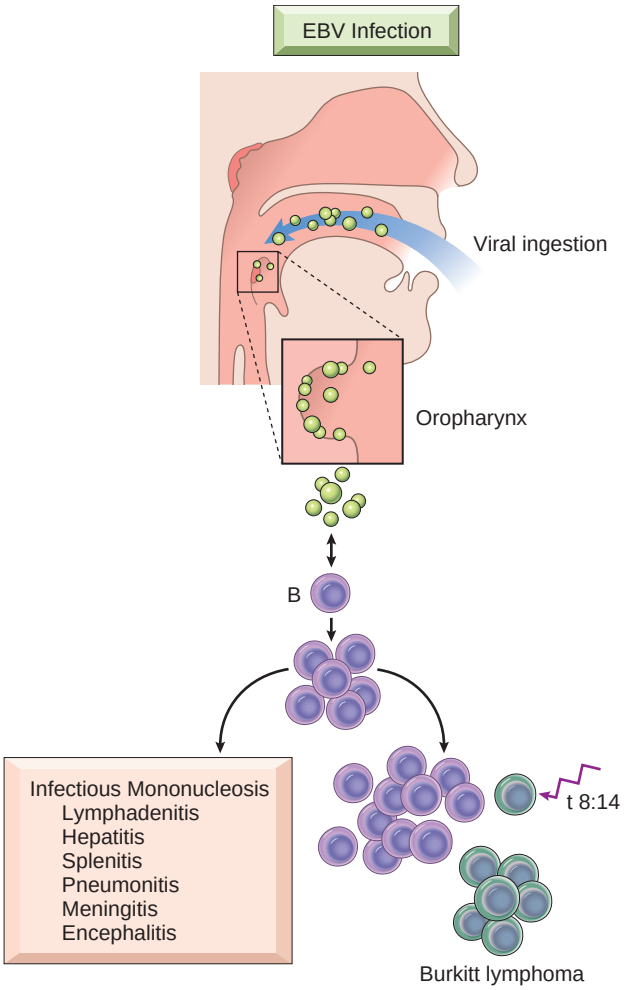

Figure 8-13 Outcomes of Epstein-Barr virus (EBV) infection. In an individual with normal immune function, infection is usually either asymptomatic or leads to mononucleosis. In the setting of cellular immunodeficiency, the proliferation of infected B cells may be uncontrolled, leading to the development of B-cell neoplasms. In other instances, persons without overt evidence of immunodeficiency develop EBV-positive tumors, which are usually (but not always) also derived from B cells. One secondary genetic event that collaborates with EBV to cause B-cell transformation is a balanced 8;14 chromosomal translocation, which is seen in Burkitt lymphoma. EBV is also implicated in the pathogenesis of nasopharyngeal carcinoma, Hodgkin lymphoma, and certain other rare non-Hodgkin lymphomas.

- *Epstein-Barr nuclear antigen 1 (EBNA1)* binds the EBV genome to host cell chromosomes during mitosis, thereby ensuring that viral episomes are partitioned evenly to daughter cells when infected cells divide.
- *Latent membrane protein 1 (LMP1)* drives B-cell activation and proliferation. LMP1 does so by mimicking a constitutively active form of CD40, a B cell surface receptor. Like activated CD40, LMP1 binds to TNF receptor–associated factors (TRAFs), adaptor molecules that trigger downstream events that activate NF-κB and the JAK/STAT signaling pathway. In addition, LMP1 prevents apoptosis by activating Bcl-2.
- *EBNA2* also promotes B-cell activation and replication. It turns on the transcription of several host cell genes, including genes that encode proteins that drive cell cycle entry, such as cyclin D.
- EBV produces a *homologue of IL-10* (vIL-10), which inhibits macrophages and dendritic cells and suppresses antiviral T cell responses.

As a result of the actions of these EBV proteins, B cells that are latently infected with EBV are activated and begin to proliferate and to disseminate. This uncontrolled, expanding polyclonal population of EBV-infected B cells secretes antibodies with many specificities, including antibodies that recognize sheep or horse red cells. These so-called heterophile antibodies are detected in diagnostic tests for mononucleosis. EBV-infected B cells may also produce autoantibodies, for example against platelets, leading to transient immune mediated thrombocytopenia in a small subset of patients with mononucleosis.

EBV is shed in the saliva. It is not known whether the source of the virus is B cells, oropharyngeal epithelial cells, or both.

The symptoms of infectious mononucleosis appear upon initiation of the host immune response. Cellular immunity mediated by CD8+ cytotoxic T cells and NK cells is the most important component of this response. The *atypical lymphocytes* seen in the blood, characteristic of this disease, are mainly EBV-specific CD8+ cytotoxic T cells, but also include CD16+ NK cells. The reactive proliferation of T cells is largely centered in lymphoid tissues, which accounts for the lymphadenopathy and splenomegaly. Early in the course of the infection, IgM antibodies are formed against viral capsid antigens; later, IgG antibodies are formed that persist for life. In otherwise healthy persons, the fully developed humoral and cellular responses to EBV act as brakes on viral shedding, resulting in the elimination of B cells expressing the full complement of EBV latency-associated genes. In hosts with acquired defects in cellular immunity (e.g., AIDS, organ transplantation), reactivation of EBV can lead to B-cell proliferation, which can progress through a multistep process to EBV-associated B-cell lymphomas. EBV also contributes to the development of some cases of Burkitt lymphoma (Chapter 13), in which a chromosomal translocation (most commonly an 8:14 translocation) involving the *MYC* oncogene is the critical oncogenic event (Fig. 8-13).

MORPHOLOGY

The major alterations involve the blood, lymph nodes, spleen, liver, CNS, and, occasionally, other organs. The **peripheral blood** shows absolute lymphocytosis; more than 60% of white blood cells are lymphocytes. Between 5% and 80% of these are large, **atypical lymphocytes**, 12 to 16 μm in diameter, characterized by an abundant cytoplasm containing multiple clear vacuolations, an oval, indented, or folded nucleus, and scattered cytoplasmic azurophilic granules (Fig. 8-14). These atypical lymphocytes, most of which express CD8, are sufficiently distinctive to strongly suggest the diagnosis.

The **lymph nodes** are typically discrete and enlarged throughout the body, particularly in the posterior cervical, axillary, and inguinal regions. On histologic examination the most striking feature is the expansion of paracortical areas due to activation of T cells (immunoblasts). A minor population of EBV-infected B cells expressing *EBNA2*, *LMP1*, and other