Lymphadenopathy
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Abstract

Lymphadenopathy can occur in any age group, in symptomatic or asymptomatic patients, and in a single site or at multiple sites. Lymphadenopathy is associated with numerous disorders. An abnormal lymph node may be observed or palpated by the patient, found by a health care worker, or discovered through radiologic evaluation. Lymphadenopathy may be a part of a complex case presentation, or the clinical cause may be straightforward. Patients with potentially curable malignant disorders may have lymphadenopathy as the first sign of their disease. This review of lymphadenopathy summarizes general considerations, discusses which patients might be considered for biopsy, reviews which nodes are most likely to be diagnostic, outlines initial diagnostic considerations on a region-by-region basis, and reviews a broad differential diagnosis for adenopathy.

FNA = fine-needle aspiration; HIV = human immunodeficiency virus

Lymphadenopathy is common and affects patients of all ages. Essential diagnostic considerations include the age of the patient, the location of the abnormal lymph nodes, the length of time the abnormal lymph nodes have been present, any associated signs and symptoms, the presence or absence of generalized lymphadenopathy, any extranodal signs or symptoms, and the presence or absence of splenomegaly and/or fever (Table 1). The critical task in approaching patients with lymphadenopathy is to determine which nodes are likely to be associated with benign, self-limited conditions and which nodes indicate malignancy or another serious condition requiring specific treatment. Even in the setting of obviously malignant lymphadenopathy, it is essential to distinguish carcinoma from lymphoma for treatment and prognostic purposes.
Table 1. Essential Considerations in Lymphadenopathy: ALL AGES

<table>
<thead>
<tr>
<th>Age</th>
<th>Location</th>
<th>Length of time present</th>
<th>Associated signs and symptoms</th>
<th>Generalized lymphadenopathy</th>
<th>Extranodal associations</th>
<th>Splenomegaly and fever</th>
</tr>
</thead>
</table>

**GENERAL CONSIDERATIONS**

**Patient Age, Node Size, and Node Location**

Age is the most important factor in predicting the probability of whether the lymphadenopathy is due to a benign or malignant lesion. Lee et al. analyzed findings from 925 patients who underwent a lymph node biopsy at Los Angeles County Hospital between 1973 and 1977 (Table 2). This total represented 0.9% of all surgical cases at the institution during that period. Lymphoproliferative disorders were not found to have an age predilection, while carcinomas, predictably, were much more common in patients older than 50 years. In younger patients, the differential diagnosis should always include infectious mononucleosis. Lymph nodes biopsied during acute infectious mononucleosis have been misdiagnosed as Hodgkin disease, as cells resembling Reed-Sternberg cells may sometimes be present in the pathologic specimen. However, immunohistochemical studies differentiate infectious mononucleosis from Hodgkin disease.
Table 2. Lymph Node Biopsy Findings*

<table>
<thead>
<tr>
<th>Biopsy findings (%)</th>
<th>Benign</th>
<th>Carcinoma</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (N=925)</td>
<td>60</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal (n=51)</td>
<td>63</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>Thoracic (n=149)</td>
<td>73</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral (n=653)</td>
<td>56</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Unspecified (n=72)</td>
<td>61</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Ages (y)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>57</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>&lt;30</td>
<td>79</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>31-50</td>
<td>59</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>51-80</td>
<td>40</td>
<td>44</td>
<td>16</td>
</tr>
</tbody>
</table>

*Data derived from Lee et al.
†Age distribution is based on 628 patients with peripheral lymph node biopsies.

The size and location of an abnormal lymph node and the duration of time that the node has been present all aid in deciding when a biopsy is necessary. It is not possible to set a strict size limit that can distinguish between normal and abnormal lymph nodes, because the size and distribution of normal lymphoid tissue vary with multiple factors, including age and background antigenic exposure. In 1 series of 220 node biopsy specimens, a lymph node size of 1.5 × 1.5 cm was the best discriminating limit for distinguishing malignant or granulomatous lymphadenopathy from other causes of adenopathy. In general, lymph nodes that have been present outside the inguinal region for longer than 1 month and measure 1 × 1 cm or larger without an obvious diagnosis should be considered for biopsy.

