PERSONAL PRACTICE

Lymphadenopathy

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Lymph node enlargement is a common finding on routine physical examination of children. The dilemma facing general practitioners is when to refer to paediatricians; the dilemma for paediatricians is deciding how extensively to investigate children. While the majority of cases will have a benign, rapidly resolving course, the well recognised associations of lymphadenopathy and potentially life threatening diseases such as cancer cause worry and anxiety to both families and doctors caring for children. This concern may in itself initiate an inappropriately rapid or over aggressive attempt at determining the diagnosis. An organised approach to children with lymphadenopathy will help the clinician make appropriate decisions regarding treatment and further investigation.

History

A detailed history should focus both on diagnostic clues, and to features suggestive of more sinister pathology. Duration of lymphadenopathy may be helpful, most infectious causes producing a short (less than two week) history. Long standing lymphadenopathy may be caused by a variety of diseases including infections (HIV, Epstein-Barr virus, tuberculosis, etc), malignancy, inflammation, and autoimmune disease, but while very long standing (over one year) lymph node enlargement is likely to be pathological, it is unlikely to be due to malignancy. Attention should be made to associated rashes (exanthemata), travel, and exposure to pets (particularly cats). Associated constitutional symptoms should be sought: weight loss (>10% over six months), fever and night sweats, pruritis, and myalgia/arthralgia. While the presence of such symptoms is important, they are not specific, as frequently believed, for lymphoma. Only one third of children with Hodgkin's disease and 10% with non-Hodgkin's lymphoma display constitutional symptoms.

Physical examination

While the child with isolated lymphadenopathy associated with erythema, tenderness, and inflammation poses little diagnostic dilemma, the chronic, non-inflamed node is more of a challenge. The first point is to decide whether nodes are abnormally enlarged. Unfortunately there is little guidance in the literature to help. While some authors suggest lymph nodes

<1 cm diameter are invariably of non-specific aetiology,¹ others agree with '1 cm rule', but add that epitrochlear nodes >0.5 cm, and inguinal nodes >1.5 cm should be regarded as abnormal nodal dimensions in these anatomical sites.^{2,3} Full examination of all nodal sites should be undertaken to determine if lymphadenopathy is localised or generalised. The distinction between localised or generalised lymphadenopathy is important, as a specific pathological cause is more likely to be found in patients with generalised lymphadenopathy.¹ The descriptive character of the lymph node(s) (firm, rubbery, fixed), is at best subjective and at worst quite misleading. Far from being pathognomonic of malignant nodes, many inflammatory lesions especially if associated with fibrotic reaction can 'feel sinister'.

Abdominal palpation should determine the presence of liver or splenic enlargement. Features of anaemia, petechiae, or bleeding will point towards a marrow infiltrative disease such as leukaemia. The skin should be examined for infective lesions or exanthematous rashes. A careful ear, nose, and throat examination, especially in children with cervical lymphadenopathy, with particular emphasis on nasal discharge, obstruction, or depression of the soft palate helps to define possible source of infection while considering some of the commoner malignant head and neck tumours such as non-Hodgkin's lymphoma, rhabdomyosarcoma, and nasopharyngeal carcinoma.

Generalised lymphadenopathy

The presence of generalised lymphadenopathy should always alert the clinician to the presence of significant pathology. Detailed history and examination will help narrow diagnostic possibilities. Any of the common viral exanthemata may produce generalised lymphadenopathy, other infective causes may include infectious mononucleosis, toxoplasmosis, and HIV infection particularly if lymphadenopathy has been present for over three months. Lymphadenopathy due to leukaemia may be generalised, but other features such as anaemia, bleeding, or bruising are likely to be present. Similarly generalised lymphadenopathy from other systemic malignancies such as lymphoma or neuroblastoma are likely to be associated with other clinical findings (for example the presence of an abdominal mass).

