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Review

Development of Cancer in Patients with Primary Immunodeficiencies

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Abstract. *Primary immunodeficiencies (PIDs) are genetic disorders that predispose to frequent and severe infections, autoimmunity and cancer. The expanded life span of such patients increases the overall risk for developing cancer, which is now estimated at 4-25%. The type of malignancy depends on the primary immunodeficiency, the age of the patient and possible viral infection, suggesting that different pathogenetic mechanisms are implicated in each case. Non-Hodgkin's lymphomas predominate, accounting for 60% of cases. The PIDs known to be associated with increased incidence of malignancy are: common variable immunodeficiency, IgA deficiency and DNA repair disorders. During recent years other types have also been included, such as severe combined immunodeficiency (SCID) and Wiskott Aldrich syndrome (WAS).*

Immunodeficiencies are genetic or acquired diseases that predispose to frequent and severe infections, autoimmunity and cancer. Patients with immunodeficiencies have an increased risk of developing malignancy due to a defective immunity towards cancer cells. Some types of immunodeficiencies, however, especially those with defective cellular immunity, predispose more frequently to cancer. The expanded life span of patients with primary and secondary immunodeficiency, due to recent therapeutic procedures and supportive care, has been connected with an increased risk for malignancies.

The incidence of primary immunodeficiencies (PIDs) is 1:10.000 births. Secondary immunodeficiencies are associated with infection with human T-cell lymphotropic virus (HTLV), immunosuppressive medication and post-transplantation immune dysfunction and although they are the most frequent, they are not addressed in this review.

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Risk and Type of Malignancy in Primary Immunodeficiencies

The overall risk for children with congenital immunodeficiency of developing malignancy is estimated at 4-25% (1). The type of malignancy is highly dependent on the primary immunodeficiency, the age of the patient and probably viral infection, suggesting that different pathogenetic mechanisms are implicated in each case (1). Non-Hodgkin's lymphomas predominate, accounting for 60% of cases (1). However, in only a few of them have distinctive features been described using current diagnostic approaches (2). Prognostic factors are not well known as yet.

There are only a few studies in the literature regarding the incidence of malignancy in primary immunodeficiencies, the histopathological types and prognosis. Filipovich *et al*. have reported the results of their research on tumours in the Immunodeficiency Cancer Registry (3). The median age of diagnosis was 7.1 years with a male predominance, due to an increased frequency of X-linked disorders. Diseases more often associated with cancer were common variable immunodeficiency (CVID), Wiskott Aldrich syndrome (WAS), ataxia-telangiectasia (AT) and severe combined immunodeficiency (SCID). Canioni *et al*. performed an interesting study from 1981-1997 among 18 children with primary immunodeficiency that developed lymphoproliferative disease (2). The patients were diagnosed as having AT, X-linked lymphoproliferative disease, combined immunodeficiency, CVID and hyper-IgM syndrome. The immunological status of the patients, as indicated by low T-cell numbers ($<1000/mm^3$) and poor to absent lymphocyte proliferative response to mitogens, was investigated in 33% and 47%, respectively. The morphological, immunochemical and molecular findings were classified as classical lymphoma, while the others were more morphologically heterogeneous.

The authors reported that the lymphomas developed usually in extranodal sites and were more frequently of the diffuse large-B cell type. The most important finding of this study was that the overall morbidity was well correlated with low T-cell number and dysfunction, rather than the type of immunodeficiency, histological classification or gene rearrangements. A third study by Frissera *et al*. presented the type of malignancy that developed in 35 patients with PIDs. Non-Hodgkin's lymphomas (60%), Hodgkin's disease (23%) and leukaemia (6%) were the most frequent lymphoproliferative diseases (4). The important point shared with the previous reports is that, although there were some differences between immunodeficiency-associated lymphoproliferative disorders, they had several common features: a tendency to present in extranodal sites, especially the central nervous system and gastrointestinal tract, rapid clinical progression when untreated, a polymorphic cell population, diffuse large cell histology, B-cell origin and association with Epstein Barr infection (5).

Possible Mechanisms of Developing Malignancy in Patients with PIDs

The immunological response to the development of tumour cells is based on the activity of cytotoxic cells, mainly natural killer (NK) cells and cytotoxic cluster CD8 cells. In addition, helper CD4 cells and chemokines, such as interleukin 2, interleukin 12 and interferons activate macrophages and protect against malignancy.

