Majalah Kedokteran Sriwijaya,
Th.56 Nomor 2, April2024

PD-L1 EXPRESSION WITH ITS INFLUENCING PROGNOSTIC FACTORS IN EXTRANODAL NK/T CELL LYMPHOMA

Esti Fitria, Krisna Murti*
Department of Anatomic Pathology, Faculty of Medicine, Sriwijaya University
Email : krisna.arinafril@unsri.ac.id

ABSTRACT

Non Hodgkin Lymphoma (NHL), especially Extranodal NK/T cell Lymphoma (ENKTL) is a rare malignancy with an incidence rate of approximately 12% (168 out of 1,403 cases) of all NHL cases. Research by Aozasa et al., the frequency of ENKTL is estimated to be 10-fold higher in Asian populations when compared to Europeans. According to WHO 2022, extranodal NK/T cell lymphoma, nasal type is often found in the respiratory tract, nasopharynx, paranasal sinuses, and palate. This type of lymphoma is closely associated with Epstein-Barr Virus (EBV) infection. Overthe past decade, immunotherapy is, once again, a promising approach to cancer treatment, due to the remarkable salutary effectiveness of Immune-Checkpoint Inhibitors (ICIs) targeting Programmed Cell Death-1 (PD-1) or Programmed Cell Death Ligand-1 (PD-L1). Programmed Death- Ligand 1 (PD-L1) is an immune checkpoint protein that manipulates the host immune response by regulating T cell function. Programmed Death- Ligand 1 is overexpressed in EBV+ lymphoma cells especially in ENKTL compared to EBV negative lymphomas and is associated with worse prognosis. In addition to determining prognosis, PD-L1 inhibitors are used as cancer therapy. Programmed Death- Ligand 1 expressed by ENKTL tumor cells as a target for PD-L1 inhibitor therapy (pembrolizumab). Programmed cell death ligand 1 (PD-L1) overexpression was associated with the clinicopathological factors of B symptoms, IPI score, and Ann Arbor Stage. Some studies examined the expression of PD-1 and PDL1 in tumor cells and found PD-L1+ tumor cells was an independent poor prognostic factor for OS.

Keywords: Extranodal NK/T cell lymphoma, Epstein-Barr Virus, Programmed Death Ligand 1, Staging Ann Arbor, Prognosis

1. INTRODUCTION

Extranodal NK/T cell lymphoma (ENKTL) accounts for less than 1% of all NHL, whereas in Asian countries and Latin American countries the incidence is more frequent at 2% to 15% of NHL.[1,2] Based on the WHO fifth edition of 2022, ENKTL has two subtypes namely nasal and non-nasal.[3,4] The nasal subtype accounts for 80% of cases, the tumor siteis initially located in the nasal cavities, nasopharynx, oropharynx, Waldeyer ring, epiglottis, and aryepiglottis fold.[5,6] Lesions in the nasal cavities may invade the face ordestroy the nasal floor, perforate the palate, and eventually become lethal midline granuloma. Lymph nodes may be involved.[6,7] In advanced staging, systemic symptoms may occur, affecting the skin, gastrointestinal tract, testis, liver, lien, and bone marrow.[8,9] The non-nasal subtype is about 20% of cases. General clinical symptoms are the same as in ENKTL, nasal type, can occur in the skin, gastrointestinal tract, testis, and miscellaneous locations.[10,11] These non- nasal cases require radiologic confirmation (PET-CT), should be reclassified as advanced staging of ENKTL, nasal type, rather than ENKTL, non-nasal type. [12,13]

The most frequent cause of this type of lymphoma is often associated with Epstein Barr Virus (EBV).[4,5,14] Although the prognosis of ENKTL, nasal type is poor, there have been recent advances in its therapy, which is in addition to using chemotherapy and radiation. Chemoradiotherapy or chemotherapy yield curative effects on ENKTL patients in the early-stage. However, the outcomes of those treatments for patients with

advanced or relapsed ENKTL are disappointing, and the estimated 3-year overall survival is 25% in advanced patients. Therefore, there is an urgent medical need to explore new therapeutic strategies for advanced ENKTL.[13,14]

Recent studies of ENKTL, nasal type with different levels of intracellular/cellular molecules, cytokines, chemokines, and microRNAs are involved in the development of ENKTL, nasal type therapy. With the application of modern therapies, clinical outcomes of patients with this disease have improved significantly.[14,15] Programmed Cell Death Ligand 1 (PD-L1), an immune checkpoint protein that manipulates the host immune response by regulating T cell function is an alternative therapy for this entity.[6,7,10] Study Gao et al., on PD-L1 expression status and corresponding prognostic features in ENKTL to date. PD-L1 expression is a new therapeutic target in cancer immunotherapy. Programmed cell death ligand 1 is overexpressed in EBV+ lymphoma cells especially in ENKTL compared to EBV negative lymphomas and is associated with worse prognosis. Programmed cell death- ligand 1expressed by ENKTL tumor cells as a target for PD-L1 inhibitor therapy (pembrolizumab).

