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CHAPTER

4

Lymphadenopathy and Diseases of the Spleen

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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, self-limited 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 found in lymph node biopsies in children.

Lymphadenopathy, however, may be a presenting sign of malignancies such as leukemia, lymphoma, or neuroblastoma. It is important to be able to differentiate benign from malignant lymphadenopathy clinically. Lymphadenopathy in the head and neck region must be differentiated from several other nonlymphatic masses due to congenital malformations (Table 4.1).

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, infraclavicular, 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.

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

History

This involves the duration of the lymphadenopathy; presence of 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

Although in young children cervical lymphadenopathy, especially in the upper cervical region, is usually due to infection, more serious disorders may have to be considered.

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 lymphoma is the more common cancer encountered.

Lanzkowsky's Manual of Pediatric Hematology and Oncology.
DOI: http://dx.doi.org/10.1016/B978-0-12-801368-7.00004-1

TABLE 4.1 Differential Diagnosis of Nonlymph Node Masses in Neck

Cystic hygroma
Branchial cleft anomalies, branchial cysts
Thyroglossal duct cysts
Epidermoid cysts
Neonatal torticollis
Lateral process of lower cervical vertebra may be misdiagnosed as supraclavicular node

TABLE 4.2 Differential Diagnosis of Lymphadenopathy

1. **Nonspecific reactive hyperplasia (polyclonal)**
2. **Infection**
   a. Bacterial: *Staphylococcus*, *Streptococcus*, anaerobes, tuberculosis, atypical mycobacteria, *Bartonella henselae* (cat scratch disease, brucellosis, *Salmonella typhi*, diphtheria, *Chlamydia trachomatis* lymphogranuloma venereum), *Calymmatobacterium granulomatis*, *Francisella tularensis*
   b. 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)
   c. Protozoal: Toxoplasmosis, malaria, trypanosomiasis
   d. Spirochetal: Syphilis, *Rickettsia typhi* (murine typhus)
   e. Fungal: Coccidioidomycosis (valley fever), histoplasmosis, *Cryptococcus*, aspergillosis
   f. Postvaccination: Smallpox, live attenuated measles, DPT, Salk vaccine, typhoid fever
3. **Connective tissue disorders**
   a. Rheumatoid arthritis
   b. Systemic lupus erythematosus
4. **Hypersensitivity states**
   a. Serum sickness
   b. Drug reaction (e.g., Dilantin, mephenytoin, pyrimethamine, phenylbutazone, allopurinol, isoniazid, antileprosy, and antithyroid medications)
5. **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. Posttransplantation lymphoproliferative disorder (PTLD)
6. **Neoplastic diseases**
   a. Hodgkin and non-Hodgkin lymphomas
   b. Leukemia
   c. Metastatic disease from solid tumors: neuroblastoma, nasopharyngeal carcinoma, rhabdomyosarcoma, thyroid cancer
   d. Histiocytosis
      i. Langerhans cell histiocytosis
      ii. Familial hemophagocytic lymphohistiocytosis
      iii. Macrophage activation syndrome
      iv. Malignant histiocytosis
7. **Storage diseases**
   a. Niemann–Pick disease
   b. Gaucher disease
   c. Cystinosis
8. **Immunodeficiency states**
   a. Chronic granulomatous disease
   b. Leukocyte adhesion deficiency
   c. Primary dysgammaglobulinemia with lymphadenopathy
9. **Miscellaneous causes**
   a. Kawasaki disease (mucocutaneous lymph node syndrome)
   b. Kikuchi–Fujimoto disease (self-limiting histiocytic necrotizing lymphadenitis)
   c. Sarcoidosis
   d. Beryllium exposure
   e. Hyperthyroidism
   f. Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome)

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., 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 intraabdominal pathology.

Localized or Generalized

Lymphadenopathy is either localized (one region affected) or generalized (two or more noncontiguous 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 lymphoma 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 and rubbery. 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 give a 2-week trial of antibiotics. If there is no reduction in the size of the lymph node within this period, careful observation of the lymph node is necessary. If the size, location, and character of the node suggest malignant disease, the node should be biopsied.

Diagnosis of Lymphadenopathy

Table 4.2 outlines the differential diagnosis of lymphadenopathy.

Figure 4.1 provides a diagnostic algorithm for evaluation of mononucleosis-like illness and Figure 4.2 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, coccidioidomycosis.
- 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 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.

