

# The Susceptive Probability: Lymphoma in Immune Deficiency

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## Abstract

The premise of immune surveillance was scripted by Burnet. The theory declares that the immune system may demonstrate a capacity to recognize and eradicate nascent and contemporary malignancies. Tumefaction may be generated by the cells of a particular organism or homo-sapiens which represent as specific antigens identifiable by the immune system. Individuals with a poor or defective immune system may engender subcategories of malignancy. The White Blood Corpuscles (WBCs) identify and ineffectively eliminate tumor cells in immune compromised subjects, in contrast to immune competent persons. Numerous immune procedures are implicated for malignant conversion with a primary immune deficiency such as enhancement and manifestation of immune cells, viral infections, modifications and reactivity to bone marrow tissue and chronic inflammation. The incidence of emerging lymphoma is augmented in congenital and acquired immune deficiency. Chronic antigenic stimulation incited by the oncogenic viruses and a lack of appropriate "antibody feedback mechanism" cogitating the lymphoid proliferation elevates the percentage of quantifiable lymphoid malignancies.

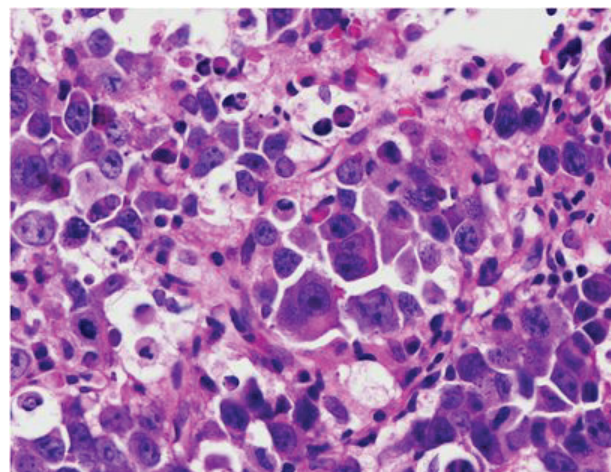
**Keywords:** Chronic antigenic stimulation; Immune compromise; Lymphoma

**Abbreviations:** WBCs: White Blood Corpuscles; WAS: Wiskott-Aldrich Syndrome; CVID: Common Variable Immune Deficiency; SCID: Severe Common Immune Deficiency; PDID: Primary Immune Deficiency Disease; EBV: Epstein Barr Virus; IALD: Immune-deficiency Associated Lympho-proliferative Disorder; ADA: Adenosine Deaminase; NK: Natural Killer; HSCT: Haematopoietic Stem Cell Transplantation; PCR: Polymerase Chain Reaction; PTLT: Post-Transplant Lympho-proliferative Disorder; HIV: Human Immune-deficiency Virus; AIDS: Autoimmune Deficiency Syndrome; PTCL: Peripheral T Cell Lymphoma; PEG: Polyethylene Glycol; ERT: Enzyme Replacement Therapy

## Introduction

### Primary immune deficiency

Individuals demonstrating a genetic immune deficiency elucidate an enhancement of tumefaction, especially lymphoma. Primary immune deficiency can be delineated with disorders such as ataxia telangiectasia, Wiskott-Aldrich Syndrome (WAS), X linked lympho-proliferative syndrome, Common Variable Immune Deficiency (CVID) and Severe Common Immune Deficiency (SCID) [1-3]. The probability of malignant transformation is enhanced in Primary Immune Deficiency Disease (PDID) at roughly 1.6% with an increment in possible emergence of non-Hodgkin's lymphoma. An estimated 10% of individuals with ataxia telangiectasia and WAS exhibit a terminal outcome with the occurrence of a lymphoma [4,5]. Lymphoid malignancy such as non-Hodgkin's lymphoma is predominant in numerous PDIDs chiefly CVID, WAS, ataxia telangiectasia, and SCID. Large B cell non-Hodgkin's lymphoma or immunoblastic lymphoma can be enunciated with WAS as localized extra-nodal aggregates. Ataxia telangiectasia can demonstrate the emergence of a Hodgkin's lymphoma (lymphocyte depletion subtype) or a non-Hodgkin's lymphoma with a concomitant 14q+ chromosomal aberration. An indicator for the primary disorder ataxia telangiectasia such as the ATM gene is cogitated which encodes a genomic signal identical to the PI3 kinase enzyme. Genetic mutation of the JAK3 network is exemplified in SCID. Microscopic analysis can be challenging in primary immune deficiency with the discernment of an aberrant lymphoid proliferation. Prognostic outcomes are linked to the immune profile of the implicated individual (Figures 1-12) [4,5].



