Lymphoproliferative disorders and lymphoreticular malignancies in the setting of immunodeficiency☆

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Abstract

Lymphoid proliferations occurring in the background of immunodeficiency range from benign lymphoid proliferations to full-blown lymphomas. They occur at a higher frequency in immunosuppressed patients compared to the general population. Immunosuppression is the main underlying pathogenic cause in these disorders and their histological appearances and immunophenotypic features are varied. Some resemble lymphoproliferative disorders seen in immune competent patients whilst others have unique characteristics; some of these also pose unique diagnostic problems. Furthermore, within some clinical contexts like the post-transplant setting, the distinction between benign and malignant proliferations is blurred. Identification of specific entities requires a clear understanding of morphology, clinical context, a wide immunohistochemistry panel, investigations for viral association, clonality investigations, and in some situations analysis of chromosomal translocations by fluorescent in-situ hybridisation studies. Precise identification of the disease entity impacts patient management and follow-up.

Keywords AIDS; HIV; immune suppression; lymphomas; lymphoproliferative disorders

Introduction

Lymphoproliferative disorders (LPDs) in the immunosuppressed are a group of diseases that can be polyclonal (reactive), oligoclonal or monoclonal (malignant). LPDs occur at a higher incidence in immunosuppressed individuals compared to the general population and develop as a consequence of impaired immune function, particularly due to defects in T-cell function rather than B-cell defects. Immunodeficiency settings may be of congenital, infectious or therapeutic origin. Immunosuppression associated lymphoproliferative disorders (IALDs) are highly heterogenous due to the various underlying causes; however, they share several features including a predilection for extranodal sites, rapid clinical progression, diffuse aggressive histology and a B-cell lineage in most cases.[1] While the majority are 'high-grade' B-cell non Hodgkin lymphomas (NHL), a few are classical Hodgkin lymphomas (cHL). Rare cases are either of T-cell or NK-cell origin.[2] Viruses such as Epstein—Barr virus (EBV) are frequently implicated in the pathogenesis of these disorders, although a proportion of them lack EBV indicating that alternative pathways must also be involved in lymphomagenesis.

The 2016 WHO classification identifies four principal categories based on the combination of morphology, immunophenotype, genetic and clinical features: — 1) LPDs associated with primary immune disorders; 2) Human immunodeficiency virus (HIV) associated LPDs; 3) post-transplant LPDs (PTLD); and 4) iatrogenic IALDs.[3]

Lymphoproliferative disorders associated with primary immune disorders

Although the incidence of lymphomas is increased in patients with primary immune disorders (PIDs), the prevalence of PID associated LPDs is low (2.4% of all paediatric lymphomas) due to the rarity of these immune disorders.[4] There are more than 60 PIDs with varying pathology and pathogenesis resulting in a high heterogeneity of the associated LPDs. PIDs that are more frequently associated with LPDs are shown in Table 1. Most PID associated LPDs occur in the paediatric age group (with the exception of CVID which presents in adults) and are more common in males due to X-linked genetic abnormalities. Epstein-Barr virus (EBV) is pathogenetically involved in most cases.[5] Lack of EBV surveillance by the T-cells is central to the pathogenesis.[6] Presentation is often in extranodal sites most commonly the gastrointestinal tract (GIT), lungs and central nervous system. Lymphoid proliferations may be the first sign of the underlying immune defect (such as in ALPS and XLP); however most cases will present with infections or infectious mononucleosis like symptoms (e.g. fatigue, fever) and a diagnosis of PID is established prior to the identification of IALD.

From a morphological point of view, the lymphoid proliferations resemble classical descriptions of lymphomas or reactive lymphoid lesions seen in immune competent individuals. Some cases are associated with polymorphous proliferations which are similar to those seen in PTLDs (discussed later). Generally the most common type of lymphoma seen in PID is diffuse large B-cell lymphoma (DLBCL) followed by Burkitt lymphoma and cHL, and rarely peripheral T-cell lymphoma. The immunophenotypes of these lymphomas are similar to those arising in immunocompetent patients. Some primary immune disorders have characteristic histological and immunophenotypical features. These will be discussed here.

Patients with *common variable immune deficiency* (CVID) may present with lymphadenopathy or extranodal lesions.[7] Lymph nodes (LNs) reveal follicular hyperplasia and paracortical expansion with presence of large atypical EBV-positive Reed Sternberg-like cells in some cases. The hyperplastic process is florid and obliterates the LN architecture. Furthermore, as

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Lymphoproliferative disorders in primary immune disorders

Primary immune disorder	Type of lymphoproliferative disorder
Combined T-cell and B-cell immunodeficiencies	
Severe combined immune deficiency	EBV-associated lesions (DLBCL & cHL); fatal IM
Hyper-IgM syndrome	EBV-associated lesions (DLBCL & cHL); T-LGL
Predominantly antibody PIDs	
Combined variable immunodeficiency	EBV-associated lesions (DLBCL & cHL); MZL, LPL, SLL & PTCL
Diseases of immune dyregulation	
X-linked LPD	EBV-associated lesions (DLBCL & BL)
ALPS	NLP-HL, cHL, DLBCL, BL, PTCL
Other well-defined immunodeficiency syndromes	
Ataxia Telangiectasia	Non-leukaemic clonal T-cell proliferations; BL, T-PLL, T-LL, cHL & NLP-HL
Wiskott-Aldrich syndrome	EBV-associated lesions (DLBCL, cHL & lymphomatoid granulomatosis)
Nijimegen breakage syndrome	DLBCL, PTCL, T-LL, cHL & NLP-HL

