Reactive lymph node conditions in childhood

Emily C Shaw
Vipul Foria
Bhumita Vadgama

Abstract

Lymph node enlargement is a common manifestation of many childhood illnesses. Chronic lymphadenopathy lasting greater than 6 weeks or persistent enlargement of a single lymph node, regional lymph node group or systemic lymphadenopathy in the absence of an obvious cause are indications for lymph node biopsy or excision. In this review we cover common and less common causes of lymph node enlargement in childhood with their characteristic histological features. The most common morphological patterns, including follicular hyperplasia, interfollicular/paracortical expansion, sinus histiocytosis and granulomatous and necrotising lymphadenitis are discussed, with a description of features suggesting specific underlying aetiology and other adjuncts to precise diagnosis.

Keywords follicular hyperplasia; lymph node; paracortical expansion; reactive; sinus histiocytosis

Introduction

Lymph node enlargement, generally defined as palpable or imaging-detected lymph nodes greater than 2 cm in size, is a common manifestation of many childhood illnesses. Chronic lymphadenopathy lasting greater than 6 weeks or persistent enlargement of a single lymph node, regional lymph node group or systemic lymphadenopathy in the absence of an obvious cause are indications for biopsy or excision. In this review we cover common and less common causes of lymph node enlargement in childhood with their morphological patterns and characteristic histological features.

Different morphological patterns of reactive lymph nodes

The morphological patterns of reactive lymphadenopathy are follicular hyperplasia, expansion of the interfollicular area, including expansion of this region by histiocytes, granulomas and/or immunoblasts, sinus histiocytosis and necrotising lymphadenitis. Reactive lymphadenopathy can be classified according to aetiology as well as morphological pattern (Table 1). For practical purposes when assessing a node, it is helpful to consider which of the anatomical and functional compartments are affected by the pathological process: the B cell areas (follicles), the T cell areas (inter- or parafollicular regions), the monocyte–macrophage areas (sinuses) or a mixed pattern combining some or all of the above compartments. The pathology should also be correlated with clinical history and there are a variety of ancillary laboratory techniques that can provide additional helpful information in making a precise diagnosis (Table 2).

Pathology of the B cell/follicular areas

Reactive follicular hyperplasia: the most common pattern of reactive hyperplasia is variable enlargement of germinal centres with or without accompanying mantle zone enlargement, initially confined to the cortical area but in florid cases causing compression of adjacent paracortex and sometimes fusion of adjacent germinal centres (Figure 1). Reactive germinal centres show prominent apoptosis, frequent tingible-body macrophages and mitotic figures. Follicular hyperplasia indicates activation and proliferation of B cells in response to any one of a number of different stimuli including infectious micro-organisms, drugs and immunisations or environmental toxins and pollutants. A specific form of follicular hyperplasia may be seen in lymph nodes of patients with human immunodeficiency virus (HIV) infection, characterised by irregular serpiginous enlargement and fusion of adjacent follicles with areas of follicular lysis and regression in older lesions. On low power microscopic examination, the follicles in a reactive condition can be seen to be evenly distributed throughout the lymph node and show polarisation with more frequent mitotic and apoptotic activity than their malignant counterparts, particularly low-grade follicular lymphoma. Absence of Bcl-2 expression by the germinal centre cells of secondary follicles on immunohistochemistry can be helpful in differentiating florid reactive hyperplasia from follicular lymphoma, although paediatric-type follicular lymphoma is usually Bcl-2 negative and care must also be taken to avoid misinterpreting the presence of small Bcl-2 expressing T lymphocytes within germinal centres. Interfollicular involvement of a lymph node by Hodgkin lymphoma may also be associated with prominent follicular hyperplasia, necessitating close examination (with or without CD15 and CD30 immunohistochemistry) to exclude the presence of Hodgkin Reed–Sternberg cells within a polymorphous interfollicular infiltrate in such cases. Clonality analysis may be used as an adjunct to differentiating reactive from neoplastic lesions, but this should be interpreted taking into account the morphological features, since the presence of a clonal (usually oligoclonal) population may indicate the product of a highly restricted immune response rather than neoplasia.

Progressive transformation of germinal centres (PTGCs): progressive transformation of germinal centres commonly affects cervical or inguinal lymph nodes, which show enlarged, reactive follicles with an influx of small mantle zone lymphocytes into some follicles, indistinct boundaries and histiocytic infiltration with or without aggregates of epithelioid histiocytes surrounding

Emily C Shaw *BM(Hons) MRCP(UK) FRCPath is a Specialty Registrar in Histopathology at the Department of Cellular Pathology, University Hospital Southampton NHS Foundation Trust, Southampton, UK. Conflicts of interest: none declared.*

Vipul Foria *FRCPath is a Consultant Cellular Pathologist at the Department of Cellular Pathology, University Hospital Southampton NHS Foundation Trust, Southampton, UK. Conflicts of interest: none declared.*

Bhumita Vadgama *FRCPath is a Consultant Paediatric Pathologist at the Department of Cellular Pathology, University Hospital Southampton NHS Foundation Trust, Southampton, UK. Conflicts of interest: none declared.*