Empiric treatment of lymphadenopathy with antibiotics or corticosteroids is a common practice but is not recommended. It is essential first to establish a diagnosis before treatment. If observation is elected, careful measurement and recording of the size of each abnormal node with a vernier-style caliper or ruler at each evaluation are prudent. Measurement of lymph nodes on computed tomographic scans may be more accurate when a loop planimeter is used.
Slap et al. 14 retrospectively evaluated 123 lymph node biopsy specimens and designed a size-based prediction model to assist clinicians in deciding when to proceed with lymph node biopsy in young patients. Clinical variables such as the presence or absence of recent ear, nose, or throat symptoms and the findings on chest x-ray films are included in the model. This model has not been tested prospectively in a large number of patients, and its validity remains uncertain.

Associated Signs and Symptoms

The signs and symptoms associated with lymphadenopathy are varied. Patients may be asymptomatic. Patients may also present with "B" symptoms, which include temperature higher than 38°C, drenching night sweats, and unexplained loss of more than 10% of body weight.15 These are characteristic of lymphoproliferative disorders but may also be present in infectious conditions. Some patients with Hodgkin disease may have pain in affected lymph nodes following alcohol ingestion.16 Lymphangitic streaking is a sign consistent with cutaneous infection. The presence or absence of associated signs or symptoms in patients with adenopathy should not alter the general approach, since both symptomatic and asymptomatic patients may have pathologic lymphadenopathy.

Abnormal nodes may be tender, warm, erythematous, or fluctuant. The nodes may be hard or rubbery, fixed or mobile. In general, qualitative characteristics such as node consistency are not particularly helpful in distinguishing benign from malignant lesions. Although rock-hard adenopathy is associated with metastatic cancer, Hodgkin disease, or tuberculosis, each of these disorders also commonly presents with soft nodes. A tender node suggests an inflammatory lesion, but malignant nodes that are rapidly expanding or contain hemorrhage may also be tender. Sinus tract formation is associated with infectious causes of lymphadenopathy (e.g., actinomycosis and mycobacterial species), but very large malignant nodes may also form sinus tracts.

Lymphadenopathy is associated with splenomegaly in a relatively limited number of disorders (4.5% of cases in 1 series 7). Infectious mononucleosis, Hodgkin disease and non-Hodgkin lymphoma, chronic lymphocytic leukemia, and acute leukemia are the most common causes. The presence of splenomegaly is rare in metastatic cancer.17

Although lymphadenopathy in the presence of fever usually represents an infection or lymphoma, the differential diagnosis is actually quite broad. The list of differential diagnoses includes infectious mononucleosis (Epstein-Barr virus), cytomegalovirus infection, toxoplasmosis, syphilis, subacute bacterial endocarditis, histoplasmosis, sarcoidosis, salmonellosis, tuberculosis, acquired immunodeficiency syndrome, Hodgkin disease, non-Hodgkin lymphoma, angioimmunoblastic lymphadenopathy, mixed essential cryoglobulinemia, systemic mastocytosis, chronic lymphocytic leukemia, agnogenic myeloid metaplasia, Waldenström macroglobulinemia, multiple myeloma, systemic lupus erythematosus, rheumatoid arthritis, Kawasaki disease, Whipple disease, serum
sickness, and Kaposi sarcoma.

Location

When considering a lymph node biopsy in a patient with more than 1 abnormal lymph node, the key issue is which of the nodes should be biopsied. In general, the largest node is most likely to yield a diagnosis. The least helpful lymph nodes to biopsy are in the inguinal region. Occasionally, however, the most accessible or most abnormal node is in the inguinal area, and it is reasonable to attempt to biopsy these. One retrospective series of inguinal biopsies demonstrated a diagnostic rate of 53%, probably because of careful patient selection by surgeons.18

If multiple nodal sites are involved, the preferable initial biopsy site is the largest peripheral node outside the inguinal area. If no peripheral nodes are available, then mediastinal nodes (if present) are often more easily accessible than abdominal or retroperitoneal nodes. If several peripheral nodes are similar in size (eg, in a patient with generalized lymphadenopathy), the most common nodes to biopsy, in descending order, are the supraventricular, cervical, axillary, epitrochlear, and inguinal nodes. Occasionally, multiple biopsies may be required from different sites at the time of initial evaluation or as a case evolves over time. Biopsy of nodes in the region of the parotid gland may injure the facial nerve or its branches, and biopsy of nodes in the posterior triangle of the neck is the most common cause of iatrogenic injury to the spinal accessory nerve.19,20

