# CHAPTER **C21**

# Less Common Hematologic Malignancies

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The most common lymphoid malignancies are discussed in Chap. 110, myeloid leukemias in Chap. 109, myelodysplastic syndromes in Chap. 107, and myeloproliferative syndromes in Chap. 108. This chapter will focus on the more unusual forms of hematologic malignancy. The diseases discussed here are listed in Table e21-1. Each of these entities accounts for less than 1% of hematologic neoplasms.

#### LYMPHOID MALIGNANCIES

Precursor B cell and precursor T cell neoplasms are discussed in Chap. 110. All the lymphoid tumors discussed here are mature B cell or T cell, natural killer (NK) cell neoplasms.

#### MATURE B CELL NEOPLASMS

#### B cell prolymphocytic leukemia (B-PLL)

This is a malignancy of medium-sized (about twice the size of a normal small lymphocyte), round lymphocytes with a prominent nucleolus and light blue cytoplasm on Wright's stain. It dominantly affects the blood, bone marrow, and spleen and usually does not cause adenopathy. The median age of affected patients is 70 years and men are more often affected than women (male/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 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 expression 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. 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 (cyclophosphamide, doxorubicin, vincristine, prednisone, or 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.

## 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, bone marrow, and peripheral blood may be involved. The circulating tumor cells have short surface villi and are called villous lymphocytes. Table e21-2 shows differences in tumor cells of a number of

# TABLE e21-1 Unusual Lymphoid and Myeloid Malignancies

# Lymphoid

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Mature B cell neoplasms	
B cell prolymphocytic leukemia	
Splenic marginal zone lymphoma	
Hairy cell leukemia	
Nodal marginal zone B cell lympho	oma
Mediastinal large B cell lymphoma	i
Intravascular large B cell lymphom	ıa
Primary effusion lymphoma	
Lymphomatoid granulomatosis	
Mature T cell and NK cell neoplasms	
T cell prolymphocytic leukemia	
T cell large granular lymphocytic l	eukemia
Aggressive NK cell leukemia	
Extranodal NK/T cell lymphoma, n	asal type
Enteropathy-type T cell lymphoma	l l
Hepatosplenic T cell lymphoma	
Subcutaneous panniculitis-like T c	ell lymphoma
Blastic NK cell lymphoma	
Primary cutaneous CD30+ T cell l	ymphoma
Angioimmunoblastic T cell lympho	ma
Myeloid	
Chronic neutrophilic leukemia	
Chronic cocinonhilic loukemic/hymer	a a in a nhilia, a un drama

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

neoplasms of small lymphocytes that aid in the differential diagnosis. SMZL cells express surface immunoglobulin and CD20, but are negative for CD5, CD10, and CD103.

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 peripheral blood with villous lymphocytes. Autoimmune

<b>FABLE e21-2</b>	Immunophenotype of	Tumors of Small	Lymphocytes
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	CD5	CD20	CD43	CD10	CD103	slg	cyclinD1
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.

anemia or thrombocytopenia 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 *CDK6* gene. The genetic lesions typically found in extranodal marginal zone lymphomas [e.g. trisomy 3 and t(11;18)] are uncommon in SMZL.

The clinical course of disease is generally indolent. Long remissions can be seen after splenectomy. A small fraction of patients undergo histologic progression to diffuse large B cell lymphoma 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 bone marrow 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 completely clear and may be mediated by both inhibitory cytokines and marrow replacement. The marrow has an increased level of reticulin fibers; indeed, hairy cell leukemia is a common cause of inability to aspirate bone marrow or so-called "dry tap" (Table e21-3). Monocytopenia is profound and may explain a predisposition to atypical mycobacterial 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

# TABLE e21-3Differential Diagnosis of "Dry<br/>Tap"—Inability to Aspirate<br/>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		

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 male/ 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 associated 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  $\alpha$  is also an effective therapy but is not as effective as nucleosides.

#### Nodal marginal zone B cell lymphoma

This rare node-based disease bears an uncertain relationship with extranodal marginal zone lymphomas, which are often mucosaassociated and are called mucosa-associated lymphoid tissue or MALT lymphomas, and splenic marginal zone lymphomas. 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 combination chemotherapy, though 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 5–10% can disseminate widely to kidney, adrenal, liver, skin, and even brain. The disease affects women more often than men (male/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 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.