**Figure 1:** Aggressive plasmablastic lymphoma in immune deficient subject [18].

X linked lympho-proliferative disease ensues on account of an immune deficient state arising from an Epstein Barr viral infection. Affected subjects elucidate sporadic instances of Burkitt's lymphoma, a large B cell lymphoma with attributes of immunoblastic proliferation, a fatal variant of infectious mononucleosis or a plasmacytoma. PDID demonstrates a possible amplification of malignant emergence by 1.42 times, in contrast to the age-adjusted population. A maximal probability appears with lymphomas arising in the male subjects with a cogitated 10 times enhanced risk and in female subjects with an estimated 8 times enhanced risk [2,4]. The elevated probability of tumor

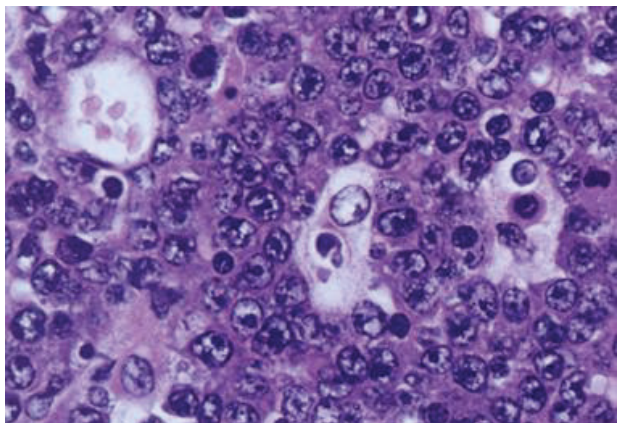
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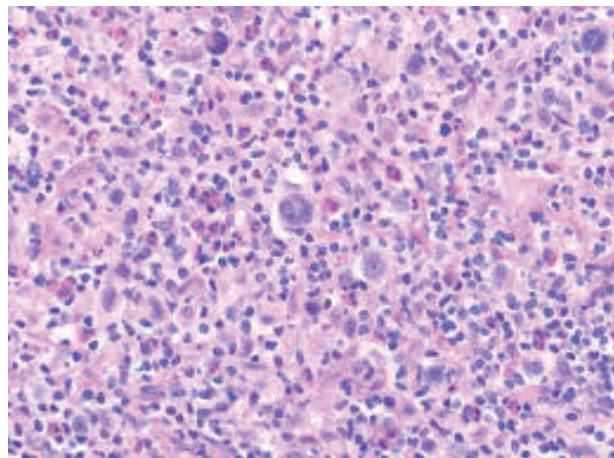
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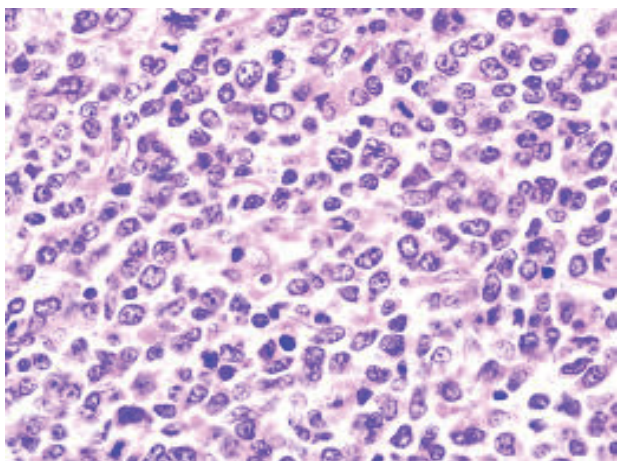




