CASE REPORT

A Rare Case of Micro-Angiopathic Hemolytic Anemia Due to Envenoming by Giant Asian Honey Bee (*Apis dorsata*)

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Giant Asian honey bee sting envenoming is a recognized cause of morbidity and mortality in rural Sri Lanka. Mass envenoming causes clinical effects, either as allergic and anaphylactic reactions or bee sting toxin-induced multiorgan damage. We report a patient who had mass envenoming from more than 1000 stingers who subsequently developed hematologic features suggestive of thrombotic microangiopathy-related hemolytic anemia. The transient acute kidney injury and acute hepatic failure seen in the patient were also considered to be secondary to thrombotic microangiopathy. A normal clotting profile and a high proportion of schistocytes in blood film ruled out disseminated intravascular coagulation as the underlying cause of the microangiopathic hemolytic anemia. The normal platelet count raised the possibility of a “partial” thrombotic microangiopathy, as has previously been reported in association with Shiga toxin-related hemolytic uremic syndrome and hump-nosed pit viper envenoming. Venom-induced direct toxicity on red cells was another possible explanation for the hemolysis, but the high proportion of schistocytes made it less likely. The place of therapeutic plasma exchange for venom-associated thrombotic microangiopathy is controversial. The patient recovered with symptomatic treatment and meticulous fluid management, without needing therapeutic plasma exchange as an adjunct treatment.

Keywords: hymenopterans, *apis dorsata*, thrombotic microangiopathy, microangiopathic hemolytic anemia, kidney injury

Introduction

The order Hymenoptera includes both bees and wasps. Most bees and wasps live solitarily and are not predisposed to stinging humans. The greatest threat to health of humans is posed by a few species of social bees (eg, different types of honey bees) and social wasps (eg, hornets, yellow jackets, and paper wasps), which produce large numbers of sterile workers.¹ The domesticated Asian honey bee (*Apis cerana*—Mee messa in the vernacular), the feral giant Asian honey bee (*Apis dorsata*—Bambara in Sinhalese and Karunge kulavi in Tamil), the feral dwarf honey bee (*Apis florea*—Danduvel mee), and the stingless bee (*Tetragonula iridipennis*—Kaneyya messa) are honey bees frequently

encountered both in rural and urban landscapes of Sri Lanka.² Giant Asian honey bees are the largest, measuring 17 to 20 mm in length, and they make large hives in open areas. The hives hang from branches of large trees, roofs, rock caves, and other similar areas. Thousands of colony members leave the nest and attack humans in defense when they are disturbed.³ Female hymenopterans have a modified ovipositor called stinger, associated with venom glands located at the tip of the abdomen. After honey bees sting, the stingers are deeply embedded in the victim's skin, detach from the insect, and continue to deliver the venom,⁴ including melittin, mast-cell degranulating peptides, phospholipase A2, hyaluronidase, acid phosphatase, and histamine.¹

Most clinically important incidents and fatalities due to Hymenoptera venom occur as a result of anaphylactic shock.¹ However, mass envenoming from hundreds of Hymenoptera stings causes life-threatening complications due to multiorgan damage. Rhabdomyolysis, acute kidney injury, noncardiogenic pulmonary edema, acute

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Figure 1. A giant Asian honey bee (*Apis dorsata*) found at the site where the hive was burnt by villagers after the incident.

myocardial infarction, bowel gangrene, and multiorgan failure have all been reported.^{1,4,5} We report a rare case of giant Asian honey bee mass envenoming in which the hematologic investigations were suggestive of a hitherto unreported complication, microangiopathic hemolytic anemia, in a Sri Lankan patient.

Case Report

A previously healthy 86-y-old male was admitted to the emergency unit of a regional hospital 30 min after a mass envenoming by giant Asian honey bees (*A dorsata*). He was stung by bees while walking outdoors. The beehive was found on a nearby Kitul (*Caryota urens*) tree. Apart from infrequent episodes of bronchial asthma, he had no hematologic, renal, or hepatic diseases in the past, no previous exposure to Hymenoptera stings, and no food or drug allergies (Figures 1 and 2).

