erythroblasts. **C)** Binucleate erythroblasts **D)** Multinuclear eryhtroblasts.

**Table 2 – Results of NGS analysis: Homozygous variant of CDIN1 gene was detected. (AR: Autosomal recessive, CDIN1: congenital dyserythropoietic anemia type 1, PRF1: perforin 1, TAF6: TATA-Box Binding Protein Associated Factor 6)**

| Gene transcript | Position | Inheritence | Genotype |
|---|---|---|---|
| CDIN1 | Chromosome 15 | AR | Homozygous |
| PRF1 | Chromosome 10 | AR | Heterosygotic |
| TAF6 | Chromosome 7 | AR | Heterosygotic |

**Table 3 – Cytogenetic analysis of the patient: With the cytogenetic analysis of the patient, tetraploid chromosome formation was detected in 17 of 18 of the metaphases as 92XXXX. (DEB: clastogenic effect of diepoxybutane, G6PD: Glucose-6-Phosphate Dehydrogenase)**

| | | | |
|---|---|---|---|
| Chromosomal analysis | 92,XXXX | TP53 deletion | %85 |
| Del20q12 | %85 | Del7q31.2 | %83 |
| Del5q31.2 | %85 | Tetrasomy7/tetrasomy8 | %85 |
| DEB | %0 | G6PD | 20,3 ıu/g Hb (normal) |
| Pyruvate kinase | 397,9 (normal) | Osmotic Fragility of Erythrocytes | Normal |

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OP 18

## DETERMINATION OF FREQUENCY AND RISK FACTORS OF SECONDARY MALIGNANCY DEVELOPMENT IN HEMATOLOGICAL MALIGNANCIES

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**Objective:** Cancer remains a significant challenge within the healthcare system. According to the 2022 GLOBOCAN report, approximately 20 million people were diagnosed with cancer, and 10 million people passed away due to the disease. A significant improvement in the prevention, diagnosis, and treatment of cancer has resulted in a greater chance of overall survival for patients. Although survival rates for these patients have improved, they may be at risk for secondary malignancies. Secondary malignancy (SM) is defined as a tumor that differ from the primary tumor in terms of location, histopathology and genetics. Secondary malignancies could be classified into two categories based on the time of occurrence: synchronous tumors occur within six months of an initial primary cancer, while metachronous tumors occur after six months. Despite various genetic and environmental factors being implicated, the pathogenesis remains unclear. There are no standard protocols for screening, prevention, diagnosis, or treatment. Additionally, most studies on this topic conducted on data from the SEER (Surveillance, Epidemiology, and End Results) database. Although this database has the advantage of including many patients, it is insufficient to examine potential risk factors because it doesn't include individual medical information such as personal and family medical history, or alcohol and smoking use. In this study, we aimed to reveal the incidence of secondary malignancy in hematological cancer patients, analyze the potential risk factors and determine which factors are associated with the development of secondary malignancies. **Methodology:** This retrospective study was conducted on 2,003 patients diagnosed with Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Essential Thrombocytosis (ET), Chronic Myeloid Leukemia (CML), Primary Myelofibrosis (PMF), Polycythemia Vera (PV), Myelodysplastic Syndrome (MDS) and Multiple Myeloma (MM) who applied to the Hematology Clinic of Bezmialem Vakif University Hospital between February 2012 and May 2024. Patients aged above 18 years and had adequate medical records were included in the study. Patients with a prior history of cancer or an inadequate medical history were excluded. The study group consisted of patients with secondary malignancies. Control subjects were matched to the study group based on age, gender, and diagnosis. Clinical parameters compared between the study and control groups included age, gender, presence of B symptoms, stage (early or advanced), primary involvement (nodal or extranodal), extranodal involvement, relapse, hematopoietic stem cell transplantation (HSCT), treatments received (radiotherapy and chemotherapy), modifiable risk factors (diabetes, hypertension, smoking, alcohol use), and a family history of cancer. For statistical analysis, occurrences of SM by the site of diagnosis were described by counts and frequencies. Differences between groups were evaluated by the pearson chi- square or fisher exact test. Logistic regression models were used to determine predictors of occurrence of SM in patients with hematological malignancies. Survival probabilities and relapse were estimated using the Kaplan-Meier method. Cox regression analysis was performed to evaluate the factors affecting survival times and relapse. The hazard ratio (HR) with corresponding 95% confidence interval was determined based on the Cox proportional hazards model. Statistical significance level was set as 0.05 and SPSS (version 28) package program was used in calculations. All p values $< 0.05$ were considered statistically significant. This study was approved

