

Survival After Anaphylaxis Induced by a Bumblebee Sting in a Dog

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ABSTRACT

A 3.5 yr old castrated male miniature schnauzer was referred with a history of collapse after a bee sting to the left hind limb. At the time of presentation, 14 hr after the sting, the dog was hypotensive, comatose, seizing, and had a brief period of cardiac arrest. Over the following 48 hr, the dog developed azotemia, severely elevated liver enzyme levels, hypertension, hematochezia, hematemesis, and disseminated intravascular coagulation (DIC). The dog's neurologic status improved slowly, but significant behavioral abnormalities remained. The dog was discharged after 7 days with ongoing polyuria, polydipsia, and behavioral changes. The polydipsia and polyuria resolved within a few days, but the behavioral changes continued for 6 wk. Reports of anaphylaxis from any cause are sparse in the veterinary literature. This is the first report of suspected anaphylaxis following a bee sting. There are no previous reports of behavioral changes after physical recovery from anaphylaxis.

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Introduction

Anaphylaxis has been broadly defined as “a serious allergic reaction that is rapid in onset and may cause death.”¹ It is considered a severe, systemic, type I hypersensitivity reaction, potentially involving multiple organ systems.^{2,3} Immunoglobulin (Ig) E is classically thought to mediate anaphylaxis, but other Igs, such as IgG1, are also significant, depending on the species.^{2,4} Anaphylactoid reactions are IgE independent, occurring without previous antigen exposure and sensitization.³ Both reactions are clinically identical, as is treatment; therefore, the terms are often used interchangeably.³ A human grading system has been proposed that classifies hypersensitivity reactions as mild, moderate, or severe, which may be more clinically useful than the anaphylaxis and anaphylactoid terminology.⁵ Moderate reactions involve ≥ 2 organ systems, with systolic blood pressure > 90 mm Hg, and severe reactions involve either neurologic compromise or systolic blood pressure < 90 mm Hg.⁵ In this report, the term anaphylaxis is used to describe a severe hypersensitivity reaction.

The pathophysiology of anaphylaxis is complex, involving both immunologic and nonimmunologic triggering mechanisms. In either case, clinical signs result from the systemic release of mediators from mast cells and basophils (e.g., histamine, tryptase, heparin, chymase, and cytokines) and the production of arachidonic acid metabolites (i.e., prostaglandins, leukotrienes).² The primary mediator of anaphylaxis is thought to be histamine, although other inflammatory amines, such as 5-hydroxytryptamine, may also be of significance in veterinary species.^{2,6}

Anaphylaxis from any cause is rarely reported in the veterinary literature. Five case reports (11 dogs) describing severe systemic reactions after Hymenoptera stings were found.^{7–11} Ten of those dogs had large numbers of simultaneous stings, and direct toxic effects of Hymenoptera venom may have contributed to their clinical signs.¹² In humans, fatalities from bee stings are usually due to anaphylaxis resulting from very few stings.¹² An additional five case reports and one study were found describing systemic hypersensitivity reactions in dogs from other causes.^{13–19} The purpose of this report was to describe the

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ALT alanine aminotransferase; BUN blood urea nitrogen; DIC disseminated intravascular coagulation; FFP fresh frozen plasma; Ig immunoglobulin; IM intramuscular(ly); MAP mean arterial blood pressure; PT prothrombin time; PTT partial thromboplastin time; SAP systolic arterial blood pressure

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clinical course of a dog that presented in suspected anaphylaxis after a bee sting.

Case Report

A 3.5 yr old castrated male miniature schnauzer weighing 8.4 kg presented to the primary care veterinarian within 1 hr of vomiting and collapsing immediately following a single bee sting to the left hind limb, which was witnessed during close supervision in an outside run. The dead bee was preserved and later identified as a bumblebee (*Bombus* sp.) The dog was fully vaccinated and had no previous medical problems.

At the time of presentation to the primary veterinarian, the dog had pale mucous membranes, tachycardia, tachypnea, a tense abdomen, obtundation, and bilateral mydriasis. A 100 mL (11.9 mL/kg) IV crystalloid bolus was delivered. IV dexamethasone (2 mg [0.24 mg/kg]) and intramuscular (IM) diphenhydramine (10 mg [1.2 mg/kg]) were administered. Results of a serum biochemical profile have been summarized (Table 1). IV crystalloids were continued at 30 mL/hr (3.6 mL/kg/hr). After 6 hr, cefazolin (dose unknown) and 1 mg (0.12 mg/kg) dexamethasone were administered IV. Nothing further was recorded for 8 hr, when the dog was found comatose and referred.

