Lymphoproliferative disorders in the immunosuppressed

Kikkeri N Naresh

Abstract

Lymphoproliferative disorders occur at a higher frequency in immunosuppressed patients than in the general population and these are a group of diseases that range from benign lymphoid proliferations to full-blown lymphomas. These proliferations develop as a consequence of immunosuppression. Their histological appearances and immunophenotypic features are varied. While some resemble lymphoid lesions seen in immune competent patients, others have unique characteristics, with some posing 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 clinical context and morphology, together with a wide immunohistochemical panel, investigations for viral association and clonality studies. Precise identification of the disease entity has an impact on patient management and follow-up.

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

Introduction

Lymphoproliferative disorders (LPD) in the immunosuppressed are a group of diseases that range from benign polyclonal to malignant monoclonal lymphoid proliferations. They develop as a consequence of immunosuppression. Immunodeficiency may be of congenital, infectious or therapeutic origin. Most immunosuppression associated lymphoproliferative disorders (IALDs) are B-cell-derived. They originate more commonly in extranodal sites, but rarely affect skin, and behave aggressively.[1,2] While most are 'high-grade' B-cell non-Hodgkin lymphomas (NHL), a few are classical Hodgkin lymphomas. Rare cases have also been shown to be either of T-cell or NK-cell origin.[3] With regards to post-transplant lymphoproliferative disorders (PTLDs), the abnormal B-cells in solid organ transplant recipients usually originate from the recipient, while in recipients of bone marrow transplant they are of donor origin.[4,5]

IALD can be broadly categorized into − 1) those associated with primary immune disorders; 2) human immunodeficiency virus (HIV) associated lymphoproliferative disorders; 3) post-transplant lymphoproliferative disorders (PTLDs); and 4) iatrogenic IALD.

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IALD associated with primary immune disorders

There are more than 60 primary immune disorders, though the prevalence of primary immune disorders is extremely low.[6] Those that are more commonly associated with IALD are shown in Table 1. Most IALDs occur in the paediatric age group and are more common in males. Epstein Barr virus (EBV) is pathogenetically involved in most cases. A lack of EBV surveillance by T-cells is central to the pathogenesis.[6]

From a diagnostic point of view, the lymphoid proliferations resemble classical descriptions of lymphomas and reactive lymphoid lesions seen in the immune competent. Some cases are associated with polymorphous proliferations similar to a subset of PTLDs (discussed later). The precursor lesions to full-blown lymphomas that are seen in some primary immune disorders have characteristic histology and immunophenotype and can still cause diagnostic problems. These will be discussed here.

Patients with *common variable immune deficiency* (CVID) may present with lymphadenopathy or extranodal lesions. Lymph nodes (LN) reveal follicular and paracortical expansion with the 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 some patients may have massive lymphadenopathy, these patients are often considered to have lymphomas clinically. The majority of the proliferations are benign, as demonstrated by clinical follow-up and gene rearrangement studies. Similar lymphoid hyperplasias may be seen in the gastrointestinal tract.[6–8]

Lymphoproliferative disorders in primary immune disorders

Primary immune disorder	Type of lymphoproliferative disorder
Severe combined immune deficiency	EBV-associated lesions (DLBCL & cHL); fatal IM
Hyper-IgM syndrome	EBV-associated lesions (DLBCL & cHL); T-LGL
Combined variable immune deficiency	EBV-associated lesions (DLBCL & cHL); MZL, LPL, SLL & PTCL
X-linked LPD	EBV-associated lesions (DLBCL & BL)
ALPS	NLP-HL, cHL, DLBCL, BL, PTCL
Ataxia Telangiectasia	Non-leukaemic clonal T-cell proliferations; BL, T-PLL, T-ALL, cHL & NLP-HL
Wiskott–Aldrich syndrome	EBV-associated lesions (DLBCL, cHL & LyG)
Nijimegen breakage syndrome	DLBCL, PTCL, T-ALL, 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 lymphocyte leukaemia; LyG: lymphomatoid granulomatosis; 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-ALL: T-cell acute lymphoblastic leukaemia/lymphoma.

