

Systemic Mastocytosis: Bone Marrow Pathology, Classification, and Current Therapies

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Key Words

Systemic mastocytosis · Histopathology · Classification · Therapies

Abstract

Mast cell disease (MCD) is characterized by the abnormal growth and accumulation of neoplastic mast cells (MC) in one or more organs. The diagnosis of systemic MCD is most commonly established by a thorough histological and immunohistochemical examination of a bone marrow (BM) trephine specimen. In cases with pathognomonic perivascular and -trabecular aggregates of morphologically atypical MC and significant BM involvement, the diagnosis may be relatively straightforward. In contrast, when a sparse, loose pattern of MC infiltration predominates, or when MCs are obscured by an associated non-MC hematological neoplasm, a high index of suspicion and use of adjunctive tests, including special stains, such as tryptase and CD25, may be necessary to reach a diagnosis. The updated classification for MCD clarifies the clinical and pathological criteria for categorizing patients into relatively discrete subgroups. Some cases, however, such those with Fip1-like-1-platelet-derived growth factor receptor α (FIP1L1-PDGFR α)⁺ clonal eosinophilia associated with elevated serum tryptase levels, with features that overlap MCD and chronic eo-

sinophilic leukemia, may not be easy to categorize on the basis of this classification. There is no standard therapy for MCD and treatment has to be tailored to the needs of the individual patient. MC-cytoreductive therapies, such as interferon- α and chemotherapy, are generally reserved for patients with progressive disease and organopathy. A subset of MCD patients with associated eosinophilia who carry the FIP1L1-PDGFR α oncogene will achieve complete clinical, histological, and molecular remissions with imatinib mesylate therapy, in contrast to those with c-kit D816V mutations. The BM pathology, consensus classification, and current therapies for MCD are further discussed in this article.

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Bone Marrow Pathology

Upon reviewing the World Health Organization (WHO) criteria for diagnosing mast cell disease (MCD), it immediately becomes obvious why the hematopathologist plays a critical role in the diagnostic process.

The diagnosis of systemic, extracutaneous MCD is most commonly established through a thorough histological and immunohistochemical examination of a bone marrow (BM) trephine specimen, which remains the most important diagnostic approach [1–7]. This is be-

cause the BM is almost always involved in systemic MCD, and standards regarding diagnostic aspects of normal and neoplastic mast cells (MCs) in other extracutaneous tissues have not been clearly defined yet [8].

Normal MC are round or oval, with a round, centrally located, nonlobated nucleus, and densely packed, uniformly distributed cytoplasmic granules. BM aspirate smears in MCD (except MC leukemia; MCL) generally show slightly increased numbers of MC, which may account for 2–5% of nucleated marrow cells [2]. Neoplastic MC vary in their morphological appearance, from the typical round MC to the larger fusiform shapes with uniformly distributed fine granules and long, polar cytoplasmic processes. The fusiform MC may also demonstrate hypogranulation and uneven granule distribution, as well as nuclear lobation [2, 3, 9–11]. BM aspirate smears from some patients show an abundant number of atypical MC (50–95% of nucleated cells), frequently with lobulated nuclei [2]. These patients with MCL have diffuse marrow infiltration with circulating MC.

The characteristic BM MC lesion, variously referred to as MC granuloma [12, 13], eosinophilic fibrohistiocytic lesion [14], or MEL (MC, eosinophil, lymphocyte) lesion [5], is usually comprised of perivascular and/or trabecular aggregates of MC. These aggregates may be relatively monomorphic, comprised mainly of fusiform MC with pale cytoplasm and inconspicuous nuclei resembling histiocytes, or more polymorphic, with MC found to be admixed with lymphocytes, eosinophils, neutrophils, histiocytes, endothelial cells, and fibroblasts [1]. Some lesions may reveal a central focus of lymphocytes, surrounded by MC, or vice versa. Eosinophils are frequently found in MC lesions, with the highest concentration being described at the periphery of the lesions. BM specimens may reveal a preponderance of fusiform or round-shaped MCs, or a mixture of round and fusiform shapes [2, 10]. While irregular trabecular thickening is commonly noted, particularly when MC aggregates about the trabeculae, other cases may be characterized by a marked thinning of BM trabeculae and osteopenia. The perivascular lesions exhibit hypertrophy of the medial and adventitial layers of the vessel wall, with a surrounding cuff of infiltrating MC [1]. BM MC infiltrates commonly exhibit a dense network of reticulin fibers. In cases with diffuse BM infiltration by monomorphous, spindled MC resembling fibroblasts, a diagnosis of idiopathic myelofibrosis may be erroneously made, especially given the accompanying decrease in normal hematopoietic elements.

