Lymph node pathology in infectious diseases

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Abstract

Lymph node biopsy is usually undertaken to investigate possible neoplastic involvement and it is appropriate that most emphasis in the teaching of lymph node pathology is placed on recognizing neoplastic diseases correctly. However, it is important also to recognize the suggestive and sometimes specific changes that occur in lymph nodes due to infection. A number of fairly standard reactive patterns involving different lymphoid and stromal components within nodes can be recognized, and different combinations can suggest specific infectious causes. It remains challenging to confirm the presence of organisms in many cases of infective lymphadenopathy and, therefore, additional clinical, serological, microbiological – and now molecular diagnostic – investigations, in response to recognition of suggestive pathology, are essential. In this review, the typical lymph node histological features associated with relatively common infectious agents are described. How the causative organisms and the effects of infection in lymph nodes may differ between individuals with intact immunity or immunocompromise is discussed.

Keywords EBV; follicular hyperplasia; granuloma; HHV8; HIV; immunocodeficiency; infection; lymph node; monocytoid B-cell hyperplasia; necrosis

Introduction

Reactive changes in lymph nodes are diverse and complex; they may be at least as challenging to interpret as neoplastic lymphoid proliferation. Among such reactive conditions, those caused by infective agents cause problems for precise diagnosis. The causative organisms may be difficult or impossible to demonstrate. Responses to different organisms within lymphoid tissue may be similar, while some agents cause changes that are only distinctive at certain stages of infection. The level of an individual's underlying immune competence also influences the ability to mount responses to many infections.

This review depicts the common reactive patterns in lymph nodes arising in response to defined infectious agents. It is not intended to provide a comprehensive catalogue of changes arising from infection with rare organisms. However, some 'rare' infections are included because of the importance of distinguishing their effects from other pathologies or because they are being recognized more frequently.

Effects of immune compromise on responses to infection in lymph nodes may be predicted in some instances; in many infections, the altered responses are well characterized. Human Immunodeficiency Virus (HIV) infection is – and will always be – a key cause of immunodeficiency, leading to altered reactions to some common infections and susceptibility to others that do not usually infect an immunocompetent individual. HIV itself causes distinct lymph node pathology and this will be described, indicating pitfalls and overlaps. The critical current roles and limitations of molecular diagnostic techniques in confirming the presence of specific micro-organisms in fixed, paraffin-embedded lymphoid tissue are also discussed.

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Common infections in immunocompetent individuals

Acute lymphadenitis

True acute inflammation of lymph nodes, with neutrophil polymorph accumulation, is rarely seen in diagnostic pathology. This is not necessarily because it is uncommon but because it is rarely biopsied. More typically, however, acute lymph node reactions to infection are short-lived expansions of lymphoid and antigen presenting components representing an immune response to infection in the drainage territory of the involved node(s). Although common, such reactive lymph nodes are also rarely biopsied since their enlargement is transient; histology, when sampled, is that of non-specific follicular and/or paracortical hyperplasia.

True acute lymphadenitis may accompany some local and systemic bacterial infections and is reflected by accumulation of neutrophil polymorphs, initially within and adjacent to sinuses. There is often extension into perinodal fat and necrosis may lead to abscess formation. Rare nowadays, severe necrotizing acute lymphadenitis is the underlying pathology of the erupting lymph node lesions ('buboes'), usually inguinal or axillary, characteristic of bubonic plague. The sites of lymphadenopathy in plague, caused by *Yersinia pestis*, reflect the lymphatic drainage from the entry site of causative organisms, via a rat-flea bite. Characteristic acute necrotizing inflammation, with large numbers of gram-negative bacilli, would be anticipated and are present.

Another classical uncommon infection (which, like plague, is potentially usable in bioterrorism) is anthrax. Inhaled spores of *Bacillus anthracis* result in bacillary proliferation and massive vascular leakage with haemorrhage and oedema. Such is found in hilar nodes, with abundant large gram-positive bacilli.

Foci of necrotizing acute inflammation accompany a florid paracortical reaction in lymphadenopathy caused by *Herpes simplex*. Lymphadenopathy is uncommon in *H. simplex* infection, usually accompanies typical oral or genital ulcerative lesions, and is painful. Regional lymph nodes are involved (cervical or inguinal) with rare cases of more widespread lymphadenopathy. Cells containing eosinophilic, ground-glass nuclear inclusions vary widely in number and may be hard to find. Infection with *Herpes zoster* may very rarely cause similar lymphadenopathy.

