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EDITORIAL

Dear readers,

As the TMSJ editorial board, we are very grateful to present to you the last issue of 2019. In this issue, you will find 1 original article, 2 case reports, and 1 review. Akay et al. have made a detailed data analysis of chronic myeloid leukemia patients regarding demographic features, treatments and treatment responses. We have also presented you a case report which can make a contribution to increasing the awareness of the differential diagnosis of multiple polyposis in the gastrointestinal tract. In a case report by Atnallar et al., the effectiveness of PET/CT in the evaluation of lymphoma has been discussed. Since PET/CT has been used very commonly in oncology, I believe that our readers will find this case report interesting to read. Today, researchers are making a great effort to investigate the role of different chemicals in cancer treatment and vanillin is a commonly used aromatic in our daily lives; the review of Mutlu et al. has presented us a different perspective by mentioning the role of vanillin in cancer treatment.

I also would like to mention International Open Access Week, 21-27th of October. This year's theme is 'Open for Whom? Equity in Open Knowledge'. I believe, this theme will encourage science enthusiasts to question the publishing community and raise awareness in equity. We should not only support open access, but also try to try to minimize the inequity and provide a fair platform for everyone. We should think of the underrepresented groups in the science community and take action by not prioritizing a specific group. Our actions today will shape the extent of the science community in the future. I invite all of our readers to consider this year's theme of Open Access Week and act upon it.

Hoping to meet all of our readers in the next issue!

Nur Gülce İŞKAN
Editor-in-Chief

CONTENTS

ORIGINAL ARTICLE

RETROSPECTIVE ANALYSIS OF CHRONIC MYELOID LEUKEMIA PATIENTS IN TRAKYA UNIVERSITY SCHOOL OF MEDICINE

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ABSTRACT

Aims: This study aims to establish the data; including demographic features, molecular response status, disease characteristics, and survival rate of chronic myeloid leukemia patients treated with tyrosine kinase inhibitors in Trakya University School of Medicine. ***Methods:*** In this study, the data of 102 patients over 18 years old who were diagnosed with chronic myeloid leukemia in Trakya University School of Medicine between January 2003-October 2019 were analyzed retrospectively. Data was analyzed using SPSS 23.0.0.0. ***Results:*** The total number of patients in the study was 102. There were 95 (93.1%) patients on chronic phase and 6 (5.9%) patients on accelerated phase. Eighty-three (81.4%) of the patients had at least a major molecular response and 17 (16.7%) patients could not achieve at least a major molecular response. ***Conclusion:*** As our study showed, first line treatment with imatinib may not be enough for some of the patients to recover and therefore different TKIs such as dasatinib, nilotinib, bosutinib, and ponatinib are being used in the treatment of CML. Inadequate response, drug side effects and incompliances are the causes of switching the drug choice. Further studies are needed to thoroughly reveal the epidemiology and treatment regimens.
Keywords: Chronic myeloid leukemia, tyrosine kinase, neoplasms

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm where most of the time a single, pluripotent hematopoietic stem cell develops a Philadelphia chromosome (t9;22) resulting with a clonal overgrowth of myeloid precursor cells (1). The pathogenesis that plays a crucial role in CML is irrepressible tyrosine kinase activity which is a by-product of translocation between 9 and 22 chromosomes giving rise to fusion genes BCR-ABL1 (1). The clinical presentation may be seen in 3 different phases: chronic, accelerated and blastic. Most patients are diagnosed at the chronic phase of the disease and if left untreated may progress to accelerated or blastic phases, which have poorer prognosis (2). Chronic myeloid leukemia represents about 15% of adults leukemias, the incidence is approximately 1-2/100,000 per year. CML may occur in all age groups, however, the median age of disease is 67 (3).

Diagnosis is made by history, physical examination and laboratory tests which comprise, which comprises spleen palpation, complete blood count, hepatitis panel and chemistry profiles. Bone marrow biopsy and aspirate are used for morphological, molecular and cytogenetic evaluation. However, diagnosis must be approved cytogenetically by using fluorescence in situ hybridization (FISH) which direclty detects the translocation (t9:22) and quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) that shows the levels of BCR-ABL1 in peripheral blood or bone marrow cells (4).

The European LeukemiaNet and National Comprehensive Cancer Network are the most common guidelines used for the diagnosis and management of CML patients in daily practice (5, 6). After patients have been diagnosed and started their first-line Tyrosine Kinase Inhibitor (TKI) treatment they are followed up on their 3rd months where a hematological response (Leukocyte < $10x10^9$/L, no immature myeloid precursors, basophils

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< 5%, platelet count < 450x10⁹/L, spleen non-palpable) is expected. In addition, quantification of BCR-ABL1 from peripheral blood is necessary every 3 months. Having an early molecular response (MR) at 3 months (BCR-ABL1 <10%) is a predictive biomarker of later on achieving a deep molecular response (7). Intervals are prolonged until the 12th month of disease expecting a major molecular response (MMR) (BCR-ABL1 0.1%, 3 log reduction from standardized baseline). Patients' relative risk scores are calculated using simple hematological and clinical data collected before any treatment. For assessing prognostic and predictive implications; Sokal, Euro and European Treatment of Outcome Study (EUTOS) scores are used (8).

First-line therapy options are first-generation (imatinib) and second-generation (nilotinib and dasatinib) TKIs. Second-line therapy options consists of second-generation TKIs (nilotinib, dasatinib, and bosutinib) and third-generation TKI, ponatinib, which is also used in third-line therapy as well as for patients with T315I mutation associated with pan-TKI resistance (8). Later on, with the introduction of imatinib, being the first targeted therapy used in treating CML patients, number of patients applying to allogenic stem cell transplantation underwent a significant decrease, however, it is still an important therapeutic option for the patients who failed at least 2 TKIs or have T315I mutation (8).

Before the 2000s, treatment strategy for CML was limited to interferon-alpha (IFN-alpha), chemotherapy, hydroxyurea and allogeneic stem cell transplantation which was the most efficient treatment strategy (9). Later on, treatment protocol completely changed with the introduction of imatinib, being the first targeted therapy used in treating CML patients (10). One of the largest phase III randomized trials done known as International Randomized Study of Interferon and STI571 (IRIS) had a major impact on providing the necessary information about the scientific and clinical background for treating Ph (+) leukemias with imatinib (10). Complete cytogenetic response rate for the patients treated with imatinib was 94% in contrast to patients that were administered IFN-alpha at the 19th month of median follow-up (10). Overall, the superiority of treating CML patients with imatinib has been proved in other prospective and retrospective studies as well (11-13).

This study aims to establish the data; including demographic features, molecular response status, disease characteristics, and survival rate of CML patients treated with TKI in Trakya University School of Medicine which is a tertiary center of the region and make a contribution to the database of CML patients in Turkey.

MATERIAL AND METHODS

This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK2019/359). Informed consent was obtained from all subjects. In this study, the data of all patients over 18 years old who were diagnosed with CML in Trakya University School of Medicine between January 2003-October 2019 were analyzed retrospectively.

There were 102 patients where their demographic data, phase of the disease, total follow-up, durations of their TKI treatments, major molecular response, reason to switch treatments and last treatment they were on were congregated from the archives of Trakya University School of Medicine.

Data was analyzed using SPSS 23.0.0.0. Continuous variables (age, total follow-up and durations of their TKI treatments) were tested for normal distribution with Shapiro-Wilk Test. Normal distribution was observed only for the duration of 4th line TKI treatment which was presented as mean and standard deviation. Non-normal distribution was observed for the rest. Thus, descriptive statistics for those are presented as median and inter-quantile range (IQR). Categorical data (gender, phase of the disease, major molecular response, distribution of TKI treatments, reasons for switching TKIs) are presented as numbers and percentages.

RESULTS

In this retrospective study 102 patients with the diagnosis of CML were included. 60 (58.8%) patients were male and 42 (41.2%) were female. There were 95 (93.1%) patients on chronic phase and 6 (5.9%) patients on accelerated phase, with 1 missing data. Eighty-three (81.4%) of the patients had at least major molecular response and 17 (16.7%) patients could not achieve at least a major molecular response, there were 2 missing data. All patients (102) in our study were admitted imatinib as the first-line treatment.

Number of patients, summary statistics of parametric (duration of 4th TKI treatment) and non-parametric variables (age, age of diagnosis, total median follow-up and duration of 1st, 2nd and 3rd TKI treatments) are presented in Table 1. Summary of categorical data (gender, phase of the disease, major molecular response, distribution TKI treatments, reasons for switching TKIs) are presented in Table 2.

In median total follow-up time of 86 (88.2%) month, 20 patients were found to be deceased, with 7 deaths being CML-related and remaining 5 deaths being non-CML-related.