Biopsy Methods and Sample Processing

Lymph nodes may be biopsied by excisional methods (via direct surgical extirpation, mediastinoscopy, open surgery, or laparoscopy) or by needle aspiration (core or fine needle). Gupta et al 21 performed concomitant fine-needle aspirations (FNAs) and excisional biopsies of lymph nodes on 100 patients in Delhi, India. In their series, the accuracy rate of FNAs was 77% in reactive hyperplasia; 77% in tuberculous lymphadenitis (the most common diagnosis); 75% in non-Hodgkin lymphoma; and 85% in metastatic carcinoma. Although FNA is simple, safe, and inexpensive, lymph node disorders such as reactive hyperplasia, Hodgkin disease, and non-Hodgkin lymphoma may be extremely difficult to distinguish from one another with FNA alone. On the other hand, FNA is very helpful in the evaluation of pancreatic and peripancreatic disorders, in the differentiation of adenocarcinomas from other disorders, and in the diagnosis of head and neck carcinoma, thyroid lesions, malignant melanoma, and relapsed lymphoproliferative disorders or carcinomas. In patients without an established diagnosis and with accessible peripheral adenopathy, however, excisional biopsy is preferred over FNA to ensure adequate sampling.

In 1996, Pinkus 22 wrote, “One would have considerable reservation regarding the routine use of needle biopsy to establish a primary diagnosis of malignant lymphoma because of the broad spectrum of lymphoid proliferations, the limitations of this
technique, and the current level of diagnostic precision required to determine treatment options. For the initial diagnosis of suspected lymphoma, the procedure of choice is surgical biopsy if the clinical condition of the patient allows. If the condition of the patient is such that surgical biopsy is contraindicated, or if the site of disease is difficult to access, a needle biopsy may be the procedure of choice. A core needle biopsy is preferred to FNA.23,24

The overall diagnostic yield of lymph node biopsies is good, but careful processing of specimens according to local institutional protocol is important. In a review 18 of 290 excisional lymph node biopsy specimens processed according to strict guidelines at Creighton University between 1970 and 1974, a “positive yield” was obtained in 63% of cases. “Positive yield” was defined as a pathologic result that confirmed, changed, or excluded the clinical diagnosis.18 Prior to the introduction of handling guidelines, the rate of positive yield at Creighton was less than 50%. Sinclair et al 25 at Massachusetts General Hospital also reported a 63% specific diagnosis rate from node biopsy, excluding patients with known malignancies, systemic diseases, or abnormal chest x-ray films. Careful selection of patients is essential. In 1 large series,26 63% of all lymph node biopsy specimens were classified as “reactive, nonspecific.” These 2 older series, compiling data on cases evaluated before the advent of modern hematopathologic technologies, provide interesting insights.

The pathologic interpretation of “atypical hyperplasia” was once common to denote biopsy specimens in which the pathologist was concerned about neoplasia but was not able to diagnose lymphoma definitively.27-29 In 1979, Schroer and Franssila 30 followed up on 70 patients who had pathologic interpretations of atypical hyperplasia at Barnes Hospital between 1961 and 1972. Thirty-seven percent were later diagnosed as having malignant lymphoproliferative disorders. On blinded reexamination of the initial 70 specimens by 2 pathologists, 19 nodes contained clearly benign lesions, 10 were clearly malignant, 37 could still be denoted only as atypical hyperplasia, and 4 had angioimmunoblastic lymphadenopathy. Suspicious but non-diagnostic lymph node specimens may be diagnosed as atypical hyperplasia with a recommendation for consideration for repeat biopsy at a later time.

With newer immunohistochemical, cytogenetic, and molecular genetic technologies, nondiagnostic biopsy findings may be seen less often.31 However, data confirming this impression have not been published. Consultation with a pathologist prior to biopsy may improve the diagnostic evaluation, and appropriate ancillary test results can then be reviewed. Formal laboratory triage systems are important. Immunohistochemical staining of frozen tissue and flow cytometric immunophenotyping are both effective in diagnosing lymphoma.32 The advantage of immunohistochemical frozen-section analysis is that the nodal morphology is intact, and the tissue can be stored for future evaluation and studies with frozen tissue. In addition, immunohistochemical analysis of paraffin-embedded tissue has improved considerably in recent years.
DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lymphadenopathy of unknown origin is similar to that of fever of unknown origin or an elevated erythrocyte sedimentation rate, in that most cases are due to an infection, a malignancy, or an immune disorder. There are 3 broad models to categorize lymphadenopathy. The extensive differential diagnosis may be grouped incorporating an acronym, CHICAGO (cancers, hypersensitivity syndromes, infections, connective tissue diseases, atypical lymphoproliferative disorders, granulomatous lesions, and other unusual causes of lymphadenopathy) (Table 3). More specifically, the letters of the alphabet serve as a method to catalog the lengthy list of causes of lymphadenopathy (Table 4). The region of the lymph node involvement can be valuable information in narrowing this lengthy differential diagnosis (Table 5).
**Cancers**
Hematologic malignancies: Hodgkin disease, non-Hodgkin lymphoma, acute and chronic leukemia, Waldenström macroglobulinemia, multiple myeloma (uncommon), systemic mastocytosis
Metastatic “solid” tumors: breast, lung, renal cell, prostate, other

