Lymph node pathology in the HIV-positive child

Komala Pillay

Abstract

Lymphadenopathy in the HIV-positive child may be due to a range of non-neoplastic (non-infective and infective) and neoplastic conditions. Reactive changes and infective diseases, mostly of mycobacterial aetiology, are encountered most often. The common neoplastic conditions include non-Hodgkin lymphoma (Burkitt lymphoma and diffuse large B-cell lymphoma) and Kaposi sarcoma.

Keywords HIV-positive; infective; kaposi sarcoma; leiomyosarcoma; lymphadenopathy; lymphoma; neoplastic; paediatric

Introduction

Enlarged lymph nodes are often biopsied in the HIV-positive paediatric patient to determine whether the adenopathy is due to reactive lymphoid hyperplasia, infection, lymphoma or Kaposi sarcoma. The aim of this review is to highlight some of the non-neoplastic (non-infective and infective) and neoplastic conditions that may be seen more commonly in lymph node biopsies from HIV-positive children, bearing in mind that some of these conditions may occur concurrently. In addition, lymphoproliferative disorders are mentioned even though these are predominantly extranodal in the HIV-positive patient.

Non-neoplastic conditions

Non-infective conditions

HIV: related lymphadenopathy: depending on the stage of the disease, lymph nodes show a variety of histological features. Enlarged lymph nodes commonly show explosive reactive follicular hyperplasia (Figure 1a), which consists of follicles of varying size (often extending into the medullary portions of the lymph node), some of which are extremely large and irregular.[1] The germinal centres show transformed cells with a high mitotic rate and prominent starry sky appearance. There is thinning of the mantle zone with invagination of the small mantle zone lymphocytes, resulting in follicle-lysis (Figure 1b) characterized by irregular clusters of germinal centre cells among collections of small mantle zone lymphocytes. The overall appearance may be mistaken for non-Hodgkin lymphoma, and a follicular dendritic cell marker such as CD21 may be useful in highlighting the germinal centres. Additional features include germinal centre haemorrhage (Figure 1b), multinucleate giant cells and distension of the sinuses with polyclonal monocytoid B cells.[2]

The interfollicular areas contain a polymorphous inflammatory infiltrate, including lymphocytes, a varying number of plasma cells, eosinophils, immunoblasts and histiocytes. There is also a proliferation of high endothelial venules.

Later in the course of the disease, there may be follicular involution characterized by small germinal centres with or without associated follicular hyperplasia (Figure 1c).[3] The germinal centres show concentrically arranged follicular dendritic cells and few residual lymphocytes with hyalinized vessels that enter the germinal centre at right angles, similar to the hyaline-vascular type of Castleman disease.

The pattern of follicular hyperplasia (more than two-thirds of the cross-sectional area of the node), mixed hyperplasia (less than two-thirds) and involution are usually typical of persistent generalized lymphadenopathy (PGL) and the acquired immunodeficiency syndrome (AIDS)-related complex (ARC).[4] In the paediatric age group, enlarged lymph nodes often show explosive reactive follicular hyperplasia. The constellation of features, although not specific, should alert the pathologist to the possibility of human immunodeficiency virus (HIV) infection. Immunohistochemically, the stain for p24 antigen may be positive in the follicular dendritic cells (Figure 1d). An abnormal T-cell population is also demonstrated with an inverted CD4-to-CD8 ratio in the paracortex as a result of decreased CD4 cells and increased CD8 cells, similar to peripheral blood changes. The follicles in these nodes also show CD8-positive T cells in contrast to the usual CD4-positive T cells in normal follicles.[4]

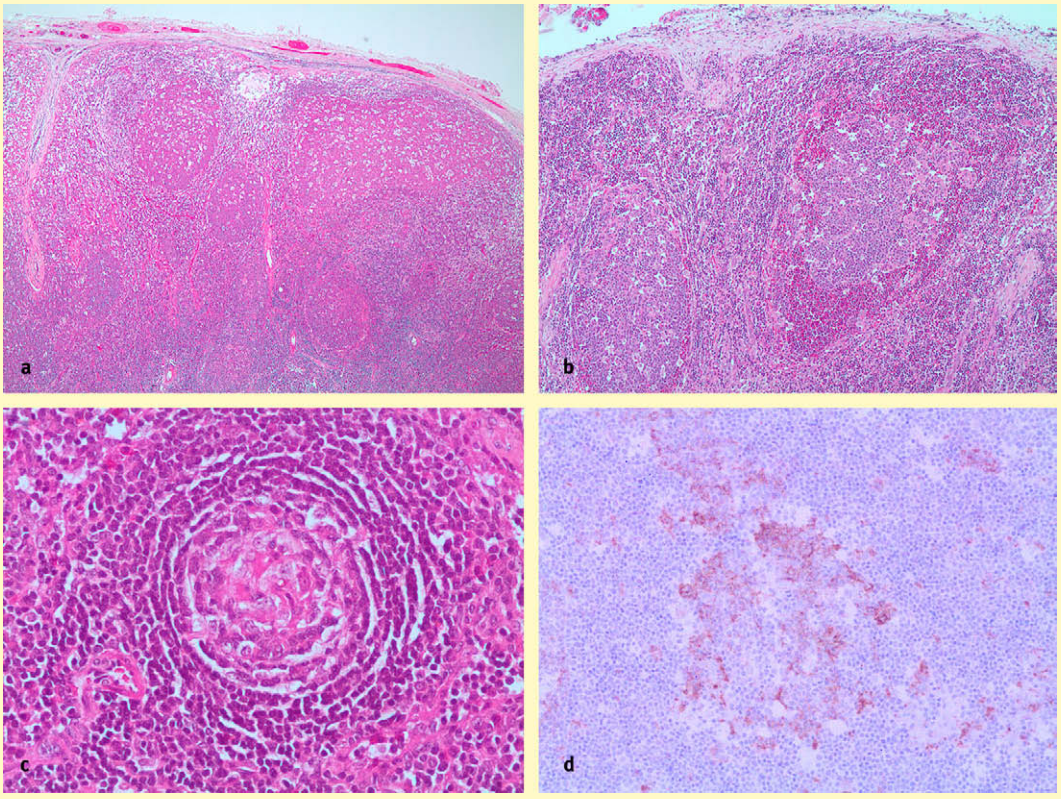
The lymph nodes with lymphocyte depletion tend to be smaller and are not often biopsied, but may be seen in autopsy sampling. These lymph nodes are characterized by a lack of cellular follicles, exposed nodal framework (vascular and sinusoidal structures) and extensive vascular proliferation. Plasma cells and histiocytes are conspicuous with relatively few lymphocytes.[1,4]