MACOP-B and R-CHOP are effective treatments, achieving 5-year survival of 75–87%. A role for mediastinal radiation therapy has not been definitively demonstrated but it is frequently used, especially in patients whose mediastinal area remains PET-avid after 4–6 cycles of chemotherapy.

#### Intravascular large B cell lymphoma

This is an extremely rare form of diffuse large B cell lymphoma characterized by the presence 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  $\beta$ -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. In general, the clinical course is aggressive and the disease is poorly responsive to therapy. Often a diagnosis is not made until very late in the course of the disease.

#### **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 Mediterranean 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 confused with Reed-Sternberg cells. The cells express CD20 and CD79a (immunoglobulin-signaling molecule), though they often do not express immunoglobulin. Some cases aberrantly express T cell markers such as CD3 or rearranged T cell receptor genes. No characteristic genetic lesions have been reported but gains in chromosome 12 and X material has been seen, similar to other HIV-associated lymphomas. The clinical course is generally characterized by rapid progression and death within 6 months.

#### Lymphomatoid granulomatosis

This is an angiocentric, angiodestructive lymphoproliferative disease comprised by neoplastic 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 lymphoma, nasal type, which can also be angiodestructive and is Epstein-Barr virus–related. The disease usually presents in adults (M>F) as a pulmonary infiltrate.

Involvement is often entirely extranodal 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 rapidly 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  $\alpha$ .

#### MATURE T CELL AND NK CELL NEOPLASMS

#### T cell prolymphocytic leukemia

This is an aggressive leukemia of medium-sized prolymphocytes involving the blood, marrow, nodes, liver, spleen, and skin. It accounts for 1-2% of all small lymphocytic leukemias. Most patients present with elevated white blood cell count (often >100,000/µL), hepatosplenomegaly, and adenopathy. Skin involvement occurs in 20%. The diagnosis is made from peripheral blood 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  $\beta$  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.

The course of the disease is generally rapid, with median survival of about 12 months. Responses have been seen with the anti-CD52 antibody, nucleoside analogs, and CHOP chemotherapy. Small numbers of patients with T cell prolymphocytic leukemia have also been treated with high-dose therapy and allogeneic bone marrow transplantation after remission has been achieved with conventionaldose therapy.

#### T cell large granular lymphocytic leukemia

T cell large granular lymphocytic leukemia (LGL leukemia) is characterized by increases in the number of LGLs in the peripheral blood (2000–20,000/ $\mu$ L) often accompanied by severe neutropenia, with or without concomitant anemia. Patients may have splenomegaly and frequently have evidence of systemic autoimmune disease, including rheumatoid arthritis, hypergammaglobulinemia, autoantibodies, and circulating immune complexes. Bone marrow involvement is mainly interstitial in pattern, with fewer than 50% lymphocytes on differential count. Usually the cells express CD3, T cell receptors, and CD8; NK-like variants may be CD3–. The leukemic cells often express Fas and Fas ligand.

The course of the disease is generally indolent and dominated by the neutropenia. Paradoxically, immunosuppressive therapy with cyclosporine, 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 aggressive 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 peripheral blood 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 less so. 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 lymphomatoid 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 gastrointestinal tract, or the testis. In some cases, hemophagocytic syndrome may influence the clinical picture. Patients may have B symptoms. 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 0 risk factors, 64% for 1, 32% for 2, and 7% for 3 or 4. 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 development 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 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 (median survival is 7 months) poor but some patients have a good response to CHOP chemotherapy. Patients who respond can develop bowel perforation from responding tumor. If the tumor responds to treatment, recurrence may develop elsewhere in the celiac disease– affected small bowel.

#### Hepatosplenic T cell lymphoma

Hepatosplenic T cell lymphoma is a malignancy derived from T cells expressing the gamma/delta T cell antigen receptor that affects mainly the liver and fills the sinusoids 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 CD8negative. 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. 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/ beta-derived but occasionally the gamma/delta receptors are involved, particularly in the setting of immunosuppression. The cells are negative for Epstein-Barr virus. Patients may have a hemophagocytic syndrome 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 hemophagocytic syndrome can be a component of a fulminant downhill course. Effective therapy can reverse the hemophagocytic syndrome.