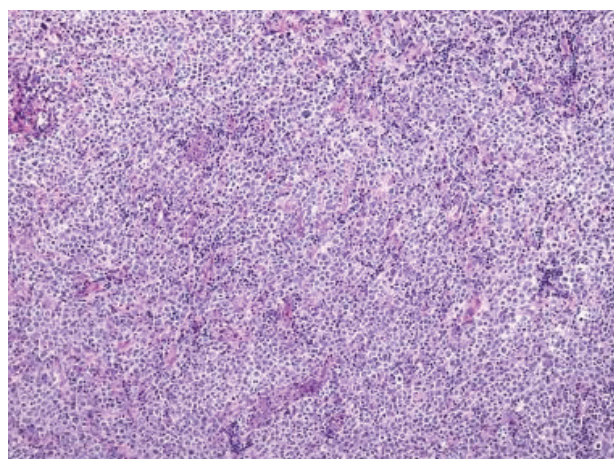
**Figure 2:** Burkitt's lymphoma with a starry sky pattern and immune compromise [19].



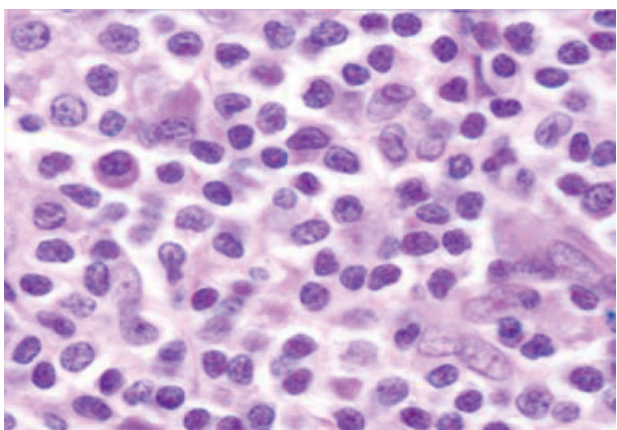
**Figure 5:** Primary effusion lymphoma associated with human immune deficiency virus infection [21].



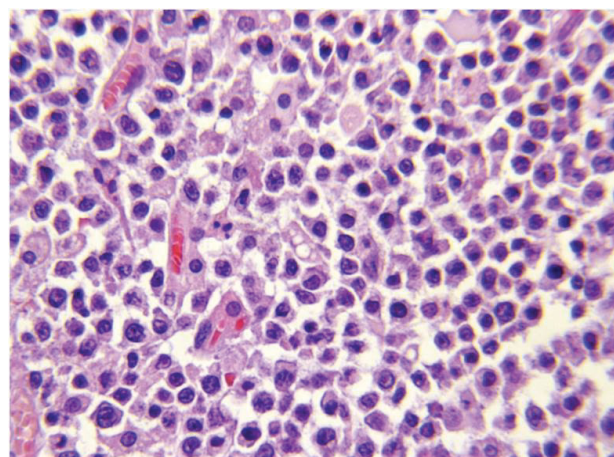
**Figure 3:** Aggressive B cell lymphoma with concurrent immune deficiency [20].



**Figure 6:** Diffuse B cell lymphoma secondary to human immune deficiency virus [19].



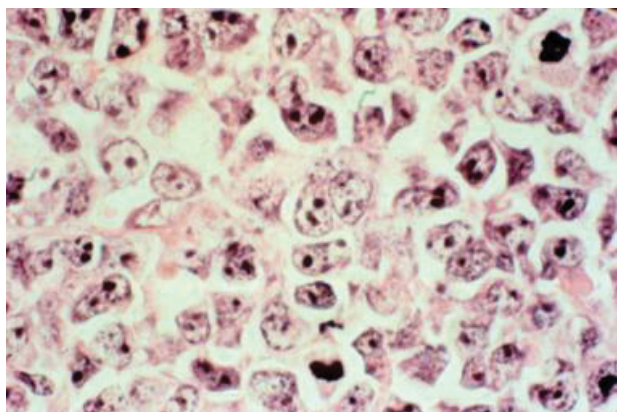
**Figure 4:** Primary cutaneous B cell lymphoma with interspersed plasmacytoid cells [19].



