45 - 115 Less Common Lymphoid and Myeloid Malignancies

115 Less Common Lymphoid and Myeloid Malignancies

SURVIVORSHIP Because of the very high cure rate in patients with HL, long-term complications have become a major focus for clinical research. In fact, in some series of patients with early-stage disease, more patients died from late complications of therapy than from HL itself. This is particularly true in patients with localized disease. The most serious late side effects include second malignancies and cardiac injury. Patients are at risk for the development of acute leukemia in the first 10 years after treatment with combination chemotherapy regimens that contain alkylating agents plus radiation therapy. The risk for development of acute leukemia is greater after MOPP-like (mechlorethamine, vincristine, procarbazine, and prednisone) and BEACOPP-like regimens than with ABVD or brentuximab-AVD. The risk of development of acute leukemia after treatment for HL is also related to the number of exposures to potentially leukemogenic agents (i.e., multiple treatments after relapse) and the age of the patient being treated, with those aged >60 years at particularly high risk. The development of carcinomas as a complication of treatment for HL is a major problem. These tumors usually occur ≥10 years after treatment and are associated with use of radiotherapy. For this reason, young women treated with thoracic radiotherapy for HL should institute screening mammograms or breast MRI exams 5–10 years after treatment, and all patients who receive thoracic radiotherapy for HL should be discouraged from smoking. Medias tinal radiation also accelerates coronary artery disease, and patients should be encouraged to minimize risk factors for coronary artery disease such as smoking and elevated cholesterol levels. Cervical radiation therapy increases the risk of carotid atherosclerosis and stroke and thyroid disease, including cancer. A number of other late side effects from the treatment of HL are well known. Patients who receive thoracic radiotherapy are at very high risk for the eventual development of hypothyroidism and should be observed for this complication; intermittent mea surement of thyrotropin should be made to identify the condition before it becomes symptomatic. Lhermitte’s syndrome occurs in ~15% of patients who receive thoracic radiotherapy. This syn drome is manifested by an “electric shock” sensation into the lower extremities on flexion of the neck. Because of the young age at which HL is often diagnosed, infertility is a concern for patients undergoing treatment for HL. Chemotherapy regimens containing alkylating agents induce

permanent infertility in nearly all men. The risk of permanent infertility in women treated with alkylat ing agent–containing chemotherapy is age-related, with younger women more likely to recover fertility. Infertility is very rare after treatment with ABVD. NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN'S LYMPHOMA NLPHL is now recognized as an entity distinct from cHL. Previous classification systems recognized that biopsies from a small subset of patients diagnosed as having HL contained a predominance of small lymphocytes and rare Reed-Sternberg–like cells; tumors had a nodular growth pattern and a clinical course that varied from that of patients with cHL. This is an unusual clinical entity and repre sents <5% of cases of HL and defines NLPHL. NLPHL has a number of characteristics that suggest its relation ship to NHL, rather than cHL, however. The HRS-like cell, or L&H (lymphocyte and histiocyte) or "popcorn" cell, is a clonal prolifera tion of B cells that are positive for B-cell markers CD45, CD79a, CD20, CD19, and BCL2. They do not express two markers nor mally found on HRS cells, CD30 and CD15. This lymphoma tends to have a chronic, relapsing course and sometimes transforms to diffuse large B-cell lymphoma, including a specific subtype of dif fuse large B-cell lymphoma known as T-cell/histiocyte–rich B-cell lymphoma, which shares an immunophenotype with the L&H cell. This natural history most closely resembles that of the indolent B-cell NHLs outlined in Chaps. 113 and 115. Patients with NLPHL are more commonly male (75%). Like cHL, the age distribution of patients with this disease has two peaks,

but unlike cHL, these peaks include children and adults age 30–40 years, respectively. The majority of patients diagnosed have stage I or II disease (75%), with a minority having advanced-stage disease at diagnosis. "B" symptoms are uncommon.

Patients with early-stage disease at diagnosis should be treated with definitive radiotherapy. This is associated with a 15-year nonrelapse survival rate of 82%. The treatment of patients with advanced-stage NLPHL is controversial. Some clinicians favor no treatment of asymptomatic disease and merely close follow-up, akin to the indolent B-cell NHLs. For patients who need therapy due to symptoms or signs of organ function impairment, both cHL regimens and B-cell NHL regimens have been used, including ABVD and R-CHOP (rituximab, cyclophosphamide, doxorubi cin, vincristine, and prednisone). A single-institution experience with R-CHOP resulted in a 100% response rate in a small group of patients without a single relapse with 42 months of follow-up. Although this is short follow-up for an indolent disease, some believe R-CHOP may be curative in this disease and advocate treat ing patients with advanced-stage disease at diagnosis, regardless of symptoms or organ function. CHAPTER 115 ■ ■FURTHER READING Ansell SM et al: Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. N Engl J Med 387:310, 2022. Chen R et al: Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood 134:1144, 2019. Gillessen S et al: Intensified treatment of patients with early stage, Less Common Lymphoid and Myeloid Malignancies unfavourable Hodgkin lymphoma: Long-term follow-up of a randomised, international phase 3 trial of the German Hodgkin Study Group (GHSG HD14). Lancet Haematol 8:e278, 2021. Herrera AF et al: Nivolumab+AVD in advanced-stage classic Hodg kin's lymphoma. N Engl J Med 391:1379, 2024. Moskowitz CH et al: Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood 132:2639, 2018. Rashidi A et al: Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: A systemic review and meta-analysis. Bone Marrow Transplant 51:521, 2016. Straus DJ et al: CALGB 50604: Risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood 132: 1013, 2018. Ayalew Tefferi, Dan L.

Less Common Lymphoid

and Myeloid Malignancies The most common lymphoid malignancies are discussed in Chaps. 111, 112, 113, 114, and 116, myeloid leukemias in Chaps. 109 and 110, myelodysplastic syndromes (MDS) in Chap. 107, and myelopro liferative syndromes in Chap. 108. This chapter will focus on the more unusual forms of hematologic malignancy. The diseases discussed here are listed in Table 115-1. Each of these entities accounts for <1% of hematologic neoplasms. RARE LYMPHOID MALIGNANCIES All the lymphoid tumors discussed here are mature B-cell or T-cell natural killer (NK) cell neoplasms.

TABLE 115-1 Unusual Lymphoid and Myeloid Malignanciesa Lymphoid Mature B-cell neoplasms B-cell prolymphocytic leukemia Splenic marginal zone lymphoma Hairy cell leukemia Nodal marginal zone B-cell lymphoma Mediastinal large B-cell lymphoma Intravascular large B-cell lymphoma Primary effusion lymphoma Lymphomatoid granulomatosis Mature T-cell and natural killer (NK) cell neoplasms T-cell prolymphocytic leukemia T-cell large granular lymphocytic leukemia Aggressive NK cell leukemia Extranodal NK/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Hepatosplenic T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma Blastic NK cell lymphoma PART 4 Oncology and Hematology Primary cutaneous CD30+ T-cell lymphoma Angioimmunoblastic T-cell lymphoma Myeloid Chronic neutrophilic leukemia Chronic eosinophilic leukemia/hypereosinophilic syndrome Histiocytic and Dendritic Cell Neoplasms Histiocytic sarcoma Langerhans cell histiocytosis Langerhans cell sarcoma Interdigitating dendritic cell sarcoma Follicular dendritic cell sarcoma Mast cells Mastocytosis Cutaneous mastocytosis Systemic mastocytosis Mast cell sarcoma Extracutaneous mastocytoma aThis list is not exhaustive. Many named entities are very rare and not discussed here. A complete listing is available in the online version of this chapter. ■ ■MATURE B-CELL NEOPLASMS B-Cell Prolymphocytic Leukemia (B-PLL) This is a malig nancy of medium-sized (about twice the size of a normal small lym phocyte), round lymphocytes with a prominent nucleolus and light blue cytoplasm on Wright’s stain. It predominantly affects the blood, bone marrow (BM), and spleen and usually does not cause adenopa thy. The median age of affected patients is 70 years, and men are more often affected than women (male-to-female ratio is 1.6). This entity is distinct from chronic lymphoid leukemia (CLL) and does not develop as a consequence of that disease. Clinical presentation is generally from symptoms of splenomegaly or incidental detection of an elevated white blood cell (WBC) count. The clinical course can be rapid. The cells express surface IgM (with or without IgD) and typical B-cell markers (CD19, CD20, CD22). CD23 is absent, and about one-third of cases express CD5. The CD5 expres sion along with the presence of the t(11;14) translocation in 20% of cases leads to confusion in distinguishing B-PLL from the leukemic form of mantle cell lymphoma. No reliable criteria for the distinction have emerged, and gene expression studies suggest a close relationship between mantle cell lymphoma and B-PLL and significant differences

with CLL. About half of patients have mutation or loss of p53, and deletions have been noted in 11q23 and 13q14. Nucleoside analogues like fludarabine and cladribine and combination chemotherapy (cyclo phosphamide, doxorubicin, vincristine, and prednisone [CHOP]) have produced responses. CHOP plus rituximab may be more effective than CHOP alone, but the disease is sufficiently rare that large series have not been reported. Splenectomy can produce palliation of

symptoms but appears to have little or no impact on the course of the disease. BM transplantation may be curative. Imatinib may also have activity. Splenic Marginal Zone Lymphoma (SMZL) This tumor of mainly small lymphocytes originates in the marginal zone of the spleen white pulp, grows to efface the germinal centers and mantle, and invades the red pulp. Splenic hilar nodes, BM, and peripheral blood (PB) may be involved. The circulating tumor cells have short surface villi and are called villous lymphocytes. Table 115-2 shows differences in tumor cells of a number of neoplasms of small lymphocytes that aid in the differential diagnosis. SMZL cells express surface immunoglobu lin and CD20 but are negative for CD5, CD10, CD43, and CD103. Lack of CD5 distinguishes SMZL from CLL, and lack of CD103 separates SMZL from hairy cell leukemia. The median age of patients with SMZL is mid-fifties, and men and women are equally represented. Patients present with incidental or symptomatic splenomegaly or incidental detection of lymphocytosis in the PB with villous lymphocytes. Autoimmune anemia or throm bocytopenia may be present. The immunoglobulin produced by these cells contains somatic mutations that reflect transit through a germinal center, and ongoing mutations suggest that the mutation machinery has remained active. About 40% of patients have either deletions or translocations involving 7q21, the site of the FLNC gene (filamin Cγ, involved in cross-linking actin filaments in the cytoplasm). NOTCH2 mutations are seen in 25% of patients. Chromosome 8p deletions may also be noted. The genetic lesions typically found in extranodal mar ginal zone lymphomas (e.g., trisomy 3 and t[11;18]) are uncommon in SMZL. The clinical course of disease is generally indolent with median sur vivals exceeding 10 years. Patients with elevated lactate dehydrogenase (LDH) levels, anemia, and hypoalbuminemia generally have a poorer prognosis. Long remissions can be seen after splenectomy. Rituximab, ibrutinib, and PI3 kinase inhibitors are also active. A small fraction of patients undergo histologic progression to diffuse large B-cell lym phoma with a concomitant change to a more aggressive natural history. Experience with combination chemotherapy in SMZL is limited. Hairy Cell Leukemia Hairy cell leukemia is a tumor of small lymphocytes with oval nuclei, abundant cytoplasm, and distinctive membrane projections (hairy cells). Patients have splenomegaly and diffuse BM involvement. While some circulating cells are noted, the clinical picture is dominated by symptoms from the enlarged spleen and pancytopenia. The mechanism of the pancytopenia is not com pletely clear and may be mediated by both inhibitory cytokines and TABLE 115-2 Immunophenotype of Tumors of Small Lymphocytes CD5 CD20 CD43 CD10 CD103 sIG CYCLIN D1 Follicular lymphoma neg pos pos pos neg pos neg Chronic lymphoid leukemia pos pos pos neg neg pos neg B-cell prolymphocytic leukemia pos pos pos neg neg pos pos Mantle cell lymphoma pos pos pos neg neg pos pos Splenic marginal zone lymphoma neg pos neg neg neg pos neg Hairy cell leukemia neg pos ? neg pos pos neg Abbreviations: neg, negative; pos, positive.

