with antibiotics is often associated with regression of the lymphoma.

Clinical Presentation

Although numerous subtypes of NHL are recognized, most disease entities may be viewed conceptually as clinically indolent (i.e., low grade) or aggressive (i.e., high grade). Indolent lymphomas typically grow slowly, do not always require therapy, and have a long natural history. A clinical history of recurring and regressing adenopathy may be elicited. Aggressive lymphomas are more likely to manifest with symptoms and are associated with limited survival in the absence of therapy.

Most patients with NHL exhibit painless lymphadenopathy involving one or more of the peripheral nodal sites. NHL can involve extranodal sites, and patients can exhibit a variety of symptoms that reflect the site of involvement. Common sites of extranodal disease include the gastrointestinal tract, bone marrow or focal bone lesions, liver, skin, and Waldeyer's ring in the nasopharynx and oropharynx, although virtually any site can be involved. Aggressive subtypes of NHL are more likely than indolent lymphomas to involve extranodal sites.

Central nervous system involvement, including leptomeningeal spread, rarely occurs with the indolent subtypes but does occur with the aggressive variants. The most aggressive NHLs (i.e., Burkitt's and lymphoblastic lymphomas) have a particular propensity to spread to the leptomeninges.

Constitutional symptoms such as fever, weight loss, or night sweats occur in about 20% of patients with NHL at the time of onset. These symptoms are more common in patients with aggressive subtypes of NHL.

Diagnosis and Differential Diagnosis

Many causes of lymphadenopathy exist in addition to lymphoid malignancies (Table 49-2). A thorough history and careful physical examination are important before performing a lymph node biopsy. The investigation of lymphadenopathy can be organized according to the location of the enlarged nodes (i.e., localized or generalized) and clinical symptoms.

Cervical lymphadenopathy is most often caused by infections of the upper respiratory tract, including infectious mononucleosis syndromes, viral syndromes, and bacterial pharyngitis. Unilateral axillary, inguinal, or femoral adenopathy may be caused by skin infections involving the extremity, including cat-scratch fever. Generalized lymphadenopathy may be caused by systemic infections (e.g., HIV, cytomegalovirus), drug reactions, autoimmune diseases, or one of the systemic lymphadenopathy syndromes. If the cause of persistent lymphadenopathy is not apparent after a thorough evaluation, an excisional lymph node biopsy should be undertaken. An enlarged supraclavicular lymph node strongly suggests malignancy and should always be sampled.

The accurate diagnosis of lymphoma requires excisional biopsy of a lymph node or generous biopsy of involved lymph tissue. Fine-needle aspiration or needle biopsy is rarely sufficient. Analysis of the pathologic specimen should include routine histologic examination and immunophenotyping. Immunophenotyping can determine the cell of origin (i.e., B cell, T cell, NK cell, or nonlymphoid cell), and the pattern of cell surface antigens aids subclassification of lymphomas. In the case of B-cell NHLs, immunophenotyping can also reveal whether the process is monoclonal in origin (i.e., neoplastic) by determining whether the surface immunoglobulin is restricted to the κ or λ light chain. In some cases, cytogenetic analysis or molecular studies of immunoglobulin or TCR gene rearrangement may be required to determine the pathologic subtype of lymphoma or to establish a monoclonal (i.e., malignant) process. If a lymph node biopsy is nondiagnostic and unexplained lymph node enlargement persists, the biopsy should be repeated.

For patients with bone marrow and peripheral blood involvement, such as in small lymphocytic lymphoma or CLL, the diagnosis may be made based on immunophenotyping of peripheral blood lymphocytes by flow cytometry. Care must be taken to exclude the possibility of aggressive lymphoma manifesting with involved lymph nodes or extranodal sites in a patient harboring a low-grade or chronic indolent lymphoma such as small lymphocytic lymphoma that is confined to the blood or bone marrow.

TABLE 49-2 CAUSES OF LYMPHADENOPATHY

INFECTIOUS DISEASES
Viral: infectious mononucleosis syndromes (cytomegalovirus, Epstein-Barr virus), acquired immunodeficiency syndrome, rubella, herpes simplex, infectious hepatitis
Bacterial: localized infection with regional adenopathy (streptococci, staphylococci), cat-scratch disease *(Bartonella henselae)*, brucellosis, tularemia, listeriosis, bubonic plague *(Yersinia pestis)*, chancroid *(Haemophilus ducreyi)*
Fungal: coccidioidomycosis, histoplasmosis
Chlamydial: lymphogranuloma venereum, trachoma
Mycobacterial: scrofula, tuberculosis, leprosy
Protozoan: toxoplasmosis, trypanosomiasis
Spirochetal: Lyme disease, syphilis, leptospirosis
IMMUNOLOGIC DISEASES
Rheumatoid arthritis
Systemic lupus erythematosus
Mixed connective tissue disease
Sjögren syndrome
Dermatomyositis
Serum sickness
Drug reactions: phenytoin, hydralazine, allopurinol
MALIGNANT DISEASES
Lymphomas
Solid tumors metastatic to lymph nodes: melanoma, lung, breast, head and neck, gastrointestinal tract, Kaposi's sarcoma, unknown primary tumor, renal, prostate
ATYPICAL LYMPHOID PROLIFERATIONS
Giant follicular lymph node hyperplasia
Transformation of germinal centers
Castleman's disease
MISCELLANEOUS DISEASES AND DISEASES OF UNKNOWN CAUSE
Dermatopathic lymphadenitis
Sarcoidosis
Immunoglobulin G4 (IgG4) Lymphadenopathy
Amyloidosis
Mucocutaneous lymph node syndrome (Kawasaki disease)
Sinus histiocytosis (Rosai-Dorfman syndrome)
Multifocal Langerhans cell (eosinophilic) granulomatosis
Lipid storage diseases: Gaucher's and Niemann-Pick diseases

Treatment

After a lymphoma has been diagnosed, patients should undergo a complete staging evaluation (Table 49-3). Staging determines