Aetiology of non-neoplastic lymphadenopathy in children. *Langerhan cell histiocytosis is in the process of being re-classified, regarded now as likely to be a neoplastic disease due to the recent discovery of a recurrent *BRAF* gene point mutation and related mitogen activated protein kinase (MAPK) pathway abnormalities in this condition. **IgG4-related disease has been included for completeness but is rare in the paediatric age group

Infections	**Viral** e.g. Epstein—Barr virus (EBV, infectious mononucleosis); cytomegalovirus (CMV); herpes; human immunodeficiency virus (HIV); measles; adenovirus, rhinovirus; Coxsackie A and B **Bacterial** e.g. Tuberculosis and other mycobacterial (including atypical) infections; cat-scratch fever (*Bartonella*); *Legionella*; Chlamydia; *Yersinia*; *Staphylococcus aureus*; group A streptococcus **Fungal** e.g. *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma* **Protozoal** e.g. Toxoplasmosis
Systemic disease	**Primary immunodeficiency disorders** e.g. Autoimmune lymphoproliferative syndrome (ALPS); X-linked hyper-IgM syndrome; common variable immunodeficiency and Wiskott—Aldrich syndrome Dermatopathic lymphadenopathy Rosai—Dorfman disease Kikuchi—Fujimoto necrotising histiocytic lymphadenitis Systemic lupus erythematosus (SLE) Kawasaki disease Sarcoidosis Crohn's disease Langerhan cell histiocytosis* Castleman disease Idiopathic juvenile arthritis/rheumatoid arthritis Kimura disease IgG4-related disease**
Iatrogenic	**Drug-induced** e.g. phenytoin; pyrimethamine; carbamazepine; allopurinol; isoniazid; phenylbutazone **Immunisation-related** e.g. live attenuated measles—mumps—rubella (MMR); diphtheria—poliomyelitis—tetanus (DPT); poliomyelitis; typhoid fever

Table 1

the follicles (Figure 2). The appearances may be 'asynchronous', with adjacent follicles exhibiting different stages of the process and the progressively transformed follicles are at least 3—4 times larger than their reactive counterparts. Immunohistochemistry with CD21 and CD23 demonstrates an expanded dendritic meshwork and the infiltrating mantle-like cells express IgM and IgD. A variable infiltrate of CD4-expressing T lymphocytes are also seen in the transformed follicle centres and there may be epithelioid histiocytes in the adjacent paracortex. The exact nature of the association between PTGC and lymphoma has yet to be elucidated, with reports in the literature of PTGC pre-dating, co-existing with and also appearing after diagnosis and treatment of lymphoma.

Immunodeficiency disorders: primary immunodeficiency disorders is an umbrella term encompassing a group of conditions caused by genetic mutations in the germline/constitutional DNA encoding key proteins involved in immune system function. These can be subdivided into combined B and T cell deficiency states, including mutation in the *CD40LG* (CD40 ligand) gene in X-linked hyper-immunoglobulin M (IgM) syndrome (Online Mendelian Inheritance in Man (OMIM) database reference #308230), antibody deficiencies such as mutations in the *ICOS* and *TNFRSF13B* genes in combined variable immunodeficiency (CVID, OMIM #607594 and #240500), immune dysregulation diseases including mutations in the FAS and FASLG (FAS ligand) genes in autoimmune lymphoproliferative syndrome (ALPS, OMIM #601859), and other defined clinical/genetic syndromes such as mutation of the *WAS* gene in Wiskott—Aldrich syndrome (OMIM #301000). The histological findings in lymph nodes that these conditions have in common include depletion of lymphoid cells from germinal centres and paracortical areas and follicular atrophy (Figure 3). The paracortical area may contain a compensatory excess of histiocytes and plasma cells and the follicles may paradoxically show hyperplasia. Atypia may be seen and progression to lymphoma may occur, reflecting loss of the normal immunosurveillance mechanisms in these patients, who are also at increased risk of developing leukaemia and solid organ tumours.

Autoimmune lymphoproliferative syndrome (ALPS) — patients with ALPS (formerly known as Canale—Smith syndrome) present with recurrent infections and constitutional symptoms associated with autoimmune phenomena such as thrombocytopaenia, haemolytic anaemia, neutropoenias or glomerulonephritis. On clinical examination patients have generalised lymphadenopathy and splenomegaly. To date five different subtypes of ALPS have been defined (Table 3). Involved lymph nodes can show a range of appearances, predominantly characterised by a preserved architecture with follicular hyperplasia and a paracortical expansion, predominantly by T immunoblasts which show prominent mitotic activity and express CD3 and the αβ T cell receptor but not CD4 or CD8 (so-called 'double-negative' T cells, dnTs) as well as polyclonal B cells which express CD5. The double negative T cells have been found to show expression of some cytotoxic markers, indicating that they may have originated from CD8 + cytotoxic T lymphocytes. ALPS subtype 3 does not show an excess of dnTs. The lymph node follicles in this condition may also show progressive transformation of germinal centres and some may appear involuted. Increased numbers of plasma cells may also be seen and these are polyclonal in nature. Grade IIIB follicular lymphoma, which can also be seen in the paediatric population, is an important differential diagnosis and represents a potential diagnostic pitfall. This is further complicated by the fact that neoplastic follicles can