TABLE 115-3 Differential Diagnosis of “Dry Tap”—Inability to Aspirate Bone Marrow Dry taps occur in about 4% of attempts and are associated with: Metastatic carcinoma infiltration 17% Chronic myeloid leukemia 15% Myelofibrosis 14% Hairy cell leukemia 10% Acute leukemia 10% Lymphomas, Hodgkin’s disease 9% Normal marrow Rare marrow replacement. The marrow has an increased level of reticulin fibers; indeed, hairy cell leukemia is a common cause of inability to aspirate BM or so-called “dry tap” (Table 115-3). Monocytopenia is profound and may explain a predisposition to atypical mycobacte rial infection that is observed clinically. The tumor cells have strong expression of CD22, CD25, and CD103; soluble CD25 level in serum is an excellent tumor marker for disease activity. The cells also express tartrate-resistant acid phosphatase. The immunoglobulin genes are rearranged and mutated, indicating the influence of a germinal center. No specific cytogenetic abnormality has been found, but most cases contain the activating BRAF

mutation V600E. The median age of affected patients is mid-fifties, and the maleto-female ratio is 5:1. Treatment options are numerous. Splenectomy is often associated with prolonged remission. Nucleosides including cladribine and deoxycoformycin are highly active but are also associ ated with further immunosuppression and can increase the risk of certain opportunistic infections. However, after brief courses of these agents, patients usually obtain very durable remissions during which immune function spontaneously recovers. Interferon α is also an effective therapy but is not as effective as nucleosides. Chemotherapyrefractory patients have responded to vemurafenib, a BRAF inhibitor. Vemurafenib does not appear to be curative, but responses can be maintained with chronic treatment. More durable remissions occur when rituximab is added to vemurafenib. Nodal Marginal Zone B-Cell Lymphoma This rare nodebased disease bears an uncertain relationship with extranodal marginal zone lymphomas, which are often mucosa-associated and are called mucosa-associated lymphoid tissue (MALT) lymphomas, and SMZLs. Patients may have localized or generalized adenopathy. The neoplastic cell is a marginal zone B cell with monocytoid features and has been called monocytoid B-cell lymphoma in the past. Up to one-third of the patients may have extranodal involvement, and involvement of the lymph nodes can be secondary to the spread of a mucosal primary lesion. In authentic nodal primaries, the cytogenetic abnormalities associated with MALT lymphomas (trisomy 3 and t[11;18]) are very rare. The clinical course is indolent. Patients often respond to combi nation chemotherapy, although remissions have not been durable. Few patients have received CHOP plus rituximab, which is likely to be an effective approach to management. Mediastinal (Thymic) Large B-Cell Lymphoma This entity was originally considered a subset of diffuse large B-cell lymphoma; however, additional study has identified it as a distinct entity with its own characteristic clinical, genetic, and immunophenotypic features. This is a disease that can be bulky in size but usually remains confined to the mediastinum. It can be locally aggressive, including progressing to produce a superior vena cava obstruction syndrome or pericardial effusion. About one-third of patients develop pleural effusions, and in 5–10% of cases, disease can disseminate widely to kidney, adrenal, liver, skin, and even brain. The disease affects women more often than men (male-to-female ratio is 1:2–3), and the median age is 35–40 years. The tumor is composed of sheets of large cells with abundant cytoplasm accompanied by variable, but often abundant, fibrosis. It is distinguished from nodular sclerosing Hodgkin’s disease by the paucity of normal lymphoid cells and the absence of lacunar variants

of Reed-Sternberg cells. However, more than one-third of the genes that are expressed to a greater extent in primary mediastinal large B-cell lymphoma than in usual diffuse large B-cell lymphoma are also overexpressed in Hodgkin’s disease, suggesting a possible pathogenetic relationship between the two entities that affect the same anatomic site. Tumor cells may overexpress MAL. The genome of tumor cells is characterized by frequent chromosomal gains and losses. The tumor cells in mediastinal large B-cell lymphoma express CD20, but surface immunoglobulin and human leukocyte antigen (HLA) class I and class II molecules may be absent or incompletely expressed. Expression of lower levels of class II HLA identifies a subset with poorer prognosis. The cells are CD5 and CD10 negative but may show light staining with anti-CD30. The cells are CD45 positive, unlike cells of classical Hodgkin’s disease.

Methotrexate, leucovorin, doxorubicin, cyclophosphamide, vin cristine, prednisone, and bleomycin (MACOP-B) and rituximab plus CHOP are effective treatments, achieving 5-year survival of 75–87%. Dose-adjusted therapy with prednisone, etoposide, vincristine, cyclo phosphamide, and doxorubicin

(EPOCH) plus rituximab has pro duced 5-year survival of 97%. A role for mediastinal radiation therapy has not been definitively demonstrated, but it is frequently used, espe cially in patients whose mediastinal area remains positron emission tomography–avid after 4–6 cycles of chemotherapy. CHAPTER 115 Intravascular Large B-Cell Lymphoma This is an extremely rare form of diffuse large B-cell lymphoma characterized by the pres ence of lymphoma in the lumen of small vessels, particularly capillaries. It is also known as malignant angioendotheliomatosis or angiotropic large-cell lymphoma. It is sufficiently rare that no consistent picture has emerged to define a clinical syndrome or its epidemiologic and genetic features. It is thought to remain inside vessels because of a defect in adhesion molecules and homing mechanisms, an idea supported by scant data suggesting absence of expression of β-1 integrin and ICAM-1. Patients commonly present with symptoms of small-vessel occlusion, skin lesions, or neurologic symptoms. The tumor cell clusters can promote thrombus formation. A subset of patients have tumors with MYD88 or CD79B mutations. In general, the clinical course is aggres sive and the disease is poorly responsive to therapy. Often a diagnosis is not made until very late in the course of the disease or at autopsy. Diagnosis may be revealed in random skin biopsies in settings where localized findings are limited. Less Common Lymphoid and Myeloid Malignancies Primary Effusion Lymphoma This entity is another variant of diffuse large B-cell lymphoma that presents with pleural effusions, usually without apparent tumor mass lesions. It is most common in the setting of immune deficiency disease, especially AIDS, and is caused by human herpes virus 8 (HHV-8)/Kaposi’s sarcoma herpes virus (KSHV). It is also known as body cavity–based lymphoma. Some patients have been previously diagnosed with Kaposi’s sarcoma. It can also occur in the absence of immunodeficiency in elderly men of Medi terranean heritage, similar to Kaposi’s sarcoma but even less common. The malignant effusions contain cells positive for HHV-8/KSHV, and many are also co-infected with Epstein-Barr virus. The cells are large with large nuclei and prominent nucleoli that can be con fused with Reed-Sternberg cells. The cells express CD20 and CD79a (immunoglobulin-signaling molecule), although they often do not express immunoglobulin. Some cases aberrantly express T-cell mark ers such as CD3 or rearranged T-cell receptor genes. No characteristic genetic lesions have been reported, but gains in chromosome 12 and X material have been seen, similar to other HIV-associated lymphomas. The clinical course is generally characterized by rapid progression and death within 6 months. CHOP plus lenalidomide or bortezomib may produce responses. Highly active antiretroviral therapy for HIV should be maintained during treatment. Lymphomatoid Granulomatosis This is an angiocentric, angiodestructive lymphoproliferative disease comprised by neoplas tic Epstein-Barr virus–infected monoclonal B cells accompanied and outnumbered by a polyclonal reactive T-cell infiltrate. The disease is graded based on histologic features such as cell number and atypia in

the B cells. It is most often confused with extranodal NK/T-cell lym phoma, nasal type, which can also be angiodestructive and is EpsteinBarr virus–related. The disease usually presents in adults (males >

females) as a pulmonary infiltrate. Involvement is often entirely extra nodal and can include kidney (32%), liver (29%), skin (25%), and brain (25%). The disease often but not always occurs in the setting of immune deficiency.

The disease can be remitting and relapsing in nature or can be rap idly progressive. The course is usually predicted by the histologic grade. The disease is highly responsive to combination

chemotherapy and is curable in most cases. Some investigators have claimed that low-grade disease (grade I and II) can be treated with interferon α. ■ ■MATURE T-CELL AND NK CELL NEOPLASMS T-Cell Prolymphocytic Leukemia This is an aggressive leu kemia of medium-sized prolymphocytes involving the blood, mar row, nodes, liver, spleen, and skin. It accounts for 1–2% of all small lymphocytic leukemias. Most patients present with elevated WBC count (often >100,000/μL), hepatosplenomegaly, and adenopathy. Skin involvement occurs in 20%. The diagnosis is made from PB smear, which shows cells about 25% larger than those in small lymphocytes, with cytoplasmic blebs and nuclei that may be indented. The cells express T-cell markers like CD2, CD3, and CD7; two-thirds of patients have cells that are CD4+ and CD8–, and 25% have cells that are CD4+ and CD8+. T-cell receptor β chains are clonally rearranged. In 80% of patients, inversion of chromosome 14 occurs between q11 and q32. Ten percent have t(14;14) translocations that bring the T-cell receptor alpha/beta gene locus into juxtaposition with oncogenes TCL1 and TCL1b at 14q32.1. Chromosome 8 abnormalities are also common. Deletions in the ATM gene are also noted. Activating JAK3 mutations have also been reported. PART 4 Oncology and Hematology The course of the disease is generally rapid, with median survival of about 12 months. Responses have been seen with the anti-CD52 anti body alemtuzumab, nucleoside analogues, and CHOP chemotherapy. Histone deacetylase inhibitors like vorinostat and romidepsin may also have activity. Small numbers of patients with T-cell prolymphocytic leukemia have also been treated with high-dose therapy, and allogeneic BM transplantation after remission has been achieved with alemtu zumab or conventional-dose therapy. T-Cell Large Granular Lymphocytic Leukemia T-cell large granular lymphocytic (LGL) leukemia is characterized by increases in the number of LGLs in the PB (2000–20,000/μL) often accompanied by severe neutropenia, with or without concomitant anemia. Pure red cell aplasia may occur in 15–20% of patients. Splenomegaly is seen in 25% of patients; adenopathy is generally absent. B symptoms are rare, but 20–30% of patients may have infections related to the severe neutropenia. Patients may have splenomegaly and frequently have evi dence of systemic autoimmune disease, including rheumatoid arthritis, hypergammaglobulinemia, autoantibodies, and circulating immune complexes. BM involvement is mainly interstitial in pattern, with <50% lymphocytes on differential count. Usually the cells express CD3, T-cell receptors, usually TCRα/β, and CD8; NK-like variants may be CD3–. Like other T-cell neoplasms, loss of expression of CD5 and/or CD7 is common. The leukemic cells often express Fas and Fas ligand. The JAK/STAT pathway is often activated. The course of the disease is generally indolent and dominated by the neutropenia. Paradoxically, immunosuppressive therapy with cyclo sporine, methotrexate, or cyclophosphamide plus glucocorticoids can produce an increase in granulocyte counts. Nucleosides have been used anecdotally. Occasionally the disease can accelerate to a more aggres sive clinical course. Aggressive NK Cell Leukemia NK neoplasms are very rare, and they may follow a range of clinical courses from very indolent to highly aggressive. They are more common in Asians than whites, and the cells frequently harbor a clonal Epstein-Barr virus episome. The PB white count is usually not greatly elevated, but abnormal large lymphoid cells with granular cytoplasm are noted. The aggressive form

