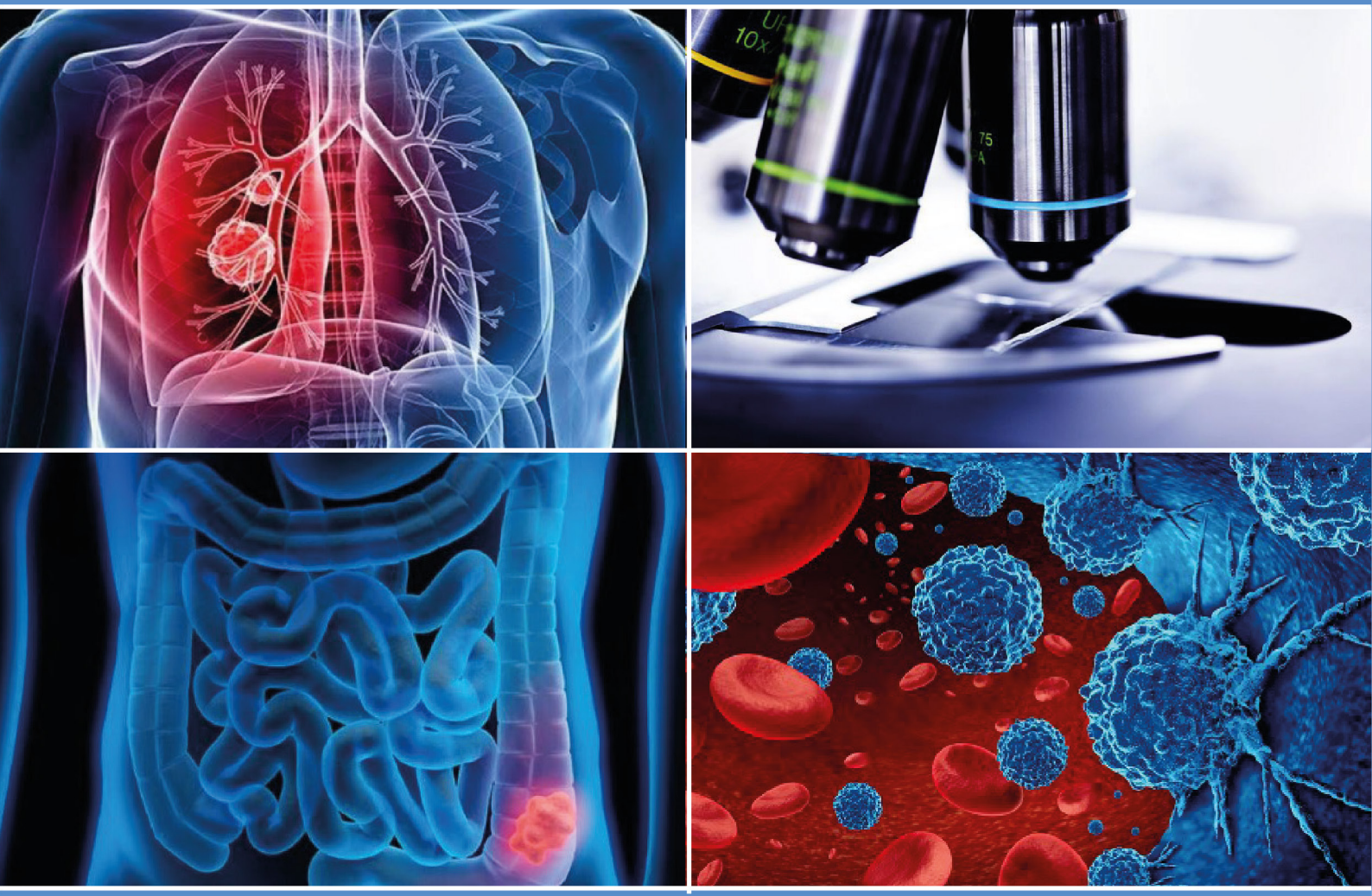
e-ISSN: 2980-0854

JCHOR

Journal of Current Hematology & Oncology Research



Volume: 2 Issue: 4 Year: 2024

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Original Article

DOI: 10.51271/JCHOR-0044

Shedding light on allogeneic hematopoietic stem cell transplantation success: exploring the relationship between donor vitamin D and parathormone levels and recipient engraftment and stem cell quantity

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Cite this article: Uzun D, Keklik M, Eser B. Shedding light on allogeneic hematopoietic stem cell transplantation success: exploring the relationship between donor vitamin D and parathormone levels and recipient engraftment and stem cell quantity . *J Curr Hematol Oncol Res.* 2024;2(4):79-82.

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Received: 08/03/2024 ◆ **Accepted**: 03/04/2024 ◆ **Published**: 14/11/2024

ABSTRACT

Aims: The aim of this study is to investigate whether pre-mobilization serum vitamin D and parathormone levels in allogeneic hematopoietic stem cell transplantation (allo-HCT) donors have an impact on the collected stem cell quantity and engraftment periods in recipients.

Methods: Data from 35 donors aged 18 and over, who served as donors in allo-HCT performed between 2019 and 2021 at Erciyes University Faculty of Medicine, Bone Marrow Transplantation and Stem Cell Treatment Center, were retrospectively analyzed. Donors with known pathologies related to the parathyroid gland, unrelated and bone marrow-derived stem cell donors were excluded from the study. Donors were grouped as low and high based on serum vitamin D and parathormone levels. The possible relationship between these values and total product CD34+ cell count, neutrophil engraftment time, and platelet engraftment time was assessed.

Results: It was found that recipients of donors with high vitamin D levels had significantly earlier platelet engraftment days compared to donors with low vitamin D levels (p=0.026). In donors with high vitamin D levels, it was observed that the peripheral CD34+ cell count was lower, and the total product CD34+ cell count was higher, although there was no significant relationship (p>0.05). Although recipients of donors with high vitamin D levels had earlier neutrophil engraftment times, no significant relationship was found (p=0.29). A moderate negative correlation was found between platelet engraftment times and vitamin D levels. There was no statistically significant relationship between parathormone levels and stem cell quantities and engraftment times.

Conclusion: Vitamin D deficiency in allo-HCT donors before mobilization was observed to prolong platelet engraftment times in recipients. Therefore, we recommend correcting vitamin D levels in donors before allo-HCT.

Keywords: Allogeneic hematopoietic stem cell transplantation, engraftment, parathormone, vitamin D

INTRODUCTION

Vitamin D plays a role not only in bone and mineral metabolism but also in various physiological events.[1] Active vitamin D exhibits its biological functions by binding to the vitamin D receptor (VDR). The discovery that most tissues and cells in the body possess VDR has led to extensive research on the potential effects of vitamin D on the hematopoietic and immune systems.[2-5] In the hematopoietic system, the presence of VDR has been identified in hematopoietic precursor cells, monocytes, activated B and T lymphocytes, and thymocytes.[3,5] In a study conducted on mice, it was observed that administration of active vitamin D to mice with VDR led to differentiation and maturation towards monocytes/macrophages in hematopoietic stem cells (HSCs); however, this effect was not observed in mice without VDR.[6,7] The presence of VDR on activated lymphocytes and natural killer cells suggests its role in differentiated cells.[8,9] Due to its immunoregulatory effects, many studies have evaluated the impact of vitamin D in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT).[10-13]

Parathyroid hormone (PTH) is another hormone shown to play a role in regulating the microenvironment of HSCs and has particularly positive effects on HSC mobilization. This

effect is believed to contribute to positive outcomes post-transplantation. In many studies, PTH has been shown to activate osteoblasts that secrete hematopoietic growth factors, thereby increasing the number of HSCs.[14]

In allo-HCT, the resolution of neutropenia and thrombocytopenia in recipients after the conditioning regimen is achieved through the reconstitution of cell lineages following stem cell infusion. Engraftment development is crucial for overall survival after stem cell transplantation.[15] The peripheral blood CD34+ cell count measured after mobilization and before the apheresis procedure is one of the most important predictors used to estimate the quantity of CD34+ cells in the product. Alongside the challenges in treating hematological diseases, inadequate stem cell collection from donors and delayed engraftment in patients can increase mortality.[16] By preventing vitamin D and PTH deficiency through measures taken during the transplant process and the administration of appropriate treatment, significant reductions in the incidence of potential complications can be achieved. Therefore, we aimed to examine the relationship between 25(OH) vitamin D and PTH levels with engraftment periods and CD34+ stem cell quantities.

METHODS

Ethics

The study was evaluated by the Ethics Committee of Erciyes University Faculty of Medicine (Date: 22.07.2020 Decision No: 2020/388). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Data from individuals who served as donors and recipients in allogeneic hematopoietic stem cell transplantation (allo-HSCT) at Erciyes University Faculty of Medicine, Bone Marrow Transplantation, and Stem Cell Treatment Center between October 2019 and March 2021 were retrospectively examined, both from written and electronic records. The study included a total of 35 adult stem cell donors aged between 18 and 65 who had undergone hematopoietic stem cell mobilization. Only peripheral stem cell donors were included, and unrelated stem cell donors were excluded.

Data such as age, sex, height, weight, peripheral blood CD34+ cell count, total product CD34+ cell count, administered granulocyte colony-stimulating factor (G-CSF) dose, duration of G-CSF administration, number of apheresis procedures, total product volume, total plasma volume, product viability (%), neutrophil engraftment time, and platelet engraftment time were obtained from medical records of allo-HSCT donors and recipients.

Evaluation of serum 25(OH) vitamin D level, PTH, and other biochemical data from donors was conducted before stem cell mobilization. Serum 25(OH) vitamin D levels were measured using the electrochemiluminescence immunoassay method with the cobas 8000 Roche device at Erciyes University Faculty of Medicine Biochemistry Laboratory.

Stem Cell Mobilization and Apheresis

As a mobilization regimen, G-CSF was subcutaneously administered to hematopoietic stem cell donors at a dose of 10 mcg/kg/day for a minimum of 4 days. Generally, on the 5th day of G-CSF administration, the CD34+ cell count in peripheral blood was evaluated using flow cytometry. Depending on the responsible physician's patient and donor-based decision, the threshold value could vary, but generally, donors with a peripheral blood CD34+ cell count >10/mcl underwent apheresis. For donors who did not reach the target CD34+ cell count, G-CSF administration was continued. Apheresis procedures were continued until the target total product CD34+ cell count was achieved, with a lower limit accepted as 2x10^6/kg CD34+ cell count.

The Optia Apheresis System device was used for apheresis procedures. Typically, when a sufficient number of CD34+ cells were obtained in peripheral blood on the 5th day of G-CSF administration, apheresis was performed to collect stem cells from donors. During the procedures, an average of 2-3 times the donors' blood volume was processed. Acid citrate dextrose solution A (ACD-A) was given to donors as an anticoagulant during the procedure, and calcium replacement was performed to prevent hypocalcemia.

Statistical Analysis

SPSS 25.0 statistical software was used for data analysis. Descriptive statistics, including counts, percentages, means, standard deviations, medians, minimum, and maximum values, were utilized. Before proceeding to analytical tests, the distribution of the data was examined using the Shapiro-Wilk test. The Mann-Whitney U test was employed for the analysis of independent quantitative variables with non-normal distribution. Spearman correlation analysis was used for the correlation analysis of non-normally distributed quantitative variables. P values less than 0.05 were considered statistically significant in all analyses.

RESULTS

There were a total of 35 allo-HCT donors, including 11 (31.4%) women and 24 (68.6%) men. The mean age in the study group was 39.4±13.8 years. All donors received at least 4 days of G-CSF, and apheresis procedures commenced after the fourth day. The mean duration of G-CSF administration was 4.9±0.36 days. A single apheresis session was applied to 97.1% of the donors, while only one donor (2.9%) received two sessions of apheresis.

The mean peripheral blood CD34+ cell count, evaluated generally on the 5th day of G-CSF administration, was 101.4±51.1/mcl, and the mean total product CD34+ cell count was 6.7±1.3x10^6/kg (Table 1). The mean neutrophil engraftment day in recipients post-transplantation was 17±4.1 days, while the mean platelet engraftment day was 14.5±5.4 days.

Tablo 1. Apheresis outcomes for donors and engraftment days for patients

	Mean	SD
Peripheral blood CD34+ cell count (/mcl)	101.4	51.1
Total product CD34+ cell count (x106/kg)	6.7	1.3
Administered G-CSF dose (mcg)	80.1	13.8
Total product volume (ml)	244.1	146.7
Product viability rate (%)	98.8	2.7
Neutrophil engraftment day	17.0	4.1
Platelet engraftment day	14.5	5.4

SD: Standard deviation, G-CSF: Granulocyte colony-stimulating factor

The mean 25(OH) vitamin D level in donors was 18.7±8 ng/ml, and the PTH level was 34.8±18.3 pg/ml. The mean B12 vitamin level was 336.4±90.2 pg/ml, and folate levels were 8.2±2.5 ng/ml.

Evaluation of Donors' 25(OH) Vitamin D Levels and Clinical Characteristics

Donors with 25(OH) vitamin D levels below 20 ng/ml were considered low, while those with 20 ng/ml and above were considered high. It was observed that 54.3% of the donors had low levels of vitamin D. The comparison of donors' clinical characteristics based on vitamin D levels is presented in **Table 2**. It was found that recipients of donors with high vitamin D levels had significantly shorter platelet engraftment times compared to donors with low vitamin D levels (p=0.026). Although donors with high vitamin D levels had a lower peripheral blood CD34+ cell count and a higher total product CD34+ cell count, there was no statistically significant relationship (p>0.05). While the neutrophil engraftment times in recipients of donors with high vitamin D levels were shorter, it was not statistically significant (p=0.29). A moderate negative correlation was found between platelet engraftment times and vitamin D levels (r: -0.36, p: 0.03).

Tablo 2. Comparison of vitamin D levels with clinical characteristics

	Low vitamin D (n=19) (mean±SD)	High vitamin D (n=16) (mean±SD)	p*
Peripheral blood CD34+ cell count (/mcl)	104.7±57.4	97.6±44.1	0.756
Total product CD34+ cell count (x10^6/kg)	6.5±1.4	7.0±1.2	0.935
Total product volume (ml)	227.6±159.5	263.7±132.3	0.317
Product viability rate (%)	99.1±2.0	98.5±3.3	0.961
Neutrophil engraftment day	18.0±4.6	15.8±3.3	0.286
Platelet engraftment day	16.4±6.0	12.3±3.5	**0.026**

*Mann-Whitney U test was used, SD: Standard deviation

Evaluation of Donors' PTH Levels and Clinical Characteristics

In donors, parathormone levels below 15 pg/ml were considered low, while those at 15 pg/ml and above were considered high. It was observed that 14.7% of donors had low parathormone levels. In donors with high PTH levels, it was found that peripheral blood CD34+ and total product CD34+ cell counts were lower, but there was no statistically significant relationship between them (p>0.05). Additionally, it was observed that recipients of donors with high PTH levels had shorter neutrophil and platelet engraftment times, but there was no statistically significant relationship (p>0.05) (**Table 3**).

Tablo 3. Comparison of donors' PTH levels with clinical characteristics

	Low PTH (n=5) (mean±SD)	High PTH (n=30) (mean±SD)	p*
Peripheral blood CD34+ cell count (/mcl)	118.6±55.4	98.6±50.8	0.506
Total product CD34+ cell count (x10^6/kg)	7.4±0.9	6.6±1.3	0.299
Total product volume (ml)	236.0±91.5	245.5±155.1	0.873
Product viability rate (%)	99.5±0.2	98.7±2.9	0.945
Neutrophil engraftment day	18.6±3.5	16.7±4.2	0.237
Platelet engraftment day	15.0±3.2	14.4±5.7	0.395

*Mann-Whitney U test was used, SD: Standard deviation, PTH: Parathyroid hormone

DISCUSSION

Allo-HCT remains an effective treatment option for many diseases, providing a chance for complete recovery. Successful allo-HCT requires an adequate infusion of HSCs in the recipient after the preparative regimen to allow hematopoietic reconstitution. Inadequate HSC infusion can negatively impact post-transplant hematopoietic reconstitution, leading to engraftment delays and graft failure, which may increase the risks of infection, bleeding, and transplant-related mortality. Mobilization failure is still a significant problem in the allo-HCT process, with reported rates ranging from 5% to 40%.[17] The generally accepted view is that the total product CD34+ cell count should reach a minimum threshold of 2x10^6/kg for successful transplantation to proceed.[18,19] However, Stiff et al.[20] suggest aiming for total product CD34+ cell counts above 4-5x10^6/kg to achieve positive effects such as faster neutrophil and platelet engraftment, shorter hospitalization periods. In our study, the median total product CD34+ cell count for all donors was 6.7x10^6/kg, surpassing the minimum threshold of 2x10^6/kg. The observed mobilization failure rate in our study appears to be lower compared to other studies.

Mikirova et al.[21] demonstrated an increase in peripheral blood CD34+ cell count in healthy adult volunteers after two weeks of receiving a dietary product containing lactobacillus, beta 1,3-glucan, ellagic acid, and vitamin D (Stem-Kine). However, since vitamin D was not administered alone in this study, evaluating the possible isolated effect of vitamin D is not feasible. In a study by Grande et al.[22] the addition of supraphysiological doses of vitamin D to the environment induced differentiation of HSCs toward monocytes/macrophages, resulting in a decrease in CD34+ CD38- cell count. Although higher levels of vitamin D were associated with a lower peripheral blood CD34+ cell count and a higher total product CD34+ cell count, this relationship was not statistically significant. In our study, we found no significant correlation between pre-mobilization 25(OH) vitamin D levels and peripheral blood or total product CD34+ cell counts in donors.

Hansson et al.[23] found that PTH positively influenced the HSC pool by stimulating the NOTCH signaling pathway. In a study by Brunner et al.[24] the effects of PTH and G-CSF on HSC mobilization in mice were compared. Similar to G-CSF, the administration of PTH increased the peripheral blood HSC count by 1.5-9.8 times. When endogenous G-CSF was targeted with antibodies, the positive effect of PTH on mobilization diminished. Therefore, it was suggested that PTH supports HSC mobilization through the release of endogenous G-CSF. In another study by Brunner et al.[25]on humans, a significant increase in circulating HSCs was found in individuals with primary hyperparathyroidism. In a study by Ballen et al.[26] patients with previous mobilization failure in autologous HSC transplantation were given PTH and G-CSF, and it was reported that the combined use of PTH and G-CSF met mobilization criteria in 45% of patients. The median neutrophil engraftment day was 11 (8-12) days, and the median platelet engraftment day was 19 (12-36) days, similar to reported engraftment times in the literature. With these data in mind, it is speculated that PTH administration, clinically approved for osteoporosis

treatment, could be a new treatment option in stem cell transplantation. In our study, we found no significant correlation between serum PTH levels measured in donors before allo-HCT mobilization and total product CD34+ cell count, neutrophil engraftment day, and platelet engraftment day.

Limitations

The main limitation of our study is its retrospective nature and the small number of donors involved. Another limitation is that it is a single-center experience, making the results less generalizable. Given the prevalence of vitamin D deficiency, its affordable and reliable treatment, further research is needed to investigate the potential effects of vitamin D in stem cell transplantation.

CONCLUSION

In allo-HSCT, high serum 25(OH) vitamin D levels in pre-mobilization donors were observed to shorten the platelet engraftment time in recipients. However, no significant correlation was observed between stem cell quantity and neutrophil engraftment time and donor 25(OH) vitamin D levels. There was no statistically significant correlation between PTH levels and engraftment times and stem cell quantities. Given the results of our study and the data in the literature, it has been concluded that the serum levels of vitamin D and PTH observed in allo-HCT pre-mobilization donors require more comprehensive and multi-centric advanced studies to shed light on the possible effects in the allo- HCT process and be incorporated into clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was a prospective cross-sectional study and the protocol of the study was approved by the Erciyes University Clinical Researches Ethics Committee (Date: 22.07.2020, Decision No: 2020/388).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0045

The Myeloid differentiation primary response 88 expression in central nervous system lymphomas

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Cite this article: Balık B, Mutlu YG, Sevindik ÖG. Myeloid differentiation primary response 88 expression in central nervous system lymphomas. *J Curr Hematol Oncol Res.* 2024;2(4):83-86.

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Received: 20/03/2024 ◆ **Accepted**: 26/06/2024 ◆ **Published**: 14/11/2024

ABSTRACT

Aims: A prominent adaptor protein that signals from many receptors called myeloid differentiation primary response 88 (MYD88) coded by MYD88 gene was evaluated. Our aim was to record the level of MYD88 expression and its relation with clinicopathological parameters in both primary and secondary central nervous system (CNS) lymphomas.

Methods: MYD88 protein expression was analyzed by two different classification using immunohistochemistry in ten patients who were diagnosed in our hospital. The samples that were collected from patients before treatment were evaluated and specified by a hematopathologist. Demographic and clinical information of the patients were obtained from hospital database and files. The primary outcome was the presence and prevalence of MYD88 expression. Secondary outcomes were determined as the evaluation of the relationship between MYD88 expression and disease prognosis.

Results: MYD88 protein expression was examined in 10 in patients of which 9/10 cases (90%) expressed the protein in wide ranges of intensity and density. Six patients (60%) expressed high-level of MYD88 protein where as one patient did not, and three patients expressed low quantity of MYD88 protein that deceased after diagnosis. Most CNS lymphoma patients had an activated B cell-like immunophenotype.

Conclusion: Primary and secondary CNS lymphomas showed expression of MYD88 protein without regards of lymphoma subtype.

Keywords: Central nervous system lymphoma, immunohistochemistry, MYD88

INTRODUCTION

A rare extra-nodal non-Hodgkin lymphoma is primary central nervous system diffuse large B-cell lymphoma (PCNS DLBCL) that primarily arises in the brain, spinal cord, leptomeninges, and vitreoretinal compartment of the eye. The term is interchangeable with primary central nervous system lymphoma (PCNSL). Rarely, other types of lymphomas can be seen in the central nervous system (CNS), the familiarity with these conditions will help in recognizing and further differentiating to establish a diagnosis.[1] Secondary CNS lymphoma (SCNSL) initially arises from another area of the body and spreads to the CNS (in contrast to primary CNS lymphoma). It may be an isolated recurrence or a part of a systemic disease at the time of presentation but usually it is a non-Hodgkin lymphoma. Myeloid differentiation primary response 88 (MYD88) coded by MYD88 gene is a prominent adaptor protein that signals from many receptors.[2]

Development of immune responses includes MYD88. The binding of ligands to different toll-like receptors or interleukin (IL)-1/IL-18 receptors induces the association of MYD88 with the Toll/IL1R domain of these receptors, resulting in the activation of the NF-κB signaling pathways in immune cells.[3] MYD88 increases IL-6 and IL-10 secretion and also promotes the secretion of interferon-β activates leading to the activation of JAK-STAT3 signaling. Interferon-β is a cytokine that has immunosuppressive effects that causes tumor cells to escape immune surveillance. STAT3 interacts physically with NF-κB heterodimers and transactivates NF-κB target genes.[4] It is recurrent in systemic DLBCL (10–20%), but more so in PCNSL (≥50%).[5,6] Bruton tyrosine kinase (BTK) integrates B-cell antigen receptor (BCR) and toll-like receptor signaling and cell survival in various B cell lymphomas.[7] Ibrutinib, a first-in-class oral inhibitor of BTK was used to show BTK being involved in oncogenic BCR signaling that controls the survival of a human activated B cell (ABC)-like subtype of DLBCL.[8]

CNSL treatment is comprised of chemotherapy and/or radiotherapy (RT) consolidated with an autologous stem-cell transplantation in eligible patients.[9] The emergence of new therapies designed for molecular targets, such as MYD88 signaling pathway, may offer alternative treatment options for patients diagnosed with these rare tumors.[10]

In this study, we aimed to retrospectively test formalin-fixed paraffin-embedded (FFPE) tissue samples obtained from

CNS tumors for the expression of MYD88 protein and their relationship with clinical and pathological variables in CNS lymphomas.

METHODS

The study was conducted with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 23.06.2021, Decision No: 02-2988). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

MYD88 protein expression was analyzed by two different classification using immunohistochemistry (IHC) in ten patients whom were diagnosed in our hospital between 2014-2020. The samples that were collected from patients before treatment were evaluated and specified by a hematopathologist. Demographic and clinical information of the patients were obtained from hospital database and patient files. IHC staining and evaluation.

Four categories were classified according to the staining intensity on a scale from 0 to 3 as follows: 0, no reaction; 1, weak reaction; 2, moderate reaction; and 3, strong reaction. In this article we identified it as first classification model.

Three categories were classified according to the widespread of staining scored as 0 (0% of tumor area stained), 1 (< 10%), 2 (10–50%), or 3 (> 50%) (**Figure**).[2] We identified it as second classification model. Staining intensity and the percentage of tumor cell positivity were evaluated and recorded by a hematopathologist.

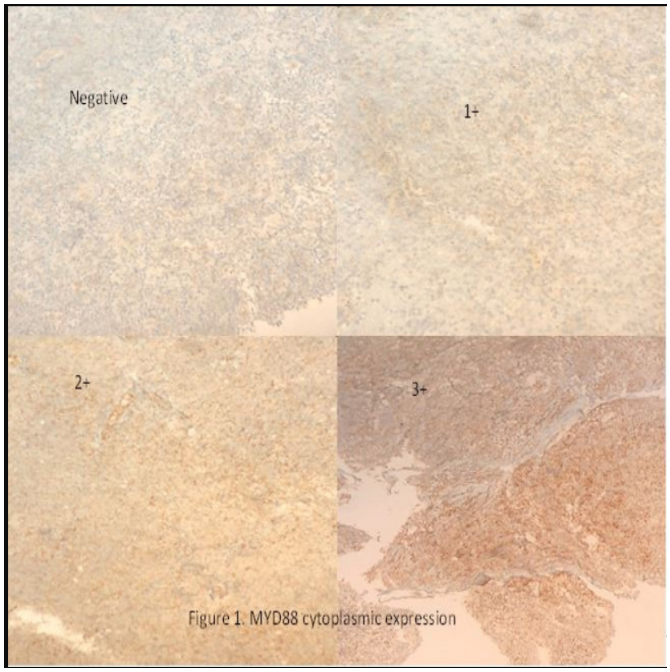

Figure. Scoring system of MYD88 expression

MYD88 protein expression in CNS lymphomas. All cases are semi-quantified in terms of intensity of MYD88 staining as score 0 (A), score 1 (B), score 2 (C), and score 3.

We also checked for the presence of Bcl-2, Bcl-6, c-Myc, MUM-1, CD10, CD20, Ki 67 and EBER with IHC. Descriptive statistics were used to define frequencies of categorical variables and mean or median (std. deviation or range) to analyze numerical variables. SPSS 17.0 were used to analyze the data.

RESULTS

A total of 10 patients; 4 females and 6 males were diagnosed between 2014-2020 were included in the study. Median age was 56.2 and 4 patients were over 65 years. Eight of them were diagnosed with DLBCL-ABC-like phenotype, 1 of them was marginal zone lymphoma and the last one was follicular lymphoma grade 3a.

Two of the patients had relapsed/refractory disease, the others were newly diagnosed. Five patients were not evaluated for lactate dehydrogenase (LDH) levels. One patient's LDH level was very high (700 U/L), 3 of them were over the laboratory reference limits, 1 was at a normal range at the time of the diagnose. Median ki67 of all cohort was 80% (10-95). Only 2 patients had B symptoms. All of the patients had neurological symptoms such as sight loss, paresthesia, hemiparesis, deafness, nystagmus, ataxia, hemiplegia, dysarthria, facial paralysis, parkinsonian symptoms and paraplegia. Cerebrospinal fluid (CSF) of only 3 patients was evaluated and involvement was detected in one. Two patients had 3, 2 had 1 and others had 2 as an Eastern cooperative oncology group (ECOG) performance status score. Disease involvement were unifocal at 4 patients and multifocal at 6 patients. Three patients were lost to follow up before treatment plan. The number of patients matching the initial treatment after the diagnosis of PCNSL or SCNSL were as follows; 2 - R-CHOP+high dose methotrexate (MTX), 1 - mini-R-CHOP+RT, 1 - De-Angelis protocol, 1 - Matrix protocol, 1–ibrutinib+nivolumab and 1 was lost before the initiation of treatment. One patient was able to proceed with autologous stem cell transplantation. The outcomes achieved with aforementioned treatment approaches are summarized at **Table 1**. MYD88 protein expression was examined in 10 in patients of which 9/10 cases (90%) expressed the protein in wide ranges of intensity and density. Six patients (60%) expressed high-level of MYD88 protein where as one patient did not, and three patients (patient 2,3,9) expressed low quantity of MYD88 protein that deceased after diagnosis. In our study most patients had ABC-like immunophenotype (8/10). Median expression of MYD88 was calculated as 95 (20-100) according to second classification (**Table 2**).

Five patients were diagnosed with supratentorial brain biopsy, 3 patients with spinal mass biopsy and 2 patients with cerebellum biopsy.

Bcl-2 was positive in 7 of 8 patients (87.5%). Bcl-6 was positive 9/10 patients (90%). C-myc was evaluated in 6 patients and 3 of them were positive (50%). Eight patients showed MUM-1 positivity. CD 10 expressions were present in 3/10 and CD 20 was 9/10. Patient that did not express CD20 expressed PAX5 and CD79a. There weren't EBER positivity in all who were examined.

DISCUSSION

Most patients in our study had ABC-like immunophenotype, that has been previously reported.[11] We analyzed MYD88 protein expression by IHC analysis in CNS lymphomas, median value of the expression level was 69%. It was present in both primary and secondary CNS lymphomas, only one patient lacked to show expression of MYD88 who was diagnosed with a PCNSL. MYD88 positivity was present 4/5 in primary CNS lymphoma and 4/4 in secondary CNS lymphoma. It is recurrent in systemic DLBCL (10–20%), but more so in PCNSL (≥50%).[5,6]

Table 1. Characteristics of patients with central nervous system lymphoma

Patient	1	2	3	4	5	6	7	8	9	10
Initial diagnosis	DLBCL-ABC	Marginal zone lymphoma	DLBCL-ABC	DLBCL-ABC	Follicular lymphoma -3a	DLBCL-ABC	DLBCL-ABC	DLBCL-ABC	DLBCL-ABC	DLBCL-ABC
Age	52	80	27	34	66	43	73	46	77	64
Gender	Female	Male	Male	Male	Female	Male	Female	Male	Male	Female
Newly diagnosed/ R/R Disease	Newly diagnosed	Newly diagnosed	Newly diagnosed	Newly diagnosed	Newly diagnosed	Newly diagnosed	R/R Disease	Newly diagnosed	Newly diagnosed	R/R Disease
Diagnosed from	Temporal lobe	Spinal epidural mass	Cerebellum	Foramen Luschka mass	Epidural mass	Parietal lobe	Temporal lobe	Cerebellum	Occipital lobe	Spinal epidural mass
Diagnosis time	26.06.2019	01.08.2019	24.02.2014	29.02.2016	13.09.2019	23.02.2017	02.02.2018	31.01.2020	24.11.2015	21.10.2020
LDH	295	Unknown	231	Unknown	Unknown	Unknown	390	176	Unknown	705
B symptoms	-	-	-	-	-	-	-	+	-	+
Neurological Symptoms	Sight loss	Paresthesia	Hemiparesis	Deafness Nistagmus Ataxia	Hemiparesis	Hemiparesis	Hemiplegia dysarthria	Facial paralysis	Parkinsonian symptoms	Paraplegia
CSF involvement	Unknown	Unknown	None	Unknown	None	Unknown	Unknown	+	Unknown	Unknown
ECOG	1	2	1	2	2	2	3	2	2	3
Multifocal/unifocal involvement	Unifocal	Unifocal	Multifocal	Unifocal	Multifocal	Unifocal	Multifocal	Multifocal	Multifocal	Multifocal
Primary/secondary CNS lymphoma	Primary	Patient was lost before evoluation	Primary	Primary	Secondary	Primary	Secondary	Secondary	Primary	Secondary
Treatment	Rtx+mtx+alxn		De Angelis	Unknown	R-CHOP+high dose mtx	Unknown	R-miniCHOP+RT	R-CHOP+high dose mtx	Unknown	Ibrutinib+ nivolumab
Autologus transplantation	+		-	Unknown	-	Unknown	-	-	Unknown	-
Treatment response	Complete Remission		Unknown	Unknown	Complete Remission	Unknown	Not achieved a response	Not achieved a response	Unknown	Not achieved a response
Last Seen on	01.04.2021		19.05.2014	01.03.2016	03.02.2021	06.03.2017	10.04.2018	25.04.2020	24.02.2016	29.11.2020
Alive/ex	Alive	Ex	Unknown	Alive	Alive	Unknown	Ex	Ex	Ex	Ex
Overall survival	646	10	85	2	510	12	69	86	93	42

LDH: Laktat dehidrogenaz, ECOG: Eastern cooperative oncology group, CNS: Central nervous system, MTX: Methotrexate, CSF: Cerebrospinal fluid

Table 2. Pathological features in patients with central nervous system lymphoma

Patient	MYD 88 first cl.	MYD 88 second cl.	Pathology	Localization	Type of lymphoma	Bcl-2	Bcl-6	C-Myc	Mum1	Cd10	Cd20	Ki 67	EBER
1	3+	90% (3)	DLBCL-ABC	Temporal lobe	Primary CNS lymphoma	+	-	-	-	-	+	40%	-
2	1+	20% (2)	Extranodal marginal zone lymphoma	Spinal mass	Patient was lost before evoluation	+	+			+	+	10%	-
3	1+	30% (2)	DLBCL-ABC	Cerebellum	Primary CNS lymphoma		+		+	-	+	80%	
4	-	-	DLBCL-ABC	Foramen Luschka mass	Primary CNS lymphoma		+		+	+	+	90%	-
5	2+	100% (3)	Follicular lymphoma grade 3a	Spinal epidural mass	Secondary CNS lymphoma	+	+	-	+	+	+	50%	
6	3+	95% (3)	DLBCL-ABC	Parietal lobe	Primary CNS lymphoma	+	+	+	+	-	+	95%	-
7	1+	100% (3)	DLBCL-ABC	Temporal lobe	Secondary CNS lymphoma	+	+	-	+	-	+	70%	-
8	3+	100% (3)	DLBCL-ABC	Cerebellum	Secondary CNS lymphoma	+	+	+	+	-	+	95%	-
9	1+	40% (2)	DLBCL-ABC	Occipital lobe	Primary CNS lymphoma	-	+		+	-	+	90%	-
10	2+	100% (3)	DLBCL-ABC	Spinal mass	Secondary CNS lymphoma	+	+	+	+	-	-	80%	-

MYD 88: Myeloid differentiation primary response 88, CNS: Central nervous system

Choi et al.[12] had examined MYD88 expression with IHC analysis in DLBCL. The results of their scoring models assessed the level of MYD88 expression. The result did not correlate between protein over-expression and clinical parameters.[12] In our study there were no significant difference between MYD88 expression and age. But our cohort was not quantitatively enough to reach statistical significance.

Caner et al.[8] determined the prevalence of MYD88 L265P mutation and the level of MYD88 expression. Consecutively they also compared their results to clinical and pathological parameters in mature B-cell NHLs. They revealed no correlation between protein over-expression and clinical parameters or a positive correlation between MYD88 mutation and expression. However they were able to document a strong positive correlation between L265P mutation and protein over-expression. Their results showed high levels of MYD88 were associated with older age and poor prognosis. Therefore, they hypothesized that MYD88 over-expression together with L265P mutation could be used as a prognostic marker. MYD88 over-expression without mutation didn't predict the prognosis of the disease.[13]

Three patients were deceased before treatment plan was initiated. Two patients were under R-CHOP chemotherapy regimen, 1 was mini-R-CHOP+RT, 1 was De-Angelis, 1 was Matrix , 1 was ibrutinib + nivolumab and 1 was exitus before the evaluation. One patient was able to achive autologous transplantation.

Prior therapies were given to five patients, 2 of them including MTX chemotherapy, 1 RT, and 1 autologous hematopoietic cell transplantation. Since our study was a retrospective study, we saw that most of the patients received MTX-based chemotherapy. The 64 year old patient that had relapsed disease and co-morbidities using 560 mg ibrutinib and nivolumab daily, died after 42 days due to fragility.

Limitations

The biggest limitations of our study were the small number of patients and the single-center experience.

CONCLUSION

Primary and secondary CNS lymphomas showed expression of MYD88 protein without regards of lymphoma subtype. Further investigations on a larger scale using homogeneous population with longer period of follow-up is required to aid the assessment of MYD88 protein role on the prognosis and treatment of CNS lymphomas. NF-κB pathway directed agents like ibrutinib and lenalidomide, understanding of MYD88's up-regulation mechanism's other than mutation and also its clinical implications. Up to our knowledge, this study is the first to document the presence of MYD88 expression on a Turkish CNS lymphoma patient group.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 23.06.2021, Decision No: 02-2988).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0046

Diagnostic white blood cells can be a predictor for mutation existence in myelodisplastic syndromes: the role of next generation sequencing

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Cite this article: Yılmaz S, Günay A, Cırık S, Baştürk A, Başdemirci M, Balasar Ö. Diagnostic white blood cells can be a predictor for mutation existence in myelodisplastic syndromes: the role of next generation sequencing. *J Curr Hematol Oncol Res.* 2024;2(4):87-92.

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Received: 09/07/2024 ◆ **Accepted**: 16/08/2024 ◆ **Published**: 14/11/2024

ABSTRACT

Aims: Myelodisplastic syndromes (MDS) are hematological disorders originating from clonal damage and characterized by inefficient bone marrow activity. The existence of mutations has been shown to play a significant role in risk, treatment response, turnover to acute myeloid leukemia, prognosis, and overall survival. Next-generation sequencing (NGS) is a technique that detects gene mutations and has been the subject of studies for detecting MDS-related mutations. We aimed to investigate the importance of the NGS method and identify mutation-related blood parameters in MDS patients.

Methods: We conducted a study on 33 MDS patients during the period of 2021–2023. Patients were analyzed for the existence of mutations with the NGS technique, and the hematological parameters, transfusion need, IPSS, and IPSS-R scores of these patients were recorded.

Results: Fifteen out of 33 patients (45.5%) were tested for mutations. White blood cell (WBC) levels at the diagnosis of patients with type 1 number somatic mutations were higher than in other groups, 7056.25, 2416.67/µL, and 3036.67/µL, respectively (p=0.048). The ratio of neutrophil and lymphocyte values recorded and NGS positive were higher than those tested negative (1.56 and 3.51, respectively). Patients with the type 1 mutation had higher WBC levels than patients with the type 2 and type 3 mutations, 7056.25/µL, 2416.67/µL, and 3036.67/µL, respectively.

Conclusion: Genetic mutations are common in MDS patients, and NGS is a useful tool to detect them. Understanding the role of mutations in the matter of risk classification, treatment response, and prognosis is quite important, and larger-scale studies are needed.

Keywords: MDS, myelodisplastic syndromes, NGS, next generation sequencing

INTRODUCTION

Myelodysplastic syndromes (MDS) are clonal bone marrow stem cell disorders associated with inefficient haematopoiesis resulting in blood cytopenias and are characterized by progression to acute myeloid leukemia in one third of patients.[1] Differential diagnosis of MDS can be challenging due to its heterogeneous nature and subjective assessment of dysplasia. The correct diagnosis and classification of MDS depends on an accurate assessment of both clinical features and laboratory or pathological findings (e.g., blast count, peripheral blood count, cytogenetics). Chromosomal abnormalities have been reported in 40% to 70% of patients with MDS and in the majority of patients with treatment-related MDS.[2]

Diagnosis of MDS can be challenging in patients with uninformative cytogenetics, a normal karyotype, or who lack robust morphological markers such as ring sideroblasts or myeloblast abundance. Important studies are underway to identify new diagnostic tools that can make the diagnosis of MDS more accurate.[3] Next-generation sequencing (NGS) is also being studied. NGS is a cytogenetic method used in diagnosis and treatment. By using targeted gene panels with NGS, it has become possible to diagnose many mutations simultaneously and to detect rare variants and changes at the chromosomal level much more sensitively than the traditional polymerase chain reaction (PCR) method.[4]

In borderline MDS and acute myeloid leukemia, where the blast rate is close to 20%, the use of NGS, in addition to other tests that detect genetic mutations, is beneficial for diagnosis. Studies have shown that NGS may be useful in the prognostic evaluation of MDS cases with persistent or refractory cytopenia and normal cytogenetics.[5] Studies have shown that TP53, SRSF2, and TET2 mutations detected by NGS are poor prognostic factors, especially SRSF2 mutations, which may accelerate the transformation of myeloproliferative neoplasms to acute myeloid leukemia.[6]

In our study, we investigated the factors influencing overall survival in MDS patients, the factors influencing the disease process when evaluating response in terms of transfusion, blasts, and fibrosis, the role of the presence of abnormalities and number somatic mutations as a result of NGS in treatment response and overall survival, and the parameters at the time of diagnosis (white blood cell (WBC), neutrophils, lymphocytes, neutrophil/lymphocyte ratio, hemoglobulin (Hb)). The aim is to determine the relationship between NGS results (e.g., platelets, blasts, etc.) and the prognostic significance of these parameters.

METHODS

Patient Selection

Our study included 33 patients (16 male and 17 female) diagnosed with MDS who were admitted to Konya City Hospital between 2021 and 2023. The ethics committee required for the study was obtained from the Hamidiye Scientific Researches Ethics Committee (Date:18.04.2024, Decision No: 5/21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who were older than 18 years of age, diagnosed with MDS, and had NGS and number somatic mutations data were included in the retrospectively designed study.

Statistical Analysis

Statistical analyses were performed using the "IBM SPSS Statistics for Windows Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)" program. Descriptive statistics are presented as frequency and % for categorical variables, mean±standard deviation, and median (IQR) for continuous variables. The data of the study were evaluated with normality assumptions using the Kolmogorov-Smirnov normality test. An independent sample t test, or Mann-Whitney U test, was used for comparisons between two independent groups. The Kruskal-Wallis H test was used for comparisons of three or more independent groups, and the Mann-Whitney U test with Bonferroni correction was applied for subgroup comparisons. Comparisons of categorical variables were made using the chi-square test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Thirty-three patients were included in the study, and the mean age was 70.21 years. Seventeen of them were male. In fifteen patients NGS test resulted positive. Number somatic mutations analysis showed that nineteen of the patients had 0, eight of them had 1, and the rest of the patients were distributed equally between 2 and 3 mutation types. Fifteen patients were treated with hypomethylating agents (HMA), and fourteen patients were treated with erythropoiesis-stimulating agents (EPO). Most of the patients (n=25) did not receive second-line treatment. Eight of the patients showed a response in blast levels. In fifteen of the patients, it is noted that the blood transfusion need was lowered. The mean WBC levels of patients at diagnosis were 5313.64/µL. The ratio of neutrophil and lymphocyte levels at diagnosis in the patients was noted at 2.62 (Table 1) .

Table 1. Characteristic features of the patients included in the study

Characteristics	
Age (years) (mean±SD)	70.21±11.43
Sex	
Male	16 (48.5)
Female	17 (51.5)
Treatment (n (%))	
HMA	15 (45.5)
Epo	14 (42.4)
Immune modulator	3 (9.1)
None	1 (3)
Second line treatment (n (%))	
HMA	2 (6.1)
Immune modulator	4 (12.1)
HMA+Venetoclax	2 (6.1)
None	25 (75.8)
Response in blast levels (n (%))	
Positive response	8 (24.2)
Negative response	5 (15.2)
No response	20 (60.6)
Response according to blood transfusion need (n(%))	
Decrease in transfusion need	15 (45.5)
No change in transfusion need	16 (48.5)
Unrelated to transfusion need	2 (6.1)
Anomalia in NGS (n(%))	
Present	15 (45.5)
None	18 (54.5)
Number somatic mutations (n(%))	
0	19 (57.6)
1	8 (24.2)
2	3 (9.1)
3	3 (9.1)
Follow up (months)	
NGS Anomaly	**Mean±SD**
Positive	13.20±4.70
Negative	18.11±12.92
Number somatic mutations (n) (mean±SD)	
0	18.84±12.47
1	13.12±3.27
2	9.66±4.72
3	10.66±0.57
SF3B1	5
ASXL1	3
TP53	3
SRSF2	2
DNMT3A	2
TET2	2
RUNX1	2
IDH2	1
NPM1	1
SETBP1	1
U2AF1	1

Abbreviations: HMA: Hypomethylating agent, Epo: Erythropoiesis stimulating agents, WBC: White blood cells, RBC: Red blood cells, HGB:Hemoglobin, SD: Standard deviation, NGS: Next generation sequencing

The WBC levels of patients according to positive and negative NGS results were 4972.67/μL and 5597.78/μL, respectively. Neutrophil and lymphocyte levels of NGS-positive patients were 2467.11/μL and 1487.33/μL, respectively. These values were 3545.55/μL and 1343.89/μL for NGS-negative patients, respectively. The ratio of neutrophil and lymphocyte values for the NGS positive and negative groups was 1.56 and 3.51, respectively. There was no significant difference between patients due to the presence of an NGS abnormality. However, the neutrophil/lymphocyte ratio at diagnosis was found to be lower in patients with NGS abnormalities (p=0.062). Eleven types of mutations were detected in NGS analyses. In five patients, the SF3B1 mutation was detected. ASXL1 and TP53 mutations were the most common mutations in each of the 3 patients (**Table 2**).

Table 2. Comparison of values recorded at diagnosis of MDS patients according to NGS anomaly group

Variables	NGS+(mean+SD)	NGS-(mean+SD)	p
WBC (10^3/μL)	4972.67±3295.58	5597.78±2507.30	0.541
RBC (x10^6/μL)	374.30±1090.99	374.30±1090.99	0.198
HGB (g/dl)	8.56±1.92	9.12±2.06	0.423
MCV (Fl)	101.39±12.99	97.90±16.45	0.511
Neutrophil (10^3/μL)	2467.11±2433.11	3545.55±2354.80	0.206
Lymphocyte (10^3/μL)	1487.33±788.76	1343.89±553.25	0.545
Neutrophil/Lymphocyte	1.56±1.03	3.51±3.76	0.062
Platelet (10^3/μL)	188.13±124.39	204.28±104.13	0.688

Abbreviations: MDS: Myelodisplastic syndromes, WBC: White blood cells, RBC: Red blood cells, HGB: Hemoglobin, MCV: Mean corpuscular volume, SD: Standard deviation

As seen in **Table 3**, there is a statistically significant difference between the WBC levels of MDS patients at diagnosis and the number somatic mutation group averages (p=0.048). Accordingly, it is possible to say that the mean of the patients with type 1 mutation for the WBC levels of MDS patients at diagnosis was greater than the mean of the 2 and 3 types of mutations, 7056.25/μL, 2416.67/μL, and 3036.67/μL, respectively. No statistically significant difference was found between the somatic mutation group averages of other variables in MDS patients (p>0.005).

There was a statistically significant difference in the platelet values recorded at diagnosis according to the transfusion needs of MDS patients (p=0.014).

Accordingly, it is possible to say that the mean of the diagnostic platelet variable in the group with no change in transfusion need is higher than the mean of the group with a change in transfusion need, 237.70/μL and 121.13/μL, respectively (p<0.05). No statistically significant relationship was found between the group averages of other variables for MDS patients (p>0.05).

Response was evaluated by treatment type for transfusion need, blast levels, and fibrosis status (**Table 4**). While a decrease in blast rate was observed in those treated with HMA (p=0.002), no statistically significant difference was detected between all 3 treatment types in terms of response to regression in fibrosis score and reduction in transfusion need. It was observed that there were more people who responded at the blast level with HMA treatment, those who did not show a change at the blast level with EPO treatment, and those who did not respond at the blast level with immune modulator treatment. No statistically significant relationship was found between the type of treatment and changes in transfusion and fibrosis levels in MDS patients (p>0.05).

Table 4. Comparison of blood levels of parameters of MDS Patients at diagnosis according to groups created based on blast level responses

Parameters	Response in blast levels	Mean±SD	p*
WBC	No response	6626.00±2729.55	0.097
	Response	3683.75±2233.58	
	No change	5637.50±2950.78	
RBC	No response	2.93±0.61	0.987
	Response	2.98±1.14	
	No change	336.97±1038.35	
HGB	No response	9.24±1.84	0.851
	Response	9.01±2.13	
	No change	8.72±2.04	
MCV	No response	96.58±14.63	0.877
	Response	99.12±15.08	
	No change	100.36±15.49	
Neutrophil	No response	2659.35±2004.48	0.201
	Response	1913.75±1712.54	
	No change	3611.00±3642.53	
Lymphocyte	No response	1096.00±329.74	0.618
	Response	1353.75±567.55	
	No change	1509.50±749.60	
Neutrophil / Lymphocyte	No response	2.44±2.10	0.376
	Response	1.46±1.11	
	No change	3.14±3.58	
Platelet	No response	155.20±85.45	**0.014**
	Response	121.13±62.36	
	No change	237.70±116.69	

Abbreviations: MDS: Myelodisplastic syndromes, WBC: White blood cells, RBC: Red blood cells, HGB: Hemoglobin, MCV: Mean corpuscular volume, SD: Standard deviation

A statistically significant difference was found between the blast levels of MDS patients and the averages of the IPSS and IPSS R scores (p<0.05) (**Table 5**).

When the data were examined according to the international prognostic scoring system (IPSS) and revised international prognostic scoring system (IPSS R) variables, it was determined that there were statistical differences in the blast level, and this difference was highest in those with responses at blast levels of 0.75 and 4.87, respectively. No statistically significant

Table 3. Comparison of values of MDS patients according to number somatic mutations group

Variables (mean+SD)	0	1	2	3	p
WBC (10^3/μL)	5396.84±2444.91	7056.25±3351.11	2416.67±1363.46	3036.67±1876.17	**0.048**
RBC (x10^6/μL)	354.75±1063.68	2.81±0.42	1.97±0.73	3.13±0.83	0.276
HGB (g/dL)	9.08±2.11	8.97±1.25	6.60±1.66	9.46±2.43	0.303
MCV (Fl)	98.27±16.31	99.47±12.20	110.30±19.45	96.43±6.02	0.700
Neutrophil (10^3/μL)	3289.47±2310.18	3723.34±3017.92	1160.00±662.04	1686.66±1574.55	0.226
Lymphocyte (10^3/μL)	1397.89±623.67	1682.50±796.75	1026.67±786.21	1133.33±258.13	0.484
Neu/Lym	3.29±3.74	1.99±1.07	1.23±0.40	1.53±1.60	0.628
Platelet (10^3/μL)	229.05±121.39	146.13±93.23	200.67±90.25	125.33±50.29	0.206

Abbreviations: MDS: Myelodisplastic syndromes, WBC: White blood cells, RBC: Red blood cells, HGB: Hemoglobin, MCV: Mean corpuscular volume, SD: Standard deviation

Table 5. Relationship between treatment type and response to treatment and blast response in MDS patients

	Response in transfusion levels					
	Unrelated to transfusion	Decrease in transfusion need	No change	χ^2	SD	p*
No treatment	0	0	1	1,752	6	0,941
HMA	1	7	7			
EPO	1	7	6			
Immune modulator	0	1	2			
	Response in blast levels					
	No response	Response	No change	χ^2	SD	p*
No treatment	0	0	1	20,499	6	**0,002**
HMA	2	8	15			
EPO	1	0	14			
Immune modulator	2	0	3			
	Response in fibrosis levels					
	No response	Response	No change	χ^2	SD	p*
No treatment	1	0		2,142	3	0.544
HMA	13	2				
EPO	10	4				
Immune modulator	3	0				

Abbreviations: MDS: Myelodisplastic syndromes, HMA: Hypomethilating agent, Epo: Erythropoiesis-stimulating agents, χ^2: Chi square, SD: Standard deviation

difference was found between the blast levels of MDS patients and the average follow-up period (p>0.05).

A statistically significant relationship was found between IPSS R risk scores and blast levels in MDS patients (p=0.017). IPSS R risk scores are categorized as very low, low, intermediate, high, or very high. Accordingly, those with no response in blast values were at the expected level; risk scores in those who responded were very low and low; and in those with no change, intermediate, high, and very high values were found to be lower. No statistically significant relationship was found between IPSS R risk scores of MDS patients and transfusion requirement and fibrosis levels (p>0.05) (**Table 6**).

No statistically significant difference was found between the average follow-up period of the NGS Anomaly variable and that of MDS patients (p=0.142) (**Table 7**).

Table 6. Comparison of responses in blast levels of MDS patients with IPSS, IPSS R and follow-up period

Parameters	Response in blast levels	Mean±SD	p*
IPSS	No response	0.40±0.41	**0.027**
	Response	0.75±0.46	
	No change	0.27±0.49	
IPSS R	No response	3.00±0.93	**0.002**
	Response	4.87±1.90	
	No change	2.27±1.30	
Follow-up (month)	No response	14.00±5.61	0.562
	Response	13.25±4.39	
	No change	17.40±12.49	

Abbreviations: MDS: Myelodisplastic syndromes IPSS: International prognostic scoring system, IPSS-R: Revised international prognostic scoring system, SD: Standard deviation

Although there was no significant difference, the mean follow-up time for those with NGS anomalies was higher than for those without, at 18.11 and 13.20 months, respectively. No

Table 7. Relationship between IPSS R risk scores of MDS patients and transfusion need, blast and fibrosis levels

		Response in transfusion need					
		Unrelated to transfusion	Decrease in transfusion need	No change	χ^2	SD	p
IPSS R risk	Very low	0	3	3	12,578	8	0,127
	Low	1	6	10			
	Intermediate	0	2	3			
	High	1	1	0			
	Very high	0	3	0			
		Response in blast levels					
		Negative response	Positive response	No change	χ^2	SD	p
IPSS R risk	Very low	0	0	6	18,551	8	**0,017**
	Low	3	2	12			
	Intermediate	2	2	1			
	High	0	2	0			
	Very high	0	2	1			
		Response in fibrosis levels					
		Negative response	Positive response		χ^2	SD	p
IPSS R risk	Very low	6	0		3,699	4	0.448
	Low	13	4				
	Intermediate	4	1				
	High	1	1				
	Very high	3	0				

Abbreviations: MDS: Myelodisplastic syndromes, IPSS R: Revised international prognostic scoring system , χ^2: Chi square, SD: Standar deviation

statistically significant difference was found between the number of somatic mutations in MDS patients and the average follow-up time (p<0.064). Although there is no statistically significant difference here, it is possible to say that those with a somatic mutation number of 2 have the lowest follow-up period, and those with a somatic mutation number of 0 have the highest (**Table 8**).

Table 8. Comparison of NGS anomaly and number somatic mutations data and follow-up periods of MDS patients

Follow up (months)		
NGS anomaly	**Mean±SD**	**p***
Positive	13.20±4.70	0.142
Negative	18.11±12.92	
Number somatic mutations		
0	18.84±12.47	0.064
1	13.12±3.27	
2	9.66±4.72	
3	10.66±0.57	

Abbreviations: NGS: Next generation sequencing, SD: Standar deviation, MDS: Myelodisplastic syndromes

DISCUSSION

Understanding genetic manifestations of hematological cancers has been the subject of studies lately, and NGS studies have been the subject of studies.[6] We conducted a study to determine the role of NGS positivity in the prognosis of MDS patients. Thirty-three MDS patients were included in the study, and 15 of them were NGS-positive. Patients were examined according to WBC levels at diagnosis. WBC levels at the diagnosis of patients with type 1 somatic mutations were higher than in other groups (7056.25, p=0.048). The ratio of neutrophil and lymphocyte values for NGS positives was higher than those tested negative (1.56 and 3.51, respectively). Patients with the type 1 mutation had higher WBC levels than patients with the type 2 and type 3 mutations (7056.25/µL, 2416.67/µL, and 3036.67/µL, respectively). Patients who did not show a change in transfusion need during the illness had higher platelet levels at diagnosis than patients with transfusion need 237.70/µL and 121.13/µL, respectively (p<0.05). Patients with NGS positivity had a longer follow-up period than the negative group (18.11 and 13.20 months, respectively).

In a study conducted by Li et al.[6] in a univariate analysis, BCORL1 was shown to be an important parameter for the OS in patients with MDS diagnosis. Yang et al.[7] used optical genome mapping and conducted comprehensive cytogenetic scoring system analysis on 101 MDS patients. They discovered that the TP53 mutation and bone marrow blasts were important parameters for the prediction of survival. In our study, we detected the TP53 mutation in three patients. In a study examining MDS patients on eltrombopag and azacitidine therapy, NGS results revealed that patients with TP53, NRAS, ASXL1, RUNX1, or TET2 mutations were more prone to progress and less susceptible to eltrombopag therapy.[8] In our study, ASXL1, RUNX1, and TET2 mutations were detected in 3, 2, and 2 patients, respectively.

NGS positivity is common in MDS patients. In a study conducted on 95 MDS patients, 91.4% of the patients tested positive for at least one mutation.[9] MDS is a clonal stem cell disorder that develops due to a complex genetic process caused by DNA damage with subtypes. Understanding the route of the disease is quite important since the MDS can turn into acute myeloid leukemia. NGS has been shown to be a useful tool for diagnosis, classification, and surveillance of treatment types.[10]

The role of mutations in treatment response in MDS patients has been the subject of studies. In an analysis made on bone marrow specimens of MDS patients, the presence of T cell receptor repertoire differences was correlated with the response to HMA treatments.[11] Takahashi et al.[12] studied the genes of 114 untreated MDS patients and concluded that the existence of four or more driver mutations was linked to poor response to HMA treatments.

It is clear to say that mutations are common among MDS patients, and the clinical significance of them is still the subject of studies. Since the diagnosis and prognosis of MDS and treatment responses to therapies require attention for better clinical outcomes, new technologies remain important for the process.[13] In a study that compares NGS with cytogenetics, NGS showed better diagnostic performance, and it is noted that karyotyping can be reduced by 30% by using NGS as a first-line approach.[14] We identified mutations in MDS patients using NGS and found a correlation with WBC levels. Therefore, patients with lower WBC levels should be tested for mutations.

CONCLUSION

We studied thirty-three MDS patients with NGS techniques for detecting mutations. Fifteen (45.5%) of the patients were positive for at least one mutation. Patients with NGS positivity had lower WBC levels than negative ones. Since MDS has a nature of clonal damage and mutations, understanding the route of the disease and planning treatments according to mutation types is quite important. Studies with larger populations should be conducted, and the use of this technique must be implemented in diagnosis and treatment processes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethics committee required for the study was obtained from the Hamidiye Scientific Researches Ethics Committee (Date:18.04.2024, Decision No: 5/21).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Case Report

DOI: 10.51271/JCHOR-0047

Can bispecific antibody therapies for multiple myeloma be a risk factor for the development of secondary haemotopoietic malignancy? A case report

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Cite this article: Tan T, Doğan İÖ, Civriz Bozdağ S. Can bispecific antibody therapies for multiple myeloma be a risk factor for the development of secondary haemotopoietic malignancy? A case report. *J Curr Hematol Oncol Res.* 2024; 2(4): 93-94.

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Received: 28/04/2024 ◆ **Accepted**: 27/05/2024 ◆ **Published**: 14/11/2024

ABSTRACT

With the introduction of many new treatments in multiple myeloma and the effective use of autologous stem cell transplantation, significant prolongation of overall survival has been achieved. Despite this, there is still no cure for this disease. Relapsed/refractory conditions seen after multiple treatments have brought the use of new agents to the agenda. Elranatamab is a humanized bispecific antibody used in relapsed or refractory multiple myeloma which targets B-cell maturation antigen on myeloma cells and CD3 on T cells . With this mechanism, elranatamab could activate T cells to induce cytotoxic T-cell response against myeloma cells. Although we have an idea and experience about the short-term adverse effect profile and management, our ideas about the long-term adverse effect and safety profile are not yet clear due to the fact that it is a very new agent. We described an unexpected hematologic event during the use of elranatamab in the following case.

Keywords: Multiple myeloma, bispecific antibodies, haemotopoietic malignancy

INTRODUCTION

With the introduction of many new treatments in multiple myeloma and the effective use of autologous stem cell transplantation, significant prolongation of overall survival has been achieved. Despite the introduction of novel agents, there is still no cure for this disease. Relapsed/refractory conditions seen after multiple treatments have brought the use of new agents to the agenda. Elranatamab, a humanized bispecific antibody utilized in the treatment of relapsed or refractory multiple myeloma, functions by targeting B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells, thereby eliciting a cytotoxic T-cell response against myeloma cells.[1] Despite our familiarity with the short-term adverse effect profile and management strategies associated with its use, the long-term adverse effects and safety profile of elranatamab remain uncertain due to its recent introduction as a therapeutic agent. Herein, we present a case detailing an unexpected hematologic event observed during elranatamab therapy, emphasizing the importance of ongoing surveillance and comprehensive understanding of its safety profile in clinical practice.

CASE

Born in 1947, female patient received radiotherapy (RT) for solitary plasmacytoma in the posterior right costal region in 2008.

In 2011, the patient received radiotherapy for a symptomatic plasmacytoma in the left thigh. Subsequent follow-up revealed a bone marrow biopsy compatible with lambda light chain predominant myeloma. The patient underwent four cycles of VAD (vincristine, adriamycin, and dexamethasone) but declined autologous Hematopoietic Stem Cell Transplantation (AHSCT). She was treated with thalidomide monotherapy for three years until 2017, when she experienced recurrence with bone plasmacytomas and associated fractures in 2017 and 2018.

During further follow-up, due to progressive myeloma, the patient was treated with VCD (bortezomib, cyclophosphamide, and dexamethasone) combination. Subsequent follow-up positron emission tomography-computed tomography (PET-CT) scans revealed new lytic lesions in the skeletal system, prompting treatment with ixazomib, cyclophosphamide, and dexamethasone. Daratumumab, bortezomib, and dexamethasone therapy was initiated following routine myeloma laboratory analyses that indicated a biochemical recurrence. The patient had progressed in 2023 and could have an access to elranatamab with the early compassionate access program.

Following six cycles of elranatamab treatment, the patient's PET-CT scan and myeloma laboratory analyses indicated

complete remission. To assess the occurrence of anemia, a bone marrow aspiration and biopsy were performed after ten cycles of elranatamab treatment. The trephine biopsy revealed diffuse dyshematopoiesis and a hypercellular bone marrow with an increase in reticulin fibers. Young-blastic morphologic cell increase with patchy-interstitial distribution was reported. The patient exhibited a moderately increased ratio of CD34 (+) precursor cells (10%-15%) and CD117 (+) precursor cells (10%-20%). Given these findings, along with the presence of excessive blasts characteristic of myelodysplastic syndrome and transformation to acute myeloid leukemia (MDS related AML), a therapeutic regimen consisting of azacitidine and venetoclax was initiated, taking into account the patient's age and performance status.

DISCUSSION

We conducted a comprehensive evaluation of a patient who developed AML during bispecific antibody therapy for relapsed/refractory myeloma. Despite the patient's history of multiple prior RT treatments, a recognized risk factor for AML development, it is of particular interest that leukemia emerged following completion of ten cycles of elranatamab treatment, coinciding with a period of controlled myeloma. Hematologic AEs related with elranatamab use were frequent anemia (68%; grades 3/4: 43%) and neutropenia (62%; grades 3/4 : 51%) are the most common ones and it's known that these effects are generally manageable with dose reductions or interruptions.[2] BCMA expression has also been identified in AML. Some studies show that BCMA mRNA expression was higher in complete remission versus no response patients.[3]

CONCLUSION

Our case underscores the necessity for a prolonged follow-up period and increased clinical experience to elucidate the potential impact of bispecific antibody therapies like elranatamab on the pathogenesis of AML in the context of myeloma treatment. The emergence of AML in our patient, despite successful control of myeloma, highlights the complexity of disease interactions and the need for vigilant monitoring during novel therapeutic interventions. Further investigation into the long-term effects of such therapies is essential for optimizing treatment strategies and minimizing adverse outcomes in patients with relapsed/refractory myeloma.

ETHICAL DECLARATIONS

Informed Consent

The patient signed the informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Case Report

DOI: 10.51271/JCHOR-0048

Kikuchi-Fujimoto disease: a rare cause of fever and lymphadenopathy in a 19-year-old male

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Cite this article: Çiftciler R, Çiftciler AE, Selim C, Çelik M. Kikuchi-Fujimoto disease: a rare cause of fever and lymphadenopathy in a 19-year-old male . *J Curr Hematol Oncol Res.* 2024;2(4): 95-97.

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Received: 02/08/2024 ◆ **Accepted**: 06/09/2024 ◆ **Published**: 14/11/2024

ABSTRACT

Kikuchi-Fujimoto disease (KFD) is also known as histiocytic necrotizing lymphadenitis or Kikuchi disease. The disease is a rare, self-limiting condition of an undetermined cause that manifests as protracted lymphadenopathy with or without systemic symptoms. Painful cervical lymphadenopathy accompanied by fever, leukopenia, and an increased erythrocyte sedimentation rate are its defining features. We reported a 19-year-old male was admitted to the hematology outpatient clinic with cervical lymphadenopathy and B symptoms. He was diagnosed with Kikuchi disease from a lymph node biopsy. He was successfully treated with intravenous immunoglobulin and steroids. The patient's complaints regressed and disappeared. Histopathological features, including lymph node necrosis and histiocytic growth, are used to diagnose KFD. It is regarded as a benign condition. To avoid incorrect diagnoses and needless treatments, medical professionals must be aware of Kikuchi disease while making a differential diagnosis for cervical lymphadenopathy.

Keywords: Kikuchi-Fujimoto, fever, lymphadenopathy, lymphoma

INTRODUCTION

Kikuchi-Fujimoto disease (KFD) is a rare self-limiting condition of undetermined cause that manifests as protracted lymphadenopathy (LAP) with or without systemic symptoms. It is also known as histiocytic necrotizing lymphadenitis or Kikuchi disease.[1] The exact role that microbial infection and non-infectious stimuli play in its etiopathogenesis is yet unknown. The majority of patients have firm to rubbery cervical LAP with sporadic fever; more severely afflicted individuals have leucopenia, splenomegaly, weight loss, and high erythrocyte sedimentation rate.[1] Young individuals of both genders are primarily affected, however the prevalence varies. Patients between the ages of 6 and 80 have been documented to have it, with a mean age of 30 at presentation; however, the majority of those affected were younger than 40 in most investigations.[2] The most prevalent signs and symptoms were LAP (100%), fever (35%), erythematous rash (10%), arthritis (7%), exhaustion (7%), and hepatosplenomegaly in 3% of patients.[3] It has also been noted that splenomegaly is a rare characteristic of KFD. The fever is usually low grade and sporadic, lasting around one week (occasionally up to one month; median length 9 days), and is the main symptom in 30–50% of individuals. A longer clinical course may be seen by patients with bigger lymph nodes, leucopenia, and fevers greater than 39.0 °C.[4,5] Due in large part to a lack of knowledge about this unusual disease, patients with KFD, particularly in its proliferative phase, have frequently been misdiagnosed as having non-Hodgkin or Hodgkin lymphoma, prompting thorough examinations and, in certain circumstances, aggressive treatment with cytotoxic medicines. The differential diagnosis of KFD includes infectious mononucleosis, tuberculous lymphadenitis, systemic lupus erythematosus, and cat scratch disease, in addition to lymphoma. In this study, we presented a 19-year-old male patient who presented with symptoms like lymphoma and was diagnosed with KFD and was successfully treated with intravenous immunoglobulin (IVIG) and steroids.

CASE

A 19-year-old male was admitted to the hematology outpatient clinic with cervical LAP and night sweats. Additionally, he had lost more than 10% of his weight in the last 6 months and had a fever of up to 39°C. He also had complaints of joint pain for about 1.5 months. He used amoxicillin and clavulanic acid for 2 weeks with the preliminary diagnosis of lymphadenitis. However, there was no improvement in the patient's complaints. On physical examination, fixed painful LAP was detected, reaching approximately 2 cm in the right and left cervical chains and extending to the supraclavicular region on the left. Laboratory tests revealed C reactive protein 28 mg/L, ferritin 562 ng/ml, hemoglobin 12.3 g/dl, leukocyte $3x10^3/mm^3$, neutrophil 1.3 $x10^3/mm^3$, platelet $209x10^3/mm^3$

and lactate dehydrogenase level 348 U/L. Contrast-enhanced neck magnetic resonance imaging revealed multiple lymph nodes in the right cervical chain, the largest of which was at level 5, 18x17 mm in size, some of them round in appearance and with increased cortical thickness. It was also reported that multiple LAPs around 1 cm were observed in the left cervical triangle. Abdominal ultrasonography revealed a spleen size of approximately 140 mm. He was admitted to the hospital for further diagnosis. Due to the patient's B symptoms and multiple pathological LAP, an excisional lymph node biopsy was performed with the preliminary diagnosis of lymphoma.

Histopathologic examination of the lymph node revealed multifocal coagulative necrosis in the paracortical area, abundant nuclear debris, and large mononuclear cells (histiocytes, plasmacytoid dendritic cells, and activated T cells) forming a pale area in the periphery (**Figure 1**). Immunohistochemically, widespread CD-68-positive histiocytes were observed around the necrosis foci (**Figure 2A**). CD-20 was immunopositive in follicular areas (**Figure 2B**), and CD-3 was immunopositive in paracortical areas. CD-8 showed more positive staining than CD-4 (**Figure 2C, 2D**). No staining with EBV was observed. Histomorphological and immunohistochemical findings were reported as compatible with 'Kikuchi Disease'. Because the patient had night sweats, painful LAP, and widespread ongoing joint pain, the patient was treated with methylprednisolone at 1 mg/kg and intravenous immune globulin (IVIG) at 400 mg/kg for 3 days. The patient, whose treatment was completed, was followed up in the hematology outpatient clinic. The patient's complaints regressed and disappeared.

DISCUSSION

Histopathological features, including lymph node necrosis and histiocytic growth, are used to diagnose KFD. It is regarded as a benign condition.[6] On the other hand, chronic and even lethal instances have been documented in the literature.[7] Hemophagocytic syndrome, rheumatic illnesses, viral diseases, neurologic disorders, lymphoma, and interstitial lung disease have all been linked to KFD.[8-11] In the case we presented, there were no laboratory or clinical findings that could be associated with these diseases. There is no set course of therapy because the signs and symptoms normally go away on their own in one to four months without causing any major problems. Fever often goes down after the afflicted lymph node is removed, indicating that excisional biopsy may be beneficial therapeutically in addition to being diagnostic since it removes the source of the inflammation.[1] Usually, the goals of pharmacotherapy are to lower morbidity and avoid problems. In moderate instances, nonsteroidal anti-inflammatory medicines are generally adequate to relieve fever and soreness in the lymph nodes. Immunomodulators, systemic corticosteroids (prednisolone 1-2 mg/kg body weight) alone or in combination, high dose corticosteroids, and IVIG have been used to treat patients with prolonged fever, severe or symptoms that have persisted for more than two weeks, and recurrent disease. This is particularly the case for patients who present with extranodal

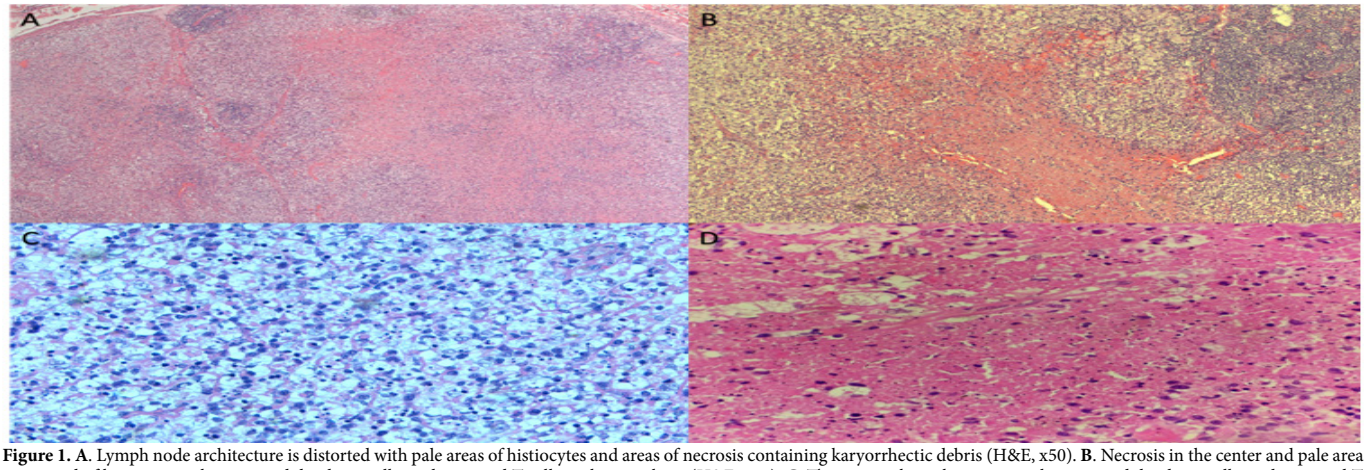

Figure 1. A. Lymph node architecture is distorted with pale areas of histiocytes and areas of necrosis containing karyorrhectic debris (H&E, x50). **B**. Necrosis in the center and pale area composed of histiocytes, plasmacytoid dendritic cells, and activated T cells in the periphery (H&E, x50). **C**. This image shows histiocytes, plasmacytoid dendritic cells, and activated T cells, which are the predominant lesional cells in Kikuchi lymphadenitis (H&E, x400). **D**. The necrotic foci in Kikuchi lymphadenitis show abundant eosinophilic karyorrhectic debris (H&E, x400).

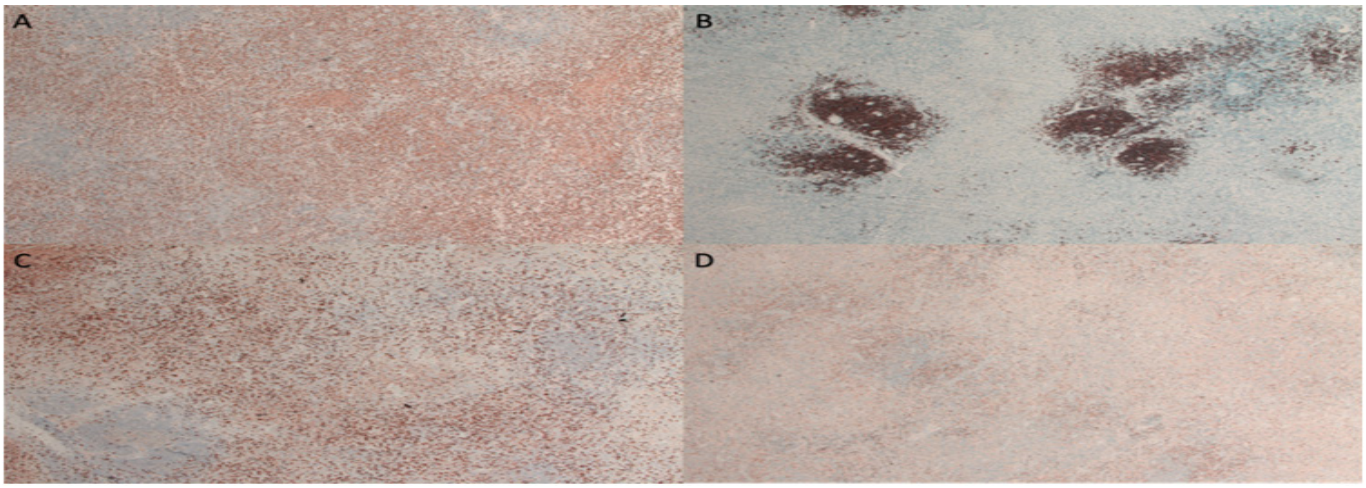

Figure 2. A. CD-68 positive in numerous histiocytes around areas of necrosis. **B**. CD-20 immunopositive in follicular areas outside of karyorrhectic areas. **C**. Many T cells in this field are CD-8 immunopositive. **D**. CD-4 immunopositive with few cells.

or generalized severe disease or hemophagocytic syndrome with good therapeutic results.[12-14]

CONCLUSION

In our case, he had lost more than 10% of his weight in the last 6 months and had a fever of up to 39 °C. Since he had constitutional symptoms and these complaints did not resolve spontaneously, the patient was treated with methylprednisolone at 1 mg/kg and IVIG at 400 mg/kg for 3 days. The patient's constitutional symptoms regressed. The lymph node shrank. The patient was followed up in the hematology outpatient clinic. To avoid incorrect diagnoses and needless treatments, medical professionals must be aware of Kikuchi disease while making a differential diagnosis for cervical lymphadenopathy.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Case Report

DOI: 10.51271/JCHOR-0049

A rare case of olfactory neuroblastoma

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Cite this article: Karatlı S, Kavak EE. A rare case of olfactory neuroblastoma. *J Curr Hematol Oncol Res.* 2024;2(4):98-99.

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Received: 02/08/2024 ◆ **Accepted**: 13/09/2024 ◆ **Published**: 14/11/2024

ABSTRACT

Olfactory neuroblastoma, also known as esthesioneuroblastoma, is a rare tumor of the nasal cavity with an incidence of approximately 0.4 per million individuals. The most common symptom is nasal obstruction, although patients may also present with epistaxis and nasal discharge. Treatment options primarily include surgical resection and radiotherapy, with a limited role for chemotherapy. There is currently no universally accepted treatment protocol for this condition. This report describes a case of olfactory neuroblastoma staged as Kadish stage C, in which the patient underwent chemoradiotherapy. Follow-up imaging revealed no evidence of disease recurrence. This case suggests that chemotherapy may play a role in the treatment regimen for advanced-stage olfactory neuroblastoma, potentially improving therapeutic outcomes.

Keywords: Olfactory neuroblastoma, chemotherapy, radiotherapy

INTRODUCTION

Olfactory neuroblastoma (ONB), also referred to as esthesioneuroblastoma (ENB), is a rare tumor originating from the olfactory neuroepithelium in the nasal cavity.[1] Its incidence is approximately 0.4 per million and it accounts for about 2% of tumors in the nasal cavity and paranasal sinuses.[2] The tumor is most commonly diagnosed in the fifth and sixth decades of life.[2,3] Although it is more frequent in males, the gender distribution is nearly equal.[2,3] The most common symptom of ONB is nasal obstruction.[2] Other frequent symptoms include epistaxis and nasal discharge.[3] Additionally, symptoms such as anosmia, excessive lacrimation, headache, and ear pain may occur due to local tumor invasion.[2,3] Paraneoplastic syndromes such as hypercalcemia and inappropriate antidiuretic hormone (ADH) syndrome are extremely rare.[3] The rarity of the tumor and its symptoms overlapping with those of upper respiratory tract infections often lead to delayed diagnosis.[1] Consequently, delayed diagnosis is common.[2-4]

Treatment for olfactory neuroblastoma generally involves surgical resection and radiotherapy (RT), with chemotherapy (CT) playing a limited role.[5] There is no established universally accepted treatment protocol.[4] It is suggested that chemotherapy may become part of the treatment regimen in advanced stages.[6] This report presents a case of a patient with Kadish stage C ONB and details the treatment plan.

CASE

A 40-year-old male patient presented to the otolaryngology clinic with persistent nasal obstruction and headaches lasting approximately 6 months. Despite receiving prolonged medical treatment for what was initially suspected to be an upper respiratory tract infection, there was no improvement in his symptoms.

Paranasal sinus computed tomography revealed soft tissue densities in the right nasal cavity, causing air loss in the ethmoid cells with indistinct borders from the middle and inferior turbinates, and extending from the accessory ostium of the right maxillary sinus into the nasal cavity, partially obstructing the nasal passage and extending to the choana (**Figure**).

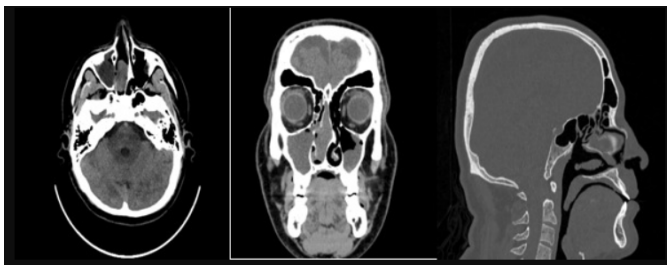

Figure. Paranasal sinus computed tomography of the patient

The brain tomography of the patient, in whom no pathological findings were detected, revealed that the punch biopsy taken from the mass was reported as ONB. Additionally, there were no PIK3CA or p53 mutations. The tumor, which invaded the posterior and anterior ethmoid cells and extended to the frontal recess, was excised via curettage through the skull base. Following surgery, the Kadish stage C patient was evaluated in the head and neck tumor board. The treatment plan included 33 fractions of radiotherapy totaling 66 gray, with concomitant systemic chemotherapy (weekly cisplatin at 40 mg/m2). During the treatment, the patient experienced minor symptoms such as dryness of the oral and nasal mucosa due to RT, and nausea

and vomiting from chemotherapy. However, these side effects did not interrupt the treatment, which continued as planned. Imaging three months after treatment showed no evidence of disease recurrence.

DISCUSSION

ONB, also known as ENB, is an extremely rare tumor.[1] It originates from olfactory neuroepithelial cells.[1] Despite its slow growth, the non-specific symptoms often lead to delayed diagnosis.[1,2] Although it can present between the ages of 35 and 70, the most common presentation age is in the fifth decade.[3] Nasal obstruction is the most frequent symptom, but epistaxis, headache, facial swelling, and ear pain can also be observed.[3]

Histopathological features may include mutations in PIK3CA, p53, NF1, and CDKN2A. Immunohistochemical markers such as vimentin, S-100 protein, neuron-specific enolase, and neurofilaments are used for diagnosing neuroblastoma.[7]

Kadish staging is the most commonly used clinical staging system for ONB.[8] Kadish A indicates the tumor is confined to the nasal cavity; Kadish B includes the nasal cavity plus one or more paranasal sinuses.[8] Kadish C indicates extension beyond the paranasal sinuses.[8] Kadish D involves regional lymph node metastasis or distant metastases.[8]

Treatment for ONB involves surgery, RT and CT.[3] Due to the tumor's rarity and the need for long-term monitoring of treatment outcomes, there is no established standard treatment protocol.[3] The role of CT remains undetermined, and data on the benefits of neoadjuvant CT or concurrent chemoradiotherapy are limited.[3,4] CT should be considered as part of the treatment regimen for advanced stages, such as Kadish C-D, or in cases where surgery is not feasible due to widespread intracranial metastases or orbital invasion.[9-12]

CONCLUSION

ONB is a very rare tumor with no established standard treatment protocol. Data on the benefits of CT are limited. CT should be considered as part of the treatment regimen in advanced stages or when surgery is not possible. More studies are needed due to the very low incidence and the small number of patients in the studies.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

No financial support has been received for this article.

Financial Disclosure

The authors declare that this study has received no financial support.

Author Contributions

All authors declare their participation in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Current Hematology & Oncology Research

Letter to the Editor

DOI: 10.51271/JCHOR-0050

A comment on 'The relationship between hepatocellular carcinoma and resolvin D1' by Erdin et al.

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Cite this article: Güven İE. The relationship between hepatocellular carcinoma and resolvin D1. *J Curr Hematol Oncol Res.* 2024;2(4):100.

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Received: 27/10/2024 ◆ **Accepted**: 11/11/2024 ◆ **Published**: 14/11/2024

Keywords: Letter to the editor, hepatocellular carcinoma, resolvin D1

Dear Editor,

We read the article entitled "The relationship between hepatocellular carcinoma and resolvin D1" by Erdin et al.[1] with great interest. First of all, we congratulate the authors and editorial board for this informative and interesting article.

In this study, they reported that resolvin D1 levels were significantly different between the control and cirrhosis group, and between the control and HCC group. Resolvin D1 levels were also found to be higher in the control group and lowest in the HCC group. In addition, a negative correlation was demonstrated between the resolvin D1 and AFP levels. Notably, resolvin D1 levels were negatively correlated with tumor stage.

In recent years, the effect of resolvin D1 on the anti-inflammatory process has been of interest. It has been demonstrated that resolvin D1 can play a significant role in the inhibition of tumor proliferation, metastasis, and epithelial-mesenchymal transition.[2] The underlying mechanism is thought to be a decrease in leukocyte infiltration, increased release of anti-inflammatory cytokines, and induction of leukocyte apoptosis.[3] In this concept, the low level of resolvin D1 in the HCC group shown in this study is promising for HCC screening in combination with AFP in cirrhotic patients. However, we believe that the sample size is relatively small for the evaluation of the association of resolvin D1 with tumor stage. Thus, a prospective study with larger sample size could provide more definitive data.

Overall, this study by Erdin et al.[1] demonstrated that resolvin D1 may be a useful biomarker for predicting the HCC as an alternative to AFP. Further studies are warranted on this topic.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author have no conflicts of interest to declare.

Financial Disclosure

The author declared that this study has received no financial support.

Author Contributions

The author made the design, execution, and analysis of the paper, and that they have approved the final version.

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