

Primary Immunodeficiencies: Genetic Risk Factors for Lymphoma¹

A. H. Filipovich,² A. Mathur, D. Kamat, and R. S. Shapiro

Immunodeficiency Cancer Registry [A. H. F.] and Division of Immunology, Department of Pediatrics, [A. H. F., A. M., D. K., R. S. S.], and the Department of Oral Sciences [A. M.], University of Minnesota, Minneapolis, Minnesota 55455

Abstract

It has been estimated that up to 25% of patients with certain genetically determined immunodeficiencies will develop tumors, primarily B-cell lymphomas, during their lifetime. Epstein-Barr virus appears to be an important cofactor in the development of lymphoproliferative disorders in patients with primary immunodeficiencies, as well as acquired immunodeficiencies. Additionally, host defects in immunoregulation and/or gene rearrangement, which are features of certain primary immunodeficiencies, probably contribute to the risk of lymphomagenesis in patients at risk.

Introduction

Lymphoproliferative disorders represent significant, potentially fatal, complications of primary immunodeficiencies. With advances in prevention and treatment of infections, patients with many of the primary immunodeficiencies can expect to survive for decades following diagnosis.

Published estimates of cancer incidence for certain primary immunodeficiencies suggest that the inheritance of these genetic defects ranks among the highest reported risk factors for tumor development in humans, ranging from 12 to 25% for patients with Wiskott-Aldrich syndrome (1), ataxia telangiectasia (2), and common variable immunodeficiency (3). In certain immunodeficiency diseases such as Wiskott-Aldrich syndrome, the risk of developing lymphoma appears to increase with age (1).

BLPDs,³ often referred to, simply, as lymphomas, are the predominant tumors in congenital immunodeficiencies. At least three major biological factors, occurring alone or in conjunction with one another, contribute to the high incidence of BLPD in the immunodeficient host. These are: (a) the ubiquity of Epstein-Barr virus; (b) host defects in immunoregulation resulting in imbalanced cytokine production; and (c) genetic defects resulting in imprecise and/or ineffective rearrangement of immunoglobulin and T-cell receptor genes during lymphopoiesis (as described later for ataxia telangiectasia).

EBV infection is a major cofactor in many, but not all, B-cell lymphoproliferative tumors. Immunodeficient hosts can acquire EBV through primary infection, through transfer of tissues at transplant (as in bone marrow transplantation), or with blood transfusions. During primary infection, EBV immortalizes B-lymphocytes *in vivo*, resulting in polyclonal activation and proliferation. In the normal host, EBV-driven lymphoproliferation is thought to be primarily controlled by EBV-specific autologous cytotoxic T-cells (which are MHC restricted), with a lesser role being played by humoral responses, antibody-dependent cellular cytotoxicity, natural killer cell activity, and possibly endogenous interferons. This complex of EBV-specific immunological control is delicately balanced to maintain the

EBV in latency following primary infection. In the immunodeficient host, suppressor and cytotoxic functions (both antigen specific and MHC restricted, as well as nonspecific) are often defective, and the production of regulatory cytokines which maintain the conditions favoring viral latency may become unbalanced. Under such circumstances EBV-infected B-cells can resume or continue proliferation.

It is hypothesized that B-cells which are already EBV-transformed may have a growth advantage in the setting of polyclonal lymphocyte proliferation. The high mitotic index of EBV-transformed cells increases the probability of genetic mutations by error, giving rise to populations of B-cells which may carry specific cytogenetic rearrangements and no longer be susceptible to ambient regulatory stimuli.

The second circumstance favoring the development of B-cell lymphoproliferative disorders in immunodeficient hosts is defective immunoregulation following B- and T-cell activation. Although their number, subset distribution, and functional repertoire may not be normal, virtually all immunodeficient patients (with the exception of certain forms of SCID) possess B- and/or T-cells capable of activation. Indeed, due to circumstances peculiar to the immunodeficient settings, stimulation of lymphocytes may be unusually intense and/or prolonged. The majority of patients with primary immunodeficiencies have defects in formation of specific protective antibodies, are unable to eliminate respiratory and gastrointestinal pathogens promptly and, thus, are prone to chronic antigenic stimulation.

