Primary Immunodeficiency and Cancer in Children: A Review of the Literature

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Abstract: The life span of patients with primary and secondary immunodeficiencies has increased due to recent advances in diagnostic and therapeutic strategies. Primary immune deficiencies (PIDs) are genetic disorders that predispose patients to frequent infections, autoimmunity and malignancies. Genomic instability due to defective DNA repair processes and other unknown mechanisms in patients with PID leads to an enhanced risk of cancer. PIDs were originally described as rare diseases occurring only in infants and young children, which are associated with severe clinical symptoms. However, advances in gene sequencing technologies, have revealed that they are much more common than originally appreciated and are present in older children, adolescents, and adults. After infection, malignancy is the most prevalent cause of death in both children and adults with PIDs. The overall risk of developing cancer in patients with PID is estimated to range from 4.7 to 5.7 percent. A 1.4 to 1.6-fold excess relative risk of cancer has been reported for PIDs. Increasing awareness among physicians regarding PID and cancer may lead to earlier diagnosis which may decrease morbidity and mortality. In this paper, we review the various categories of PIDs in children and highlight their association with various malignancies. MEDLINE was searched to identify articles for inclusion. Three authors have independently screened literature search results from MEDLINE and abstracted data from studies dealing with cancers of children among primary immune deficiencies.

Keywords: Malignancy, primary immune deficiency, children, lymphoma, genomic, tumor.

1. INTRODUCTION

1.1. Why is the Risk of Cancer Increased for PID?

The immune system is known to be protective against non-self antigens like viruses, bacteria, and parasites. However, less is known about tumor surveillance among immune cells. The immunological surveillance of cancer was proposed by Lewis Thomas and Frank Macfarlane Burnet more than 50 years ago [1-4]. Various lines of evidence support the hypothesis that the immune system plays an important role in tumor surveillance; 1) primary immunodeficiencies in mice and humans are associated with increased cancer risk; 2) patients receiving immunosuppressive drugs following organ transplantation have a tendency to develop cancers; 3) patients with acquired immunodeficiency due to human immunodeficiency virus (HIV-1) infection have an increased risk of cancer; 4) immune cell infiltrates in tumors represent a prognostic factor for survival according to their quality and quantity; 5) malignant cells carry mutations in protein-coding genes which are recognized by the adaptive immune system, 6) tumor cells selectively accumulate mutations to survive immune destruction (“immunoediting”); 7) lymphocytes carrying NKG2D receptor can recognize and eliminate stressed premalignant cells; 8) novel therapeutic approaches focus on molecules critical in immune checkpoints such as CTLA-4, PD-1, or PD-L1. Our current knowledge supports the protective nature of the immune system against non-self and self-antigens [5].

Several mechanisms are exerted to explain the occurrence of malignancies in patients with PID including intrinsic and extrinsic causes. Intrinsic disorders arise from defects in differentiation or apoptosis including; cytoskeleton, lymphocyte co-signaling, metabolism, cytotoxicity and impairment of the genetic material including chromosome stability, telomere maintenance, and DNA repair. On the other hand, extrinsic causes include transforming infections (HPV and EBV virus infections) and chronic tissue inflammation. The lack of control of chronic inflammation and oncogenic vi-
ruses along with the loss of tumor surveillance facilitates the development of malignancies [6].

