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PIV PEDIATRIC INFECTION & VACCINE

Original Article

Malignancy in Patients With Inborn Errors of Immunity Beyond Infectious Complication: Single Center Experience for 30 Years

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ABSTRACT

Purpose: Cancer incidence is known to be higher in patients with inborn errors of immunity (IEI) compared to the general population in addition to traditionally well-known infection susceptibility. We aimed to investigate cancer occurrence in patients with IEI in a single center.
Methods: Medical records of IEI patients treated at Samsung Medical Center, Seoul, Korea were retrospectively reviewed from November 1994 to September 2023. Patients with IEI and cancer were identified.
Results: Among 194 patients with IEI, seven patients (3.6%) were diagnosed with cancer. Five cases were lymphomas, 4 of which were Epstein-Barr virus (EBV)-associated lymphomas. The remaining cases included gastric cancer and multiple myeloma. The median age at cancer diagnosis was 18 years (range, 1–75 years). Among patients with cancer, underlying IEIs included X-linked lymphoproliferative disease-1 (XLP-1, n=3), activated phosphoinositide 3-kinase delta syndrome (APDS, n=2), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) haplo-insufficiency (n=2). Seventy-five percent (3/4) of XLP-1 patients, 40.0% (2/5) of APDS patients, and 50.0% (2/4) of CTLA-4 haplo-insufficiency patients developed cancer. Patients with XLP-1 developed cancer at earlier age (median age 5 years) compared to those with APDS and CTLA-4 (P<0.001). One patient with APDS died during hematopoietic cell transplantation.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Conclusions: Cancer occurred in 3.6% of IEI patients at a single center in Korea. In addition to infectious complications and inflammation, physicians caring for IEI patients should be aware of the potential risk of cancer, especially in association with EBV infection.

Keywords: Primary immunodeficiency diseases; Epstein-Barr virus; Malignancy; Lymphoma

INTRODUCTION

Human inborn errors of immunity (IEI) include more than 480 diseases caused by single gene variants that exhibit autoimmunity, immune dysregulation, and syndromic features as well as increased susceptibility to infection by pathogens.[1] In addition, an increased incidence of cancer is known to be one of the well-known characteristics of IEI.[2,3] Cancer incidence in patients with IEI is associated with several factors including persistent chronic inflammation, susceptibility to oncogenic virus infection caused by impaired immunity, and reduced capacity for sensing and repairing damaged DNA.[2,4,5] As the survival rate of IEI patients is improving with an early, accurate diagnosis, and proper management of the disease, it is noteworthy that cancer development in these patients needs more attention. Therefore, it is important to judiciously monitor the possibility of cancer as well as opportunistic infections and other clinical features of IEI.[6] The purpose of this study was to investigate the cancer incidence rate and the type of cancer that occurred in IEI patients to increase awareness among physicians because most IEI patients are being followed by infectious disease physicians or immunologists in Korea.

MATERIALS AND METHODS

The medical records of patients with IEI at the department of pediatrics of Samsung Medical Center (SMC), Seoul, Korea from November 1994 to September 2023 were retrospectively reviewed. Patients who had visited an outpatient clinic or received in-patient care at least once at SMC were included. IEI patients were defined when there were typical clinical phenotypes or genetic confirmations according to the International Union of Immunological Societies (IUIS) phenotypical classification.[1] Cancer patients were defined as patients with cancer codes (C00-D49 based on International Classification of Diseases, 10th Revision). Information was obtained on the type of cancer, the underlying IEI, the age at diagnosis of cancer/IEI, the status of hematopoietic cell transplantation (HCT), and survival.

The Kaplan-Meier curve for survival in the entire cohort was illustrated. In addition, the cancer frequency in each type of IEI was calculated. Comparisons between Kaplan-Meier curves for cancer-free follow-up in each IEI were performed using the Log-rank test. Cases per person-year for malignancy were calculated. Analysis and visualization were carried out using GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA). This study was approved by the Institutional Review Board of SMC (SMC 2022-12-103, 2023-11-100).

