Letters to the Editor

In Response to *Xylocopa tranquebarica* Fatal Stinging by Kularatne et al

To the Editor:

In a very interesting report published in *Wilderness & Environmental Medicine*,¹ a 59-year-old healthy male manual laborer who had been stung by the insect *Xylocopa tranquebarica* on the face in the right malar region, with the bee remaining attached to the skin, felt faint with shortness of breath and then collapsed. He was pronounced dead on arrival in the hospital, to which he had been brought approximately 90 minutes after the sting. Despite his lungs being slightly congested and with secretions in the bronchial tree, all other organs including the heart and coronary arteries were normal on postmortem examination. The authors correctly anticipated that the pattern of allergy and anaphylaxis in humans has wide variations, and it is quite possible that the victim in this report had severe hypersensitivity to some components of the venom of *X. tranquebarica*. However, this report raises important questions concerning anaphylactic death as well as the laboratory and histological procedures necessary to elucidate the cause of death and especially the manner of death:

1. Postmortem tryptase estimation: Tryptase, a serine protease stored in the mast cell granules and released together with histamine, is relatively stable postmortem and can be found in blood from a few minutes up to several hours after mast cell degranulation. In anaphylactic deaths, postmortem tryptase blood samples have shown consistently raised values.² However, increased tryptase levels have also been found in a few cases of death from nonanaphylactic causes. These cases include sudden infant death syndrome, acute deaths after heroin injection, traumatic deaths, atherosclerotic cardiovascular disease, asphyxia, tissue trauma, hemolysis, and postmortem diffusion from tissue to blood. Aortic postmortem tryptase measurements can be of value when taken as soon as possible after death in cases of anaphylaxis. Tryptase can be measured up to 4 days after death even when blood samples are stored at room temperature because it is very stable with a long half-life.³ For the diagnosis of anaphylaxis in the postmortem setting, a level of 10 µg/L or greater is found to have a sensitivity of 86% and specificity of 88%.⁴

2. Coronary artery histology: In anaphylactic death, the myocardium and especially the coronary arteries are usually infiltrated by inflammatory cells such as mast cells

and eosinophils and should be always examined. However, medications, infectious agents or organisms, malignant neoplasms, chemicals that stimulate the immune system, hypereosinophilic syndrome, hypersensitivity drug reactions, asthmatic bronchitis, parasitic and fungal infections, Kounis syndrome, hypersensitivity drug-induced myocarditis, Churg-Strauss syndrome, Wegener granulomatosis, microscopic polyangiitis, and Goodpasture syndrome have overlapping clinicopathologic characteristics and can also induce mast cell and eosinophilic infiltration in various human organs. We have recently emphasized that the heart and especially the coronary arteries should be regarded as the main organs⁵ and primary target of anaphylaxis,⁶ serving as the primary door through which life crosses to death, and should be scrutinized histologically in any postmortem examination.

3. Kounis syndrome and bee stings: The Kounis acute hypersensitivity-associated coronary syndrome is a combination of acute coronary syndromes with conditions that can lead to mast cell activation, involving interrelated and interacting inflammatory cells such as macrophages and T-lymphocytes and including anaphylactic or anaphylactoid and allergic or hypersensitivity insults.⁷ In Kounis syndrome manifesting as coronary artery spasm (type I Kounis syndrome) and sudden death, histologic examination of coronary arteries and Giemsa stain for mast cells with positive control have found scattered mast cells in the tunica adventitia.⁸ Bee sting-induced Kounis syndrome has been described on several occasions, and this syndrome is occasionally associated with fatal cardiac arrhythmias such as ventricular fibrillation that can lead to sudden death.⁹

4. Mastocytosis and bee stings: Patients with severe hypersensitivity reactions to hymenoptera stings have been found to have an increased serum baseline total tryptase level of >11.4 ng/mL and underlying clonal mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome. In these patients, bone marrow aspiration has shown mast cell granulomas and spindle-shaped mast cells. Flow cytometric analysis of mast cells has revealed mast cells expressing CD2 or CD25 on their surface, and KIT mutation analysis found KIT mutation at codon 816. KIT is the mast receptor for the stem cell factor that is essential for mast cell development, proliferation, survival, adhesion, and homing. Therefore, patients with serum baseline tryptase greater than normal might have KIT mutations that lower the stimulus threshold for anaphylaxis and hyperresponsive mast cell phenotype

resulting in severe allergic reaction and/or development of Kounis syndrome.¹⁰

Therefore, practicing physicians and pathologists should keep in mind all of these pathologies in cases of fatal bee stinging events, and when pathologic examination is regarded as necessary, they should always look for myocardium and especially coronary artery infiltration by inflammatory cells such as mast cells and eosinophils. This, together with postmortem bone marrow examination and serum tryptase estimation, would help in elucidating the cause of sudden death and in particular the manner of death.

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In Reply to Drs Kounis, Kounis, Soufras, and Patsouras

To the Editor:

Professor Nicholas G Kounis and colleagues¹ are owed high appreciation for expressing their expert opinion on confirming the diagnosis of anaphylaxis and mechanisms of sudden cardiac arrest associated with acute anaphylaxis. They agree with our findings that anaphylaxis was the probable cause of the tragic of death caused by *Xylocopa tranquebarica* sting in our report.

The value of postmortem tryptase analysis has been highlighted as a sensitive and specific measurement to diagnose anaphylaxis. It is interesting to read their remarks on coronary artery histology: “We have recently emphasized that the heart and especially the coronary arteries should be regarded as main organs and primary target of anaphylaxis serving as a primary door through which life crosses to death.”¹ We fully agree with this statement, which is applicable to the index case where the patient died without leaving time for development of mucocutaneous and pulmonary manifestations of anaphylaxis.² We are aware of Kounis syndrome and have experienced this specific manifestation in hornet stings and drug allergies leading to acute coronary syndrome in Sri Lanka.^{3,4} In type 1 Kounis syndrome, coronary artery spasm is the mechanism of cardiac ischemia that may result in sudden cardiac arrest and death. In such events, histological examination of the coronary arteries will assist in establishing the diagnosis. In addition, undue host susceptibility to anaphylaxis has been highlighted as a possible KIT mutation. Finally, dissemination of these novel concepts will lay the foundation for development of new therapeutic agents and strategies to prevent deaths from acute anaphylaxis.

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