2. CANCER EPIDEMIOLOGY IN PIDS

An increased risk of cancer among PIDs was reported by The Australasian Society of Clinical Immunology and Allergy PID registry (including 1132 patients from 79 centers in Australia). Within this report, PID diagnoses included, predominantly, antibody deficiencies (77.8%), complement deficiencies (6.9%), combined T-cell and B-cell immunodeficiencies (4.8%), well-defined immunodeficiency syndromes (5.8%), congenital defects of phagocyte number, function, or both (3.5%) and diseases of immune dysregulation (1.2%). A 1.6-fold relative excess risk of cancer for all PID and a relative increased risk for non-Hodgkin lymphoma (NHL), leukemia, gastric cancer and thymoma were observed compared to age-matched general population [7]. There was an 8-fold increased risk for NHL for all types of PID and B-cell lymphomas were more common [7]. Non-Hodgkin lymphoma was found to be higher in patients with ‘antibody deficiencies’ and ‘well-defined immunodeficiency syndromes’, leukemia was found to be higher in patients with ‘disorders of immune dysregulation’ and IgG subclass deficiency. They did not show an increased risk of leukemia in Ataxia telangiectasia (AT) patients [7]. The authors speculated that due to decreased gastric IgA and hydrochloric acid production along with facilitated Helicobacter pylori colonization and gastric inflammation, the risk of stomach cancer was high in all PIDs [7-9]. The largest study included 3658 patients with PID enrolled in the United States Immune Deficiency Network (USIDNET) registry between 2003 and 2015, and among them approximately 4.7% percent of patients reported cancers [10]. Within this report, common variable immune deficiency (CVID) was the most encountered (35%) PID which was followed by chronic granulomatous disease (CGD) (13%), DiGeorge syndrome (12%), severe combined immunodeficiency (SCID) (7%), Wiskott-Aldrich syndrome (WAS) (7%), and Hyper IgM syndrome (4%). Within the included subjects, male to female ratio was 1.4. In The Surveillance, Epidemiology and End Results Program (SEER) population-based cancer registry in United States, there was a 1.42 fold increased relative risk in PID. Although lymphoma was more frequent in patients with PID, common malignancies were similar (i.e. lung, colon, breast and prostate) [10]. Within 171 different cancers reported in the cohort; lymphoma constituted 48%, skin cancers 15%, genitourinary 8% and gastrointestinal cancers 8%. Among PID cases, cancer was the most frequent in CVID by 47% followed by patients with unclassified hypogammaglobulinemia and patients with agammaglobulinemia. None of the patients with CGD were diagnosed with cancer [10].

Within the Dutch patients with PID registered in European Society for Immunodeficiencies (ESID) database, 8.1% had malignancy. Lymphoma was the most frequent cancer (28.3%) with NHL taking the lead [11].

3. LYMPHOMA AND IMMUNE DEFICIENCY

Since lymphoma is the leading cancer type among patients with PID, there are studies focusing especially on it. Tanyıldız et al., assessed 100 childhood lymphoma cases (57 NHL, 43 HL) [12]. They compared the survival rates among immunodeficient and immunocompetent patients and they also sought the efficacy of rituximab in patients with PID. Seventeen (17%) of these patients with PID developed lymphoma (NHL in 10 of 17) and the median age was 6 years (3–16) at diagnosis with an increased female/ male ratio. The diagnoses included AT (n=7), CVID (n=2), selective IgA deficiency (n=2), autoimmune lymphoproliferative syndrome (ALPS:n=1), WAS (n=1), interleukin-2-inducible T-cell kinase (ITK) deficiency (n=1), X-linked lymphoproliferative syndrome (XLPS; n=1), and Epstein-Barr virus (EBV)-associated lymphoproliferative syndrome (n=1) [12]. Rituximab was administered to patients with DLBCL or Burkitt lymphoma (BL) with an AT or renal transplant background as a first-line treatment, and also in the relapse protocol for the BL cases with an EBV-associated lymphoproliferative disease background and the B-cell lymphoblastic lymphoma cases with an AT background. Rituximab was not found to increase survival compared to other treatment modalities without rituximab [12]. In patients with lymphomas that expressed CD20, reduced-dose chemotherapy with rituximab as the first-line treatment showed a beneficial effect [12]. Seidemann et al., reported 19 patients with PID who developed NHL within a total of 1413 cases [13]. The PID diagnoses included predominantly antibody deficiencies (n=6) and combined immune deficiencies (CID) (AT n=3; Nijmegen breakage syndrome (NBS) n=4; Purine nucleoside phosphorylase deficiency n=1; IL 2 receptor defect n=1, other combined PID n=4). T-NHL was diagnosed in 4 of 13 and B-NHL in 9 of 13 CID patients, whereas in 6 patients, with humoral PID, 2 developed T-NHL and 4 B-NHL. The types of NHL differed in PID and non-PID cases such as centroblastic and immunoblastic lymphomas (31.6% vs. 8.1%), anaplastic large cell lymphoma (26.3% vs. 10.7%), BL and B-ALL (21% vs. 47.8%). Therapy-related toxicity was observed more in PID cases. The causes of death in these cases were sepsis (n=3); tumor progression (n=3); relapsing of the disease (n=1); bone marrow transplantation (BMT)-related toxicity (n=1) and secondary malignancy (n=1). The median age at diagnosis was lower among patients with PID (7.8 years versus 9.3 years). The lymphoma was diagnosed in 6 of 19 children before 3 years of age and in 3 prior to PID diagnosis. Fifteen of nineteen patients had multiorgan involvement and extranodal disease, and in 3 of them, tumor was located in rare sites [13]. In 10 patients, treatment was modified due to comorbid factors such as severe infections and toxicity. The toxicity was not compared with patients with cancer who did not have PID. The methotrexate dose was low in chromosome breakage syndromes, alkylating agents and epipodophyllotoxines were either decreased or skipped in DNA repair defects. Three patients died due to multiorgan failure and sepsis. The tolerance to therapy was not different among patients with humoral or combined immunodeficiencies. Twelve patients achieved remission. The majority of PID cases were misdiagnosed as infection prior to the diagnosis of cancers. Due to increased risk of lymphoproliferative neoplasms and higher treatment-related side effects, early suspicion for lymphoma is crucial in these cases. Due to the rarity of immunodeficiency and lymphoma, optimal treatment is not clear. Each patient may need his/her own individual regimen like initiating treatment with decreased doses and modifying the inten-
4. EBV AND LYMPHOPROLIFERATIVE DISEASES