EBV: Epstein Barr virus; DLBCL: diffuse large B-cell lymphoma; cHL: Classical Hodgkin lymphoma; IM: infectious mononucleosis; LGL: T-cell large granular lymphocytic leukaemia; MZL: marginal zone lymphoma; LPL: lymphoplasmacytic lymphoma; SLL: small lymphocytic lymphoma; PTCL: peripheral T-cell lymphoma; BL: Burkitt lymphoma; NLP-HL: nodular lymphocyte predominant Hodgkin lymphoma; T-PLL: T-cell prolymphocytic leukaemia; T-LL: T-cell lymphoblastic leukaemia/lymphoma.

Table 1

some patients may have massive lymphadenopathy, these patients are often considered to have lymphomas clinically. Majority of the proliferations are benign as demonstrated by clinical follow-up and gene rearrangement studies. Similar nodular lymphoid hyperplasias may be seen in the GIT.[8]

Patients with *hyper-IgM syndrome* can present with extranodal lesions in the GIT, gall bladder or liver. In the LNs, germinal centres are absent. Histologically, these lesions demonstrate accumulations of IgM producing plasma cells at all the involved sites. The peripheral blood B-cells express IgM and IgD only; cells expressing other heavy chains are not seen. These patients harbour mutations in CD40 or CD40 ligand, which impair B-cell-T-cell interactions affecting class-switching in B-cells.[9]

Autoimmune lymphoproliferative syndrome (ALPS) is an uncommon disease which occurs due to mutations in the FAS or FASL gene resulting in lymphoid proliferations due to the accumulation of lymphoid cells that fail to undergo apoptosis.[10] Young patients usually present with generalised lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, B-cell lymphocytosis and autoimmune manifestations like hemolytic anemia, idiopathic thrombocytopenic purpura, urticarial rash, glomerulonephritis, or Guillain-Barré syndrome. The median age at initial presentation is around 24 months, but may be up to 15 years. Most patients have lymphadenopathy, while some patients may present with splenomegaly without evidence of peripheral lymphadenopathy. The LNs show relative preservation of architecture with florid reactive follicular hyperplasia and marked paracortical expansion with presence of immunoblasts and plasma cells. Majority of the cells in the expanded paracortex are CD3-positive T-cells which are characteristically negative for both CD4 and CD8 (double negative cells) (Figure 1). A good proportion of the paracortical cells are positive for CD57 and cytotoxic molecules (TIA-1 and perforin), but CD56 or CD16 positive cells (NK cells) are not seen. These paracortical lymphoid cells often have high Ki-67 expression and show frequent mitoses. In contrast to other reactive conditions, apoptotic cells and histiocytes containing apoptotic bodies are conspicuously absent in the paracortex. The paracortical expansion is often extensive and a differential diagnosis of immunoblastic lymphoma may be considered. The lymphoid cell expansion is non-clonal by gene rearrangement studies. Apart from florid follicular hyperplasia, changes in follicles akin to Castleman's disease, follicular involution and progressive transformation of germinal centres may be seen. Spleen reveals prominent white pulp and expanded red pulp. Red pulp shows an infiltrate similar to those of the LN paracortex. Some of these patients later develop nodular lymphocyte predominant Hodgkin lymphoma or a T cell rich B cell lymphoma.[11]

HIV-associated lymphoproliferative disorders

HIV infects CD4-positive T-cells, monocytes and dendritic cells, and has profound immunological effects. These lymphoproliferative disorders encompass pathologies of both neoplastic and non-neoplastic nature (infective or otherwise). The introduction of combination antiretroviral therapy has significantly reduced the incidence of NHL by 50% (Engels, 2006), however, the incidence in HIV-positive patients remains at 60-200 times compared to that in the general population. The risk of HIV-associated cHL remains stable. Non-neoplastic lesions may precede or coexist with neoplasms.[12]

Several pathogenetic mechanisms are implicated in HIV-associated LPDs; they include chronic antigen stimulation, genetic abnormalities, cytokine deregulation, and oncogeneic viruses EBV and HHV8.[13] EBV is identified in 40% of HIV-associated LPDs and nearly all cases of cHL arising in HIV-positive individuals are associated with EBV.[14]

Extranodal sites are more commonly involved in HIV-associated LPDs, in particular the GIT, liver, bone marrow and central nervous system. LNs are involved in one third of cases.[15] Patients usually present at an advanced clinical stage and a markedly elevated lactate dehydrogenase is usually present.

Morphological overlaps are observed between neoplasms, infective pathologies and non-neoplastic/non-infective pathologies. Histological appearances and IALDs seen in HIV patients are enumerated in Table 2. Viral associations and genes involved in HIV-lymphomas are summarised in Table 3.

Reactive lymph node lesions: the microscopic appearance of LNs in HIV infection vary with the duration of the disease, from florid follicular hyperplasia in the early phases, followed by follicular involution and, in the late stages to complete effacement of nodal architecture with disappearance of germinal

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