While MC atypia has been proposed as a criterion for aggressive MCD [3, 15], other studies have questioned the precise prognostic value of such morphological abnormalities [4, 10]. Lennert and Parwaresch [3] proposed cytological and cytochemical characteristics of MC as one feature that distinguishes 'benign' from 'malignant' MCD. The latter exhibits MC with large, irregularly shaped nuclei, increased mitotic activity, and decreased metachromatic granules, sometimes resembling monocytes [1, 3].

Three major histological patterns of BM MC infiltration have been described [2]. The commonest, Type I, exhibits focal MC infiltration, with a normal distribution of fat cells and hematopoietic elements in the uninvolved marrow space. Patchy MC infiltration with osteosclerosis and fibrosis also characterizes the Type II pattern, but, in contrast to Type I, marked hypercellularity is noted in the non-MC involved marrow space. The increased cellularity results from a variable increase in the number of immature granulocytes, eosinophils, immature monocytes, small megakaryocytes, or blast cells. A subset of these cases will meet WHO criteria for diagnosis of a clonal, non-MC lineage hematological disorder associated with MCD (MCD-AHNMD). Type III pattern represents MCL, and is characterized by a diffuse marrow infiltration with neoplastic, morphologically atypical MC, commonly with circulating MC. Not all cases can be neatly categorized on the basis of this histological classification, such as those with borderline findings between Types I and II, and those with diffuse BM MC infiltration, but without other features of MCL [16].

In general terms, MC are not readily recognized by hematoxylin-and-eosin staining, and may be confused with a variety of other cells that include fibroblasts, histiocytes, hairy cells, and monocytes [1, 17]. In addition, BM MC lesions may be significantly polymorphic, with MC being admixed with lymphocytes, eosinophils, neutrophils, histiocytes, endothelial cells, and fibroblasts [1]. Metachromatic stains, such as Giemsa or toluidine blue, are useful for demonstrating the basophilic MC granules [18], but such staining is diminished or often lost with the decalcification process with acidic solutions that is necessary for sectioning of paraffin-embedded BM tissue [17]. The cytoplasmic granules of MC, including those of immature MC, are also intensely stained with naphthol-AS-D-chloroacetate esterase [19], which has been historically useful. Among the immunohistochemical markers, staining for tryptase is considered the most sensitive, being able to detect even small-sized MC infiltrates [6, 20]. Given that virtually all MC, irrespective of their stage of mat-

uration, activation status, or tissue of localization, express tryptase, staining for this marker detects even those infiltrates that are primarily comprised of immature, non-granulated MC [21]. Tryptase immunostaining is particularly useful for the diffuse pattern of MC infiltration, where a loose MC distribution, in lieu of the discrete MC aggregates, is seen [20]. It must be emphasized that neither tryptase, nor other immunohistochemical markers, such as chymase, KIT/CD117, and CD68, can distinguish between normal and neoplastic MC [22]. Also, abnormal basophils seen in some cases of acute and chronic basophilic leukemia, as well as in chronic myeloid leukemia, and blasts in some acute myelogenous leukemia cases may be tryptase⁺, and may prove difficult to distinguish from MC [23]. Recently, CD25, a low-affinity receptor for interleukin-2, has been proposed as an immunohistochemical marker that reliably distinguishes between normal and neoplastic MC, for all major subgroups of MCD [21]. In 72 of the 73 MCD cases analyzed, a strong, annular, membrane-staining pattern for CD25 was detected across all subgroups, and in these, the number of CD25⁺ cells was closely correlated with the number of tryptase⁺ cells. Cells coexpressing tryptase and CD25 in the setting of hematological disease are highly likely to be neoplastic MC. In contrast, none of the 75 control cases showed CD25⁺ expression on BM MC by immunohistochemistry. Significantly, 2 urticaria pigmentosa (UP) cases, who did not exhibit the pathognomonic compact BM MC infiltrates on initial review, were re-examined by CD25 immunostaining. Both patients were found to have CD25⁺ MC, of which >25% had a spindled morphology, in a loosely scattered, interstitial pattern. These 2 patients were reclassified as having indolent MCD given that 3 minor criteria of the WHO system were satisfied. CD25 expression was correlated with presence of the c-kit D816V mutation in 72 of 73 systemic MCD and 2 of 3 UP cases. Consistent with our previously published flow cytometry data [24], screening for CD2 expression on BM MC by immunohistochemistry has low diagnostic value because a significant proportion of cases stain negative, and CD2 expression on BM MC is generally weak in the cases that are positive [6, 21, 22]. In one study, CD2-positivity by immunohistochemistry was 81% (35/43) in indolent MCD, 55% (11/20) in MCD-AHNMD, 29% (2/7) in aggressive MCD, and 67% (2/3) in MCL [21]. CD2-positivity, as determined by flow cytometry, was: 46% (6/13) in indolent MCD, 29% (2/7) in MCD-AHNMD, 13% (1/8) in aggressive MCD, and 0% (0/2) in MCL [24].