#### **Blastic NK cell lymphoma**

The neoplastic cells express NK cell markers, especially CD56, and are CD3 negative. They are large blastic-appearing 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 typical 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, about 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 complication of silicone on saline breast implants. Cutaneous CD30+ T cell lymphoma often responds to therapy. Radiation therapy can be effective and surgery can also produce long-term disease control. Five-year survival exceeds 90%.

#### Angioimmunoblastic T cell lymphoma

Angioimmunoblastic T cell lymphoma is a systemic disease that accounts for about 15% of all T cell lymphomas. Patients frequently have fever, advanced stage, diffuse adenopathy, hepatosplenomegaly, skin rash, polyclonal hypergammaglobulinemia, 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 nonneoplastic inflammatory cells together with proliferation of high endothelial venules and follicular dendritic cells. 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 lymphoma treatments more likely to produce infectious complications.

#### **MYELOID MALIGNANCIES**

#### CHRONIC NEUTROPHILIC LEUKEMIA

Chronic neutrophilic leukemia is a rare myeloproliferative disorder that may be confused with the much more common chronic myeloid leukemia. Patients present with increased peripheral blood neutrophil counts (>25,000/µL) and hepatosplenomegaly, but unlike those with chronic myeloid leukemia, no Philadelphia chromosome or BCR/ABL fusion gene is detectable and immature forms comprise less than 10% of circulating white blood cells. The diagnosis is one of exclusion. One must rule out leukemoid reactions and other myeloproliferative and myelodysplastic syndromes. No morphologic dysplasia of myeloid precursors is present. Some patients with chronic neutrophilic leukemia appear to have an underlying plasma cell disorder but the relationship between the entities is not defined. In the vast majority of patients, cytogenetic analysis is normal. The disease course is variable from 1 to 20 years or more. A small number of patients may develop acute leukemia or myelodysplasia. Most have progressive marrow replacement with myeloid cells and crowding out of red cell and platelet precursors. Hydroxyurea can control the white blood cell count, but this is generally unnecessary even at counts >100,000/µL because, unlike the cells of acute leukemia, the cells of chronic neutrophilic leukemia are not invasive and not likely to cause leukostasis. Patients do not respond to splenectomy and no therapy has been shown to alter the natural history of the disease.

#### CHRONIC EOSINOPHILIC LEUKEMIA/HYPEREOSINOPHILIC SYNDROME

The diagnostic criteria for chronic eosinophilic leukemia/hypereosinophilic syndrome are provided in Table e21-4. The presence of eosinophilia is critical, defined as eosinophils  $\geq$ 1500/µL in blood, increased marrow eosinophils, and myeloblasts <20% in blood or marrow for at least 6 months, in the absence of other symptoms requiring more immediate treatment. The eosinophilic disorders are much more common in men than women (9:1). Patients may be totally asymptomatic and have the eosinophilia detected incidentally in routine blood work or they may have any of a myriad of symptoms including fever, fatigue, cough, edema, shortness of breath, central nervous system dysfunction, muscle aches and pains, itching, abdominal pain, diarrhea, peripheral neuropathy, or rheumatologic findings. The key diagnostic issue is distinguishing clonal eosinophilia, a neoplastic proliferation of eosinophils, from the many entities and drug exposures that can cause secondary eosinophilia. Because of the paucity of markers of eosinophil clonality, the diagnosis tends to be one of exclusion.

The first condition to rule out is eosinophilia accompanying a *FIP1L1-PDGFRA*-associated myeloproliferative disorder. If a mutation is noted in the peripheral blood, patients are treated with imatinib, which inhibits the platelet-derived growth factor receptor activated in this condition. If mutation is absent, a bone marrow analysis is done with cytogenetics looking for a 5q33 (*PDGFRB*), 4q12 (*PDGFRA*), or 8p11.2 (*FGFR1*) translocation. These clonal eosinophilias are part of the clinical picture of myeloid malignancies involving these genes. The PDGF receptor abnormalities predict a favorable response to imatinib whereas the FGF receptor abnormality is associated with chemotherapy-refractory disease.