Table 1: Summary statistics of parametric and non-parametric variables.

	Number of patients*	Median (IQR)
Current age of patients (years)		62.00 (26)
Age of the patients at the time of diagnosis (years)		51.98(23)
Total follow-up (months)		86.00 (84)
Duration of 1st line TKI treatment (months)	44	15.00 (39)
Duration of 2nd line TKI treatment (months)	21	16.00 (19)
Duration of 3rd line TKI treatment (months)	9	8.00 (8)
Duration of 4th line TKI treatment (months)**	4	20.0 ± 19.408

**All 102 patients started off with Imatinib as the first line treatment, these are the number of patients who were switched to next line treatment and their durations.*

***TKI:** Tyrosine Kinase Inhibitor, **IQR:** Inter-quartile Range*

*** Since the data of duration of the 4th line TKI treatment is normally distributed, it is given as mean ± standard deviation.*

Table 2: Summary statistics of categorical variables.

		Number (%)
Gender	**Male**	60 (58.8)
	Female	42 (41.2)
Phase	**Chronic**	95 (93.1)
	Accelerated	6 (5.9)
	N/A	1
Distribution of 2nd line TKI treatments	**Dasatinib**	17 (38.6)
	Nilotinib	26 (59.1)
	N/A	1
Distribution of 3rd line TKI treatments	**Dasatinib**	8 (38.1)
	Nilotinib	10 (47.6)
	Bosutinib	3 (14.3)
Reasons to switch 2nd line TKI treatment	**Side effect**	5 (11.4)
	Loss of MR	37 (84.1)
	Incoordination	2 (4.5)
Reasons to switch 3rd line TKI treatment	**Side effect**	9 (39.1)
	Loss of MR	12 (52.2)
	Incoordination	1 (4.3)
	Refractory	1 (4.3)
Last treatment	**Dasatinib**	9 (8.8)
	Nilotinib	22 (21.6)
	Bosutinib	4 (3.9)
	Imatinib	57 (55.9)
	Ponatinib	4 (3.9)
	Hydroxyurea	2 (2.0)
	Cytarabine	1 (1.0)
	No drug	1 (1.0)
	N/A	2
Major molecular response (BCR-ABL1 ≤0.1%	**Responsive**	83 (81.4)
	No response	17 (16.7)
	N/A	2 (1.96)
Survival status	**Alive**	90 (88.24)
	Deceased	12 (11.76)
	CML-related	7 (6.8)
	Non-CML-related	5 (4.9)

***TKI:** Tyrosine Kinase Inhibitor, **N/A:** Not Available*

DISCUSSION

Before 2013, epidemiological data from the End Results Program of United States National Cancer Institute were used in daily practice, however with the Turkish CML study, which was a multicentral study with 1133 patients, Turkey managed to establish its database and found the median age for Turkish CML patients to be 46.1±14.8 (9, 14). Our study has found the mean age of CML patients to be 51.98 years. This proves the need for similar studies to be conducted since different genetic and environmental factors can make up different mean ages. These demographic data are also important for different clinical approaches in daily practice. Since there are higher rates of durable complete molecular response with second-generation TKIs, second-generation TKIs may be considered in younger patients (e.g. <50 years) in comparison to older patients. This could lead to potential molecular responses where the patients may end up with the discontinuation of TKI treatments (15).

According to the previous studies, most patients diagnosed with CML present themselves in the chronic phase, however, 5-7% may advance to accelerated or blastic phases (9, 16). Our data was in line with the Turkish CML study, during the initial diagnostic evaluations, where 93.1% of patients were in the chronic phase whereas 5.9% of patients were in the accelerated phase (9).

All the patients (n=102) in our study used imatinib as the first-line of TKI treatments with no regards to the phase of the disease. In IRIS study, only 55% of the patients were remained on imatinib in 8 year follow-up time (15). This highlighted the need for supplementary treatment options for patients who had to switch their imatinib treatments, which led to the development of second-generation TKIs.

In our study, due to several reasons such as side effects, loss of molecular response and patient incompliance; imatinib was switched to dasatinib or nilotinib in 44 patients. In the study carried out by Şahin et al. (9), 90.8% of patients had to have their imatinib treatment altered due to their loss of molecular response and 9.2% had it altered due to drug intolerance. In comparison, 44.11% of the patients in our study had to switch their imatinib treatment due to inadequate response, side effects or their incompliances.

The study conducted by Russo et al. (17) with 82 CML patients, 34 had nilotinib and 48 of them had dasatinib as their second line TKIs, with prior TKI being imatinib in all patients. In the previously-mentioned Turkish CML study, the first choice after imatinib treatment in 194 patients was dasatinib, in 138 patients the first choice was nilotinib and 114 patients had to use both nilotinib and dasatinib during their treatment (9). In our study, out of 44 patients who had to switch first-line TKI treatment, 17 of them had dasatinib and 26 of them had nilotinib as a part of their second-line TKI treatment. Nine of the patients receiving second-line TKI treatment had their treatment switched due to generated side effects, 12 of the patients as a result of a loss in molecular response, 2 of the patients because of incompliances and 1 of the patient had to switch their treatment due to refraction.

Comparing our data concerning the distribution of third-line TKI treatments, while 3 out of 21 patients in our study used bosutinib as their third-line TKI treatment; in the study of Khoury et al. (18) 115 out of 118 patients used bosutinib in third-line TKI treatment. Moreover, 10 patients in our study used nilotinib and 8 patients used dasatinib.

Furthermore, 83 patients enrolled in our study had an MMR following their last treatments where 17 patients had less than MMR. In the IRIS study, patients who had been assigned to take imatinib had a 10-year MMR rate of 93% (15). In the study conducted by Şahin et al. (9) evaluation of molecular response was not carried out due to a lack of available data in the majority of patients.

In a median total follow-up time of 86 (88.2%) months, total number of 12 patients was found to be deceased, where 7 deaths were associated with CML and 5 deaths were non-CML-related. Causes of CML-related deaths are included but not limited to cardiac complications, blastic transformation, incompliance with treatment plans. In the IRIS study, for the patients who had been assigned to use imatinib, the estimated survival rate was 83.3% (15).

The main limitations in our study were the lack of data in molecular (RT-PCR and BCR-ABL1), cytogenetic (FISH) and hematologic responses in the following 3rd, 6th and 12th months of patients' treatment, which are highly important in making decisions when to switch their treatments with the addition to planning future treatment strategies. Our study also lacks the patients' clinical risk scores such as Sokal, Hasford and EUTOS due to the missing data in patients' files.

In conclusion, CML is a myeloproliferative neoplasm which is seen mostly in older adults. As our study showed, first line treatment with imatinib may not be enough for some of the patients to recover and therefore different TKIs such as dasatinib, nilotinib, bosutinib, and ponatinib are being used in the treatment of CML. Inadequate response, drug side effects and incomplian-

ces are the causes of switching the drug choice. Further studies are needed to thoroughly reveal the epidemiology and treatment regimens.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TUTF-BAEK2019/359).

Informed Consent: Informed consent was obtained from all subjects.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: FEA, BK, BT, HOK Supervision: FEA, BK, BT, HOK Resources: FE, BK, BT, EİA, VB, HOK Materials: FEA, BK, BT, EİA, VB, HOK Data collection and/or processing: FEA, BK, BT, EİA, VB, HOK Analysis and/or Interpretation: FEA, BK, BT, HOK Literature Search: FEA, BK, HOK Writing Manuscript: FEA, BK, BT, HOK Critical Review: FEA, BK, BT, HOK

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TMSJ
CASE REPORT

EFFECTIVENESS OF PET/CT IN EVALUATION OF THE LYMPHOMA

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ABSTRACT

Aims: Prognosis and survival of Hodgkin lymphoma have been improved dramatically by the development of treatments as well as the sensitivity of evaluation tools. In this case report, we aimed to emphasize the importance of positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography in the initial staging of Hodgkin's lymphoma, evaluating the response to treatment, and to demonstrate residual tissue or recurrence. ***Case Report:*** A 25-year-old male patient presented to Trakya University Hospital with swelling in the right groin and was diagnosed with Hodgkin's lymphoma. Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography scan was used for initial staging and assessment of response to treatment. ***Conclusion:*** Positron emission tomography is a feasible imaging modality for the evaluation of lymphomas. It is sensitive to detect minimal recurrence as well as alterations of lesions' metabolic activity. ***Keywords:*** Positron emission tomography, lymphoma, hodgkin disease

INTRODUCTION

Lymphoproliferative disorders are classified as Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) based on the histopathological as well as clinical features (1). Hodgkin's lymphoma generally originates from a single lymph node, especially cervical or mediastinal lymph nodes and it is expected to progress to adjacent lymph nodes in a localized fashion. The prevalence of HL is observed in two age groups, first, between the ages of 20-40 years and the second at 50 years and over (2). Histological feature of HL is characterized with featured cells which are called Reed-Sternberg cells on a background rich with inflammatory cells. The most common subtype is the nodular sclerosing type that contains fibrous bands within the involved lymph node (1).