A number of rarer causes of generalised lymphadenopathy should also be considered in

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the list of differential diagnoses. A wide range of autoimmune and connective tissue disease may be associated with generalised lymphadenopathy. Drugs (particularly phenytoin and carbamazepine) are reported to be associated with lymphadenopathy, but this complication appears to be very rare.⁴ X linked lymphoproliferative disease is characterised by a rapidly progressive and often fatal Epstein-Barr virus infection mimicking severe infectious mononucleosis.⁵ The Sézary syndrome is a form of cutaneous T cell non-Hodgkin's lymphoma with similarities to mycosis fungoides.⁶ Although more typically a disease of older patients, it has been reported to occur in children and is associated with generalised lymphadenopathy.

Regional lymphadenopathy

Due to the anatomical arrangement of the lymphatic system and drainage, regional lymphadenopathy usually represents the clinical manifestation of local pathological processes. Infection is undoubtedly the commonest cause of localised lymphadenopathy, and careful examination of the skin, ear, nose, and throat, teeth, scalp, etc will help define the source of infection in a proportion of children. Common infecting organisms will be streptococcal and staphylococcal species.⁷ Axillary and cervical lymphadenopathy should always prompt questioning about pets, as cat scratch disease is commonly associated with this pattern of lymph node enlargement.⁸ Long standing lymphadenopathy may suggest tuberculosis and a history of contact should be sought. Tuberculin skin testing may help in clarification, however, both false positive and false negative results may lead to confusion.⁹

In developed countries, lymphadenopathy due to mycobacteria is likely to be non-tuberculous and one recent report has suggested the incidence of *Mycobacterium avium* and *Mycobacterium malmoense* infections in children is increasing.¹⁰ The cervical, submandibular, and preauricular nodes are usually involved, and in most cases the lymphadenopathy is unilateral. Systemic illness appears to be unusual. Diagnosis may be made by Mantoux testing with different mycobacterium species antigens, however, results may not be conclusive. In addition cross reactivity with tuberculin purified protein derivative may further confuse the situation by producing both false positive and false negative results. The diagnostic test of choice is excisional biopsy with the specimen being sent for both mycobacterial culture and for routine histology. Excision is likely to be curative, as antituberculous drug treatment seems to have no role in the treatment of non-tuberculous mycobacterial infection. Incision and drainage or needle biopsy produces sinus formation and scarring in a significant number of children.¹¹

Regional lymphadenopathy may of course be due to malignancy. Indeed cancers such as Hodgkin's disease commonly present with enlarged nodes. Overall the incidence of cancer induced lymphadenopathy is small. One series presenting data on lymph node

biopsies in children reported about one sixth of cases being due to malignancy.¹² Of 13 malignant cases in this report, nine were due to Hodgkin's disease, three non-Hodgkin's lymphoma, and one Langerhans' cell histiocytosis. Although other malignancies such as soft tissue sarcomas may involve locoregional nodes, it is uncommon for lymphadenopathy to be present without additional physical signs due to the primary tumour.

Rarer pathologies

A seemingly bewildering assortment of reactive lymphadenopathies, lymphadenitides, and lymphoproliferative disorders underlies a small proportion of children with enlarged lymph nodes.¹³ A few warrant further discussion as confusion with malignant nodes is not uncommon.¹⁴

Rosai-Dorfmann disease (sinus histiocytosis with massive lymphadenopathy)¹⁵ may present with alarming, bulky, and often matted lymph nodes. The majority of cases present with cervical lymphadenopathy, although other nodal sites and extranodal involvement (skin, soft tissues, bone, central nervous system) can be seen. Although the disease is usually seen in young adults, cases in children have been reported.¹⁶ Constitutional symptoms such as fever and malaise may be present in a proportion of cases. Common laboratory findings are raised erythrocyte sedimentation rate (ESR), hypergammaglobulinaemia, and anaemia. Although the lymph nodes undergo spontaneous regression with time, mortality from progressive disease in vital sites is recognised.¹⁷ A variety of therapeutic interventions have been tried in order to halt the progression of this disease including corticosteroids, a variety of chemotherapeutic agents, immunosuppressants such as cyclosporin, and radiotherapy. All have been shown to have some effect in individual patients, but at best the responses are variable, and no consistent approach can be recommended other than observation in the majority of cases. A small number of cases will develop persistent, non-progressive disease, or demonstrate a chronically relapsing picture over several years.