Programmed cell death ligand 1(PD-L1) overexpression was associated with the clinicopathological factors of B symptoms, IPI score, and Ann ArborStage. There are four stages in this method.[5,8] A number of studies have examined the prognostic effects of PD- L1+ tumor cells in NK/T lymphoma and showed inconsistent results. In 79 patients with nasal NK/T-cell lymphoma (ENKTL), nasal type PDL1+ tumor cells were observed in 79.7% of patients and these patients seemed to have a better OS compared with that in patients with PD- L1-negative tumor cells. However, in another study of 49 patients with ENKTL, the PD-L1 expression in tumor cells showed an unfavorable impact for OS and PFS. Zeng et al., analyzed 88 ENKTL to screen out the prognostic markers to establish the molecular model for ENKTL prognosis. This study examined the expression of PD-1 and PDL1 in tumor cells and found PD-L1+ tumor cells was an independent poor prognostic factor for OS with hazard ratio of 9.36.[9]

2. METHODS

This literature review is organized in several steps. In the first step, the authors determined the topic to be explored. In the second step, the authors collected articles, either in Indonesian or English, from various databases including PubMed, ScienceDirect, Cochrane Library, Google Scholar, Directory of Open Access Journal (DOAJ), and Garda Rujukan Digital (GARUDA). The search keywords were *Extranodal NK/T cell lymphoma, Epstein-Barr Virus, Programmed Death Ligand 1, Staging Ann Arbor, Prognosis.* Step three, the author sorted out relevant articles through the Patient/Population, Intervention, Comparison, Outcome (PICO) approach. Step four, the author discussed and drew conclusi.

3. DISCUSSION

Extranodal NK/T-cell lymphoma (ENKTL), nasal type is a rare subtype of non-Hodgkin lymphoma, a lymphoid malignancy originating from the NK/T cell lineage. It is characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype and associated with Epstein-Barr virus (EBV).[8]

Definition, Epidemiology And Etiology

According to the International T cell lymphoma project (ITCLP), with 22 institutions from North America, Asia, and Europe, ENKTL is found in approximately 2.7% of all cases. By geographical region, the difference becomes clear with ENKTL

associated with 5.1% of cases in North America, South America, 4.3% in Europe, and 22.4% of cases occurring mostly in Asia.[13,14]

Although the exact mechanism remains unclear, EBV appears to play a role in the pathogenesis of ENKTL, nasal type, as it is a common cause in all ethnic groups.[1] In addition to the EBV infection, diverse genetic alterations appear to be involved in the pathogenesis of ENKTL, nasal type. The chromosomal area at 6q21-23 is frequently deletion (36-60% of cases), and contains various tumor suppressor genes, such as PRDM1, ATG5, HACE1, and FOXO3, through comparative genomic hybridization, recognized as candidate triggers of ENKTL, nasal type tumorigenesis. A multicentric study in Asia revealed an increased frequency of ENKTL, nasal type in farmers (pesticide users) and chemical plant workers.[14,15]

Clinical Symptoms

The peak incidence of ENKTL, nasal type occurs at the age of 40-50 years, and the male-female ratio is about 2:1. More than 70% of patients are diagnosed at an early stage, based on the Ann Arbor classification. The lesions are initially found as necrotic and ulcerated granulomas in the nasal cavity, which is its extranodal location.[8] The most common initial symptoms are nasal congestion and discharge. Additionally, prolonged fever, as a systemic symptom, is also common. A study by Miki et al composed of 62 subjects with ENKTL, nasal type with majority patients complaints of nasal obstruction, bloody nasal discharge, and persistent fever.[6,8,13]

Extranodal NK/T-cell lymphoma, nasal type can cause highly aggressive systemic symptoms and the mostcommonly affected sites are skin, soft tissue, testis and intestine. In aretrospective cohort analysis study in Brazil, nearly 20% of cases were extranasal in origin, but bone marrow involvement is also possible.[8,16,17]