The diagnosis of all lymphoproliferative disorders is based on the pathological assessment of the involved tissue, obtained preferably with excision of the whole lymph node (3). Pre-treatment staging is paramount due to the decision of the length of treatment and the evaluation of the response. The whole-body metabolic scan is the choice to treatment with advantages including the sensitivity of the metabolic status of the lesions as well as the lack of radio-contrast medium requirement (3). Positron Emission Tomography/Computed Tomography (PET/CT) can perfectly and sensitively estimate the whole-body tumor burden (4).

Staging is based on revised Ann Arbor system and it consists of 4 stages; stage 1 and 2 are considered as a limited disease and stage 3 and 4 are known as advanced disease. In stage 3, there was dissemination in both sides of the diaphragm and in stage 4, there was extranodal involvement including non-lymphoid tissues and bone marrow (5). Internationally accepted and suggested treatment of HL is a combination of 4 individual cytotoxic drugs, abbreviated as Adriamycin-Bleomycin-Vincristine-Dacarbazine (ABVD) regimen which has been proven to be effective in approximately 80% of patients regardless of the stage (5). As HL is a fluorodeoxyglucose (FDG)-avid lymphoma, PET/

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CT changed the staging up to 44% of the lymphomas and 62% of the first-line treatment (3, 6, 7). FDG/PET imaging has a value of showing both nodal and extranodal involvement, especially in the evaluation of liver, spleen and bone marrow. CT and Magnetic Resonance Imaging (MRI) have been replaced with the introduction of PET/CT (6, 8).

In advanced-stage patients, response evaluation is suggested after the completion of 2 cycles of treatment while in early stage patients, it is suggested to be performed after the completion of 4 cycles. Subocz et al. (9) reported that after two to three ABVD chemotherapy cycles, the sensitivity and specificity of transient PET were reported as 81% and 97%, respectively. Post-treatment follow-up is in the first 2 years, every 3 months; the next 3 years, every 6 months, then annually, but it may be longer if there is no clinical evidence of disease or absence of any complaints and may be performed with a physical examination alone to avoid further radiation exposure and left to clinician's discretion (2). Although routine PET/CT examination is not recommended during follow-up, PET/CT scanning can distinguish between active tumor and necrosis or fibrosis in residual masses (10). The negative predictive value of PET/CT, or the ability of a negative scan to exclude persistent disease or future relapse, averages 80 to 90 percent (11).

The aim of this case report is to present a 25-year-old male patient with HL and emphasize the role of PET/CT in both the staging and the treatment process.

CASE REPORT

A 25-year-old male patient presented with a non-tender and painless growth in the right groin which he incidentally noticed. He did not report any previous medical illness and his physical examination showed generalized lymphadenomegalia in the cervical, axillary and inguinal regions. Ultrasonographic evaluation of lymphatic stations demonstrated lymphadenomegalias with obliterated fatty hilum and thickened cortex.

The whole-body CT was performed. Bilateral cervical, mediastinal, abdominal and inguinal lymphadenomegalies and sclerotic lesions in right iliac bone were observed. A hypodense lesion in the spleen with a diameter of 4.5 cm and a nodular lesion in the liver with a diameter of 3.5 cm were observed (Figure 1). Excisional biopsy was performed and the patient was diagnosed with nodular sclerosing type Hodgkin lymphoma.

The staging was performed with 18F-FDG PET/CT. The largest lymph node was 2.3 cm with SUVMax (PET/CT Standardized Uptake Values) of 13.7 gr/ml.

Increased diffuse metabolic activity was observed in the entire vertebral column, bilateral proximal head of humerus and femur, and bilateral iliac crest. A single focal uptake in the left patella was regarded as a benign process. The patient was classified as Stage IV ES (extranodal splenic involvement) according to the revised Ann Arbor system. ABVD treatment was commenced.

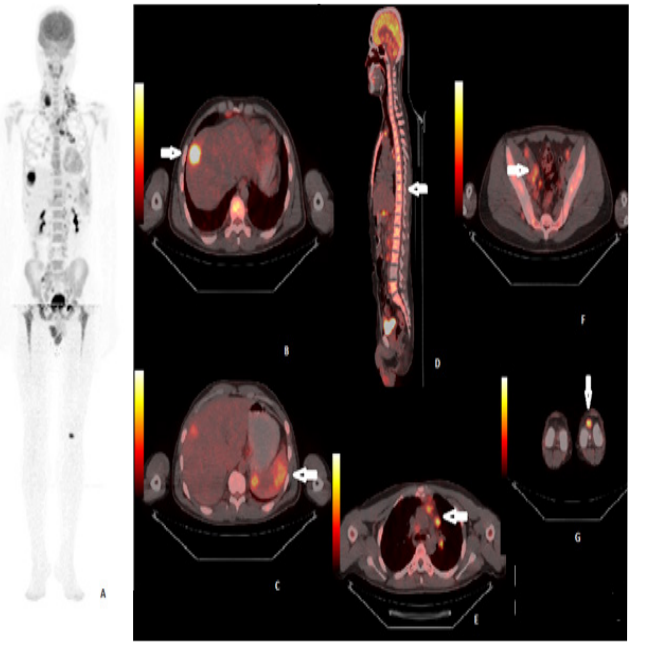

Figure 1: The whole-body PET/CT: A) Maximum intensity projection (MIP) images, B) liver lesion, C) splenic lesion, D) vertebral colon uptake, E) mediastinal lymph node involvement, F) pelvic lymph nodes, G) focal patellar uptake (white arrows).

After 2 cycles of treatment, the patient was re-staged with interim 18F-FDG PET/CT and bilateral supraclavicular, pretracheal lymph nodal involvement and nodular lesion with a substantial metabolic activity within the spleen were observed (Figure 2). This response was regarded as a partial response to the first-line treatment.

After the completion of the 6th ABVD cycle, the patient was re-evaluated. Increased metabolic activity was observed in the right antero-cervical and supraclavicular lymph nodes with bilateral paratracheal lymph nodes (Figure 3). The patients was accepted as non-responsive, and salvage treatment with cisplatin, high dose Ara-C and dexamethasone (DHAP) for 2 cycles was commenced.

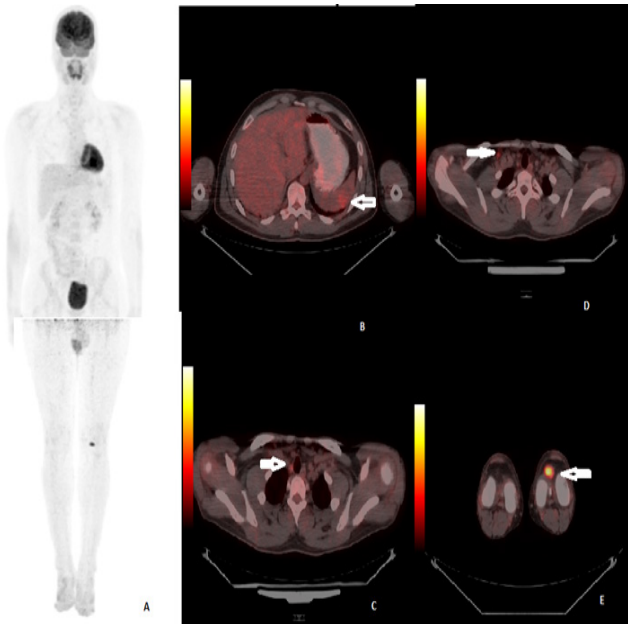

Figure 2: Interim PET/CT scans after 2 cycles of first-line treatment: A) MIP images, B) splenic lesion, C-D) lymph nodes, E) focal patellar uptake (white arrows).

