

Multiple Hornet Stings With Features of Reye's Syndrome

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Hornet's venom is known to possess a variety of toxic effects. A 19-mo-old girl who developed a Reye-like syndrome following multiple stings by the Oriental hornet (*Vespa orientalis*) is described. She presented with encephalopathy associated with hepatomegaly, elevated transaminase levels, low prothrombin time, and hyperammonemia. Liver biopsy demonstrated microvesicular fatty infiltration and diffuse mitochondrial changes. Additional features were acute renal tubular necrosis and massive hemolysis.

Stinging insects of the order of Hymenoptera (bees, hornets, and wasps) may cause systemic reactions that are usually allergic in origin (1). Most fatal allergic reactions are in the respiratory or cardiovascular system, or both (2,3). Only a few studies have dealt with nonallergic reactions attributed to the direct toxic effects of venom (4). Toxic nonimmunologic reactions are usually produced when an individual is stung by multiple insects within a short period of time (5,6). The venom of the Oriental hornet (*Vespa orientalis*) has been shown, mostly in animal studies, to cause toxic effects such as neurotoxicity (7), deranged blood clotting (8), hemolysis (9), rhabdomyolysis (10), hepatotoxicity (11-13), and acute renal tubular necrosis (14).

We report the development of a Reye-like syndrome in an infant, following multiple stings by the Oriental hornet—an association not reported previously.

Case Report

A 19-mo-old girl was in good health until 1 h before admission when she was the victim of multiple hornet stings. Two hornets were brought with the patient and were identified as the Oriental hornet (*Vespa orientalis*).

On admission the patient was afebrile, alert, and oriented, with stable vital signs and no respiratory distress. She was extremely edematous over the face and scalp, with erythema and signs of multiple stings. Forty-two sting lesions were identified, mostly over the head, neck, and upper extremities. Examination of the cardiovascular, respiratory, and neurologic systems was unremarkable. The abdomen was soft with no organomegaly. Within the first 24 h the patient vomited several times, became drowsy, and deteriorated rapidly to develop stupor, jaundice, hepatomegaly, and papilledema. Twenty hours after admission, liver transaminases peaked at >5000 U, alkaline phosphatase at 1750 U, SGPT at 304 U, and total bilirubin at 43 mg/dl with about half direct-reacting. Prothrombin time decreased to 26% and arterial ammonia rose to 248 mg% (normal 40-60 mg%). Electroencephalography demonstrated slow high-amplitude δ -activity compatible with stage C hepatic coma. Liver biopsy, following fresh plasma infusion and prothrombin time correction, revealed diffuse microvesicular fatty infiltration by oil-red staining of frozen sections. Light microscopy (hematoxylin and eosin) demonstrated a preserved architecture, foamy cytoplasm, and a mild acute inflammatory infiltrate with occasional cholestasis and rare cell necrosis (Figure 1). Electron microscopy revealed diffuse microvesicular lipid accumulation. Pleomorphism was noted in the mitochondria, which showed a dense matrix and changes of cristae (Figure 2). The severe hepatic dysfunction, which was most prominent on the second day, was associated with renal dysfunction, initially presenting with oliguria; blood urea nitrogen peaked at 30 mmol/L on the third day, with blood creatinine peaking at 223 mmol/L and uric acid at 767 mmol/L. Kidney biopsy revealed changes compatible with acute tubular necrosis and hemoglobinuric nephrosis.

During the first 12 h after admission, the patient developed a severe hemolysis with hemoglobin falling to 7.6 g%