by Bezmialem Vakif University Ethical Committee (2024/50). **Results:** 1,757 of 2,003 hematological malignancies were analyzed, 51 of whom developed SM. There was no SM in patients with PV, and one patient with MDS was excluded for inadequate records. A total of 248 cases were selected as controls. The 299 patients with hematological malignancies had a median follow-up of 70 months (95% CI 46.7-93.2) and a median age of 64 years (range 24-89), and 154 (51.50%) were female. Among these 51 cases of SM, the mean time to secondary malignancy development was 103.61 months (95% CI 88.7-118.4), and 11 had synchronous (21.6%) and 40 had metachronous (78.4%) tumors (Figure-1A). A majority of SM were found in Non-Hodgkin Lymphoma (NHL) (n=26, 51%). The most common type of SM was lung cancer (n=9, 17.6%) (Figure-1B). In terms of age, gender, B symptoms, stage, primary and extranodal involvement, HSCT, chemotherapy, or modifiable risk factors, there was no statistically significant difference between patients with and without SPM. However, relapse and radiotherapy were significantly more common in the control (p=0.023 and p=0.038, respectively). Moreover, a family history of cancer was statistically significant in the study group (p= <0.001) (Table-1). In the multivariate logistic regression analyses, family history of cancer, no relapse, and no radiotherapy were associated with an increased risk of secondary cancer (Table-2). There were no significant differences in survival times between the groups (Figure-2A). Cox multivariate analysis showed advanced age and male gender to be risk factors for OS (Table-3). The mean time to relapse for hematologic malignancies was 106.6 months (range 98.8–114.4 months). SM patients had a longer time to relapse than controls (p=0.004) (Figure-2B). Cox multivariate analysis showed that patients who got autologous transplantation and those who did not develop secondary malignancy were at higher risk of relapse (Table-3). **Conclusion:** In conclusion, this study indicates that a family history, no relapse history, and no radiotherapy are associated with an increased risk of secondary malignancy development. Survival times between patients with and without secondary malignancy didn't differ significantly. It's also important to note that both synchronous and metachronous cases were included in our study. Interestingly, the study group had better clinical outcomes than the control group. The findings may be a result of a conscious and meticulous approach taken by patients with multiple malignancies and their clinicians. Therefore, early screening, follow-up, and a multidisciplinary approach should be considered in managing these patients from the moment of initial diagnosis. Further studies are needed to validate our findings and provide a more comprehensive understanding of the risk factors and outcomes associated with secondary malignancies.

| | **Synchronous n (%)** | **Metachronous n (%)** | **Total n (%)** |
|---|---|---|---|
| HL | 0 (0.0%) | 7 (17.5%) | 7 (13.7%) |
| NHL | 7 (63.6%) | 19 (47.5%) | 26 (51.0%) |
| CLL | 2 (18.2%) | 3 (7.5%) | 5 (9.8%) |
| ET | 0 (0.0%) | 5 (12.5%) | 5 (9.8%) |
| CML | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| PMF | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| MM | 2 (18.2%) | 4 (10.0%) | 6 (11.8%) |
| TOTAL | **11 (100.0%)** | **40 (100.0%)** | **51 (100.0%)** |

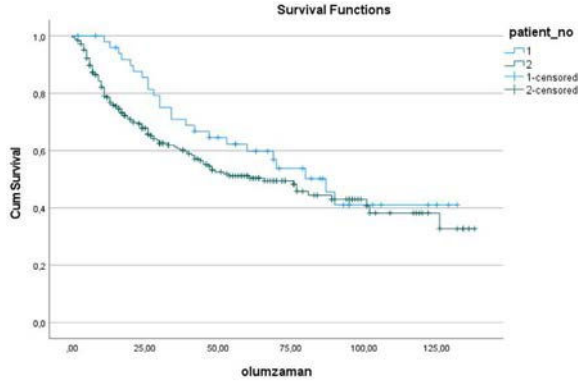
**Figure-1A**. The distrubution of secondary malignancies based on hematological malignancies.