RESULTS

A total of 194 patients were identified with IEI. Of those, 129 patients (66.5%) were male. The median age at the time of IEI diagnosis was 2.8 years (range, 0–75 years). In 78% of the

patients, the diagnosis of IEI was based on genetic testing, while the remaining patients were diagnosed through cytogenetic testing, immunophenotyping, or a definite clinical presentation, with or without familial histories. According to the IUIS classification, IEIs belonging to the category "Combined immunodeficiencies (CID) with associated or syndromic features" were the most common type (28.4%, 55/194), followed by "Predominantly antibody deficiencies" (20.6%, 40/194) and "Congenital defects of phagocyte number, function or both" (19.6%, 38/194). **Fig. 1**. shows the survival curve for the entire cohort. There were 22 deceased patients with a median age of 4.1 years old. The overall survival rate was 82.6%.

Seven patients (3.6%) were diagnosed with cancer; 3 patients with X-linked lymphoproliferative disease 1 (XLP-1), 2 with activated phosphoinositide 3-kinase delta syndrome (APDS), and two with cytotoxic T lymphocyte antigen 4 (CTLA-4) haplo-insufficiency. The proportions of cancer for each IEIs were as follows; 75.0% (3/4) in patients with XLP-1, 40.0% (2/5) in patients with APDS, and 50.0% (2/4) in patients with CTLA-4 haplo-insufficiency. The most common cancer type was lymphoma (n=5); diffuse large B-cell lymphoma (DLBCL) (n=3), Hodgkin lymphoma (HL) (n=1), and mucosa-associated lymphoid tissue lymphoma (MALToma) (n=1). Of note, 4 out of 5 (80.0%) lymphomas were associated with Epstein-Barr virus (EBV) infection. The other two cancers were gastric cancer and multiple myeloma.

The characteristics of the seven IEI patients with cancer are shown in **Table 1**. Four were male and three were female. The median age at cancer diagnosis was 18 years (range, 1–75 years). Three patients were initially diagnosed with common variable immunodeficiency (CVID; patients 3, 4, and 5) and developed cancer later during follow-up. The median period from diagnosis of CVID to cancer development was 11 years (range, 2–19 years). They were later genetically confirmed with XLP-1, APDS, and CTLA-4 haplo-insufficiency. One (14.3%) died from complications during HCT.

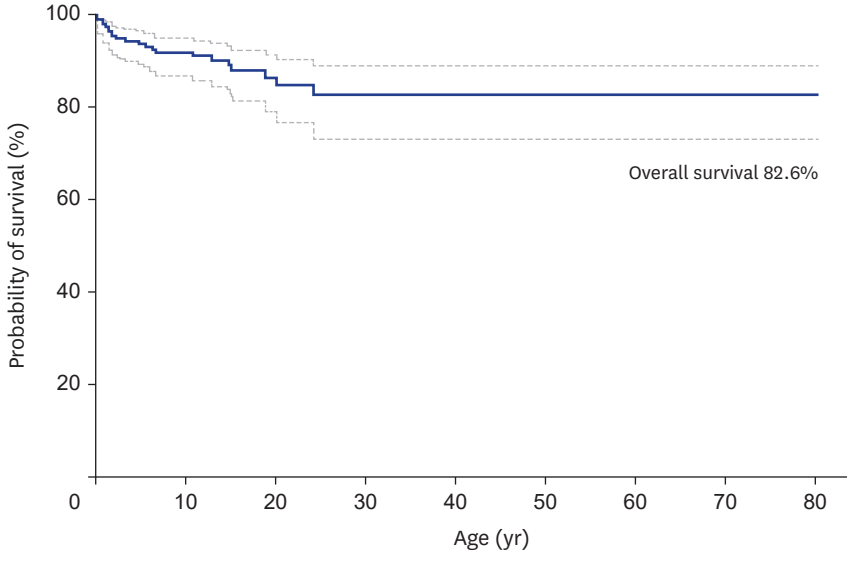

Fig. 1. The overall survival curve for 194 patients with IEI. "Censor" refers to the current age of patients. Out of the total patients, 22 patients died with a median age of 4.1 years. The overall survival rate was 82.6%.
Abbreviations: IEI, inborn errors of immunity.