Table 1. Classification of mast cell neoplasms [3]

Benign	
1	Mastocytoma (mast cell nevus)
2	Cutaneous mastocytosis
	a) diffuse (mostly urticaria pigmentosa)
	b) localized
3	Systemic mastocytosis with skin involvement (mostly urticaria pigmentosa)
Malignant	
1	Malignant mastocytosis (mast cell reticulosis)
	a) primary
	b) secondary to cutaneous or systemic mastocytosis
2	Mast cell sarcoma
3	Mast cell leukemia, occurring with 1 or 2

Classification

MCD is characterized by the abnormal growth and accumulation of neoplastic MC in one or more organs of the body. In general terms, MCD exhibits immense diversity in its clinical presentation and disease course, its pattern of organ involvement, histological features, its potential overlap with other hematological neoplasia, and increasingly, in the molecular lesions that are associated with this disease. Historically, these factors have made the task of classifying MCD into discrete clinicopathological entities a challenging endeavor.

The classification of MCD has evolved over the years; the first recognition of cutaneous MCD came from Unna's [25] recognition in 1887 that UP lesions were histologically comprised of MC infiltrates. Subsequently, although the systemic nature of MCD was alluded to in case descriptions in the early 1900s by Sézary et al. [26] and Jeanselme and Touraine [27], systemic MC infiltrates were histologically demonstrated by Ellis [28] only in 1949, thus differentiating skin delimited MCD from the more extensive systemic MCD. Subsequently, a dichotomous view prevailed, wherein 'benign' MCD was separated from 'malignant' MCD, based upon the presence or absence of associated UP, organomegaly, cytological and cytochemical features of BM MC, as well as the clinical course (table 1) [3, 29–31]. Following this, based on the recognition that not all patients classified as having 'benign' MCD have a favorable outcome, and that 'malignant' MCD was comprised of relatively distinct clinicopathological entities, revised classifications that proposed four or five broad MCD subgroups were proposed [1, 32]. More recently, updated diagnostic criteria (table 2) and

Table 2. WHO criteria for diagnosis of systemic MCD [35]

Major	Multifocal dense infiltrates of mast cells in bone marrow or other extracutaneous organs (>15 mast cells aggregating)
Minor	<ol style="list-style-type: none"> 1 Mast cells in bone marrow or other extracutaneous organs show an abnormal (spindling) morphology (>25%) 2 Codon 816 c-kit mutation D816V in extracutaneous organs 3 Mast cells in the bone marrow express CD2, CD25, or both 4 Serum tryptase >20 ng/ml (does not count in patients who have an associated clonal hematological non-mast cell disease; AHNMD)

Table 3. WHO variants of mastocytosis [35]

1	Cutaneous mastocytosis (CM): <ol style="list-style-type: none"> a) Maculopapular CM b) Diffuse CM c) Mastocytoma of skin
2	Indolent systemic mastocytosis <ol style="list-style-type: none"> a) Smoldering SM b) Isolated BM mastocytosis
3	Systemic mastocytosis with an associated clonal hematological non-MC lineage disease (MCD-AHNMD)
4	Aggressive systemic mastocytosis <ol style="list-style-type: none"> With eosinophilia
5	Mast cell leukemia (MCL) <ol style="list-style-type: none"> Aleukemic MCL
6	Mast cell sarcoma
7	Extracutaneous mastocytoma

Table 4. 'C'-findings = indication of impaired organ function due to MC infiltration (has to be confirmed by biopsy in most cases) [35]