Chronic antigenic stimulation in a host with impaired immunological response was thought to be the main cause of cancer (5).

Infection induced carcinomas include some of the commonest malignancies, accounting for over 20% of the total. Epstein Barr virus (EBV) appears to be an important co-factor for the development of disease and can affect the host, either primarily or by reactivation, during an immunocompromised state (1). EBV infection results in polyclonal activation and proliferation of B-cells. Immunity to this virus is mainly controlled by specific MHC (major histocompatibility complex)-restricted cytotoxic cells and to a lesser degree by humoral responses, antibody dependent cellular toxicity, natural killer activity and cytokines. When the above mechanisms are defective, EBV-B cells can resume and continue unfavorable proliferation (5). Oncogenic DNA viruses, such as papoviruses, herpesviruses, adenoviruses and retroviruses, lead to the transduction of copies of the viral genome into cellular genes that could activate proto-oncogenes, inactivate tumour suppressor cells or stimulate growth factors causing transformation of the infected cell (1). It seems, however, that immunoregulation, imbalanced cytokine production and genetic defects, resulting in imprecise or ineffective rearrangememnt of immunoglobulin and T-cell receptor genes during lymphopoiesis, influence cancer development.

Primary Immunodeficiencies Associated with Cancer

The PIDs, known to be associated with the increased incidence of malignancy are CVID, IgA deficiency and DNA repair disorders. During recent years, patients with SCID and WAS have also been included and the above list has been further expanded. In most PIDs when the molecular defect is known, the molecular mechanism leading to malignancy can be determined.

Cancer in patients with impaired humoral immunity. Table I summarizes the malignancies reported in the literature in patients with humoral immunity defects. CVID is a heterogeneous group of disorders caused by an intrinsic defect of B-cells or B/T-cell coordination. The incidence of cancer has been estimated to be 2.5%, when the onset is before the age 16 years and 8.5% when it is later.

Non-Hodgkin's lymphomas were described in 50% and epithelial tumours, including carcinomas of the stomach, breast, bladder and cervix, in 39% of cases (1). Lymphomas are more often of the B-cell type and of extranodal location (1). Recently, in patients with CVID, a low grade malignancy was described, arising from mucosal lymphohyperplasia due to chronic inflammatory or autoimmune stimulation of the lungs and gastrointestinal tract, classified as mucosa-associated lymphoid tissue-lymphomas (MALT) (6). Twenty per cent of patients with CVID and a history of diffuse parenchymal lung disease exhibited a nearly 30% increased risk of developing B-cell lymphoproliferative disease, especially non-Hodgkin's lymphoma, possibly due to human herpesvirus type 8 infection (7).

The molecular defect in patients with CVID is variable and in most cases is not determined. Recently, it has been shown that homozygous loss of the inducible co-stimulator (ICOS) on activated T-cells may result in an adult onset form, in 5% of cases of CVID. Patients present with hypogammaglobulinaemia and defective secondary responses. Murine models have demonstrated an insufficient generation of germinal centres in the absence of ICOS. Carcinoma of the vulva has been described in one patient with ICOS deficiency (8).

An additional 5-10% of cases with CVID carry at least one mutation in the tumor necrosis factor receptor superfamily (TNFRSF13B) gene. One patient with monoallelic mutation in this gene developed tonsillar carcinoma of epithelial origin and died. More data from murine and human TNFRSF13B are needed, however, to show any possible predisposition to malignancy (9).

Table I. *Malignancies reported in the literature in patients with humoral defects.*

PID	Frequency	Malignancy
CVID*	2.5-8.5 %	Non-Hodgkin's lymphoma (50%) Epithelial tumours (carcinomas of stomach, breast, bladder,cervix) (39%) Carcinoma of the vulva (ICOS** deficiency) Tonsillar carcinoma of epithelial origin (*TNFRSF13B****)
X-linked agammaglobulinaemia	6%	Lymphoproliferative disorders, gastric adenocarcinoma, colorectal cancer
IgA and IgG subclass deficiency	Rare	Hodgkin's disease

CVID*: common variable immunodeficiency, ICOS**: inducible co-stimulator, TNFRSF13B***:Tumour Necrosis Factor Receptor Superfamily.

