



Case Report

Acute kidney injury due to multiple bee stings in a 3 years old girl

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Abstract

Background : Bee stings can lead to mild to severe allergic reaction . Serious complications of bee stings include hypersensitivity to the venom, which can develop after a single sting, and acute renal failure which has been reported mostly secondary of intravascular hemolysis developing after multiple bee stings. We report here a child who developed multiorgan system involvement.

Case presentation : A-3 years-old-girl was admitted to Kariadi Hospital with multiple bee stings and referred due to acute kidney injury stage failure by local hospital. Clinical finding were anasarca edema, gastrointestinal bleeding, oliguria (0.8ml/kgBW/hours), stage II hypertension (124/99mmHg), flaccid paraparesis inferior. Laboratory finding were hypoalbuminemia (2.4g/dL), anemia (6g/dl), leukocytosis (35.800/mm³), electrolyte imbalance (hypocalcemia : 1.66mg/dL) and estimated glomerular filtration rate (eGFR) 8.09 ml/min/1.73m². Chest-X ray showed pulmonary edema and duplex pleural effusion. The renal function recovered with supportive management including four sessions of haemodialysis. Patient discharged from the hospital on the nineteenth day.

Conclusion : Multiple bee stings can lead multiorgan system involvement.

Keywords : Bee sting, acute kidney injury, hemodialysis

INTRODUCTION

A history of systemic allergic reaction appears in the medical records of at least 0.8% of children, but the true prevalence among the pediatric population is likely to be higher and fatal reactions have been reported.¹ Hymenoptera envenomation may result in systemic damage but with early commencement of standard care, chances of survival are increased. Acute Kidney Injury in children following bee sting envenomation is rare and survival is hinged on early recognition and prompt appropriate management.²

Bee sting is frightening, especially when masses of bee attack, not only because of the severe pain but also the possibility of fatal reaction. In the literature, there have been many reports of serious complications of multiple bee stings. Three major reactions occur after bee envenomation. The first is local swelling and irritation, which is produced by vasoactive components of bee venom. The second, less common reaction, is a generalized anaphylactic responses with urticaria,

angioedema, dyspnea and hypotension. These more extensive reactions are caused by an immediate hypersensitivity reaction. The third reaction is serum-sickness-like symptoms including thrombocytopenia, DIC, hemolysis, rhabdomyolysis and acute renal failure. It is possibly mediated through circulating immune complex or delayed hypersensitivity reaction.³

CASE

A three years-old-girl was admitted to Kariadi Hospital with multiple bee stings and referred by a local hospital. On the first day of care, she still had edema all over the body. Her blood pressure was 124/99 mmHg (P₉₅₊₁₂) and diuresis was 0.8 ml/kg/hours. She was assessed with acute kidney injury stage failure (GFR of 8.09 ml/minute/1,73m²), stage II hypertension, anasarca edema, post multiple bee sting on her head, pulmonary edema and duplex pleural effusion, liver function disorders, hypoalbuminemia (2.4 mg/dL), anemia (6 mg/dl),

leukocytosis (35.800/mm³), hypocalcemia (1,66 mg/dL), and gastrointestinal bleeding. She was given D10% intravenous 10 ml/hours + NaCl 3% (2 meq) 89 ml + KCl (2 meq) 45 ml, Aminofusin intravenous 5%, intravenous 20% lipid, furosemide 4 mg/kgBW/day (60 mg/24 hours), ceftriaxone injection 1 gram/24 hours, methylprednisolone injection 30 mg/24 hours, paracetamol injection 150 mg/6 hours (for analgesic use), calcium gluconate injection 6 ml/12 hours, omeprazole injection 6 mg/12 hours, sodium bicarbonate 1 tablet/8 hours, nifedipine 5 mg/8 hours, sucralfate 5 ml/8 hours, and was given gentamicin ointment at the sting marks lesion. On the third day of care, her diuresis were 0,3 cc/kg/hours. She was performed hemodialysis on second day of care continued every two days. She was administered by 50 ml of 20% albumin. The eGFR were increase from 8.09 ml/min/1.73m² to 15, 98 and then 25, and 51.15ml/min/1.73m² after she undergo 4 session hemodialysis. The urea was decreased from 271 mg/dL to 199mg/dL, 120mg/dL, 73 mg/dL and then 34 mg/dL. She had experienced seizure on the seventh day and

flaccid paraparesis inferior.

We tapered off the methylprednisolone dose. Last results the eGFR was 83,33 ml/minute/1,73 m². On the nineteenth day, she was discharged from the hospital with good clinical conditions.