**Hypersensitivity syndromes**
Serum sickness
Drug sensitivity: diphenylhydantoin, carbamazepine, primidone, gold, allopurinol, indomethacin, sulfonamides, others
Silicone reaction
Vaccination related
Graft-vs-host disease

**Infections**
Viral: infectious mononucleosis (Epstein-Barr virus), cytomegalovirus, infectious hepatitis, postvaccinial lymphadenitis, adenovirus, herpes zoster, human immunodeficiency virus/acquired immunodeficiency syndrome, human T-lymphotropic virus 1
Bacterial: cutaneous infections (staphylococcus, streptococcus), cat-scratch fever, chancroid, melioidosis, tuberculosis, atypical mycobacteria, primary and secondary syphilis
Chlamydial: lymphogranuloma venereum
Protozoan: toxoplasmosis
Mycotic: histoplasmosis, coccidioidomycosis
Rickettsial: scrub typhus
Helminthic: filariasis

**Connective tissue diseases**
Rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease, Sjögren syndrome

**Atypical lymphoproliferative disorders**
Angiofollicular (giant) lymph node hyperplasia (Castleman disease), angioimmunoblastic lymphadenopathy with dysproteinemia, angiocentric immunoproliferative disorders, lymphomatoid granulomatosis, Wegener granulomatosis

**Granulomatous disorders**
Tuberculosis, histoplasmosis, mycobacterial infections, cryptococcus, silicosis, berylliosis, cat-scratch fever

**Other unusual causes of lymphadenopathy**
Inflammatory pseudotumor of lymph nodes, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), Rosai-Dorfman disease, nodular transformation of silicones
Table 3. Causes of Lymphadenopathy: CHICAGO*

<table>
<thead>
<tr>
<th>A</th>
<th>Acquired immunodeficiency syndrome (AIDS), 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>AIDS-related lymphadenopathy syndrome, 2,4,13</td>
</tr>
<tr>
<td>C</td>
<td>Amyloidosis, 2,15,16 Chronic myeloid leukemia, 17</td>
</tr>
<tr>
<td>D</td>
<td>Castlemans disease, 18 Cat-scratch fever, 19</td>
</tr>
<tr>
<td>E</td>
<td>Chickenpox, 20 Drug eruptions, 21 Exanthems, 22</td>
</tr>
<tr>
<td>F</td>
<td>Fatigue, 23 Familial Mediterranean fever, 24</td>
</tr>
<tr>
<td>G</td>
<td>Fever, 25 Feline syndrome, 26 Filariasis, 27</td>
</tr>
<tr>
<td>H</td>
<td>Gaucher disease, 28 Glanzmanns thrombasthenia, 29</td>
</tr>
<tr>
<td>I</td>
<td>Hairy cell leukemia, 30 Hematologic malignancy, 31</td>
</tr>
<tr>
<td>J</td>
<td>Herpes zoster, 32 Histoplasmosis, 33 Inclusion body meningoencephalitis, 34</td>
</tr>
<tr>
<td>K</td>
<td>Histiocytosis, 35 Hepatitis B, 36 Hepatitis C, 37</td>
</tr>
<tr>
<td>L</td>
<td>Human immunodeficiency virus infection, 38 Human neutrophilic leukemia, 39</td>
</tr>
<tr>
<td>M</td>
<td>Human T-cell leukemia/lymphoma, 40 Hyperparathyroidism, 41</td>
</tr>
<tr>
<td>N</td>
<td>Hydroxyapatite deposits, 42 Immunodeficiency, 43</td>
</tr>
<tr>
<td>O</td>
<td>Leukemia, 44 Lymphoma, 45</td>
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<tr>
<td>P</td>
<td>Myeloma, 46 Myelodysplasia, 47</td>
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<tr>
<td>Q</td>
<td>Mycosis fungoides, 48 Nonspecific lymphadenopathy, 49</td>
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<tr>
<td>R</td>
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<td>S</td>
<td>Niemann-Pick disease, 53 Occult malignancy (malignant), 54</td>
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<tr>
<td>T</td>
<td>Ossudary hyperplasia, 55 Rheumatoid arthritis, 56</td>
</tr>
<tr>
<td>U</td>
<td>Sarcoidosis, 57 Systemic lupus erythematosus, 58</td>
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<tr>
<td>V</td>
<td>Sjogrens syndrome, 59 Systemic granulomatous disease, 60</td>
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<td>W</td>
<td>Tuberculosis, 61 Varicella-zoster virus infection, 62</td>
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<tr>
<td>X</td>
<td>Vascular collapse, 63 Vasculitis, 64</td>
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<tr>
<td>Y</td>
<td>Waldenstrom macroglobulinemia, 65 Wegener granulomatosis, 66</td>
</tr>
<tr>
<td>Z</td>
<td>Wiskott-Aldrich syndrome, 67 X-linked lymphoproliferative disease, 68</td>
</tr>
</tbody>
</table>

