Fatal Cerebral Events Following Insect Stings May be Due to Inappropriate Mast Cell Activation

Sir,

The description of delayed complication of fatal ischemic stroke following beesting in a 41-year-old man by Elavarasi and colleagues,[1] merits testing for mast cell tryptase level as excessive mast cell degranulation is one explanation for neurological or cardiac fatalities following insect stings. An elevated baseline mast cell tryptase level could mean an underlying clonal mast cell disease such as systemic mastocytosis that can present in myriad ways with insect stings and perioperative anaphylaxis leading to fatal outcomes being extreme examples.[2-4] Mast cells reside in tissues and therefore, rely on local signals to decide the next course of action. For example, experiments have shown cardiac ischemia as a signal to increase mast cell numbers in cardiac tissues.[5] However, oxygen and glucose deprivation in cerebral tissues led to increase in thalamic mast cell numbers and this increase in mast cell infiltration appears to be dependent on the duration of the anoxic insult,[6] similar to a clinical presentation of prolonged anaphylaxis.

The well-understood pathway of mast cell activation is via allergen-IgE-IgE receptor crosslinking but complement pathway activation following insect envenomation, including positive biofeedback loops involving interleukin-5 (IL-5) and tryptase also merits attention. Non-IgE-dependent pathways that cause mast cell degranulation are beginning to be understood that include Mas-related G-protein receptor X2 (MRGPRX2) on mast cells that can be activated by substance P, small molecule antibiotics, and wasp venom.[7] The release of mediators following mast cell degranulation such as histamine (causes vasodilatation), tryptase, chymase, matrix metalloproteinases (damage blood-brain barrier) including various inflammatory cytokines (that activates microglia and recruits neutrophil and macrophages) lead to inflammation of neurons and brain edema. Mast cells have the capacity to amplify the inflammatory responses inflicting more damage to the nervous system that has been seen in both models of ischemic and hemorrhagic stroke.[6]

The patient discussed in the report may have been sensitized to beestings, or perhaps the system was simply overwhelmed with the amount of venom injected (bees release a large amount of venom 50–140 μg per sting compared to wasp 2–17 μg, 50 beestings would be anywhere between 2500–7000 μg), or how long he had been unconscious in the field (prolonged anaphylaxis) leading to the fatal outcome. Gain-of-function KIT mutations are increasingly recognized in patients post Hymenoptera anaphylaxis and unexplained anaphylaxis, with some studies reporting that as high as 27% of patients with systemic reactions to insect venoms can have a clonal mast cell disorder with increased baseline mast cell tryptase levels (cutoff at 11.4 ng/mL).[8-10] Immunologists, therefore, recommend that mast cell tryptase level be checked in all patients who present with anaphylaxis to insect venoms.

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Conflicts of interest

There are no conflicts of interest.

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