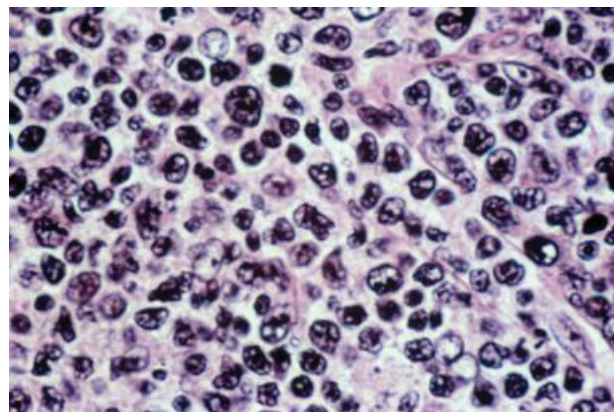
**Figure 7:** Diffuse large B cell lymphoma with immune compromise [22].

appearance is enunciated with CVID, a frequent PDID. The incidence of non-Hodgkin's lymphoma is augmented in individuals with CVID. Lymphomas arise with a probable incidence of 8.2% in CVID and incur elevated mortality. Dysfunctional DNA reparative mechanisms with

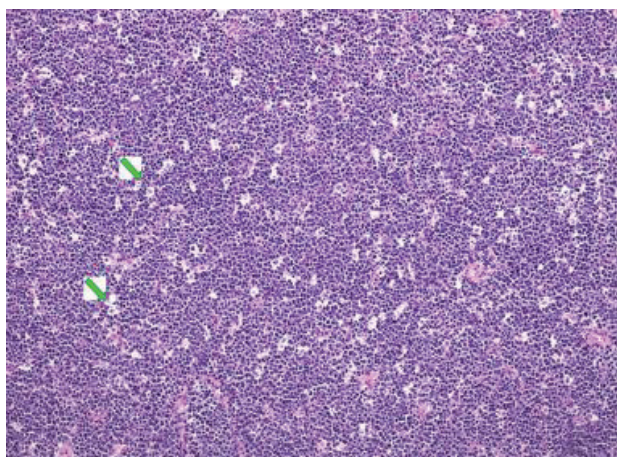




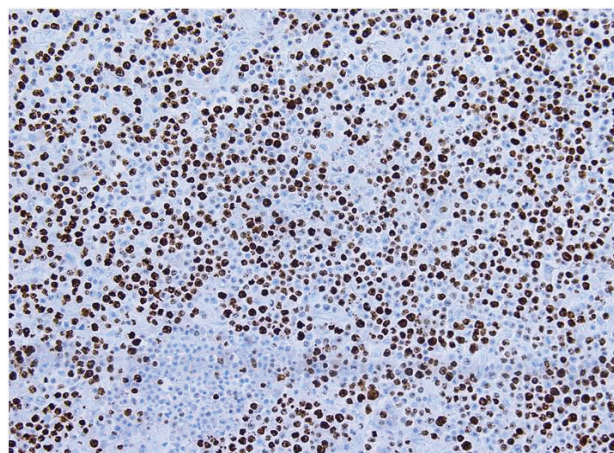
**Figure 8:** Immunoblastic lymphoma with prominent nucleoli and concomitant immune deficiency [19].