Relative or selective deficiencies in the production of down-regulating lymphokines are found in many immunodeficient settings. It appears likely that T-cell subsets (perhaps similar to the murine TH 1 population) (4) which produce interferons and interleukin 2 are quantitatively or qualitatively reduced in many primary immunodeficiency states. Imbalances of cytokines which are believed to be critical to normal terminal B-cell differentiation have been documented in patients with primary immunodeficiencies who have developed EBV-associated BLPD (see Table 3 and discussion below).

Materials and Methods

Primary, genetically determined, immunodeficiency diseases are a heterogeneous group of syndromes sharing in common inherent abnormalities in the development or maintenance of specific immune responses. The clinical presentations of primary immunodeficiencies occur variably from birth until the later decades of life. The genetic basis for the majority of primary immunodeficiency syndromes identified by the WHO Scientific Group on Immunodeficiency (5) is currently unknown. The premature lethality of primary immunodeficiencies is most often attributed to overwhelming infections or the sequelae of recurrent and chronic infections, such as pulmonary insufficiency. Tumors, particularly lymphoproliferative disorders, are the second leading cause of death in persons with many of the primary immunodeficiency syndromes.

Because primary immunodeficiencies are rare, few cases of cancer in patients with primary immunodeficiency will be diagnosed at any given medical institution. Therefore, the idea of an international registry of these cases was conceived by Dr. Robert Good and his colleagues at the University of Minnesota in the early 1970s (6). The concept was realized in 1973 with the support of the National Cancer Institute, and the ICR was maintained for a number of years through the efforts of Dr.

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² To whom requests for reprints should be addressed.

³ The abbreviations used are: BLPD, B-cell-origin lymphoproliferative disorder; EBV, Epstein-Barr virus; MHC, major histocompatibility complex; SCID, severe combined immunodeficiency; ICR, Immunodeficiency Cancer Registry; IgE, immunoglobulin E; IFN, interferon; ELISA, enzyme-linked immunosorbent assay; IL-4, interleukin 4; XLP, X-linked lymphoproliferative syndrome; A-T, ataxia telangiectasia.

John Kersey and B. D. Spector, with later contributions by Val Stoker, Karen Heinitz, and Ann Mertens. Immunodeficiency Cancer Registry cases have been identified through voluntary case reports and literature review. Histopathological review of tumors in the ICR was performed by Dr. Glauco Frizzera using a classification system developed during the review of postallograft lymphomas (7) as well as other contemporary classification systems. *In situ* probing of paraffin sections of ICR lymphomas for EBV DNA used hybridization with the S³⁰ *BAMHI* probe previously described for posttransplant lymphomas (8). Studies of serum IgE and cytokine levels, IL-4, and IFN- α were performed by A. Mathur and D. Kamat. IgE was measured by sandwich ELISA assay, IL-4 by a commercially available ELISA kit (R & D Systems, Minneapolis, MN), and IFN was assayed at Lee Biomolecular, LaJolla, CA.

Results

Table 1 shows the distribution of cancers in the ICR according to immunodeficiency diagnoses, and Table 2 summarizes characteristics of the non-Hodgkin's lymphomas/B-cell lymphoproliferative disorders reported to the ICR. The median age at diagnosis for ICR lymphoma cases was 7.1 yr. The overall male predominance reflects the contribution of several X-linked disorders including SCID and Wiskott-Aldrich syndrome, as well as the surprising observation of excess tumors in males with ataxia telangiectasia, an autosomal recessive disorder.

B-cell lymphomas in the ICR vary in histopathological appearance and immunological typing from polyclonal B-cell hyperplasia at one end of the spectrum to monoclonal malignant lymphomas at the other. In many cases BLPDs were associated with rapid clinical deterioration and death, irrespective of clonality or histopathological similarity to non-Hodgkin's lymphomas (see Ref. 9 for detailed description of clinical outcomes).

While EBV has been found in virtually all tumor samples of posttransplant BLPD [both solid organ (10) and bone marrow

(8)], the association between EBV and primary immunodeficiencies has not been universal when using the same technique of *in situ* hybridization with an S³⁰ *BAMHI* probe for EBV. In studies by Dr. Lawrence Berg at the University of Minnesota, paraffin sections from 13 cases of non-Hodgkin's lymphoma/BLPD in the ICR were reviewed. EBV was detected in only 4 of 13 cases, including 3 of 5 tissues from patients with Wiskott-Aldrich syndrome and one of 3 from patients with SCID.