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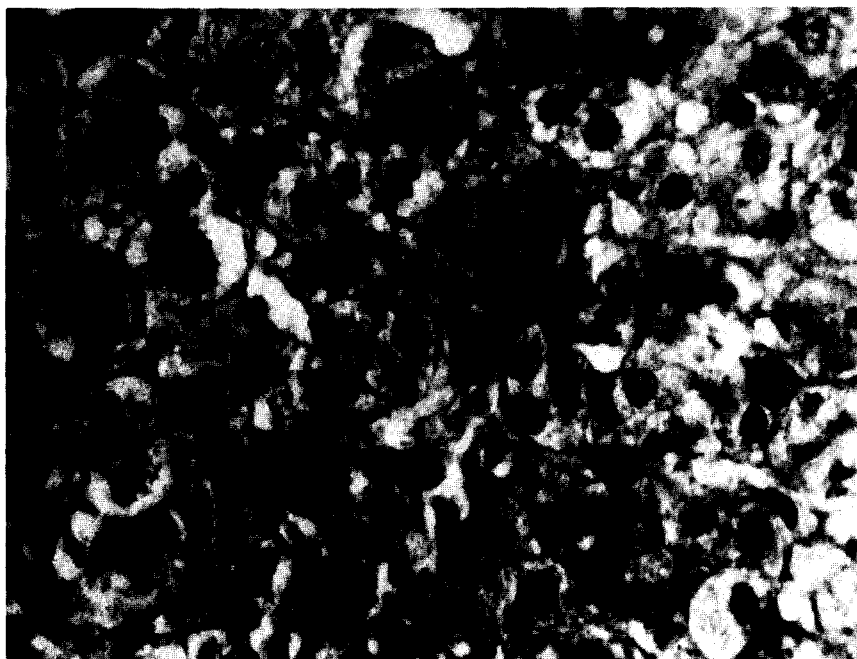


Figure 1. Liver biopsy specimen demonstrating diffuse foamy cytoplasm (H&E, $\times 700$).

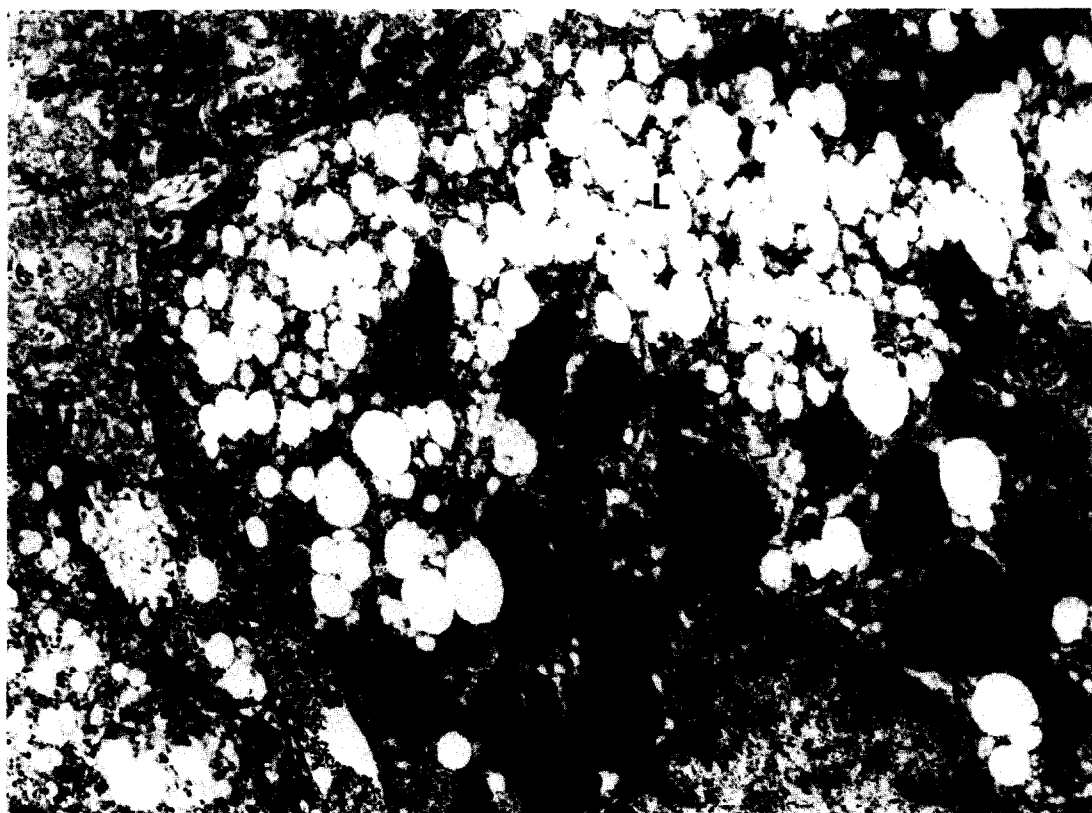


Figure 2. Electron micrograph of the liver ($\times 12,000$) showing foam cell appearance of two hepatocytes filled by microvesicular lipid droplets (L). The mitochondria (M) demonstrate pleomorphism with irregular shapes and matrix space filled by dense, fibrillar material. Irregularities of the cristae are present. N, nucleus.