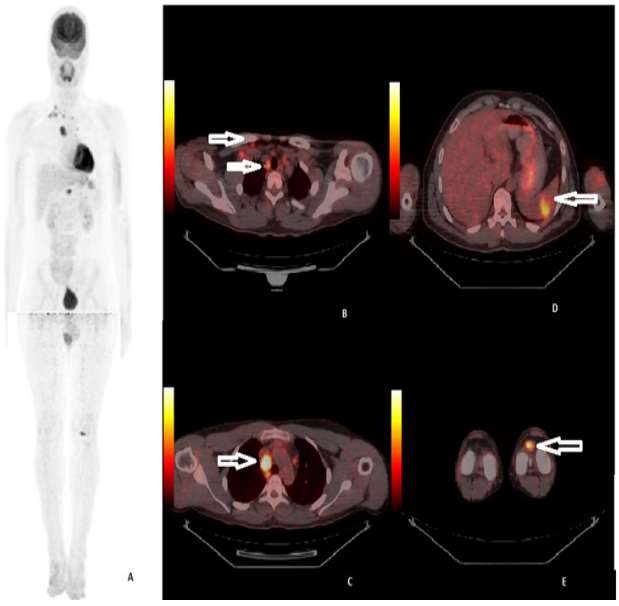

Figure 3: 18 FDG PET/CT after 6 cycles of ABVD treatment A) MIP images, B-C) multiple lymph node involvement, D) splenic lesion, E) focal patellar uptake (white arrows).

After salvage treatment, a remaining lesion in the spleen was observed and regarded as a partial response to gemcitabine-irinotecan and sequential 2 cycles of brentuximab vedotin treatment was selected for bridging to autologous stem cell transplantation (Figure 4).

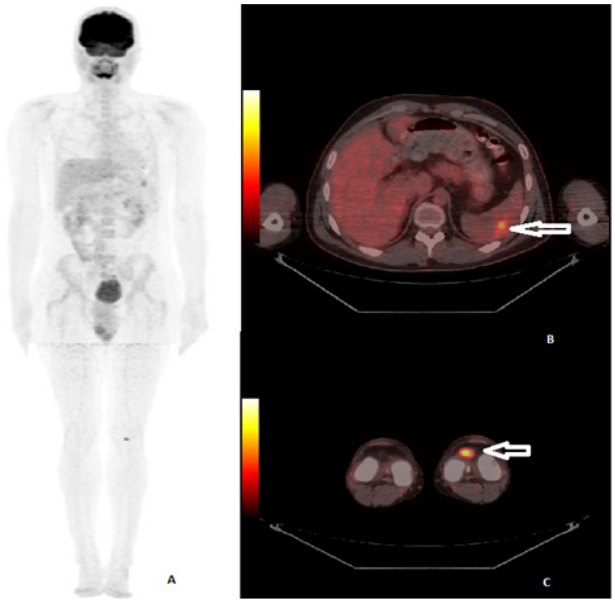

Figure 4: 18F-FDG PET/CT scan after gemcitabine-irinotecan treatment A) MIP images, B) splenic lesion (white arrows).

The patient was re-evaluated with 18F-FDG PET/CT after autologous stem cell transplantation and complete remission status was observed.

Two years later, the patient was re-scanned with 18F-FDG PET/CT for the newly developed lymphadenomegalies detected during follow up examination. Subtle metabolic activity was observed in the cervical region, suggesting an inflammatory condition (Figure 5).

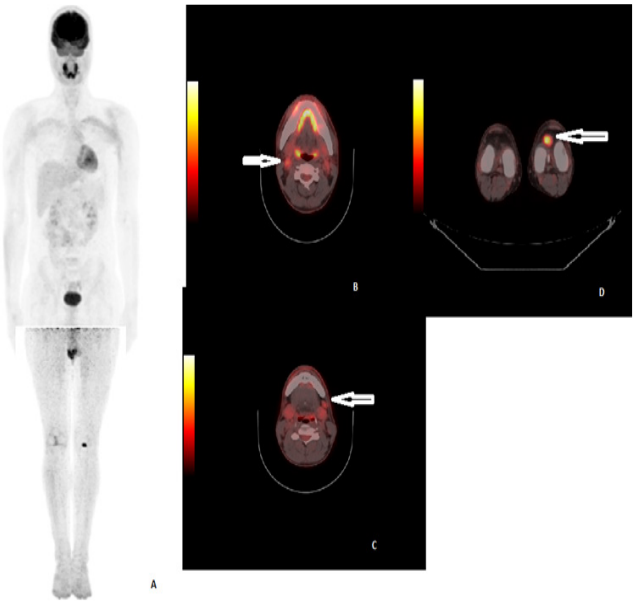

Figure 5: 18F-FDG PET/CT scan 2 years after transplantation A) MIP images, B) right deep jugular lymph node, C) left submandibular lymph node, D) focal patellar uptake (white arrows).

In 2016, the patient was re-scanned with 18F-FDG PET/CT. FDG uptake in the bilateral jugular, left submandibular, right posterior triangle lymph nodes and bilateral external–internal iliac lymph nodes were observed and regarded as inflammatory (Figure 6).

He was followed up frequently with physical examinations, biochemistry tests, and ultrasonography; considering he was on remission.

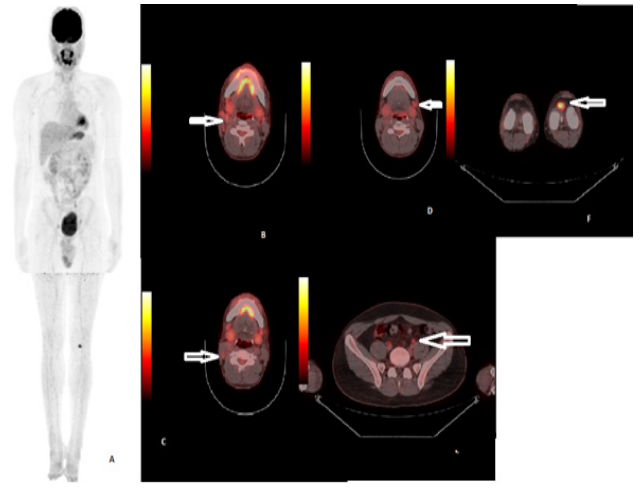

Figure 6: Latest 18F-FDG PET/CT scan A) MIP images, B-C-D-E) multiple lymph nodes, F) focal patellar uptake (white arrows).

DISCUSSION

This case is an example of the utility of PET/CT in HL. In this case, we showed that PET/CT is a highly sensitive evaluation tool in HL combined with clinical assessment.

In our case, post-treatment PET/CT showed that the patient did not response to the first-line therapy. After that the patient has gone under second-line therapy and autologous stem cell transplantation. The patient was re-evaluated with 18 F-FDG PET/CT and complete remission status was observed. As we know from the Hodgkin Lymphoma Diagnosis and Treatment Guide, Turkish Hematology Association; PET/CT leads us to choose the appropriate therapy regimen (2).

PET/CT is widely used for treatment evaluation, detecting recurrence and relapses (10). It can also be used for the follow-up period, if there is any suspicion of the recurrence.

The importance of PET/CT in the assesment of lymphoma has increased significantly. Clinicians should acknowledge the advancement of PET/CT and its value in the assesment of lymphoma.

Ethics Committee Approval: N/A

Informed Consent: Informed consents was obtained from the patient for this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: GDA, Supervision: BÖ, Materials: GDA, Data collection and/or processing: BÖ, Analysis and/or Interpretation: GA, Literature Search: GA, Writing Manuscript: BÖ, Critical Review: GA.

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CASE REPORT

GASTROINTESTINAL TRACT MULTIPLE LYMPHOMATOUS POLYPOSIS PRESENTED AS MANTLE CELL LYMPHOMA

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ABSTRACT

Aims: Mantle cell lymphoma is a mature B cell non-Hodgkin lymphoma which may be presented with the involvement of the gastrointestinal tract as multiple lymphomatous polyposis. The aim of this case report is to increase the awareness of including lymphomatoid polyposis as an entity in the differential diagnosis of multiple polyposis of the gastrointestinal tract. ***Case Report:*** A 69-year-old male patient was admitted to the Trakya University Emergency Department with acute abdominal pain. His clinical findings were anorexia that started 3-4 months ago together with constipation and nausea causing him to lose 10-15 kg in 7-8 months, with denial of other parameters of B-symptoms (fevers and night sweats). Endoscopic biopsies that were taken from bulbus and duodenum were investigated and he was diagnosed with mantle cell lymphoma. The patient went through an ileocecal resection due to his intussusception that caused abdominal pain in the first place. ***Conclusion:*** Although being an infrequent disease, gastrointestinal lymphomatoid polyposis should be an entity comprised in differential diagnosis for multiple polyposis of the gastrointestinal tract. On the other hand, there is still not a therapeutic protocol with a definitive cure for gastrointestinal tract mantle cell lymphoma. Elderly patients in high risk group such as our patient should be given treatment by taking their conditions into consideration. ***Keywords:*** Mantle cell lymphoma, polyp, non-Hodgkin lymphoma

INTRODUCTION

Within large group non-hodgkin lymphomas (NHL) mantle cell lymphoma (MCL) is an infrequent type of B-cell NHL in the World Health Organization (WHO) classification, accounting for nearly 5–10% of all lymphoid malignancies (1). Primarily occurring in elderly males with a mean age of 65-75 years. MCL has an incidence of 2–3/100.000 per year (1).

