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Review Article

Hematological Malignancies Associated With Primary Immunodeficiency Disorders

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ABSTRACT

Primary Immunodeficiency disorders (PID) have been increasingly recognized in association with hematologic malignancies. To better appreciate this association, a systemic search of the Ovid MEDLINE database was performed with terms related of hematologic malignancies and all PID described in the 2017 International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. More than 60 PID distinct PID, caused by cell-intrinsic and extrinsic mechanisms were associated with diverse hematologic malignancies. These occurred among all subgroups of PID, including syndromic and non-syndromic combined PID affecting cellular and humoral immunity, predominantly antibody deficiencies and defects of immune regulation. In addition, defects in phagocyte numbers or functions, or in innate immunity were associated with hematologic malignancies. Increased awareness and vigilance for the possibility of malignancy is required when caring for patients with PID.

1. Introduction

Traditionally, primary immunodeficiency disorders (PID) were identified by increased susceptibility to infections. Subsequently, the association of PID with autoimmunity and uncontrolled inflammation was recognized, while in recent years the increased incidence of malignancies, particularly hematological malignancies is being explored [1]. Retrospective registry cohort studies in patients with Ataxia Telangiectasia [2] and Nijmegan Breakage Syndrome [3] found 25–42% incidence of malignancies. Moreover, a recent survey of 3658 patients with diverse PID enrolled in the United States Immune Deficiency Network database found an 8–10 fold excess relative risk of lymphoma compared with the age-adjusted population [4], further establishing the association recognized already in the early 1970's [5].

As recently emphasized in a review in this journal, several mechanisms can explain the association between PID and malignancies [6]. These mechanisms can be broadly categorized into intrinsic versus extrinsic to the defective immune cell [7]. These factors include impaired cell development, intra-cellular signalling, chromosome instability, chronic infection, tissue inflammation, and impaired immune surveillance [7]. Distinguishing between the different mechanisms, although challenging at times, is critical for employing the most appropriate management.

Increased awareness of clinicians, coupled with advances in genetics, has led to a surge in the diagnosis of malignancies associated with PID. More than 300 distinct single-gene inborn errors of immunity have been identified, which are often categorized by the dominant affected immune cell or mechanism [8]. These include defects in cellular and humoral immunity with or without associated non-immune features, defects in number and function of neutrophils and phagocytes, as well as intrinsic and innate immunity or complement deficiencies. Given the increasing association of hematologic malignancies with PID, described recently in broad terms [6]; [7], there is a need for a complimentary detailed review of this association. To provide a useful tool to immunologists, hematologists, oncologists and other health care providers, we provide below a comprehensive review of the PID associated with hematological malignancies.

2. Methods

A systemic search using the Ovid MEDLINE database was performed for all PID described in the 2017 International Union of Immunological Societies (IUIS) Expert Committee for Primary Immunodeficiency classification system, combined with terms for hematological

Abbreviations: AD, Autosomal dominant; ADA, Adenosine deaminase; AML, Acute myeloid leukemia; AR, Autosomal recessive; CID, combined immunodeficiency; HL, Hodgkin lymphoma; HLH, Hemophagocytic lymphohistiocytosis; IUIS, International Union of Immunological Societies; MDS, Myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma; PID, Primary immunodeficiency diseases; SCN, Severe congenital neutropenia; WHIM, Warts, hypogammaglobulinemia, infections, and myelokathexis

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malignancies. Search terms for PID were based on the listed names and affected genes as classified by the IUIS 2017. Search terms for hematological malignancies included the following from Ovid MEDLINE: hematologic neoplasms, leukemia, and lymphoma, myelodysplastic syndromes (MDS) and lymphoproliferative disorders. Abstracts of the results were reviewed to find relevant case reports, case series, and review articles of PID associated with hematological malignancies. Relevant articles were included if there was genetic confirmation of the PID when possible. References from relevant articles were further reviewed for additional references. In addition, abstracts from recent conferences were reviewed for completion.

Relevant findings were grouped in accordance with the IUIS 2017 classification system with the exception of a few conditions with similar clinical findings that were grouped together, including Hyper-IgE syndrome and Constitutional mismatch repair deficiency. With each PID, clinical features of the PID were described, followed by description of the underlying genetic, if known, the mechanistic defect of the PID and associated hematological malignancies.

3. Results

PID associated with hematological malignancies, grouped in accordance to IUIS 2017 classification system are detailed below and summarized in Table 1. Additionally, the types of PID that should be considered with specific haematological malignancies are provided in Table 2. Unless otherwise specified, the hematological malignancies described below are not secondary to hematopoietic stem cell transplant (HSCT), medications, or any other therapies.

3.1. Immunodeficiencies affecting cellular and humoral immunity

3.1.1. T-B+ SCID

Severe combined immunodeficiencies (SCID) are a group of rare inherited disorders with profound defects in T-lymphocyte function (designated as T-), with or without associated B and NK-lymphocyte defects (designated as B- and NK-, respectively). Infants with SCID suffer from fatal opportunistic infections caused by bacteria, viruses, or fungi.