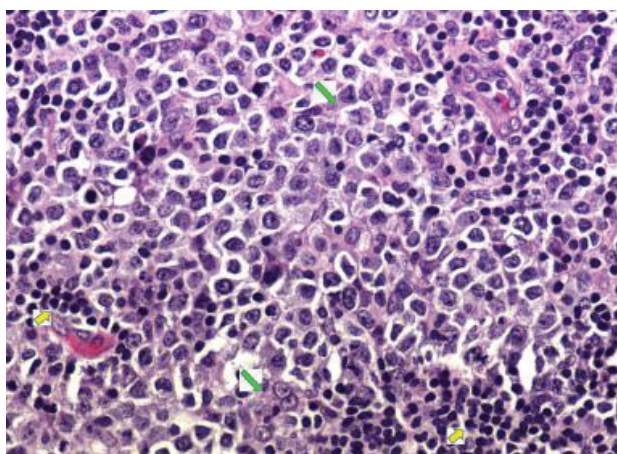
**Figure 11:** Diffuse large B cell lymphoma with anaplasia and pleomorphic nuclei [19].



**Figure 9:** Burkitt's lymphoma secondary to human immune deficiency viral infection [19].



**Figure 12:** Ki67 immune reactivity in diffuse B cell lymphoma (DLBCL) [22].



**Figure 10:** Diffuse B cell lymphoma subsequent to human immune deficiency virus infection [19].

ensuing primary immune deficiency are accompanied by attributes such as elevated cellular sensitization to radiation, the emergence of

developmental disorders and the appearance of various malignancies. Ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, and Nijmegen breakage syndrome display defective reparative mechanisms of the DNA which are secondary to enhanced susceptibility to radiation. The percentage probability of tumefaction can be diverse in various forms of primary immune deficiency disorder. The subjects demonstrate an increased possibility of appearing lymphoma or leukemia and adjunctive cancers induced by aggregates of decimated DNA. Elevation in the emergence of lymphomas is induced by factors such as defective functioning of lymphoid proliferation incited by Epstein Barr Virus (EBV) along with genetic instability of lymphocytes on account of persistent activation and lymphoid proliferation following chronic infection, an attribute which is cogitated with CVID [6,7]. Lymphoma arising in individuals with PDID is frequently and concurrently accompanied by Epstein Barr viral infection. The virus (EBV) significantly impacts lymphocytic proliferation on account of supersession of T cell surveillance with a modified apoptotic response and cytokine emergence within the B lymphocytes. Evolution of Immune-deficiency Associated Lympho-proliferative Disorder (IALD) is especially concurrent with Epstein Barr viral infection and incites considerable mortality. Prevalence of IALD in PDID varies from 0.7%-1.8% in implicated subjects on account of diverse genetic discrepancies



[2,3]. Adenosine Deaminase (ADA) deficient SCID is enunciated as an inherited disorder which delineates the aggregation of enzyme substrates such as adenosine-2'deoxy adenosine and deoxyribonucleotides (dAXP) which incites a severe lymphopenia along with an absence of cellular and humoral immunity resulting in reoccurring and severe infections. An elevation of adenosine values restricts the differentiation of thymocytes, encourage thymic hypoplasia with consequent apoptosis and concurrent depletion of T lymphocytes, B lymphocytes, and Natural Killer (NK) cells. Delayed characterization of the disorder implicates the immunological and autoimmune system along with the genesis of hemolytic anemia and immune thrombocytopenia as a component of the severe disease. As the ADA gene appears to be universal, non-hematological manifestations are frequently discerned in subjects of ADA deficiency. Disease complexities incriminate organs such as the liver, kidney, bone and central nervous system [3,4].

### Disease pathogenesis

The pathogenesis of emerging lymphomas in primary immune deficiency such as ADA SCID is obscure. Lymphocytes devoid of ADA reduces possible genesis of tumors and inhibitors of ADA are competent in treating lymphomas. Aggregation of adenosine and purine metabolites in ADA deficient individuals enhances the apoptosis of T and B lymphocytes. Subjects receiving Polyethylene Glycol (PEG) modified ADA therapy or those with Haematopoietic Stem Cell Transplantation (HSCT) demonstrate an appropriate disbursal of adenosine metabolites. Lymphoma cells spontaneously revert on account of an ADA mutation in subjects of ADA SCID. A lack of appropriate immune surveillance is cogitated, recapitulating adjunctive primary immune deficiencies. B lymphocytes are clone specific, as elucidated by the Polymerase Chain Reaction (PCR) applicable to the lymph node and bone marrow, thereby indicating an inferior prognosis. The aforementioned disease aspects exhibit a negative predictive value within a miniature cohort of lymphoid proliferation [3,4].