Most patients are diagnosed with advanced disease (Ann Arbor stage III/IV) presenting with hepatosplenomegaly, extensive lymphadenopathy, and bone marrow involvement, with some additionally having extranodal involvements including the gastrointestinal (GI) tract, lacrimal glands, central nervous system and skin (2-6). Patients can also exhibit pancytopenia or have a leukemic presentation with massive leukocytosis (4).

Overall, GI tract involvement is the most prevalent extranodal involvement among all lymphomas (5). Mucosal involvement of the small bowel or colon displays itself as a polyp-like lesion (lymphomatoid polyposis) (5, 6). Gastrointestinal polyposis, found in up to 10% of cases, comprising a condition such as multiple lymphomatous polyposis (MLP) is an entity defined by the existence of multiple GI polypoid lesions featured in several segments of the digestive tract (7, 8). This case report presents multiple polypoid involvements of the bulbus, ileum, and caecum by aiming to raise awareness of including lymphomatoid polyposis as an entity in the differential diagnosis of multiple polyposis of the GI tract.

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CASE REPORT

A 69-year-old male patient was admitted to the Trakya University Emergency Department with acute abdominal pain. He had a history of anorexia that started 3-4 months ago together with constipation and nausea causing him to lose 10-15 kg (more than 10% of total body weight) in 7-8 months. However, he did not have other B symptoms such as fevers and night sweats. The patient also had a medical history of systemic lupus erythematosus and hypertension. He was a 40 pack-year smoker and an occasional consumer of alcohol. He was later administered to General Surgery Department with a pre-diagnosis of intussusception.

On his abdominal magnetic resonance imaging (MRI) he had bilateral pleural effusion, ascites and multiple nodular infiltrations in his spleen and liver. Starting from the antropyloric region of the stomach extending to the first part of the duodenum, a mass lesion forming a prominent expansion in the posterior region was observed. Intussusception and proximal obstruction at the terminal ileum level were observed in the right lateral side of the abdomen. The patient also had a positron emission tomography (PET/CT), revealing extensive lymph node adenopathy throughout his whole body and had a diffuse heterogeneous uptake in his skeletal system, being more in the proximal bilateral humerus (Figure 1, 2).

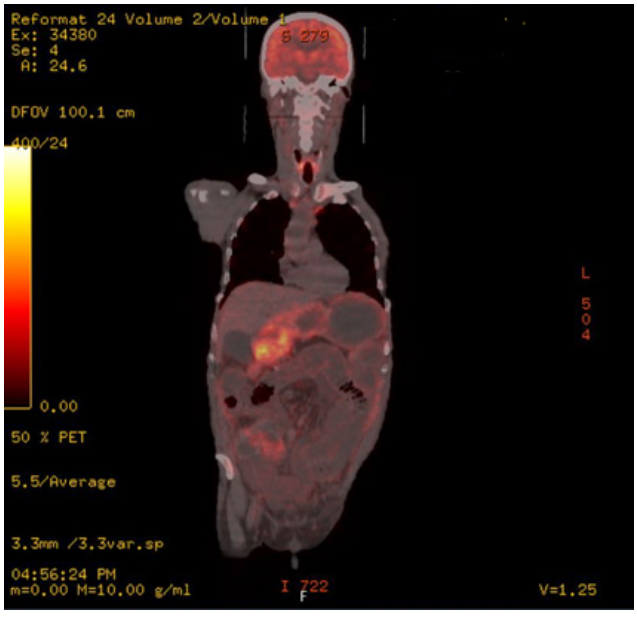

Figure 1: Coronal fused F-18 FDG PET/CT image showing increased FDG uptake throughout the thickened distal gastric wall, in right inferior cervical, bilateral mediastinal and abdominal lymph nodes.

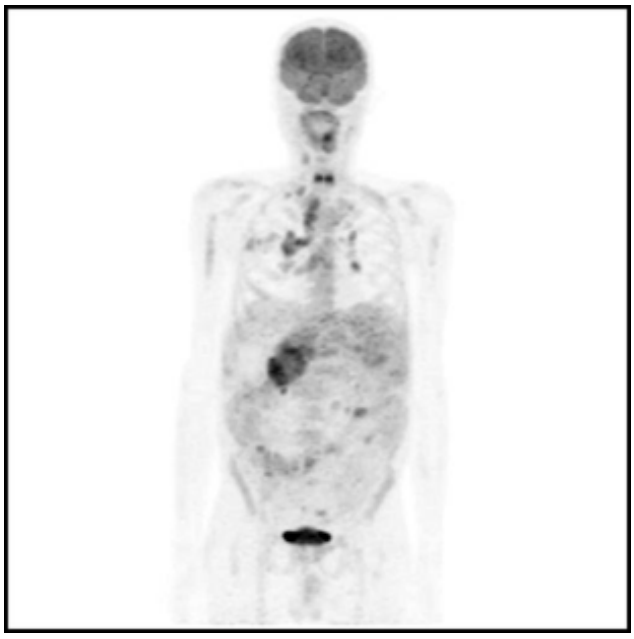

Figure 2: Whole- body MIP (maximum intensity projection) image demonstrating increased FDG uptake in cervical, abdominal and mediastinal lymph nodes, stomach, duodenum, spleen and heterogeneous uptake in the bone marrow.

Endoscopic biopsies that were taken from bulbus and duodenum were investigated by the Pathology department and the patient was diagnosed with MCL. At the same time, the patient urgently went through an ileocecal resection due to his intussusception. Endoscopic samples and resection specimens revealed diffuse infiltration of the intestinal wall by MCL (Figure 3). Immunohistochemical analysis showed positive staining for CD5, CD20, Sox11, and Cyclin D1 and negative for CD10, CD23, blc6, and p53; 70% of tumor cells were found to be positive for Ki-67 (Figure 4).

After his diagnosis, he was directed to Hematology Clinic for his treatment. On account of his clinical staging, bone marrow biopsy was performed and revealed an infiltration of MCL as well. Bone marrow biopsy revealed minimal involvement of MCL with a less than 10% positive staining of Cyclin D1 and SOX-11. Patient's MCL International Prognostic Index (MIPI) score was 7.7, which places him into a high-risk category (9, 10). According to local and international guidelines, his treatment was planned with autologous stem cell transplantation (ASCT) and high dose chemotherapy. The patient's Eastern Cooperative Oncology Group (ECOG) performance status was 3-4 and cardiac status was low to apply an anthracycline

based high dose therapy (11).Due to his performance and cardiac status, the patient received rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) chemoimmunotherapy. It was planned for him to undergo at least three cycles of chemoimmunotherapy with a re-staged evaluation using PET/CT.

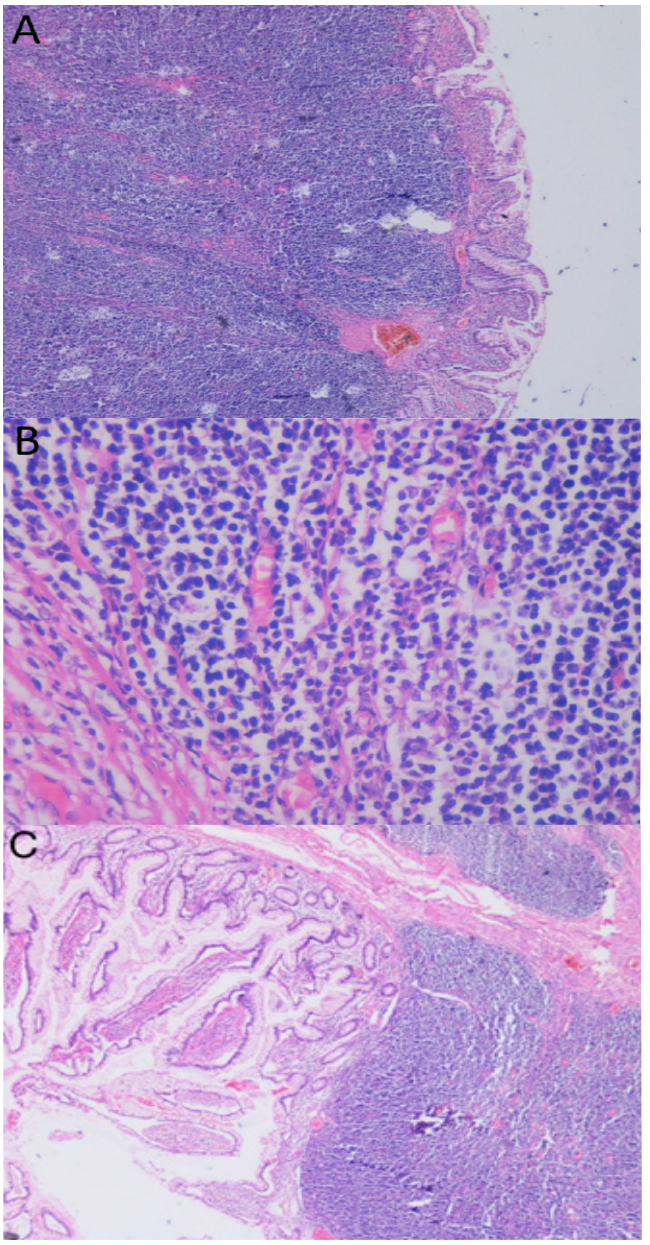

Figure 3: Lymphoid infiltration of tumor cells beneath intestinal mucosa(A: Hematoxyline & eosin stain, x40, B: Hematoxyline & eosin stain, x100), transition zone (C: Hematoxyline & eosin stain, x40).

