To the editor:

Proposal for a revised classification of systemic mastocytosis

Historically, mast cell disease (MCD) signified overt infiltration of one or more organs by cytologically abnormal mast cells.\(^1\) In adults, the condition almost always involves the bone marrow (BM), a cardinal feature of systemic mastocytosis (SM). We now recognize SM as a hematopoietic stem cell disease that often harbors a KIT mutation and is sometimes associated with non–mast cell lineage clonal myeloproliferation. The World Health Organization (WHO) classification system recognizes 4 major SM subcategories: indolent SM (ISM; little or no evidence of organ dysfunction), aggressive SM (ASM; presence of disease-related organopathy), SM associated with a clonal hematologic non–mast cell lineage disease (SM-AHNMD), and mast cell leukemia (MCL; presence of ≥20% mast cells in BM aspirate).\(^2\) Although we fully endorse the current classification system, it has its limitations, and we hope to initiate a constructive dialogue that may lead to a consideration for revisions.

1. Unlike the case with blast-phase chronic myelogenous leukemia (CML) or leukemic conversion of BCR-ABL\(^{-}\)negligible myeloproliferative neoplasms (MPN), most MCL cases develop de novo rather than represent transformation of preexisting SM. Such was the case in the majority of MCL cases identified in a recent review of 342 MCD patients from our institution.\(^3\) The mere presence of KITD816V in some MCL cases (the sole MCL case tested in the aforementioned study was negative for the mutation) does not justify the status quo, because the pathogenetic contribution of KITD816V in SM and its use as a therapeutic target are uncertain and definitely not as well defined as they are for BCR-ABL or FIP1L1-PDGFRα. From a practical standpoint, the clinical features and treatment of MCL are more akin to acute leukemia than SM.

2. The clinical relevance of the SM-AHNMD subcategory has not been convincingly made, since the SM component is often not the dominant process from the standpoint of clinical features, diagnosis, bone marrow histology, or treatment. Again, for the reasons outlined in the previous paragraph, the presence of KITD816V should not be used as an excuse to lump together a clinicopathologically heterogenous group of diseases that are prognostically diverse. The observations from our recent review of 123 cases with SM associated with other myeloid malignancies underscore this point.\(^4\)

3. The current proposal fails to address the prognostic relevance of the provisional ISM subvariants, smoldering SM (SSM) and BM mastocytosis (BMM).

Based on the above discussion, we propose the following revisions to the current SM classification (Table 1):

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Indolent systemic mastocytosis (ISM)</td>
<td>Meets criteria for SM; no “C” findings; no evidence of SM-MDS, SM-CMML, SM-AL, or AML with BM mastocytosis; minimal or no MPN features</td>
</tr>
<tr>
<td>II</td>
<td>Smoldering systemic mastocytosis (SSM)</td>
<td>As above for ISM; 2 or more “B” findings</td>
</tr>
<tr>
<td>III</td>
<td>Aggressive systemic mastocytosis (ASM)</td>
<td>Meets criteria for SM; no evidence of SM-MDS, SM-CMML, SM-AL, or AML with BM mastocytosis; 1 or more “C” findings; MPN features allowed</td>
</tr>
<tr>
<td>IV</td>
<td>Systemic mastocytosis associated with myeloproliferative neoplasm, unclassifiable (SM-MPN)</td>
<td>No “C” findings</td>
</tr>
</tbody>
</table>

SM indicates systemic mastocytosis; MPN, myeloproliferative neoplasm; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; AL, acute leukemia; AML, acute myeloid leukemia; and BM, bone marrow.
occurrence of KITD816V may be emphasized by naming the entity “MCL with KITD816V,” similar to other entities in the “AML with recurrent genetic abnormalities” subcategory. Similarly, “myelomatosic leukemia” and “AML with BM mastocytosis” (ie, SM-AML) can be included in the same “AML and related myeloid neoplasms” category.

2. SM-AHNMD should be eliminated as a subcategory of SM; instead, “SM–chronic myelomonocytic leukemia” (SM-CMML) and “SM–myelodysplastic syndrome” (SM-MDS) should be placed under the WHO category of “Myelodysplastic/myeloproliferative neoplasms” (MDS/MPN), given their similar prognosis and morphologic characteristics. In contrast, there is a firm basis for adopting a SM-MPN subcategory: it has been recognized since at least the early 1980s that a proportion of SM patients have BM features that are consistent with a coexisting MPN that is otherwise unclassifiable.5 The rare cases of SM with associated lymphoid or plasma cell neoplasm can be classified in the relevant category as, for example, “multiple myeloma with BM mastocytosis.”