On admission, the patient was anxious and in pain with large numbers of stingers embedded in the skin over the head, neck, and hands. His body was swollen and his skin was erythematous. His pulse rate was 112 beats·min⁻¹ and blood pressure was 150/90 mm Hg. All stingers, numbering more than a 1000, were removed with utmost care. Hematologic and biochemical investigations performed on admission were unremarkable except for an elevated white blood cell count. He was treated with intravenous hydrocortisone, normal saline infusion, oral chlorpheniramine, cefuroxime, paracetamol, and tetanus toxoid. He passed normal amounts of urine, and the color of the urine was normal.

Figure 2. The patient with swelling and small ulcers over the stinging sites.

On Day 2, he reported feeling dizzy and lifeless, and investigations were repeated. The white blood cell count was further elevated ($29 \times 10^9 \text{ L}^{-1}$ [normal $4\text{--}11 \times 10^9$]) with neutrophils comprising 90% of cells. Hemoglobin had decreased (9.1 g·dL^{-1} [normal $13\text{--}17$]), but platelet count remained within the normal range. Total bilirubin was elevated (3.9 g·dL^{-1} [normal $0.2\text{--}1.0$]), and the predominant rise was in the indirect fraction (Table 1). The blood picture examination revealed polychromatic cells, ovalocytes, and schistocytes. The schistocytes constituted approximately 5% of the red cell population. White cells appeared increased with a left shift of the neutrophils. The hematologist concluded that the blood picture was suggestive of microangiopathic hemolytic anemia. A normal direct antiglobulin test ruled out immune hemolysis. Because the clotting profile was normal, disseminated intravascular coagulation was considered unlikely and a thrombotic microangiopathy was considered the most likely cause of hemolysis. Renal impairment was present with a serum creatinine of 1.9 mg·dL^{-1} (normal $0.8\text{--}1.3$) on Day 2. Urinalysis was normal with no hemoglobinuria. Hepatic function impairment was also noted by Day 2, with elevated alanine transaminase (91 U·L^{-1} [normal $5\text{--}30$]) and a marginally increased direct bilirubin fraction.

A diagnosis of thrombotic microangiopathy associated with hemolysis, acute kidney injury, and acute liver injury as a result of giant Asian honey bee envenoming was made. The patient recovered by Day 5 with antihistamines for symptomatic alleviation, antibiotics for prevention of skin sepsis, and meticulous fluid management. He did not require renal dialysis for renal impairment or therapeutic plasma exchange for microangiopathic hemolytic anemia (Table 1).

Table 1. Investigations results on admission, Day 2, and discharge

	<i>On admission</i>	<i>Day 2</i>	<i>On discharge</i>
White blood cells (normal 4–11 L ⁻¹)	20.8×10 ⁹	29.0×10 ⁹	11.4×10 ⁹
Hemoglobin (normal 12–16 g·dL ⁻¹)	12.4	9.1	11.1
Platelet count (normal 150–450×10 ³ μL ⁻¹)	332×10 ³	259×10 ³	264×10 ³
Serum bilirubin (normal 0.2–1.0 mg·dL ⁻¹)	1.1	3.9	1.0
Alanine transaminase (U·L ⁻¹)	56	91	44
Serum creatinine (mg·dL ⁻¹)	1.2	1.9	1.3
PT/INR (s)	Not done	13/1.1	12/1.0
aPTT (s)	Not done	32	32
D-dimer (normal <500 ng·mL ⁻¹)	Not done	256	250

PT, prothrombin time; INR, international normalized ratio; aPPT, activated partial thromboplastin time.