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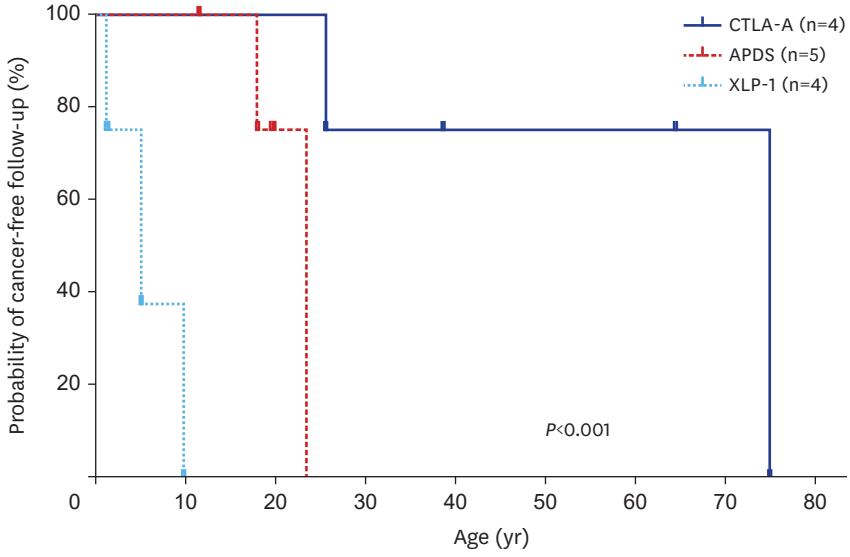
Table 1. Characteristics of the patients with IEI and cancer

Patient No.	Sex	IEI			Cancer			HCT (age, yr)	Current status (age, yr)
		Diagnosis	Age at IEI diagnosis (yr)	Identified variant	Diagnosis	Age at cancer diagnosis (yr)	EBV-associated		
1	Male	XLP-1	10	*SH2D1A*:Exon 3-4 deletion, hemizygous	DLBCL	9	Yes	Yes (11)	Alive (14)
2	Male	XLP-1	1.2	*SH2D1A*:Exon 3-4 deletion, hemizygous	DLBCL	1.2	Yes	Yes (1.7)	Alive (5)
3	Male	CVID→XLP-1	3→5.3	*SH2D1A*:c.162_201+31delinsTACAAGGACATATACA, hemizygous	HL	5.2	Yes	Yes (5.7)	Alive (7)
4	Female	CVID→APDS	4→23.9	*PIK3CD*:c.1246T>C, p.(Cys416Arg) missense, heterozygous	DLBCL	23.5	Yes	Yes (23.9)	Deceased (24)
5	Female	CVID→CTLA-4 haplo-insufficiency	14→28	*CTLA-4*:c.406C>T, p.(Pro136Ser), missense, heterozygous	Gastric cancer	25	No	No	Alive (34)
6	Male	CTLA-4 haplo-insufficiency	75	*CTLA-4*:c.406C>T, p.(Pro136Ser), missense, heterozygous	Multiple myeloma	75	No	No	Alive (80)
7	Female	APDS	31	*PIK3CD*:c.1573G>A, p.(Glu525Lys), missense, heterozygous	MALToma	18	No	No	Alive (32)

Abbreviations: IEI, inborn errors of immunity; EBV, Epstein-Barr virus; HCT, hematopoietic cell transplantation; XLP-1, X-linked lymphoproliferative disease-1; DLBCL, diffuse large B cell lymphoma; CVID, common variable immunodeficiency; HL, Hodgkin lymphoma; APDS, activated phosphoinositide 3-kinase delta syndrome; CTLA-4, cytotoxic T-lymphocyte antigen 4; MALToma, mucosa-associated lymphoid tissue lymphoma.



No. at risk (censored)									
CTLA-A	4 (0)	4 (0)	4 (0)	3 (0)	2 (1)	2 (1)	2 (1)	1 (2)	0 (2)
APDS	5 (0)	5 (0)	1 (3)	0 (3)					
XLP-1	4 (0)	0 (1)							

Fig. 2. Kaplan-Meier curves for cancer-free follow-up according to age in patients with 3 types of IEI. Censor means the current age (if alive) or age at death (if deceased). Patients with XLP-1 developed cancer at an earlier age compared to those with APDS and CTLA-4 (P<0.001 by Log-rank test).
Abbreviations: IEI, inborn errors of immunity; XLP-1, X-linked lymphoproliferative disease-1; APDS, activated phosphoinositide 3-kinase delta syndrome; CTLA-4, cytotoxic T-lymphocyte antigen 4.

