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

The World Health Organization (WHO) system uses peripheral blood counts and smear analysis, bone marrow morphology, and cytogenetic and molecular genetic tests in order to classify myeloid malignancies into five major categories (Table 135e-4). In this chapter, we focus on chronic neutrophilic leukemia; atypical chronic myeloid leukemia, *BCR-ABL1* negative; chronic myelomonocytic leukemia; juvenile myelomonocytic leukemia; chronic eosinophilic leukemia, not otherwise specified; mastocytosis; myeloproliferative neoplasm (MPN), unclassifiable (MPN-U); myelodysplastic syndrome (MDS)/MPN, unclassifiable (MDS/MPN-U); refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T); and myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*. This chapter also includes histiocytic and dendritic cell neoplasms, transient myeloproliferative disorders, and a broader discussion on primary eosinophilic disorders including hypereosinophilic syndrome (HES).

TABLE 135e-4 WORLD HEALTH ORGANIZATION CLASSIFICATION OF MYELOID MALIGNANCIES

1. **Acute myeloid leukemia (AML) and related precursor neoplasms**[a]
2. **Myeloproliferative neoplasms (MPN)**
   - **2.1.** Chronic myelogenous leukemia, *BCR-ABL1* positive (CML)
   - **2.2.** *BCR-ABL1*-negative MPN
     - **2.2.1.** Polycythemia vera
     - **2.2.2.** Primary myelofibrosis
     - **2.2.3.** Essential thrombocythemia
   - **2.3.** Chronic neutrophilic leukemia
   - **2.4.** Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
   - **2.5.** Mastocytosis
   - **2.6.** Myeloproliferative neoplasm, unclassifiable (MPN-U)
3. Myelodysplastic syndromes (MDS)
   - **3.1.** Refractory cytopenia[b] with unilineage dysplasia (RCUD)
     - **3.1.1.** Refractory anemia (ring sideroblasts <15% of erythroid precursors)
     - **3.1.2.** Refractory neutropenia
     - **3.1.3.** Refractory thrombocytopenia
   - **3.2.** Refractory anemia with ring sideroblasts (RARS; dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow erythroid precursors)
   - **3.3.** Refractory cytopenia with multilineage dysplasia (RCMD; ring sideroblast count does not matter)
   - **3.4.** Refractory anemia with excess blasts (RAEB)
     - **3.4.1.** RAEB-1 (2–4% circulating *or* 5–9% marrow blasts)
     - **3.4.2.** RAEB-2 (5–19% circulating *or* 10–19% marrow blasts *or* Auer rods present)
   - **3.5.** MDS associated with isolated del(5q)
   - **3.6.** MDS, unclassifiable (MDS-U)
4. **MDS/MPN overlap**
   - **4.1.** Chronic myelomonocytic leukemia (CMML)
   - **4.2.** Atypical chronic myeloid leukemia, *BCR-ABL1* negative (aCML)
   - **4.3.** Juvenile myelomonocytic leukemia (JMML)
   - **4.4.** MDS/MPN, unclassifiable (MDS/MPN-U)
     - **4.4.1.** *Provisional entity: Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T)*
5. **Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA, PDGFRB,* or *FGFR1*[c]**
   - **5.1.** Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
   - **5.2.** Myeloid neoplasms with *PDGFRB* rearrangement
   - **5.3.** Myeloid and lymphoid neoplasms with *FGFR1* abnormalities

[a]AML-related precursor neoplasms include therapy-related MDS and myeloid sarcoma. [b]Either monocytopenia or bicytopenia: hemoglobin level <10 g/dL, absolute neutrophil count $<1.8 \times 10^9$/L, or platelet count $<100 \times 10^9$/L. However, higher blood counts do not exclude the diagnosis in the presence of unequivocal histologic/cytogenetic evidence for MDS. [c]Genetic rearrangements involving platelet-derived growth factor receptor α/β (*PDGFRA/PDGFRB*) or fibroblast growth factor receptor 1 (*FGFR1*).

CHRONIC NEUTROPHILIC LEUKEMIA

Chronic neutrophilic leukemia (CNL) is characterized by mature neutrophilic leukocytosis with few or no circulating immature granulocytes. CNL is associated with 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 also display constitutional symptoms, splenomegaly, anemia, and thrombocytopenia. Median survival is approximately 2 years, and causes of death include leukemic transformation, progressive disease associated with severe cytopenias, and marked treatment-refractory leukocytosis. CNL is rare, with less than 200 reported cases. Median age at diagnosis is approximately 67 years, and the disease is equally prevalent in both genders.