Histopatology

Histopathological features of ENKTL, nasal type show diffuse, dense tumor cells and infiltrative pattern, generally with coagulative necrosis and mixed with apoptotic bodies.[8,17] Angiocentric-angiodestructive and fibrinoid changes in blood vessels are common. There may also be a heavy inflammatory cell background (small lymphocytes, plasma cells, histiocytes and eosinophils), similar to that of an inflammatory process. Bone marrow involvement is rare, usually with interstitial infiltration.[17,18]

Lymphoma cells vary in size from small, medium, large to anaplastic cells. Medium-sized cells or mixed with small and large cell sizes are common. Lymphoma cells with irregular nuclei and pale eosinophilic cytoplasm. Granular chromatin, except in very large size cells, usually vesicular chromatin. Nuclei are generally invisible or small. Mitoses are easily found (Figure 1).[17] Progression of cell histology to large cells indicates progressive, residual or metastatic disease.[8,17]

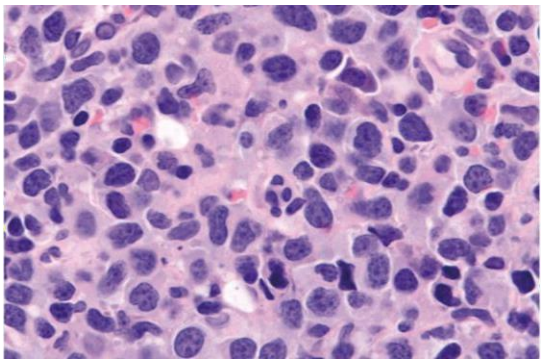

Figure 1. Nodal EBV-positive T- and NK-cell lymphoma. This lymphoma shows diffuse infiltrates of monotonous, medium to large sized cells, sometimes resembling centroblasts.[8]

Immunohistochemistr

Recent studies have shown that EBV can infect NK or T cells, suggesting a new concept of EBV-associated lymphoma.The tumor cells give positive expression of

EBNA1 and CD2, indicating the origin of ENTKL, nasal type is NK cells or T cells, which express surface CD3, CD56, and T Cell Receptor (TCR) proteins and TR gene rearrangement. The difference betweenNK or T cell origin is not important for diagnosis and prognosis.[19,20] In many cases, tumor cells are also positive for CD2, cytoplasmic surface CD3, and CD56, while surface CD3 is negatively expressed. Cytotoxic T cell lineages areexpressed on CD5, CD8 and TCR, often CD56 negative. Cytotoxic molecules (e.g. TIA1, granzyme B, and perforin) are positively expressed. HLA-DR, CD25, FAS (CD95), FAS ligand, CXCL13, IRF4/MUM1, pSTAT3 and MATK proteins are positively expressed. PD-L1 and CD68 immunohistochemistry were generally positive. In situ hybridization for EBV encoded RNA (EBER) showed the presence of EBV in the majority of lymphoma cell cases (Figure 2).[8,19,20]

