

Clinical Communications

Fatal anaphylaxis following a hornet sting in a yellow jacket venom-sensitized patient with undetected monoclonal mast cell activation syndrome and without previous history of a systemic sting reaction

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Clinical Implications

- Fatal anaphylaxis may occur in vespid venom-sensitized individuals suffering from mast cell disorders without a previous history of a systemic sting reaction. A detailed necropsy including serologic measurements of tryptase and specific IgE levels is able to corroborate the diagnosis.

TO THE EDITOR:

IgE-mediated fatal anaphylaxis after Hymenoptera stings is a rare but well-recognized cause of sudden death. However, the number of cases might be underestimated as establishing the diagnosis of fatal anaphylaxis without a clinical history is not always straightforward due to reasons such as the nonspecificity of macroscopic and microscopic autopsy findings or the presence of accompanying, potentially lethal diseases. Here, we report a detailed clinical history, necropsy, and serology of a case of fatal Hymenoptera anaphylaxis in a patient without a previous history of Hymenoptera venom allergy suffering from an undetected monoclonal mast cell activation syndrome (MMAS).

A 32-year-old Caucasian man (182 cm, 90 kg) without a clinical history of a systemic sting reaction or serious health problems was stung by a hornet while sitting in his car. As he took a photograph of the insect with his mobile phone and sent it to his colleague, later, it could be clearly confirmed as a hornet (*Vespa crabro*) (Figure 1). Only minutes after the sting, he called his colleague and reported serious health problems. The colleague made an emergency call, and when the ambulance arrived, the man was found lifeless in cardiac arrest. Prolonged resuscitation by the emergency doctor as well as in the hospital was unsuccessful, and the patient was declared dead approximately 2 hours after the hornet sting.

At autopsy, 1 day postmortem, a 1-cm-diameter hyperemic and edematous macula was identified at the gluteal fold and was the presumed location of the insect sting. Skeletal muscles, interstitial soft tissues, and serous membranes were characterized by a pronounced exocisosis due to a massive shift of the body fluid to the internal organs (Figure 2, A). The patient showed massive subcutaneous edema of the face, especially in the region of the eyelids,

lips, and neck. Moreover, massive cyanosis of the lips and tongue was observed. The respiratory tract was characterized by laryngeal edema of the glottis with petechial bleeding, exaggerated mucus production, and spastic constriction of the bronchial muscle. The lung displayed high-grade interstitial and intraalveolar edema and the interstitium contained abundant eosinophils and mast cells (Figure 2, B). In the pulmonary venules and capillaries, massive microthrombosis, microglobules, and erythrocyte sludge were present. Moreover, thromboembolic and hemorrhagic phenomena were found in several organs. Interestingly, no urticarial was visible; however, it is described to be absent in up to 20% of cases of anaphylaxis.¹ In addition to these typical signs of anaphylactic shock, acute hepatopathy and pancreatitis, shock-induced hemorrhagic gastritis, enteritis, nephropathy, splenomegaly, cerebral edema, and cardiac shock with biventricular heart failure were diagnosed. The detailed autopsy results are given in this article's Online Repository and Figure E1 at www.jaci-inpractice.org. As the cause of death, an anaphylactic peracute cardiogenic shock with massive generalized edema, hypovolemia, pulmonary edema, and asphyxia was determined.

The mother of the patient reported that he received 3 to 4 stings from yellow jackets (none from hornets) within the last 4 years. In these cases, the patient reacted with a considerable swelling and local erythema with slow regression. Except the male sex and moderate alcohol consumption (blood alcohol: 0.11 g/L), no other risk or cofactors for severe anaphylaxis were found.