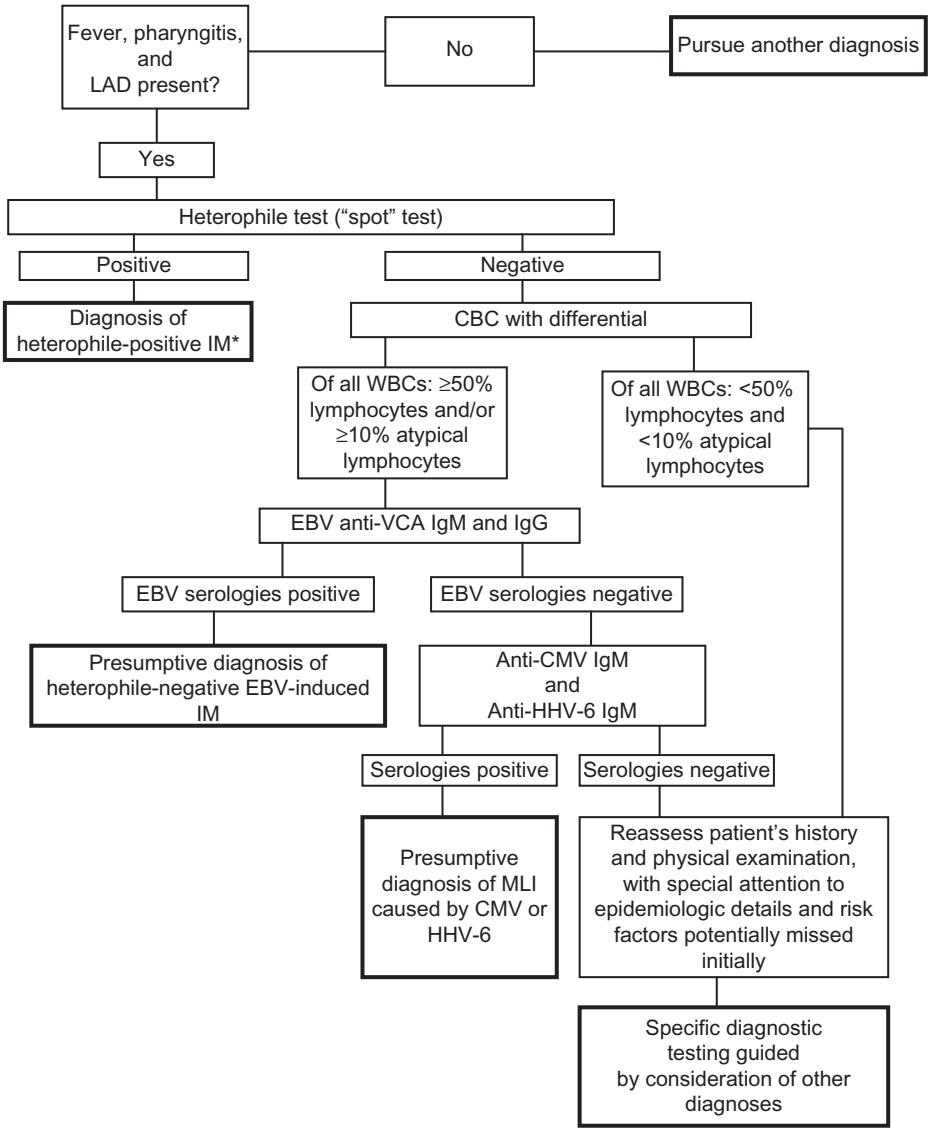

FIGURE 4.1 Diagnostic algorithm for evaluation of mononucleosis-like illness (MLI). CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV-6, human herpes virus 6; IM, infectious mononucleosis; LAD, lymphadenopathy; VCA, viral capsid antigen; WBC, white blood cell. *Consider possibility of false-positive heterophile test due to HIV-1 before finalizing diagnosis. *Source: Adapted from Hurt and Tammaro (2007), with permission.*