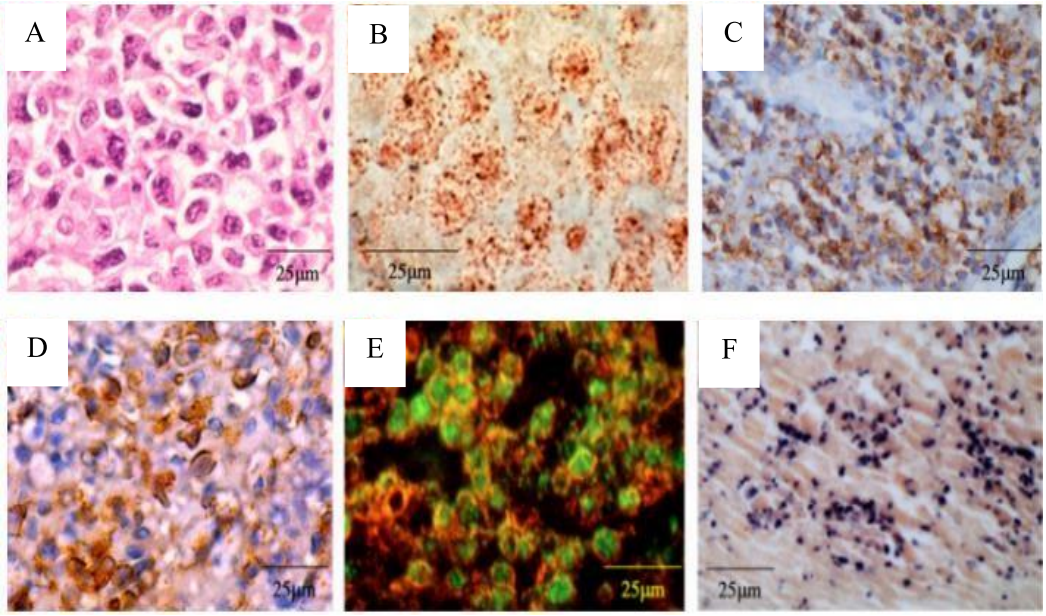

Figure 2. Microscopic features of extranodal NK/T cell lymphoma, nasal type. (a) Hematoxylin and eosin staining; (b) CD56 immunohistochemical staining; **(c)** In situ hybridization for EBV DNA; (d) Dual fluorescence staining with CD2 (red) and EBV nuclear antigen 1 (EBNA1) (green); (e) EBV-encoded latent membrane protein 1 (LMP) 1 immunohistochemical staining; (f) In situ hybridization of EBV-encoded small nuclear early region (EBER).[17]

Pathogenesis of ENKTL

Several major mechanisms of pathogenesis are involved in ENKTL, namely pathogenesis involving mechanisms of tumor cell proliferation, increased angiogenesis, genomicinstability, immune evasion, inhibiting apoptosis and inactivation of tumor suppressor genes (Figure 3).[21] However,the current literature review discusses the mechanism of immune evasion regarding the pathogenesis associated with PD-L1.

Programmed Cell Death Ligand 1 (PD-L1)

Programmed cell death ligand 1 (PD-L1), otherwise known as B7-H1 or CD274 is the first functionally characterized ligand of the coinhibitory programmed death receptor 1 (PD-1).Programmed cell death ligand 1 (PD-L1) along with its co-ligand PD-L2, plays a role in peripheral and central immune cell tolerance through binding to the PD-1 receptor. PD-L1 expression can be constitutive or inducible. Constitutive PD-L1 expression can be found on Antigen Presenting Cells (APCs), dendritic cells, macrophages, vascular endothelial cells and pancreatic islet cells. In the context of

inflammation and/or infection, PD-L1 is induced as a signal that suppresses hematopoiesis, endothelial and epithelial cells. Several studies have shown PD-L1 expression on the surface of several types of tumor cells such as ENKTL, melanoma, renal cell carcinoma and so on. [21]

Natural Killer (NK) cells can also increase PD-L1 expression on the surface of tumor cells through IFN-γ secretion via JAK1, JAK2, and STAT1 pathways. TLR-assisted PD-L1 regulation is dependent on activation by MEK/ERK kinases that increase PD-L1 mRNA transcription through nuclear factor kappa B. In conclusion, both T cells and NK cells jointly secrete IFN-γ which will induce PD-L1 expression on the surface of target cells including tumor cells. PD-L1 expression can also be suppressed by tumor suppressor genes such as Phosphatase and Tensin Homolog (PTEN) (Figure 3). [21,22]