Kikuchi's disease (histocytic necrotising lymphadenitis) was first described in Japan but is now recognised to occur world wide,¹⁸ usually in young adults, but also reported in children.¹⁹ The disease is benign and self limiting, however, the pattern of lymphadenopathy and prominent constitutional symptoms commonly leads to confusion with malignant lymphomas. Cervical lymph nodes are usually involved, although other nodal sites (including generalised lymphadenopathy) may be seen. Nodes are commonly tender to touch, classical rubbery or firm, but not matted together. A prodromal flu-like illness may precede the onset of lymphadenopathy and fever is commonly reported. Laboratory findings include raised ESR and leucopenia. Due to the self limiting nature of the disease a conservative approach should be taken with symptomatic antipyretic treatment. The majority of

Flow chart for the management of children with lymphadenopathy.

cases will resolve within a few weeks but a few will persist for some months or up to a year.

Kawasaki disease presents with a combination of fever, rash, changes to the peripheral extremities, mucosal changes, conjunctival injection, and cervical lymphadenopathy. The association with coronary artery disease and sudden death makes recognition of the disease important.²⁰ Diagnosis is rarely a problem if the full spectrum of clinical features is present, however, cases presenting with fever and cervical lymphadenopathy mimicking infective lymphadenitis have been reported.²¹

Management of lymphadenopathy

With an organised approach, careful history taking and physical examination, the majority of children with lymphadenopathy will not pose a diagnostic dilemma. The presence of unexplained generalised lymphadenopathy, significant constitutional symptoms, hepatic or splenic enlargement, anaemia, or bleeding tendency should prompt urgent referral to a paediatrician. Where the diagnosis is not immediately obvious and other clinical signs are absent, a period of observation should be undertaken, and some authors would recommend the initial empirical use of antibiotics during the early follow up period.²⁷ Regular evaluation of both the lymph node(s) and patient's general condition should be undertaken. Progressive lymph node enlargement over two to three weeks, no diminution in lymph node masses after five to six weeks, or failure or complete resolution by 10 weeks should prompt further referral and investigation (figure).³

If at the time of referral there are no diagnostic clues in the history or the examination of the child, an exhaustive battery of detailed investigations is likely to be time consuming, unpleasant for the child, expensive, and of little diagnostic value. The most direct way to a

diagnosis is likely to be a biopsy preceded by a few simple investigations. These should include a full blood count and differential white cell count, tuberculin skin test, and chest radiography (particularly important to exclude mediastinal masses before general anaesthesia). ESR is a very non-specific test and is of limited benefit as it is commonly raised in a wide range of inflammatory, reactive, and malignant conditions. Similarly a normal ESR does not necessarily exclude significant pathology. Lymph node fine needle aspiration may have a role, but experience in the technique is limited, and interpretation of samples requires a degree of expertise and can at times be very misleading. The procedure of choice is either incisional or excisional lymph node biopsy. Pathological diagnosis can be notoriously difficult, and appropriate handling of biopsies, and experienced pathological opinion, is vital. Certainly if the possibility of malignancy is being considered, advice from a paediatric oncologist should be sought *before* biopsy. Complex immunohistochemistry, cytogenetic analysis, and molecular biology studies can be vital clues in clinching or excluding the possibility of cancer and also help define a wide range of non-malignant entities. All these techniques rely on fresh biopsy material, and the days of a wedge of tissue fixed in formalin in the operating theatre are numbered. Unfortunately inappropriate handling of biopsy material still frequently occurs. These issues may be compounded by the present nature of contracting within the health service and the incentive to deal with these children 'in house' rather than to refer or consult specialist centres early in the diagnostic process. This can result in further delays in diagnosis and the need for repeat biopsies. Appropriate consultation and referral at an early stage can avoid many of the pitfalls outlined above.

Conclusions

Lymphadenopathy is a common finding in children. Although a myriad of possible diagnoses are possible, very few cases will be associated with significant pathology. Untimely, inappropriate, and unnecessary investigations can be avoided in children presenting with lymphadenopathy and should be achieved through good clinical skills and interdisciplinary communication and cooperation.

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