is characterized by symptoms of fever and laboratory abnormalities of pancytopenia. Hepatosplenomegaly is common; node involvement is less common. Patients may have hemophagocytosis, coagulopathy, or multiorgan failure. Serum levels of Fas ligand are elevated. The cells express CD2 and CD56 and do not have rearranged T-cell receptor genes. Deletions involving chromosome 6 are common. The disease can be rapidly progressive. Some forms of NK

neoplasms are more indolent. They tend to be discovered incidentally with LGL lymphocytosis and do not manifest the fever and hepatosplenomegaly characteristic of the aggressive leukemia. The cells are also CD2 and CD56 positive, but they do not contain clonal forms of Epstein-Barr virus and are not accompanied by pancytopenia or autoimmune disease. Extranodal NK/T-Cell Lymphoma, Nasal Type Like lym phomatoid granulomatosis, extranodal NK/T-cell lymphoma tends to be an angiocentric and angiodestructive lesion, but the malignant cells are not B cells. In most cases, they are CD56+ Epstein-Barr virus–infected cells; occasionally, they are CD56–Epstein-Barr virus–infected cytotoxic T cells. They are most commonly found in the nasal cavity. Historically, this illness was called lethal midline granuloma, polymorphic reticulosis, and angiocentric immunoproliferative lesion. This form of lymphoma is prevalent in Asia, Mexico, and Central and South America; it affects males more commonly than females. When it spreads beyond the nasal cavity, it may affect soft tissue, the gastro intestinal tract, or the testis. In some cases, hemophagocytic syndrome (HPS) may influence the clinical picture. Patients may have B symp toms. Many of the systemic manifestations of disease are related to the production of cytokines by the tumor cells and the cells responding to their signals. Deletions and inversions of chromosome 6 are common. Many patients with extranodal NK/T-cell lymphoma, nasal type, have excellent antitumor responses with combination chemotherapy regimens, particularly those with localized disease. Radiation therapy is often used after completion of chemotherapy. Four risk factors have been defined, including B symptoms, advanced stage, elevated LDH, and regional lymph node involvement. Patient survival is linked to the number of risk factors: 5-year survival is 81% for zero risk factors, 64% for one risk factor, 32% for two risk factors, and 7% for three or four risk factors. Combination regimens without anthracyclines have been touted as superior to CHOP, but data are sparse. High-dose therapy with stem cell transplantation has been used, but its role is unclear. Enteropathy-Type T-Cell Lymphoma Enteropathy-type T-cell lymphoma is a rare complication of longstanding celiac disease. It most commonly occurs in the jejunum or the ileum. In adults, the lymphoma may be diagnosed at the same time as celiac disease, but the suspicion is that the celiac disease was a longstanding precursor to the develop ment of lymphoma. The tumor usually presents as multiple ulcerating mucosal masses but may also produce a dominant exophytic mass or multiple ulcerations. The tumor expresses CD3 and CD7 nearly always and may or may not express CD8. The tumor may express CD30, but therapies directed at CD30 have not been adequately tested. The normal-appearing lymphocytes in the adjacent mucosa often have a similar phenotype to the tumor. Most patients have the HLA genotype associated with celiac disease, HLA DQA1∗0501 or DQB1∗0201. The prognosis of this form of lymphoma is typically poor (median survival is 7–11 months), but some patients have a good response to CHOP chemotherapy. Patients who respond can develop bowel per foration from responding tumor. If the tumor responds to treatment, recurrence may develop elsewhere in the celiac disease–affected small bowel. An indolent form of T-cell or NK cell lymphoma occurs rarely that affects mainly the small intestine and presents with dyspepsia, vomit ing, and diarrhea. The cells often contain genetic changes that result in JAK-STAT activation. The disease is most often chronic with little or no propensity to spread and develop aggressive growth. A variety of approaches have been tested; none are reliably curative. Hepatosplenic T-Cell Lymphoma Hepatosplenic T-cell lym phoma is a malignancy derived from T cells expressing the gamma/delta

T-cell antigen receptor that affects mainly the liver and fills the sinu soids with medium-size lymphoid cells. When the spleen is involved, dominantly the red pulp is infiltrated. It is a disease of young people, especially young people with an underlying immunodeficiency or with an

autoimmune disease that demands immunosuppressive therapy. The use of thiopurine and infliximab is particularly common in the history of patients with this disease. The cells are CD3+ and usually CD4– and CD8–. The cells may contain isochromosome 7q, often together with trisomy 8. The lymphoma has an aggressive natural history. Combination chemotherapy may induce remissions, but most patients relapse. Cytarabine/etoposide/platinum-based regimens appear more effective than CHOP-based regimens. Median survival is about 2 years. The tumor does not appear to respond to reversal of immunosuppressive therapy. Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma involves multiple subcutaneous collections of neoplastic T cells that are usually cytotoxic cells in phenotype (i.e., contain perforin and granzyme B and express CD3 and CD8). The rearranged T-cell receptor is usually alpha/betaderived, but occasionally, the gamma/delta receptors are involved, par ticularly in the setting of immunosuppression. The cells are negative for Epstein-Barr virus. A history of autoimmune disease, particularly lupus erythematosus, in the patient or the family is present in almost one-third of patients. Patients may have an HPS in addition to the skin infiltration; fever and hepatosplenomegaly may also be present. Nodes are generally not involved. Patients frequently respond to combination chemotherapy, including CHOP. When the disease is progressive, the HPS can be a component of a fulminant downhill course. Effective therapy can reverse the HPS. Blastic NK Cell Lymphoma The neoplastic cells express NK cell markers, especially CD56, and are CD3 negative. They are large blasticappearing cells and may produce a leukemia picture, but the dominant site of involvement is the skin. Morphologically, the cells are similar to the neoplastic cells in acute lymphoid and myeloid leukemia. No characteristic chromosomal abnormalities have been described. The clinical course is rapid, and the disease is largely unresponsive to typi cal lymphoma treatments. Primary Cutaneous CD30+ T-Cell Lymphoma This tumor involves the skin and is composed of cells that appear similar to the cells of anaplastic T-cell lymphoma. Among cutaneous T-cell tumors, ~25% are CD30+ anaplastic lymphomas. If dissemination to lymph nodes occurs, it is difficult to distinguish between the cutaneous and systemic forms of the disease. The tumor cells are often CD4+, and the cells contain granules that are positive for granzyme B and perforin in 70% of cases. The typical t(2;5) of anaplastic T-cell lymphoma is absent; indeed, its presence should prompt a closer look for systemic involvement and a switch to a diagnosis of anaplastic T-cell lymphoma. This form of lymphoma has sporadically been noted as a rare com plication of silicone or saline breast implants. The natural history of breast implant–associated lymphoma is generally indolent. Cutaneous CD30+ T-cell lymphoma often responds to therapy. The anti-CD30 immunotoxin conjugate brentuximab vedotin is active. Radiation therapy can be effective, and surgery can also produce long-term dis ease control. Five-year survival exceeds 90%. Angioimmunoblastic T-Cell Lymphoma Angioimmunoblastic T-cell lymphoma is a systemic disease that accounts for ~15% of all T-cell lymphomas. Patients frequently have fever, advanced stage, dif fuse adenopathy, hepatosplenomegaly, skin rash, polyclonal hypergam maglobulinemia, and a wide range of autoantibodies including cold agglutinins, rheumatoid factor, and circulating immune complexes. Patients may have edema, arthritis, pleural effusions, and ascites. The nodes contain a polymorphous infiltrate of neoplastic T cells and non neoplastic inflammatory cells together with proliferation of high endo thelial venules and follicular dendritic cells (FDCs). The most common chromosomal abnormalities are trisomy 3, trisomy 5, and an extra X chromosome. Aggressive combination chemotherapy can induce

regressions. The underlying immune defects make conventional lym phoma treatments more likely to produce infectious complications.

RARE MYELOID MALIGNANCIES The World Health Organization (WHO) and the International Consensus Classification (ICC) systems use PB counts, PB smear analysis, BM mor phology, and cytogenetic and molecular genetic tests in order to classify myeloid malignancies into several major categories (Table 115-4). Among them, acute myeloid leukemia (AML) and AML-related disorders are discussed in Chap. 109, MDS and MDS/AML in Chap. 107, chronic myeloid leukemia (CML) in Chap. 110, and JAK2 mutation–prevalent myeloproliferative neoplasms (MPN), including essential thrombocy themia, polycythemia vera, and primary myelofibrosis, in Chap. 108. In this chapter, we focus on some of the remaining myeloid neoplasms listed in Table 115-4, which are less frequent: (1) other MPNs includ ing chronic neutrophilic leukemia (CNL), chronic eosinophilic leu kemia, not otherwise specified (CEL-NOS), and MPN, unclassifiable (MPN-U); (2) MDS/MPN overlap including chronic myelomonocytic leukemia (CMML), atypical CML (aCML), MDS/MPN with mutated SF3B1 and thrombocytosis, MDS/MPN with ring sideroblasts and thrombocytosis, not otherwise specified (MDS/MPN-RS-T-NOS), and MDS/MPN, not otherwise specified (MDS/MPN-NOS); (3) juvenile myelomonocytic leukemia (JMML); (4) transient myeloproliferative disorder (TMD); (5) hypereosinophilia including those associated with tyrosine kinase gene fusions (TKGFs) and hypereosinophilic syn drome (HES); (6) mastocytosis; and (7) histiocytic and dendritic cell neoplasms (hemophagocytic lymphohistiocytosis [HLH] is discussed in Chap. 68). CHAPTER 115 Less Common Lymphoid and Myeloid Malignancies ■ ■CHRONIC NEUTROPHILIC LEUKEMIA CNL is a clonal proliferation of mature neutrophils with few or no circulating immature granulocytes. Other clinical features include hepatosplenomegaly and constitutional symptoms. The disease is molecularly characterized by activating mutations of the gene (CSF3R) encoding for the receptor for granulocyte colony-stimulating factor (G-CSF), also known as colony-stimulating factor 3 (CSF3). Patients with CNL might be asymptomatic at presentation but can also display constitutional symptoms, splenomegaly, anemia, and thrombocytope nia. A population-based study suggested an overall incidence of 0.1 cases/million individuals, using combined Surveillance, Epidemiology, and End Results and National Cancer Database data. CNL typically presents in elderly patients with a median age at diagnosis of 66.5 years (range, 15–86 years) and slight male preponderance (56–58% of cases). Median survival is ~2 years, and causes of death include transforma tion to acute leukemia, progressive disease associated with severe cyto penias, and marked treatment-refractory leukocytosis. CSF3 is the main growth factor for granulocyte proliferation and differentiation. Accordingly, recombinant CSF3 is used for the treat ment of severe neutropenia, including severe congenital neutropenia (SCN). Some patients with SCN acquire CSF3R mutations, and the frequency of such mutations is significantly higher (~80%) in patients who experience leukemic transformation. SCN-associated CSF3R mutations occur in the region of the gene coding for the cytoplasmic domain of CSF3R and result in truncation of the C-terminal–negative regulatory domain. In 2013, Maxson et al described a different class of CSF3R mutations in ~90% of patients with CNL; these were mostly membrane proximal, the most frequent being a C-to-T substitution at nucleotide 1853 (T618I). In a subsequent confirmatory study, CSF3R mutations were found to be specific to WHO-defined CNL. About 40% of the T618I-mutated cases also harbored SETBP1 mutations. CSF3R T618I has been shown to induce lethal myeloproliferative disorder in a mouse model and to have in vitro sensitivity to JAK inhibition. Diagnosis of CNL requires exclusion of the more common causes of neutrophilia including infections and inflammatory processes (Table 115-5). In addition, one should be mindful of the association between some forms of metastatic cancer