Recently we have had the opportunity to quantify some of the immunoregulatory parameters that are felt to be important in regulation of terminal B-cell differentiation in patients with newly diagnosed EBV-associated BLPD. As the data indicate in Table 3, BLPD patients with primary as well as secondary immunodeficiencies had elevated serum levels of IL-4, the cytokine which promotes B-cell proliferation, and markedly decreased levels of α -interferon, an important cytokine responsible for downregulation of IL-4-mediated B-cell proliferation when compared with normal EBV-seropositive controls. IgE levels, which are often increased in the face of such immunoregulatory dysfunction, were also elevated in the immunodeficient patients. Four of the six patients in Table 3 are evaluable for response to recombinant α -interferon therapy used as the sole therapy of BLPD. All four of these patients demonstrated significant objective tumor responses, and 2 of 4 achieved complete remission.

Imbalances in T-cell regulatory cytokines involved in terminal B-cell proliferation have also been measured in patients with primary immunodeficiencies who have not yet developed lymphoma, including patients with Wiskott-Aldrich syndrome, hyper-IgE syndrome, and common variable immunodeficiency. XLP, first published as Duncan's syndrome (11), has been postulated to represent an unusual susceptibility to overwhelming EBV infection. This disorder carries a high risk of BLPD in the

Table 1 Immunodeficiency Cancer Registry cases: distribution of tumors and immunodeficiencies

Immunodeficiency	Adenocarcinoma	Lymphoma	Hodgkin's disease	Leukemia	Other tumors	Total tumors
Severe combined immunodeficiency	1 (2.4) ^a	31 (73.8)	4 (9.5)	5 (11.9)	1 (2.4)	42 (8.4)
Hypogammaglobulinemia	3 (14.3)	7 (33.3)	3 (14.3)	7 (33.3)	1 (4.8)	21 (4.2)
Common variable immunodeficiency	20 (16.7)	55 (45.8)	8 (6.7)	8 (6.7)	29 (24.2)	120 (24.0)
IgA ^b deficiency	8 (21.1)	6 (15.8)	3 (7.9)	0 (0)	21 (55.3)	38 (7.6)
Hyper-IgM syndrome	0 (0)	9 (56.3)	4 (25.0)	0 (0)	3 (18.8)	16 (3.2)
Wiskott-Aldrich syndrome	0 (0)	59 (75.6)	3 (3.8)	7 (9.0)	9 (11.5)	78 (15.6)
Ataxia telangiectasia	13 (8.7)	69 (46.0)	16 (10.7)	32 (21.3)	20 (13.3)	150 (30.0)
Other immunodeficiencies	1 (4.0)	12 (48.0)	1 (4.0)	4 (16.0)	7 (28.0)	25 (5.0)
Total immunodeficiency categories	46 (9.2)	252 (50.4)	43 (8.6)	63 (12.6)	96 (19.2)	500 (100)

^a Numbers in parentheses, percentage of total tumors.

^b IgA, immunoglobulin A; IgM, immunoglobulin M.

Table 2 Characteristics of non-Hodgkin's lymphomas in the Immunodeficiency Cancer Registry

This table excludes cases of non-Hodgkin's lymphoma in immunodeficiency categories with fewer than two cases reported.

Immunodeficiency	n	M:F ratio ^a	Median age (yr) at diagnosis	Primary tumor sites (%) ^b			
				Brain, CNS	Gastrointestinal tract	Lymph node	Multiple
Severe combined immunodeficiency	31	23:7	1.6	6.5	3.2	9.7	48.4
Hypogammaglobulinemia	7	7:0	1.2	0	14.3	14.3	14.3
Common variable immunodeficiency	55	30:23	23.0	1.8	12.7	12.7	25.5
IgA ^c deficiency	6	4:1	9.4	16.7	0	0	0
Hyper-IgM syndrome	9	7:2	7.8	11.1	22.2	22.2	0
Wiskott-Aldrich syndrome	59	59:0	6.2	23.7	6.8	8.5	20.3
Ataxia telangiectasia	69	40:24	8.5	0	8.7	10.1	14.5
Other immunodeficiencies	4	4:0	4.0	0	0	0	0
Total immunodeficiency categories	240	174:57	7.1	7.9	8.8	10.4	21.7

^a Sex reported where known.

