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Lymphadenopathy and splenomegaly are common findings in children. Both benign and malignant processes can produce these findings and it is important to distinguish between the two so that appropriate management can be undertaken.

LYMPHADENOPATHY

Enlarged lymph nodes are commonly found in children. Lymphadenopathy might be caused by proliferation of cells intrinsic to the node, such as lymphocytes, plasma cells, monocytes or histiocytes or by infiltration of cells extrinsic to the node, such as neutrophils and malignant cells. In most instances, lymphadenopathy represents transient proliferative responses to local or generalized infections. Reactive hyperplasia, defined as a polyclonal proliferation of one or more cell types, is the most frequent diagnosis in pediatric lymph node biopsies.

Lymphadenopathy is also a presenting sign of malignancies such as leukemia, lymphoma, or neuroblastoma and it is important to be able to differentiate benign from malignant lymphadenopathy.

Lymphadenopathy in the head and neck region must be differentiated from several other masses due to congenital malformations (Table 15-1).

Systematic palpation of the lymph nodes is important and should include examination of the occipital, posterior auricular, preauricular, tonsillar, submandibular, submental, upper anterior cervical, lower anterior cervical, posterior upper and lower cervical, supraclavicular, infracavicular, axillary, epitrochlear and popliteal lymph nodes. Many children have small palpable nodes in the cervical, axillary and inguinal regions which are usually benign in nature. However, adenopathy in the supraclavicular regions is usually pathologic.

When a child presents with lymphadenopathy, management is based on the following factors.

History

This involves the duration of the lymphadenopathy; fever; recent upper respiratory tract infection; sore throat; skin lesions or abrasions, or other infections in the lymphatic region.
drained by the enlarged lymph nodes; immunizations; medications; previous cat scratches, rodent bites, or tick bites; arthralgia; sexual history; transfusion history; travel history and consumption of unpasteurized milk. Significant weight loss, night sweats, or other systemic symptoms should also be recorded as part of the patient’s history.

**Age**

In children younger than 6 years, the most common cancers of the head and neck are neuroblastoma, rhabdomyosarcoma, leukemia and non-Hodgkin lymphoma. In children 7–13 years of age, non-Hodgkin lymphoma and Hodgkin lymphoma are equally common followed by thyroid carcinoma and rhabdomyosarcoma; and for those older than 13 years Hodgkin disease is the more common cancer encountered.

**Location**

Enlargement of tonsillar and inguinal lymph nodes is most likely secondary to localized infection; enlargement of supraclavicular and axillary lymph nodes is more likely to be of a serious nature. Enlargement of the left supraclavicular node, in particular, should suggest a malignant disease (e.g., malignant lymphoma or rhabdomyosarcoma) arising in the abdomen and spreading via the thoracic duct to the left supraclavicular area. Enlargement of the right supraclavicular node indicates intrathoracic lesions because this node drains the superior areas of the lungs and mediastinum. Palpable supraclavicular nodes are an indication for a thorough search for intrathoracic or intra-abdominal pathology.

Lymphadenopathy is either localized (one region affected) or generalized (two or more non-contiguous lymph node regions involved). Although localized lymphadenopathy is generally due to local infection in the region drained by the particular lymph nodes, it may also be due to malignant disease, such as Hodgkin disease or neuroblastoma. Generalized lymphadenopathy is caused by many disease processes. Lymphadenopathy may initially be localized and subsequently become generalized.

**Size**

Nodes in excess of 2.5 cm should be regarded as pathologic. In addition, nodes that increase in size over time are significant.
Character
Malignant nodes are generally firm, rubbery and matted. They are usually not tender or erythematous. Occasionally, a rapidly growing malignant node may be tender. Nodes due to infection or inflammation are generally warm, tender and fluctuant. If infection is considered to be the cause of the adenopathy, it is reasonable to perform a 2-week trial of antibiotic therapy. Failure to produce a reduction in the size of the lymph node within this period is an indication for careful observation. If the size, location and character of the node suggest malignant disease, the node should be biopsied.

Diagnosis of Lymphadenopathy
Table 15-2 outlines the differential diagnosis of lymphadenopathy.

Figure 15-1 provides a diagnostics algorithm for evaluation of mononucleosis-like illness and Figure 15-2 for diagnostic evaluation of cervical lymphadenitis.