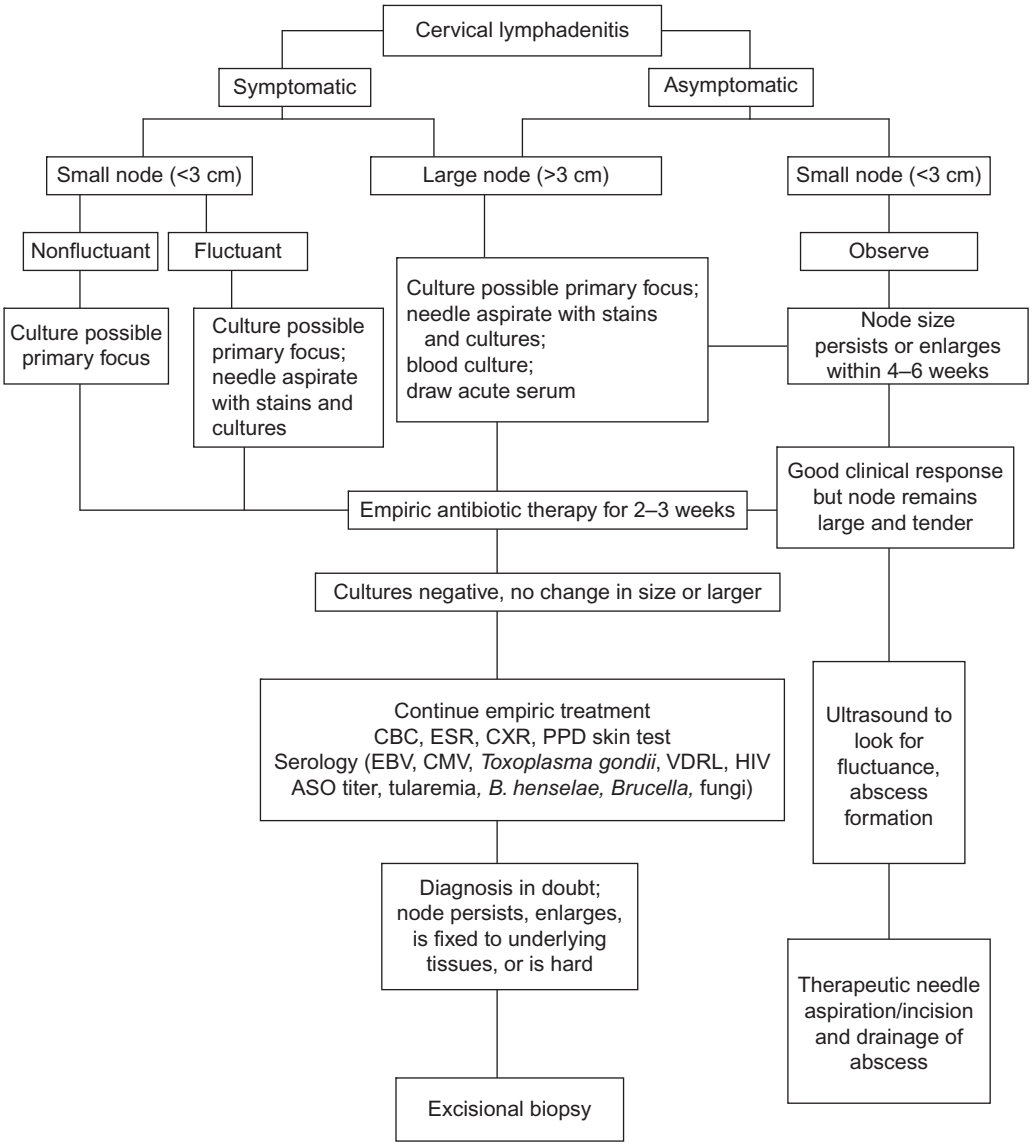

FIGURE 4.2 Diagnostic evaluation of cervical lymphadenitis. ASO, antistreptolysin titer; CXR, chest radiography; CBC, complete blood cell count; CMV, cytomegalovirus; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; PPD, purified protein derivative; VDRL, Venereal Disease Research Laboratories. *Source: Adapted from Gosche and Vick (2006), with permission.*

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.
- 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.

DISEASES OF THE SPLEEN

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.

Asplenia

Congenital asplenia is found in the rare Ivemark syndrome—trilobed lungs, centralized liver, and cardiac defects as well as a risk of infection. Diagnosis of asplenia (congenital or postsurgical) is made by the presence of Howell–Jolly bodies and the presence of intracellular vesicles (appearing as pits or pocks) in erythrocytes and no uptake by Tc99 colloid sulfur radionuclide.