| | **Synchronous n (%)** | **Metachronous n (%)** | **TOTAL n (%)** |
|---|---|---|---|
| Lung | 0 (0.0%) | 9 (22.5%) | 9 (17.6%) |
| Thyroid | 3 (27.3%) | 3 (7.5%) | 6 (11.8%) |
| Breast | 1 (9.1%) | 3 (7.5%) | 4 (7.8%) |
| RCC | 1 (9.1%) | 3 (7.5%) | 4 (7.8%) |
| BCC | 0 (0.0%) | 3 (7.5%) | 3 (5.9%) |
| Bladder | 1 (9.1%) | 2 (5.0%) | 3 (5.9%) |
| Colon | 0 (0.0%) | 3 (7.5%) | 3 (5.9%) |
| DLBCL | 0 (0.0%) | 2 (5.0%) | 2 (3.9%) |
| Endometrium | 1 (9.1%) | 1 (2.5%) | 2 (3.9%) |
| Pancreas | 1 (9.1%) | 1 (2.5%) | 2 (3.9%) |
| Mesothelioma | 1 (9.1%) | 0 (0.0%) | 1 (2.0%) |
| Larynx | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| Rectal | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| CMML | 1 (9.1%) | 0 (0.0%) | 1 (2.0%) |
| Prostate | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| GIST | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| SCC | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| Stomach | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| Ovary | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| Testicular | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| Gallbladder | 1 (9.1%) | 0 (0.0%) | 1 (2.0%) |
| Bowen | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| Cervix | 0 (0.0%) | 1 (2.5%) | 1 (2.0%) |
| **TOTAL** | **11 (100.0%)** | **40 (100.0%)** | **51 (100.0%)** |

**Figure-1B.** Distribution based on the types of secondary malignancies.

**Table 1 – Clinical features of patients**

| | With SM (N=51) Count (%) | Without SM (N=248) Count (%) | p |
|---|---|---|---|
| Age median (range) | 66 (24-89) | 63 (24-89) | 0.423 |
| Gender | | | 0.934 |
| Female | 26 (51.0%) | 128 (51.6%) | |
| Male | 25 (49.0%) | 120 (48.4%) | |
| Status | | | 0.887 |
| Alive | 27 (52.9%) | 134 (54.0%) | |
| Death | 24 (47.1%) | 114 (46.0%) | |
| B Symptoms | | | 0.566 |
| Absent | 30 (58.8%) | 135 (54.4%) | |
| Present | 21 (41.2%) | 113 (45.6%) | |
| Stage | | | 0.083 |
| Early | 26 (51.0%) | 94 (37.9%) | |
| Advanced | 25 (49.0%) | 154 (62.1%) | |
| Primary Involvement | | | 0.326 |
| Nodal | 18 (35.3%) | 106 (42.7%) | |
| Extranodal | 33 (64.7%) | 142 (57.3%) | |
| Extranodal Involvement | | | 0.911 |
| No | 14 (27.5%) | 70 (28.2%) | |
| Yes | 37 (72.5%) | 178 (71.8%) | |
| Relapse | | | **0.023** |
| No | 48 (94.1%) | 201 (81.0%) | |
| Yes | 3 (5.9%) | 47 (19.0%) | |
| HSCT | | | 0.140 |
| No | 43 (84.3%) | 226 (91.1%) | |
| Autologous | 8 (15.7%) | 22 (8.9%) | |
| Radiotherapy | | | **0.038** |
| No | 36 (70.6%) | 136 (54.8%) | |
| Yes | 15 (29.4%) | 112 (45.2%) | |
| Chemotherapy | | | 0.335 |
| No | 6 (11.8%) | 19 (7.7%) | |
| Yes | 45 (88.2%) | 229 (92.3%) | |
| Modifiable Risk Factors *(Diabetes, Hypertension, Smoking, Alcohol)* | | | 0.206 |
| No | 8 (15.7%) | 59 (23.8%) | |
| Yes | 43 (84.3%) | 189 (76.2%) | |
| Family History of Cancer | | | **<0.001** |
| No | 36 (70.6%) | 242 (97.6%) | |
| Yes | 15 (29.4%) | 6 (2.4%) | |