*Some entities with more than 1 common name are listed more than once. Boldface indicates more common etiologies.

Table 4. Differential Diagnosis of Lymphadenopathy*

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Cervical
Infections: pharyngitis, dental abscess, otitis media and otitis externa, infectious mononucleosis, toxoplasmosis, cytomegalovirus, hepatitis, adenovirus, rubella
Malignancies: Hodgkin disease, non-Hodgkin lymphoma, squamous cell carcinoma of the head and neck
Kikuchi disease

Supraclavicular and prelaryngeal
Virchow node: abdominal or thoracic neoplasm
Delphian node: thyroid or laryngeal disease
Infections: mycobacterial (eg, scrofula), fungal

Axillary
Infections: staphylococcal and streptococcal arm infections, cat-scratch fever, tularemia, sporotrichosis
Malignancies: breast carcinoma, Hodgkin disease, non-Hodgkin lymphoma, melanoma

Epitrochlear
Lymphoproliferative disorders
Connective tissue diseases and sarcoidosis
Dermatologic diseases
“Historical” associations: syphilis, leprosy, leishmaniasis, rubella

Inguinal
Benign reactive (especially in shoeless walkers)
Malignancies: Hodgkin disease, non-Hodgkin lymphoma, melanoma, squamous cell carcinoma of the penis and vulva, anal cancer
Infections: cellulitis, venereal diseases

Hilar
Unilateral
Infections: bacterial pneumonia, mycobacterial diseases, fungal infections, tularemia, psittacosis, pertussis
Other granulomatous diseases
Malignancies: bronchogenic carcinoma, metastatic breast cancer and gastrointestinal cancers, non-Hodgkin lymphoma, Hodgkin disease

Bilateral
Granulomatous diseases: sarcoidosis, berylliosis, etc
Bilateral infections
Malignancies: non-Hodgkin lymphoma, Hodgkin disease, metastatic carcinoma
Calcified: tuberculosis, histoplasmosis, silicosis

Mediastinal
Exclude other causes of mediastinal widening
Differential diagnosis is similar to that for hilar lymphadenopathy

Abdominal
Malignancies: metastatic adenocarcinoma (including gastric), non-Hodgkin lymphoma, transitional cell carcinoma of the urinary collecting system, chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin disease (rarely mesenteric)

Tuberculosis

Generalized
Hematologic malignancies: non-Hodgkin lymphoma, Hodgkin disease, chronic lymphocytic leukemia, acute lymphocytic leukemia
Infectious: infectious mononucleosis, cytomegalovirus, human immunodeficiency virus, tuberculosis, toxoplasmosis, histoplasmosis, coccidioidomycosis, brucellosis
Rheumatoid arthritis, systemic lupus erythematosus
Sarcoidosis
Angioimmunoblastic lymphadenopathy
Table 5. Regional Differential Diagnosis of Lymphadenopathy

Cervical Lymphadenopathy

The differential diagnosis of cervical lymphadenopathy primarily consists of infections and malignancies. Common infectious etiologies include bacterial pharyngitis, dental abscesses, otitis media and otitis externa, infectious mononucleosis, gonococcal pharyngitis, cytomegalovirus, toxoplasmosis, hepatitis, and adenovirus. The most common malignancies presenting in the cervical region include non-Hodgkin lymphoma, Hodgkin disease, and squamous cell carcinoma of the head and neck. Isolated posterior cervical and occipital adenopathy is associated with rubella, toxoplasmosis, and Kikuchi disease (histiocytic necrotizing lymphadenitis). Kikuchi disease is a syndrome of unknown etiology that was first described in 1972 in Japan. The classic patient is a young woman who presents with painless lymphadenopathy that is unilateral in the posterior cervical region and resolves in 3 months.