An unusual and alarming pattern of acute reaction has been described in mesenteric lymph nodes accompanying severe gastro-intestinal inflammation, including acute appendicitis and intestinal perforation. An accumulation of pleomorphic CD30-positive B-cell immunoblasts may occur, limited to the subcapsular sinus and the immediately adjacent lymph node parenchyma (Figure 1). There is grave danger of misinterpreting such

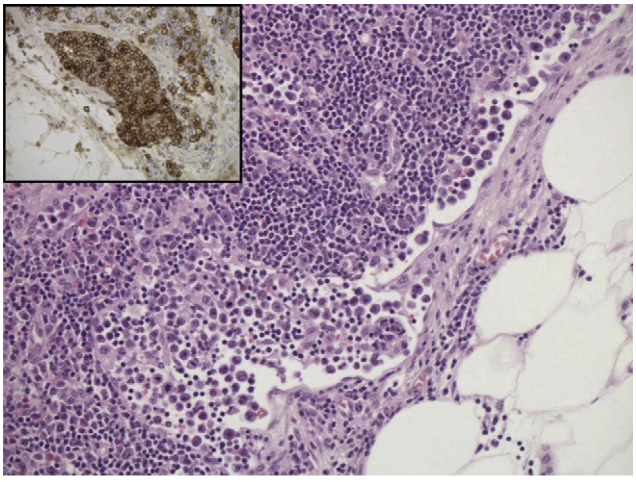

Figure 1 Immunoblastic, predominantly intrasinusoidal reaction following repeated intra-abdominal surgery. Inset shows CD30 expression by the large cells, which were polytypic for kappa and lambda and showed polyclonal IGH rearrangements. (Case available by kind courtesy of Dr Vivek Mudaliar, Consultant Histopathologist, Royal Shrewsbury Hospital).

reactions as large B-cell lymphoma if this phenomenon is not recognized. Careful investigation with immunohistochemistry (including exclusion of ALK-positive large B-cell lymphoma and primary effusion-based lymphoma, which may express an incomplete B-cell immunophenotype), plus consideration of FISH and PCR to investigate MYC and IGH rearrangements, is advisable in all such cases to avoid error in either direction.

Mycobacterium tuberculosis

Extra-pulmonary tuberculosis (TB) is ever-present, even in apparently immunocompetent individuals. Solitary or localized lymphadenopathy, with few systemic symptoms, is a relatively frequent presentation of TB today. Increasing use of endobronchial ultrasound (EBUS)-guided fine-needle aspiration to sample mediastinal and peribronchial lymph nodes also contributes to increasing detection of lymph node involvement accompanying pulmonary disease via sampling of the draining lymph nodes. It therefore remains essential for cellular pathologists to recognize TB-associated lymph node pathology in cytology and histology specimens.

The classical pathology of TB is granuloma formation with caseation and this is found in lymph nodes as at other sites (Table 1). Caseation may be absent from early lesions and can be so extensive in advanced cases that the granulomatous nature of the process is obscured. Distribution of granulomas within lymph nodes is generally random. Epithelioid macrophages usually predominate; multinucleated macrophage giant cells may be sparse or abundant and do not always have classical Langhans type appearances. There is not usually any significant fibrosis accompanying TB granulomas in active disease; tombstone nodules of hyaline fibrosis, however, may be left in healed lesions, often associated with dystrophic calcification. Abundant lymphocytes accompany the epithelioid cells; these are predominantly T-cells of CD4-positive type, including Th1 and Th2 subsets. CD8-positive T-cells are fewer and mainly confined to the periphery of granulomas plus the surrounding

Granulomatous lymphadenitis histopathology: associated characteristic histological features in immunocompetent patients

Disease/infection	Langhans giant cells	Caseous or fibrinoid necrosis	Suppurative inflammation
Sarcoidosis	+	+/−	−
Tuberculosis and non-TB mycobacteria	+	+	−
Cat scratch disease, lympho-granuloma venereum, tularaemia (*Francisella tularensis*), brucellosis (*Brucella* spp) & melioidosis (*Burkholderia pseudomallei*)	+	+	+
Syphilis (*Treponema pallidum*)	+	+	−
Whipple's disease	−	−	−
Toxoplasmosis	−	−	−
Leishmaniasis	+	+	−

Table 1

lymphoid tissue. Acid-fast bacilli (AFB) may be demonstrated using Ziehl–Neelsen (ZN) or auramine staining in fixed tissue sections but are typically rare. A high content of organisms would suggest that the patient has immune impairment, or that the organism might be an atypical (non-TB) mycobacterium. It is important to remember that in standard histological sections, the density of AFB in tissue needs to be >1000 per cubic centimetre for a histopathologist to be able to see any at all. Thus the statement "AFB not seen" is not synonymous with a lesion not being mycobacterial.

Granulomatous pathology in lymph nodes should always prompt staining for AFB and fungi, even if the granulomas lack caseation and appear incidental to additional pathology, such as metastasis or lymphoma. Patients with malignant diseases are often subtly or overtly immunocompromised, by the disease itself or its treatment, and are susceptible to new or reactivated infection by organisms such as TB. Conversely, even if caseating granulomas dominate the histological picture in a lymph node, careful exclusion of additional pathology, particularly lymphoma or subtle cancer, is essential.

Atypical mycobacteria

There are no consistent differences between TB and non-TB (atypical) mycobacterial infections in terms of the detail of granulomatous inflammation that they cause in immunocompetent persons. Individual lesions in nodes may be less well defined and show greater coalescence with neighbouring granulomas; a serpiginous aggregation of necrotic granulomas is characteristic. A classic scenario is children presenting with enlarged neck nodes, but otherwise well. *Mycobacterium avium-intracellulare, Mycobacterium scrofulacaeum* and *Mycobacterium kansasii* are environmental mycobacteria commonly consumed by children, causing local neck lymphadenopathy; usually the