## Supplementary Materials

**Table S1.** Consensus criteria for mast cell activation syndrome (MCAS) *.

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|---|
| i) Typical clinical signs of severe, recurrent (episodic) systemic mast cell activation are present (often in form of anaphylaxis) (definition of systemic: involving at least two organ systems) |
| ii) Involvement of MC is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual´s baseline to plus 20% plus 2 ng/mL ** |
| iii) Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production or drugs blocking mediator release or effects of MC-derived mediators *** |

* The consensus criteria for MCAS were first published in (27). All three MCAS criteria (i+ii+iii) must be fulfilled to call a condition MCAS.** Other MC-derived markers of MC activation (histamine and histamine metabolites, PGD2 metabolites) have also been proposed but are less specific compared to tryptase. Abbreviations: MC, mast cells; PGD2, prostaglandin D2. *** Example: histamine receptor blockers.

**Table S2.** Conditions and Disorders (Co-Morbidities) predisposing to MCA/MCAS.

| Predisposing Condition | Estimated Frequency of Anaphylaxis / MCAS (% of patients affected) |
|---|---|
| **Isolated**: | |
| Hereditary Alpha Tryptasemia (HAT) | 5–10% |
| Hymenoptera Venom Allergy (HVA) | 10–20% |
| Other IgE-Dependent Allergies (IgE-A) | |
| Atopic Dermatitis (AD) | 10% |
| Other Atopic Disorders | |
| Cutaneous Mastocytosis (CM) | <5% |
| Systemic Mastocytosis (SM) | <5% |
| **Combined** *: | |
| HAT + CM | 10% |
| HAT + SM | 10% |
| IgE-A + CM/SM | 5–10% |
| HAT + SM + HVA | 50% |

* Patients suffering from the combined MCAS type are at high risk to develop life-threatening anaphylaxis despite prophylactic anti-mediator therapy. Abbreviations: MCAS, mast cell activation syndrome; IgE, immunoglobulin E; HAT, hereditary alpha tryptasemia; HVA, hymenoptera venom allergy.

**Table S3.** Variants of MCAS and diagnostic features (criteria).

| Variant of MCAS | Main Diagnostic Features |
|---|---|
| Primary MCAS | the *KIT* D816V mutation is detected and mast cells |
| (= Clonal MCAS) * | the *KIT* D816V mutation is detected and mast cells<br>a) with confirmed mastocytosis (CM or SM) **<br>b) with only two minor SM criteria ** |
| Secondary MCAS | an IgE-mediated allergy, another hypersensitivity reaction or another immunologic disease that can induce MCA and thus MCAS, is diagnosed, but no neoplastic MC or *KIT* D816V is found *** |
| Idiopathic MCAS | criteria to diagnose MCAS are met, but no related reactive disease, no IgE-dependent allergy, and no neoplastic/clonal MC are found |

* The terms clonal MCAS, monoclonal MCAS (=MMAS) can be used synonymously with the term primary MCAS. ** Most of the patients suffer from CM or SM. However, in some cases, only two minor SM criteria are detected and criteria for SM and CM are not fulfilled. *** No *KIT* mutation at codon 816 is detected, and flow cytometry (if performed) will not detect a clonal population of CD25-positive MC. Abbreviations: MC, mast cells; MCA, MC activation; CM, cutaneous mastocytosis; SM, systemic mastocytosis.