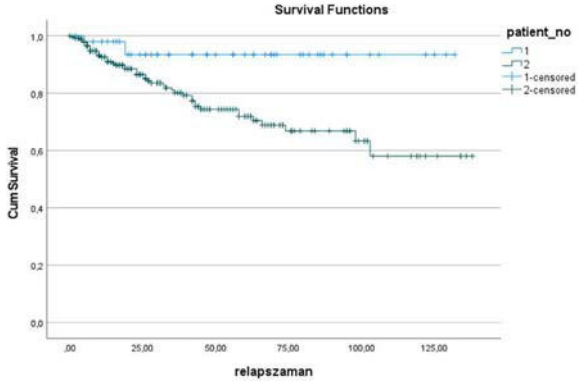




**Table 2 – Multivariate analysis result to determine risk factors for SM development**

| | Multivariate OR (95% CI) | p |
|---|---|---|
| Stage | | 0.262 |
| Early | 1.47 (0.74-2.91) | |
| Advanced | 1.00 | |
| Relapse | | **0.022** |
| No | 5.18 (1.27-21.16) | |
| Yes | 1.00 | |
| Radiotherapy | | **0.020** |
| No | 2.44 (1.15-5.20) | |
| Yes | 1.00 | |
| Modifiable Risk Factors *(Diabetes, Hypertension, Smoking, Alcohol)* | | 0.179 |
| No | 1.00 | |
| Yes | 1.86 (0.75-4.64) | |
| Family History | | **<0.001** |
| No | 1.00 | |
| Yes | 21.90 (7.30-65.64) | |

**Table 3 – Risk factors for overall survival and relapse in patients.**

| | Multivariate HR (95% CI) | p |
|---|---|---|
| **OVERALL SURVIVAL (OS)** | | |
| Age | | **0.009** |
| Young | 1.00 | |
| Old | 1.07 (1.01-1.13) | |
| Gender | | **0.009** |
| Female | 1.00 | |
| Male | 3.60 (1.37-9.44) | |
| Type of SM | | 0.157 |
| Synchronous | 1.00 | |
| Metachronous | 2.23 (0.73-6.78) | |
| Stage | | 0.779 |
| Early | 1.13 (0.43-2.93) | |
| Advanced | 1.00 | |
| Primary Involvement | | 0.089 |
| Nodal | 3.32 (0.83-13.26) | |
| Extranodal | 1.00 | |
| Extranodal Involvement | | 0.214 |
| No | 1.00 | |
| Yes | 2.13 (0.64-7.06) | |
| Relapse | | 0.879 |
| No | 1.34 (0.03-58.09) | |
| Yes | 1.00 | |
| HSCT | | 0.233 |
| None | 1.00 | |
| Autologous | 5.771 (0.32-102.5) | |
| Radiotherapy | | 0.622 |
| No | 1.00 | |
| Yes | 1.32 (0.42-4.07) | |
| **RELAPSE** | | |
| Patients | | **0.006** |
| with SM | 1.00 | |
| without SM | 5.16 (1.59-16.17) | |
| Stage | | 0.429 |
| Early | 1.00 | |
| Advanced | 1.29 (0.68-2.45) | |
| Extranodal Involvement | | 0.969 |
| No | 1.00 | |
| Yes | 1.01 (0.48-2.12) | |

**Table 3 (continued)**

| | Multivariate HR (95% CI) | p |
|---|---|---|
| HSCT | | <0.001 |
| None | 1.00 | |
| Autologous | 6.25 (3.40-11.51) | |
| Chemotherapy | | 0.203 |
| No | 1.00 | |
| Yes | 3.63 (0.49-26.44) | |