During autopsy no signs for the presence of mastocytosis were observed. Although a slight accumulation of mast cells was present in the lung, mast cells were not aggregated and were normally shaped (Figure 2, C). Interestingly, the mast cell-activating *c-kit* D816V mutation, which is a minor criterion for the diagnosis of systemic mastocytosis and for a clonality of mast cells, could be detected in the DNA of a low

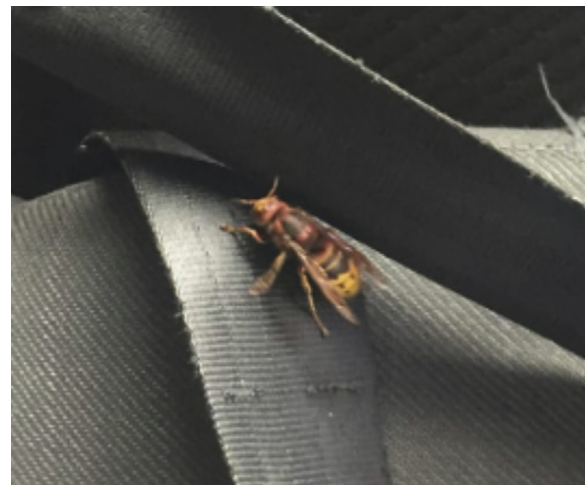


FIGURE 1. European hornet (*Vespa crabro*). The insect was the elicitor of the fatal anaphylaxis. The photograph was taken by the patient immediately after the sting with his mobile phone.

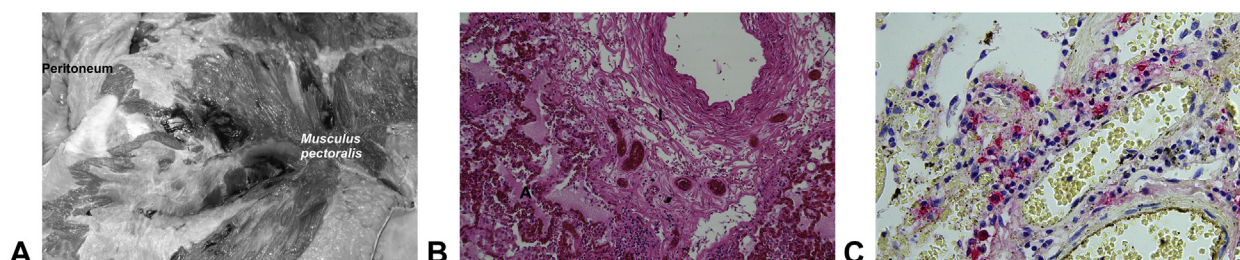


FIGURE 2. Autopsy findings. **A**, Thoracic aperture demonstrates exicosis of skeletal muscles and interstitial soft tissue due to massive shift of body fluid to internal organs. **B**, Pulmonary interstitial, perivascular edema (l), intraalveolar edema (A), and intravascular microthrombosis (hematoxylin and eosin staining, $\times 150$). **C**, Mast cells in lung tissue (red, partially degranulated, $\times 400$) visualized using anti-mast cell tryptase monoclonal antibody in an automated staining system.

percentage of cells from the spleen, liver, skeletal muscles, and adrenal gland (mutation level: 0.001%-0.03% of cells) using a highly sensitive and highly specific previously published quantitative PCR method.² No blood or bone marrow samples that are routinely used for detection of the *c-kit* D816V mutation were available.

MMAS is a disease that has been diagnosed in patients with systemic reactions to Hymenoptera venoms as well as in patients with unexplained episodes of anaphylaxis, in whom the activating *c-kit* mutation can be detected while the diagnostic requirements for systemic mastocytosis are not met.³ The fact that the patient most likely suffered from MMAS may in part explain both the unexpected severity of the allergic sting reaction and the clinical presentation with cardiovascular involvement without skin changes. Nowadays, the strong connection between clonal mast cell disorders and severe allergic reactions to Hymenoptera venoms in untreated patients as well as after discontinuation of venom immunotherapy is well established.^{4,5}

In a serum sample taken before death at the hospital, the tryptase level was highly elevated at 195 ng/mL (normal range, <11.4 ng/mL). Unfortunately, the baseline tryptase level is unknown. Although elevated tryptase levels can also be found in nonanaphylactic fatalities, it was demonstrated that levels >110 ng/mL are a diagnostic criterion of anaphylaxis-associated deaths in postmortem samples with a sensitivity of 80%.⁶ In the living, elevated mast cell tryptase is almost absolutely specific for anaphylaxis.⁷

Specific IgE (sIgE) to *Vespa crabro* venom (i75) was detectable with 2.41 kU_A/L (normal range, <0.35 kU_A/L). Notably, sIgE to yellow jacket venom (i3) was even higher with 4.96 kU_A/L. In addition, sensitization to vespine venom was confirmed by the positive sIgE test result to the recombinant yellow jacket venom components rVes v 1 (i211) (3.2 kU_A/L) and rVes v 5 (i209) (1.4 kU_A/L).