1	Cytopenia(s): Absolute neutrophil count <1,000/ μ l, or hemoglobin <10 g/dl, or platelets <100,000/ μ l
2	Hepatomegaly with ascites and impaired liver function
3	Palpable splenomegaly with hypersplenism
4	Malabsorption with hypoalbuminemia and weight loss
5	Skeletal lesions: large-sized osteolysis or severe osteoporosis causing pathological fractures
6	Life-threatening organopathy in other organ systems that definitively is caused by an infiltration of the tissue by neoplastic mast cells

an updated consensus classification (table 3), based on refinements of prior systems, was proposed for MCD in 2001 [33], and was subsequently adopted by the WHO [34]. This version incorporates recent advances in our understanding of MCD, including the role of activating c-kit receptor mutations, presence of cell surface markers that reliably distinguish neoplastic from normal MC, and detection of elevated levels of circulating MC mediators as a surrogate measure of systemic MC burden. The WHO classification takes into account the gamut of clinical manifestations of MCD, from the relatively benign pediatric-onset MCD with skin-limited disease, to the persistent, clonal, myeloproliferative variants seen in adults that may exhibit an inexorably progressive disease course, and that are often associated with a non-MC hematological malignancy.

The diagnosis of systemic MCD is established when either 1 major and 1 minor criterion, or 3 of the minor criteria, are satisfied (table 2). Described below are the major clinicopathological categories (except cutaneous MCD) included in the WHO classification:

Indolent Systemic MCD. The majority of adult systemic MCD patients have indolent disease, with a low systemic MC burden, associated UP, and, generally, a good prognosis. A subgroup of these patients, however, may have severe symptoms from MC-mediator release, and may die from anaphylactic shock [2, 15, 32]. Transformation of disease into an aggressive variant or development of an associated malignancy, while possible, is infrequent in this group of patients [2, 4, 9, 32]. The following have to be ruled out before a patient is classified as having indolent disease: (1) manifestations of end-organ dysfunction ('C' findings – table 4) such as cytopenias, weight loss secondary to malabsorption, ascites, hypersplenism, and pathological fractures, all of which have to be proven to result from MC infiltration of underlying organs, (2) clear evidence of an AHNMD, and (3) MCL [34]. Previous studies, both prospective and retrospective, have identified other prognostic variables in multivariate analyses that may be partially correlated with 'C' findings (i.e. MC-related organopathy), including older age [9, 32], absence of UP [9], type of BM MC infiltration pattern [2, 9], BM eosinophilia [35], atypical BM MC morphology [3, 7, 15, 29, 32], high BM MC burden [15, 35], and presence of c-kit D816V mutation [36]. Identification of favorable prognostic features at the time of MCD diagnosis may help identify those patients more likely to experience an indolent clinical course.

In general, the BM MC burden in indolent MCD is less than 5–10%, depending upon the methodology used for MC quantification [15, 35]. Typically, a patchy infiltration pattern with a perivascular and/or -trabecular MC aggregates is noted, with noninfiltrated regions exhibiting a normal distribution of fat cells and other hematopoietic elements [2, 35]. Less commonly, a diffuse interstitial pattern of MC with little tendency to form compact MC aggregates may be seen [8]. A spectrum of atypical morphological features including cell ‘spindling’, cytoplasmic hypogranulation, uneven granule distribution, cytoplasmic processes, and nuclear abnormalities characterize BM MC from these patients. Less commonly, MC morphology may be relatively normal [3, 8, 10, 15, 32]. When such MC predominate, a diagnostic challenge may result, and may require the use of adjunctive tests, such as screening for MC CD25 expression and for the c-kit D816V mutation. Whether a unilateral BM biopsy is sufficient to rule out BM MC infiltration in indolent MCD has recently been questioned. In 23 patients who underwent bilateral BM biopsies as part of the diagnostic workup, 4 cases (17%) had only a unilateral positive BM result [37]. Three of the four patients had a serum tryptase value of less than 25 ng/ml, and hence would not have been classified as systemic MCD, as per the WHO consensus classification, without the second BM biopsy. It is recommended that BM trephines from adult patients with clinically proven cutaneous MCD (usually UP) be screened for MC infiltrates by tryptase immunostaining, which can detect even very small infiltrates comprised of 10–15 cells.

In one study, MCD patients with a Type I pattern of BM MC infiltration (largely found in indolent disease) had an actuarial 5-year survival rate of 0.75, as compared to patients with Type II (aggressive MCD or MCD-AHNMD) or III (MCL) patterns, who had 5-year survival rates of 0.17 and 0.0, respectively [2].

The relatively infrequent smoldering MCD and isolated BM MCD subcategories of indolent systemic MCD are not discussed here.

