Table 13-7 Differences between Hodgkin and Non-Hodgkin Lymphomas

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Waldeyer ring and mesenteric nodes commonly involved
Extranodal presentation rare	Extranodal presentation common

anatomically contiguous lymphoid tissues. HL also has distinctive morphologic features. It is characterized by the presence of neoplastic giant cells called *Reed-Sternberg cells*. These cells release factors that induce the accumulation of reactive lymphocytes, macrophages, and granulocytes, which typically make up greater than 90% of the tumor cellularity. In the vast majority of HLs, the neoplastic Reed-Sternberg cells are derived from germinal center or postgerminal center B cells.

Hodgkin lymphoma accounts for 0.7% of all new cancers in the United States; there are about 8000 new cases each year. The average age at diagnosis is 32 years. It is one of the most common cancers of young adults and adolescents, but also occurs in the aged. It was the first human cancer to be successfully treated with radiation therapy and chemotherapy, and is curable in most cases.

Classification. The WHO classification recognizes five subtypes of HL:

1. Nodular sclerosis
2. Mixed cellularity
3. Lymphocyte-rich
4. Lymphocyte depletion
5. Lymphocyte predominance

In the first four subtypes—nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte depletion—the Reed-Sternberg cells have a similar immunophenotype. These subtypes are often lumped together as *classical* forms of HL. In the remaining subtype, lymphocyte predominance, the Reed-Sternberg cells have a distinctive B-cell immunophenotype that differs from that of the "classical" types.

Pathogenesis. The origin of the neoplastic Reed-Sternberg cells of classical HL has been explained through elegant studies relying on molecular analysis of single isolated Reed-Sternberg cells and variants. In the vast majority of cases, the Ig genes of Reed-Sternberg cells have undergone both V(D)J recombination and somatic hypermutation, establishing an origin from a germinal center or postgerminal center B cell. Despite having the genetic signature of a B cell, the Reed-Sternberg cells of classical HL fail to express most B-cell–specific genes, including the Ig genes. The cause of this wholesale reprogramming of gene expression has yet to be fully explained, but presumably is the result of widespread epigenetic changes of uncertain etiology.

Activation of the transcription factor NF-κB is a common event in classical HL. This can occur by several mechanisms:

- NF-κB may be activated either by EBV infection or by some other mechanism and turns on genes that promote lymphocyte survival and proliferation.
- EBV^+ tumor cells express latent membrane protein-1 (LMP-1), a protein encoded by the EBV genome that transmits signals that up-regulate NF-κB.
- Activation of NF-κB may occur in EBV-tumors as a result of acquired loss-of-function mutations in IκB or A20 (also known as *TNF alpha-induced protein 3, or TNFAIP3*), which are both negative regulators of NF-κB.
- It is hypothesized that activation of NF-κB by EBV or other mechanisms rescues "crippled" germinal center B cells that cannot express Igs from apoptosis, setting the stage for the acquisition of other unknown mutations that collaborate to produce Reed-Sternberg cells.

Little is known about the basis for the morphology of Reed-Sternberg cells and variants, but it is intriguing that EBV-infected B cells resembling Reed-Sternberg cells are found in the lymph nodes of individuals with infectious mononucleosis, strongly suggesting that EBV-encoded proteins play a part in the remarkable metamorphosis of B cells into Reed-Sternberg cells.

The florid accumulation of reactive cells in tissues involved by classical HL occurs in response to a wide variety of cytokines (e.g., IL-5, IL-10, and M-CSF) chemokines (e.g.,eotaxin), and other factors (e.g., immunomodulatory factor galectin-1) that are secreted by Reed-Sternberg cells. Once attracted, the reactive cells produce factors that support the growth and survival of the tumor cells and further modify the reactive cell response. For example, eosinophils and T cells express ligands that activate the CD30 and CD40 receptors found on Reed-Sternberg cells, producing signals that up-regulate NF-κB. Other examples of "cross-talk" between Reed-Sternberg cells and surrounding reactive cells are provided in Figure 13-28. Some of the factors produced by RS cells give rise to a state of immunodeficiency by impairment of T helper and cytotoxic cells and enhancing the generation of regulatory T cells (as discussed later).

Reed-Sternberg cells are aneuploid and possess diverse clonal chromosomal aberrations. Copy number gains in the *REL* proto-oncogene on chromosome 2p are particularly common and may also contribute to increases in NF-κB activity.

MORPHOLOGY

Identification of Reed-Sternberg cells and their variants is essential for the diagnosis. **Diagnostic Reed-Sternberg cells are large cells (45 μm in diameter) with multiple nuclei or a single nucleus with multiple nuclear lobes, each with a large inclusion-like nucleolus about the size of a small lymphocyte (5 to 7 μm in diameter)** (Fig. 13-24*A*). The cytoplasm is abundant. Several Reed-Sternberg cell variants are also recognized. **Mononuclear variants** contain a single nucleus with a large inclusion-like nucleolus (Fig. 13-24*B*). **Lacunar cells** (seen in the nodular sclerosis subtype) have more delicate, folded, or multilobate nuclei and abundant pale cytoplasm that is often disrupted during the cutting of sections, leaving the nucleus sitting in an empty hole (a lacuna) (Fig.