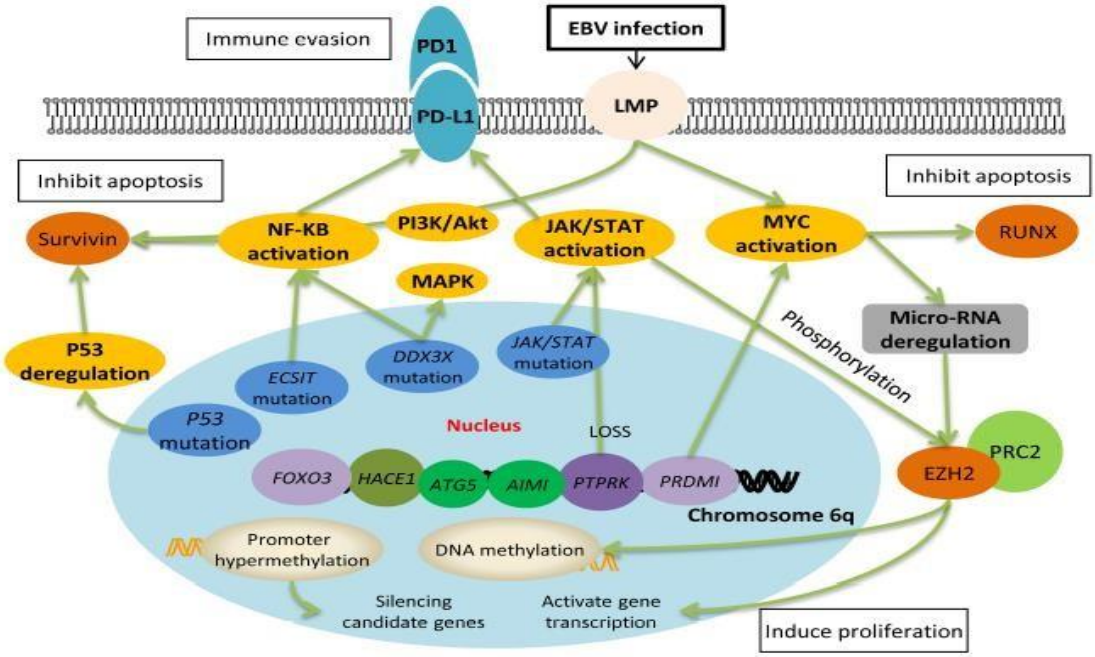

Figure 3. Molecular pathogenesis of Epstein-Barr virus-positive NK/T-cell lymphoma. EBV's latent membrane protein-1 (LMP-1) activates downstream signaling pathways, one of which is the NF-kB pathway. Together with the PI3K/Akt pathway, NF-kB leads to the upregulation of survivin, which further inhibits cell apoptosis. JAK/STAT activation is associated with the upregulation of EZH2, which results in DNA methylation and gene transcription, and ultimately induces cell proliferation. Both the NF-kB pathway and the JAK/STAT pathway upregulate PD-L1 expression on the surface of lymphoma cells and both escape immune system surveillance by activated T cells. Deletion of chromosome 6q suppresses many tumor suppressor genes, such as PTPRK and PRDMI, which directly results in activation of the JAK/STAT and myc pathways. In addition, mutations of genes including P53, ECSIT, DDX3X are also involved in ENKTL oncogenesis.[21]

In the case of ENKTL, the nasal type of PD-L1 expression calculation is conducted based on the cut-off value. Research by Wook et al showed PD-L1 is positive in tumor cells. In this study, 56% (41 out of 73 ENKTL cases) with positive PD-L1 with a cut-off value > 10%, were positively expressed in lymphoma (Figure 4).[7,24]

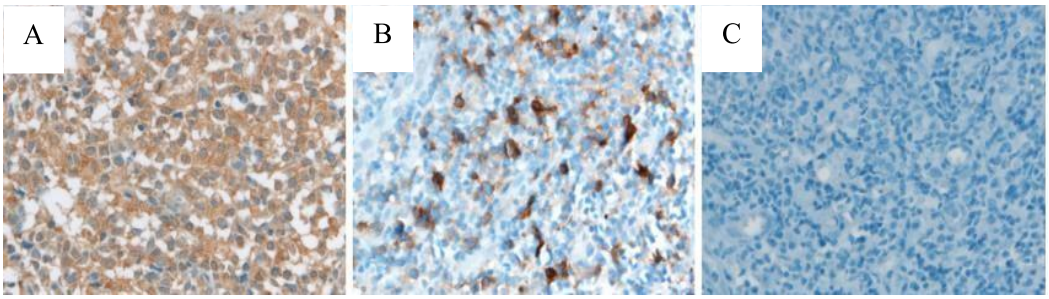

Figure 4. PD-L1 expression pattern in ENKTL tissue. Three examples of ENKTL expressed PD-L1 in 80% (a), 20% (b), and 0% (c) of lymphoma cells and reactive cells, respectively (×400 magnification).[25]

Management

Extranodal NK/T cell Lymphoma (ENKTL), nasal type therapy utilizes anthracycline-based chemotherapy. P-glycoprotein (P-gp), an efflux pump capable of excreting chemotherapeutic drugs, is frequently expressed in ENKTL. The SMILE regimen (dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide) in a prospective trial has greatly improved the success rate for treating advanced disease, reported with a five-year survival of 50%.The newer regimen, DDGP (dexamethasone, cisplatin, gemcitabine, pegasparginase) compared to SMILE leads to a 2-year overall survival rate of 74% versus 45% respectively.[26] The greater understanding of the pathology, particularly with regard to apoptosis resistance, epigenetic changes and immune evasion has identified a number of therapeutic targets that are now in clinical trials or could be used in the near future. Response rates from single agents used so far such as PD-L1 blockade or JAK-STAT inhibition remain low and effective combination therapies may be required.[26,27]

Staging

Computed tomography (CT) scan and MRI are used for assessment of local lesions, lymph node involvement and distal metastasis. In addition, bone marrowbiopsy and gastric fiberscope are required for evaluation of bone marrow and other organ involvement. Staging of ENKTL, nasal type can use the Lugano classification. Fluorodeoxyglucose (FDG) PET-CT is the standard and most accurate radiological staging, ENKTL tumor cells are FDG-avid. Lymphoma staging can be determined based on Ann Arbor staging: [28]