Systemic MCD-AHNMD. The association of MCD with a broad spectrum of hematological disorders has previously been well described [1–3, 16, 31, 32, 38–40]. The frequent coexistence of systemic MCD with dysmyelopoiesis and myeloid neoplasms is consistent with the view that systemic MCD is a clonal myeloproliferative disorder (MPD) that involves a hematopoietic progenitor, commonly a myeloid progenitor. However, the independent codevelopment of two discrete hematological neoplasms, such as a monoclonal gammopathy of uncertain

significance and systemic MCD, cannot be discounted in some cases [23, 40]. The diagnosis of MCD-AHNMD should be made cautiously, and according to well-established WHO criteria, for both the MCD, as well as the associated hematological neoplasm [41].

MCD-AHNMD is the second most common MCD category; more frequent than aggressive systemic MCD and the rare true MCL [23]. Sagher and Even-Paz [30] described malignant transformation in 7% of patients with childhood-onset MCD, and in 33% of patients with adult-onset systemic MCD. Lennert and Parwaresch [3] described MCL or AML developing in 16 of 43 systemic MCD cases (37%), and Horny et al. [2] have reported a coexistent leukemia in 14 of 45 (29%) and in 25 of 61 (40%) [31] MCD patients. In a study by Travis et al. [16], 22 of 66 (33%) systemic MCD patients had an associated hematological disorder.

Most hematological disorders associated with systemic MCD involve dysmyelopoiesis or neoplasia of the myeloid elements, and are associated with characteristic cytogenetic abnormalities that are known to occur in acute leukemias, MPD, and myelodysplastic syndromes (MDS) [16, 23]. While most case series describe chronic MPD (except Philadelphia⁺ chronic myeloid leukemia) and acute leukemias as the most frequent hematological neoplasia associated with systemic MCD [31], myelodysplasia may have been relatively under-appreciated [10, 16]. The recognition in several case series that the commonest myeloid neoplasm associated with systemic MCD is chronic myelomonocytic leukemia, an MPD/MDS hybrid, supports the contention that dysmyelopoiesis is a prominent feature of systemic MCD [23, 40, 42, 43].

In general, the BM examination reveals a hypercellular marrow (Type II or III pattern of MC infiltration [2]) with effacement of the underlying architecture, although some patients cannot be neatly categorized on this basis, and MDS, which may represent the largest group of associated hematological disorders, may present with either a normo- or hypocellular marrow [16, 32]. In many cases, the BM MC infiltrates may be obscured by the associated hematological neoplasm if only hematoxylin-and-eosin or Giemsa stains are employed [23]. In such cases, the MC infiltrates are relatively easy to identify within sheets of monotonous blast cells than within more polymorphous infiltrates seen in MPD and MDS. A thorough examination of the BM specimen after tryptase immunostaining, however, will often reveal foci of spindled MC, thus allowing the diagnosis of MCD to be established. Infrequently, compact MC infiltrates, the major diagnostic criterion as per the WHO classification, are not de-

tected in MCD-AHNMD. In such cases, adjunctive testing, including screening for the c-kit D816V mutation and for CD25 expression on BM MC, as well as demonstration of MC atypia ('spindling'), is critical towards reaching a diagnosis of MCD [34]. A pattern of loosely scattered atypical/neoplastic MC without focal aggregates has been described in MCD with associated Chronic myelomonocytic leukemia, AML, multiple myeloma [23], as well as in cases with prominent eosinophilia that carry the Fip1-like-1platelet-derived growth factor receptor α (FIP1L1-PDGFR α) oncogene [44]. Most MCD-AHNMD cases are positive when tested for the c-kit D816V mutation [23], although other mutations have also been described [45].

In most cases, a diagnosis of MCD is made incidentally, usually after an examination of BM and other tissues for evaluation of the associated hematological disorder [16, 23]. In such cases, it is difficult to ascertain if systemic MCD existed prior to the onset of the hematological disorder, although some cases have UP lesions as well as symptoms of MC-mediator release that clearly predate the diagnosis of the associated hematological disorder.

The median age of systemic MCD patients with an associated hematological disorder is greater than patients without them, and the length of the prediagnostic intervals is significantly shorter in the former [16, 31]. MCD-AHNMD patients are more likely to present with constitutional symptoms, but less likely to experience symptoms of MC-mediator release, including skin symptoms, and also less likely to present with UP lesions. In 2 published series, 5-year survival of MCD-AHNMD patients as compared to those with systemic MCD alone was 17 versus 75%, and 28 versus 61%, respectively [2, 16]. The adverse prognosis of this group of patients largely stems from the unfavorable clinical course of the specific associated hematological disorder, rather than the systemic MCD component. In general, patients with refractory anemia with ringed sideroblasts, polycythemia vera, or essential thrombocytosis, expectedly have a more indolent course than patients with chronic myelomonocytic leukemia or AML [16]. Thus, in most cases, the associated hematological disorder tends to overshadow MCD in terms of both, the clinical presentation, as well as the clinical course of the patient, reflecting its more aggressive biological nature.

