# 09 - 366 Mastocytosis

## 366 Mastocytosis

less for BRCA mutation carriers), and sensitized patients typically have type I symptoms with pruritus, flushing, urticaria, throat tightening, and hypotension with elevated tryptase (Fig. 365-2). ST is positive in >85% of patients with recent reactions. In a prospective study of 126 women who received six or more carboplatin treatments, repeat ST before each exposure identified reactors, with seven anaphylactic reactions in seven patients who agreed to be reexposed to carboplatin despite positive ST. Oxaliplatin reaction phenotypes include CRR and mixed reactions with conversion from type I to CRR and mixed phenotypes during DD. Oxaliplatin-induced immune-mediated thrombocytopenia (OIIT) with bleeding is a rare complication that precludes further DD. Carboplatin DD started in early 2000 and a large study in 2016 with 370 patients (212 carboplatin-allergic and 13 cisplatin-allergic patients), who underwent 2177 DDs, mostly in the outpatient setting with three- or four-bag protocols, showed 20% mild BTRs, non superior costs compared to regular infusions, and a life expectancy advantage at 5 years in ovarian cancer patients compared to nonallergic patients. A study of 272 patients allergic to platins, taxanes, and mono clonals who underwent 1471 DDs with three-bag 12-step protocols reported similar safety. Oxaliplatin DD poses challenges due to the heterogeneity of phenotypes and phenotype switching. A study of 48 patients with 200 DDs who underwent three-bag 12-step protocols showed mild to moderate BTRs in 18 patients, 1 patient with OIIT, and 2 patients with hemolytic anemia. A study of patients with type I, CRR, and mixed reactions who underwent 273 DDs indicated a switch from type I to CRR and mixed reactions during DD, with elevated IL-6, and two patients developed OIIT. The survival of platinum-desensitized patients is noninferior to nonallergic patients. Doxorubicin and Other Chemotherapy Drugs Doxorubicin reactions are rare, occurring at first exposure, and a study of 30 patients and 128 DDs, mostly with three-bag 12-step protocols, showed 16% mild BTRs, and one patient required epinephrine. DDs for etoposide, cyclophosphamide, methotrexate, gemcitabine, and other chemother apy drugs have shown similar safety. ■ ■MONOCLONALS/BIOLOGICALS Infusion reactions of the type I IgE/non-IgE mediated, CRR, mixed, and delayed-reaction phenotypes have been reported for monoclonal antibodies (MoAbs). Hypersensitivity reactions can occur on first exposure or after multiple exposures (Fig. 365-2). Reactions are more frequent with chimeric MoAbs but also occur with humanized and fully humanized MoAbs. Skin testing is limited by cost. Patients with cetuximab-induced anaphylaxis react to galactose-alpha-1-3-galactose, a nonhuman carbohydrate in the Fab chain of cetuximab, due to pre existing IgE acquired through tick bite sensitization. DDs have been reported for most IV and SC available MoAbs (Fig. 365-3). The first series of MoAb desensitizations included 23 patients with moderate to severe type I and mixed reactions to trastuzumab, infliximab, and ritux imab who underwent 105 DDs with three bags and 12 steps and had 29% mild BTRs. A study of 104 patients who reacted to 16 MoAbs with type I, CRR, mixed, and delayed reactions and received 526 DDs, mostly with three bags and 12 steps in the outpatient setting, presented with 23% mild BTRs. Tryptase was elevated in type I and

IL-6 in CRR BTRs. ■ ■SMALL MOLECULES Epidermal growth factor receptor and tyrosine kinase inhibitors such as imatinib, osimertinib, and olaparib can induce type I and type IV reac tion phenotypes, and successful DDs with multiple oral doubling doses have been reported, allowing for continued long-term maintenance. ■ ■NONSTEROIDAL ANTINFLAMMATORY

DRUGS (NSAIDS) Aspirin (ASA) and other NSAIDs can induce type I reactions with urticaria and anaphylaxis thought to be IgE-mediated and, in patients with asthma and dysregulated lipid metabolism, a syndrome termed aspirin-exacerbated respiratory disease (AERD) with bronchospasm. Patients with AERD have universal intolerance to COX-1 inhibitors but tolerate COX-2 inhibitors. The American Academy of Allergy, Asthma, and Immunology Work Group Report in 2020 reviewed 14

series of ASA DDs with intranasal ketorolac or oral aspirin in >900 AERD patients. More than 70% of patients reported improvement of asthma, lack of polyp recurrence, recovery of sense of smell, and less steroid usage, with cross-desensitization and tolerance to all COX-1 inhibitors while maintained on daily ASA. For type I reactions in car diac and neurologic patients, DD with rapid doubling doses has been proven safe and effective.

