Review Article

HONEY BEE STINGS AND ANAPHYLAXIS: REVIEW
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Abstract:
Arthropod bites and stings are capable of inflicting injury, allergic reactions and transmitting infectious diseases. Hymenoptera order members are particularly important because of being nearly ubiquitous in the nature. Their stings may lead to fatal allergic reactions. The severity and duration of reaction to bee venom can differ from one person to another. Most people experience a local non-serious allergic reaction to bee venom. However, depending on the location and number of bee stings, previous history of allergic reactions may increase possibility of severe life-threatening events. Hymenoptera venom consists of a mixture of biologically active substances including enzymes which causes localized and systemic reactions which may be fatal. Diagnostic test are helpful in identifying allergy to venom and also to differentiate between bee, wasp, yellow jackets or hornets. Postmortem findings in bee stings are those of local reactions and internally upper respiratory tract edema found in anaphylaxis cases apart from systemic findings due to shock and venom allergens in treated cases. Absence of these finding doesn’t rule out possibility of anaphylaxis.

Key words: Honey bee sting, Anaphylaxis, Autopsy.

Introduction:
Anaphylactic shock is an unexpected, sudden and sometimes deadly event that affects the patient in 75% of the cases without pre-existent history of allergy. According to the recent concept most common causes are drugs, hymenopteric poisons and nutrients.¹

The severity and duration of reaction to bee venom can differ from one person to another. Most people experience a local non-serious allergic reaction to bee venom. However, depending on the location and number of bee stings, previous history of allergic reactions may increase possibility of severe life-threatening events.

Insects of the order Hymenoptera, which include honey bees, wasps, ants and hornets, are frequently involved in accidental stings to human beings around the globe. Hymenoptera venom consists of a mixture of biologically active substances including enzymes which causes localized and systemic reactions which may be fatal.

Case Report:
The deceased was a 70 year male, who sustained accidental, multiple honey bee stings while he was grazing cows in field. He was taken to local hospital where stings were removed, first aid given and referred to higher centre. He died on his way to tertiary centre. On examination his face, neck and upper limbs were swollen. Multiple punctured stings with oozing of straw color fluid were observed around eyes (Fig-1). In-situ dissection of upper airway (Fig-2) revealed severe edema of tracheal and laryngeal mucosa. The thickness of this edema was comparable to the width of little finger. On cut section straw color fluid oozed out. Uvula and pharyngeal mucosa was edematous. Lungs were edematous and congested. Cause of death was ascertained as asphyxia due to upper airway edema in a case of multiple honey bee stings (Anaphylactic shock).
Fig. 1: Showing Multiple honey bee stings with oozing of straw color fluid.

Fig. 2: In-situ dissection showing edema of laryngeal and tracheas mucosa with oozing of fluid.

Discussion and review:
Entomology: Arthropod bites and stings are capable of inflicting injury, allergic reactions and transmitting infectious diseases. Hymenoptera order members are particularly important because of being nearly ubiquitous in the nature. Their stings may lead to fatal allergic reactions.

The well-known members of the Hymenoptera order are bees, wasps, hornets, yellow jackets and ants. This order in fact consists of about 100,000 species of bees, wasps and ants. Many of these animals have poison glands and stinging apparatus. Two distinct families exist, the Apidae and the Vespidae. The genus Apis contains only the honeybee, while the genus Polistes and the genus Vespula contain wasp, yellow jacket and hornet (Fig 1). The various subspecies occur with different frequencies in different parts of the world.

Among the species of Hymenoptera, bees are the most commonly encountered species because of beekeeping activities. Two of the more commonly encountered species of bee are honeybee Apis mellifera and the bumblebee (Bombus species). The venom of apis mellifera (honey bee) extensively used in oriental medicine. Honey bee venom has both analgesic and anti-inflammatory effects. Therefore, it has been used for a variety of conditions, including pain syndrome, herniated nucleus pulposus, cervical disc protrusion, and progressive muscle atrophy.

Pathogenesis: Bees sting only in defence, and during a sting approximately 50 µg of venom is injected into the skin. The barbed sting is normally left in situ, resulting in evisceration and death of the bee. Bees venom contains three main allergens: Phospholipase A (to which most patients are sensitive), hyaluronidase (to which a smaller number are allergic) and mellitin (which is an important allergen in only a few patients).