As no former hornet stings but several yellow jacket stings were reported, the patient most likely was primarily sensitized to yellow jacket venom. However, this is speculative as many patients are not able to correctly identify the insect they were stung by. Nevertheless, it was demonstrated before that the vast majority of patients with anaphylactic reactions to hornet venom seem to be primarily sensitized to yellow jacket venom.⁸ Here,

this assumption might also be supported by the higher sIgE level to yellow jacket venom and rVes v 1 compared with hornet venom. Nevertheless, it could be speculated whether hornet venom might be more potent in eliciting a severe allergic reaction by reasons such as the amount of delivered venom or stronger potential for mast cell activation.

As reported earlier,⁹ this case demonstrates that anaphylactic death may occur without a previous history of a systemic allergic sting reaction, particularly in patients with MMAS. Although fatal anaphylaxis is not always easy to prove, a detailed post-mortem diagnostic workup including serologic testing for tryptase and sIgE levels can be extremely helpful to confirm the diagnosis in unexplained deaths, also without a previous clinical history.

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AUTOPSY RESULTS

At autopsy, 1 day postmortem, a 1-cm-diameter hyperemic and edematous macula was identified at the gluteal fold as presumed location of the insect sting. However, the accessibility of this site was limited due to the presence of death spots, multiple small blisters, and acne-like eruptions.

Skeletal muscles, interstitial soft tissues, and serous membranes were characterized by a pronounced exicosis due to a massive shift of the body fluid to the internal organs (Figure E1, A).

The patient showed a massive subcutaneous edema of the face, especially in the region of the eyelids, lips, and neck. Moreover, massive cyanosis of the lips and tongue was observed.

The respiratory tract was characterized by a larynx edema of the glottis with petechial bleeding, exaggerated mucus production, and spastic constriction of the bronchial muscle (Figure E1, B). The lung displayed a high-grade interstitial and intraalveolar edema (each side of the lung 850 g) and the interstitium contained abundant eosinophils and mast cells (Figure E1, C). A slight accumulation of mast cells was observed mainly in perivascular areas of the lung. However, mast cells were not present in larger aggregates and normally shaped (Figure E1, D). In the pulmonary venules and capillaries, massive microthrombosis, microglobules, and erythrocyte sludge were present (Figure E1, C). The endothelia were swollen and vacuolated. Moreover, hyperinflation of the alveoli with acute emphysema and interstitial emphysema of the soft tissue at the pulmonary hilum were observed. In addition, pronounced mucus plugging of the airways and hyperemia were detected.

The lymph nodes showed a massive hyperemia with dilation of the marginal sinus (Figure E1, E) as well as congestion and microthrombosis (Figure E1, F).

The liver was characterized by massive necrosis and dissociation of the hepatocytes, microthrombosis, and hyaline globules in the sinusoids as well as dilatation of the perisinusoidal spaces (Figure E1, G). In addition, many mast cells and eosinophils were found in the sinusoids. The pancreas was characterized by peripancreatic fat necroses (Figure E1, H).

The shock-induced gastro- and enteropathy was manifested as multiple petechial gastric erosions, autodigestion, and ischemic necroses of the foveolar epithelial cells, particularly in the corpus ventriculi.

The kidneys showed a cortical anemia and massive congestion of the medulla. Moreover, necrosis of the tubular epithelia and hyperemia of the glomerula were observed (Figure E1, I).

The spleen was characterized by a congestive splenomegaly (300 g) with a red and congested pulp (Figure E1, J).

In the brain, congestion of the meninges, ischemic lesions of the ganglion cells as well as in asphyxia-prone regions such as the hippocampus were found (Figure E1, K).

The heart was affected by a cardiogenic shock with biventricular heart failure and both the left and right ventricle showed a massive dilatation (Figure E1, L). The myocardium cells were dissociated and hyaline banding of myofibrils was observed. In addition, an interstitial edema and massive microthrombosis of capillary and venous blood vessels were found. The left coronary showed arteriosclerosis with a 40% asymmetric stenosis. Finally, no myocardial infarction or interstitial fibrosis could be identified.

