B-cell Lymphoproliferative Disorders Associated with Primary and Acquired Immunodeficiency

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KEYWORDS

• Primary immunodeficiency • Acquired immunodeficiency • B-Cell lymphoma
• Post-transplant lymphoproliferative disorder

ABSTRACT

The diagnosis of lymphoproliferative disorders associated with immunodeficiency can be challenging because many of these conditions have overlapping clinical and pathologic features and share similarities with their counterparts in the immunocompetent setting. There are subtle but important differences between these conditions that are important to recognize for prognostic and therapeutic purposes. This article provides a clinicopathologic update on how understanding of these B-cell lymphoproliferations in immunodeficiency has evolved over the past decade.

Key Features

- Knowledge of the clinical history is an important step in the evaluation of lymphoproliferative disorders associated with immunodeficiency.
- There is some overlap in morphologic and phenotypic features between lymphoproliferative disorders in immunedeficient versus immunocompetent settings. Viral infection by Epstein-Barr virus (EBV) and/or human herpes virus 8 (HHV8), however, seems more commonly associated with immunodeficiency.
- EBV-positive mucocutaneous ulcer (EBV MCU) is an important entity to recognize due to its indolent nature compared with other EBV-positive lymphoproliferations.
- Newer genomic approaches have revealed that the expression of key viral genes can alter the normal function of cell survival and proliferation pathways. Additional knowledge of how these pathways are altered may play an integral role in the future diagnosis and treatment of immunodeficiency-associated lymphomas.

OVERVIEW

B-cell lymphoproliferative disorders represent a heterogeneous group of diseases. Epidemiologic and experimental studies in the past 40 years have revealed a correlation between the development of a subset of B-cell lymphoproliferative disorders and a defect in immune surveillance. These defects in immune surveillance often occur as a result of an inherited or acquired immunodeficiency. Primary causes of inherited immunodeficiency include common variable immunodeficiency, severe combined immunodeficiency, and Wiskott-Aldrich syndrome; their associations with various types of lymphoproliferative processes are listed (**Table 1**). Acquired immunodeficiencies, on the other hand, can arise in the settings of HIV infection (**Table 2**), post-transplant, or iatrogenic-associated immune

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Table 1
Primary immunodeficiency and associated lymphoproliferative disorders

Disease	Genetic/Protein Defect	Immune Deficiency	Lymphoproliferative Disorders/ Lymphomas
Combined B-cell and T-cell immunodeficiencies			
Severe combined[118,119] immunodeficiency syndrome	Many subtypes	Decreased T-cells, B-cells, and Ig depends on subtype	EBV-associated lesions (DLBCL and HL), mostly B-cell NHL, fatal infectious mononucleosis
Hyper-IgM syndrome[120]	CD40 ligand or CD40	Neutropenia	EBV-associated lesions (DLBCL and HL) and LGL leukemia
Wiskott-Aldrich syndrome[121]	*WAS*	Progressive decrease of T-cells, B-cells, low IgM, increased IgE	EBV-associated lesions (DLBCL and HL) and mostly B-cell NHLs; may involve CNS
Antibody deficiency			
Common variable immune deficiency[122]	Unknown	Decreased IgG, IgA, and/or IgM; decreased B-cells	EBV-associated lesions (DLBCL and HL), MALT lymphoma, SLL, LPL, and PTCL (rare)
DNA repair defects			
Ataxia-telangiectasia[123]	*ATM*	Progressive decrease of T-cells and B-cells; increased IgM and decreased IgA, IgE, IgG	HL, DLBCL, BL, nonleukemic clonal T-cell proliferations, T-PLL (children), T-ALL (young adults)
Nimegen breakage syndrome[124]	*NBN*	Progressive decrease of T-cells, normal/ reduced B-cells; decreased IgA, IgE, and IgG	B-cell and T-cell NHL, T-LBL/ALL, and HL
Immune dysregulation			
X-linked lymphoproliferative syndrome[125]	*SH2D1A*	Normal/reduced B-cells, normal/reduced immunoglobulin	EBV-associated lesions (DLBCL and BL)
Autoimmune lymphoproliferative syndrome[126]	FAS (type 1a), FASL (type 1b), CASP10 (type 2a) or CASP8 (type 2b)	Increased $CD4^-/CD8^-$ T-cells	HL, DLBCL, BL, and PTCL (rare)
Chédiak-Higashi syndrome[127]	*LYST*	No immune deficiency	EBV-associated lesions

Abbreviations: Ig, immunoglobulin; LGL, large granulocyte lymphocyte; LPL, lymphoplasmacytic lymphoma; MALT, mucosa-associated lymphoid tissue; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; T-LBL, T-cell lymphoblastic lymphoma; T-PLL, T-cell prolymphocytic leukemia.