Supraclavicular Lymphadenopathy

The Virchow node, a pathological anterior left supraclavicular lymph node also known as the signal node or Troisier ganglion, heralds the presence of an abdominal or thoracic neoplasm. Common causes include breast carcinoma, non-Hodgkin lymphoma, Hodgkin disease, gastrointestinal neoplasms, and bronchogenic carcinoma. Chronic fungal and mycobacterial infections (eg, scrofula) can also cause supraclavicular adenopathy. The Delphian node is a midline prelaryngeal lymph node that has traditionally been believed to be an oracle of thyroid disease or laryngeal malignancy, but objective data are lacking and patients with lymphoma may have lymphadenopathy in this region.

Axillary Lymphadenopathy

Axillary adenopathy, like cervical adenopathy, is usually secondary to infection or malignancy. Hodgkin disease, non-Hodgkin lymphoma, carcinoma of the breast, and melanoma are common. Characteristic infectious causes of axillary lymph nodes include staphylococcal and streptococcal bacterial infections of the arm, cat-scratch fever, tularemia, and sporotrichosis.

Epitrochlear Lymphadenopathy

Selby et al performed a prospective study of epitrochlear adenopathy in 324 patients. None of the 140 healthy controls in the study had any epitrochlear nodes palpable. A total of 184 consecutive patients with conditions associated with adenopathy in other regions were examined; of these, 49 patients (27%) had palpable epitrochlear adenopathy. The 2 most common diagnoses in the patients with epitrochlear adenopathy were lymphoma/chronic lymphocytic leukemia (22 patients) and infectious mononucleosis (12 patients). Other diagnoses included sarcoidosis, human immunodeficiency virus (HIV) infection, dermatologic diseases, and some connective
tissue disorders. Historically, epitrochlear adenopathy has been associated with secondary syphilis, lepromatous leprosy, leishmaniasis, and rubella.

Inguinal Lymphadenopathy

Most adults have some degree of inguinal lymph node enlargement. Benign reactive inguinal lymphadenopathy is more common in patients who walk shoeless outdoors. Common malignant causes include non-Hodgkin lymphoma, Hodgkin disease, malignant melanoma, squamous cell carcinoma of the penis, and squamous cell carcinoma of the vulva. Benign causes include cellulitis and venereal disease (syphilis, chancroid, genital herpes, and lymphogranuloma venereum). The node of Cloquet (also known as the Rosenmüller node) is a deep inguinal lymph node located near the femoral canal; when pathologically enlarged, it may be mistaken for an inguinal hernia.

Popliteal Lymphadenopathy

Little data exist on popliteal adenopathy in humans, although rat popliteal nodes are a common immunologic research model. One author does not routinely check for popliteal nodes, stating, "the physical examination must not be stretched beyond its limits."

Hilar and Mediastinal Lymphadenopathy

The most common causes of hilar prominence on chest x-ray films are vascular engorgement and adenopathy. On chest x-ray evaluation alone, it may be difficult to distinguish vascular enlargement from nodal enlargement. The differential diagnosis of hilar lymphadenopathy is extensive. Fraser et al have articulated an extensive differential diagnosis, evaluation approaches, and radiologic findings. Unilateral hilar adenopathy may be related to pneumonitis or neoplasia. Any bacterial pneumonia can cause unilateral hilar adenopathy; granulomatous disease, tuberculosis, atypical mycobacterial infections, histoplasmosis, coccidioidomycosis, tularemia, psittacosis, and pertussis are also considerations. Common neoplastic etiologies of unilateral hilar disease include bronchogenic carcinoma, metastatic carcinoma of the breast and gastrointestinal tract, non-Hodgkin lymphoma, and Hodgkin disease. Bilateral hilar adenopathy is commonly caused by sarcoidosis, non-Hodgkin lymphoma, Hodgkin disease, metastatic carcinoma, chronic granulomatous infections, or berylliosis. Calcified hilar adenopathy may be secondary to tuberculosis, histoplasmosis, or silicosis (classically egg-shaped nodes).