### Organ transplant recipients

Organ transplantation depicts an augmented incidence of lymphomas on account of direct or indirect immune suppression. Renal transplant recipients demonstrate an estimated prevalence of malignant transformation at 4-6%. Skin tumors, malignant lymphomas, Kaposi's sarcoma, and cervical carcinoma may be frequently elucidated with solid organ transplants. Lymphomas emerge at an estimated 350 folds, in contrast to the age-matched general population. Disease prevalence is elevated in recipients of adult cardiac transplant and in individuals on muromonab (OKT-3) containing therapeutic regimens. The central nervous system is implicated in approximately half (50%) of the individuals and the recipient allograft is incriminated in about one third (30%) of subjects [5].

### Morphological elucidation

Majority of the emerging lymphomas exhibit a prominent cytological polymorphism with an admixture of miniature and enlarged follicular center cells. Zones of atypical immunoblast infiltration and predominant necrosis can coexist. The pre-emptive lymphocytic infiltrate delineates a polyclonal B cell phenotype identical to a reactive cellular egress. Subsequently, a monoclonal component arises with concomitant chromosomal aberrations and a progression to lymphoma. Nomenclature of a "polymorphic B cell lymphoma" can be adopted for the tumefaction. The gradual transition from an active polyclonal B lymphocyte aggregate to an oligoclonal B lymphocytic proliferation which terminates in a monoclonal B cell lymphoma is

elucidated. Segregation of clone-specific B lymphocyte proliferation is clinically significant. Immunoglobulin rearrangements suggest a monoclonal lymphocytic aggregation in the preliminary stage of malignant transformation, prior to a morphological demonstration and evolution of an overt lymphoma. Instances of Post-Transplant Lymphoproliferative Disorder (PTLD) display the Epstein Barr viral genome [5]. The clone specific virus localizes within progenitor B lymphocytes and thus is incriminated in the generation of lymphomas and associated tumors. Perpetual latent viral activity appears in concurrence with an overt, lytic viral activity, occasionally represented in reoccurrences. Rearrangements of the MYC gene are infrequent in lymphomas associated with PTLDs, in contrast to lymphomas occurring with Human Immune-deficiency Virus (HIV). T lymphocytic lymphoma or a Burkitt's lymphoma can co-exist. Lymphoma arising subsequent to PTLDs displays an aggressive clinical course. The aforementioned lymphomas are managed by an appropriate reduction of immune suppression with concordant administration of a standardized therapy as applicable to lymphomas. Chemotherapy and radiation therapy can also be opted for [5,6].