or plasma cell neoplasms with secondary neutrophilia. Neoplastic neutrophilia also occurs in other myeloid malignancies, which should be excluded during the

TABLE 115-4 International Consensus Classification of Myeloid Neoplasms 6. Acute myeloid leukemia (AML) a. AML diagnosis requiring ≥10% bone marrow (BM) or peripheral blood (PB) blasts

i. Acute promyelocytic leukemia

ii. Core binding factor AML

iii. AML with KMT2A rearrangement

iv. AML with DEK::NUP214

v. AML with MECOM rearrangements

vi. AML with NPM1 mutation

vii. AML with in-frame bZIP CEBPA mutations

viii. AML with other rare recurring translocations

ix. Myelodysplastic syndrome (MDS)/AML with TP53 mutations

x. MDS/AML with myelodysplasia-related mutations

xi. MDS/AML with myelodysplasia-related karyotype

xii. MDS/AML not otherwise specified (NOS) b. AML diagnosis requiring ≥20% BM or PB blasts

i. AML with t(9;22)-BCR::ABL1

ii. AML with TP53 mutations, other than pure erythroid leukemia

iii. AML with myelodysplasia-related gene mutations

iv. AML with myelodysplasia-related karyotype

v. AML NOS 7. AML-related disorders PART 4 Oncology and Hematology a. Pure erythroid leukemia (PEL; TP53 mutated) b. Myeloid sarcoma c. Blastic plasmacytoid dendritic cell neoplasm d. Acute leukemia of ambiguous lineage e. Acute undifferentiated leukemia f. Mixed phenotype acute leukemia 8. Myelodysplastic syndromes (MDS) a. MDS with mutated TP53 b. MDS with excess blasts (5–9% BM or 2–9% PB) c. MDS without excess blasts (<5% BM and <2% PB)

i. MDS with del(5q) [isolated or accompanied by only one other cytogenetic abnormality other than 7/del(7q); no multi-hit TP53]

ii. MDS with SF3B1 [variant allele frequency ≥10%/no RUNX1 or multi-hit TP53; no del(5q), –7/del(7q), complex karyotype, or abnormal 3q26.2]

iii. MDS, NOS–single-lineage dysplasia

iv. MDS, NOS–multilineage dysplasia

v. MDS, NOS without dysplasia 9. MDS/AML a. MDS/AML (BM/PB blasts 10–19%) b. MDS/AML with mutated TP53 10. Myeloproliferative neoplasms (MPN) a. Chronic myeloid leukemia b. Polycythemia vera c. Essential thrombocythemia d. Primary myelofibrosis (PMF)

i. Early/prefibrotic PMF

ii. Overt PMF e. MPN, unclassifiable (MPN-U) f. Chronic neutrophilic leukemia g. Chronic eosinophilic leukemia, NOS 11. MDS/MPN a. Chronic myelomonocytic leukemia (CMML) (≥0.5 × 109/L absolute and ≥10% PB monocytes)

i. CMML-1 (<10% BM and <5% PB blasts)

ii. CMML-2 (10–19% BM or 5–19% PB blasts) b. Atypical chronic myeloid leukemia c. MDS/MPN with mutated SF3B1 and thrombocytosis d. MDS/MPN with ring sideroblasts and thrombocytosis, NOS e. MDS/MPN, NOS

i. MDS/MPN with isolated isochromosome (17q) 12. Eosinophilic disorders 13. Mastocytosis 14. Hematologic neoplasms with germline predisposition 15. Pediatric myeloid malignancies 16. Premalignant clonal hematopoiesis

diagnostic workup (Table 115-5). Accordingly, the ICC diagnostic crite ria for CNL are designed to exclude the possibilities of both secondary/

reactive neutrophilia and leukocytosis associated with myeloid malig nancies other than CNL (Table 115-5). The discovery of CSF3R mutations (see above) and their almost invariable association with ICC-defined CNL has allowed its incorporation in the ICC diagnostic criteria (Table 115-5). In general, the presence of a membrane proxi mal CSF3R mutation in a patient with predominantly neutrophilic granulocytosis should be sufficient for the diagnosis of CNL, regard less of the degree of leukocytosis. Unfortunately, several exclusionary criteria still need to be met for diagnosing CNL in the absence of CSF3R mutations (Table 115-5). Current treatment in CNL is largely palliative and suboptimal in its efficacy. Several drugs alone or in combination have been tried, and none have shown remarkable efficacy. As such, allogeneic hema topoietic stem cell transplant (ASCT) is reasonable to consider in the presence of symptomatic disease, especially in younger patients. Oth erwise, cytoreductive therapy with hydroxyurea is probably as good as anything, and a more intensive combination chemotherapy may not have additional value. However, response to hydroxyurea therapy is often transient, and some have successfully used interferon α as an alternative drug. JAK inhibitor therapy has emerged as an additional therapeutic option but is not necessarily superior to hydroxyurea (estimated response rate of 30%). It is thus recommended that CNL patients first and foremost be evaluated for eligibility and disposition for ASCT, with the remaining therapeutic agents being aimed at con trolling myeloproliferation (targeting leukocytes

<25–30 × 109/L) and alleviating symptoms. ■ ■CHRONIC EOSINOPHILIC LEUKEMIA, NOT OTHERWISE SPECIFIED In a Mayo Clinic survey of 1416 patients with PB eosinophilia evalu ated between 2008 and 2019, 17 patients (1.2%) fulfilled the ICC crite ria for CEL-NOS (Table 115-5); median age was 63 years, with the vast majority of patients (88%) presenting with systemic symptoms. Organ involvement was a prominent feature including spleen, cardiac, pulmo nary, and distal esophagus. Laboratory abnormalities included anemia, leukocytosis, and eosinophilia (median eosinophil count of 6.4 × 109/L; range, 2.0–53.1 × 109/L). The most common bone marrow abnormali ties included abnormal eosinophils, abnormal and increased mega karyocytes, and fibrosis (18%). Cytogenetic abnormalities occurred in 88% of patients and included trisomy 8, complex karyotype, 13q–, 20q–, and chromosome 1 abnormalities. All seven patients with next-generation sequencing studies harbored one or more mutations including ASXL1 (43%) and IDH1 (29%). Half of patients treated with hydroxyurea-based regimens responded with a persistent decline in eosinophil count for a median duration of 18 months. One-third of patients treated with prednisone responded, with a median duration of response at 13 months. Three patients were treated with imatinib, of whom two had normalization of eosinophil count. At a median follow-up of 13 months, nine patients had died, including three who underwent leukemic transformation. ■ ■MYELOPROLIFERATIVE NEOPLASM, UNCLASSIFIABLE The category of MPN-U includes MPN-like neoplasms that cannot be clearly classified as one of the other subcategories of MPN listed in Table 115-1. Examples include patients presenting with unusual thrombosis or unexplained organomegaly with normal blood counts but found to carry MPN-characteristic mutations such as JAK2 and CALR or display bone marrow morphology that is consistent with MPN. It is possible that some cases of MPN-U represent earlier disease stages in polycythemia vera (PV) or essential thrombocythemia (ET), which, however, fail to meet the threshold hemoglobin levels or platelet counts that are required per WHO diagnostic criteria. Specific treat ment interventions might not be necessary in asymptomatic patients with MPN-U, whereas patients with arterial thrombotic complications might require cytoreductive and aspirin therapy and those with venous thrombosis might require systemic anticoagulation.

TABLE 115-5 International Consensus Classification (ICC) Diagnostic Criteria for Chronic Neutrophilic Leukemia (CNL), Atypical Chronic Myeloid Leukemia (aCML), and Chronic Myelomonocytic Leukemia (CMML) VARIABLES CNLa aCML CMML PB leukocyte count ≥13 × 109/Ld ≥13 × 109/L PB segmented neutrophils/bands ≥80% PB neutrophil precursorsb <10% ≥10% PB blasts Usually absente <20% <20% PB monocyte count <10% of leukocytes No or minimal monocytosis ≥0.5 × 109/Lg Cytopeniah Yes Yes Dysgranulopoiesis Yes PB basophil/eosinophil percentage <10% PB monocyte percentage <10% ≥10% BM Hypercellular ↑ Neutrophils, number and % <5% blasts Normal neutrophilic maturation BCR-ABL1 No No No Tyrosine kinase gene fusionsf No No No CSF3R T618I or other activating CSF3R mutation or persistent neutrophilia, splenomegaly, no identifiable cause of reactive neutrophilia,c if plasma cell neoplasm is present, need demonstration of clonality of myeloid cells by cytogenetic or molecular studies Yes PB and BM blasts/promonocytes <20% <20% Evidence for other MPN: CML, PV, ET, PMF No No No Evidence for reactive leukocytosis or monocytosis No No No aDiagnosis requires meeting all criteria. bNeutrophil precursors include myeloblasts, promyelocytes, myelocytes, and metamyelocytes. cCauses of reactive neutrophilia include plasma cell neoplasms, solid tumor, infections, and inflammatory processes. d≥25 × 109/L in cases lacking CSF3R T618I or another activating CSF3R mutation. e10–19% blasts constitute accelerated phase and ≥20% blast phase. fTyrosine kinase gene fusions involve PDGFRA, PDGFRB, FGFR1, ABL1, JAK2, and FLT3. gPB