^b For 51.3% of Immunodeficiency Cancer Registry cases, primary tumor site is other or unknown.

^c IgA, immunoglobulin A; IgM, immunoglobulin M.

Table 3 Serum α -interferon in immunodeficient patients with EBV-associated BLPD

Patient	Diagnosis	Biological parameters at diagnosis			Response to IFN- α therapy
		IL-4 (pg/ml)	IFN- α (Iu/ml)	IgE (Ku/dl)	
2-yr-old male	SCID s/pTd BMT ^a (autologous recovery)	190	<5	10	PR
1.9-yr-old male	Combined immunodeficiency	18	<5	2500	CR
14.5-yr-old female	s/p liver transplant	155	<5	425	PR
56-yr-old female	s/p heart transplant	187	<5	168	NE
6.5-yr-old male	s/p heart/lung transplant	118	<5	145	CR
57-yr-old female	10-yr s/p kidney transplant	35	10	920	Surgical excision only
Normal seropositive controls		<5	31 \pm 3 ^b	43 \pm 9	

^a s/p, status post; Td BMT, T-depleted bone marrow transplant; PR, partial response; CR, complete response; s/p liver; s/p heart; NE, not evaluable; s/p heart/lung; s/p kidney.

^b Mean \pm SD.

boys who survive infectious mononucleosis. Information regarding quantification of immunoregulatory cytokines in XLP is not yet available.

A-T is an autosomal recessive disorder associated with chromosomal breakage that can serve as a model for the association between abnormal chromosomal rearrangement and lymphoid malignancies. Roughly half of reported tumors in A-T are non-Hodgkin's lymphomas: 69 of 150 ICR cases (46%). In addition, 21.3% of ICR cases (32 of 150) were reported as leukemias. Both B- and T-cell malignancies occur.

It has been observed that, following exposure to DNA damaging agents, such as X-irradiation, A-T cells fail to pause and repair damage, but rush on to DNA replication. It appears that, in A-T, a variably limited number of lymphocytes carry productive rearrangements of immunoglobulin and T-cell receptor chains. This finding may explain the variable development of the immune repertoire and the continuous predisposition to acquired cytogenetic changes which can lead to malignant transformation of lymphocytes in this disorder.

The study of translocations observed in B- and T-cell malignancies from A-T patients suggests that two mechanisms are commonly associated with malignant transformation: (a) translocations between members of the pair of No. 14 chromosomes followed by clonal deletion of one of two translocation partners; and (b) translocations of 14q32, the joining regions of immunoglobulin heavy genes (and less often 2p12 and 22q11, the immunoglobulin light chain genes) with 8q24 (*c-myc*) (12). The latter cytogenetic changes in A-T lymphoid malignancies bear remarkable similarities to rearrangements observed in lymphoid tumors from normal individuals (13). Thus, the A-T defect appears to magnify a common mechanism of lymphomagenesis.

Conclusion

Life-threatening lymphoproliferative disorders are major complications of secondary immunodeficiencies as well as primary immunodeficiencies. The continuing requirement for immunosuppressive therapy in growing numbers of organ and tissue recipients, as well as the spread of human immunodeficiency virus infection, contributes to the expansion of the numbers of individuals at risk for such tumors. There are multiple similarities among the clinical features of lymphoproliferative disorders in both primary and secondary immunodeficiencies including: diffuse morphologies at diagnosis; frequent extranodal primary sites and oligoclonal immunological features; young age at diagnosis (for primary immunodeficiencies) or shorter latency period to tumor diagnosis related to intensity of

posttransplant immunosuppression; and frequent association with primary or reactivated EBV infection. Most often lymphoproliferative disorders involve terminally differentiating B-cells and arise under circumstances of chronic immunostimulation and immunoregulatory imbalance. Detailed and sequential investigation of immunoregulatory abnormalities in patients with primary immunodeficiencies at highest risk of lymphomas may prove particularly useful in extending our understanding of biological changes underlying the development of lymphomas in both immunosuppressed individuals and the apparently nonimmunodeficient population. In both groups evidence for genetic predisposition as well as environmental exposure should be sought.

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