Aggressive Systemic MCD. This is the third commonest subcategory of systemic MCD [23]. As per the WHO classification [34], this condition is characterized by <20% MC in BM smears, and <10% circulating MC in

the peripheral blood. The sine qua non for diagnosing aggressive MCD is demonstrating impaired organ function (i.e. 'C' findings; table 4) resulting directly from neoplastic MC infiltration of the involved organ(s) [46]. In reality, however, biopsy of an organ other than that of BM is rarely undertaken, and organopathy is generally demonstrated by clinical tests alone.

Patients with aggressive systemic MCD are a subset of the erstwhile 'malignant mastocytosis' category that also includes MCD-AHNMD and MCL (see relevant sections in this review), and thus all share common features, such as older age, absence of UP lesions, presence of organomegaly, anemia, eosinophilia, a high BM MC burden, MC morphological atypia (i.e. high-grade morphology), BM features of dysmyelopoiesis/myeloproliferation, an elevated serum tryptase level, activating c-kit receptor mutations, and/or a rapid clinical course [1–3, 9, 15, 32, 35].

The BM shows a high, but variable degree of MC infiltration, with features of myelodysplasia and/or myeloproliferation, except that WHO criteria for an associated hematological malignancy (MCD-AHNMD) and MCL are not satisfied [34]. Given the degree of BM involvement, testing for CD25 expression on BM MC, or for c-kit D816V mutations, is often less critical in this subgroup of systemic MCD.

MCL. This is an aggressive hematological malignancy characterized by progressive organopathy, including BM failure from MC infiltration, and the presence of a considerable number of atypical MC in the BM smear (generally >20% of nucleated cells), as well as in the peripheral blood (generally >10% of leukocytes) [47–59].

MCL may arise de novo, or evolve from known pre-existing systemic MCD. In a review of 17 published MCL cases, the median age of MCL patients was noted to be 49 years (range: 18–75 years), with a mean survival time of only 6.6 months (range: 2–14 months) [60]. Anemia is virtually always present, as are circulating MC (range: <1–96% of leukocytes); however, cutaneous UP lesions are usually absent. MCL patients may present with peptic ulcer disease (often severe) [55], hepatosplenomegaly, high serum tryptase levels reflecting a high systemic MC burden [59], and the c-kit D816V mutation [60, 61].

In MCL, the BM generally reveals a dense, diffuse infiltration by markedly atypical MC which may comprise the majority of nucleated BM cells, with effacement of the underlying architecture (Type III pattern [2]). The MC are immature, sometimes blastic, and often have sparse metachromatic granules, and hence may be missed on routine staining unless tryptase [8, 15] and/or CD25

immunostaining is performed [21, 60]. Rare aleukemic variants of MCL have also been described [60]. Rarely, patients may present with large numbers of metachromatically granulated, primitive, blast-like cells, with prominent mediator-release symptoms. In such cases, differentiating MCL from tryptase- and/or c-kit D816V-positive AML [62, 63], acute basophilic leukemia [64], and the myelomastocytic overlap syndrome [65] is a diagnostic challenge, in the absence of well-defined criteria.

Current Therapy of Systemic MCD

Historically, therapy for systemic MCD has been largely empirically derived, given the relative rarity of this disease, its biological heterogeneity, and the lack of simple, widely agreed upon criteria to assess treatment response. Presently, while there is no standard therapy for systemic MCD, several general statements can be made, albeit with important caveats [41, 66–72]: (1) Cytoreductive therapy, especially chemotherapy, is generally reserved for patients with progressive disease and documented organopathy ('C' findings; table 4) from tissue MC infiltration. In select patients, however, the distinction as to whether the organopathy has resulted from MC infiltration, an immunological component of the disease, or from an associated hematological disorder (MCD-AHNMD) may be difficult or impossible to make, which may complicate the selection of appropriate therapy; (2) patients with recurrent or persistent mediator-related symptoms may require treatment with appropriate 'anti-mediator' drugs, which include histamine receptor-blockers, glucocorticoids, sodium cromolyn, acetylsalicylic acid, leukotriene antagonists, and in patients who have developed or are at risk of developing anaphylactic shock, on-demand epinephrine via a self-injector (Epi-Pen). In all cases, avoidance of triggers for MC degranulation remains the cornerstone for therapy. In the rare case of patients with severe and/or recurrent life-threatening episodes of mediator-release events that are refractory to antimediator drugs, cautious consideration may be given to the use of cytostatic or -reductive agents, keeping in mind the severe side effects and potential mutagenic effects of the latter, and only after a full discussion of potential risks and benefits of such treatment with the patient; (3) for MCD-AHNMD patients, it is recommended that a treatment plan that takes into account both components of disease, as well as the individual patient's performance status, be formulated. Given that in