DISCUSSION

Allergic reactions to insect bites result most frequently from stings of flying insects of the Hymenoptera order. Hymenoptera venoms contain low-molecular weight compounds (e.g., biogenic amines, such as histamine) as well as potentially allergenic peptides (e.g. melittin in bee stings) and proteins, which are species-specific.⁴ Bee venom is related, though not identical, to bumblebee venom; likewise, wasp venom is related, though not identical, to the venom of other Vespidae. Immunological cross-reactions to allergens in bee and wasp venom -or the venoms of other Hymenoptera- are often encountered, as are cross-reactions to pollen and food allergens.⁴⁻⁶



Figure 1. Tawon ndas (*Vespa Affinis*) and head location of bee stings



Figure 2. Peripheral left seventh cranial nerve palsy (Arrow showed the nasolabial angle was drawn in the right sight)



Figure 3. Chest–X ray showed pulmonary edema and pleural effusion

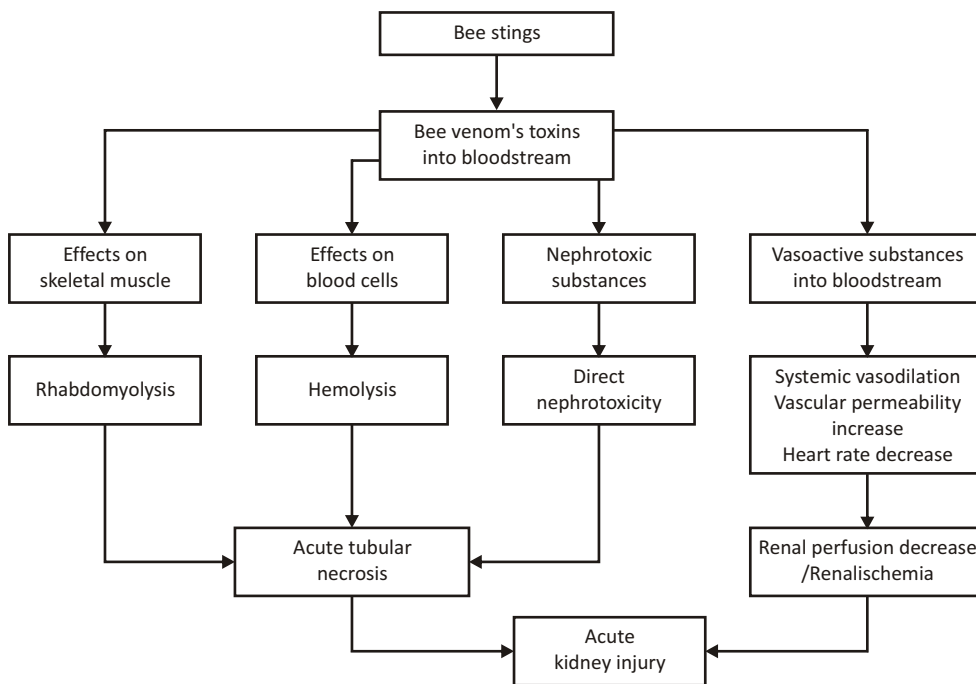


Figure 4. Pathophysiology of AKI induced by bee sting⁷

The patient had attack of many bees in the area of head, neck and leg. The stinger remain in the skin after the bees attack the child. It called “tawon ndas” (*Vespa affinis*) that usually attack the victim in the area of head and neck. It generally mainly black, with the first two abdominal segments being a deep yellow, forming a conspicuous band and it size reaching up to 30mm (Figure 1).

Patophysiology

The allergic reaction can be triggered by a single sting, and the greater the number of stings, the worse the prognosis because multiple stings lead to inoculation of a higher amount of venom. Insect venom of the *Hymenoptera* order (bees and wasps) is responsible for

14% of the cases of anaphylactic reactions, constituting the second place among the causes, second only to food antigens (33 to 34%).The effects of the poison can be systemic and can eventually cause death. Mortality rates for multiple bee stings were approximately 15–25% in previously published studies.⁷(*Level of evidence 2*)

The venom components act on vascular resistance, thereby altering blood pressure and activating the immune system. Phospholipase A2 is the major allergen and melitin is the most abundant substance of venom composition. Both are neuromuscular blocking agents, which can cause respiratory paralysis. Melitin promotes the release of catecholamines and has depressive and cardiotoxic effects. The set of functions of the venom

components generates a systemic hypoperfusion and it decreases renal blood flow, which can predispose to AKI.^{7,8}

