Research Article / Araştırma Makalesi

Childhood Lymphoproliferative Disorders with Inborn Errors of Immunity from the Perspective of Oncology

Onkoloji Perspektifinden Konjenital İmmün Yetmezliklerle Birlikteliği Olan Çocukluk Çağı Lenfoproliferatif Bozuklukları

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Abstract

Background: Malignancy is an important issue for immunodeficiency patients and management could be challenging. This study aims to review inborn errors of immunity (IEI) patients with lymphoproliferative disorders.
Materials and Methods: Age at diagnosis, gender, type of immunodeficiency, tumor type and location, Ebstein-Barr virus (EBV) status, comorbidity, treatment schemes for malignancy, and follow-up time were evaluated in 12 patients between 2007-2023, retrospectively.
Results: Ten of twelve patients (83,3%) were male. Median age was 8 years. In terms of immunodeficiency type, 11 had a definitive diagnosis of IEI, 5 of which had DNA repair defects. One had been diagnosed with DOCK8 disorder without any history of frequent and/or severe infections previously. Nine patients (75%) were diagnosed with IEI after malignancy. Lymphoma was the leading lymphoproliferative disorder (n=10) and most of them were diffuse large B-cell lymphoma (n=4). Lymphoid nodal involvement was the prominent location (n=9), but primary central nervous system and gastric mucosal involvement were unusual. Three patients were EBV positive. All patients were treated with several chemotherapy regimens. Median follow-up time was 32,6 months. Seven patients (58.3%) died because of infection or malignancy or other causes. All other patients are still under follow-up with disease-free. The 5-year event-free survival was 38.9% and overall survival was 51.9%.
Conclusions: All patients with IEI should be monitored for malignancy. Furthermore patients with unusual findings of malignancy shouldalso be examined for IEI.

Keywords: Ebstein-Barr virus, Inbor nerrors of immunity, DOCK8 disorder, Lymphoproliferative disorder, Malignancy

Öz

Amaç: Malignite, immün yetmezlik hastaları için önemli bir sorundur ve yönetimi zor olabilir. Bu çalışma, lenfoproliferatif bozuklukları olan konjenital immun yetmezlik (KIY) hastalarını incelemeyi amaçlamaktadır.
Materyal ve Metod: 2007-2023 yılları arasında 12 hastada tanı yaşı, cinsiyet, immün yetmezlik türü, tümör çeşidi ve yeri, Ebstein-Barr virüs (EBV) durumu, eşlik eden hastalıklar, malignite için tedavi şemaları ve takip süresi retrospektif olarak değerlendirildi.
Bulgular: On iki hastanın on tanesi (%83,3) erkekti. Ortanca yaş 8 idi. İmmün yetmezlik türü açısından 11 hastaya kesin KIY tanısı kondu, bunların beşinde DNA onarım kusurları vardı. Birine daha önce sık ve/veya şiddetli enfeksiyon öyküsü olmadan DOCK8 bozukluğu tanısı konuldu. Dokuz hastaya (%75) malignite tanısından sonra KIY tanısı kondu. Lenfoma en sık saptanan lenfoproliferatif bozukluk (n=10) olup çoğu diffüz büyük B hücreli lenfomaydı (n=4). Lenfoid nodal tutulum en sık tümör yerleşim yeri (n=9) olmakla birlikte primer merkezi sinir sistemi ve gastrik mukozal tutulumlar alışılmışın dışında idi. Üç hastada EBV pozitif saptandı. Tüm hastalara çeşitli kemoterapi rejimleri uygulandı. Ortanca takip süresi 32,6 aydır. Yedi hasta (%58,3) enfeksiyon veya malignite veya diğer nedenlerden dolayı öldü. Diğer tüm hastalar hala hastalıksız olarak takip altındadır. 5 yıllık olaysız sağkalım %38,9 ve genel sağkalım %51,9 idi.
Sonuç: Konjenital immun yetmezlik tanılı tüm hastalar malignite gelişimi açısından izlenmelidir. Ayrıca, beklenenden farklı malignite özellikleri sergileyen hastalar da immun yetmezlikler açısından incelenmelidir.