Fig. 2. displays Kaplan-Meier curves for cancer-free follow-up according to age in patients with XLP-1, APDS, and CTLA-4 haplo-insufficiency. The curves for the three IEI types showed significant differences (P<0.001). Three out of four XLP-1 patients developed cancer at younger ages with a median age of 5 years (1, 5, and 9 years, respectively) than those with APDS (18 years and 23 years) and CTLA-4 haploinsufficiency patients (25 and 75 years). The remaining one patient with XLP died from EBV-associated hemophagocytic lymphohistiocytosis (HLH) at 17 months of age and was later diagnosed with XLP-1

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through genetic testing. Among five patients with APDS, two developed lymphomas, while the remaining three younger patients did not develop cancer, yet (11, 19, and 19 years, respectively). Among the four CTLA-4 haplo-insufficiency patients, two developed gastric cancer and multiple myeloma, respectively while two other patients were free of cancer yet (38 and 62 years). Cases per person-year for malignancy were as follows; 0.1714 for XLP-1, 0.022 for APDS, and 0.010 for CTLA-4 haplo-insufficiency patients, respectively.

Following are the details of each patient who developed cancer. Patients 1 and 2 are siblings. Patient 1 was evaluated for recurrent fever and weight loss for six weeks by an infectious disease physician. During the follow-up, blood EBV DNA was detected at 84,850 IU/mL and a tonsil biopsy revealed EBV-associated DLBCL. He was referred to a hemato-oncologist for chemotherapy. During the chemotherapy, he had persistently high EBV DNAemia and cancer progression was detected, but IEI was not suspected. Around this time, his younger brother, patient 2 presented with refractory Kawasaki disease. After a very convoluted clinical course, he was eventually diagnosed with EBV-associated DLBCL with high EBV DNAemia at 78,143 IU/mL. At that point, a familial genetic test was performed. Both patients had the same pathogenic variant in *SH2D1A* (exon 3–4 deletion, hemizygous) gene. These 2 patients were finally diagnosed with XLP-1. After final IEI diagnosis, both of them received HCT.

Patient 3 had a family history of a maternal uncle's early death due to meningoencephalitis without additional information. Patient 3 was diagnosed with CVID around 3 years old, based on hypogammaglobulinemia and a history of recurrent pneumonia. The genetic test result from outside hospital was non-diagnostic at that time. Monthly intravenous immunoglobulin G (IVIG) therapy has continued since then. At the age of 5, he developed prolonged fever with an EBV DNAemia (peak titer 78,272 IU/mL) for five months. Eventually, EBV-associated HL was confirmed by radiologic and pathologic evaluation. At this point, genetic testing was performed repeatedly, and XLP-1 was finally diagnosed by confirmation of a novel pathogenic variant in the *SH2D1A* gene (c.162_201+31delinsTACAAGGACATATACA, hemizygous).[7] After the confirmation of final diagnosis, he received HCT and is alive.

Patient 4 was diagnosed with CVID at the age of four and had been on regular IVIG therapy. EBV-associated DLBCL was diagnosed at 23 years old. About five months after her cancer diagnosis, a pathogenic variant of the *PIK3CD* gene (c.1246T>C, p.[Cys416Arg] missense, heterozygous) was confirmed by genetic testing. After the final IEI diagnosis of APDS, she received HCT. However, this patient died of complications during HCT.

Patient 5 was diagnosed with CVID at 14 years old and had been on IVIG therapy. She developed early gastric cancer at 25 years old without evidence of *Helicobacter pylori* infection. At the age of 28 years old, a genetic test was performed, which confirmed CTLA-4 haplo-insufficiency (c.406C>T, p.Pro136Ser, missense, heterozygous).

Patient 6 was a maternal uncle of patient 5 and was diagnosed with multiple myeloma and later confirmed with CTLA-4 haplo-insufficiency through family genetic testing.

Patient 7 had a history of recurrent sinopulmonary infection and bronchiectasis since childhood. She developed MALToma of the parotid gland at 18 years old and received chemotherapy. She developed additional cancers later; HL (not EBV-associated) at 25 years old and vulva intraepithelial neoplasia III at 29 years old. She was referred to the IEI clinic due to a recurrent infection history with bronchiectasis. Genetic testing confirmed a likely

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pathogenic variant of the *PIK3CD* gene (c.1573G>A, p.Glu525Lys, heterozygous) and she was finally diagnosed with APDS at 31 years old.