Table 1

Patients with *hyper-IgM syndrome* can present with extranodal lesions in the gastrointestinal tract, 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, and cells expressing other heavy chains are not seen. These patients harbour mutations in the genes encoding CD40, CD40 ligand, activation-induced cytidine deaminase (AID), uracil DNA glycosylase (UNG) or NF-κB essential modulator (NEMO), which impair B-cell—T-cell interaction affecting class-switching in B-cells.[6,9]

Autoimmune lymphoproliferative syndrome (ALPS) is an uncommon disease that can cause diagnostic problems. Young patients usually present with generalized lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, B-cell lymphocytosis and autoimmune manifestations like haemolytic anaemia, idiopathic thrombocytopaenic 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 their architecture with florid reactive follicular hyperplasia and marked paracortical expansion with the presence of immunoblasts and plasma cells. The 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, a subtype of diffuse large B-cell 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. The spleen reveals prominent white pulp and expanded red pulp. The red pulp shows an infiltrate similar to those of the LN paracortex. The lymphoid proliferation in ALPS is related to an impairment of apoptosis as a consequence of inherited heterozygous mutations in the Fas, Fas ligand, caspase 10 or caspase 8 genes. Some of these patients later develop nodular lymphocyte predominant Hodgkin lymphoma or a T-cell rich B-cell lymphoma.[2,6,10,11]

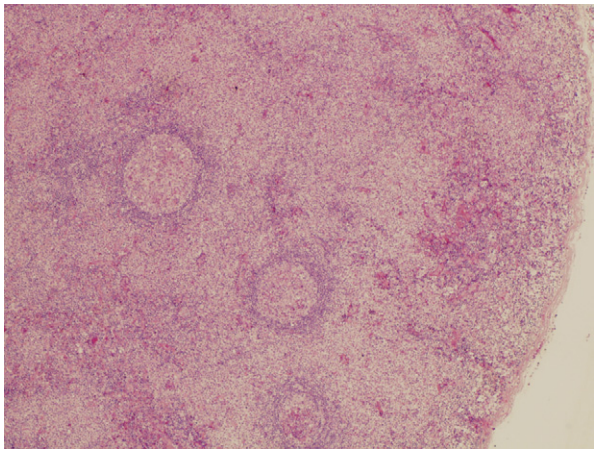

Figure 1 LN in a child with documented autoimmune lymphoproliferative syndrome (ALPS). The LN shows reactive follicles with expanded interfollicular areas. The interfollicular area shows a prominent infiltrate of T-cells positive for CD3 and negative for CD4 and CD8.

HIV-associated lymphoproliferative disorders

HIV infects CD4-positive T-cells, monocytes and dendritic cells, and has profound immunological effects. The effects on the immune system include cellular and tissue manifestations throughout the 'lymphoreticular' system — LN, spleen, extranodal lymphoid tissues, bone marrow and peripheral blood. These 'lymphoproliferative' disorders encompass pathologies of both neoplastic and non-neoplastic nature (infective or

Lymphoproliferative disorders in HIV patients

'Reactive' lymph nodal alterations
1) Florid follicular hyperplasia and acute viral lymphadenitis-like changes
2) Follicular involution
3) Depleted lymph node
4) Castleman-like changes

T-cell expansions
1) Diffuse infiltrative lymphocytosis syndrome & HIV-associated CD8+ lymphocytosis syndrome

Plasma cell infiltrates
1) Florid plasma cell expansion in lymph nodes, tissues and bone marrow with polyclonal hypergammaglobulinemia

HHV-8-associated pathologies
1) Multicentric Castleman disease
2) Multicentric Castleman disease with so-called microlymphoma
3) Multicentric Castleman disease with lymphoma
4) Multicentric Castleman disease with Kaposi sarcoma
5) Multicentric Castleman disease with HHV-8-associated haemophagocytic syndrome

Lymphomas specifically occurring in HIV-positive patients
1) Plasmablastic lymphoma
2) Primary effusion lymphoma — classical and 'solid' forms
3) Lymphomas arising in multicentric Castleman disease

Lymphomas occurring in other immunodeficient states
1) Lesions similar to polymorphic post-transplant lymphoproliferative disorder

Lymphomas also occurring in immune competent patients
1) Classical Hodgkin lymphoma
2) Burkitt lymphoma
3) Diffuse large B-cell lymphoma
4) Primary diffuse large B-cell lymphoma of the CNS
5) Marginal zone lymphoma (of mucosa-associated lymphoid tissue (MALT) type)
6) Peripheral T-cell and NK-cell lymphoma

Table 2