monocytes ≥1 × 109/L in cases without evidence of clonality; the latter is signified by abnormal karyotype or a myeloid neoplasm associated mutation with ≥10% variant allele frequency. hHemoglobin <12 g/dL in females and <13 g/dL in males, absolute neutrophil count <1.8 × 109/L, and/or platelets <150 × 109/L, that is not explained by another condition. Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; PB, peripheral blood; PMF, primary myelofibrosis; PV, polycythemia vera. ■ ■CHRONIC MYELOMONOCYTIC LEUKEMIA CMML is classified under the ICC category of MDS/MPN neoplasms and is defined by sustained (>3 months) PB monocytosis (≥0.5 × 109/L; monocytes ≥10% of leukocyte count), consistent BM morphology, <20% BM or PB blasts (including promonocytes), and cytogenetic or molecular evidence of clonality. The median age at CMML diagno sis is ~73–75 years, with a male preponderance (1.5–3:1). The exact incidence of CMML remains unknown but is estimated at 4 cases per 100,000 persons per year. Clinical presentation is variable and depends on whether the disease presents with MDS-like (MDS-CMML) or MPN-like (MP-CMML) phenotype, based on the presence or absence of leukocyte count of ≥13 × 109/L; the former is associated with cyto penias and the latter with splenomegaly and features of myeloprolif eration such as fatigue, night sweats, weight loss, and cachexia. About 20% of patients with CMML experience unique symptoms including systemic inflammatory syndromes (e.g., arthritis, pericardial effusion, pleural effusion, ascites), autoimmune diseases, leukemia cutis, and lysozyme-induced nephropathy. During the diagnostic workup of CMML, it is important to first exclude reactive causes of monocytosis, including tuberculosis, fungal infections, subacute bacterial endocarditis, viral and protozoal infec tions, connective tissue diseases, sarcoidosis, lipid storage disorders, postsplenectomy state, and the recovery phase of an acute infection or BM regeneration after chemotherapy. Other myeloid neoplasms in the differential diagnosis include CML (BCR::ABL1-defined) and other fusion gene-associated entities including those with rearrangements of PDGFRA, PDGFRB, FGFR1, JAK2, FLT3, and ABL1. Similarly, it

Persistent and lasting for at least 3 months Hypercellular ↑ Granulocyte proliferation Granulocytic dysplasia ± erythroid/megakaryocyte Dysplasia <20% blasts Hypercellular due to myeloproliferation and increased monocytes and lacking diagnostic features of AML, MPN, or other conditions associated with monocytosis CHAPTER 115 Less Common Lymphoid and Myeloid Malignancies should be noted that monocytosis can be associated with MPN such as primary myelofibrosis (PMF) and PV, where its presence adversely impacts survival. BM examination often shows morphologic dysplasia in at least one hematopoietic lineage and granulocytic and monocytic proliferation. On immunophenotyping, the abnormal cells often express myelomonocytic antigens such as CD13 and CD33, with variable expression of CD14, CD64, CD68, and CD163. Monocyticderived cells are almost always positive for the cytochemical non specific esterases (e.g., butyrate esterase), while normal granulocytic precursors are positive for lysozyme and chloroacetate esterase. In CMML, it is common to have a hybrid cytochemical staining pattern with cells expressing both chloroacetate and butyrate esterases simul taneously (dual esterase staining). Based on flow cytometric expression of CD14/CD16, monocytes can be classified into classical MO1 (CD14+/CD16–), intermediate MO2 (CD14+/CD16+), and nonclassical MO3 (CD14−/CD16+) frac tions, with MO1 constituting the major monocyte population (85%) in healthy conditions. CMML patients have a characteristic increase in classical monocytes, distinguishing CMML from other causes of reactive and clonal monocytosis. Almost all patients with CMML har bor somatic mutations that are neither specific nor disease-defining, including (1) mutations in

epigenetic control of transcription, such as histone modification (EZH2, ASXL1, UTX), and DNA methylation (TET2, DNMT3A, IDH1, IDH2); (2) mutations in the spliceosome machinery (SF3B1, SRSF2, U2AF1, ZRSR2, PRPF8); (3) mutations in genes that regulate cell signaling (JAK2, KRAS, NRAS, CBL, PTPN11, NF1, FLT3); (4) mutations in transcription factors and nucleosome

assembly regulators (RUNX1, GATA2, SETBP1); and (5) mutations in DNA damage response genes such as TP53 and PHF6. Of these, those involving TET2 (~60%), SRSF2 (~50%), ASXL1 (~40%), and the oncogenic RAS pathway (~30%) are the most frequent, with only frameshift and nonsense ASXL1 mutations consistently and indepen dently adversely impacting survival. Clonal cytogenetic abnormalities are seen in about a third of patients with CMML and include trisomy 8 and abnormalities of chromosome 7.

Several risk models serve similar purposes in identifying high-risk patients who are considered for ASCT earlier than later. Risk factors in the Mayo Molecular Model (MMM) include presence of truncating ASXL1 mutations, absolute monocyte count >10 × 109/L, hemoglobin <10 g/dL, platelet count <100 × 109/L, and the presence of circulating immature myeloid cells. The resulting four-tiered risk categorization includes high (three or more risk factors), intermediate-2 (two risk factors), intermediate-1 (one risk factor), and low (no risk factors); the corresponding median survivals are 16, 31, 59, and 97 months, respectively. ASCT is the only treatment modality that secures cure or long-term survival and is appropriate for MMM high/intermediate-2 risk disease. In one of the largest retrospective cohorts involving 513 CMML patients (median age, 53 years), the European Group for Blood and Marrow Transplantation reported a 4-year relapse-free survival rate of 27% and an overall survival rate of 33%. At present, for younger patients with higher risk disease and an acceptable comorbidity index, ASCT is the preferred treatment modality. Drug therapy is currently not disease-modifying and includes hydroxyurea and hypomethylat ing agents; a phase 3 study (DAKOTA) comparing hydroxyurea and decitabine in high-risk MP-CMML showed similar overall survival at 23.1 versus 18.4 months, respectively, despite response rates being higher for decitabine (56 vs 31%). PART 4 Oncology and Hematology ■ ■ATYPICAL CHRONIC MYELOID LEUKEMIA aCML is formally classified under the MDS/MPN category of myeloid malignancies and is characterized by left-shifted granulocytosis and dysgranulopoiesis. Diagnostic criteria are listed in Table 115-2 and include leukocyte count of ≥13 × 109/L, dysgranulopoiesis, cytopenia, ≥10% immature granulocytes, <20% PB or BM myeloblasts, <10% PB monocytes, <10% PB eosinophilia, absence of otherwise specific mutations such as BCR::ABL1 or TKGFs (involving PDGFRA, PDG FRB, FGFR1, JAK2, ABL1, or FLT3; Table 115-6), and not meeting WHO criteria for CML, PMF, PV, or ET. The BM in aCML is hyper cellular with granulocyte proliferation and dysplasia with or without erythroid or megakaryocytic dysplasia. The differential diagnosis of aCML includes CML, which is distinguished by the presence of BCR::ABL1; CNL, which is distinguished by the absence of dysgranu lopoiesis and presence of CSF3R mutations; and CMML, which is distinguished by the presence of monocytosis (absolute monocyte count ≥0.5 × 109/L). TABLE 115-6 Primary Eosinophilia Classification EOSINOPHILIA ASSOCIATED WITH TKGF (M/LN-EO-TK) VARIABLES Absolute eosinophil count ≥1500 × 109/L ≥1500 × 109/L ≥1500 × 109/L ≥1500 × 109/L PB eosinophil % ≥10% ≥10% ≥10% ≥10% Documentation of chronicity of eosinophilia Advised Advised Advised Advised Comorbidity associated with secondary eosinophilia Absent Absent Absent Absent PB blast ≥2% or BM blast ≥5% Yes or no Yes or no No No Abnormal karyotype Yes or no Yes or no No No TKGF Yes No No No BCR-ABL1 No No No No Abnormal T lymphocyte phenotype or clonal T-cell clones No No Yes No Eosinophil-mediated tissue/organ

damage Yes or no Yes or no Yes or no Yes Abbreviations: ABL1 (e.g., ETV6::ABL1); BM, bone marrow; FGFR1 (e.g., ZMYM2::FGFR1); FLT3 (ETV6::FLT3); JAK2 (PCM1::JAK2); M/LN-eo-TK, myeloid/lymphoid neoplasms with eosinophilia and TKGF; PB, peripheral blood; TKGF, tyrosine kinase gene fusions, often involving PDGFRA (e.g. FIP1L1::PDGFRA) or PDGFRB (e.g., ETV6::PDGFRB).

The molecular pathogenesis of aCML is incompletely understood; about one-fourth of patients express SETBP1 mutations, which are, however, also found in several other myeloid malignancies, including CNL and CMML. SETBP1 mutations in aCML were prognostically detrimental and mostly located between codons 858 and 871; similar mutations are seen with Schinzel-Giedion syndrome (a congenital disease with severe developmental delay and various physical stigmata including midface retraction, large forehead, and macroglossia). A somatic missense mutation in ethanolamine kinase 1 (ETNK1 N244S) was described in 9% of patients with aCML but was also seen in 14% of patients with CMML, 6% of patients with mastocytosis (especially in association with eosinophilia), and rarely in other MPNs. In a series of 55 patients with WHO-defined aCML, median age at diagnosis was 62 years, with female preponderance (57%); sple nomegaly was reported in 54% of the patients, red cell transfusion requirement in 65%, abnormal karyotype in 20% (20q– and trisomy 8 being the most frequent), and leukemic transformation in 40%. Median survival was 25 months. Outcome was worse in patients with marked leukocytosis, transfusion requirement, and increased imma ture cells in the PB. In a more recent Mayo Clinic study of 25 molecu larly annotated and strictly WHO-defined aCML patients, median age was 70 years and 84% were male. Cytogenetic abnormalities were seen in 36% and gene mutations in 100%. Mutational frequencies were as follows: ASXL1 28%, TET2 16%, NRAS 16%, SETBP1 12%, RUNX1 12%, ETNK1 8%, and PTPN11 4%. Median survival was 10.8 months, and at last follow-up (median, 11 months), 17 (68%) deaths and 2 (8%) leukemic transformations were documented. In multivariable analysis, advanced age, low hemoglobin, and TET2 mutations were shown to carry independent prognostic significance; other mutations, includ ing ASXL1 and SETBP1 lacked prognostic significance. Conventional chemotherapy is largely ineffective in the treatment of aCML. Similarly, treatment response to the JAK1/2 inhibitor ruxolitinib has not been impressive. However, a favorable experience with ASCT was reported in nine patients; after a median follow-up of 55 months, the majority of the patients remained in complete remission. ■ ■MDS/MPN WITH MUTATED SF3B1 OR WITH RING SIDEROBLASTS, BOTH ASSOCIATED WITH THROMBOCYTOSIS OR NOT OTHERWISE SPECIFIED The ICC classifies patients with morphologic and laboratory features that resemble both MDS and MPN as “MDS/MPN overlap.” This cat egory is broad and is distinguished from MPN by the presence of “cyto penia.” Leukocytosis is also part of the definition for the subcategories of MDS/MPN, including MDS/MPN with mutated SF3B1 (MDS/ MPN-T-SF3B1), MDS/MPN with ring sideroblasts and thrombocyto sis, NOS (MDS/MPN-RS-T-NOS), and MDS/MPN-NOS. Diagnostic criteria for MDS/MPN-T-SF3B1 include thrombocytosis (≥450 ×

109/L), anemia, blasts <1% in PB and <5% in BM, presence of SF3B1 CHRONIC EOSINOPHILIC LEUKEMIA, NOT OTHERWISE SPECIFIED (CEL-NOS) LYMPHOCYTIC VARIANT HYPEREOSINOPHILIA HYPEREOSINOPHILIC SYNDROME