A polyclonal polymorphic B-cell lymphoproliferative disorder (PBLD), probably Epstein–Barr virus (EBV) driven, can also occur in the HIV-infected child. This is usually part of a systemic process and includes features such as generalized lymphadenopathy, hepatosplenomegaly and extranodal involvement, especially of the lung.[5] Histologically, the cellular infiltrate comprises an admixture of lymphocytes, plasma cells, plasmacytoid lymphocytes and immature lymphoid cells or immunoblasts. This lesion is considered to be atypical lymphoid hyperplasia that is intermediate between benign and definite malignant lesions.[6] It is possible that EBV alone or in concert with human lymphotrophic virus type-III (HTLV-III) may be related to the development of these lymphoproliferative lesions in children.[6]

Other associated reactive changes may include focal dermatopathic lymphadenitis characterized by pulp histiocytosis and melanin pigment, and haemophagocytosis demonstrated by sinus histiocytosis with engulfed red blood cells and/or leucocytes.[7]

Castleman disease (CD) is probably a result of low-grade chronic inflammation induced by human herpes virus 8 (HHV8), which stimulates interleukin-6 (IL-6) secretion and subsequent hyperplasia of the immune system. This virus is also involved in

Komala Pillay *MBChB FCPath (SA) FRCPath (UK) MMed Anat Path (UCT) Consultant Histopathologist is at the National Health Laboratory Services and Division of Anatomical Pathology, University of Cape Town, Red Cross Children's Hospital, Cape Town, South Africa.*



HIV associated lymphadenopathy. **a** Enlarged irregular germinal centre in HIV associated lymphadenopathy, **b** follicle-lysis and germinal centre haemorrhage, **c** follicular involution and **d** positive p24 immunohistochemistry.

Figure 1

Kaposi sarcoma (KS), which explains the co-existence of these two lesions in certain instances.

The systemic form of CD (multicentric plasma cell type) usually occurs in AIDS, whereas the localized (hyaline vascular or plasma cell type) usually occurs in immunocompetent individuals.[8] Multicentric CD is characterized by follicles with variable morphology (hyperplastic, atrophic or fibrotic) surrounded by expanded mantle zones with scattered plasmablasts that have moderate amounts of amphophilic cytoplasm, large vesicular nuclei and prominent nucleoli. These cells may form small monoclonal proliferations (plasmablastic microlymphoma). Of note, HHV-8 positive plasmablastic lymphoma in the setting of multicentric CD is an entity with a poor prognosis.[9] Follicles characteristic of the hyaline vascular type with prominent follicular dendritic cells, increased vascularity, concentric layering of the mantle cells and vessels entering the follicle at right angles may be also be seen. The interfollicular region shows abundant mature plasma cells and is heavily vascularized.[9]

Reactive changes attributed to HIV infection may have features similar to CD, especially follicles showing the characteristics of hyaline-vascular type CD. Therefore, all children with this diagnosis should be tested for HIV.[8] The changes are usually more diffuse in CD compared to reactive HIV-related adenopathy and there is usually HHV8 staining by immunohistochemistry.

Lympho-epithelial cysts: in 1958, Bernier and Bhaskar defined lympho-epithelial cysts as solitary or multiple cysts within intraparotid lymph nodes, probably as a result of cystic degeneration of salivary gland inclusions. With progression of disease, the process involves the entire lobe.[10] However, Ihler and colleagues showed with computer assisted three-dimensional reconstruction that these lesions may be derived from salivary lobules with accompanying reactive lymphoid hyperplasia.[11]

According to Dave *et al.* there are 16 reported cases in HIV-positive children.[12] It is uncertain whether persistent generalized lymphadenopathy, HIV-associated benign lympho-epithelial lesions and HIV-associated benign lympho-epithelial cysts represent a continuous spectrum or distinct entities.[12] Lympho-epithelial lesions are characterized by infiltration of ductal epithelium by lymphocytes which are small to medium in size with irregular nuclear contours and condensed chromatin.[13] These lesions are similar to those encountered in myoepithelial sialadenitis (MESA) and mucosa-associated lymphoid tissue (MALT) lymphoma.[13] Lympho-epithelial cysts show cystic structures filled with proteinaceous fluid containing foamy macrophages and reactive lymphocytes, lined by squamous or cuboidal epithelium with numerous intra-epithelial lymphocytes and surrounded by hyperplastic lymphoid follicles (Figure 2). When these lesions are suspected clinically, fine needle aspiration cytology is recommended to exclude other pathology such as Warthin tumour, lymphoma or KS.[6]

Chetty reported nine paediatric cases, all of whom had trucut biopsies and therefore intact cystic structures were not present. However, most of the cases showed prominent lympho-epithelial lesions, centrocyte-like cells, centroblastic cells, plasma cells and histiocytes.[13]