the vast majority, the MCD component is only coincidentally detected [23], the treatment plan primarily takes into account the generally more aggressive associated hematological malignancy. Here, it is important to keep in mind the inherent resistance of neoplastic MC to chemotherapy, which may lead to persistent MCD even when the associated disease is in remission [73]; (4) in cases carrying the FIP1L1-PDGFR α oncogene, with clonal eosinophilia, elevated serum tryptase levels and BM involvement by neoplastic MC, imatinib mesylate ought to be considered as first-line therapy given the dramatic clinical and molecular responses to this drug (see below) [44, 74, 75]. Such patients, however, are a minority and the durability of the therapeutic response is unknown.

Commonly employed first- and second-line cytostatic/-reductive agents for the treatment of systemic MCD at the present time include:

(1) *Interferon alpha (IFN- α)*: It is often considered the first-line therapy for aggressive systemic MCD, both with and without an associated hematological malignancy. Since the original report of its efficacy [76], several groups have studied its therapeutic efficacy in systemic MCD [77–92]. In published case reports/series, IFN- α therapy has been described to improve mediator-related symptoms [88], decrease BM MC burden [76, 83, 84, 86, 89, 93], and ameliorate MCD-related ascites [76, 89], cytopenias [94], and osteoporosis [84, 86]. A recent review identified 14 cases of aggressive systemic MCD in the literature, who were treated with IFN- α . Of these, only 3 patients (20%) achieved a 'major' response to therapy [67]. Other studies have reported clinically significant responses ranging from 0% [87] to 60% [94].

Issues relating to the use of IFN- α in MCD include: (a) variability in reported response rates. This is related not only to the underlying biological heterogeneity of MCD, but also to the use of nonuniform treatment response criteria. For instance, some studies have used the recently proposed response criteria [67], wherein resolution of one 'C'-finding (e.g. increase in the absolute neutrophil count from <1.0 to $\geq 1.0 \times 10^9/l$), without progress in other 'C'-findings, constitutes a 'major response' [94]. In contrast, other studies have required normalization of histological abnormalities in addition to resolution of all symptoms and signs of disease, to define the best response [88]; (b) uncertainties regarding the optimal dose and duration of therapy. In a prospective, multicenter study, patients receiving the highest doses of IFN- α (i.e. >3 MU/m²/day) all responded to therapy [88]. The time to best response may be up to 12 months or longer [94] and delayed responses to therapy have been de-

scribed [95]. Data from one study suggested that treatment duration of 6 months or less may not be sufficiently long enough to reduce the systemic MC burden [88]; (c) occurrence of significant toxicity. There is a variable, but significant incidence (up to 50%) of dose-limiting toxicity related to IFN- α treatment, including flu-like symptoms, bone pain, fever, cytopenias, depression, and hypothyroidism [88, 89]. Anaphylaxis, as a response to IFN- α injections, has also been described [79]. (d) are IFN- α combinations superior to IFN- α monotherapy? Several investigators have used IFN- α in combination with prednisone [76, 94] to avert treatment-induced untoward reactions. Whether this combination is superior to IFN- α monotherapy in terms of efficacy and/or tolerance is currently unknown in the absence of a randomized clinical trial; (e) how durable are the objective responses? A significant proportion of patients have been reported to experience clinical and/or biochemical relapse within months of IFN- α treatment being discontinued, outlining the largely 'static' effect of IFN- α on neoplastic MC [88, 89].