CHAPTER 366 ■ ■OTHER DRUGS Symptoms of progestogen hypersensitivity (PH) are cyclical and include type I and delayed phenotypes. PH can lead to miscarriage, and oral and vaginal DD protocols have resulted in viable pregnancies. Reactions to iron formulations include type I, CRR, mixed, and delayed phenotypes that are responsive to DD. Allopurinol-induced delayed rashes respond to PO and IV DD protocols. Corticosteroids, glatiramer acetate, vaccines, and other medication DDs have been reported with doubling multistep PO, IV, and SC protocols. Mastocytosis IMPACT Discontinuing drugs inducing allergic symptoms affects patients for whom second-line therapies may not be available, are more expensive, or do not provide similar therapeutic benefits. DD protocols allow for the safe reintroduction of first-line therapies, and their use should be extended to all patients in need. ■ ■FURTHER READING Adnan A, Acharya S: Multistep IgE mast cell desensitization is a dose- and time-dependent process partially regulated by SHIP-1. J Immunol 210:709, 2023. Castells M et al: Penicillin allergy. N Engl J Med 381:2338, 2019. Dhopeshwarkar N: Drug-induced anaphylaxis documented in elec tronic health records. J Allergy Clin Immunol Pract 7:103, 2019. Isabwe GAC: Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. J Allergy Clin Immunol 142:159, 2018. Sloane D: Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. J Allergy Clin Immunol Pract 4:497, 2016. Matthew P. Giannetti, Joshua A. Boyce

Mastocytosis ■ ■DEFINITION AND EPIDEMIOLOGY Mastocytosis is defined by accumulation of clonally expanded mast cells in tissues such as skin, bone marrow, liver, spleen, and gut. Diag nostically, mast cell expansion is most readily identified in skin and/ or bone marrow. Mastocytosis occurs at any age, although it is most commonly diagnosed in infancy and young adulthood. The prevalence of mastocytosis is estimated at ~1 in 10,000 people. Most forms of the disease are characterized by somatic gain-of-function mutations in the stem cell factor receptor (KIT) gene, and >90% of patients carry the KIT D816V mutation. Familial occurrence is rare, and atopy is not increased compared with the general population. ■ ■CLASSIFICATION AND PATHOPHYSIOLOGY A consensus classification for mastocytosis recognizes cutaneous mas tocytosis with variants, systemic mastocytosis with five variants, and mast cell sarcoma (Table 366-1). Cutaneous

mastocytosis is the most common diagnosis in children and indicates disease limited to skin with absence of pathologic infil trates in internal organs. It is usually diagnosed within the first year

TABLE 366-1 Classification of Mastocytosis Cutaneous mastocytosis (CM) Maculopapular cutaneous mastocytosis (MPCM) Solitary mastocytoma of skin Diffuse cutaneous mastocytosis Systemic mastocytosis Indolent systemic mastocytosis (ISM) Smoldering systemic mastocytosis Systemic mastocytosis with associated clonal hematologic non–mast cell PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders lineage disease (SM-AHNMD) Aggressive systemic mastocytosis (ASM) Mast cell leukemia (MCL) Mast cell sarcoma (MCS) Source: Modified from DA Arber et al: International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 140:1200, 2022. of life with demonstration of fixed, maculopapular, polymorphic, and hyperpigmented lesions (known as maculopapular cutaneous mas tocytosis [MPCM]), solitary mastocytoma(s), or diffuse cutaneous mastocytosis. Although mast cell accumulation is limited to the skin, children often have systemic symptoms. Systemic mastocytosis (SM) refers to involvement of an extracutaneous site (most often bone mar row). There are five distinct variants of SM. Indolent systemic mastocy tosis (ISM) accounts for >70% of adult patients. ISM is diagnosed when there is no evidence of organ dysfunction due to mast cell infiltration, an associated hematologic disorder, or mast cell leukemia. ISM is asso ciated with a normal life expectancy. Smoldering systemic mastocytosis (SSM) is characterized by high mast cell burden including bone mar row infiltration of >30% and a baseline serum tryptase >200 ng/mL (B findings), but absence of systemic mastocytosis associated with clonal hematologic non–mast cell lineage disease (SM-AHNMD) or aggressive systemic mastocytosis (ASM) (Table 366-2). In SM-AHNMD, the prog nosis is determined by the nature of the associated disorder, which can range from dysmyelopoiesis to leukemia. In ASM, mast cell infiltration may occur in multiple organs such as liver, spleen, gut, bone, and bone marrow resulting in one or more C findings and a poor prognosis (Table 366-2). Mast cell leukemia (MCL) is the rarest form of SM and is invariably fatal at present; the peripheral blood contains circulating, metachromatically staining, atypical mast cells. An aleukemic form of MCL is recognized without circulating mast cells when the percentage of high-grade immature mast cells in bone marrow smears exceeds 20% in a nonspicular area. Mast cell sarcoma is a rare solid mast cell tumor with malignant invasive features. TABLE 366-2 B and C Findings for Diagnosis of SSM and ASM B Findings (2 or more in the absence of any C findings are required for a diagnosis of SSM):