(variant allele frequency [VAF] >10%), and not otherwise classified as another myeloid neoplasm; corresponding criteria for MDS/MPN-RST-NOS also include thrombocytosis and anemia and absence of excess blasts but, in addition, require presence of ≥15% BM ring sideroblasts and absence of

SF3B1 mutation. The term MDS/MPN-NOS is reserved for MDS/MPN that does not meet criteria for either of the aforemen tioned MDS/MPN entities despite displaying thrombocytosis (≥450 × 109/L) or leukocytosis (≥13 × 109/L). ■ ■JUVENILE MYELOMONOCYTIC LEUKEMIA JMML is primarily a disease of early childhood and is now considered a unique clonal disorder of childhood, separated from MDS/MPN. Both CMML and JMML feature leukocytosis, monocytosis, and hepa tosplenomegaly. Additional characteristic features in JMML include thrombocytopenia and elevated fetal hemoglobin. Myeloid progenitors in JMML display granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity that has been attributed to dysregulated RAS/MAPK signaling. The latter is believed to result from mutually exclusive mutations involving RAS, PTPN11, and NF1. A third of patients with JMML that is not associated with Noonan syndrome carry PTPN11 mutations, while the incidence of NF1 in patients without neurofibromatosis type 1 and RAS mutations is ~15% each. In general, ~85% of JMML cases have one of the classical RAS pathway mutations (PTPN11, NRAS, KRAS, NF1, or CBL); in addition, a myriad of other mutations, such as ASXL1, RUNX1, SETBP1, JAK3, and CUX1, among others, have recently been reported. Taken together, it is cur rently believed that almost all patients with JMML harbor mutations in the RAS pathway; clonal disorders that mimic JMML but do not harbor a RAS pathway mutation are classified as JMML-like neoplasms. The 2022 ICC diagnostic criteria for JMML require the presence of PB monocyte count ≥1 × 109/L, <20% blasts in PB or BM, splenomeg aly, and absence of BCR::ABL1. Diagnosis also requires the presence of one of the following: (1) somatic mutations of PTPN11, KRAS, NRAS, or RRAS; (2) germline NF1 mutation and loss of heterozygosity of NF1 or clinical diagnosis of neurofibromatosis type 1; and (3) germline mutation and loss of heterozygosity of CBL. Drug therapy is relatively ineffective in JMML, and the treatment of choice is ASCT, which results in a 5-year survival of ~50%. ■ ■TRANSIENT MYELOPROLIFERATIVE DISORDER TMD, also referred to as transient abnormal myelopoiesis (TAM), constitutes an often but not always transient phenomenon of abnor mal megakaryoblast proliferation, which occurs in ~10% of infants with Down syndrome. TMD is usually recognized at birth and either undergoes spontaneous regression (75% of cases) or progresses to acute megakaryoblastic leukemia (AMKL; 25% of cases). Almost all patients with TMD and TMD-derived AMKL display somatic GATA1 muta tions. TMD-associated GATA1 mutations constitute exon 2 insertions, deletions, or missense mutations, affecting the N-terminal transactiva tion domain of GATA-1 and resulting in loss of full-length (50 kD) GATA-1 and its replacement with a shorter isoform (40 kD) that retains friend of GATA-1 (FOG-1) binding. In contrast, inherited forms of exon 2 GATA1 mutations produce a phenotype with anemia, whereas exon 4 mutations that affect the N-terminal, FOG-1-interactive domain produce familial dyserythropoietic anemia with thrombocytopenia or X-linked macrothrombocytopenia. ■ ■HYPEREOSINOPHILIA Eosinophilia refers to a PB absolute eosinophil count (AEC) that is above the upper normal limit of the reference range. The term hype reosinophilia (HE) is used when the AEC is ≥1500 × 109/L. The ICC recommends both BM and PB examination for diagnostic evaluation of HE. The former should include cytogenetic and molecular analysis as well as immunohistochemistry for mast cells (CD117, tryptase, CD25), and the latter should include lymphocyte flow cytometry with T-cell panel, TCR gene rearrangement studies, and serum tryptase. The most frequent causes of HE include infections, especially those related to tissue-invasive helminths, allergic/vasculitic diseases, drugs, and meta static cancer. Primary HE is the focus of this chapter and is considered when a cause for secondary eosinophilia is not readily apparent.

In the presence of normal BM morphology and absence of genetic abnormalities, the two major diagnostic possibilities are lymphocytic variant HE and idiopathic HE (Table 115-3); the former is

character ized by the presence of an abnormal T-cell phenotype or clone. Both conditions might be associated with tissue/organ dysfunction due to eosinophilic infiltrates, in which case their nomenclature is modified into lymphocytic variant hypereosinophilic syndrome and idiopathic hypereosinophilic syndrome (iHES), respectively. In the presence of a TKGF, a diagnosis of myeloid/lymphoid neoplasm with eosinophilia and TKGF is considered (Table 115-3). The genes involved in TKGFassociated HE are listed in Table 115-6: PDGFRA, PDGFRB, FGFR1, ABL, JAK2, and FLT3. Once the latter possibility is excluded, other ICC-defined myeloid or lymphoid neoplasms (e.g., systemic mastocy tosis, acute myeloid or lymphoblastic leukemia, CML, MPN or MDS/ MPN, Hodgkin's and non-Hodgkin's lymphoma) must be considered and excluded. CEL-NOS is considered in the presence of cytogenetic abnormalities, excess blasts, or morphologic evidence of dysplasia, including that of megakaryocytes.

The diagnostic workup for HE that is not associated with morpho logically overt myeloid malignancy should start with PB mutation screening for PDGFRA and PDGFRB mutations using fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction. If mutation screening is negative, a BM examination with cytogenetic and molecular studies is indicated. In this regard, one must first pay attention to the presence or absence of TKGF or associ ated cytogenetic abnormalities (Table 115-6). CEL-NOS is a subset of clonal eosinophilia that is neither molecularly defined nor classified as an alternative clinicopathologically assigned myeloid malignancy. We prefer to use the term strictly in patients with an HES phenotype who also display either a clonal cytogenetic/molecular abnormality, excess blasts in the BM or PB, or abnormal BM morphology (Table 115-6). CHAPTER 115 Less Common Lymphoid and Myeloid Malignancies ■ ■HYPEREOSINOPHILIA ASSOCIATED WITH TYROSINE KINASE GENE FUSIONS Both platelet-derived growth factor receptors α (PDGFRA; located on chromosome 4q12) and β (PDGFRB; located on chromosome 5q31q32) are involved in MPN-relevant activating mutations. Clinical phe notype in both instances includes prominent blood eosinophilia and excellent response to imatinib therapy. In regard to PDGFRA muta tions, the most popular is FIP1L1-PDGFRA, a karyotypically occult del(4)(q12), which was described in 2003 as an imatinib-sensitive acti vating mutation. Functional studies have demonstrated transforming properties in cell lines and the induction of MPN in mice. Cloning of the FIP1L1-PDGFRA fusion gene identified a novel molecular mecha nism for generating this constitutively active fusion tyrosine kinase, wherein an ~800 kb interstitial deletion within 4q12 fuses the 5′ por tion of FIP1L1 to the 3′ portion of PDGFRA. FIP1L1-PDGFRA occurs in a very small subset of patients who present with the phenotypic features of either systemic mastocytosis (SM) or HES, but the presence of the mutation reliably predicts complete hematologic and molecular response to imatinib therapy. In a retrospective survey of 151 patients with FIP1L1-PDGFRA– associated eosinophilia (143 males; mean age at diagnosis, 49 years), organopathy involved the spleen (44%), skin (32%), lungs (30%), heart (19%), and CNS (9%); none of 31 patients initially treated with corticosteroids achieved complete hematologic remission, whereas all 148 patients treated with imatinib achieved complete hematologic responses and also molecular responses, when evaluated. Treatment discontinuation was documented in 46 patients followed by a 57% relapse rate; the 1-, 5-, and 10-year overall survival rates in imatinibtreated patients were 99%, 95%, and 84%, respectively. Other studies have confirmed the possibility of treatment-free remissions in some patients after imatinib discontinuation. Infrequent occurrence of FIP1L1-PDGFRA–mutated AML associated with eosinophilia has also been shown to respond to low-dose imatinib therapy (100 mg/d). The association between eosinophilic myeloid malignancies and PDGFRB rearrangement was first characterized and published in 1994 when fusion of the tyrosine

kinase encoding region of PDGFRB to the ets-like gene, ETV6 (ETV6-PDGFRB, t(5;12)(q33;p13), was

demonstrated. The fusion protein was transforming to cell lines and resulted in constitutive activation of PDGFRB signaling. Since then, several other PDGFRB fusion transcripts with similar disease pheno types have been described, cell line transformation and MPD induction in mice have been demonstrated, and imatinib therapy was effective when employed.

The 8p11 myeloproliferative syndrome (EMS) (also known as human stem cell leukemic/lymphoma syndrome) constitutes a clini cal phenotype with features of both lymphoma and eosinophilic MPN and is characterized by a fusion mutation that involves the gene for fibroblast growth factor receptor 1 (FGFR1), which is located on chro mosome 8p11 [e.g., ZMYM2::FGFR1, t(8;13)(p11.1;q12.1)]; disease phenotypes include T-cell acute lymphoblastic leukemia, large B-cell lymphoma, and MPN-like disease with HE. In EMS, both myeloid and lymphoid lineage cells exhibit the 8p11 translocation, thus demon strating the stem cell origin of the disease. The disease features several 8p11-linked chromosome translocations, and some of the correspond ing fusion FGFR1 mutants have been shown to transform cell lines and induce EMS- or CML-like disease in mice depending on the specific FGFR1 partner gene (ZNF198 or BCR, respectively). Consistent with this laboratory observation, some patients with BCR-FGFR1 mutation manifest a more indolent CML-like disease. The mechanism of FGFR1 activation in EMS is similar to that seen with PDGFRB-associated MPN; the tyrosine kinase domain of FGFR1 is juxtaposed to a dimer ization domain from the partner gene. EMS is an aggressive disease often requiring combination chemotherapy followed by ASCT. Pemi gatinib, which targets FGFR1/2/3, has been introduced and shown to induce hematologic and cytogenetic response in >70% of patients with FGFR1-rearranged myeloid/lymphoid neoplasms. PART 4 Oncology and Hematology The 2022 ICC includes a number of other subcategories of myeloid/ lymphoid neoplasms with eosinophilia and TKGFs (M/LN-eo-TK): (1) ETV6::ABL1, t(9;12)(q34.1;p13.2), phenotypically similar to CML and treated the same way with imatinib or similar tyrosine kinase inhibitors (TKIs) with good response; (2) PCM1::JAK2 or BCR::JAK2 or other JAK2 partners, t(8;9)(p22;p24.1), phenotypically similar to MPN or MDS/MPN with >90% response rate to ruxolitinib but not durable and requiring bridging to ASCT; and (3) ETV6::FLT3, t(12;13) (p13.2;q12.2), phenotypically similar to lymphoblastic leukemia or lymphoma, CEL, or MDS/MPN, with some responses seen with FLT3 inhibitor therapy. ■ ■HYPEREOSINOPHILIC SYNDROME Blood eosinophilia that is neither secondary nor clonal is operationally labeled as being “idiopathic.” HES is a subcategory of idiopathic eosin ophilia with persistent increase of the AEC to ≥1.5 × 109/L and pres ence of eosinophil-mediated organ damage, including cardiomyopathy, gastroenteritis, cutaneous lesions, sinusitis, pneumonitis, neuritis, and vasculitis. In addition, some patients manifest thromboembolic com plications, hepatosplenomegaly, and either cytopenia or cytosis. BM histologic and cytogenetic/molecular studies should be exam ined before a working diagnosis of HES is made. Additional blood studies that are currently recommended during the evaluation of HES include serum tryptase (an increased level suggests mastocytosis and warrants molecular studies to detect FIP1L1-PDGFRA), T-cell immunophenotyping, and T-cell receptor antigen gene rearrangement analysis (a positive test suggests an underlying clonal or phenotypically abnormal T-cell disorder). In addition, initial evaluation in HES should include echocardiogram and measurement of serum troponin levels to screen for myocardial involvement by the disease. Initial evaluation of the patient with eosinophilia should include tests that facilitate assessment of target organ damage, including com plete blood count, chest x-ray, echocardiogram, and serum troponin level. Increased level of serum cardiac troponin has been