If these genetic lesions are absent, peripheral blood lymphocytes are studied for immunophenotype and T cell receptor gene rearrangements. The presence of clonal lymphocytes makes the diagnosis of lymphocyte variant hypereosinophilia and implies a cytokinedriven process. If the peripheral blood T cells are normal, one is left with chronic eosinophilic leukemia/hypereosinophilic syndrome as the diagnosis, and these two related entities are distinguished mainly by peripheral blood and bone marrow blast counts. If the peripheral blood has >2% blasts and the marrow has >5% blasts, chronic eosinophilic leukemia is the diagnosis; if the peripheral blood has <2% blasts and the marrow has <5% blasts, the diagnosis is hypereosinophilic syndrome.

The heart, lungs, and central nervous system are the organ systems often most affected by eosinophil-mediated tissue damage. Patients should have chest radiographs, echocardiography, and troponin level measured to assess lung and cardiac involvement. In the absence of abnormalities in the platelet-derived growth factor receptors, asymptomatic patients can be observed. When treatment is indicated based on symptoms, glucocorticoids are the initial treatment. Hydroxyurea, interferon  $\alpha$ , cladribine, and cyclosporine have also been used. The anti-IL5 antibody mepolizumab is being tested. Responses are noted but are not durable. Anti-CD52 antibody (alemtuzumab) has also produced responses but is profoundly immunosuppressive.

## HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Tumors derived from histiocytes or dendritic cells are exceedingly rare. Through the past century, a number of disorders have been labeled initially as histiocytic disorders but, upon further study with newer analytic tools, the origin has been found to be nonhistiocytic; often, rare T cell disorders like anaplastic large cell lymphoma

# TABLE e21-4 Diagnosis of Chronic Eosinophilic Leukemia and Hypereosinophilic Syndrome

Required: Persistent eosinophilia  $\geq$ 1500/µL in blood, increased marrow eosinophils, and myeloblasts <20% in blood or marrow.

- 1. Exclude all causes of reactive eosinophilia: allergy, parasites, infection, pulmonary disease (e.g., hypersensitivity pneumonitis, Loeffler's), and collagen vascular diseases
- Exclude primary neoplasms associated with secondary eosinophilia: T cell lymphomas, Hodgkin's disease, acute lymphoid leukemia, mastocytosis
- 3. Exclude other primary myeloid neoplasms that may involve eosinophils: chronic myeloid leukemia, acute myeloid leukemia with inv(16) or t(16;16)(p13;q22), other myeloproliferative syndromes and myelodysplasia
- 4. Exclude T cell reaction with increased IL-5 or other cytokine production

If these entities have been excluded and no evidence documents a clonal myeloid disorder, the diagnosis is hypereosinophilic syndrome.

If these entities have been excluded and the myeloid cells show a clonal chromosome abnormality or some other evidence of clonality and blast cells are present in the peripheral blood (>2%) or are increased in the marrow (but <20%), the diagnosis is chronic eosinophilic leukemia.

were initially thought to be derived from histiocytes. Histiocytes and macrophages are not cell types that routinely circulate and, therefore, neoplasms derived from them tend to produce localized tumor masses in the site of origin. The range of markers that characterize these cells is not as broad as those available for lymphocyte subsets. However, the four main types of macrophages and dendritic cells have some distinguishing features. Langerhans cells are bone marrow-derived and reside in the skin; their main function is to present antigen to T cells. They are MHC class II, Fc receptor, and S100 protein positive; they express CD4 and CD1a, and they are not phagocytosing cells. They contain distinctive morphologic features such as Birbeck granules, rod or tennis racket-shaped structures of uncertain function. Interdigitating dendritic cells are also bone marrow-derived antigen-presenting cells and they can be in any tissue. They are MHC class II and S100 positive but do not express other known markers. Follicular dendritic cells appear to be derived from a mesenchymal stem cell and reside in lymph node follicles; they present antigen to B cells. They are CD21 and CD35 positive and CD68 and CD45 negative. Macrophages are also CD21 and CD38 positive, but they express CD68 and are phagocytic and express lysozyme.