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OP 19

## FLT3-ITD POSITIVE ACUTE MYELOİD LEUKEMIA MIMICKING ACUTE PROMYELOCYTIC LEUKEMİA

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**Objective:** Acute myeloid leukemia (AML) is a heterogeneous disease due to genetic abnormalities and differences in immunophenotypes. The diagnosis of AML requires a careful evaluation of clinical morphology, immunophenotyping, cytogenetics, and molecular analyses. [1] In current practice, flow cytometry-based immunophenotyping provides a rapid and reliable method for diagnosing AML, including acute promyelocytic leukemia (APL). APL is a subtype of AML with distinct morphological, biological, and clinical characteristics. It can be effectively treated with ATRA-based therapy protocols. However, if not treated quickly, it can be fatal due to the risk of disseminated intravascular coagulation (DIC). Therefore, the diagnosis and treatment of APL represent a true medical emergency.[2] The absence of CD34, HLA-DR, and CD11b is a characteristic immunophenotypic feature that often distinguishes APL from other AML subtypes. However, AML subtypes other than APL that lack CD34 and HLA-DR expression have also been reported. APL accounts for 8% to 17% of AML patients. In AML patients without the PML-RARA fusion gene, 12% to 21% of cases have been identified as HLA-DR negative. These HLA-DR negative AML cases are distinct from APL because they do not carry the characteristic PML-RARA fusion.[3] HLA-DR and CD34 negativity is generally observed in AML-M1 and AML-M2 subtypes and is associated with nucleophosmin (NPM1) gene mutations and FMS-like tyrosine kinase-internal tandem duplication (FLT3-ITD) mutations.[4] NPM1 mutations are among the most common genetic abnormalities in AML, occurring in 27-35% of adult AML cases. Although rare, an "APL-like" immunophenotype has been reported in some de novo acute myeloid leukemia (AML) cases with NPM1 gene mutations. These cases show some immunophenotypic similarities to APL, despite being genetically different. AML cases with NPM1 mutations have unique clinical and biological characteristics.[5] In this study, we aimed to highlight the association of FLT3-ITD positivity, as opposed to NPM1, in HLA-DR negative non-APL AML cases in our clinic. **Methodology:** We examined three acute leukemia patients who were referred to our clinic within one month and were initially reported as APL based on flow cytometry analysis. Our focus on these patients stemmed from the fact that a condition with an incidence of 1-2 cases per 1 million people per year was diagnosed consecutively as APL in flow cytometry analysis within a short period. Fluorescent in situ hybridization (FISH) analysis for the 15;17 translocation and polymerase chain reaction (PCR) for FLT3-ITD and FLT3-TKD mutations were performed on the patients' peripheral blood. NPM1 mutations could not be analyzed in these patients. **Results:** Morphological examination of the patients' peripheral blood smears showed prominent nucleoli, Auer rods, and cup-like nuclei. Due to the CD34 and HLA-DR negativity in the flow cytometry analysis, these cases were initially considered APL. However, cytogenetic results revealed a negative t(15;17) translocation in all three patients, excluding APL. Additionally, all three patients tested positive for FLT3-ITD mutations. The peripheral blood white blood cell (WBC) count, blast percentage, and D-dimer levels were significantly elevated at the time of presentation in all patients. (Table 1) **Conclusion:** In cases with APL-like immunophenotypes, these similarities pose diagnostic challenges in daily practice. In this study, the APL-like AML cases exhibited CD34 and HLA-DR negativity and carried FLT3-ITD mutations. These de novo cases were characterized by high WBC counts, blast percentages, and elevated D-dimer levels. NPM1 is one of the most frequently mutated genes in AML, often seen alongside FLT3-ITD. Morphological and immunophenotypic similarities between many AML cases with NPM1 mutations and APL are well-known. In the first case, the blasts resembled the abnormal promyelocytes of APL (Figure 1.A). In the second case, a blast with a cup-like nucleus was observed (Figure 1.B). The "cup-like" nucleus morphology is specifically associated with acute myeloid leukemia (AML) with NPM1 gene mutations. The WBC count was very high in all cases a feature that is unusual for APL, especially the hypergranular variant. High WBC counts and blast cell percentages are typically described in NPM1-mutated AML.[6] Similarly, this could also be considered for FLT3-ITD, based on our findings. However, further studies with more cases are needed to confirm this. All patients demonstrated elevated D-dimer levels, which is more strongly associated with APL.[7] Unlike high D-dimer levels, fibrinogen levels were within acceptable limits. One patient had prominent gum hypertrophy, and frequent gum bleeding was observed during clinical follow-up. In conclusion, for cases with APL-like features but negative PML-RARA results by FISH and/or molecular methods, it is important to consider AML with NPM1 and/or FLT3-ITD mutations.

**Table 1 – Clinical-Pathological Parameters of the Patients**

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age | 34 | 35 | 57 |
| Gender | Female | Female | Female |
| Hemoglobin(gr/dl) | 6,3 | 9,4 | 8,8 |
| Plateletes | 12,000 | 75,000 | 91,000 |
| Leukocytes(WBC) | 159,000 | 120,000 | 307,000 |
| LDH | 841 | 405 | 471 |
| Fibrinogen | 246 | 419 | 341 |
| D-dimer | 7499 | 7853 | 1020 |