Anahtar Kelimeler: Ebstein-Barr virüs, Konjenital immun yetmezlikler, DOCK8 bozukluğu, Lenfoproliferatif hastalıklar, Malignite

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Introduction

Malignancy is one of the major cause of morbidity and mortality for children with immunodeficiency (1). While inborn errors of immunity (IEI) are a heterogeneous group of diseases characterized by congenital disorders of immune system that can occur at any age from birth, secondary immunodeficiencies are acquired immune disorders usually caused by immunosuppressive medications. In both cases, risk of infections, autoimmune diseases, lymphoproliferation and malignancy are increased (2). While the most common cancer detected in patients with IEI is reported to be non-Hodgkin lymphoma (NHL), Hodgkin lymphoma and acute leukemias are also common (3).

Although it is thought that there are various mechanisms in development of malignancy in immunodeficiency, viral factors are found to be the most common triggering agents and Epstein-Barr virus (EBV) is a leading cause (4). It has been well established that EBV is involved in pathophysiology of various cancers such as lymphomas and nasopharyngeal carcinoma, and serious and prolonged EBV infection is seen as an important risk factor, especially in development of NHL (4, 5).

There are some unique features of tumors in immunocompromised patients. It should not be forgotten that in IEI, tumors may occur at an earlier age than expected, and unexpected malignancies can arise in unusual or rare locations. Furthermore there are more undiagnosed immunodeficiencies than thought in children with malignancies, it should be known that the first symptom of these patients might be malignancy and then they can be diagnosed with immunodeficiency through examinations (5). Taking these facts into consideration, this study aims to review clinical and laboratory features, diagnostic course and 'individualized' treatment approaches of the cases with IEI with a lymphoproliferative disorder at our center.

Materials and Methods

In this study, data of patients with lymphoproliferative disorders who were under 18 years old and had an accurate diagnosis of IEI at Başkent University Faculty of Medicine Adana Dr Turgut Noyan Application and Research Center Department of Pediatric hematology and oncology, between 2007 and 2023, were retrospectively analyzed. Age, time of immunodeficiency and/or malignancy diagnosis, gender, type of immunodeficiency, type and location of tumor, EBV status, comorbidity, treatment regimens for malignancy, follow-up period and outcome were recorded. Quantitative immunoglobulin levels, lymphocyte subgroup analysis and vaccine response of all patients were examined before chemotherapy and/or radiotherapy in the evaluation during the diagnosis of malignancy at first admission. The results were evaluated according to age percentiles. Additionally, patients underwent specific genetic variant analysis for suspected disease, whole exome sequencing (WES) or next generation sequencing (NGS) if possible. EBV status were studied for all patients by serology and PCR. The European Society for Immunodeficiencies (ESID) clinical diagnostic criteria and the 2022 International Union of Immunological Societies (IUIS) phenotypical classification for IEI had been used for immunological classification of patients in retrospective manner (6,7).

Statistical analysis

Statistical analysis were carried out using the SPSS 22.0. Categorical measurements were summarized as frequency and percentages, and continuous measurements as mean, minimum-maximum and median. Kaplan-Meier method was used for survival curves.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration (as revised in 2013) and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants' legal guardians or parents included in the study. This study was approved by Başkent University Non-Interventional Clinical Research Ethics Committee (Date: 12.02.2025, Decision number: 25/40).

Results

Among 12 patients in study, there was a predominance of male gender (M:F =8:4). Median age was 8 years (min: 3 – max: 14). In five cases combined immunodeficiency with associated or syndromic features were detected as DNA repair defects ((Nijmegen breakage syndrome (NBS) = 3, Ataxia telangiectasia (AT) = 2)) (Table 1). Patients with AT were previously diagnosed with immunodeficiency and admitted to our department after development of malignant disease. Patient 3 was diagnosed with AT at the age of 8 due to frequent infections and ataxia. Nine months later, while he was being monitored for a lung infection, diagnosis of Hodgkin lymphoma was made in our center by excision of a 13X7 mm palpable lymph node in left axilla. Patient 9 had a sibling with AT and recognised during family screening. This patient's diagnosis of acute lymphoblastic leukemia (ALL) was made in our center at 3 years old, with a mediastinal mass and bone marrow involvement due to respiratory distress. The immunoglobulin levels of both AT patients were normal because they were receiving regular intravenous immunoglobulin (IVIG). Patient 1, 5 and 10 were diagnosed with NBS upon phenotypic and laboratory findings at the ages of 12, 5 and 14 years respectively during the evaluation of lymphoproliferative disease (Figure 1). Patient 5 was diagnosed with ALL, and Patient 1 and 10 had diffuse large B cell lymphoma (DLBCL). The IgM level of Patient 5 was low (35 mg/dL (45-200)), isolated decrease of IgA (IgA: 29

mg/dL (65-421)) was detected in Patient 10, and panhypogammaglobulinemia (IgA: 6.4 mg/dL (65-690)), IgM: 13.1 mg/dL (56-560), IgG: 452 mg/dL(663-2635)) was detected in Patient 1 (Table 1).