Table II. *Malignancies reported in the literature in patients with cellular defects.*

PID	Frequency	Malignancy
SCID*	1.5%	Non-Hodgkin's lymphoma, Hodgkin's disease, Leukaemia Multiple renal and pulmonary leiomyomata EBV**-associated lymphoma (Artemis) Burkitt lymphoma (ADA deficiency treated with PEG-ADA***)
X-linked lymphoproliferative disease	30%	Hodgkin's B cell lymphoma, non-Hodgkin lymphomas in the intestinal region
Autoimmune lymphoproliferative syndrome (ALPS)		Hodgkin's and non-Hodgkin's lymphoma
Wiskott-Aldrich syndrome	13%	Diffuse large B-cell lymphomas, non-Hodgkin's lymphoma of larynx, leukaemia, cerebellar astrocytoma, Kaposi sarcoma, smooth muscle tumours
Chromosome 22q11 deletion syndromes		B-cell lymphomas, hepatoblastoma, renal cell carcinoma, neuroblastoma
Hyper-IgM syndromes		Carcinomas of liver, pancreas, biliary tract

SCID*: severe combined immunodeficiency, EBV**: Epstein Barr Virus, PEG-ADA***: polyethylene glycol-adenosine deaminase.

Table III. *Malignancies reported in the literature in patients with DNA repair defects.*

Type	Frequency	Malignancy
ATM*	33%	Lymphoid leukemias, lymphomas, epithelial tumours
ATM heterozygous	3.8%	Breast and gastrointestinal cancer
Nijmegen breakage syndrome	rare	Brain tumors, lymphomas, leukemia
Fanconi anemia	26%	Acute myeloid leukaemia(10%) MDS (10%), squamous cell carcinomas (6%)
Artemis	13%	Lymphoma
DNA ligase IV defect	rare	T-cell acute lymphoblastic leukemia, non-Hodgkin's lymphoma
Xeroderma pigmentosum, cartilage hair hypoplasia	rare	Basal cell carcinomas

ATM*: ataxia telangiectasia mutated.

IgA deficiency, which is the commonest type of immunodeficiency, is associated with a high frequency of epithelial tumours, due to defective defence of the mucosa against pathogens, especially of the respiratory and gastrointestinal tract. In addition to immunological impairment, other local conditions such as chronic atrophic gastritis or pernicious anaemia, usually observed in these patients, may play an important role in tumour development (1).

Other defects of humoral immunity, rarely associated with malignancy, are X-linked agammaglobulinaemia (XLA) and subclass deficiency. XLA has a risk of 6% for tumour development mainly of lymphoproliferative disorders, gastric adenocarcinoma and colorectal cancer (10, 11). Adenocarcinoma develops in combination with local immunological impairment and chronic gastritis. Rapidly progressive colorectal cancer is diagnosed 30-times more frequently in patients with XLA and

for this reason screening of these patients has been proposed (11). In one study two patients with selected IgA and IgG subclass deficiency without hypoglobulinaemia developed Hodgkin's disease (12).

A multi-centre retrospective study in patients with antibody deficiency and lymphoproliferative disease revealed that B-cell lymphoma is frequent in CVID and rare in patients with agammaglobulinemia and isolated IgG subclass deficiency (13).

Hyper-IgM syndromes. Hyper-IgM syndromes are caused by mutations in the genes encoding for the CD40/CD40L interaction pathway leading to defects in the switching of the genes of immunoglobulins in different classes. Patients with X-linked hyper-IgM syndrome suffer from chronic hepatitis and cholecystitis due to defective clearance of cryptosporidia that is a possible mechanism for the development of carcinomas of the liver, pancreas, billiary tract and associated neoectodermal endocrine cells (14). Expression of CD40 has been detected in most B-cell neoplasias, such as Hodgkin's disease and Reed-Sternberg cells (15).