DISCUSSION

In this study, we investigated cancer development among IEI patients in a single center, in Korea. Out of 194 patients with IEI, 3.6% were diagnosed with cancer with a median age of 18 years. The underlying IEI included XLP-1 (n=3), APDS (n=2), and CTLA-4 haplo-insufficiency (n=2). Lymphoma was the most frequently diagnosed cancer in patients with IEI and EBV-associated lymphoma accounted for 80.0% (4/5).

Traditionally, the most important disease manifestations were infectious complications in IEI patients. Therefore, most IEI patients have been followed by infectious disease physicians. However, since IEI patients also have several other manifestations such as allergy, autoimmunity, and cancer, physicians who take care of IEI patients should be aware of these disease entities during their follow-up period.

It is well known that cancer risk is increased in patients with IEI, reported as 4–25%.[8,9] Another study reported that the incidence of cancer in IEI patients was about 10,000 times higher than that of a similar age group.[10] The rate of cancer occurrence observed in this study was higher than the age-standardized cancer incidence rate of the general population in Korea (0.027%, 269.7 per 100,000); 0.015% for children aged 0–14 years, 0.078% for individuals aged 15–34 years, 0.478% for adults 35–64 years and 1.484% for seniors aged over 65 years.[11,12] Delays in detection and treatment of cancer may be associated with more fatal outcomes. Therefore, cancer surveillance in IEI patients may contribute to improved survival.

In this study, there were three types of IEI with cancer development: XLP-1, APDS, and CTLA-4 haplo-insufficiency, which presented with cancer occurrence rates of 75%, 40%, and 50%, respectively. According to previous studies, IEIs with cancer occurrence were reported in ataxia telangiectasia mutated (33%), XLP (30%), Wiskott-Aldrich syndrome (WAS) (13%), CVID (2.5-9.3%), X-linked agammaglobulinemia (XLA) (6%), and severe combined immune deficiency (SCID) (1.5%).[13,14] In our cohort, there were 8 patients with WAS, 19 patients with XLA, and 13 patients with SCID, none of whom developed cancer yet. In cases of WAS and SCID, all except one patient have received HCT. Recent advances in curative treatment and conservative management appear to reduce the rate of cancer development. However, judicious monitoring is still needed when caring for these types of IEI patients.

XLP-1 is an IEI caused by a deficiency of signaling lymphocyte activation molecule (SLAM)-associated protein (SAP), and is characterized by EBV-triggered immune dysregulation, lymphoproliferation, hypogammaglobulinemia, and lymphoma.[15,16] XLP-1 is an X chromosome-related disease, found in one to three individuals out of one million male individuals.[17] Previous studies demonstrated that one-third of patients with XLP-1 develop lymphoma, predominantly B cell non-HL, with or without EBV infection.[18] In our study, all four XLP-1 patients had EBV infection, and three of them developed EBV-associated lymphoma. A previous study showed that preemptive HCT in patients with XLP-1 before symptom onset such as HLH, lymphoma, severe infection might be beneficial.[19] Still, HCT can lead fatal complications including graft failure, graft-versus-host disease and even mortality. Therefore, cooperation with hematologists considering the benefit and risk of HCT is needed for tailored management.

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APDS is an IEI caused by either a gain-of-function variant in the *PIK3CD* gene (type 1 APDS) or a loss-of-function variant in the *PIK3R1* gene (type 2 APDS).[20] APDS is a disease characterized by severe infection, lymphadenopathy, and autoimmunity.[21] According to previous studies, 13% of patients with APDS developed malignancies, mostly, B cell lymphoma with a median age of 18 years.[22-24] There were reports of other malignancies, including dysgerminoma and rhabdomyosarcoma in patients with APDS.[22,25,26] In our study, 2 out of 5 APDS patients developed cancer (MALToma and EBV-associated DLBCL). Given that the median age of cancer diagnosis is over 18 in patients with APDS, surveillance for malignancies of APDS patients in the adolescent period may be important.