The non-allergic local reaction is a toxic response to venom constituents, while the large local reaction appears to be caused by an allergic reaction to venom proteins. The IgE-mediated late-phase reaction is probably responsible for most of these reactions; however, a cell-mediated mechanism, or a combination of the two, is possible.

Mellitin, a peptide component of bee venom, hydrolyses cell membranes, changes cell permeability, causes histamine and catecholamine release and is responsible for local pain. It acts with phospholipase-A2 to trigger the release of arachidonic acid, which causes cell membrane breakdown, damage of the vascular endothelium, and activation of the inflammatory response. Peptide 401 (mast cell degranulating peptide), triggers mast cells to degranulate, releasing histamine and other vasoactive peptides. Vasoactive amines, including
histamine, dopamine and noradrenaline can provoke ischemia and even myocardial infarction through profound hypotension and arrhythmia, or by increasing oxygen demands through direct inotropic and chronotropic effects in the presence of preexisting ischemic heart disease.\(^\text{12}\)

The “allergic angina syndrome” which could progress to acute myocardial infarction (“allergic myocardial infarction”) was first described in 1991 by Kounis and Zavras. Allergic angina and allergic myocardial infarction are now referred to as “Kounis syndrome” this syndrome is associated with mast cell degranulation.\(^\text{13-15}\)

Jae Woo Jung et al reported a fatal case of a 65-year-old woman with DIC (Disseminated intravascular Coagulation), following anaphylactic shock after bee sting acupuncture.\(^\text{16}\)

Mesothelium damage, thrombocyte and macrophage activation, cytokine, leukotriene release vascular coagulation, bradykinin and Platelet activating factor (PAF) and sometimes even the deposition of immune complexes in the basement membrane of small blood vessels and activation of the complement system may contribute to the pathogenesis of DIC\(^\text{17}\).

**Lethal dose and fatal period:** The estimated lethal dose is approximately 20 stings/kg in most mammals. Anaphylactic reactions to Hymenoptera stings are not dose dependent or related to the number of stings. Onset of life-threatening, anaphylactic signs typically occur within 10 minutes of the stings\(^\text{18}\). Massive honey bee envenomation is defined as more than 50 stings at a time\(^\text{19}\).

**Venom Allergens:** Hymenoptera venom consists of a mixture of biologically active substances including enzymes (phospholipases, hyaluronidas), peptides (melitin, apamin, bombolitins) and other low molecular weight compounds (biogenic amines, acetylcholine, lipids and free amino acids\(^\text{19,20}\)).

**Clinical Features:** Hymenoptera sting envenomation results in a number of clinical presentations (i) Non-allergic, local reactions (pain, minor edema, redness at the sting site); (ii) Allergic, large local reactions (extensive swelling >10 cm persisting more than 24hrs); (iii) Anaphylaxis (generalized urticaria, angioedema, bronchospasm, hypotension, cardiovascular collapse and loss of consciousness); (iv) Systemic toxic reactions (edema, vomiting, diarrhea, headache, seizures and altered sensorium); (v) Unusual reactions (cardiac ischemia, encephalomyelitis and cerebral infarctions).\(^\text{19,21,22}\)

**Localized reactions:** These vary in size from swellings a few centimetres in diameter to marked oedema of the entire hand, the forearm or even most of the leg.\(^\text{5}\) In most individuals hymenoptera stings cause nonallergic local reactions of limited size and duration. Some subjects experience an allergic local reaction (large local reaction) to a sting that is greater than 10 cm in diameter and may last for up to 5 days\(^\text{23}\).

The most alarming localized reactions are those involving the eyelid or the subcutaneous tissues of the neck, although these are smaller than many of the swellings affecting the limbs. Whilst such reactions are frightening and may cause considerable discomfort, they are not dangerous. Large swellings take several days to subside.\(^\text{6}\).

**Systemic or generalized reaction:** The commonest clinical features of the anaphylactic reaction to bee and wasp venom are cutaneous (pruritus, urticaria and angio-oedema) and respiratory (asthma and laryngeal oedema). Features particular to insect sting allergy are gastrointestinal symptoms (diarrhoea, abdominal pain and incontinence) and visual problems,
including transient amblyopia. Patients may also suffer from tachycardia, sweating, hypotension, fainting and loss of consciousness. In some patients a severe generalized reaction can occur very rapidly, sometimes within a few minutes of the sting. Many patients suffer from a sensation of impending doom.