shown to correlate with the presence of cardiomyopathy in HES. Typical echo cardiographic findings in HES include ventricular apical thrombus, posterior mitral leaflet or tricuspid valve abnormality, endocardial thickening, dilated left ventricle, and pericardial effusion. In a Mayo Clinic study of 98 consecutive patients with idiopathic eosinophilia, including HES, median age was 53 years (55% male),

and overt organ involvement was seen in >80% of the cases, including 54% involving organs other than the skin. The frequencies of cardiac involvement, hepatosplenomegaly, and increased serum tryptase and interleukin (IL) 5 levels were 8%, 4%, 24%, and 31%, respectively. The study also revealed that 11% of the affected patients harbored pathoge netic mutations including TET2, ASXL1, and KIT; the presence of such mutations did not appear to influence phenotype, and the number of informative cases was too small to assess prognostic relevance. Instead, the study identified anemia and presence of cardiac involvement or hepatosplenomegaly as risk factors for survival. Glucocorticoids are the cornerstone of therapy in HES. Treatment with oral prednisone is usually started at 1 mg/kg per day and contin ued for 1–2 weeks before the dose is tapered slowly over the ensuing 2–3 months. If symptoms recur at a prednisone dose level of >10 mg/d, either hydroxyurea or interferon α is used as steroid-sparing agent. In patients in whom usual therapy fails as outlined above, mepolizumab or alemtuzumab might be considered. Mepolizumab is a monoclonal antibody that targets IL-5, which is a well-recognized growth factor for eosinophils. Alemtuzumab targets the CD52 antigen, which has been shown to be expressed by eosinophils but not by neutrophils. In a recently reported placebo-controlled phase 3 study, HES patients received subcutaneous mepolizumab (300 mg) every 4 weeks, in addi tion to their preprotocol therapy, and experienced significantly fewer disease flare-ups or treatment discontinuations (28 vs 56% for pla cebo), without excess adverse events. Mepolizumab was U.S. Food and Drug Administration approved for use in HES on September 25, 2020. In a smaller phase 2 study, benralizumab (monoclonal antibody target ing the receptor for IL-5; 30 mg given subcutaneously every 4 weeks) was also shown to reduce eosinophil count more efficiently compared to placebo (90 vs 30%). ■ ■MASTOCYTOSIS SM is characterized by proliferation of neoplastic mast cells (MCs) in BM and/or other extracutaneous organs and is distinguished from cutaneous mastocytosis (CM; skin involvement only) and mast cell sarcoma (MCS; high-grade focal MC tumor). According to the ICC and WHO-proposed fifth edition (WHO5) classification systems (Table 115-4), SM is subclassified into indolent (ISM), smoldering (SSM), aggressive (ASM), SM with associated myeloid (SM-AMN, per ICC) or hematologic (SM-AHN, per WHO5) neoplasm, and mast cell leukemia (MCL). WHO5 also includes an additional “low-grade” SM subtype, namely BM mastocytosis (BMM); the latter is described as consisting of (1) absence of skin lesions, (2) absence of B findings, and (3) serum tryptase level <125 ng/mL. The ICC considers BMM as a clinicopathologic variant and not an SM subtype. Both ICC and WHO5 have also refined their diagnostic criteria for SM in general. Diagnosis per ICC requires the presence of a major criterion (multifo cal aggregates of ≥15 MCs) or, in its absence, the presence of at least three minor criteria, including (1) BM biopsy or extracutaneous organ section with >25% MCs with atypical morphology; (2) MC expres sion of CD25, CD2, and/or CD30; (3) KIT D816V or other activating KIT mutation; and (4) increased serum tryptase >20 ng/mL (needs to be adjusted in the presence of hereditary α-tryptasemia); in addi tion, presence of myeloid/lymphoid neoplasm with eosinophilia with TKGRs must be excluded. SM diagnosis per WHO5 requires the pres ence of the major criterion as well as one other minor criterion or at least three minor criteria. The term advanced SM (AdvSM) includes ASM, SM-AMN/AHN, and MCL; AdvSM is distinguished from non-AdvSM by the presence of either an associated myeloid/hematologic

neoplasm (e.g., AML, CMML, MDS, MPN) or organopathy resulting from MC infiltra tion. MC-associated organopathy is defined by the presence of one or more C findings: (1) ≥1 cytopenia (hemoglobin <10 g/dL, absolute neutrophil count <1 × 109/L, or platelet count <100 × 109/L); (2) pal pable hepatomegaly with abnormal liver function tests, ascites, or por tal hypertension; (3) palpable splenomegaly with thrombocytopenia attributed to hypersplenism; (4) MC infiltration of the gastrointestinal system with resultant malabsorption with weight loss; and (5) large osteolytic lesions with or without pathologic fractures.

The ICC system requires the AHN component in SM-AHN to be of myeloid lineage, resulting in a revised nomenclature (i.e., SM-AMN). By contrast, WHO5-defined SM-AHN allows the AHN component to be of either myeloid or lymphoid lineage. Additional divergence between ICC and WHO5 concerns the definition of MCL; both systems require the presence of ≥20% MCs in BM aspirate, but ICC criteria require, in addition, immature cytomorphology (i.e., promastocytes, metachro matic blast-like cells, or multinucleated or highly pleomorphic MC) of the excess MCs; furthermore, ICC no longer differentiates between leukemic (≥10% circulating MC) versus aleukemic MCL variants. Both the ICC and WHO5 use similar B findings to distinguish indolent from smoldering SM, with the latter requiring the presence of two or more B findings, including (1) MCs >30% of BM cellularity on BM biopsy and serum tryptase >200 ng/mL; (2) cytopenia not meeting criteria for C findings or cytosis; and (3) palpable hepatomegaly without liver func tion impairment or splenomegaly without thrombocytopenia or >1 cm lymphadenopathy on palpation or imaging; in addition, KIT D816V VAF ≥10% qualifies as a B finding, per WHO5. In a study of 329 patients with AdvSM, including WHO5 subcat egories of SM-AHN (64%), ASM (30%), and MCL (6%) or ICC subcat egories of SM-AMN (64%), ASM (33%), and MCL (3%), multivariable analysis that included the Mayo Alliance risk factors for survival in SM (age >60 years, anemia, thrombocytopenia, increased alkaline phosphatase) revealed more accurate survival prediction with the ICC versus WHO5 classification order: (1) survival was significantly worse with ICC-defined MCL versus WHO5-defined MCL with otherwise mature MC cytomorphology; (2) prognostic distinction was con firmed for ICC-defined MCL versus ICC-defined SM-AMN but not for WHO5-defined MCL versus WHO-defined SM-AHN; (3) survival was similar between WHO5-defined MCL with mature cytomorphol ogy versus ICC-defined SM-AMN; and (4) ICC-defined SM-AMN but not WHO-defined SM-AHN with lymphoid lineage was prognostically distinct from ASM. Accordingly, our views on the classification of AdvSM are in line with those of the ICC system. We believe that these details are therapeutically relevant considering the emergent nature of ICC-defined MCL and the fact that SM-AMN, as opposed to SMAHN, carries a prognostically worse designation that might require therapeutic intervention with ASCT sooner than later. Currently available drugs for treatment include KIT inhibitors (KITi), which exhibit remarkable activity in reducing MC and mutant KIT burden but have not been shown to extend survival. On the other hand, we are impressed by the remarkable activity of currently available KITi on the MC component of SM, with the caveat that such drugs are expensive, have significant side effects, and need long-term use. The first step in treatment decision-making is to identify whether the AMN component takes priority over the SM component of the disease, for treatment purposes. High-grade AMNs, including AML, high-/veryhigh-risk MDS or CMML, or those with >10% BM blasts, likely take precedence in this regard. Accordingly, in a fit patient with SM-AML or SM-high/very-high-risk MDS, intensive remission induction therapy or hypomethylating agent (HMA) therapy can be considered. If the SM is incidentally diagnosed or is associated with minimal symptoms, we generally limit SM therapy to supportive/symptomatic care, includ ing with antihistamine and/or antileukotriene agents or cromolyn, as well as taking precautions for

anaphylaxis prevention/treatment. For SM with significantly high MC or symptom burden, concurrent MC cytoreduction can be considered, particularly for those with relapsed/ refractory disease, although there are no clear protocols in this regard. ASCT has an important role in the treatment of SM-high-grade AMN, although there is no consensus regarding optimal timing, deb ulking strategy, and so on; overall survival appears to be most favorable for SM-AMN patients compared to other subgroups, and survival was superior in those receiving myeloablative versus reduced-intensity conditioning, thereby indicating the need for effective cytoreduction prior to stem cell transplantation. For SM-AMN patients with a lowgrade AMN, such as PV or ET, or low-risk MDS, conventional therapy for the AMN including therapeutic phlebotomies, low-dose aspirin, hydroxyurea or interferon α, or erythropoiesis-stimulating agents is pursued. If the SM disease component does not warrant cytoreduction

(e.g., no C findings), supportive/symptomatic care, as described earlier, is pursued, along with intermittent monitoring of disease status. If MC cytoreduction is warranted, monotherapy with a TKI or cladribine can be pursued, depending on individual risk, benefit considerations, treat ment availability, cost considerations, and so on.