EBV is known to be associated with the development of lymphoma in patients with PID [15] associated with cytotoxicity and T-cell dysfunctions [16]. These susceptible patients with PID may manifest with haemophagocytic lymphohistiocytosis (HLH), dysgammaglobulinemia or chronic lymphoproliferative/lymphoma disease following EBV infection [16]. In some PIDs, EBV-associated lymphoproliferative disorders are more frequent than other PIDs [17]. Susceptibility to EBV is classified as a new entity within the diseases of immune dysregulation in the International Union of Immunological Societies 2017 report [18]. This group includes CTPS1, ITK, XLP type 1 and type 2, CD27, FAAP24, RAS guanyl-releasing protein 1 (RASGRP1), CD70, CARMIL 2, MAGT1 and PRKCD deficiencies.

ITK deficiency is clinically characterized by EBV-induced immune dysregulation and susceptibility to lymphoma. Previously reported patients exhibited EBV related NHL or most frequently HL with variable results to chemotherapy and HSCT [15, 18-21].

XLP patients may present with the triad of fulminant infectious mononucleosis, HLH, dysgammaglobulinemia and/or lymphoma [22]. Besides patients developing lymphoma following EBV infection, some patients demonstrate no evidence of a prior EBV infection [23]. Reduced-intensity conditioning (RIC) HSCT is the only curative therapy according to the current approach [24].

RASGRP1 deficiency is a recently described PID, in which a decrease in CD4+ T cells and EBV associated B cell lymphoma may be seen. The reported three cases showed recurrent sinopulmonary infections, EBV-related lymphoproliferation and B cell lymphoma, increased susceptibility to herpes virus (HSV, VZV and CMV) and pyogenic infections and autoimmune manifestations [25].

CD70–CD27 signaling is critical in T and B cell-mediated immunity and has a major role in EBV immunity [26]. Both CD70 and CD27 deficiencies share some clinical and immunological features such as autoinflammatory diseases, EBV-associated Hodgkin’s lymphoma and hypogammaglobulinemia [26, 27].

5. COMBINED IMMUNE DEFICIENCIES (CID) AND MALIGNANCIES

This group includes DNA repair defects and other disorders with associated syndromic features [18]. Bloom syndrome, NBS, and AT are the best-known DNA repair defects predisposing to lymphomas. Besides the increased rates of malignancies, these diseases are challenging regarding the toxicity observed following chemo-radiotherapy. Suarez et al., reported malignant diseases in 69 (24.5%) among 279 AT patients of the French population. Although the majority of the patients developed NHL, ALL, AML, HL, NHL, T-ALL, carcinomas were also reported. All NHLs were high-grade mostly of B-cell origin. HL and NHL had mostly extranodal involvement. Epstein-Barr virus was highly prevalent in lymphomas [28].