Congenital Polysplenia

This condition is characterized by the presence of several spleens of varying size and function, hepatobiliary abnormalities and cardiac anomalies.

Accessory Spleen

Accessory spleens occur in 15% of normal people and are usually present with no other abnormalities. The most frequent location is the splenic hilum or the tail of the pancreas or other locations in the abdomen or pelvis. Its identification is important when splenectomy is carried out for hematologic indications and the desired clinical effect is not obtained due to a functional accessory spleen.

Splenosis

Splenosis is autotransplantation of splenic tissue into the peritoneum or omentum and results from rupture of the spleen and spillage and subsequent implantation of splenocytes.

Sequestration of Spleen

Sequestration of the spleen refers to splenic enlargement when blood enters the spleen but is unable to exit properly, for example, sickle cell anemia in young infants and congenital spherocytosis, and is characterized by a sudden severe drop in hemoglobin, occasionally hypovolemic shock, and abdominal pain in the left upper quadrant.

Splenoptosis (Splenic Visceroptosis)

Splenoptosis occurs when the spleen is not fixed within the retroperitoneum, and a palpable spleen may 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 differentiating true splenomegaly from visceroptosis of the spleen.

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 4.3 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. History of neonatal omphalitis, umbilical venous catheterization leading to inferior vena cava, or portal vein thrombosis resulting in portal hypertension.
3. Jaundice (evidence of liver disease) leading to portal hypertension.
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).

TABLE 4.3 Causes of Splenomegaly

1. **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, coccidioidomycosis, South American blastomycosis
2. **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 thrombocythemia)
3. **Infiltrative splenomegaly**
   a. Nonmalignant
      i. Langerhans cell histiocytosis
      ii. 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
      i. Leukemia
      ii. Lymphoma: Hodgkin and non-Hodgkin
4. **Congestive splenomegaly**
   a. Intrahepatic (portal hypertension): Cirrhosis of the liver (e.g., neonatal hepatitis, α_1-antitrypsin deficiency, Wilson disease, cystic fibrosis)
   b. Prehepatosplenic or portal vein obstruction (e.g., thrombosis, vascular malformations)
5. **Immunologic diseases**
   a. Serum sickness, graft-versus-host disease (GVHD)
   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)
6. **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

Physical Examination

1. Size of spleen (measured in centimeters below costal margin); consistency, tenderness, audible rub. It is critical to differentiate splenoptosis from true enlargement of the spleen.
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 SLE.
8. Cardiac murmurs, Osler nodes, Janeway lesions, splinter hemorrhages, fundal hemorrhages as evidence of 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 reexamine 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).
- *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, serum bilirubin, urinary urobilinogen, direct antiglobulin test (Coombs test), and red cell enzyme assays (if indicated).
- *Evaluation for liver disease*: Liver function tests, α_1-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, CH_{50}, antinuclear antibody, rheumatoid factor, urinalysis, blood urea nitrogen, 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 and other storage diseases.
- *Lymph node biopsy*: If there is significant lymphadenopathy, lymph node biopsy may provide the diagnosis.
- *Imaging studies*:
  - Abdominal CT scan, if indicated.
  - Magnetic resonance imaging (MRI) if indicated.
  - Liver−spleen scans with ^{99m}Tc-sulfur colloid.
- *Splenectomy or partial splenectomy*: If less invasive studies have failed to provide the diagnosis, it may be necessary to perform a splenectomy or a partial splenectomy on rare occasions to establish a diagnosis. Splenic tissue 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.

Surgery Involving Spleen

Splenectomy is usually done laparoscopically and partial splenectomy has become a therapeutic alternative to total splenectomy. Partial splenectomy leaving at least 20% splenic tissue is sufficient to preserve immune competence and is suitable when splenectomy is performed for indications other than for immune-mediated hematologic disorders such as autoimmune hemolytic anemia or immune thrombocytopenic purpura.

The primary risk of splenectomy is overwhelming postsplenectomy infection (OPSI) and sepsis. Risk factors for OPSI are:

1. age of splenectomy—under 5 and especially infants under 2 years of age,
2. failure to receive presplenectomy immunization, and
3. noncompliance with prophylactic antibiotics

Reduction in incidence of OPSI can be achieved by:

1. presplenectomy immunization with protein conjugated vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.
2. postsplenectomy prophylactic antibiotics.
3. prompt, early, and effective medical treatment for fever.

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