We find cladribine, midostaurin, and avapritinib to be reasonable drug considerations for AdvSM as well as MCL. While avapritinib has theoretical advantages over midostaurin, including a more potent inhibitory effect on KIT D816V and proven efficacy in patients previ ously treated with midostaurin, we are agnostic regarding the choice of TKI given the lack of head-to-head comparison; instead, we recom mend an individualized approach to TKI selection that weighs drug accessibility/affordability, comorbid conditions, risk tolerance for anticipated adverse events, and provider/center experience with the particular TKI. We continue to utilize cladribine as a reasonable alter native to TKI therapy, based on decades-long experience, long-term safety record, and qualitatively better toxicity profile that is mostly limited to cytopenias, as opposed to cognitive impairment and other side effects with avapritinib and intolerance due to diarrhea with midostaurin. For ASM patients who exhibit disease progression and/ or leukemic transformation despite adequate TKI dosing or cladribine, we recommend ASCT as salvage therapy. We consider “true” MCL an oncologic emergency, and collaboration with an experienced hema topathologist to expeditiously confirm the diagnosis is critical, as is expedited molecular testing for KIT D816V and other AMN-relevant mutations. CHAPTER 115 ■ ■DENDRITIC AND HISTIOCYTIC NEOPLASMS Dendritic cell (DC) and histiocyte/macrophage neoplasms are extremely rare. DCs are antigen-presenting cells, whereas histiocyte/ macrophages are antigen-processing cells. BM myeloid stem cells (CD34+) give rise to monocyte (CD14+, CD68+, CD11c+, CD1a–) and DC (CD14–, CD11c+/–, CD1a+/c) precursors. Monocyte precursors, in turn, give rise to macrophages (CD14+, CD68+, CD11c+, CD163+, lysozyme+) and interstitial DCs (CD68+, CD1a–). DC precursors give rise to Langerhans cell DCs (Birbeck granules, CD1a+, S100+, langerin+) and plasmacytoid DCs (CD68+, CD123+). Follicular DCs (CD21+, CD23+, CD35+) originate from mesenchymal stem cells. Dendritic and histiocytic neoplasms are operationally classified into macrophage/histiocyte-related and DC-related. The former includes histiocytic sarcoma/malignant histiocytosis and the latter Langerhans cell histiocytosis, Langerhans cell sarcoma, interdigitating DC sarcoma, and follicular DC sarcoma. Less Common Lymphoid and Myeloid Malignancies Histiocytic Sarcoma/Malignant Histiocytosis Histiocytic sarcoma represents malignant proliferation of mature tissue histiocytes and is often localized. Median age at diagnosis is estimated at 46 years with slight male predilection. Some patients might have a history of lymphoma, MDS, or germ cell tumors at time of

disease presentation. The three typical disease sites are lymph nodes, skin, and the gastro intestinal system. Patients may or may not have systemic symptoms including fever and weight loss, and other symptoms include hepato splenomegaly, lytic bone lesions, and pancytopenia. Immunopheno type includes presence of histiocytic markers (CD68, lysozyme, CD11c, CD14) and absence of myeloid or lymphoid markers. Prognosis is poor, and treatment is often ineffective. The term malignant histiocytosis refers to a disseminated disease and systemic symptoms. Lymphomalike treatment induces complete remissions in some patients, and median survival is estimated at 2 years. In one of the largest series of histiocytic sarcoma, 330 cases were included with median age of 61 years (59% male). In the latter study, the most common sites of pre sentation were skin, connective tissue, lymph nodes, gastrointestinal tract, and hematopoietic system; median overall survival was 6 months, and treatment included systemic chemotherapy, radiotherapy, and surgery. Factors associated with poor outcome included older age, high comorbidity index, and disease involving the hematopoietic and reticuloendothelial system. Langerhans Cell Histiocytosis Langerhans cells (LCs) are spe cialized DCs that reside in mucocutaneous tissue and upon activation

become specialized for antigen presentation to T cells. LC histiocytosis (LCH; also known as histiocytosis X) represents neoplastic proliferation of LCs (S100+, CD1a+, and Birbeck granules on electron microscopy). LCH incidence is estimated at 5 per million, and the disease typically affects children, with a male predilection. Presentation can be either unifocal (eosinophilic granuloma) or multifocal. The former usually affects bones and less frequently lymph nodes, skin, and lung, while the latter is more disseminated. Unifocal disease often affects older chil dren and adults, while multisystem disease affects infants. LCH of the lung in adults is characterized by bilateral nodules. Prognosis depends on organs involved. Only 10% of patients progress from unifocal to multiorgan disease. LCH of the lung might improve upon cessation of smoking. Approximately 55% of patients with LCH harbor BRAF V600E gain-of-function mutations, which indicates high-risk disease and resistance to first-line therapy, while responses to targeted therapy with vemurafenib have been reported. Other forms of treatment for LCH include combination chemotherapy and MEK inhibitors in BRAF wild-type but with other MAPK pathway mutations. Unfortunately, such targeted therapy has not secured long-lasting treatment-free remissions.

In one retrospective study, 33 adult patients with LCH were studied including 21 with single-system LCH, 10 with multisystem LCH, and 2 with pulmonary LCH. Patients with single-system unifocal involve ment were successfully treated with local therapies such as surgery and radiotherapy. Most of the multisystem LCH patients and patients with single-system multifocal involvement were treated with systemic chemotherapy. Cladribine was the first choice in 10 of 11 patients who received chemotherapy. Among all patients, the overall response rate (ORR) was 97%. Among those who had cladribine in the first line, the ORR was 81%. All these patients achieved a complete remission and were alive at the last visit. The median follow-up was 38 months (range, 2–183 months). The median progression-free survival (PFS) has not yet been reached. Ten-year PFS was 90.9%. Expert consensus recommenda tions for treatment include local therapies for unifocal disease, smoking cessation as first-line therapy for pulmonary LCH, and systemic therapy for multifocal and multisystem disease; the latter might include cladrib ine, cytarabine, and targeted therapy with BRAF and MEK inhibitors. PART 4 Oncology and Hematology In one study, 26 adult patients with non-LCH, including 17 with Erdheim-Chester disease (ECD), 3 with Rosai-Dorfman disease (RDD), 5 with ECD/RDD, and 1 with ECD/LCH, were treated with the MEK inhibitor

trametinib; the most common treatment-related toxicity was rash (27%), whereas the response rate of the 17 evaluable patients was 71%, including 73% without a detectable BRAF V600E; median time-to-treatment failure was 37 months; most patients har bored mutations in BRAF (either classic BRAF V600E or other BRAF alterations) or alterations in other genes involved in the MAPK path way (e.g., MAP2K, NF1, GNAS, or RAS). Langerhans Cell Sarcoma Langerhans cell sarcoma (LCS) also represents neoplastic proliferation of LCs with overtly malignant mor phology. The disease can present de novo or progress from antecedent LCH. There is a female predilection, and median age at diagnosis is estimated at 41 years. Immunophenotype is similar to that seen in LCH, and liver, spleen, lung, and bone are the usual sites of disease. Prognosis is poor, and treatment is generally ineffective. Interdigitating Dendritic Cell Sarcoma Interdigitating DC sarcoma (IDCS), also known as reticulum cell sarcoma, represents neoplastic proliferation of interdigitating DCs. The disease is extremely rare and affects elderly adults with no sex predilection. Typical presen tation is asymptomatic solitary lymphadenopathy. Immunophenotype includes S100+ and negative for vimentin and CD1a. Prognosis ranges from benign local disease to widespread lethal disease. Follicular Dendritic Cell Sarcoma Follicular dendritic cells (FDCs) reside in B-cell follicles and present antigen to B cells. FDC neoplasms (FDCNs) are usually localized and often affect adults. FDCN might be associated with Castleman’s disease in 10–20% of cases, and increased incidence in schizophrenia has been reported. Cervical lymph nodes are the most frequent site of involvement in FDCNs, and other sites include maxillary, mediastinal, and retroperitoneal lymph

nodes; oral cavity; the gastrointestinal system; skin; and breast. Sites of metastasis include lung and liver. Immunophenotype includes CD21, CD35, and CD23. Clinical course is typically indolent, and treatment includes surgical excision followed by regional radiotherapy and some times systemic chemotherapy. Hemophagocytic Lymphohistiocytosis (see Chap. 68) Hemo phagocytic lymphohistiocytosis (HLH) represents nonneoplastic pro liferation and activation of macrophages and cytotoxic lymphocytes that induce cytokine-mediated bone marrow suppression, features of intense phagocytosis in bone marrow and liver, and multiorgan dysfunction including cytopenias, coagulopathy, and fever. HLH may result from genetic (primary) or acquired (secondary) disorders of macrophages. The former entail genetically determined inability to regulate macrophage proliferation and activation and might include alterations in familial HLH genes, including those of perforin (PRF1, UNC13D, STXBP2, and STX11), granule/pigment abnormality genes (RAB27A, LYST, and AP3B1), or X-linked lymphoproliferative disease genes (SH2D1A and XIAP). Acquired HLH is often precipitated by viral infections, including Epstein-Barr virus. HLH might also accom pany certain malignancies such as T-cell lymphoma and autoimmune diseases, ASCT, and chimeric antigen receptor (CAR) T-cell therapy. In a recent population-based study from Sweden, the annual incidence of malignancy-associated HLH had increased 10-fold and was at least 0.71 per 100,000 adults from 2012 to 2018, and early survival improved significantly, likely due to increased awareness and more HLH-directed therapy. Regardless of the cause, the common tissue/organ-damaging pathway involves excessive inflammatory cytokine release, including IL-6, IL-2, IL-1, interferon γ, and tumor necrosis factor (TNF). Clinical presentation of HLH includes fever, severe constitutional symptoms, enlarged lymph nodes, hepatosplenomegaly, neurologic dysfunction, and abnormalities in multiple organ function tests. Diagnosis is accomplished by either detection of HLH-related muta tions or meeting five of the following eight conventional criteria: (1) hemophagocytosis in the bone marrow/spleen/lymph nodes; (2) serum ferritin ≥500 μg/L; (3) hypofibrinogenemia (fibrinogen ≤1.5 g/L) or hypertriglyceridemia (triglycerides ≥3 mmol/L); (4) low NK cell activ ity; (5) elevated soluble IL-2 receptor (CD25) ≥2400 U/mL; (6) bi- or tri-cytopenia

(platelets <100 × 109/L, hemoglobin <9 g/dL, absolute neutrophil count <1 × 109/L); (7) splenomegaly palpable >3 cm below left costal margin; and (8) fever. Clinical course is often fulminant and fatal with reported 1-year survival rates of <30% in patients with hematologic malignancy. Current therapeutic approaches for primary or secondary HLH include the so-called HLH-94 protocol, which con sists of weekly treatments with etoposide and dexamethasone, stem cell transplant, emapalumab (a monoclonal antibody that binds and neu tralizes interferon γ and is approved in primary HLH), and the JAK1/2 inhibitor ruxolitinib. The latter has recently been shown to increase survival rate in affected patients to >80%. ■ ■FURTHER READING Alaggio R et al: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid neoplasms. Leukemia 36:1720, 2022. Arber DA et al: International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 140:1200, 2022. de Leval L et al: A practical approach to the modern diagnosis and classification of T- and NK-cell lymphomas. Blood 144:1855, 2024. Khoury JD et al: The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and histio cytic/dendritic neoplasms. Leukemia 36:1703, 2022. Miranda RN et al: The 5th edition of the World Health Organization Classification of Hematopoietic and lymphoid tissues: Mature T-cell, NK-cell, and stroma-derived neoplasms of lymphoid tissues. Mod Pathol 37:100512, 2024. Szuber N et al: Chronic neutrophilic leukemia: 2022 update on diagno sis, genomic landscape, prognosis, and management. Am J Hematol

97:491, 2022.

Revision #1
Created 2026-01-06 16:32:02 UTC by Omar Ayman
Updated 2026-01-06 16:32:02 UTC by Omar Ayman