CTLA-4 haplo-insufficiency, caused by a germline heterozygous variant of *CTLA-4*, was demonstrated to be associated with severe immune dysregulation.[27,28] In addition, they may exhibit lymphoproliferation, autoimmune cytopenia, hypogammaglobulinemia, with increased susceptibility to recurrent infections.[29,30] In a large global CTLA-4 multicenter study, cancer occurred in about 13.0% (17/131) of CTLA-4 haplo-insufficiency patients. Among these 17 patients, lymphoma was the most common type of cancer diagnosed (10/17) with a median age of 32, followed by gastric adenocarcinoma (5/17) with a median age of 34.[31] In our study, 2 of 4 CTLA-4 haplo-insufficiency patients developed cancer.

CVID is a group of heterogenous disorders diagnosed by exclusion of definite cause of hypogammaglobulinemia.[32,33] Patients with CVID seem to have a higher incidence of cancer than the general population, and it has been reported that gastric cancer and lymphoma were common.[34] There are increasing number of patients who were previously diagnosed with CVID and are confirmed with another IEI later through genetic testing. As mentioned, among the seven patients who developed cancer, three patients' initial diagnosis was CVID (Patients 3, 4, and 5).

Various cancers can occur in several types of IEI patients. Among those, EBV-associated lymphoma may be most common as observed in our study and also in the literature. According to IUIS classification, patients with CID, antibody deficiency, immune dysregulation, and defects in intrinsic and innate immunity have increased susceptibility to EBV infection and serious outcomes such as HLH and cancer development. In our cohort, 1 patient with antibody deficiency (APDS) and 3 patients with immune dysregulation (XLP-1) developed EBV-associated lymphoma. Therefore, it is important to suspect the possibility of cancer and test for EBV when patients develop symptoms such as lymphadenopathy, hepatosplenomegaly, prolonged fever, or blood laboratory values abnormality.

The overall cancer incidence in this study seemed to be lower than the 4–25% reported in previous studies in the 1990s.[9] This finding could be associated with recent advances in the diagnosis and management of IEI, reducing the risk of cancer development. In addition, early detection and treatment of precancerous lesions may have contributed to lowering the cancer incidence.

In conclusion, cancer occurred in 3.6% of IEI patients at a single center in Korea. In addition to the infectious complications and inflammation aspects of IEI, physicians caring for IEI patients should also be aware of the potential risk of cancer, especially in association with EBV infection.

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요약

목적: 선천면역장애 환자들은 감염에 취약할 뿐만 아니라, 면역이 정상인 사람들에 비해 암 발생률도 높은 것으로 알려져 있다. 본 연구는 단일 기관에서 추적 중인 선천면역장애 환자들에서의 암 발생을 조사하여 보고자 하였다.
방법: 1994년 11월부터 2023년 9월까지 삼성서울병원에서 선천면역장애 진단 하에 추적하는 환자를 대상으로 후향적으로 의무기록을 리뷰하였다. 선천면역장애 환자 중에서 암으로 진단된 환자를 확인하였다.
결과: 총 194명의 선천면역장애 환자 중, 7명(3.6%)의 환자에서 암이 진단되었다. 5명의 환자가 림프종으로 진단받았으며 그 중 4명의 환자는 Epstein-Barr 바이러스 연관 림프종이었다. 나머지 암은 위암과 다발 골수종이었다. 암 진단 당시 나이는 중앙값 18세 (범위, 1세–75세)였다. 암이 발생한 환자들의 면역결핍 질환은 X-linked lymphoproliferative disorder-1 (XLP-1) 3명, activated phosphoinositide 3-kinase delta disease (APDS) 2명, cytotoxic T-lymphocyte antigen 4 (CTLA-4) haplo-insufficiency 2명이었다. 개별 질환별로 분석하였을 때, XLP-1 환자의 75.0%, APDS 환자의 40.0%, CTLA-4 환자의 50.0%에서 암이 발생하였다. XLP-1 환자는 APDS 및 CTLA-4 haplo-insufficiency 환자에 비해 더 이른 나이에 암이 발생하였다 (중앙연령 5세, $P<0.001$). 한 명은 조혈모세포 이식 치료 중 사망하였다.
결론: 국내 단일 기관에서 진료받는 선천면역장애 환자들의 3.6%에서 암이 발생하였다. 선천면역장애 환자들을 진료하는 의료진들은 이들 환자에서 감염이나 염증 등의 문제외에도 암 발생의 가능성, 특히 Epstein-Barr 바이러스 감염과 연관된 암의 비중이 높은 것에 대한 인식을 갖는 것이 중요하다.