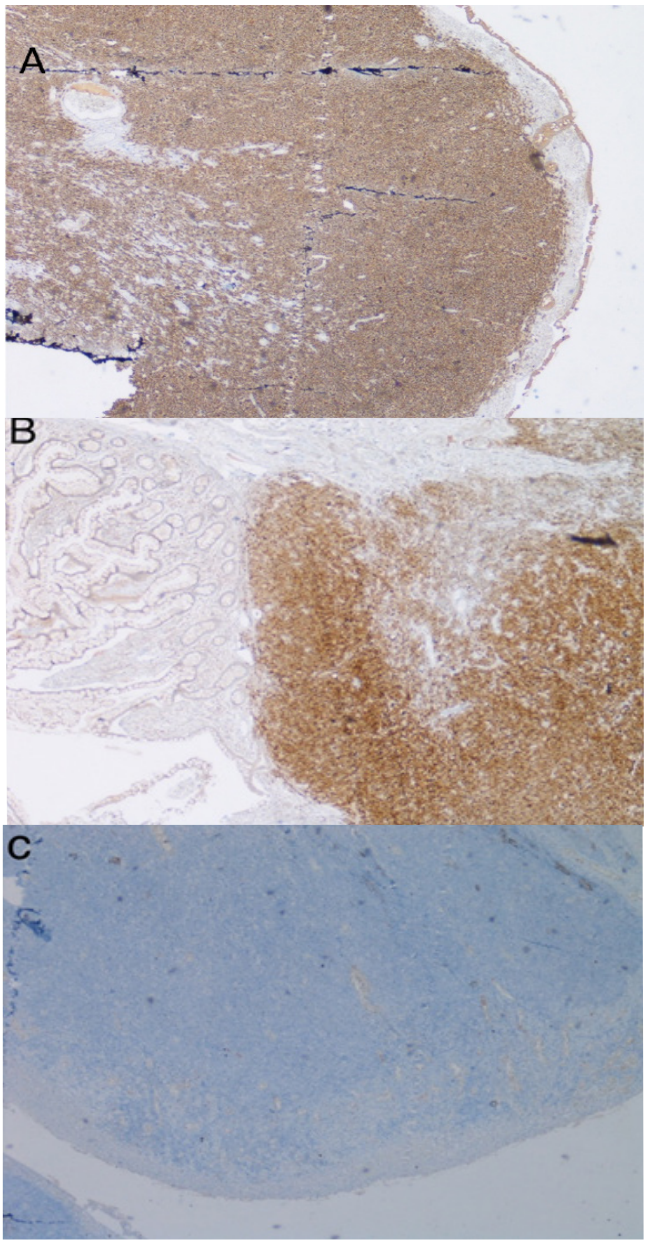

Figure 4: Diffuse positive staining of CD20 (A: Hematoxyline & eosin stain, x40), diffuse positive staining of SOX-11 (B: x40), negative staining of CD23 (C: x40).

DISCUSSION

Multiple lymphomatous polyposis was described by the appearance of diffuse proliferation of atypical lymphocytes accompanied by multiple polypoid lesions throughout GI sites first depicted by Cornes et al. (8) in 1961. The involvement of the GI tract remains ambiguous; however, it has been put forward to be associated with the manifestation of adhesion molecules such as the mucosal homing receptor α4β7 (12, 13).

As the name indicates, malignant cells closely resemble B cells that normally surround the germinal center of the lymph node creating the mantle zone. The molecular pathogenesis is resulting from the chromosomal translocation t(11;14)(q13;q32) catalyzing deregulation of the Bcl-1 oncogene on chromosome 11, causing overexpression of cyclin D1 (13). Immunohistochemistry is used for differentiating MLP from other NHL, in which malignant cells usually express positivity for CD20, CD5 and Cyclin D1 while being negative for CD3, CD10 and Bcl6. Immunohistochemical analysis of our patient showed positive staining for CD5, CD20, Sox11 and Cyclin D1 whereas negative for CD10, CD23, bcl6 and p53.

Having a heterogeneous clinical picture, the most prevalent symptoms of GI MCL are abdominal pain, hematochezia, and diarrhea (5,6). It should be noted that our patient was admitted to the hospital with acute abdominal pain. The differential diagnosis for GI MCL includes hereditary polyposis syndromes adenomatous polyps, colorectal carcinoma, lymphoid nodular hyperplasia, GI lipomatosis, with hypogammaglobulinemia, among others (8). Mucosa-associated lymphoid tissue lymphoma may present as multiple but has lymphoepithelial lesions and is negative for CD5 and cyclin D1.

International prognostic index risk score for mantle cell lymphoma is currently practiced evaluating patients' prognosis, which encompasses the factors of age, leukocyte count, lactate dehydrogenase level (LDH), performance status, and the percentage of Ki-67 dividing patients into high, intermediate, and low-risk categories (15, 16). Our patient was in the high-risk group with a poor prognosis due to his Ki-67 proliferation index of 70% and MIPI of 7.7. Unfortunately, most patients up to 70% are diagnosed at stage IV, with a 29-month survival (10). MCL reported overall survival rate is 3-4 years (10).

The present medical method is primarily based on the patient's clinical risk factors, stage of disease and symptoms. Our patient fits the category of elderly or physically unfit patients who are mainly autologous stem-cell transplant-ineligible. Even though the 'gold standard' therapy for young and fit patients (transplant eligible and <66 years) is a high dose of chemoimmunotherapy accompanied by ASCT, for the elderly patients ineligible for ASCT, conventional chemoimmunotherapy (e.g. R- CHOP) supported by rituximab, seems to be the 'gold standard' (10). Other agents such as Bendamustine, combined with Rituximab (BR) were also used in elderly group patients, however, one study displays a higher incidence of second cancer in the BR group (19%) than the R-CHOP group (11%) (16). Different combinations with agent lenalidomide have been also tested (16, 17). Owing to our patients' low cardiac status he was administered a 3-cycle R-CVP chemoimmunotherapy with a re-staged evaluation using PET/CT.

In conclusion, albeit being an infrequent disease, GI lymphomatoid polyposis should be an entity comprised in the differential diagnosis for multiple polyposis of the GI. On the other hand, there is still not a therapeutic protocol with a definitive cure for GI tract MCL. Elderly patients in high risk group such as our patient should be given treatment by taking their conditions into consideration.

Ethics Committee Approval: N/A

Informed Consent: Informed consents was obtained from the patient fort his study.

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TMSJ
REVIEW

VANILLIN: IS IT JUST AN AROMATIC OR A CURE FOR CANCER?

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ABSTRACT

Abstract: Cancer is one of the most challenging diseases mankind has confronted, and it is listed as the second most common reason of death according to the World Health Organization. Its damage to global economy is valued trillions of dollars and it is increasing day by day. This literature review is aiming to reflect on vanillin's anticancer potential, a natural chemical being used in different industrial areas. Beside flavour, it is a powerful antioxidant and a strong antimutagenic. Oxidative stress and mutations are two major reasons for carcinogenesis. Therefore, the cancer prevention and/or therapeutic potential of vanillin is being investigated. Many studies using different cell lines have noted that vanillin had positive effects on cancer. ***Keywords:*** Cancer, reactive oxygen species, oxidative stress, vanillin

INTRODUCTION

Heretofore, a wide range of organic and inorganic chemicals have been searched to observe their antioxidant effects for cells and antimutagenic potential against the cancer tissue. Among these chemicals, vanillin is an outstanding one that has been researched since the late '80s. Vanillin, 4-hydroxy-3-methoxybenzaldehyde, has always been an economically important flavor of daily lives (Figure 1). It is being used in a wide scale of products, from drinks to perfumes; with different aims to heal wounds, or to increase physical performance since the 14th century. Until the late '80s, vanillin was not a center of focus as a chemical of modern medicine and oncological pharmacology. A study by Ohta et al. (1) changed the perspective to vanillin rapidly. In this study, vanillin's antioxidant effects, as well as antimicrobial and anti-inflammatory potential, were mentioned and lead up to new clinical usages of vanilin (2-4). Since the publication of the forenamed article, vanillin has influenced cancer research and treatment modalities.