## HISTIOCYTIC SARCOMA

This is a tumor of histiocytes or macrophages that may present as a solitary mass with or without systemic symptoms of fever and weight loss. The tumor is composed of sheets of large cells effacing the tissue architecture. The cells resemble the cells of diffuse large B cell lymphoma but they do not express lymphocyte markers and are CD68, lysozyme, CD11c, and CD14 positive. The tumor is not highly responsive to treatment and the natural history is usually aggressive.

#### LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis is a disease of childhood that has been called histiocytosis X, Letterer-Siwe disease, Hand-Schuller-Christian disease, and eosinophilic granuloma. Patients with Langerhans cell histiocytosis are at increased risk of acute lymphoid leukemia or other lymphoid malignancy. Three clinical syndromes are recognized. Solitary bone lesions, particularly those involving the skull, femur, pelvis, or ribs, are frequently called eosinophilic granuloma. The presence of multiple lesions affecting a single tissue, most often bone, is called Hand-Schuller-Christian disease. The presence of multiple lesions in multiple organs including bones, skin, liver, spleen, and nodes is called Letterer-Siwe disease. The characteristic Birbeck granules are pathognomonic but only visible on electron microscopy. The clinical course tends to be inversely related to the number of lesions. Patients with solitary lesions may progress to multiple lesion and multiorgan involvement in 10% of cases; however, most patients respond to chemotherapy. Long-term survival is seen in 70-90% of cases.

#### LANGERHANS CELL SARCOMA

Langerhans cell sarcoma is distinguished from Langerhans cell histiocytosis by the presence of a high degree of cellular atypia; it can arise de novo or progress from prior Langerhans cell histiocytosis. The natural history is more aggressive, but the disease is responsive to treatment and the long-term survival is about 50%.

#### INTERDIGITATING DENDRITIC CELL SARCOMA

Interdigitating dendritic cell sarcoma is a proliferation of spindleto ovoid-shaped cells that usually present in lymph nodes but also can form skin nodules. The initial mass is usually asymptomatic but fatigue, fever, or night sweats may accompany the lesion. The cells express \$100 and are negative for follicular dendritic cell markers like CD21 and CD35. The clinical course is variable. Localized disease is curable with local therapy.

#### FOLLICULAR DENDRITIC CELL SARCOMA

Follicular dendritic cell sarcoma is a tumor of follicular dendritic cells that originates in lymph nodes in about two-thirds of cases, usually cervical nodes. Extranodal sites may also be involved. The presentation is usually a slow-growing painless mass. The microscopic anatomy of the tumor is similar to that of the interdigitating dendritic cell tumors but the tumor cells express different markers (i.e., they are CD21 and CD35 positive and negative for CD1a). The tumor is typically indolent and can be controlled with surgery. There is no clear role for radiation therapy or chemotherapy.

#### MASTOCYTOSIS

Mastocytosis is a proliferation and accumulation of mast cells in one or more organ systems. In about 80% of cases, only the skin is involved. In the other 20%, the skin and at least one other organ system are involved.

#### **CUTANEOUS MASTOCYTOSIS**

Three major variants of cutaneous mastocytosis are described: (1) urticaria pigmentosa, the most common form, is a maculopapular pigmented rash affecting the papillary dermis; (2) diffuse cutaneous mastocytosis, occurring rarely but almost entirely in children, does not produce the maculopapular rash; instead, the skin is relatively smooth but may be red or thickened and on biopsy have infiltration in the papillary and reticular dermis with mast cells; (3) mastocytoma of skin, a single lesion, most often on the trunk or wrist, in which a tumor mass composed of mast cells forms.

#### SYSTEMIC MASTOCYTOSIS

Clinical manifestations of systemic mastocytosis may be mediated either by the infiltration of organs with mast cells or the release of mediators from the mast cells, including proteases, histamine, eicosanoids, or heparin. The signs and symptoms can be grouped into the following categories: (1) constitutional symptoms (fatigue, fever, weight loss, sweats); (2) skin manifestations of mast cell infiltration (pruritus, urticaria, rash, dermatographism); (3) mediatorrelated symptoms (abdominal pain, flushing, syncope, hypertension, headache, tachycardia, diarrhea); and (4) bone-related symptoms (fracture, pain, arthralgia). Patients may have splenomegaly, anemia, and either increases or decreases in platelet count and white blood cell count. Bone marrow involvement is common and can progress to crowd out normal hematopoietic elements. Eosinophilia can be seen to such a marked degree that a primary eosinophilic disorder is suspected. Serum tryptase is a useful marker for mast cell mass. Tryptase levels >20 ng/mL indicate the presence of systemic mastocytosis. Tryptase levels tend to be <15 ng/mL in cutaneous mastocvtosis.