Cancer in patients with combined immunodeficiencies. Patients with SCID soon die unless successful bone marrow transplantation is performed. The incidence of developing cancer is 1.5% before the age of 1 year, mainly non-Hodkgin lymphoma, Hodgkin's disease and leukaemia (Table II). A defect in variable diversity and joining [V(D)J] recombination leads to SCID, while a deregulation of this process may participate in the onset of lymphoid malignancy, since this mechanism is a critical checkpoint in the development of both B and T lymphocytes (16). It has been reported that a child transplanted for X-linked SCID developed multiple renal and pulmonary leiomyomata 8 years after haploidentical transplantation (17). Also, a patient with adenosine deaminase (ADA) deficiency and replacement therapy with PEG-ADA developed Burkitt lymphoma 13 years later (18).

All combined immunodeficiencies are more or less associated with malignancy. X-linked lymphoproliferative disease is a T-cell regulatory defect that leads to uncontrolled B-cell proliferation after EBV infection. Thirty percent of patients develop lymphoma of B-cell phenotype at a median age of 4.9 years. Rarely, non-Hodgkin's lymphomas occur in the intestinal region (19).

Autoimmune lymphoproliferative syndrome (ALPS) is a variable clinical condition manifesting as lymphoproliferative disease, autoimmune cytopenia and susceptibility to malignancy and is known to be due to defective apoptosis (20). Mutations have been described in different genes of the Fas mediated signalling pathway, Fas gene and caspases 8 and 10. Somatic Fas mutations have been found in multiple myeloma. The patients have an increased risk of developing Hodgkin and non-Hodgkin's lymphoma, underscoring the critical role played by cell surface receptor-mediated apoptosis in eliminating redundant proliferating lymphocytes with autoreactive and oncogenic potential (21, 22).

WAS is a combined immunodeficiency characterized by thrombopenia from infancy, eczema and progressive immunodeficiency. A function of the WAS protein is to link signalling pathways to actin cytoskeleton reorganization which is involved in the establishment of immunological synapses between T lymphocytes and antigen presenting cells, as well as between cytotoxic T and natural killer cells and their targets. NK-cell cytotoxicity, chemotaxis and chemokinesis are also impaired (23). An abnormal response of lymphocytes to EBV infection and reduced surface expression and aberrant proteolysis of CD23 in patients with WAS has also been described (24). Approximately 13% of individuals with WAS developed malignancy, which was the second reason of morbidity, mainly diffuse large B-cell lymphomas, that were extranodal and frequently involved the brain (24). These patients may also have a variety of malignancies including non-Hodgkin's lymphoma of the larynx (25), leukaemia, cerebellar astrocytoma, Kaposi sarcoma (26, 27) or rarely smooth muscle tumours (24). WAS-associated malignancies have a poor prognosis, as illustrated by the fact that only 1 of the 21 patients was alive for more than 2 years after diagnosis (24).

Chromosome 22q11 deletion syndromes are associated with a wide variety of phenotypic abnormalities including a variable degree of immunodeficiency. Patients with severely impaired T-cell function are few (5-10%) and need thymus transplantation. However, there are also reports of developing, usually B-cell lymphomas induced by Epstein Barr virus (28). Hepatoblastoma and renal cell carcinoma, as well as neuroblastoma, have also been reported (29).

The ICF syndrome (immunodeficiency, centromeric instability and facial anomalies) is a recessive disease affecting humoral immunity and causing DNA rearrangements targeted to the centromere-adjacent heterochromatin region of chromosomes 1 and 16 (30).

Cancer in patients with DNA repair defects. DNA double-strand breaks, arising after ionizing radiation, are a serious form of DNA damage, potentially leading to replication errors, loss or rearrangement of genomic material and eventually cell death or carcinogenesis. Syndromes well known to be associated with cancer are those caused by DNA repair defects, including AT, Bloom syndrome, Fanconi anaemia, Nijmegen syndrome, Cartilage Hair Hypoplasia and other rare diseases (Table III). These defects are associated with an increased risk for malignancy, mainly the B-cell non-Hodgkin's lymphomas. Hodgkin's, Burkitt and non-Hodgin's lymphohyperplasia B- or T- cell type have also been reported (31).

AT is a rare neurodegenerative disease. The defective Ataxia-telangiectasia mutated protein (ATM protein) is the

central component of the signal-transduction pathway responding to double-strand breaks. Increased incidence of cancer is observed in one third of AT patients, mainly lymphoid leukaemias and lymphomas, but there is also a substantial risk of epithelial tumours later in life (32). Carriers are estimated to be 0.5%-1% of the population and have an increased risk of developing malignancy, especially breast and gastrointestinal cancer. Loss of heterozygosity has been found in 30-40% of breast cancer cases and defective protein in 50-70% (33).