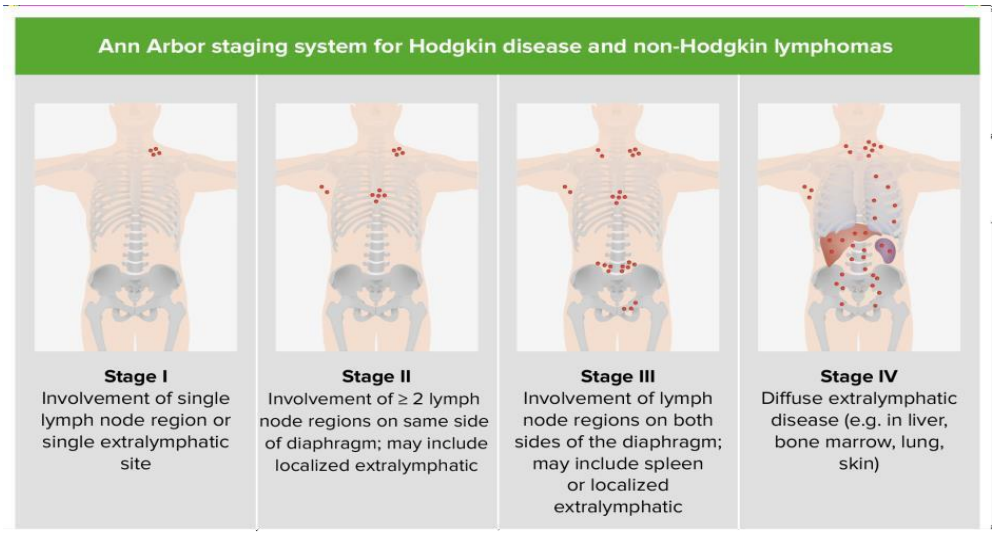

Figure 5. Ann Arbor staging system. Stage I is involvement of one KGB or extralymphatic. Stage II is the involvement of ≥ 2 KGB on the same side of the diaphragm. Stage III is KGB involvement on both sides of the diaphragm. Stage IVis involvement of many extralymphatic areas. [28]

Prognosis

The prognosis of ENKTL patients was assessed using the Ann Arbor staging system. Early staging does not correlate with poor prognosis. Recent research by several Asian lymphoma study groups published a new and improved prognosis system, namely staging I which is defined as limited to the nasal area, without tumor invasion of surrounding structures. Staging II non-nasal location or nasal location with tumor invasion. Staging III nasal dysfunction with regional lymph node involvement, and staging IV dysfunction with non-regional lymph node metastases or lymph node metastases on both sides of the diaphragm. The prognosis of extranodal NK/T cell lymphoma depends on the localization. The cumulative probability of survival at a nasal location at 5 years is 37.9% to 45.3%, being the worst in presentations that occur outside the nasal cavity. As mentioned by several studies, the staging system needs to be validated, preferably in the future in prospective studies.[8,28]

The International Prognostic Index (IPI) and the NK/T cell lymphoma prognostic index were previously used for risk stratification. After the introduction of nonanthracycline-containing treatment regimens, these scoring systems were no longer adequate, and in 2016, the ENKTL (PINK) prognostic index was introduced in table 1. [28]

This new scoring system attributes 1 point to each risk factor, and the modified PINK score is the prognostic index ENKT, an EBV score that includes all factors from the PINK score along with EBV plasma loading. Since 2017, the prognostic index PINK ENKTL-EBV (PINK-E) score that includes all factors from the PINK score along with EBV plasma loading. Since 2017, the PINK prognostic index has been incorporated into the NCCN for PTCL. However, for ENKTL patients at RSMH Palembang Ann Arbor staging is still used. [29,30]

Programmed Cell Death Ligand 1 (PD-L1) and Prognosi

It is known that EBV infection can induce PD-L1 expression. Program Death Ligand 1 itself as previously described contributes to modulating the peripheral immune system such as APCs, macrophages, dendritic and endothelial cells. Several authors have notified an association between PD-L1 expression and a better prognosis. Kim et al stated that ENKTL patients with positive PD-L1 expression had a better 5-year survival rate. However, different results were shown by the study of He et al., where PD-L1 expression was an independent predictor of a worse prognosis. Furthermore, other researchers who actually show no relationship between PD-L1 and prognosis, namely the study of Feng et al.[9,22] The study by Hai Xia et al that to further evaluate the prognostic significance of PD-L1, a univariate analysis wasperformed. In addition to lésions' location ($p = 0.013$), distal lymph node metastasis ($p = 0.006$), Ann Arbor stage ($p < 0.001$), NRI score ($p = 0.027$), PINK score ($p = 0.023$), and chemotherapy regimens ($p < 0.001$), patients with high PD-L1expression were associated with increased risks of disease progression, compared with patients with low PD-L1 respectively ($p = 0.005$). Kaplan-Meier analysis showedthat the high PD-L1 expression was significantly associated with shorter progression free survival (PD-L1: $p = 0.004$).[25] In terms of overall survival, univariate analysis demonstrated that