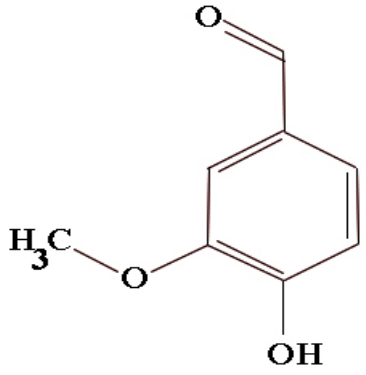

Figure 1: Chemical structure of 4-hydroxy-3-methoxybenzaldehyde.

According to the World Health Organization (WHO) data, in 2018 alone, 18.1 million people were diagnosed with cancer and 9.9 million people died of this disease. While the global cancer bill was estimated to rise to $1.5 trillion in 2018, the United States made the most cancer related spendings with $90 billion (5).

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The formation of normal cells into tumor cells in multiple steps causes cancer. Various genetic and epigenetic related factors such as mutation, chromosome aberration, nuclear exchange, and exogenic stress factors like tobacco and/or alcohol use, radiation can start this formation (5, 6). Most of the stages causing this formation are still unknown, but studies have shown that reactive oxygen species (ROS), namely hydrogen peroxide (H2O2), hydroxyl radical (HO•) and superoxide anion (O2–) have a major role in cancer's exhibition, also known as malignancy (7). ROS are produced as endogens in every cell as the result of mitochondrial oxidative metabolism and each cell has its compensation limit called "ROS scavenging capacity". In the case of exceeding this limit, the cellular antioxidant defense system remains incapable and that leads to cellular oxidative stress. As a result, chemical stress factors can damage mitochondrial deoxyribonucleic acid (mtDNA) and nuclear deoxyribonucleic acid (nuclear DNA). It can also cause lipid peroxidation, and reversible or irreversible modifications of cellular proteins. It is well known that mtDNA is more sensitive than nuclear DNA to oxidative conditions (8). However, the effect of mtDNA mutation on the development of pseudo-hypoxic conditions and creation of metastatic potential have not been explained thoroughly yet (9). The latest studies demonstrated that abnormality in citric acid (Krebs) cycle, which creates more ROS than the ROS-suppressing machinery can compensate, is originated from nuclear DNA mutation, not mtDNA mutation. This mutation pushes the cell to work like, there is a hypoxic environment even in normal conditions, and this process controls the tumor's aggressiveness (10).

REACTIVE OXYGEN SPECIES AND THEIR ROLES IN CANCER DEVELOPMENT

Reactive oxygen species are highly reactive molecules, usually produced by the aerobic respiratory system in all aerobic organisms. Molecular oxygen (O2), the terminal receiver of electron transport chain (ETC), is an unreactive molecule compared to ROS. ROS definition includes different kinds of radicals, also known as free radicals, and described as molecules which have unpaired electrons (11). Hydrogen peroxide (H2O2), hydroxyl radical (HO•) and superoxide anion (O2–) are the examples of ROS molecules produced by aerobic respiratory mechanisms (12). Aerobic organisms use mitochondria, ETC to produce enough adenosine triphosphate (ATP) to maintain vital activities. In this aerobic process, electrons pass through different complexes until they reach O2, but electron leakage results in excessive O2- production (13). In addition to the aerobic mechanism and nicotinamide adenine dinucleotide phosphate oxidases (NOX), which are the two major endogenous ROS sources, different ROS sources can also cause ROS activities in organism (14). Exergonic sources such as ionizing radiation, drugs, lipoxygenases, cytochrome p450, peroxisome, and inflammatory cells are the additional ROS sources to the aerobic respiratory system (15).

It is well known that ROS and cellular redox changes have major roles in the development of carcinogenesis and various diseases since they have been held responsible for having a significant impact on hemostatic cellular signaling pathways (16). H2O2, one of the major ROS molecules, is a fundamental component of epidermal growth factor, angiotensin II and platelet-derived growth factor as intracellular messengers. Messenger effects of H2O2 were noticed with specific inhibition of it in A431 human epidermoid carcinoma cells (17). ROS molecules' production in high levels and oxidative stress in the cells are defined as characteristic features of the carcinoma with in vivo and in vitro studies (12, 15, 16). Hypoxia starts the butterfly effect. Butterfly effect defines major changes caused by very small changes at the beginning of the situation. This butterfly effect continues with macrophage infiltration into the tumor and followed by an oxidative upsurge in the damaged vascular tissue at the reperfusion phase (18).

In 1970, Cameron et al. (19, 20) have published two studies about antioxidants' effects on cancer. He substantiated this relation with applying intravenous ascorbic acid, an important antioxidant, in patients with terminal period cancer, and noted clinical improvement. Sabharwal et al. (21) also pointed out that, ROS promote cancer cells' proliferation and survival in rat models and cell lines. Therefore, if ROS are causing carcinogenesis, it should be prevented by antioxidants. However, some studies have turned the tables. In these studies, dietary supplemented antioxidant, N-acetylcysteine (NAC), has accelerated the tumorigenesis and mortality in v-raf murine sarcoma viral oncogene homolog BV600E or Kirsten rat sarcoma viral oncogene G12D induced lung cancer model in mice (22). NAC has also accelerated tumorigenesis in melanoma human xenografts (23). Different antioxidants have been tried in different cancer types such as colorectal, prostate, lung, head and neck, but it was noted that applied antioxidants like ß-carotene, NAC, vitamin A or ascorbic acid have not caused progress in treatment of these cancer types, on the contrary accelerated the mortality in used cancer models (24).

VANILLIN

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a natural aromatic used in various industrial areas like food, perfumes, and medicines. It grows in the pods of Vanilla planifolia (25, 26). Vanillin is one of the most studied antimutagenic and antioxidant chemicals over the past three decades, thanks to the study of Ohta et al. (1). Vanillin has also shown antimutagenic effects on X-ray, ultraviolet light, methylmethane sulphonate and mitomycin C induced mutations in mammalian cells (27). Although antimutagenic effects have been shown in studies, this effect does not always occur. On N-methyl-N'-nitro-N-nitrosoguanidine induced mutations, vanillin has shown no significant antimutagenic effects (28). This contradiction is based on different repair pathways to overcome different mutagenic effects. For example, ROS scavenging and non-homologous end joining, and recA-dependent recombination repair enhancement is shown as one of them (29).

Besides vanillin's effective antimutagenic ability, its antioxidant abilities are not outstanding. It has weak O2- scavenging activity, and also its effect on lipid peroxidation has been undefined (30). In different studies, different assays were used to control the antioxidant effects of vanillin but some specific assays showed negative results whilst some showed positive. It has shown negative results in 1,1-diphenyl-2-picrylhydrazyl radical scavenging, carotene decolorization, and cholesterol oxidation and linoleic acid assays (31). However, its lipid peroxidation and protein oxidation inhibiting activities against the HO• in rat liver were positive (32). It also showed strong antioxidant activity against peroxynitrite-mediated reactions, and inhibited DNA-dependent protein kinase of cancer cells (33).

VANILLIN AND CANCER

Reactive oxygen species' effects on cancer formation was discussed in detail before. It is known that ROS and genetic mutations are the main reasons for cancer formation. Since vanillin has the antioxidant ability in suitable conditions and an efficient antimutagenic ability, its anticarcinogenic and anti-metastatic abilities were an area of interest. Different cell lines have been used and different parameters have been researched.

Many organisms have developed different mechanisms to survive from hypoxia and the hypoxia-inducible factor 1 (HIF-1) gene is one of these mechanisms. This gene can interact with transcription factors and enzymes to control tissue development and vascularity (34). This adaptation to hypoxia is also used by the tumor microenvironment and accelerates the tumor's development. Park et al. (35) used A2058 and A375 malignant melanoma cells and investigated the effects of vanillin. They have noted that vanillin has no significant effects on cell viability under hypoxic conditions. However, vanillin has had a major effect on HIF-1α metabolism. It has suppressed HIF-1α accumulation due to hypoxia. Whilst inhibiting the HIF-1α, no A2058 and A375 cytotoxic effects have noted. It suppresses the HIF-1α accumulation pathway in the nucleus and also decreases HIF-1α protein levels, not only transcriptional factors (35).