The following investigations should be carried out to elucidate the cause of either localized or generalized lymphadenopathy:

- Thorough history of infection, contact with rodents or cats and systemic complaints
- Careful examination of the lymphadenopathy including size, consistency, mobility, warmth, tenderness, erythema, fluctuation and location. All the lymph-node-bearing areas as outlined above should be carefully examined
- Physical examination for evidence of hematologic disease, such as hepatosplenomegaly and petechiae
- Blood count and erythrocyte sedimentation rate (ESR)
- Skin testing for tuberculosis
- Bacteriologic culture of regional lesions (e.g., throat)
- Specific serologic tests for Epstein–Barr virus (EBV), Bartonella henselae (IFA), syphilis (VDRL) toxoplasmosis, cytomegalovirus (CMV), human immunodeficiency virus (HIV), tularemia, brucellosis, histoplasmosis, coccidiomycosis
- Chest radiograph and CT scan (if necessary); abdominal sonogram and CT, if indicated
- Ultrasonography is useful in an acute setting in assessing whether a swelling is nodal in origin, an infected cyst or other soft tissue mass. It may detect an abscess requiring drainage
- EKG and echocardiogram if Kawasaki disease is suspected
- Lymph node aspiration and culture; helpful in isolating the causative organism and deciding on an appropriate antibiotic when infection is the cause of the lymphadenopathy
- Fine needle aspiration; may yield a definite or preliminary cytologic diagnosis and occasionally obviate the need for lymph node biopsy; it provides limited material in the
## Table 15-2  Differential Diagnosis of Lymphadenopathy

| I. Nonspecific reactive hyperplasia (polyclonal) |
| --- |
| II. Infection |
| Bacterial: |
| Staphylococcus, streptococcus, anaerobes, tuberculosis, atypical mycobacteria, *Bartonella henselae* (cat scratch disease, brucellosis, *Salmonella typhi*, diphtheria, *C. trachomatis* lymphogranuloma venereum), calymmatobacterium granulomatis, francisella tularensis |
| Viral: |
| Epstein–Barr virus, cytomegalovirus, adenovirus, rhinovirus, coronavirus, respiratory syncytial virus, influenza, coxsackie virus, rubella, rubeola, varicella, HIV, herpes simplex virus, human herpes virus 6 (HHV-6) |
| Protozoal: |
| Toxoplasmosis, malaria, trypanosomiasis |
| Spirochetes: |
| Syphilis, rickettsia typhi (murine typhus) |
| Fungal: |
| Coccidioidomycosis (valley fever), histoplasmosis, cryptococcus, aspergillosis |
| Postvaccination: |
| Smallpox, live attenuated measles, DPT, Salk vaccine, typhoid fever |
| III. Connective tissue disorders |
| A. Rheumatoid arthritis |
| B. Systemic lupus erythematosus |
| IV. Hypersensitivity states |
| A. Serum sickness |
| B. Drug reaction (e.g., Dilantin, mephenytoin, pyrimethamine, phenylbutazone, allopurinol, isoniazid, antileprosy and antithyroid medications) |
| V. Lymphoproliferative disorders (Chapter 16) |
| A. Angioimmunoblastic lymphadenopathy with dysproteinemia |
| B. X-linked lymphoproliferative syndrome |
| C. Lymphomatoid granulomatosis |
| D. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) |
| E. Castleman disease benign (giant lymph node hyperplasia, angiofollicular lymph node hyperplasia) |
| F. Autoimmune lymphoproliferative syndrome (ALPS) (Canale-Smith syndrome) |
| G. Post-transplantation lymphoproliferative disorder (PTLD) |
| VI. Neoplastic diseases |
| A. Hodgkin and non-Hodgkin lymphomas |
| B. Leukemia |
| C. Metastatic disease from solid tumors: neuroblastoma, nasopharyngeal carcinoma, rhabdomyosarcoma, thyroid cancer |
| D. Histiocytosis |
| 1. Langerhans cell histiocytosis |
| 2. Familial hemophagocytic lymphohistiocytosis |
| 3. Macrophage activation syndrome |
| 4. Malignant histiocytosis |
| VII. Storage diseases |
| A. Niemann–Pick disease |
| B. Gaucher disease |
| C. Cystinosis |

(Continued)
event flow cytometry is required and negative results cannot rule out a malignancy because the sample may be inadequate

- Bone marrow examination if leukemia or lymphoma is suspected
- Lymph node biopsy is indicated if:
  - Initial physical examination and history suggest malignancy
  - Lymph node size is greater than 2.5 cm in absence of signs of infection
  - Lymph node persists or enlarges
  - Appropriate antibiotics fail to shrink node within 2 weeks
  - Supraclavicular adenopathy.

