

Anaphylaxis to quinolones in mastocytosis: Hypothesis on the mechanism

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Clinical Implications

- Quinolones are potential triggers of anaphylaxis in mastocytosis and should be avoided in this disease.

TO THE EDITOR:

Systemic mastocytosis (SM) is a disease associated with anomalous proliferation and accumulation of mast cells in different tissues. Most cases are represented as lifetime clonal diseases in adults, with anaphylaxis risk of approximately 50%.^{1,2} Anaphylaxis is a serious, acute, and life-threatening systemic hypersensitivity reaction (HSR) resulting from mast cell and basophil degranulation, through IgE- and non-IgE-mediated mechanisms. Understanding the patient-specific triggers and promoting their avoidance is key to the prevention of anaphylaxis.³

The present case report shows 2 agents, *Hymenoptera* venom and quinolone, triggering anaphylaxis in a patient with mastocytosis. Our objective is to provide evidence of quinolones as a previously underrecognized trigger of anaphylaxis in mastocytosis.

A 46-year-old woman presented with recurrent anaphylaxis, reporting 5 severe reactions over the last 7 years. The first 3 episodes were induced by stinging of insects, which were not identified by the patient. These reactions were characterized by flushing, dizziness, blurred vision, and loss of consciousness. There were vomiting and generalized tonic-clonic seizure in 2 reactions and respiratory distress in the remaining 1. After these 3 events, she had 2 more reactions associated with ciprofloxacin, which was used to treat urinary tract infection: one reaction with flushing and laryngeal edema and the other with flushing and syncope. Physical examination between the reactions was normal.

Her basal serum tryptase level was 17.7 µg/L. Upper digestive endoscopy showed increased number of anomalous CD25⁺ mastocytes in the gastric and duodenal mucosae. Bone marrow biopsy revealed aggregates of 15 or more mast cells and spindle-shaped mast cells expressing CD2 and CD25. Genetic study for KIT mutation was not done. Therefore, SM without cutaneous involvement was diagnosed.

Serum specific IgE (sIgE) levels to bee, wasp, fire ant, and phospholipase A were measured twice and were undetectable. Microarray evaluation of sIgE to allergen components (ISAC) was negative. Skin testing to *Hymenoptera* venoms and ciprofloxacin was performed twice, in duplicate, and the results were

negative. All investigation was done 3 months after the last anaphylactic reaction.

We reported a patient with SM and 5 anaphylactic reactions, 3 being induced by insect venom and 2 by ciprofloxacin. It took 7 years to the diagnosis of SM, a rare and underrecognized disease. As observed in our case, 20% of the patients with SM do not present urticaria pigmentosa, which makes the diagnosis more difficult.¹ Mastocytosis must be investigated in all patients with *Hymenoptera* allergy due to the known association between these diseases.^{4,5} Besides, quinolones are an unknown cause of anaphylaxis in mastocytosis and patients are currently not oriented to avoid this class of antibiotics.

A novel mechanism was recently described to explain some nonallergic anaphylactic reactions (Figure 1).³ Cationic substances acting as basic secretagogues activate mouse mast cells *in vitro* and *in vivo* through a single receptor, the Mrgprb2, which is ortholog of the human MAS-related G protein-coupled receptor-X2 (MRGPRX2).^{6,7} Several basic exogenous substances have been involved in MRGPRX2-mediated mast cell activation based on *in vitro* studies. Neuromuscular blocking agents and all fluoroquinolones have a tetrahydroisoquinoline motif, which can bind and activate this receptor.⁷ Compound 48/80, vespid mastoparan, opioids, and icatibant are other examples of agonists of MRGPRX2.⁷ Targeting human MRGPRX2 is a promising way to prevent or treat nonallergic drug hypersensitive reactions and other inflammatory diseases.^{8,9}