Hemolysis and rhabdomyolysis were observed in many cases reported in the literature, demonstrated by elevated serum levels of indirect bilirubin and creatine kinase. The main mechanisms involved in AKI caused by rhabdomyolysis are renal vasoconstriction, formation of intratubular deposits of myoglobin and direct cytotoxicity of myoglobin to the renal tubule cell.⁷

Renal vasoconstriction is due to hypovolemia and heme protein binding to nitric oxide. The direct cytotoxicity of myoglobin to the renal tubule cell occurs through the heme portion, which induces the production of free radicals causing lipid peroxidation and cell damage. Another factor that contributes to renal impairment is the possible occurrence of disseminated intravascular coagulation, described in rhabdomyolysis. This phenomenon leads to the release of thromboplastin, causing the formation of micro thrombi in the glomeruli, with the consequent glomerular filtration rate reduction.⁷

Myoglobin released from lysis of muscular cells does not have a specific binding protein, and it is freely filtered by the glomeruli. Casts are produced after filtration of myoglobin through the glomerular basement membrane. Moreover, myoglobin can, through the heme fraction, induce the release of free iron, which catalyses free radical production and further enhances ischemic tubule damage. In the absence of hypovolemia and acid urine, myoglobin has a less nephrotoxic effect.⁹

Clinical Manifestation

According to the reports by Muller et al, and Ring and Messmer et al, systemic anaphylactic reactions to wasp venom was graded into 4 classes, ranging from generalized urticaria and itching, to anaphylactic shock, cardiac arrest and apnea. It has classified hymenopteran sting reactions as local, large local, systemic grades I to IV, and unusual delayed reactions.⁶ (Level of evidence 2)

Bee venoms contain 9–13 different peptide antigens that all may trigger allergic reactions. The most well known allergic reaction is the Type I anaphylactic or immediate hypersensitivity reaction. This reaction is mediated by immunoglobulin E antibodies, which trigger mast cell degranulation when they are cross-linked by the appropriate antigen. Symptoms usually occur distant to the sting site and include hives, pruritis, require intensive supportive care including airway control and restoration of hemodynamic stability with aggressive fluid resuscitation and pressor support. Nearly all deaths caused by *Hymenoptera* envenomation occur by Type I immediate hypersensitivity.⁸

Other immune-mediated reactions to *Hymenoptera* envenomation include immune complex (Type III) and cell-mediated (Type IV) reactions. Type III (serum sickness) reactions occur 3–14 days after the sting and

present with fever, headache, urticaria, lymphadenopathy, polyarthritis, and polyarthralgias. Type II hypersensitivity reactions (antibody mediated) do not commonly occur following *Hymenoptera* envenomation. Major local reactions are usually the result of a Type IV hypersensitivity reaction. The associated local edema and erythema can last up to a week.⁸ (Level of evidence 2)

The patient came into the hospital seven days after the attack, she came with chief complain generalized edema. She also complain painful and pruritic and edematous on sting lesion. According to this, it is belong to hypersensitivity type IV. She also shows some delayed reaction like acute kidney injury, seizure and paralysis (several days after admission) which is include hypersensitivity type III.

Mass Stinging Events

Mass stinging events can be acutely life-threatening due to the toxic action of large amounts of injected venom. Toxicity from massive honey bee envenomation occurs directly from the systemic effects of the venom, as opposed to immune-mediated anaphylaxis. Death may result from exposure to hundreds or thousands of stings.⁸

The very young and the very old may be at greater risk for morbidity and mortality from massive bee attacks. Children have smaller body mass and are exposed to a greater amount of venom per kilogram. Children are more likely to be stung due to carelessness and are less able to escape when stung. The elderly often have comorbidities that increase their risk of severe outcome after mass envenomation.⁸ (Level of evidence 2)

The patient is 3 years old girl that attacked with the bees when playing in the outdoor. Her friends were intrude the nest of bees so the bee attacked them as a threat to their colony. She can not escape when stung because she was the youngest among them.