patients with high PD-L1 expression experienced significantly increased overall mortality than those with low PD-L1, respectively (PD-L1: HR = 2.44, 95% CI: 1.45 to 4.11. It is well known that both PD-L1 and VISTA are capable ofsuppressing antitumor T-cell responses. Interestingly, multivariate analysis demonstrated that type III had a significant influence on PFS and OS, with high hazard ratios (PFS: p = .010; OS: p = 0.012) after adjusting for possible confounding variables. In conclusion, PD- L1 showed synergistic functions in predicting the poor prognosis in ENKTL.[25]

4. CONCLUTION

In conclusion, comprehensively explore the expression profile of numerous B7 family proteins PD-L1 in ENKTL. PD-L1 was significant associated with worse clinical outcomes. PD-L1 was an independent predictor of poor prognosis, and patients with high expressions of PD-L1 suffered from the worst prognosis. More importantly, PD-L1 blockadeaffordable for ENKTL immunotherapy.

REFERENSI

1. Storck K, Markus B, Ulrich K, Andreas K. (2019). Clinical presentation and characteristics of lymphoma in the head and neck region. *Head Face Med* ,15(1):1.
2. Park HS, Lacey M, Marta BA, Atul BS, Katherine MK. (2017). T-cell non-Hodgkin lymphomas: spectrum of disease and the role of imaging in the management of common subtypes. *Korean J Radiol* ,18(1):71-83.
3. Zhang N, Dalal MR. (2019).Incidence and prevalence of T cell lymphoma in the EMA member states:methodology for estimation in rare malignancies of CTCL an PTCL (VISTA and PD-L1 synergistically predict poor prognosis in patients with extranodal natural killer/T-cell lymphoma *Value,* 3:853.
4. Liu S, Weiping L, Huichao L, Lei Y, Yuqin S, Xi Z, et al. (2022). Epidemiological characteristics of peripheral T-cell lymphoma: a population-based study. *Front Oncol,* 12:863-69.
5. Gao L-M, Zhang Y-H, Shi X, Liu Y, Wang J, Zhang W, et al. (2022). The Role of PD-L1 expression in prediction and stratification of recurrent or refractory extranodal natural killer/T-cell lymphoma. *Front Oncol,* 12:821-8.
6. Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. Extranodal NK/T cell lymphoma. In: World health organization classification of tumors of haematopoietic and lymphoid tissues. 4thth ed. Lyon: IARC 2017.*P536-54*
7. Wook Y, Ho Y, Soo J, Tae M, Dae S, Chul-W, Yoon K. (2016). Expression of programmed cell death ligand 1 (PD-L1) in advanced stage EBV-associated extranodal NK/T cell lymphoma is associated with better prognosis. *Virchows Arch,* 469(2):581-90
8. Shih S. Extranodal NK/T cell lymphoma. In: WHO classification of Tumors of hematopoetic and lymphoid tissue. 5thth ed. Lyon: International agency for research on cancer 2022. p368-70.
9. Kim S, Ryu K, Park B, Yoon S, Cho J, Park Y, Kim W. (2022). Exosomal and soluble programmed death-ligand 1 (PD-L1) predicts pembrolizumab responses in patients with extranodal NK/T-cell lymphoma. *Cancers* 14(1):56-61.
10. Randolph GJ, Stoyan I, Bernd HZ, Joshua PS. (2017). The lymphatic system: integral roles in immunity. *Annu Rev Immunol,* 35:31-52.
11. Kumar V, Abbas AK, Aster JC.

Hematopoietic and lymphoid systems.