### Lymphomas associated with HIV

Infection with HIV primarily engenders a Kaposi's sarcoma and malignant lymphoma. An estimated 3% of individuals with Autoimmune Deficiency Syndrome (AIDS) demonstrate a non-Hodgkin's lymphoma. A probability of emerging lymphomas in AIDS is 60 fold higher, in contrast to the general population. Subjects with hemophilia depict the greatest prevalence of arising lymphomas. Discernment of lymphoid malignancy can be at a younger age than cogitated with the immune competent persons. Majority of instances demonstrate extra nodal variants of the lymphoma with tumefaction appearing in the gastrointestinal tract, central nervous system, bone marrow, liver, oral cavity, adjunctive body cavities, and the heart. Lymphomas with a predominantly B lymphocyte lineage exhibit concomitant clone specific immunoglobulin gene rearrangements [7,8]. On morphological grounds, the majority may appear as Burkitt's lymphoma or a large B cell lymphoma displaying prominent immunoblastic or plasmablastic configurations. Primary effusion lymphoma along with Peripheral T Cell Lymphoma (PTCL) with coexistent touton giant cells is also cogitated. A polymorphic variant of post-transplant lymphoproliferative disorder arises in subjects of solid organ transplantation. Lymphomas engendered by the *Human herpesvirus8* (HHV8) exhibit an anaplastic morphology with enlarged cells. Molecular and cytogenetic aspects of Burkitt's lymphoma originating in individuals infected by HIV+ recapitulate the sporadic instances of Burkitt's lymphoma, particularly with genomic modifications of MYC gene. BCL2 and T cell receptor lack implication in lymphoma genesis on account of the viral ingress. Concomitant infection with EBV is commonly elucidated. Hodgkin's lymphoma may appear in accordance with the global incidence ratio. However, initial representation with stage III or IV is elucidated with aggressive histological subcategories arising at uncommon sites such as liver and skin. Dissemination of lymphoma is non-contiguous. Variable and atypical Reed Sternberg cells are multitudinous. The non-lymphoid stromal cell population is quantifiably enhanced. Epstein Barr viral genome can be comprehensively elucidated within the Reed Sternberg cells (nearly 100% concurrence). Demography, clinical attributes and prognostic outcomes of Hodgkin's lymphoma secondary to HIV infection simulate the aforementioned aspects of non-Hodgkin's lymphoma arising on account of human immune deficiency viral infection [8,9].

Acquired diseases with immune deficiency

Amplification of lymphoma is cogitated in disorders of acquired immune deficiency such as rheumatoid arthritis, Sjogren’s syndrome, Hashimoto’s thyroiditis and adjunctive autoimmune disorders. Certain specific conditions are designated as a pre-malignant phase of malignant lymphoma [5].

Sub-categorization of lesions

A diffuse lymphoma (DLBCL) frequently arises in predominantly extra-nodal sites. Epstein Barr viral infection is elucidated in an estimated 55% instances with extra-nodal lymphoma emerging in the lung (10%) and brain (10%). Hodgkin’s lymphoma is infrequent (10%) while Burkitt’s lymphoma non-reactive to the EBV occurs in two-thirds (66%) of instances. Subjects exhibit a malignant transformation following 3 years of commencement of PEG-modified ADA therapy. Haplo-identical HSCT and a T lymphocyte gene therapy articulated on peripheral blood can be opted for, although lymphomas subsequently emerge [9,10]. Depleted T lymphocyte quantification and/or aberrant T lymphocyte function influence the prognosis of lymphoid proliferation to a greater degree than histological or genetic modifications. Anomalous secretion of interleukins, particularly interleukin 6 is crucial for the lymphoid proliferation incorporating autocrine and paracrine cytokine stimulations. Interleukins impact the malignant cells by contributing to self-perpetuation of B lymphocytes immortalized by the EBV with concomitant tumor progression [5].

The methodology of malignant transformation

Lymphoma appears as a frequent malignancy in primary immune deficiency, displaying an amplified 8-13 fold probable emergence as compared to the immune competent population. B lymphocyte lymphomas primarily emerge in the extra-nodal sites and are preceded by an organ-specific, polyclonal lymphocytic infiltrate. Lymphomas originate on account of modified lymphocytes secondary to primary immune deficiency. Augmentation of emerging lymphomas is concurrent to persistent and reoccurring viral and/or bacterial infections [10,11]. Infections are characteristic of a majority of primary immune deficiency disorders, particularly with an antigen-specific representation. Defective and expressly mobilized lymphoid tissue incur lymphoid hyperplasia in approximately half (50%) of the subjects with CVID. Implicated individuals elucidate a lymph node enlargement and hepatosplenomegaly with concurrent environmental conditions which favor the transformation of lymphocytes into a lymphoma. Additionally, immune disorders enhance the incidence of lymphomas in particular, in contrast to alternative forms of cancer. The hypothesis debates emergent protective manifestations of the immune system in carcinogenesis. Nijmegen breakage syndrome amplifies the emergence of lymphomas concordant to chronic stimulation of impaired lymphocytes [11,12]. Chromosomal breakage syndrome with an accompanying deficient regeneration of deoxyribonucleic acid (DNA repair defect) concurs with a primary immune deficiency such as ataxia-telangiectasia,