The initial symptoms after massive envenomation include edema, fatigue, fever, nausea, vomiting, localized pain, and loss of consciousness. Rapid onset of diarrhea and urinary incontinence may be secondary to endogenous histamine release. Multisystem derangements include hemolysis, rhabdomyolysis, transaminitis, thrombocytopenia, and disseminated intravascular coagulation. Rhabdomyolysis may lead to oliguria, acute tubular necrosis, and renal failure. With excellent supportive care, the systemic toxicity is usually reversible. No specific antidotes are available. Death from mass envenomation has been reported in victims with 500–1000 stings. With aggressive supportive care, survival is possible in such situations.^{7,8} The multicenter retrospective study of 1091 hospitalized wasp sting patients in China report major clinical characteristics of these patients are toxic reactions, and the wasp venom toxicity is attributed to hemolytic, myotoxic, neurotoxic, vasodilatory, nephrotoxic and hepatotoxic enzymes.^{10–13}

One cohort study at Turkey revealed that severe systemic reactions were associated with mild eosinophilia (>5%) (OR 12.6; CI 1.5-109.7; $p = 0.022$), female sex (OR 6.4; CI 1.5-26.9; $p = 0.011$) and accompanying atopic disease (OR 3.4; CI 1.2-12.3; $p = 0.016$) as significant risk factors for severe systemic reactions.¹² (*Level of evidence 2*)

The patient had edema, vomiting, localized pain as the initial symptom after the attack. She also complain difficult to breath, the rapid reaction occur in the previous hospital. When came to our hospital she showed transaminitis, rhabdomyolysis which was lead to acute kidney injury.

A common complication in bee sting accidents is acute kidney injury (AKI). The onset of the first manifestations of this complication occurs 24 to 48 hours after the accident, and it is due to the great amount of inoculated poison. Other signs and symptoms resulting from the toxic effects of bee venom are nausea, vomiting, hyperventilation (acid breathing), generalized edema, myalgia, arthralgia, headache, restlessness and consciousness alteration. The severity of AKI seems to be associated with the number of stings, since creatinine levels were higher.^{8,11-14}

Previously, some studies have shown that AKI due to wasp stings was secondary to pigment-induced acute tubular necrosis. We also suspect a direct toxic effect from the venom on the renal tubules, particularly in those lacking elevated CK levels. The severity of clinical manifestation is related to the number of stings.¹⁵ In one study of 45 children that developed acute renal failure after mutiple bee sting show that the levels of almost all the laboratory tests were elevated, including Cr, ALT, CK, extended PT, APTT and descended Haemoglobin, which were higher in patients with >10 stings than those in patients with 10 stings. The in-hospital mortality in the >10 stings group was 5 times higher than that in 10 stings group, which was statistically significant. This indicates that the severity of clinical features and the prognosis depend on the number of stings in patients with toxic reactions.¹⁰ (*Level of evidence 2*)

Initial laboratory work up of our patient revealed deranged serum urea and serum creatinine. There was a decrease in the hemoglobin to 6 g/dL on admission day. A transient elevation of hepatic transaminases was evident with a peak alanine aminotransferase of 525 IU/L on admission day before gradually returning to normal. CPK was show level in fourteenth hospital day. Urinalysis revealed proteinuria and haematuria. On admission, she had an estimated GFR of 8,09 ml/min/1.73m² which better over days to 83,3 ml/min/1.73m² because she had haemodialysis and subsequent improvement in serum biochemistry.

Hymenoptera stings can lead to a myriad of neurologic manifestations in children, such as encephalitis, peripheral neuritis, optic neuropathy,

myasthenia gravis, cerebral infarction, acute inflammatory polyradiculopathy, acute disseminated encephalomyelitis, encephalomyelorradiculoneuritis, stroke and neuromuscular paralysis.¹⁶⁻¹⁸ (*Level of evidence 2*)

Our patient developed inferior paraparesis that can be caused by acute inflammatory polyradiculopathy on the seventh day admission. She also experienced focal seizure for about 5 minutes. Peripheral left seventh cranial nerve paresis with a differential diagnosis of Bell's Palsy was suspected on patient. The neurological complication of this patient completely recovered after corticosteroid treatment.

Management

Local Reactions

Large local reactions may require the addition of antihistamines and corticosteroids to manage symptoms. Antihistamines, such as diphenhydramine, can be given by mouth or via IV depending on the severity of the reaction. H2 blockers can also be administered and have been found to be just as efficacious as H1 blockers in urticaria and anaphylaxis. The combination of H1 and H2 blockers appears to be superior to either agent alone and should be given in severe anaphylaxis. Acute severe urticaria may also benefit from a single dose of epinephrine, but this is usually not necessary since there is no acute threat to life. In the future, the patient should be instructed to take oral antihistamines as soon as possible if they are stung again to prevent the establishment of a local reaction.¹⁹⁻²² (*Level of evidence 3*)