The approach to evaluating hilar adenopathy includes a detailed history and physical examination, evaluation of old chest x-ray films, judicious use of serologic studies (fungal, serum angiotensin-converting enzyme, etc), cultures when appropriate, and lymph node biopsy. Mediastinoscopy is the preferred initial approach; other potential approaches include limited anterior thoracotomy or needle biopsy.
It may be difficult to distinguish mediastinal lymph-adenopathy from the many other causes of mediastinal widening. Diffuse mediastinal widening may be related to acute mediastinitis, hemorrhage, lipomatosis, or fibrosing mediastinitis. Acute mediastinitis is usually bacterial and related to entities such as esophageal rupture (secondary to Boerhaave syndrome, foreign body ingestion, invasive esophageal carcinoma, penetrating or blunt chest trauma, or therapeutic esophageal dilatation), empyema, lung abscess, bacterial pericarditis, retropharyngeal abscess, or an infected bronchogenic cyst. Anterior mediastinal masses may represent a thymoma, a teratoma or other germ cell tumor, an intrathoracic goiter, Hodgkin or non-Hodgkin lymphoma, a parathyroid mass, choriocarcinoma, or benign tumors such as lipomas, fibromas, hemangiomas, and lymphangiomas. Middle mediastinal masses may be secondary to non-Hodgkin and Hodgkin lymphoma, carcinoma of the trachea, metastatic carcinoma, granulomatous mediastinitis, bronchogenic cyst, pleuroperticardial cyst, diaphragmatic hernia through the foramen of Morgagni, Castleman disease, or vascular dilatation. Posterior mediastinal masses are usually due to neurogenic tumors, neuroenteric cysts, gastroenteric cysts, thoracic duct cysts, esophageal neoplasms and diverticula, diaphragmatic hernia through the foramen of Bochdalek, disease of the thoracic spine, or extramedullary hematopoiesis.

The initial approach to the mediastinal mass is similar to that of the hilar mass, including detailed history and physical examination, review of old chest x-ray films, and judicious laboratory testing, followed by other evaluations that may include a computed tomographic scan with subsequent biopsy.

Abdominal Lymphadenopathy

Lymphadenopathy limited to the abdomen (mesenteric and/or retroperitoneal) is often malignant. Causes include non-Hodgkin lymphoma, metastatic adenocarcinoma, gastric adenocarcinoma, Hodgkin disease (characteristically retroperitoneal node involvement and rarely mesenteric involvement), transitional cell carcinoma of the bladder, chronic lymphocytic leukemia, hairy cell leukemia, and tuberculosis. A classic sign of gastric adenocarcinoma is the Sister (Mary) Joseph nodule in the umbilical area, which may represent a direct metastatic deposit or an enlarged anterior abdominal lymph node. Umbilical metastases may also be seen in other malignancies. This physical sign is named after surgeon William J. Mayo's scrub nurse, who was able to predict the findings at laparotomy if she felt a periumbilical mass while scrubbing the patient's abdomen. It has been suggested that the "Mary" in "Sister Mary Joseph" is incorrect, but there is clear historical evidence to the contrary. Generalized Lymphadenopathy

Common malignant causes of generalized lymphadenopathy include the hematologic malignancies, especially non-Hodgkin lymphoma, Hodgkin disease, chronic lymphocytic leukemia, and acute lymphocytic leukemia. Benign causes include infectious
mononucleosis, cytomegalovirus, toxoplasmosis, tuberculosis, histoplasmosis, coccidioidomycosis, brucellosis, sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, HIV infection, and angioimmunoblastic lymphadenopathy.

**SPECIAL CLINICAL AND LABORATORY ASSOCIATIONS**

Historical and laboratory associations may aid in establishing the diagnosis in difficult cases associated with lymph-adenopathy (Table 6). The differential diagnosis of lymph-adenopathy with malabsorption includes gluten-sensitive enteropathy, Crohn disease, amyloidosis, and Whipple disease. Rheumatoid arthritis, systemic lupus erythematosus, Wegener granulomatosis, or Whipple disease may cause lymphadenopathy associated with arthralgias or arthritis. Renal disease and lymphadenopathy are seen together with systemic lupus erythematosus, mixed connective tissue disease, amyloidosis, Whipple disease, and Hodgkin disease with paraneoplastic minimal change disease. Hypogammaglobulinemia and lymphadenopathy may be associated with chronic lymphocytic leukemia, amyloidosis, common variable immunodeficiency, and Whipple disease.133 Monoclonal proteins in the serum or urine may be associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, or amyloidosis.

| **Malabsorption:** amyloidosis, gluten-sensitive enteropathy (celiac sprue), Crohn disease, amyloidosis, Whipple disease |
| **Arthralgias and arthritis:** rheumatoid arthritis, systemic lupus erythematosus, Wegener granulomatosis, Whipple disease, non-Hodgkin lymphoma, vasculitis |
| **Renal disease:** amyloidosis, Hodgkin disease (paraneoplastic minimal change disease), mixed connective tissue disease, systemic lupus erythematosus, Whipple disease |
| **Hypogammaglobulinemia:** chronic lymphocytic leukemia, non-Hodgkin lymphoma, common variable immunodeficiency disorder, amyloidosis, Whipple disease |
| **Monoclonal proteins:** amyloidosis, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma |

Table 6. Historical and Laboratory Associations With Lymphadenopathy

**CONCLUSION**

Lymphadenopathy is an important physical finding with an extensive differential diagnosis that often presents interesting challenges to the clinician. Skill in palpating
peripheral lymph nodes improves with time. Clinicians should be encouraged to consistently measure the peripheral nodes that are discovered on physical examination with calipers. Node biopsies, when appropriate, should be performed in a manner most likely to yield a useful result. Knowledge of the broad differential diagnosis of lymphadenopathy, the relationships of other signs and symptoms, and key laboratory associations all aid in a thoughtful and expeditious diagnosis.

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### Table 4

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical</strong></td>
<td>Infections: pharyngitis, dental abscesses, otitis media and otitis externa,</td>
</tr>
<tr>
<td></td>
<td>infectious mononucleosis, toxoplasmosis, cytomegalovirus, leptospira,</td>
</tr>
<tr>
<td></td>
<td>adenovirus, rubella. Maligunancies: Hodgkin disease, non-Hodgkin lymphoma,</td>
</tr>
<tr>
<td></td>
<td>squamous cell carcinoma of the head and neck.</td>
</tr>
<tr>
<td>**Supravacuolar and</td>
<td>Lymphadenopathy.</td>
</tr>
<tr>
<td>preauricular**</td>
<td>Erythematous lymph nodes: abdomen or thoracic neoplasms.</td>
</tr>
<tr>
<td><strong>Axillary</strong></td>
<td>Infections: streptococcal and staphylococcal skin infections, cat-scratch</td>
</tr>
<tr>
<td><strong>Epistaxis</strong></td>
<td>Maligunancies: breast carcinoma.</td>
</tr>
<tr>
<td><strong>Inguinal</strong></td>
<td>Maligunancies: Hodgkin disease, non-Hodgkin lymphoma, melanoma, squamous</td>
</tr>
<tr>
<td></td>
<td>cell carcinoma of the penis and vulva. Melanoma, vulvar cancer.</td>
</tr>
<tr>
<td><strong>Hilar</strong></td>
<td>Infections: bacterial pneumonia, mumps, meningitis, pneumonia, atypical</td>
</tr>
<tr>
<td></td>
<td>infections, tuberculous infection.</td>
</tr>
<tr>
<td><strong>Unilateral</strong></td>
<td>Maligunancies: non-Hodgkin lymphoma, melanoma, squamous cell carcinoma of</td>
</tr>
<tr>
<td></td>
<td>the penis and vulva.</td>
</tr>
<tr>
<td><strong>Bilateral</strong></td>
<td>Maligunancies: non-Hodgkin lymphoma, melanoma, squamous cell carcinoma of</td>
</tr>
<tr>
<td></td>
<td>the penis and vulva.</td>
</tr>
<tr>
<td><strong>Infiltrative</strong></td>
<td>Maligunancies: melanoma, squamous cell carcinoma of the penis and vulva.</td>
</tr>
<tr>
<td><strong>Abdominal</strong></td>
<td>Maligunancies: metastatic adenocarcinoma (including gastric), non-Hodgkin</td>
</tr>
<tr>
<td></td>
<td>lymphoma, transitional cell carcinoma of the urogenital tract, chronic</td>
</tr>
<tr>
<td></td>
<td>lymphocytic leukemia, hairy cell leukemia.</td>
</tr>
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<td><strong>Generalized</strong></td>
<td>Maligunancies: non-Hodgkin lymphoma, Hodgkin disease, chronic lymphocytic</td>
</tr>
<tr>
<td></td>
<td>leukemia, acute lymphocytic leukemia.</td>
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<tr>
<td><strong>Hematologic</strong></td>
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</tr>
<tr>
<td></td>
<td>lymphocytic leukemia.</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Maligunancies: mononucleosis, cytomegalovirus, human immunodeficiency virus,</td>
</tr>
<tr>
<td></td>
<td>toxoplasmosis, histoplasmosis, coccidioidomycosis, brucellosis.</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis, systemic lupus erythematosus. Asthmatic.</td>
</tr>
</tbody>
</table>

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### Table 5

Maligunancies: multiple myeloma, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma.