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FIGURE 113-7 Adult T-cell leukemia/lymphoma. Peripheral blood smear showing leukemia cells with typical “flower-shaped” nucleus. EBV infection in nearly all cases and more common in Asia and native populations in Peru. It usually presents with a mass and obstructive symptoms in the upper aerodigestive tract with occasional extranodal sites, but over two-thirds of patients will have localized disease. It is more common in men, and the median age at diagnosis is 60. This disease has its own prognostic score, which takes into account the presence or absence of “B” symptoms, disease stage, whether LDH is elevated, and whether there is lymph node involvement. EBV viral load at diagnosis and at the end of therapy is also predictive. PART 4 Oncology and Hematology Treatment for early-stage disease is usually with combined-modality therapy of chemotherapy (commonly using etoposide, ifosfamide, cisplatin, and dexamethasone) and intensity-modulated radiation therapy (50–55 Gy), and patients with localized disease involving the nasal passages do quite well, with 3-year OS of ~85%. Patients with more advanced-stage disease do poorly, with disseminated extranodal relapse occurring frequently, and the median OS is only 4.3 months. The most commonly used treatment regimen is the SMILE regi men (dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide). ■ ■FURTHER READING Horwitz S et al: The ECHELON-2 Trial: 5-year results of a random ized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma. Ann Oncol 33:288, 2022. Morschhauser F et al: Rituximab plus lenalidomide in advanced untreated follicular lymphoma. N Engl J Med 379:934, 2018. Tille H et al: Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med 386:351, 2022. Westin JR et al: Survival with axi-cabtagene ciloleucel in large B-cell lymphoma. N Engl J Med 389:148, 2023. Caron A. Jacobson, Dan L. Longo

Hodgkin’s Lymphoma Hodgkin’s lymphoma (HL) is a malignancy of mature B lymphocytes. It represents ~10% of all lymphomas diagnosed each year. The majority of HL diagnoses are classical HL (cHL), but there is a second subtype of HL, nodular lymphocyte-predominant HL (NLPHL). While this diagnosis does resemble cHL morphologically in certain respects, there is some evidence that it is more related to the indolent B-cell non-Hodgkin’s lymphomas (NHLs) biologically than it is to cHL. The

majority of this chapter will be specific to cHL, with a discussion of NLPHL at the end. cHL is one of the success stories of modern oncology. Until the advent of extended-field radiotherapy in the mid-twentieth century, it was a highly fatal disease of young people. Radiation therapy cured some patients with early-stage disease, and the introduction of mul tiagent chemotherapy in the 1970s

resulted in further improved cure rates, for both patients with early- and advanced-stage disease. Cure rates now are >85%. The new challenge in the treatment of HL is late therapy-related toxicity, including a high rate of secondary malignan cies and cardiovascular disease. Current clinical trials are aimed at minimizing this risk while preserving efficacy. ■ ■EPIDEMIOLOGY AND ETIOLOGY HL is of B-cell origin. The incidence of HL appears fairly stable, with an estimated 8830 new cases diagnosed in the United States in 2023. HL is more common in whites than in blacks and more common in males than in females. A bimodal distribution of age at diagnosis has been observed, with one peak incidence occurring in patients in their twen ties and the other in those in their eighties. Some of the late age peak may be attributed to confusion among entities with similar appearance such as anaplastic large-cell lymphoma and T-cell/histiocyte–rich B-cell lymphoma. There are four distinct subtypes of cHL that are differentiated based on their histopathologic features (Table 114-1): nodular scle rosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. Patients in the younger age groups diagnosed in the United States largely have the nodular sclerosing subtype of HL. Elderly patients, patients infected with HIV, and patients in developing countries more commonly have mixed-cellularity HL or lymphocyte-depleted HL. Together, nodular sclerosis and mixed-cellularity types account for nearly 95% of cases. Infection by HIV is a risk factor for developing HL. In addition, an association between infection by Epstein-Barr virus (EBV) and HL has been suggested. A monoclonal or oligoclonal pro liferation of EBV-infected cells in 20–40% of the patients with HL has led to proposals for this virus having an etiologic role in HL. However, the matter is not settled definitively. Viral oncogenesis appears to play a greater role in HIV-related cHL: EBV can be detected in nearly all cases of HIV-associated cHL, compared to only one-third of cases of non–HIV-associated cHL. Reed-Sternberg (HRS) cells are the malig nant cells in HL. HRS cells in HIV-associated cHL express the EBVtransforming protein latent membrane protein 1 (LMP-1), and the EBV genomes from multiple disease sites in the same HIV-associated cHL patient are episomal and clonal, suggesting that EBV is directly involved in early lymphomagenesis. Histologically, the HRS cell is diagnostic of cHL (Fig. 114-1). These cells are large cells with abundant cytoplasm with bilobed and/ or multiple nuclei. By immunohistochemistry, they are often PAX-5 positive but have low to no expression of other B-cell antigens like CD19 and CD20. They express CD15 and CD30 in 85 and 100% of cases, respectively. These cells, though, comprise <1% of the tumor cellularity, with the majority of the tumor made up of a surround ing inflammatory infiltrate of polyclonal lymphocytes, eosinophils, neutrophils, macrophages, plasma cells, fibroblasts, and collagen. The HRS cell interacts with its microenvironment via cell-cell contact and elaboration of growth factors and cytokines, which results in a sur rounding cellular milieu that protects it from host immune attack. The surrounding environmental cells likewise support the HRS cells via cell-cell signaling and cytokine production, which provides signals TABLE 114-1 World Health Organization Classification of Hodgkin’s Lymphoma Nodular lymphocyte-predominant Hodgkin’s lymphoma Classical Hodgkin’s lymphoma Nodular sclerosis Lymphocyte-rich Mixed cellularity Lymphocyte-depleted

FIGURE 114-1 Hodgkin’s disease: A classic Reed-Sternberg (RS) cell is present near the center of the field. RS cells are large cells with a bilobed nucleus and prominent nucleoli surrounded by a pleiomorphic cellular infiltrate. (From DL Kasper: Harrison’s Principles of Internal Medicine, 16th ed. New York, NY: McGraw-Hill; 2005, Fig. 97-11, p. 654.) that promote proliferation and survival of the HRS cell itself. Interest ingly, 97% of HRS cells in cHL harbor genetic aberrations in the PD-L1 locus on chromosome 9p24.1, resulting in overexpression of PD-L1, the ligand for the inhibitory PD-1 receptor on immune cells. This is one mechanism whereby the HRS cell may be able to avoid

immune destruction in its inflammatory microenvironment and may contribute to the generalized immune suppression in HL patients. APPROACH TO THE PATIENT Classical Hodgkin's Lymphoma Most patients with cHL present with palpable lymphadenopathy that is nontender; in most patients, these lymph nodes are in the neck, supraclavicular area, and axilla. More than half of the patients will have mediastinal adenopathy at diagnosis, and this is some times the initial manifestation. Subdiaphragmatic presentation of cHL is unusual and more common in older males. One-third of patients present with fevers, night sweats, and/or weight loss, or "B" symptoms. Occasionally, HL can present as a fever of unknown ori gin. This is more common in older patients who are found to have mixed-cellularity HL in an abdominal site. Rarely, the fevers persist for days to weeks, followed by afebrile intervals and then recurrence of the fever. This pattern is known as Pel-Ebstein fever. HL can occa sionally present with unusual manifestations. These include severe and unexplained itching, cutaneous disorders such as erythema nodosum and ichthyosiform atrophy, paraneoplastic cerebellar degeneration and other distant effects on the CNS, nephrotic syn drome, immune hemolytic anemia and thrombocytopenia, hyper calcemia, and pain in lymph nodes on alcohol ingestion. Evaluation of patients with HL will typically begin with a careful history and physical examination. Patients should be asked about the presence or absence of "B" symptoms. Comorbid diagnoses that may impact therapy should be reviewed, including a history of pulmonary disease and congestive heart failure given the use of chemotherapy drugs that can cause both lung and heart toxicity. A physical examination should pay attention to the peripherally accessible sites of lymph nodes and to the liver and spleen size. Laboratory evaluation should include a complete blood count with differential; erythrocyte sedimentation rate (ESR); chemistry stud ies reflecting major organ function including serum albumin; and HIV and hepatitis virus testing. A positron emission tomography (PET)/computed tomography (CT) scan is used for staging and is more accurate than a bone marrow biopsy for evaluation of bone marrow involvement as the bone marrow involvement in cHL tends to be patchy and therefore potentially missed on a unilateral bone

TABLE 114-2 The Ann Arbor Staging System for Hodgkin's Lymphoma STAGE DEFINITION I Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) II Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease) III Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm III1 Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes III2 Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III1 IV Involvement of extranodal site(s) beyond that designated as "E" More than one extranodal deposit at any location Any involvement of liver or bone marrow A No symptoms B Unexplained weight loss of >10% of the body weight during the

6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month CHAPTER 114 Recurrent drenching night sweats during the previous month E Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow Hodgkin's Lymphoma marrow biopsy. The initial evaluation of a patient with HL or NHL is similar. In both situations, the determination of an accurate ana tomic stage is an important part of the evaluation. Staging is done using the Ann Arbor staging system (Table 114-2). The diagnosis of HL is established by review of an adequate biopsy specimen by an expert

hematopathologist. HL is a tumor characterized by rare neoplastic cells of B-cell origin (immunoglob ulin genes are rearranged but not expressed) in a tumor mass that is largely polyclonal inflammatory infiltrate, probably a reaction to cytokines produced by the tumor cells. The differential diagnosis of a lymph node biopsy suspicious for HL includes inflammatory processes, mononucleosis, NHL, phenytoin-induced adenopathy, and nonlymphomatous malignancies. Staging for cHL is anatomically based given the propensity of the disease to march from one lymph node group to the next group, often contiguous to the first. Staging is important for selecting therapy of appropriate duration and intensity, but the outcome of optimal therapy for all the stages is excellent. Patients are stratified based on whether they have early-stage disease (stage I or II) or advanced-stage disease (stage III or IV). Patients with early-stage disease have a better prognosis overall but are further classified as favorable or unfavorable based on a variety of factors. These fac tors vary from study to study but include bulky disease, number of lymph node areas involved, an elevated ESR (>30 if “B” symptoms are present; >50 if “B” symptoms are absent), and age. Prognosis in advanced-stage disease is best predicted by the International Prog nostic Score (IPS), which ascribes 1 point for male sex, older age (>45 years), stage IV disease, serum albumin <4 g/dL, hemoglobin <10.5 g/dL, white blood cell count ≥15,000/μL, and a lymphocyte count <600/μL and/or <8% of white blood cell count. Five-year progression-free survival ranges from 88% for patients with no risk factors to 62% for patients with four or more factors, but very few patients have multiple risk factors. TREATMENT Classical Hodgkin’s Lymphoma The overwhelming majority of patients with HL will be cured with either chemotherapy alone or a combination of chemotherapy and radiation therapy. It has long been appreciated that patients

with advanced-stage disease do not benefit from the addition of radiation therapy to chemotherapy and are thus treated with chemotherapy alone. For early-stage disease, however, treatment with combined-modality therapy has been associated with a small decrease in risk of relapse but with an increased risk of late toxicity including secondary malignancies, thyroid disease, and prema ture cardiovascular disease and stroke resulting in minimal or no improvement in long-term survival. Much of this risk can be attrib uted to radiation therapy. Thus, investigation into the treatment of early-stage HL at present is aimed at trying to maximize treatment outcome without using radiotherapy. This is an area of controversy in the treatment of HL.

EARLY-STAGE DISEASE The most common chemotherapy regimen used to treat early-stage HL in the United States is ABVD (doxorubicin, bleomycin, vin blastine, and dacarbazine). This regimen is given every other week, with each cycle including two treatments. In patients with low-risk, or favorable, disease, the use of four to six cycles of ABVD alone, without radiation therapy, results in progression-free and overall survival rates of 88–92% and 97–100%, respectively, at 5–7 years. This may be associated with a slightly increased risk of relapse when compared with abbreviated chemotherapy (ABVD for four cycles) followed by involved field radiation therapy (30 Gy), but with no difference in overall survival owing to the excellent salvage strate gies used for relapsed HL and to the late toxicities seen following radiation therapy to the chest. German studies have examined a very abbreviated chemotherapy regimen (ABVD for two cycles) and low-dose radiation (20 Gy) for particularly good-risk disease with two or fewer lymph node areas involved and found that this was equally effective to standard combined-modality therapy of ABVD for four cycles and 30 Gy of radiation. However, long-term followup is not yet available to assess the impact of the lower radiotherapy dose on late toxicities. Finally, the use of an early interim PET/CT scan can aid

decisions regarding the duration and extent of therapy. In one study, a negative PET/CT scan after three cycles of ABVD predicted for excellent outcomes with no additional therapy; in another, a negative PET/CT scan after two cycles of ABVD pre dicted for good outcomes with two additional cycles of ABVD alone, without radiation therapy. PART 4 Oncology and Hematology For unfavorable-risk disease, the omission of radiation ther apy following chemotherapy is associated with a more significant increased risk of relapse compared to favorable-risk disease, but again with no change in overall survival. For these patients, treat ment options would include ABVD for four cycles followed by involved field radiation therapy or ABVD alone for six cycles. Treatment decisions are often based on the extent of the radiation field and the unfavorable risk factor, with patients with nonbulky disease being candidates for chemotherapy alone if radiation would be contraindicated for another reason. Combined modality therapy has typically been used for patients with bulky disease, although patients with bulky disease who have a negative PET/CT scan after chemotherapy may not benefit from additional radiation therapy. Alternative chemotherapy regimens to ABVD have been devel oped and include the Stanford V regimen and escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincris tine, procarbazine, and prednisone). Neither of these regimens has resulted in improved outcomes in patients with early-stage disease. ADVANCED-STAGE DISEASE Patients with advanced-stage disease do not benefit from the addi tion of radiation therapy after a complete response to chemotherapy alone and should be treated with chemotherapy alone. The most common regimens used in the United States include ABVD or brentuximab vedotin plus doxorubicin, vinblastine, and dacarba zine (AVD) for six cycles. Brentuximab is an antibody-drug con jugate (ADC) that targets CD30 on the HRS cell and is conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE). It was approved in the relapsed setting as a single agent and then was

tested in phase 1 and 2 trials in combination with AVD chemo therapy for the upfront treatment of advanced-stage cHL. A phase 3 study, ESCHELON-1, randomized patients with advanced-stage cHL to either ABVD or brentuximab-AVD and demonstrated both a progression-free and overall survival benefit with brentux imab-AVD. Again, Stanford V and escalated BEACOPP have been evaluated in advanced-stage disease and are not associated with an improvement in overall survival but are associated with increased toxicity. The small fraction of patients who do not achieve complete remission with chemotherapy alone (partial responders with persis tent PET scan positivity account for <10% of patients) may benefit from the addition of involved field radiotherapy. Drugs that target the PD-1/PD-L1 axis have been developed for the treatment of relapsed HL based on the known genomic alterations leading to PD-L1 overexpression on the HRS cell (see “Relapsed Disease,” below). In the setting of relapsed disease, these drugs, which include pembrolizumab and nivolumab, have very high response rates and are associated with durable responses. Phase 2 studies combining these drugs with either brentuximab (nivolumab) or ICE (nivolumab; ifosfamide, carboplatin, and etopo side) or GND (pembrolizumab; gemcitabine, vinorelbine, and doxo rubicin) chemotherapy have demonstrated high complete response rates in order to get patients to autologous stem cell transplantation. A multicenter randomized trial comparing brentuximab-AVD to nivolumab-AVD in the upfront treatment of advanced-stage cHL has been presented, and there was a progression-free survival ben efit with nivolumab-AVD and the regimen had an arguably more favorable toxicity profile. We await longer follow-up and U.S. Food and Drug Administration review of these results to determine if this study establishes a new standard of care for the upfront treatment of advanced-stage cHL. RELAPSED DISEASE Patients who relapse after primary therapy of HL can frequently still be cured. Patients who relapse after an effective chemother apy regimen are usually not curable with subsequent chemotherapy administered at standard doses. Alternative

salvage chemotherapy administered at standard doses, then, is given in order to document sensitivity to chemotherapy and to achieve maximum reduction of tumor mass. For patients who respond completely or nearly so, autologous stem cell transplantation can cure over half of patients. Standard salvage chemotherapy regimens have historically included ICE and GND. Newer combinations, including brentuximab with immune checkpoint inhibitors such as nivolumab, have also been tested with promising results for patients who have not seen brentuximab in the frontline setting. The combinations of ICE or GND with nivolumab or pembrolizumab, respectively, are similarly highly effective and lead to high complete remission rates and success in getting patients to definitive autologous stem cell trans plantation. These novel combinations have largely replaced standard sal vage chemotherapy approaches, as the chemotherapy/immunotherapy combinations appear to be more effective and are associated with higher rates of durable response after autologous stem cell trans plantation, perhaps owing to the chemosensitizing effects that have been observed following immune checkpoint inhibition. Studies are ongoing to investigate whether autologous transplant is necessary for patients who have a favorable response to chemotherapy/immu notherapy combinations based on this observed phenomenon. For patients with early-stage disease who do not respond sufficiently to salvage chemotherapy, radiation therapy can be very effective to achieve a remission; whether to consolidate such a remission with an autologous stem cell transplant is debated. Brentuximab is also used as a maintenance therapy following successful autologous stem cell transplantation based on results of the AETHERA study, a randomized trial of brentuximab maintenance versus observation. Finally, anti-CD30 chimeric antigen receptor (CAR) T-cell therapy has been tested in multiply relapsed cHL with promising early results; these products are now being tested in multicenter phase 2 clinical trials.

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