Constitutional mismatch repair deficiency (CMMRD) and antibody deficiency-related immunodeficiency were detected in 2 patients. Several examinations were performed due to simultaneous or consecutive multiple malignancies in these cases. Both patients were 14 years old at first admission. Patient 2 was first followed up for primary central nervous system lymphoma. Six years later malignant epithelial ovarian tumor had been detected; after the course of treatment for ovarian tumor, colon adenocarcinoma had developed in last 2 years. In MLH1, c.1415_1416delGA; p.Arg472ThrfsX5 andMSH2, c.1030C>T; (p.Gln344Ter) genes, double heterozygous mutations were detected in NGS and she was followed up as CMMRD for 11 years. IgG2 level (76 mg/dL(110-480)) was also low in her examinations. In Patient 8, three different tumors were detected simultaneously; gastric DLBCL, glioblastoma multiforme (GBM) and gastric adenocarcinoma. The patient's immunological evaluations revealed low initial IgA level (<5mg/dL (65-421)).

Figure 1. Patient 1 (1a) and Patient 5 (1b) with Nijmegen Breakage syndrome

Patient 7 had the diagnosis of common variable immunodeficiency (CVID) at the age of 13 due to severe lung infection and recurrent asthma-like attacks from the group of predominant antibody deficiencies by the absence of hepatitis B and tetanus vaccine responses and low levels of IgM (13 mg/dl (26-184)), IgE (1.5 IU/ml (1.9-170)), IgG2 (60mg/dL (100-455)) and IgG4 (<0.3mg/dL (3.7-136)). One year after, a swollen lymph node biopsy from cervical area revealed DLCBL in our center. After completion of treatment for lymphoma he admitted with walking disorder and ataxia 5 years later. Radiological imaging and excisional biopsy from involved brain tissue had no neoplastic infiltration, but pathological findings were primarily suggestive of viral infection, characterized by microglial nodules, perivascular inflammation and reactive gliosis. He died after being followed up for 1.5 years with progressive encephalopathy.

Patient 4 was diagnosed with autoimmune lymphoproliferative syndrome (ALPS) at the age of 3. Direct Coombs test was positive with hemolytic anemia and thrombocytopenia; Evans syndrome was suspected. In the course of condition, concurrent widespread lymphadenopathy and hepatosplenomegaly, and high double negative T lymphocyte ratio led to consider an immunodeficiency state related to immundysregulation and autoimmunity. Except IgG (2478 mg/dL (400-1300)), quantitative immunoglobulin levels tested at that time were within normal

range for his age. With immunosuppressive treatments (corticosteroids, mycophenolate mofetil, IVIG), clinical and laboratory findings displayed remission. But similar findings recurred 6 months later, and T-cell lymphoma was detected in an excisional biopsy performed from cervical area. Three months after starting of lymphoma treatment, patient had secondary hemophagocytic lymphohistiocytosis. Genetic diagnosis could not be performed for this patient.