X-linked SCID is among the most common causes of SCID. X-linked SCID is caused by mutations in the common gamma chain of the interleukin (IL) -2 receptor, which is also shared by receptors to the IL-4, IL-7, IL-9, IL-15, and IL-21. Lymphoproliferative disease and lymphoma have been described in patients with X-linked SCID. A 7-month Caucasian male presented with oral thrush, chronic diarrhea and left periorbital edema caused by a retro-orbital diffuse large cell B-cell NHL, which was EBV-negative. He was found to have a mutation in the common gamma chain [9]. The tumor resolved 6 months after HSCT. In addition, two patients have been described with Hodgkin-like polymorphous lymphoproliferative lesions. The first patient presented at 2 months of life with pneumocystis pneumonia and a cranial soft tissue mass, which was shown to be an EBV negative lymphoproliferative lesion. He had a c.676C > T mutation in exon 5 of gamma common chain. The second child presented with hepatomegaly and lytic lesion in the rib which was shown to be an EBV-negative lymphoproliferative lesion [10]. Another patient with X-linked SCID was found to have a nodular liver mass caused by non-transplant related multi-focal polymorphic lymphoproliferative disease [11].

Coronin-1A deficiency is a rare form of SCID characterized by recurrent ear, sinus, and respiratory infections. The Coronin family of proteins are important in the regulation of actin cytoskeleton. Autosomal recessive (AR) mutations in *CORO1A,* the gene encoding Coronin-1A cause T-cell lymphopenia and immune dysregulation. Mutations in Coronin-1A are associated with the development of EBV-associated lymphoproliferative disease and/or lymphoma at a very young age [12]; [13]; [14].

3.1.2. T-B- SCID

Recombination-activating genes 1 and 2 encode the proteins RAG1 and RAG2, respectively, which play an essential role in V(D)J recombination and initiate DNA cleavage for gene rearrangement in the generation of T-cell receptors. The spectrum of PID associated with RAG mutations varies based on the specific defect. Most patients present with SCID, while other may present with Omenn's syndrome, characterized by skin erythroderma, lymphoadenopathy, hepatosplenomegaly, hepatitis and colitis. There have been rare cases of lymphoma associated with RAG1 mutations [15], [16]. One case was a 5-year-old female with compound heterozygous mutations in *RAG1* who developed a diffuse large B-cell lymphoma [15]. A second case was a male with a history of recurrent infections, who was initially diagnosed with common variable immunodeficiency before genetic sequencing revealed mutation in RAG1. He developed a mucosa-associated lymphoid tissue lymphoma at 11-years of age.

DCLRE1C deficiency can cause SCID and Omenn's syndrome. The *DCLRE1C* gene encodes for the Artemis protein that acts in the non-homologous end-joining pathway [17]. Patients' cells have defective chromosome rearrangement, and demonstrate increased sensitivity to ionizing radiation. DCLRE1C deficiency is associated with the development of EBV-associated lymphoproliferative disease, EBV-associated lymphoma, and leukemia [18]; [19]; [20].

XRCC4-Like Factor, also known as Cernunnos- deficiency is an AR form of SCID characterized by radiation sensitivity and clinical features of microcephaly, recurrent infections, autoimmune cytopenias, and growth delay, caused by defects in the *NHEJ1* gene. There has been a case report of a 2-year-old boy who presented with EBV-negative diffuse large B cell lymphoma of the brain, and was later confirmed to have homozygous mutations in the *NHEJ1* gene [21].

DNA ligase IV deficiency is characterized by chromosomal instability, radiation sensitivity, immunodeficiency, developmental abnormalities, and growth delay. It is caused by mutations in the *LIG4* gene and impaired B and T lymphocyte development due to impaired repair of double strand breaks in V(D)J recombination. Patients might present with SCID or with Omenn's syndrome, attributed to uncontrolled inflammatory response, particularly targeting the skin, liver and gastrointestinal tract cause often by few T cells that escape thymus selection [22]. There have been described cases of patients with DNA ligase IV deficiency who have developed hematological malignancies including lymphoproliferative disorder, lymphoma and leukemia [23]; [24]; [25]; [26]; [27]; [28].

Adenosine deaminase (ADA) deficiency is the second most common cause of SCID and is characterized by growth failure, opportunistic infections, and severe thrush. ADA deficiency is caused by AR mutations in the *ADA* gene, which leads to accumulation of intracellular adenosine and deoxyadenosine as well as disruption of purine metabolism, affecting rapidly replicating cells, such as lymphocytes. Other cells and tissues, such as bone, marrow, lungs and liver might also be affected [29]. ADA deficiency has been shown to be associated with MDS and lymphoma [30]; [31]; [32]. A female patient with ADA deficiency who received ADA enzyme replacement therapy developed Burkitt's lymphoma at 15 years of age in another case report [32]. There has also been a male patient with ADA deficiency, also receiving ADA replacement therapy who developed EBV-positive cerebral lymphoma at 10-years of age. Recently, plasmablastic Lymphoma was reported in an ADA deficient patient following gene therapy [33].

3.1.3. Combined immunodeficiencies generally less profound than SCID

Purine nucleoside phosphorylase deficiency is a rare form of combined immunodeficiencies (CID) characterized by progressive immune abnormalities, neurological impairment, and autoimmunity. It is caused by mutations in the *PNP* gene and leads to the accumulation of toxic metabolites in T cells. In one case report, a 2.5-year-old female was diagnosed with B-cell anaplastic large cell lymphoma and subsequently found to have PNP deficiency [34].