Nijmegen breakage syndrome and Bloom’s syndrome and elucidates an enhanced appearance of lymphomas. Disorders with a chromosomal breakage syndrome and an associated DNA repair defect in the absence of coexistent immune deficiency such as xeroderma pigmentosum, Fanconi’s anemia, Werner’s syndrome, Rothmund Thomson syndrome delineate the emergence of adjunctive cancers other than lymphoid malignancies [12,13]. Primary immune deficiency exemplifies a possible and moderate emergence of tumors at an estimated twice the incidence than immune competent individuals. Actual assessment of malignant appearance can be reduced. The spectrum of developing malignancies in primary immune deficiency is restricted and incidence of tumefaction such as malignant melanoma, renal cell carcinoma and non-small cell carcinoma of the lung is identical in the immune competent and immune compromised individuals. Prevalence of malignant conversion is not augmented during the neonatal phase despite the inadequate immune system. Aggressive and malignant neonatal tumors such as neuroblastoma, leukemia and pontine glioma undergo spontaneous regression. Thus the neonatal period is cogitated as an “oncogenic grace period”. Additionally, adults with Down’s syndrome depict a 50% decline in the incidence of tumors such as breast, prostate, and lung. Adjunctive malignancies or lymphomas arise on account of enhanced mobilization of the lymphocytes. Malignant conversion is contingent to primeval, untransformed tissue. Tissue inflammation and fibrosis with restricted malignant transformation can be elucidated in neonates [13,14]. “Cancer immune surveillance” aptly describes the premise that the immune system procures an appropriate identification and eradication of developing tumors in the absence of extraneous therapeutic intervention. Immune surveillance suitable for tumors cogitates the surmise that possible malignant conversion is elevated amongst particular categories of immune compromised individuals infected with HIV, HSCT, and Solid Organ Transplant (SOT) recipients. A coterie of three hundred simplistic genetic malformations implicating the immune system can be enunciated in Primary Immune Deficiency (PID). Immune protection with specific genetic and chromosomal pathways which analyze immune surveillance applicable to malignancies arising in subjects with the compromised immune system is thus exemplified [14,15]. Secondary immune deficiency enunciates innumerable attributes which impact the possible emergence of tumefaction, especially acquired or iatrogenic derangement of the immune system from pharmacotherapy induced genetic toxicity.

Therapeutic options

Enzyme Replacement Therapy (ERT) cogitate a transient augmentation of the immune function. Various clinical manifestations and tumor evolution emerge, although an indolent immunological decline ensues. Several transfusions of genetically altered T lymphocytes engender a T cell compartment composed of chiefly transformed T lymphocytes [15,16]. Polyclonal T lymphocyte coterie thus generated is not competent in curbing the concomitant B lymphocyte transformation incurred by infection of EBV. Incompetent

Immune disorder	Frequency of discernment	Risk elevation	Elucidated malignancies
Selective Ig A deficiency	1/143-1/965	X1.31	Gastric carcinoma or Lymphoma
CVID	1/10,000-1/100,000	X1.19-1.3	Gastric carcinoma or Lymphoma
X-linked agammaglobulinemia	1/200,000	Enhanced	Gastric or intestinal carcinoma
X-linked hyper IgM syndrome	1/1000,000	Enhanced	Liver, gall bladder and pancreas carcinoma
Wiskott-Aldrich syndrome	1/10,000	Enhanced	Lymphoma

Table 1: Primary immune deficiency with probable malignancies [2].

elucidation of associated transformed cellular subcategories such as NK cells mounts an inadequate immune reaction against the EBV.

Intense monitoring of subjects with ADA SCID administered an extensive ERT is mandated, especially in individuals with infusions of genetically altered T lymphocytes. Gene therapy with retroviral vectors and an autologous CD34+ lymphocyte infusion transformed with ADA is cogitated as an appropriate therapy for individuals lacking an HLA-identical or a sibling donor for a stem cell transplant (Table 1) [16,17].

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