that is accompanied by either the presence of myeloblast excess (either >2% in the peripheral blood or 5–19% in the bone marrow) or evidence of myeloid clonality. Cytogenetic abnormalities in CEL, other than those that are associated with molecularly defined eosinophilic disorders, include trisomy 8 (the most frequent), t(10;11)(p14;q21), and t(7;12)(q11;p11). CEL-NOS does not respond to imatinib, and treatment strategies are often not different from those used in other similar MPNs and include ASCT for transplant-eligible patients with poor risk factors and participation in experimental treatment protocols otherwise.

***PDGFR*-Mutated Eosinophilia** Both platelet-derived growth factor receptors α (*PDGFRA* located on chromosome 4q12) and β (*PDGFRB* located on chromosome 5q31-q32) are involved in MPN-relevant activating mutations. Clinical phenotype in both instances includes prominent blood eosinophilia and excellent response to imatinib therapy. In regard to *PDGFRA* mutations, the most popular is *FIP1L1-PDGFRA*, a karyotypically occult del(4)(q12) that was described in 2003 as an imatinib-sensitive activating 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 mechanism for generating this constitutively active fusion tyrosine kinase, wherein a ~800-kb interstitial deletion within 4q12 fuses the 5′ portion 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 or HES, but the presence of the mutation reliably predicts complete hematologic and molecular response to imatinib therapy.

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 phenotypes have been described, cell line transformation and myeloproliferative disease (MPD) induction in mice has been demonstrated, and imatinib therapy was proven effective when used.

***FGFR1*-Mutated Eosinophilia** The 8p11 myeloproliferative syndrome (EMS) (also known as human stem cell leukemic/lymphoma syndrome) constitutes a clinical phenotype with features of both lymphoma and eosinophilic MPN and characterized by a fusion mutation that involves the gene for fibroblast growth factor receptor 1 (*FGFR1*), which is located on chromosome 8p11. In EMS, both myeloid and lymphoid lineage cells exhibit the 8p11 translocation, thus demonstrating the stem cell origin of the disease. The disease features several 8p11-linked chromosome translocations, and some of the corresponding 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 MPD; the tyrosine kinase domain of *FGFR1* is juxtaposed to a dimerization domain from the partner gene. EMS is aggressive and requires combination chemotherapy followed by ASCT.

Hypereosinophilic Syndrome (HES) Blood eosinophilia that is neither secondary nor clonal is operationally labeled as being idiopathic. HES is a subcategory of idiopathic eosinophilia with persistent increase of the AEC to $\geq 1.5 \times 10^9$/L and presence of eosinophil-mediated organ damage, including cardiomyopathy, gastroenteritis, cutaneous lesions, sinusitis, pneumonitis, neuritis, and vasculitis. In addition, some patients manifest thromboembolic complications, hepatosplenomegaly, and either cytopenia or cytosis.

Bone marrow histologic and cytogenetic/molecular studies should be examined 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 systemic 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 complete blood count, chest x-ray, echocardiogram, and serum troponin level. An increased level of serum cardiac troponin has been shown to correlate with the presence of cardiomyopathy in HES. Typical echocardiographic findings in HES include ventricular apical thrombus, posterior mitral leaflet or tricuspid valve abnormality, endocardial thickening, dilated left ventricle, and pericardial effusion.

Glucocorticoids are the cornerstone of therapy in HES. Treatment with oral prednisone is usually started at 1 mg/kg per day and continued 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 who do not respond to usual therapy as outlined above, mepolizumab or alemtuzumab might be considered. Mepolizumab targets interleukin 5 (IL-5), a well-recognized survival factor for eosinophils. Alemtuzumab targets the CD52 antigen, which has been shown to be expressed by eosinophils but not by neutrophils.

MASTOCYTOSIS

Mast cell disease (MCD) is defined as tissue infiltration by morphologically and immunophenotypically abnormal mast cells. MCD is classified into two broad categories: cutaneous mastocytosis and systemic mastocytosis (SM). MCD in adults is usually systemic, and the clinical course can be either indolent or aggressive, depending on the respective absence or presence of impaired organ function. Symptoms and signs of MCD include urticaria pigmentosa, mast cell mediator release symptoms (e.g., headache, flushing, lightheadedness, syncope, anaphylaxis, pruritus, urticaria, angioedema, nausea, diarrhea, abdominal cramps), and organ damage (lytic bone lesions, osteoporosis, hepatosplenomegaly, cytopenia). Aggressive SM can be associated with another myeloid malignancy, including MPN, MDS, or MDS/MPN overlap (e.g., CMML), or present as overt mast cell leukemia. In general, life expectancy is near normal in indolent SM but significantly shortened in aggressive SM.

Diagnosis of SM is based on bone marrow examination that shows clusters of morphologically abnormal, spindle-shaped mast cells that are best evaluated by the use of immunohistochemical stains that are specific to mast cells (tryptase, CD117). In addition, mast cell immunophenotyping reveals aberrant CD25 expression by neoplastic mast cells. Other laboratory findings in SM include increased levels of serum tryptase, histamine and urine histamine metabolites, and prostaglandins. SM is associated with *KIT* mutations, usually *KIT* D816V, in the majority of patients. Accordingly, mutation screening for *KIT* D816V is diagnostically useful. However, the ability to detect *KIT* D816V depends on assay sensitivity and mast cell content of the test sample.

Both indolent and aggressive SM patients might experience mast cell mediator release symptoms, which are usually managed by both H_1 and H_2 histamine receptor blockers as well as cromolyn sodium. In addition, patients with propensity to vasodilatory shock should wear a medical alert bracelet and carry an Epi-Pen self-injector for self-administration of subcutaneous epinephrine. Urticaria pigmentosa shows variable response to both topical and systemic glucocorticoid therapy. Cytoreductive therapy is not recommended for indolent SM. In aggressive SM, either interferon α or cladribine is considered first-line therapy and benefits the majority of patients. In contrast, imatinib is ineffective in the treatment of *PDGFR*-unmutated SM.

DENDRITIC AND HISTIOCYTIC NEOPLASMS

Dendritic cell (DC) and histiocyte/macrophage neoplasms are extremely rare. DCs are antigen-presenting cells, whereas histiocyte/