Systemic Reactions

The most common symptoms of bee and wasp envenomation are dermal in nature and include generalized urticaria, flushing, and angioedema. The more severe but less common anaphylactic reactions may cause upper airway edema and circulatory collapse, ultimately resulting in death.^{8,23}

Epinephrine is the most rapid-acting and effective medication to reverse the life-threatening complications of anaphylaxis and should be administered immediately for any patient with evidence of an anaphylactic reaction. Delays in administration of epinephrine may allow the airway obstruction or cardiovascular collapse to progress to the point of irreversibility and death.⁷ Patients should be treated with 0.01 mg/kg (maximum dose 0.5 mg) of the 1:1000 dilution of epinephrine intramuscularly, preferably in the lateral thigh. Epinephrine can be continued in a dose of 0.01 mg/kg IM at 20 minute intervals or an epinephrine drip can be considered (0.05-1 µg/kg/min).²⁴⁻²⁷ (*Level of evidence 1*)

Corticosteroids are recommended for all anaphylactic patients. Though corticosteroids have no immediate benefit, they are thought to speed the resolution of angioedema and urticaria. Dosages similar

to status asthmaticus should be initiated for anaphylaxis, such as methylprednisolone 2 mg/kg IV bolus followed by 1 mg/kg every 6–8 hours. In milder cases, oral corticosteroids such as prednisolone or prednisone can be dosed at 1 mg/kg twice a day.²⁶ (Level of evidence 4)

Early treatment with steroids and antihistamines, copious saline hydration for intravenous volume replacement and sodium bicarbonate for urine alkalization is advised. Treatment of acute kidney injury following bee stings with haemodialysis, hemofiltration or peritoneal dialysis has been reported, although exchange blood transfusion or plasmapheresis is equally effective because it directly reduces the circulating mediators of inflammation caused by the venom.²⁷ (Level of evidence 2)

Our patient came on the seventh day after the treatment so she was not show the sign of anaphylaxis reaction. However on the previous hospital she received some treatment furosemide, ceftriaxon, methylprednisolone, diphenhydramine and paracetamol. Initial laboratory result on admission day show decreased of glomerular filtration rate (8,89 ml/mnt/1,73 m²) then she programmed to haemodialysis.

Literature search shows as few as 30–50 stings in children carries grave prognosis while very sensitive individuals may develop fatal anaphylaxis even after just one bite. Our patient had over 50 stings and survived. The time between the accident and medical treatment, and the prompt removal of stingers seem to be important in determining our patient's prognosis. Prognosis is also improved when systemic toxic effect is anticipated, with anticipatory management instituted.²⁸

The time between the accident and medical treatment seems to be important in determining the patient's prognosis in many cases. In one study of case report at Brazil, the patient who received medical support seven hours after the bee stings had severe acute renal failure whereas in the patient whose treatment was given half an hour after the attack the renal dysfunction was mild and rapidly reversed after aggressive fluid infusion. Another point to consider is the removal of bee stings. The sting continue to inject venom after be detached from the insect body. The patient should remove it as quickly as possible in order to reduce the amount of venom inoculated. In the cases presented here the removal of the stings were made in the hospitals. The patient had this performed 24 hours after bee stung. This made the case more serious, because a larger quantity of venom must be injected.²⁹

SUMMARY

The case reported a girl that was stung by around 50 bees at the face, head, and hands seven days before admission. She developed swelling throughout all over the body. Because the swelling increases over time, the

girl was taken to Kendal General Hospital. During the treatment in the hospital, the urine output decreased and there were no improvement so she referred to Kariadi General Hospital. On admission to Kariadi General Hospital Emergency Room, she was conscious but was less active. She had edema all over the body. There were sting marks on his face, scalp, hands, and feet. Physical examination shows hepatomegaly, splenomegaly, and minimal crackles on both lungs. Laboratory workup reveals low haemoglobin and the peripheral blood smear showed evidence of hemolysis. Blood chemistry tests shows elevated ureum level, creatinine level and ALT. Urinalysis shows proteinuria and hematuria. She assessed with acute kidney injury with GFR 8,89 ml/minute/1,73m² then she undergo hemodialysis. The GFR better over days to 83,3 ml/min/1.73m² on the fourteenth day because she had haemodialysis and subsequent improvement in serum biochemistry. She also developed acute inflammatory polyradiculopathy and improved with given corticosteroid for about 4 weeks. We encourage rapid transfer of patients with multiple bee stings to tertiary hospitals as renal lesions might occur. Dialysis should be initiated as needed to achieve better outcomes in patients with AKI following bee sting.

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