(2) *2-chlorodeoxyadenosine (Cladribine/2-CdA)*: The therapeutic activity of this investigational agent, first described in a case with aggressive systemic MCD [96], has been confirmed in other studies involving a small number of patients, mostly with either IFN- α -refractory disease, or IFN- α intolerance, albeit with variable treatment schedules [97–100]. The rationale for its use in this setting stems from its known potent activity against monocytes both in vitro and in vivo [101], and the concept that MC and monocytes arise from a common progenitor [102]. 2-CdA is a purine analog, which accumulates in cells as 2-CdA 5'-phosphate after its phosphorylation by deoxycytidine kinase [103]. In this form, it blocks DNA synthesis in dividing cells by inhibiting the enzyme ribonucleotide reductase, and DNA repair in resting cells, leading to DNA strand breaks and apoptosis. In a prospective, multicenter, pilot study, 2-CdA was found to be therapeutically active in patients with indolent MCD (n = 3), smoldering MCD (n = 1), aggressive MCD (n = 3), and in MCD-AHNMD (n = 3) [98]. All patients had a favorable clinical response, with a median time to best response of 6 months. Objective responses included a decrease in serum tryptase levels and urine methylhistamine excretion in all patients, partial remission of UP lesions in all 7 patients with such lesions, and BM MC cytorreduction in 9 of 10 patients. While 2-CdA was generally well tolerated, treatment complications seen in this cohort included cytopenia(s), with fever of unknown origin (n = 2, includes herpes zoster in 1 patient) and need

for transfusions (n = 3), deep venous thrombosis (n = 1), and Sweet syndrome/toxicodermia (n = 1). One patient with an associated myelodysplastic syndrome with trisomy 8 experienced prolonged BM aplasia, and subsequently received a stem cell allotransplant. One initial responder experienced a primarily biochemical relapse 6 months after completion of 2-CdA therapy, and achieved a second response after retreatment with the same agent.

Despite 2-CdA's considerable activity in treating MCD, its precise indication(s), as well as the dose and schedule of administration in this setting remain unclear. Given the potential for prolonged BM aplasia and lymphopenia, its use is probably best restricted to select cases with IFN- α -refractory disease, after careful consideration of the risk:benefit ratio, as well as other available therapies for individual patients.

(3) *Imatinib mesylate (Gleevec)*: With molecular testing, subgroups of MCD patients with specific mutations in imatinib-responsive molecular targets can be identified. Based on these mutation(s), it may be possible to predict a priori, whether a patient will either respond, or be refractory to imatinib therapy.

FIP1L1-PDGFR α fusion: Eosinophilia (BM and/or peripheral blood) commonly accompanies systemic MCD (in 20–40% of cases – termed MCD-eos) [9, 32, 35, 104], and is demonstrably clonal in a proportion of such cases [105]. Approximately one half of MCD-eos patients carry the FIP1L1-PDGFR α fusion oncogene [44], which results from an ~800-kb interstitial deletion of chromosome 4q12, thereby generating a constitutively active PDGFR α tyrosine kinase [106]. These patients exhibit clinical and histological features of myeloproliferation and generally have an elevated serum tryptase level, but lack pathognomonic clusters of atypical MC in the BM on routine hematoxylin-and-eosin staining [44, 74, 75, 107]. Regardless of whether the FIP1L1-PDGFR α + cases are classified as a unique subtype of systemic MCD [44, 75] or a 'myeloproliferative variant' of hypereosinophilic syndrome [74, 107], or as chronic eosinophilic leukemia [108], or a myelomastocytic overlap syndrome [65], they generally exhibit a complete and durable (4–30 months) response to 'low-dose' (100 mg/day) imatinib [44, 108, 109], which is currently considered first-line therapy for these patients [110]. It is currently recommended that all suspected MCD-eos cases be screened for the FIP1L1-PDGFR α fusion by either fluorescence in situ hybridization or reverse transcriptase-polymerase chain reaction [70, 72]. Imatinib therapy in FIP1L1-PDGFR α + clonal eosinophilia has occasionally been associated with car-

diogenic shock [111, 112]. It is currently recommended that patients receive concomitant corticosteroids (1 mg/kg/day) for 1–2 weeks in the presence of either an abnormal echocardiogram or elevated serum troponin levels pretreatment.

C-kit Mutations. The c-kit point mutation, D816V, is found in all subsets of systemic MCD, and may occur with or without accompanying eosinophilia. This mutation maps to the receptor enzymatic site and renders it resistant to inhibition by imatinib, both in vitro [113, 114] and, as shown preliminarily, in vivo as well [75, 117,

118]. Imatinib, thus, is unlikely to be beneficial for the treatment of those adult and atypical pediatric patients who carry the D816V mutation. Preliminary studies, however, reveal the enzymatic site mutations to be inhibited by newer generation small molecule inhibitors, which will likely enter clinical trials soon [119]. In contrast to D816V, the rare germ-line F522C mutation, which is associated with an unusual variant of systemic MCD, is inhibited by imatinib [120]. These data underscore the importance of performing a mutational analysis of c-kit prior to contemplating therapy with imatinib mesylate.

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