Nijmegen breakage syndrome, a disease of the same repair pathway, is frequently associated with brain tumours, lymphomas and leukaemia (34).

Similar clinical phenotypes in addition to microcephaly, developmental delay and failure to thrive have been described in patients with DNA ligase IV defect which also demonstrates in non homologous recombination of DNA double strands (31).

Fanconi anaemia is a hereditary disorder that includes bone marrow failure, congenital abnormalities and cancer predisposition, including acute myeloid leukaemia and squamous cell carcinomas (35). The Fanconi anaemia-Breast Cancer Risk Assessment (BCRA) pathway is frequently implicated in human cancer, such as breast cancer and familiar ovarian cancer (36, 37).

Mutations of the Artemis gene cause SCID and Epstein Barr positive lymphoma in 6% of patients (38). Xeroderma pigmentosum is also associated with an increased risk of skin cancer (39). Cartilage hair hypoplasia is an inherited syndrome characterized by short stature, sparse hair and immunodeficiency, frequently associated with malignancy and increased risk of basal cell carcinomas (40).

Cancer in patients with defects of phagocytes. Defects of phagocytes are infrequently associated with malignancy. Congenital neutropenia is a heterogenous disorder that includes Kostmann syndrome and predisposes to myelodysplasia and acute myelogenous leukaemia especially caused by mutations of neutrophil elastase, granulocyte-colony stimulating factor (G-CSF), RAS and monosomy of chromosome 7 (41). Interestingly, mutations of neutrophil elastase have been identified experimentally in several cell lines from metastases of human breast and lung cancer (42).

Schwahmann syndrome is associated with an increased incidence of acute myelogenous leukaemia (43). Several malignancies have been observed in hyper-IgE syndromes (Job syndrome), such as anaplastic large cell lymphoma, peripheral T- cell lymphoma and pulmonary adenocarcinoma (44, 45). Chronic granulomatous disease is caused by a defect of the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase pathway that results in defective killing of intracellular pathogens phagocytosed by neutrophils. Only one patient with chronic granulomatous disease who developed acute lymphoblastic leukaemia has been reported (46). WHIN syndrome, the acronym for warts, hypoglobulinemia, immunodeficiency and myelokathexis, is a congenital neutropenia syndrome. Two cases of B-cell lymphoma following EBV infection have been reported (47). Defects of lysosomal enzymes (Chediak-Higashi, Griscelli and perforin disorders) are known to be associated with haemophagocytic disease and an increased risk of leukaemia.

Therapeutic Process

The therapeutic process for patients with immunodeficiency is not different from other patients with the same malignancy. Short chemotherapeutic protocols, however, are better and prophylaxis from bacteria and pneumonocystii carinii is needed. Patients with combined immunodeficiency can be cured with haematopoietic stem cell transplantation. In most cases, the preparative chemotherapy conditioning does not include radiation. Engraftment can be accomplished in 70-90% of the cases when an identical human leukocyte antigen (HLA) donor is available. The risk for lymphoma, however, in the transplanted patients is not well known (6).

The treatment of malignancy in patients with DNA repair defects may be difficult, balancing the risk of adequate doses of chemotherapy against toxicity. Radiomimetic agents or treatment with cyclophosphamide, methotrexate, vincristine and etoposide should be avoided.

It seems, however, that knowledge of the type of malignancy developed in each patient is limited and most of the reports are from the last decade, when both the lifespan of these patients and the treatment have changed. Furthermore, the most effective treatment is not as yet known, but bone marrow transplantation with an identical HLA donor has saved the lives of some patients (48).

Gene therapy is considered an alternative therapy to bone marrow transplantation for the correction of single gene defects. This curative treatment would avoid the side effects of graft *versus* host disease (GVHD), allogeneic graft rejection and toxicity of myeloablative drugs (49). Nevertheless, the development of T-cell leukaemia, following the otherwise successful treatment of patients with X-linked severe combined immunodeficiency, has led to the re-evaluation of this approach (50).

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