Lirdprapamongkol et al. (36) have noted the positive effects of vanillin on tumor growth and metastasis suppression by tamoxifen comparison. Tamoxifen is a highly effective chemotherapeutic used to prevent or treat breast cancer. It binds to the estrogen receptor and prevents mammalian cell's proliferation by a complicated mechanism (37). At 4T1 cell line used in vivo studies, vanillin has decreased the number of tumor colonies in the lungs whilst tamoxifen has shown no effect (36). Despite vanillin's positive result at fighting with metastasis, vanillin and tamoxifen have not shown any significant effect on primer tumor growth (37).

A colon cancer cell line, HCT-116 carries a mutation in KRAS proto-oncogene. King et al. (38) have reported the positive effect of vanillin at repairing various mutations in the HCT-116 cell line. Furthermore, study of the Ho et al. (2) confirmed this profound anti-mutagenic effect of vanillin on human colon cancer. HT-29 is also a human colon adenocarcinoma cell line (39). Ho et al. (2) noted that vanillin against HT-29 cells showed cytolytic and cytostatic effects. Vanillin's half-maximal inhibitory concentration (IC50) was 400 μg/ml against HT-29 cells (2).

DISCUSSION

Many different therapies have been tried to cure cancer. The combined procedure of surgery, chemotherapy, and radiotherapy is the standard procedure of cancer treatment, but 5-year and 10-year mortality rates are showing us that this standard procedure and different drug therapies are not enough to fight against cancer. To increase the success rate, different therapy methods have been developed. For this aim, multiple plants and their products have been tried with different chemotherapeutics. The potential synergistic effects and decreasing toxicity against the healthy cells of these molecules with drugs are the most important parameters in these researches. Vanillin, the focal point of

this literature review, is not a major molecule in cancer research area but previous studies, which have a small part in cancer studies, have promising results. Its anti-oxidant and antimutagenic effects were studied and exemplified with different studies from the literature. Even the lack of up-to-date studies was a major problem while writing this review, cited articles were briefly showing the aforementioned positive effects against carcinogenesis.

CONCLUSION

Vanillin is a promising molecule with its antioxidant and antimutagenic abilities. In the rapidly developing cancer research area, vanillin's effects with other drugs or alone should be researched and new studies should be made to expose the vanillin's potential against carcinogenesis.

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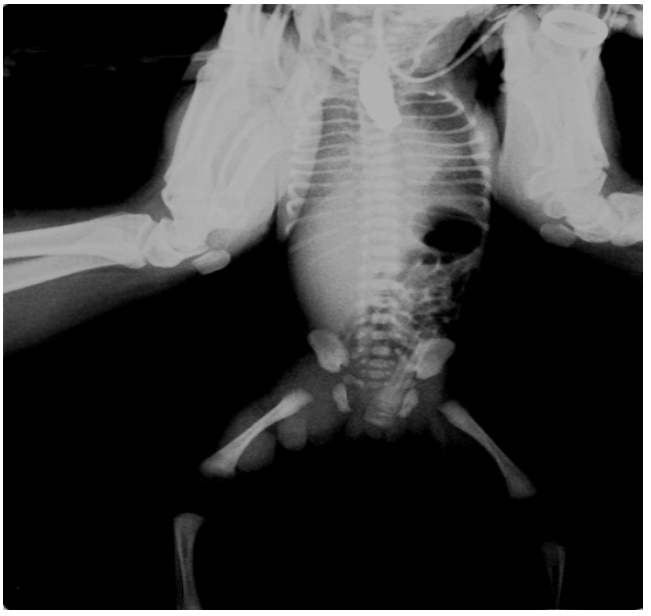
RETRACTIONS & ERRATA

Date: 2019, October

Errata

In the article by Mutlu et al., entitled "A Newborn With Esophageal Atresia, Tracheoesophageal Fıstula And Feeding Problems" (Turkish Med Stud J 2019:6(2);60-3.) Figure 1 was reflected on the y axis by mistake and caused a misunderstand like the patient had situs inversus. The figure is corrected as follows:



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3. All authors are responsible for approval of the final proofs of the article
4. Those authors who do not fulfill the required number of contributions or do not meet criteria should be listed in the Acknowledgement section at the end of the manuscript.
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Contribution	Explanation	Contributing Authors
CONCEPT	The idea for research or article/hypothesis generation	
DESIGN	Planning the methods to generate hypothesis	
SUPERVISION	Supervision and responsibility for the organization and course of the project and the manuscript preparation	
RESOURCES	Supplying financial resources, equipment, space, and personnel vital to the project	
MATERIALS	Biological materials, reagents, referred patients	
DATA COLLECTION AND/OR PROCESSING	Responsibility for conducting experiments, management of patients, organizing and reporting data	
ANALYSIS AND/OR INTERPRETATION	Responsibility for presentation and logical explanation of results	
LITERATURE SEARCH	Responsibility for conducting literature search	
WRITING MANUSCRIPT	Responsibility for creation of an entire or the substantial part of the manuscript	
CRITICAL REVIEW	Reworking the final, before submission version of the manuscript for intellectual content, not just spelling and grammar check	
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TMSJ Form for Disclosure of Potential Conflicts of Interest

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receiv and understand your work. The form is designed to be completed electronically and stored electronically. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information.
* The form is in four parts.

1. Identifying information.
Type your full name. If you are NOT the corresponding author please check the box "No" and type the name of the corresponding author. Provide the requested manuscript information.
*If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare under Sections 2, 3, or 4 below, you can check "Nothing to disclose" (see Section 1, line 7, page 2). In this case only, the disclosure applies to all authors, and the form is complete.

2. The work under consideration for publication.
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party—that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation, or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work.
Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. I there is any question, it is usually better to disclose a relationship than not to do so.
For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations, or academic institutions, need not be disclosed here (but can be acknowledged on the title page of the manuscript). For example, if a government agency sponsored a study in which yo have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships.
Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
*If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare under Sections 2, 3, or 4 below, you can check "Nothing to disclose" (see Section 1, line 7, page 2). In this case only, the disclosure applies to all authors, and the form is complete.

Section 1. Identifying Information
Complete by providing the requested information in the white boxes.

1. Given Name (First Name):		2. Surname Last Name):		3. Current Date:	
4. Are you the corresponding author?	___Yes	___No	If "No", name of corresponding author:		
5. Manuscript Title:					
6. Manuscript Identifying Number (if you know it):					
7. If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare, check here:				___**Nothing to Disclose**	

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information in the white boxes. Add rows as needed.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Grant					
2. Consulting fee or honorarium					
3. Support for travel to meetings for the study or other purposes					
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like					
5. Payment for writing or reviewing the manuscript					
6. Provisions of writing assistance, medicines, equipment, or administrative support					
7. Other					

*This means money that your institution received for your efforts this study.

Section 3. Relevant financial activities outside the submitted work.

Please indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information in the white boxes.

Relevant Financial Activities Outside the Submitted Work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Board membership					
2. Consultancy					
3. Employment					
4. Expert testimony					
5. Grants/grants pending					
6. Payment for lectures including service on speakers bureaus					
7. Payment for manuscript preparation					
8. Patents (planned, pending or issued)					
9. Royalties					
10. Payment for development of educational presentations					
11. Stock/stock options					
12. Travel/accommodations/ meeting expenses unrelated to activities listed**					
13. Other (err on the side of full disclosure)					

*This means money that your institution received for your efforts.

**For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

____No other relationships/conditions/circumstances that present a potential conflict of interest.

____Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, we ask that you update your disclosure statements if anything has changed. On occasion, we may ask you to disclose further information about reported relationships.

This form is adapted from the Author Disclosure Form created by the International Committee of Medical Journal Editors (ICMJE). The ICMJE has not endorsed nor approved the contents here. The official version of the ICMJE Author Disclosure Form is located at http://www.icmje.org/coi_disclosure.pdf

CONSENT FORM for CASE REPORT

Title of Project:_____

1. I have read, and understood the Participant Information Sheet dated _____
2. I freely agree to the use of my medical records for the purpose of this study.
3. I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.
4. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant_____

Signature of Participant _____ Date _____

The participant was informed through phone call and a verbal consent was obtained.

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure.

Name of witness (if appropriate)_____

Signature of witness_____ Date _____

Name of Researcher_____

Signature of Researcher_____ Date_____

Name of Researcher

Signature of Researcher_____ Date_____