The prevalence of *Hymenoptera* venom allergy (HVA) is higher in mastocytosis (around 25%), especially in adults, compared with that in the general population. In addition, the frequency of clonal mast-cell disease in screened subjects with HVA ranges from 1% to 7.9%.^{4,5} The risk of anaphylaxis in mastocytosis increases with higher levels of tryptase. Moreover, more severe *Hymenoptera* HSRs are also associated with higher baseline serum tryptase levels in patients without SM.^{4,5} Our patient had an abnormal serum tryptase level (17.7 µg/L). Serum tryptase levels above 20 µg/L are a minor criterion for the diagnosis of SM, but in 50% of cases, baseline serum tryptase level is less than 20 µg/L.^{1,2} A study assessing indolent SM showed the highest prevalence (50%) of HVA in patients with tryptase levels ranging from 20.4 to 29.9 µg/L, whereas in patients with levels below 6.1 µg/L or above 191 µg/L, the prevalence was lower than 10%.^{4,5}

Currently, only those patients with mastocytosis who have anaphylaxis to an insect sting are candidates for diagnostic testing.^{4,5} Anaphylaxis to *Hymenoptera* venom is typically IgE-mediated, but some substances in the venom, such as vespid mastoparan, can induce direct degranulation of mast cells.⁷ Serum sIgE measurement is the first and safer test to be done, at least 4 to 6 weeks after the last reaction.^{4,5} The patient reported here was tested twice to the 3 *Hymenoptera* insects, because she did not identify the insect involved in the anaphylactic reactions. The test results were negative. Serum sIgE measurement is more often negative or presents lower levels in mastocytosis than in the HVA population without mastocytosis.^{4,5} Our results can be interpreted as false negatives, or, alternatively, *Hymenoptera* venom may have nonspecifically stimulated mast cells. Skin testing in mastocytosis can be

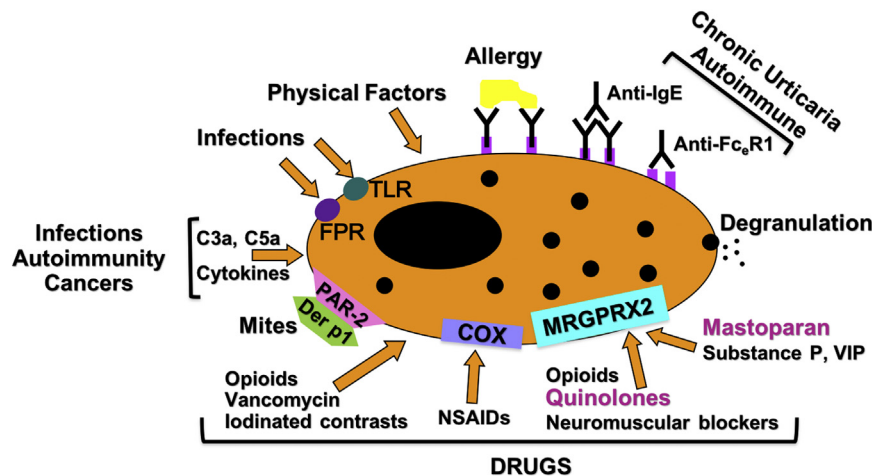


FIGURE 1. Mechanisms of mast cell activation. COX, cyclooxygenase; Der p1, *Dermatophagoides pteronyssinus* allergen 1; FPR, *N*-formyl peptide receptor; NSAID, nonsteroidal anti-inflammatory drug; PAR-2, proteinase-activated receptor-2; TLR, Toll-like receptor; VIP, vasoactive intestinal peptide. Figure adapted with permission from Giavina-Bianchi et al.³

complicated by anaphylaxis, and we probably should use lower concentrations than the ones standardized for patients without the disease. Sting challenge test is contraindicated in patients with mastocytosis who are not receiving venom immunotherapy, and many experts suggest life-long immunotherapy for HVA in mastocytosis.^{4,5}

Quinolones are a class of antibiotics frequently associated with drug-induced HSRs, probably due to their chemical structure and increased consumption. HSRs to quinolones can be both nonallergic and allergic, but an IgE-mediated mechanism is hardly demonstrated. Actually, the diagnosis is challenging, because drug-specific sIgE tests are unavailable and skin testing presents undetermined sensitivity and specificity.³ Quinolones are one of the substances that may activate mast cells through MRGPRX2, resulting in non-IgE-mediated release of mediators, as described above.⁷

In conclusion, the excess of mast cells and their MRGPRX2 receptors in patients with mastocytosis may induce anaphylaxis on activation by quinolones. Based on the current knowledge and on this case report, it is advisable to be cautious when prescribing quinolones for patients with mastocytosis until further studies address this issue.

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