3. Given its significantly worse prognosis and different age distribution, as demonstrated in our recent study of 159 cases with ISM,6 SSM should be separated from ISM as a distinct entity. In contrast, the clinical relevance of retaining the provisional entity “BMM” as an ISM subvariant is limited and can be removed.

We hope that this document serves to open the dialogue among interested parties regarding the classification of SM, to make it more practical and clinically relevant. In this regard, we strongly believe that the current WHO framework for the classification of hematologic malignancies is the best venue to facilitate the relevant discussions and debates.

To the editor:

Induction of p53 and up-regulation of the p53 pathway in the human 5q− syndrome

There is mounting evidence from the study of animal models of human disorders of defective ribosome biogenesis, including Diamond-Blackfan anemia and Treacher Collins syndrome, that ribosomal stress leads to activation of the p53 pathway.1-3 Stabilization of p53 leads to cell-cycle arrest and apoptosis. We read with interest the manuscript by Danilova showing that deficiency of RPS19 in the zebrafish results in developmental abnormalities and defective erythropoiesis through the activation of the p53 protein family.3 The 5q− syndrome is the most distinct of all the myelodysplastic syndromes (MDS), and is defined under the World Health Organization (WHO) classification as refractory anemia with the del(5q) as the sole karyotypic abnormality [MDS with del(5q)].4-5 We have recently generated a mouse model of the human 5q− syndrome (with haploinsufficiency of RPS14) that shows the key features of the human disease, including a macrocytic anemia.6 p53 is activated in this mouse model of the human 5q− syndrome and intercrossing with p53-deficient mice completely rescued the progenitor cell defect.6 We thus hypothesized that activation of p53 and of the p53 pathway may underlie the pathogenesis of the human 5q− syndrome.

Data from several laboratories suggests that up-regulation of the p53 pathway is a common response to haploinsufficiency of ribosomal proteins. We now present an analysis of the p53 pathway in the 5q− syndrome; gene expression profiling (performed as previously described7 on Affymetrix U133 Plus2.0 arrays) was used to compare CD34+ cells from 16 patients with 5q− syndrome with CD34+ cells from 17 healthy controls, and 1570 significantly differentially expressed genes (P < .05, Benjamini-Hochberg correction) were identified. We then imported this gene list into the DAVID gene ontology application, and the p53 pathway was returned as significantly deregulated (p = .031) in the 5q− syndrome (Figure 1A). Ten genes in the p53 pathway were significantly deregulated: FAS, CD82, WIG1, CASP3, SESN3, TNFRSF10B (DR5), MDM4, BAX, DDB2 and BID. All these genes were expressed at higher levels in 5q− syndrome compared with healthy controls, with the exception of MDM4 (a negative regulator of p53) which was expressed at lower levels in 5q− syndrome patients. Moreover, 5 of the 8 most significantly up-regulated known genes in 5q− syndrome are p53 targets, including WIG1 and BAX.5 The p53 pathway was not significantly deregulated in non-5q− syndrome patients with a del(5q) (n = 30) or in non-del(5q) patients (n = 136).

Next, we performed an immunohistochemical analysis of p53 protein expression in bone marrow trephine sections from 3 patients with 5q− syndrome and 6 normal bone marrow samples. Strong p53 expression was found in all 3 cases of 5q− syndrome compared with healthy controls, with the exception of MDM4 (a negative regulator of p53) which was expressed at lower levels in 5q− syndrome patients. Moreover, 5 of the 8 most significantly up-regulated known genes in 5q− syndrome are p53 targets, including WIG1 and BAX.5 The p53 pathway was not significantly deregulated in non-5q− syndrome patients with a del(5q) (n = 30) or in non-del(5q) patients (n = 136).

Next, we performed an immunohistochemical analysis of p53 protein expression in bone marrow trephine sections from 3 patients with 5q− syndrome and 6 normal bone marrow samples. Strong p53 expression was found in all 3 cases of 5q− syndrome while only rare p53-positive cells were observed in normal bone marrow. By double immunostaining6 we showed that clusters of p53-positive cells with the morphologic appearance of erythroblasts were positive for Glycophorin in all 3 patients with 5q− syndrome (Figure 1B).

References


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Contribution: A.P. and A.T. conceived and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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