In: Robin basic pathology. 10th rev. ed. Philadelpia: Elsevier 2018. p442-93.
12. Wallentine JC. Hematopoietic and immune systems. In: Lindberg MR, Laura WL, editors. Diagnostic pathology normal histology. 2ndnd ed. Philadelphia: Elsevier; 2018. p118-47.
13. Jaap A, Van D, Anne G, Niezink H, Gerwin A. Huls, Max B, et al. (2021). Extranodal natural killer/T-cell lymphoma, nasal type: diagnosis and treatment. *Euro Heme Associate,* 5(2):523.
14. Kuper CF, Marcel VW, Serge AL. Mucosa associated lymphoid tissues. In: Parker GA, editor. Immunopathology in toxicology and drug development. 2ndnd ed. Durham: Springer; 2017. p81-122.
15. Huang Y, De L, Gaulard P. (2013). Molecular underpinning of extranodal NK/Tcell lymphoma. *Best Pract Res Clin Haematol,* 26:57-74.
16. Costa R, Pereira J, Lage L, Baiocchi O. (2023). Extranodal NK-/Tcell lymphoma, nasal type: what advances have been made in the last decade? *Front Oncol,* 13(11):75-95.
17. Takahara M, Takumi K, Kan K, Toshihiro N, Yasuaki H. (2021). Extranodal NK/T-cell lymphoma, nasal type: genetic, biologic, and clinical aspects with a central focus on Epstein-Barr virus relation. *Microorganisms* 9:1381.
18. Takada H, Imadome KI, ShibayamaH, Yoshimori M, Wang L, Saitoh Y, etal. (2017). EBV induces persistent *NF-κB* activation and contributes tosurvival of EBV positive neoplastic T- or NK-cells. *PloS One,* 12:174-86.
19. Tang T, Tay K, Tao M, Quek R, Farid M, Lim ST. (2016). A phase II study of bortezomib-GIFOX (gemcitabine, ifosfamide, oxaliplatin) in patients with newly diagnosed natural-killer T-cell lymphoma. *Blood,* 128:53.
20. Tomoka T, Powers E, Van G, Amuquandoh A, Dhungel, BM, Kampani C, et al. (2017). Extranodal natural killer/T-cell lymphoma in Malawi: a report of three cases. *BMC Cancer,* 17:633.
21. Kimura H, Karube K, Ito Y, Hirano K, Suzuki M, Iwata S, et al. Rare occurrence of JAK3 mutations in natural killer cell neoplasms in Japan. *Leuk Lymphoma* 2014;55:962-3.
22. Wen H, Ma H, Cai Q, Lin S, Lei X,He B, et al. (2018). Recurrent ECSIT mutation encoding V140A triggers hyperinflammation and promotes hemophagocytic syndrome in extranodal NK/T cell lymphoma. *Nat Med,* 24(2):154-64.
23. Tse E, Au-Yeung R, Kwong YL. (2019). Recent advances in the diagnosis and treatment of natural killer/T-cell lymphomas. *Expert Rev Hematol,* 12:927-35.
24. Hai X, Yan G, Jian C, Qiang-H, Xiao-X, Bing B, et al. (2021). VISTA and PD-L1 synergistically predict poor prognosis in patients with extranodal natural killer/T-cell lymphoma. *Onco Immunol,* 1(10):11-21.
25. Lee S, Park HY, Kang SY, Kim SJ, Hwang J, Lee S, et al. (2015). Genetic alterations of JAK/STAT cascade and histone modification in extranodal NK/T-cell lymphoma nasal type. *Oncotarget,* 6:17764-76.
26. Wen H, Ma H, Cai Q, Lin S, Lei X,He B, et al. (2018). Recurrent ECSIT mutation encoding V140A triggers hyperinflammation and promotes hemophagocytic syndrome in extranodal NK/T cell lymphoma. *Nat Med,* 24(2):154-64.
27. Eladl AE, Kazuyuki S, Yuka S, Taishi T, Seiichi K, Kei K, et al. (2020). EBV status has prognostic implications among young patients with angioimmunoblastic T-celllymphoma. *Cancer Med,* 9(2):678-88.
28. Jaap A, Van D, Anne G, Niezink H, Gerwin A. Huls, Max B, et al. (2021). Extranodal natural killer/T-cell lymphoma, nasal type: diagnosis and

treatment. *Euro Heme Associate,* 5(2):523.
29. Bhatkule Ma, Dhawle MS, Kumbhakarna NR, Bindu RS. (2014). Nasal natural killer/T cell lymphoma. *Indian J Hematol Blood Transfus*, 30:292-3.
30. Su YJ, Wang PN, Chang H, Shih LY, Lin TL, Kuo M, et al. (2018). Extranodal NK/T-cell lymphoma, nasal type: clinical features, outcome, and prognostic factors in 101 cases. *Eur J Haematol* 101:379-88.