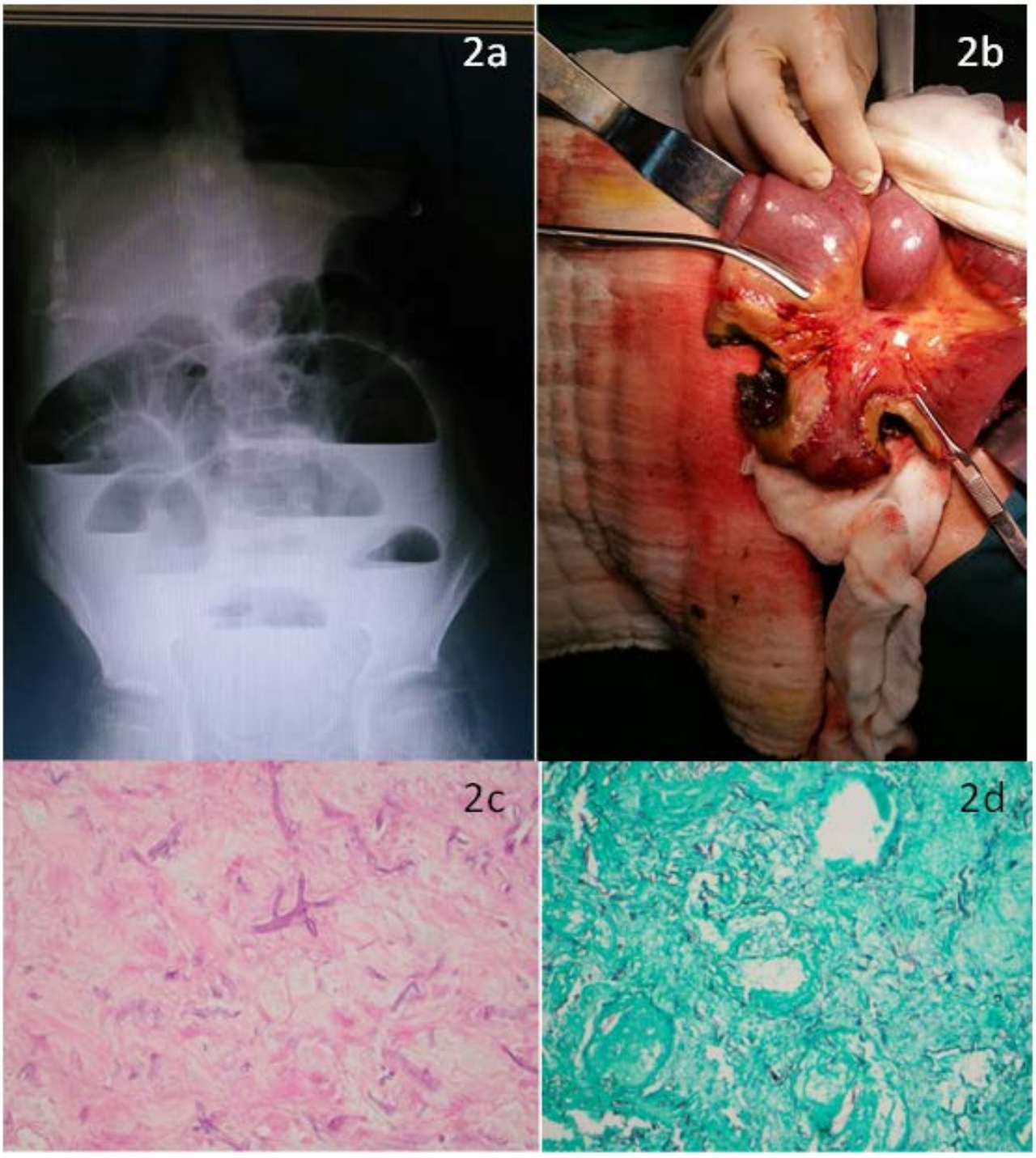

Figure 2. Preoperative abdominal radiography (a), intraoperative appearance of intestinal mucormycosis (b) histopathology of intestinal mucormycosis (Hematoxylin-Eosin staining&Gomori Metanamin-Silver staining) (c,d) in Patient 6

When Patient 6 was 8 years old, he was taken to a medical center due to cough and respiratory distress, and a mass was detected in his abdomen. He was diagnosed with Burkitt lymphoma and medical history revealed that IVIG was given due to hypogammaglobulinemia at first diagnosis. After receiving 2 cycles of chemotherapy, patient's treatment continued in our center. Although he was receiving regular IVIG

in our center, hypogammaglobulinemic state persisted. Furthermore he needed surgical intervention and long-term antifungal treatment and intensive care support due to intestinal mucormycosis and septic shock, it was decided that his chemotherapy tolerance was poor and treatment modality was modified (Figure 2a-2b). The patient's lymphoma treatment was completed and IgA level (41 mg/dL (46-218)) and IgG level (531 mg/dL (650-1600)) were low within first year follow-up. He had remission for 3 years. Then he admitted with fever and sorethroat at 12 years old, atypical lymphocytes were seen in peripheral blood smear; bone marrow examinations were found to be compatible with t(9;22) positive B-cell ALL. After four chemotherapy blocks, he needed long-term intensive care support again due to febrile neutropenia, septic shock and multiorgan failure. Considering all these, it was decided that patient had an immunodeficiency compatible with "unclassified antibody deficiency".