Close communication between surgeon, oncologist and pathologist is critical to maximize results from lymph node biopsy. In addition the following precautions should be observed:

- Upper cervical and inguinal areas should be avoided; lower cervical and axillary nodes are more likely to give reliable information
- The largest node should be biopsied, not the most accessible one. The oncologist should select the node to be biopsied in consultation with the surgeon
- The node should be removed intact with the capsule, not piecemeal
- The lymph node should be immediately submitted to the pathologist fresh or in sufficient tissue culture medium to prevent the tissue from drying out. The node must not be left in strong light, where it will be subject to heat and it should not be wrapped in dry gauze, which may produce a drying artifact. Fresh and frozen samples should be set aside for additional studies, as noted below.

Intraoperative frozen section and cytologic smears should be performed. These findings, together with the clinical data, will determine which of the following additional studies may be required:

- Gram stain and culture (bacterial including mycobacterial, viral and/or fungal) if clinically warranted or if intraoperative frozen section suggests an infection
Figure 15-1  Diagnostic Algorithm for Evaluation of Mononucleosis-like Illness (MLI).

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpes virus 6; IM, infectious mononucleosis; LAD, lymphadenopathy; VCA, viral capsid antigen; WBC, white blood cell.

*Consider possibility of false-positive heterophile test due to HIV-1 before finalizing diagnosis.

Adapted from: Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. Am J Med 2007;120(10):911el–911e8, with permission.
Figure 15-2  Diagnostic Evaluation of Cervical Lymphadenitis.

Abbreviations: ASO, anti-streptolysin titer; CXR, chest radiography; CBC, complete blood cell count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; PPD, purified protein derivative; VDRL, venereal disease research laboratories.

Adapted from: Gosche JR, Vick L. Acute, subacute and chronic cervical lymphadenitis in children. Semin Pediatr Surg 2006;15:99–106, with permission.
• Tissue in tissue culture medium for cytogenetic analysis in cases of suspected malignancy. Smears or touch preparations of the node on slides can be air dried for fluorescent in situ hybridization studies to confirm certain malignancies
• Tissue frozen immediately for molecular studies
• Immunohistochemical stains to help differentiate and classify tumor types
• Flow cytometry for classifying and subtyping leukemias and lymphomas
• Gene rearrangement studies for the T-cell receptor and the immunoglobulin gene may be required to determine monoclonality in leukemia or lymphoma
• These can be performed on fresh frozen tissue, or less optimally in formalin-fixed paraffin-embedded tissue
• Formalin fixation for light microscopic analysis.

Once the cause of the lymphadenopathy is ascertained, appropriate management can be undertaken.

SPLENOMEGALY

The tip of the spleen is frequently palpable in otherwise normal infants and young children. It is usually palpable in premature infants and in about 30% of full-term infants. It may normally be felt in children up to 3 or 4 years of age. At an older age, the spleen tip is generally not palpable below the costal margin and a palpable spleen usually indicates splenic enlargement two to three times its normal size.

Splenoptosis

In children, a palpable spleen may occasionally be due to visceroptosis rather than true splenomegaly. This distinction is important to make so that extensive investigations for the cause of splenomegaly are not undertaken unnecessarily. Visceroptosis may result from congenital or acquired defects in the supporting mechanism responsible for maintaining the spleen in the correct position. The visceroptosed spleen may be felt anywhere from the upper abdomen to the pelvis and may undergo torsion. When the spleen is felt in the upper abdomen, it can easily be pushed under the left costal margin. This finding is helpful in diagnosing visceroptosis and in differentiating it from true splenomegaly.

In addition to this finding, an abdominal radiograph in the upright position may reveal intestinal gas bubbles between the left dome of the diaphragm and the spleen. This sign may be helpful in suggesting the diagnosis.

Splenomegaly

The significance of splenomegaly depends on the underlying disease. Splenomegaly can be caused by diseases that result in hyperplasia of the lymphoid and reticuloendothelial systems (e.g., infections, connective tissue disorders), infiltrative disorders (e.g., Gaucher
disease, leukemia, lymphoma), hematologic disorders (e.g., thalassemia, hereditary spherocytosis) and conditions that cause distention of the sinusoids whenever there is increased pressure in the portal or splenic veins (portal hypertension). Table 15-3 lists the various causes of splenomegaly.