Hymenoptera antigen, when injected, can cause a wide range of severe delayed effects like serum sickness, neurological disturbances like polyradiculomyelitis (Guillain- Barre syndrome) and seizures, acute renal failure, haemolysis, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), myocardial infarction or cardiac arrhythmias. Atypical and unusual reactions were similarly seen in this case, some of which occurred a few hours or even a few days after the bee stings.

Song et al. and Cho et al. reported a case of serum sickness reaction caused by honeybee acupuncture, and there was one report of fatal anaphylaxis to a bee sting after sensitization through repeated honeybee acupuncture. Zhang Ling et al. reported a case of multiple organ dysfunction due to massive bee stings in which diagnosis was based on autopsy findings of acute pulmonary edema, acute kidney injury, hepatic and cardiac dysfunction, and cerebral edema. Acute myocardial ischemia, severe rhabdomyolysis and angioedema following massive bee envenomation was also reported.

**Diagnostic tests:** Diagnosis is based on history, skin tests and estimation of venom specific serum IgE-antibodies (RAST). To diagnose insect venom allergy a good patient history is important. Allergological tests (skin test, specific IgE titre) confirm the diagnosis.

Investigations are of value to confirm the clinical impression, and can be helpful to determine whether the allergy is to bee or wasp venom, if the insect has not been identified. Skin-prick tests to the venoms and measurement of specific IgE antibodies in the serum are helpful in such conditions.

Specific IgE (CAP-FEIA), CAST-ELISA (leukocyte sulfidoleukotriene release) and Flow-CAST (basophil CD63 expression) are valuable additional diagnostic tools for establishing the true culprit insect in patients with unclear clinical history or sensitization to both insects.

A serum tryptase and specific IgE to bee venom on serum obtained at autopsy can assist in confirming anaphylactic reaction to bee venom as the cause of death, particularly in the absence of observable stings.

**Treatment:**

**Symptomatic:** The majority of Hymenopteran stings are self-limiting events, which resolve in a few hours without treatment. Treatment of uncomplicated envenomations (stings) consists of conservative therapy with antihistamines, ice or cool compresses, topical lidocaine, or corticosteroid lotions.

Epinephrine is the only effective drug in case of respiratory (bronchial asthma, laryngeal edema) or cardiovascular (hypotension, arrhythmias, hypovolemic shock) manifestation. It has to be administered as rapidly as possible.

**Immunotherapy:** For individuals with a specific allergy to Hymenoptera venom, immunotherapy may be a relatively safe and effective treatment option. Immunotherapy leads to complete protection in more than 98% of patients with wasp (yellow jacket) venom allergy and in 75-80% of patients with bee venom allergy. The efficacy of venom immunotherapy is well documented but this treatment is expensive. It is therefore mainly indicated in patients with a history of severe systemic reactions and a high degree of exposure.
**Autopsy Findings:** Multiple puncture mark over body with surrounding edema is found in death due to bee stings. On squeezing straw color edematous fluid oozes in fresh cases. There is swelling of whole limbs, face and neck. Stings are found in-situ, if not treated. Dead honey bees may be found on body.

In anaphylaxis there may be laryngeal (or pharyngeal, or other upper airway) oedema. Pulmonary oedema, if present, may indicate epinephrine (adrenaline) overdose. Recommended blocks for histological examination are: Heart, Coronary artery, Lung with airways, Vocal cord mucosa. Anaphylactic shock is likely to be misdiagnosed as myocardial infarction. Myocardial ischaemia is very probable (almost inevitable) in shock deaths, which may therefore be mistaken for primary myocardial infarction. Mode of death in anaphylaxis is asphyxia and respiratory arrest due to upper airway edema and Cause of death is anaphylactic shock.

Nezih Anolay et al observed pulmonary edema and swelling in laryngeal area in a case of honey bee sting. In many cases of fatal anaphylaxis no specific macroscopic findings are present at postmortem examination. This reflects the rapidity and mode of death, which is often the result of shock rather than asphyxia. Investigations that might help determine whether anaphylaxis was the cause of death had rarely been performed. In the presence of a typical clinical history, absence of postmortem findings does not exclude the diagnosis of anaphylaxis.

**Conclusion:**
Honey bee stings most commonly occurs accidentally in rural population in fields. Honey bee keepers allergic to bee venom are advised to carry epinephrine or undergo immunotherapy by pure venom extract. In deaths due to Honey bee stings early postmortem and in-situ dissection of larynx and trachea will detect upper airway edema which will help to conclude cause of death as anaphylactic shock.

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