Patient 11 was found EBV-PCR positive in examinations due to fever, massive hepatosplenomegaly and painless enlargement of lymph nodes, was followed up for more than 1 year with diagnosis of chronic active EBV disease. Despite corticosteroid, IVIG, rituximab treatments, patient's lymph nodes continued to grow and he complained of bone pain on his left hip. In the last of serial lymph node biopsies performed at different periods, Hodgkin lymphoma was diagnosed at the age of 7. The patient's quantitative immunoglobulin levels, lymphocyte subgroups and hepatitis B and tetanus vaccine responses were normal. Total IgE level was checked for hyperIgE syndrome (HIES). It was around 195 IU/mL (0-90), but he had no history of frequent infections and/or eczematous lesions. In WES analysis, 4 copy duplications were detected in exons 8-14 in the DOCK8 gene (NM_203447.4). In extended analysis investigating functional significance of this genetic abnormality, it was considered that patient had immunodeficiency associated with dedicator of cytokinesis 8 (DOCK8) disorder, since functionality was also impaired at protein syntesis level.

In Patient 12, ep300 c1889A>G (p.TYR630Cys) heterozygote mutation associated with Rubinstein Taybi syndrome and c.2689.c>g (p.arg897Gly) heterozygote mutation associated with neurofibromatosis type 1 were detected in a center due to short stature and syndromic facial appearance. An excisional biopsy performed at the age of 4 for painless enlargements in multipl lymph nodes was found to be compatible with Hodgkin lymphoma. Simultaneously EBV-PCR was profoundly high and quantitative immunoglobulin levels, lymphocyte subgroups and hepatitis B and tetanus vaccine responses were normal. But after completion of lymphoma treatment, total IgE levels were high at 2 different times (713 IU/mL vs 1440 IU/mL (0-90)) in the examinations upon cough attacks and eczematous lesions. Therefore, it was planned to perform WES for HIES.

All patients were evaluated for EBV serology and in case of positive results, it has been confirmed by PCR. Patient 1, 11 and 12 were EBV-PCR positive (199200 copy/ml vs 266000 copy/ml vs 205827 copy/ml). EBV-PCR of all patients became negative after treatment.

The treatment modalities used in all patients are shown in Table 1. Additionally, all patients were administered IVIG.

Median follow-up time was 32,6 months (range 1-180 months). Seven patients died due to infections, uncontrolled and/or newly diagnosed malignancies, or other causes (e.g. progressive encephalopathy, sudden death at home after six years from malignancy treatment). Five patients are alive without disease. One of them is treated with additional hematopoietic stem cell transplantation. The 5-year event-free survival was 38.9% and overall survival was 51.9% (Figure 3).