1. High MC burden: MC infiltration in bone marrow of >30%, basal serum tryptase level >200 ng/mL, and/or KIT D816V >10% VAF in bone marrow
2. Hypercellular bone marrow with signs of dysmyelopoiesis but without cytopenias meeting C criteria or WHO criteria for an MDS or MPN
3. Palpable hepatomegaly, palpable splenomegaly, or lymphadenopathy (on CT or ultrasound: >2 cm) without impaired liver function or hypersplenism C Findings (1 or more required for a diagnosis of ASM). C findings should be reasonably attributable to high tissue MC infiltration:
4. Cytopenia(s): ANC <1000/μL or Hb <10 g/dL or PLT <100,000/μL
5. Hepatomegaly with ascites and impaired liver function
6. Palpable splenomegaly with associated hypersplenism
7. Malabsorption with hypoalbuminemia and weight loss

8. Skeletal lesions: large area(s) of osteolysis with pathologic fractures (presence of osteoporosis alone without osteolytic lesions does not satisfy this criterion) Abbreviations: ANC, absolute neutrophil count; ASM, aggressive systemic mastocytosis; CT, computed tomography; Hb, hemoglobin; MC, mast cells; MDS, myelodysplastic syndromes; MPN, myeloproliferative disorders; PLT, platelets; SSM, smoldering systemic mastocytosis; VAF, variant allele frequency; WHO, World Health Organization.

Somatic activating mutations in the KIT gene are characteristic of mastocytosis. KIT D816V is most common, although other mutations have been reported. KIT mutations are found in mast cells and some times in other cell lineages in patients with mastocytosis. KIT muta tions are observed in patients with all forms of SM but are also present in some children with cutaneous mastocytosis in lesional skin. Addi tional mutations in genes such as TET2, SRSF2, ASLX1, and RUNX1 known to be associated with other hematologic neoplastic disorders can be detected in patients, usually with advanced variants of SM. The life expectancy for patients with cutaneous mastocytosis and for most patients with ISM is normal, whereas that for patients with SMAHNMD is determined by the non–mast cell component. ASM and MCL have a poor prognosis, while patients with SSM have an inter mediate prognosis. Progression from ISM to a more advanced form is uncommon (~5% lifetime risk); however, patients should be monitored for emergence of hematologic disease and end-organ manifestations of ASM. In infants and children with cutaneous manifestations, namely, maculopapular cutaneous mastocytosis, mastocytoma(s), or bullous lesions, visceral involvement is usually lacking, and spontaneous reso lution is common prior to adolescence. Polymorphic maculopapular cutaneous mastocytosis usually resolves spontaneously. Progression from cutaneous mastocytosis (CM) to ISM may occur in ~10% of chil dren, especially in those with high mast cell burden (diffuse cutaneous mastocytosis) or hematologic abnormalities and those who present with smaller uniform lesions with diameters measuring <2 cm (mono morphic MPCM). ■ ■CLINICAL MANIFESTATIONS The clinical manifestations of SM are due to the release of bioactive substances acting at both local and distal sites, tissue infiltration by mast cells, and the tissue response to the cellular infiltrate. Clinical manifestations include intermittent urticaria, flushing, tachycardia and vascular collapse, gastric acid hypersecretion, crampy lower abdominal pain, and diarrhea. The increased local mast cell burden in the skin (MPCM), bone marrow, and gastrointestinal tract may be a direct cause of pruritus, bone pain, and malabsorption, respectively. Mast cell–mediated fibrotic changes may occur in liver, spleen, and bone marrow but not in gastrointestinal tissue or skin. The cutaneous lesions of MPCM are reddish-brown macules, pap ules, or plaques that respond to trauma with urtication and erythema (Darier’s sign). Two distinct forms of MPCM are recognized: poly morphic MPCM and monomorphic MPCM. Children with CM may present with MPCM, mastocytomas, or diffuse cutaneous mastocyto sis (DCM). Mastocytomas are generally solitary elevated lesions that are yellow, brown, or red in color. Their size may vary from a few millimeters to several centimeters. Rubbing or irritation of a masto cytoma lesion may lead to systemic symptoms such as flushing and urticaria. Children with DCM present without distinct lesions, but rather a generalized thickening of skin and “peau d’orange” appear ance due to diffuse mast cell infiltration. DCM is associated with bul lae formation and more severe systemic symptoms, including upper gastrointestinal irritation and vascular collapse in the first few years of life. Maculopapular skin lesions of mastocytosis may be present in patients with adult-onset systemic disease. The apparent incidence of cutaneous lesions is ≥80% in patients with ISM and <50% in those with SM-AHNMD or ASM. In the upper gastrointestinal tract, gas tritis and peptic ulcer are significant problems. In the lower intestinal tract, the occurrence of diarrhea and abdominal pain is attributed to increased motility due to mast cell mediators. The periportal fibrosis

associated with mast cell infiltration may lead to portal hypertension and ascites. In some patients, anaphylaxis may occur with rapid and life-threatening vascular collapse. Anaphylaxis is most commonly induced by Hymenoptera stings and nonsteroidal anti-inflammatory drugs (NSAIDs). The neuropsychiatric disturbances are clinically most evident as impaired recent memory, decreased attention span, and “migraine-like” headaches. Patients may experience exacerbation of a specific clinical sign or symptom variably with alcohol ingestion, temperature changes, stress, use of mast cell–interactive opioids, or ingestion of NSAIDs.

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