In the Mayo Clinic series, 40% of patients with systemic mastocytosis had an associated myeloid neoplasm; in about 45% of these patients, the associated tumor was a myeloproliferative syndrome; in 29% it was chronic myelomonocytic leukemia, and in 23% it was a myelodysplastic syndrome. Eosinophilia was noted in about onethird of the patients with an associated myeloid neoplasm. Median survival for patients with systemic mastocytosis and another myeloid neoplasm was about 2 years.

In the absence of a myeloid neoplasm, systemic mastocytosis can have an indolent or an aggressive clinical course. Patients who follow a more indolent course do not have high levels of tryptase or bone marrow mastocytosis, no dysplasia, no hepatosplenomegaly, no skeletal involvement, normal blood counts, and no symptoms of malabsorption with weight loss. Such patients comprised 46% of the Mayo Clinic experience and had a median survival of 16+ years.

By contrast, about 12% of the Mayo Clinic patients with systemic mastocytosis had an aggressive course. They often had anemia and

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thrombocytopenia, B symptoms, and hepatosplenomegaly. Their median survival was about 3.5 years.

#### However, many of these patients were diagnosed and treated before it became widely known that the majority of patients with systemic mastocytosis have activating mutations of c-KIT, most notably KITD816V. KIT is one of the kinases that are inhibited by imatinib, but this mutation is relatively resistant to its effects. The second- and third-generation inhibitors have not been tested. Interferon $\alpha$ produces response in about half of patients and the responses last about 1 year. Hydroxyurea may unpack the marrow sufficiently to restore hematopoiesis. Median responses last 2.5 years. Cladribine produced responses in 55% of patients, with responses lasting about a year, and is a reasonable first-line therapy.

#### MAST CELL SARCOMA/LEUKEMIA

Mast cell sarcoma is very rare but consists of a destructive tumor mass composed of atypical-looking immature mast cells. They may appear de novo or in the setting of systemic mastocytosis as a solitary mass that is growing unusually fast compared with other involved sites. When the bone marrow becomes >50% mast cells, one may see circulating mast cells accounting for >10% of the white blood cell count. This finding permits a diagnosis of mast cell leukemia.

#### **EXTRACUTANEOUS MASTOCYTOMA**

These rare tumors of normal-appearing mast cells often present in the lung. The treatment experience is anecdotal.

## FURTHER READINGS

- CHANDESRIS MO et al: Enteropathy-associated T-cell lymphoma: A review on clinical presentation, diagnosis, therapeutic strategies, and perspectives. Gastroenterol Clin Biol 34:590, 2010
- ELLIOTT MA et al: WHO-defined chronic neutrophilic leukemia: A long-term analysis of 12 cases and a critical review of the literature. Leukemia 19:313, 2005
- FARIS JE, LACASCE AS: Primary mediastinal large B-cell lymphoma. Clin Adv Hematol Oncol 7:125, 2009
- FORCONI F: Hairy cell leukaemia: Biological and clinical overview from immunogenetic insights. Hematol Oncol Nov 2, 2010 [Epub ahead of print]
- GREER JP, MOSSE CA: Natural killer cell neoplasms. Curr Hematol Malig Rep 4:245, 2009
- KOTLYAR DS et al: A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 9:36, 2011
- PARDANANI A, TEFFERI A: Systemic mastocytosis in adults: A review on prognosis and treatment based on 342 Mayo Clinic patients and current literature. Curr Opin Hematol 17:125, 2010
- TEFFERI A et al: Hypereosinophilic syndrome and clonal eosinophilia: Point-of-care diagnostic algorithm and treatment update. Mayo Clin Proc 85:158, 2010