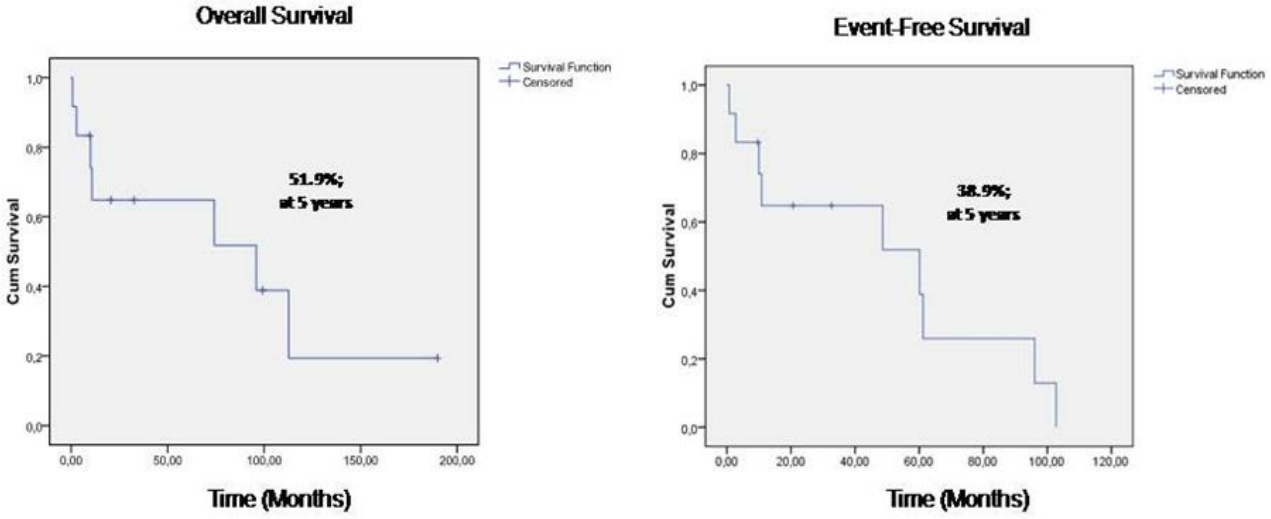

Figure 3. Overall (a) and event-free (b) survival of patients

Table 1. Inborn errors of immunity in patients with lymphoproliferative disorders

Patient no	Sex	IEI age (year)	Tumor age (year)	Inborn errors of immunity	Mutation analysis	Comorbidity	Lymphoproliferative disorder type	Tumor location/Stage-Risk group	EBV status	Treatment	Final status	Follow-up time (month)
1	F	15	12	Panhypogammaglobulinemia Nijmegen Breakage syndrome	NBN	Growth retardation Hypothyroidism Ovarian failure Psoriasis	1. Diffuse large B cell lymphoma 2. EBV-associated lymphoproliferative disorder	Generalized lymphadenopathy/ Stage III	Positive (second tumor diagnosis)	For the first diagnosis: NHL-BFM-90 For the second diagnosis: R-CHOP	After HSCT alive	180
2	F	22	14	IgG2 deficiency CMMRD	MLH1 heterozygosity + MSH2 heterozygosity	Epilepsy Epithelial malign ovarian tumor Adenocarsinoma in the colon	T cell lymphoma	Central nervous system /Stage IV	Negative	NHL-BFM-90	Exitus (due to malignancy)	132
3	M	7	8	Ataxia telangiectasia	ATM	-	Hodgkin lymphoma	Axilla /Stage IIBE	Negative	ABVD	Exitus (due to infection)	3
4	M	3	3	ALPS	NA	Evans syndrome HLH	T cell lymphoma	Generalized lymphadenopathy /Stage III	Negative	NHL-BFM 90	Exitus (due to malignancy)	11
5	M	5	5	IgM deficiency Nijmegen Breakage syndrome	NBN	Syndromic appearance Left renal atresia	B cell ALL	MRG	Negative	ALL-IC BFM 2002	Exitus (due to other causes)*	84
6	M	8	8	Hypogammaglobulinemia	NA	-	1. Burkitt lymphoma 2. Ph (+) B cell ALL	Abdominal/ Stage III	Negative	1. COPADM 2. EsPhALL	Alive	84
7	M	13	14	CVID	NA	Progressive ensephalopahy	Diffuse large B cell lymphoma	Submandibular/ Stage III	Negative	R-CHOP	Exitus (due to other causes)**	72
8	F	14	14	IgA deficiency CMMRD	MSH6 homozygosity	-	1. Diffuse large B cell lymphoma 2. Glioblastoma multiforme 3. Adenocarsinoma	1. Stomach 2. Central nervous system 3. Stomach /Stage NA	Negative	R-CHOP Nivolumab Bevacizumab VIT	Exitus (due to malignancy)	9
9	M	1	3	Ataxia telangiectasia	ATM	-	T cell ALL	MRG	Negative	ALL-IC BFM 2009	Alive	20
10	F	14	14	IgA deficiency Nijmegen Breakage syndrome	NBN	Syndromic appearance	Diffuse large B cell lymphoma	Cecum/ Stage III	Negative	-	Exitus (due to infection)	1
11	M	8	7	DOCK8 duplication abnormality	DOCK8 homozygosity	-	Hodgkin lymphoma	Generalized lymphadenopathy/ Stage IVSB	Positive	Rituksimab GPOH-HD 2002 Radiotherapy	Alive	24
12	M	5	4	HyperIgE syndrome ?	NA	Syndromic appearance Growth retardation	Hodgkin lymphoma	Generalized lymphadenopathy/ Stage IIISB	Positive	Rituksimab GPOH-HD 2002 Radiotherapy	Alive	9