Discussion

The feral giant Asian honey bee sting is an environmental hazard in rural Sri Lanka. In an observational study of 322 patients admitted to a rural hospital after Hymenoptera sting, 292 were instances of giant Asian honey bee stings.³

In this case report, the hematologic investigations were suggestive of the occurrence of a rare complication, microangiopathic hemolytic anemia. Microangiopathic hemolytic anemia is caused by the destruction of red cells as they squeeze through capillaries that have damaged endothelial linings covered by fibrin clots. The fragmented cells appear as schistocytes in a blood picture. The causes of microangiopathic hemolytic anemia are either a thrombotic microangiopathy or disseminated intravascular coagulation. These 2 conditions are differentiated based on the clotting profile. If disseminated intravascular coagulation is the cause of microangiopathic hemolytic anemia, the clotting profile is abnormal with prolonged prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), and high D-dimer levels. In contrast, in thrombotic microangiopathy, the clotting profile is normal. The patient's normal clotting profile was suggestive of hemolysis being part of a thrombotic microangiopathy. The other useful distinguishing feature is the proportion of schistocytes in blood picture. In a normal person, it is <0.5%. A person with disseminated intravascular coagulation will have a higher proportion of schistocytes, but it will be less than 1%. If the cause of the schistocyte formation is thrombotic microangiopathy, the proportion will be higher than 1%.⁶ In this patient, the proportion of schistocytes was approximately 5%, providing further evidence to support thrombotic microangiopathy as the probable etiology of hemolysis.

In a thrombotic microangiopathy, it is usual to see thrombocytopenia in the blood counts and the blood picture. This occurs due to platelet adherence to the damaged vascular endothelium. The patient described

had normal platelet counts. There are 2 possible explanations for this finding. Thrombotic microangiopathy related to Shiga toxin-induced hemolytic uremic syndrome has been shown to occur in some instances with normal platelet counts. This entity is described as “partial HUS.”⁷ Thrombotic microangiopathy sans thrombocytopenia has also been described after envenoming by hump-nosed pit vipers.^{8,9} A similar “partial” thrombotic microangiopathy could explain the giant Asian honey bee-induced hemolytic anemia without thrombocytopenia. The second possible explanation is direct toxicity on the red cells by the toxin, thus leaving platelet counts unaffected. Although such direct toxicity has not been demonstrated after bee sting envenoming, there is evidence for toxin-induced hemolysis after viper bites.^{10–12} Although direct venom-induced hemolysis needs to be considered, the presence of a high proportion of schistocytes favors a microangiopathic genesis for the hemolysis. Further research into mechanisms of hematotoxicity of bee venom is needed in the future.

Vascular injury associated with thrombotic microangiopathy causes organ failure. The patient's transiently elevated serum creatinine was suggestive of damage to renal vasculature. Liver enzyme alanine transaminase elevation and the direct fraction of bilirubin elevation were suggestive of injury to hepatic vasculature. The mixed picture of indirect and direct bilirubin rise is consistent with thrombotic microangiopathy-associated hemolysis and acute liver injury.

The standard management for microangiopathic hemolytic anemia secondary to primary thrombotic microangiopathic syndromes such as thrombotic thrombocytopenic purpura is therapeutic plasma exchange.¹³ In venom-associated thrombotic microangiopathy, however, the value of therapeutic plasma exchange is controversial. There are a few case reports suggesting a useful role as an adjunct treatment.¹⁴ More robust evidence is awaited. There is presently a systematic review of the literature being conducted, and its results are likely to give us more evidence-based guidance.¹⁵ We were spared the dilemma

of whether to perform therapeutic plasma exchange in this patient because he recovered from the hemolysis and renal and hepatic injuries with symptomatic treatment, meticulous fluid management, and antibiotic therapy.

Conclusions

This case report highlights the need to add microangiopathic hemolytic anemia to the growing list of probable life-threatening complications associated with mass envenoming due to giant Asian honey bee sting. Thrombotic microangiopathy being the underlying cause of microangiopathic hemolytic anemia provides a pathophysiological explanation for the transient renal and hepatic failure that occurred in the patient.

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