and hemoglobinuria. Associated muscular damage was noted with a creatine phosphokinase peak of 7850 U on the second day. Although the platelet count, thrombin time, and fibrinogen were all within normal limits, the level of fibrinogen degradation products was elevated at 20 $\mu\text{g/ml}$ (control 2.5 $\mu\text{g/ml}$).

The patient was treated with intravenous glucose-electrolyte solutions, blood and plasma transfusions, antibiotics, and corticosteroids. The hepatic dysfunction and hemolysis improved gradually from the fourth day, with amelioration of renal status starting about 36 h later. A continuous gradual improvement was noted over the next 3 wk, and the patient was discharged with normal liver and renal functions. The only residual physical findings were a right central-type facial nerve paralysis and mild nonpitting edema over the face and scalp.

The patient's serum was analyzed by double-immunodiffusion, using as positive controls antisera to Oriental hornet venom extract that was raised in rabbits, as described elsewhere (15). Serum obtained on day 1 was negative for antibodies to hornet venom, but serum obtained 90 days later demonstrated such antibodies.

Discussion

The reactions described in the present patient are likely the result of a nonallergic toxic effect of a massive venom dose. The lack of antibodies in the patient's serum on admission as opposed to the presence of antibodies 90 days later confirms this hypothesis. Venom from the Oriental hornet has been shown to cause a significant elevation of liver enzymes in hepatocyte culture (13) as well as in the intact animal (12,13). Lipid accumulation in liver cells treated in vitro with a venom sac extract of the same hornet has been previously reported (11). Hepatocellular necrosis following multiple hornet stings has been described in one fatal case (16) which, however, bore no similarity to the present patient. Another report of reversible cholestatic liver damage is presented elsewhere, but contains very limited data (17).

The Oriental hornet is widely distributed throughout the Mediterranean region and the Near East. Although this particular species is uncommon in North America, other social Hymenoptera, including ants, bees, wasps, and hornets, possess venoms with identical toxins, that is, biogenic amines like histamine and serotonin, kinins, or common enzymes, such as hyaluronidase and phospholipase A and B (18). One would expect these common active constituents of various animal venoms to produce similar cytotoxic effects in different tissues and particularly in hepatocytes. Fractionation of the Oriental hornet venom has shown that the fraction containing

mainly phospholipases induced a lipid accumulation in hepatocytes similar to that produced by a whole venom sac extract (11).

The clinical features of the present case resemble Reye's syndrome; the patient deteriorated rapidly through a stage of confusion and vomiting into a stuporous condition associated with abnormal liver function. The elevated transaminases were accompanied by a prolonged prothrombin time and hyperammonemia, and typical histologic changes of cytoplasmic microvesicular steatosis and mitochondrial abnormalities were evident. Certain features, however, distinguish this venom-induced hepatic dysfunction from a classical Reye's syndrome, including the severe hemolysis and hyperbilirubinemia, elevation of alkaline phosphatase and SGGTP, and the presence of mild inflammatory and cholestatic lesions in liver parenchyma. The hyperbilirubinemia is probably a result of the associated massive hemolysis, with hepatocellular edema, leading to intrahepatic cholestasis. Renal tubular damage is also a feature of Reye's syndrome. Histology usually demonstrates glomerular mesangial cellularity and focal tubular degeneration with occasional microvesicular fatty infiltration (19). The elevated level of fibrinogen degradation products may present a mild form of disseminated intravascular coagulopathy, which is also a described feature of the syndrome (20). The hornet venom is well known to cause both features: the renal tubular damage as well as the coagulopathy (8,14,15).

The present case demonstrates that massive envenomization by hornets is another potential source of toxic mitochondriopathy resembling Reye's syndrome. As the venom of many Hymenoptera share common toxic constituents, other wasps and bees are likely to produce a similar syndrome upon stinging.

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