F; female, M; male, EBV; Ebstein Barr virus, NHL-BFM; non hodgkin lymphoma- Berlin Frankfurt Munich, HSCT; hematopoietic stem cell transplantation, R-CHOP; Rituximab-Cyclophosphamide Doxorubicin Vincristine Prednisone, ABVD; Doxorubicin Bleomycin, Vinblastine Dacarbazine, HLH; hemophagocytic lymphohistiocytosis, ALPS; autoimmune lymphoproliferative syndrome, ALL; acute lymphoblastic leukemia, ALL-IC BFM; acute lymphoblastic leukemia - Berlin Frankfurt Munich; COPADM; cyclophosphamide vincristine prednisone doxorubicin methotreksat, EsPhALL; Philadelphia-chromosome-positive acute lymphoblastic leukemia, CVID; common variable immunodeficiency, CMMRD; constitutional mismatch repair deficiency syndrome, VIT; vincristine irinotecan temozolomide, GPOH-HD; German Society of Pediatric Oncology and Hematology-Hodgkin's Disease, ; MRG; intermediate risg group, StageNA: because of triple malignancy at the same time, staging is unnecessray

*Sudden death at home

** Due to progressive ensephalopathy

Discussion

In patients with IEI, after infections, most important cause of mortality is malignancy (8,9). DLBCL is a common lymphoproliferative malignancy in this situation (10). Compatible with literature, in our cases profound lymphoproliferative malignancy was lymphoma, and DLBCL was the frequent type (Table 1).

Patients with medical history of recurrent/serious infections, autoimmune disease, low immunoglobulin levels, serious toxicity and infections during cancer treatment, detection of lymphoma/immunodeficiency-related genetic mutations, syndromic findings and growth retardation can be suggestive of any IEI. Variety of these features were present in some patients in this study. For example, all patients with NBS had previously been examined in various centers due to short stature, growth retardation and syndromic facial appearance however they were all undignosed before detection of cancer. At first evaluation for malignancy, the immunoglobulin levels of NBS patients were low compared to their age percentile, and certain diagnosis was confirmed with subsequent genetic analysis. On the other hand, patients with AT were initially diagnosed as IEI at pediatric neurology and immunology departments and they had been referred after malignancy development.

Constitutional mismatch repair deficiency syndrome is a rare and serious cancer predisposition syndrome that has taken attention in recent years. It is associated with solid tumors that may occur at an early age and may be the first-sign of this condition (11). Defects in DNA repair due to mutations in the *MSH* genes and others are explanatory for development of malignancy (12). There are some studies suggesting that MMR system is also related to immune system and some CMMRD patients with varying degrees of immunodeficiency are identified (12-14). In genetic analysis of Patient 8, a homozygous mutation was detected in the *MSH6* gene, and IgA level was low. This patient, who was diagnosed with GBM in central nervous system, DLBCL and adenocarcinoma in stomach simultaneously, appeared as a serious and rare pediatric CMMRD case that displayed a fatal course. Patient 2 had also double heterozygosis mutation in *MLH1* and *MSH2* genes and IgG2 level was low. Although in 2022 IEI classification, MSH6 deficiency is classified under the group of predominantly antibody deficiencies (IIIb), this patient had a low level of IgG2 which is a novel finding in this case. In this patient, which had a fatal course similar to Patient 8, malignant epithelial ovarian tumor and then adenocarcinoma in colon were diagnosed during follow-up after lymphoma.

In IEI, according to ESID criteria, for diagnosis of CVID and unclassified antibody deficiency, secondary causes of hypogammaglobulinemia must have been excluded like infection, protein loss, medication and malignancy (6). In one of our cases with CVID, diagnosis of IEI had been established one year ago before NHL. However other case with unclassified antibody deficiency who had severe intestinal mucormycosis, did not have any measurement of quantitative immunoglobulin levels until admission to oncology department. So in this case, two different malign diseases occurence and severe opportunistic infection and febrile neutropenic episodes (*Klebsiella oxitoca*, *Enterococcuss spp*, *Acinetobacter baumannii*, etc.) were remarkable for IEI.

According to the 2022 IUIS phenotypic classification for primary immunodeficiencies, there are some cases with EBV susceptibility due to immune dysregulation (7). Several studies indicate that lymphomas are frequently associated with EBV in immunodeficiencies (15-17). Only three patients with IEI included in this study were EBV positive at the time of lymphoproliferative disorders, while others were negative. Here we come across to the fact that occurrence of malignancy in children is a multifactorial process and cannot be associated only with viral factors. With immunosupressive treatment for lymphoma, EBV viral load had gradually decreased and became negative as expected in our cases.

A‘*unique’* patient (Patient 11) in this study is the case who had chronic active EBV disease for almost a year and subsequently had been diagnosed with Hodgkin lymphoma. In patient's WES analysis, 4 copy duplications were detected in exons 8-14 in *DOCK8* gene (NM_203447.4). DOCK8 deficiencies were associated with HIES previously, but according to the IUIS 2022 classification they are in combined immunodeficiencies (7). Patients with this disease often have clinical signs such as atopy, recurrent infections and cutaneous manifestations such disseminated HPV, molluscum, recurrent herpes, varicella, and laboratory findings of eosinophilia and abnormal immunoglobulin levels (18,19). In our patient, there were no clinical or laboratory findings for this disorder previously. While abnormalities such as deletions, nonsense and splice site mutations in *DOCK8* gene have been described in literature (20-22), due to duplications in our patient, further analyzes were performed in terms of gene function which revealed significant loss. Although, it has been shown that some neurodevelopmental disorders (cognition and communication abnormalities, behaviour and mood problems, etc.) are related with *DOCK8* duplications (23,24) ,this is a very rare case associated with a lymphoproliferative malignancy with duplications in *DOCK8* gene. Since this is not a deficiency involving *DOCK8*, there were no other classical findings of HIES. Unlike this case, Patient 12 was diagnosed with Hodgkin lymphoma at a younger age than expected. Then he had eczematous skin lesions and lung symptoms during follow-up after completing lymphoma treatment. Patient’s total IgE levels are significantly high at this time and genetic analysis is crucial for possible HIES.

There is no certain approach to treatment of malignancies with immunodeficiency. Generally, these patients are treated according to institutional protocols. For example in this study, for Hodgkin lymphoma patients, drug doses were not reduced. Only one patient with AT (Patient 3), died due to an invasive fungal infection that occurred while chemotherapy was ongoing. NHL patients diagnosed in early stages

of the study were applied full doses of chemotherapy according to the NHL-BFM 90 protocol. Two of them died,one is followed without disease after HSCT (Table 1). CD20 positive NHL patients diagnosed in last 8 years were treated with rituximab and CHOP protocol to avoid side effects due to drug toxicity. Treatment of these patients was completed without any problem. However, one patient died due to progressive encephalopathy after 5 years from initial chemotherapy and other one was due to progressive GBM (Table 1). Patients diagnosed with AT and ALL were treated according to the ALL-IC BFM protocols, in protocol M process, standard dose (2 g/m^2) methotrexate was given to patient with B cell ALL, while methotrexate was administered to patient with T cell ALL at 2 g/m^2 instead of 5 g/m^2.

An important point is that these patients are more likely to develop serious infections and have higher mortality rates due to medications in the treatment of malignancy compared to other children. Beyond this, the malignancy may not be treated optimally because of modifications of drug doses. Considering all, it is necessary to treat them in experienced centers with multidisciplinary approach where pediatric infection, pediatric immunology and pediatric hematology oncology experts exist. Development of international treatment protocols should also be helpful for these kind of cases.

The primary limitation of the study is that it was conducted retrospectively in a single center with few cases since it is rare condition to have both immunodeficieny and a lymphoproliferative disorder. The main themes we want to mention about this study are the definition of accompanying immunodeficiency and management of these patients. In conclusion, malignancies associated with immunodeficiencies are rare but compelling to manage. Although it is difficult to overcome malignancies due to additional problems (especially severe infections and drug side effects), the fight against the malignancy itself can also be difficult as resistant or recurrent disease. Inborn errors of immunity should be evaluated in cases of severe, frequent or opportunistic infections; early-onset autoinflammatory situations and associated syndromic features likely before diagnosis of malignancy.

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Ethical Approval: *All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration (as revised in 2013) and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants' legal guardians or parents included in thes tudy. This study was approved by Başkent University Non-Interventional Clinical Research Ethics Committee (Date: 12.02.2025, Decision number: 25/40).*

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Analysis and interpretation: E.H.A., N.Y., B.H., N.E.K.
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