As a cause of death, an anaphylactic peracute cardiogenic shock with massive generalized edema, hypovolemia, pulmonary edema, and asphyxia was determined.

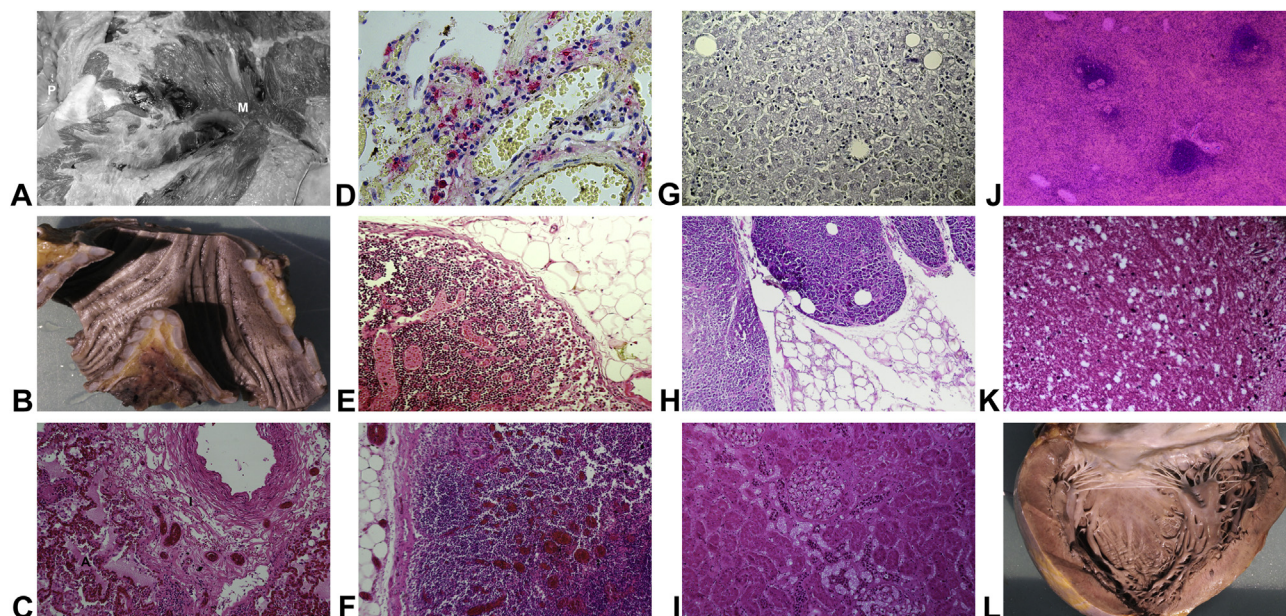


FIGURE E1. Macroscopic and histological findings at autopsy. **A**, Thoracic aperture demonstrates exicosis of skeletal muscles and interstitial soft tissue due to massive shift of body fluid to internal organs. P: peritoneum, M: *Musculus pectoralis*. **B**, Spastic constriction of the bronchial muscle. **C**, Pulmonary interstitial, perivascular edema (I), intraalveolar edema (A), and intravascular microthrombosis (hematoxylin and eosin [H&E], $\times 150$). **D**, Mast cells in lung tissue (red, partially degranulated, $\times 400$) visualized using an antimast cell tryptase monoclonal antibody in an automated staining system. **E**, Massive hyperemia of lymph nodes with dilation of the marginal sinus (H&E, $\times 150$). **F**, Congestion and microthrombosis in paratracheal lymph nodes. **G**, Hypoxic and toxic vacuolization of the liver by lipids and water. Accumulation of mast cells, eosinophils, monocytes, and macrophages in the sinusoids and perisinusoidal spaces (H&E, $\times 150$). **H**, Prefinal acute pancreatitis with adipose tissue necrosis (H&E, $\times 90$). **I**, Tubulonephrosis and necrosis in kidney. Massive vacuolation of glomerular endothelia (H&E, $\times 100$). **J**, High-grade splenomegaly due to massive blood congestion (H&E, $\times 10$). **K**, Edema of the brain (H&E, $\times 50$). **L**, Acute dilatation of the left ventricle of the heart.