it can be as a result of cancer treatment it self [23,24]. Previously, anemia that occurred in cancer patients was always associated with anemia of chronic disease. This type of anemia was now referred as cancer-related anemia or cancer-related anemia (CRA). This effect was known as the paraneoplastic syndrome [25].

White blood cells or leucosyite were part of polymorphonuclear cells which has a function for the defence to infection and inflamation. Due to this function, leukocytes usually surrounded the cancer cells or spread between epithelial cells. The increase of leukocytes may promote by the released of various interleukins (IL-1 and IL-18) and chemokines (CXCL10 and CCL20) by the NPC cells [26]. In addition, this pathway referred to assumed that the more advance the cancer progresses, it will involve more leukocytes number. It will also increase the possibility of leukocyte interactions with other cells activated such as endothelial cells, platelets and cancer cells through their ligands [27].

Leukopenia was one of the side effects that occur due to the toxicity of chemotherapy drugs. Post-chemotherapy leukopenia was an important problem that has a negative impact on the quality of life of cancer patients and altered the morbidity and mortality of patients. Leukopenia can occur immediately or several days after chemotherapy. Leukocytes reached the lowest value on the 7th to 14th day post-chemotherapy and could continue after the drug was discontinued. Generally recovery occurs 2 weeks after discontinuation of therapy [28]. The presence of hematopoietic suppression due to the effects of chemotherapy, including leukopenia, can be influenced by several factors, including the patient's nutrition, age, radiation administration, chronic diseases and diseases affecting the hematopoietic system. The occurrence of leukopenia after chemotherapy can cause complications that have a negative impact on the patient's condition, such as infection. Furthermore, immediate treatment was needed to increase the number of leukocytes [29].

Thrombocytosis was associated with the advanced cancer stage or metastasis. Thrombositosis was one of a poor prognostic marker for most tumors. In the study of Gao et al., found 11.8% of cases of nasopharyngeal carcinoma with a platelet count >300,000/mm3, with a platelet count above this value has a poor prognosis and a tendency to metastasized [30]. Cancer cells can interact with all components of the hemostatic system including platelets [31]. Cancer cells have the ability to aggregate platelets (known as tumor cell-induced platelet aggregation or TCIPA). This ability occurs due to cancer cells could expressed the receptors and adhesion molecules own by the platelets. The existence of TCIPA will provide an advantage for the survival of cancer cells [32,33]. The similarity of the phenotype of cancer cells with platelets is also accompanied by the ability of cancer cells to produce various platelet agonists such as ADP and thrombin [34].

The occurrence of thrombocytopenia in some solid tumors is considered to be part of the paraneoplastic syndrome. In NPC, thrombocytopenia rarely occurs unless it has diffuse infiltrated of the bone marrow. Yang K, et al. found that there were only two reports of thrombocytopenia in nasopharyngeal cancer [31]. According to the present study, thrombocytopenia was 2.1%, thrombocytopenia with anemia was 4.2%.

The novelty on the present study revealed the trend that more advance the stage, the more complicated the hematologic disorder found. However, the advanced research with prospective approach is needed to prove this finding.

4. CONCLUSION

A routine hematological examination is an important determinant in NPC patients to established the presence of hematological abnormalities. Hematologic abnormalities are more complicated with the increasing stages of NPC. Furthermore, an appropriate treatment should be given to increase the NPC patient's quality of life.

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