**Diagnostic Approach to Splenomegaly**

**Detailed History**

1. Fever or rigors indicative of infection (e.g., subacute bacterial endocarditis [SBE], infectious mononucleosis, malaria).
2. Neonatal omphalitis, umbilical venous catheterization (inferior vena cava or portal vein thrombosis).
3. Jaundice (evidence of liver disease).
4. Abnormal bleeding or bruising (hematologic malignancy).
5. Family history of hemolytic anemia (e.g., hereditary spherocytosis or thalassemia major).
6. Travel to endemic areas (e.g., malaria).
7. Trauma (splenic hematoma).

**Physical Examination**

1. Size of spleen (measured in centimeters below costal margin); consistency, tenderness, audible rub.
2. Hepatomegaly.
3. Lymphadenopathy.
4. Fever.
5. Ecchymoses, purpura, petechiae.
6. Stigmata of liver disease such as jaundice, spider angiomata, or caput medusa.
7. Stigmata of rheumatoid arthritis or systemic lupus erythematosus (SLE).
8. Cardiac murmurs, Osler nodes, Janeway lesions, splinter hemorrhages, fundal hemorrhages (SBE).

**Laboratory Investigations**

The extent to which the following investigations are undertaken must be guided by clinical judgment. It is not necessary to perform all the evaluations. If the child appears well and the index of suspicion is low, it is reasonable to do no further investigations and re-examine the child in 1–2 weeks. If the splenomegaly persists, the following investigations should be done:

- **Blood count**: Red cell indices, reticulocyte count, platelet count, differential white blood cell count and blood film (which may demonstrate evidence of hematologic malignancy, hemolytic disorders, viral and protozoal infections)
Table 15-3  Causes of Splenomegaly

| Category                  | Description                                                                                       |
|---------------------------|--------------------------------------------------------------------------------------------------|
| I. Infectious splenomegaly| (due to antigenic stimulation with hyperplasia of the reticuloendothelial and lymphoid systems) |
| A. Bacterial:            | acute and chronic systemic infection, subacute bacterial endocarditis, abscesses, typhoid fever, |
|                          | miliary tuberculosis, tularemia, plague                                                          |
| B. Viral:                | infectious mononucleosis (Epstein–Barr virus), cytomegalovirus, HIV, hepatitis A, B, C          |
| C. Spirochetal:          | Syphilis, lyme disease, leptospirosis                                                             |
| D. Rickettsial:          | Rocky Mountain spotted fever, Q fever, typhus                                                    |
| E. Protozoal:            | malaria, babesiosis, toxoplasmosis, toxocara canis, toxocara catis, leishmaniasis, schistosomiasis, |
|                          | trypanosomiasis                                                                                   |
| F. Fungal:               | Disseminated candidiasis, histoplasmosis, coccidiodomycosis, South American blastomycosis         |
| II. Hematologic disorders|                                                                                                  |
| A. Hemolytic anemias,    | such as thalassemia, splenic sequestration crisis in sickle cell disease, hereditary spherocytosis |
|                          | B. Extramedullary hematopoiesis as in osteopetrosis and myelofibrosis                             |
|                          | C. Myeloproliferative disorders (e.g., polycythemia vera, essential thrombocytthemia)            |
| III. Infiltrative splenomegaly|                                                                                                    |
| A. Nonmalignant          | 1. Langerhans cell histiocytosis                                                                 |
|                          | 2. Storage diseases such as Gaucher disease, Niemann–Pick disease, GM-1 gangliosidosis, glycogen |
|                          | storage disease type IV, Tangier disease, Wolman disease, mucopolysaccharidoses,                  |
|                          | hyperchylomicronemia types I and IV, amyloidosis and sarcoidosis                                 |
| B. Malignant             | 1. Leukemia                                                                                      |
|                          | 2. Lymphoma: Hodgkin and non-Hodgkin                                                             |
| IV. Congestive splenomegaly|                                                                                                     |
| A. Intrahepatic (portal hypertension):| cirrhosis of the liver (e.g., neonatal hepatitis, α1-antitrypsin deficiency, Wilson’s disease, cystic fibrosis) |
| B. Prehepatosplenic or portal vein obstruction (e.g., thrombosis, vascular malformations)    |
| V. Immunologic diseases  |                                                                                                  |
| A. Serum sickness,       | graft-versus-host disease                                                                         |
|                          | B. Connective tissue disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis–Felty    |
|                          | syndrome, mixed connective tissue disorder, Sjogren syndrome, macrophage activation syndrome,    |
|                          | systemic mastocytosis                                                                             |
|                          | C. Common variable immunodeficiency                                                               |
|                          | D. Autoimmune lymphoproliferative syndrome (ALPS) (Canale-Smith syndrome)                        |
| VI. Primary splenic disorders|                                                                                                      |
| A. Cysts                 |                                                                                                  |
| B. Benign tumors (e.g., hemangioma, lymphangioma)                                              |
| C. Hemorrhage in spleen (e.g., subcapsular hematoma)                                             |
| D. Partial torsion of splenic pedicle leading to congestive splenomegaly, cyst and abscess formation |