NBS, and DNA ligase IV deficiency are autosomally recessively inherited combined immunodeficiencies characterised by microcephaly, abnormal facies, radiosensitivity, developmental delay and susceptibility to malignancies [29-32]. In an NBS cohort, 42% of the patients with cancer were diagnosed with lymphoma, especially NHL. Other malignancies included: medulloblastoma, neuroblastoma, dysgerminoma and thyroid cancer [29]. On the other hand, leukemia, and B-cell lymphoma have been reported in DNA ligase IV deficient patients [31-33]. The reported malignancies among patients with Bloom syndrome included lymphoma, leukemia and a variety of cancers of gastrointestinal system, skin, breast, lung and endometrium. Medulloblastoma, Wilms tumor and osteosarcoma were also reported [34].

Mutations in WAS gene are implicated in two immune deficiencies; classical WAS characterized by the clinical triad of thrombocytopenia, eczema, and immunodeficiency and X-linked neutropenia (XLN) with the latest results from the gain of function. The WAS protein regulates actin polymerization in hematopoietic cells. The median age for developing cancer in WAS patients is 9.5 years [35, 36]. The tumors seen in WAS include NHL, HL and less frequently myelodysplastic syndrome, ALL, myelomonocytic leukaemia and nonhematopoietic malignancies [35-40]. Bone marrow arrest at the promyelocyte stage seen in XLN patients may be associated with myelodysplastic syndrome and AML [41].

DiGeorge syndrome (DGS) is associated with conotruncal cardiac defects, recurrent infections and hypoparathyroidism [42, 43]. In a study, 0.9% of 687 patients with DGS suffered from malignancy. The majority of the patients were diagnosed with cancer prior to 9 years of age [44]. The malignancies in DGS patients were found to be thyroid carcinoma, hepatoblastoma, neuroblastoma, ALL, Wilms tumor, teratoid/rhabdoid tumor, MALT lymphoma, EBV associated T-cell lymphoma and B-cell NHL [42-48].

6. CANCERS AMONG PREDOMINANTLY ANTIBODY DEFICIENT (PAD) PATIENTS

One of the biggest cohorts investigating cancers in humoral immune deficiencies was reported by Mellemkjaer et al. [49]. Patients with CVID (n=176), IgA deficiency (n=386) and 2071 relatives were included. In IgA deficiency, cancer incidence was not high, however, in CVID patients, the incidence of lymphoma, especially NHL and mucosa-associated lymphoid tissue (MALT) lymphomas, and stomach cancer increased [49]. The reason for CVID patients developing cancer has not been fully understood although innate genetic instability, proliferation of the lymphoid cells due to infections, and impaired clearance of oncogenic viruses are suspected [50].

7. MALIGNANCIES IN QUANTITATIVE AND QUALITATIVE PHAGOCYTE DISORDERS

Severe congenital neutropenia (SCN) predispose to recurrent and life-threatening infections. The concomitant use
of granulocyte colony-stimulating factor (G-CSF) may reduce sepsis and mortality. However, the use of G-CSF has been reported to be associated with a higher incidence of MDS and AML [51]. Rosenberg et al., reported results of the 10 year cumulative incidence for MDS/AML as 21% in patients with SCN (n=374) and Shwachman-Diamond syndrome (SDS) (n=29) who used G-CSF for a long time [51]. However, the studies are still confusing: patients with cyclic and idiopathic neutropenia who used G-CSF for a long time do not seem to be at increased risk. There are also cases of malignant transformation with chronic neutropenia not treated with G-CSF as well [51, 52]. According to Germe- shausen et al.; patients with CSF3R mutations have a higher risk for secondary malignancies compared to patients without mutations [52]. Seven patients of fifty-five SDS patients developed MDS or AML in the French Severe Chronic Neutropenia Registry with an estimated risk of 19% and 36% at 20 and 30 years, respectively [53]. Contrary to the neutropenias, chronic granulomatous disease (CGD) known to impair neutrophil functions was not observed to be associated with increased cancer risk [10]; however, Wolach et al., reported for the first time a child with CGD who developed ALL [54].

CONCLUSION

The immune system is unique by protecting us from infectious non-self pathogens and also from malignant cells. The tumor surveillance hypothesis is still significant among cancer development mechanisms. Owing to the newly identified immune deficiencies, the pathways underlying malignancies are being exhibited one by one. Pediatricians should be aware of PID and of the increased tendency of cancer in patients with PID. Early diagnosis may provide better treatment options before severe organ damage occurs including liver, lungs and bone marrow.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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