- **Evaluation for infection**: Blood culture and viral studies (CMV, EBV panel, HIV, toxoplasmosis, smear for malaria, tuberculin test)
- **Evaluation for evidence of hemolytic disease**: Blood count, reticulocyte count, blood smear, haptoglobin level, serum bilirubin, urinary urobilinogen, direct antiglobulin test (Coombs test), osmotic fragility, autohemolysis and red cell enzyme assays, if indicated
• **Evaluation for liver disease**: Liver function tests, α₁-antitrypsin deficiency, serum copper, ceruloplasmin (to exclude Wilson disease) and liver biopsy (if indicated)

• **Evaluation for portal hypertension**: Ultrasound and Doppler of portal venous system and endoscopy (if indicated to exclude esophageal varices)

• **Evaluation for connective tissue disease**: ESR, C3, C4, CH₅₀, antinuclear antibody (ANA), rheumatoid factor, urinalysis, blood urea nitrogen (BUN) and serum creatinine

• **Evaluation for infiltrative disease (benign and malignant)**:
  - Bone marrow aspiration and biopsy, looking for blasts, Langerhans cell histiocytes, or storage cells
  - Enzyme assay for Gaucher disease

• **Lymph node biopsy**: If there is significant lymphadenopathy, lymph node biopsy may provide the diagnosis

• **Imaging studies**:
  - CT scan
  - Magnetic resonance imaging (MRI)
  - Liver – spleen scans with ⁹⁹ᵐTc-sulfur colloid

• **Biopsy**: If less invasive studies have failed to provide the diagnosis, it may be necessary to perform a splenectomy or a partial splenectomy. Biopsy and splenic aspiration are rarely performed because there is a significant risk of bleeding. Biopsy material must be processed for cultures and Gram stain, as well as for histology, flow cytometry, histochemical stains, electron microscopy and gene rearrangement studies. Once the etiology of the splenomegaly is ascertained, further management for the underlying disorder can be instituted.

**Suggested Reading**

Behrman R, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics. 17th ed. Elsevier; 2004.
Gosche JR, Vick L. Acute, subacute and chronic cervical lymphadenitis in children. Semin Ped Surg. 2006; 15(2):99–106.
Hoffman R, Benz EJ, Shattil SJ, et al. Hematology: Basic Principles and Practice. 3rd ed. Churchill Livingstone; 2000.
Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. Am J Med. 2007;120(10):911.e1–911.e8.
Kim DS. Kawasaki disease. Yonsei Med J. 2006;47(6):759–772.
La Barge 3rd DV, Salzman KL, Harnsberger HR, et al. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): imaging manifestations in the head and neck. Am J Roentgenol. 2008;191(6):W299–W306.
Leung AKC, Robson WLM. Childhood cervical lymphadenopathy. J Pediatr Health Care. 2004;18:3–7.
Nathan D, Orkin S. Nathan and Oski’s Hematology of Infancy and Childhood. 6th edn. Philadelphia: Saunders; 2003.
Paradela S, Lorenzo J, Martinez-Gomez W, et al. Interface dermatitis in skin lesions of Kikuchi-Fujimoto’s disease: a histopathological marker of evolution into systemic lupus erythematosus? Lupus. 2008;17 (12):1127–1135.
Tracy Jr TF, Muratore CS. Management of common head and neck masses. Semin Pediatr Surg. 2007;16(1):3–13.
Twist CJ, Link MP. Assessment of lymphadenopathy in children. Pediatr Clin N Am. 2002;49:1009–1025.