On presentation at the authors' institution (14 hr after being stung), the dog was comatose. During triage, there was a 2 min generalized seizure, which was followed by cardiac arrest. External cardiac compressions were initiated. Continuous electrocardiographic monitoring showed return of a spontaneous rhythm after 30 sec. The heart rate was 40 beats/min. An IV catheter was placed, and a minimum database, venous blood gas, and electrolytes were measured. The systolic arterial blood pressure (SAP) measured by ultrasonic Doppler flow monitor^a was 80 mm Hg. Physical examination showed pale mucous membranes, absent capillary refill, and no palpable pulse. Petechiae were noted on a clipped area of the forelimb. There were clear breath sounds

in all lung fields, and the respiratory rate was 24 breaths/min. No heart murmur was ausculted. Abdominal palpation was unremarkable, although hematochezia was evident. Rectal body temperature was 35.4°C. The dog had bilateral ventral strabismus, and the pupils could not be assessed.

Packed cell volume was 62% (reference range, 37–55%) with a total protein of 46 g/L (reference range, 60–80 g/L). Hypoglycemia (2.1 mmol/L; reference range, 3.6–6.2 mmol/L) and hyperlactatemia (3.4 mmol/L; reference range, 0.5–2.0 mmol/L) were noted. Blood urea nitrogen (BUN) was elevated, and creatinine was normal (Table 1).

Dextrose^b (0.5 g/kg), diluted 1:1 with 0.9% saline^c, was administered, followed by a 6 mL/kg bolus of hetastarch^d over 30 min, and additional fluid boluses (6 mL/kg hetastarch and 12 mL/kg of a balanced isotonic electrolyte replacement fluid^e) over 1 hr. The heart rate was then 96 beats/min and the SAP was 135 mm Hg. Repeat blood work showed normal lactate and glucose. Ongoing infusions of hetastarch (1 mL/kg/hr) and electrolyte replacement fluid (4.8 mL/kg/hr containing 2.5% dextrose) were started. A complete blood count, serum biochemical profile, blood type, and coagulation panel were performed. An indwelling urinary catheter was placed, and urinalysis was performed.

The complete blood count, obtained after volume resuscitation, showed neutropenia ($2.07 \times 10^3/\mu\text{L}$; reference range, $3.1\text{--}14.4 \times 10^3/\mu\text{L}$), lymphopenia ($0.29 \times 10^3/\mu\text{L}$; reference range, $0.9\text{--}5.5 \times 10^3/\mu\text{L}$), monocytopenia ($0.03 \times 10^3/\mu\text{L}$; reference range, $0.1\text{--}0.4 \times 10^3/\mu\text{L}$), and mild nonregenerative anemia (packed cell volume was 30% and hematocrit was 30.7% [reference range, 40.3–60.3%]). Results of the serum biochemical panel have been summarized in Table 1. Urinalysis showed proteinuria, hematuria, glucosuria, and a specific gravity of 1.015. The coagulation panel was suggestive of disseminated intravascular coagulation (DIC). Specifically, prothrombin time (PT) was 45.0 sec (reference range, 6.8–10.2 sec) and partial thromboplastin time

TABLE 1

Results of Serial Serum Biochemical Panels Taken at Various Time Points Following the Bee Sting

Serum level (U)	Within 1 hr of the sting at the primary care veterinarian (reference range)	14 hr after referral (reference range)	36 hr after referral (reference range)
Aspartate aminotransferase ($\mu\text{kat/L}$)	38.02 (0.25–1.10)	399.83 (0.38–1.09)	296.59 (0.38–1.09)
ALT ($\mu\text{kat/L}$)	16.43 (0.20–1.97)	151.90 (0.27–1.52)	106.55 (0.27–1.52)
Albumin (g/L)	32 (27–44)	9 (25–37)	17 (25–37)
BUN (mmol/L)	10 (2.1–11.1)	12.5 (1.7–10.7)	14.3 (1.7–10.7)
Creatinine ($\mu\text{mol/L}$)	133 (44–141)	159 (62–159)	212 (62–159)
Phosphorus (mmol/L)	1.8 (0.8–1.9)	2.4 (0.9–1.9)	N/A

ALT, alanine aminotransferase; BUN, blood urea nitrogen; N/A, not available.

(PTT) was 54.4 sec (reference range, 10.7–16.4 sec). D-dimers were 2.39 $\mu\text{g/mL}$ (reference range, $< 0.2 \mu\text{g/mL}$), with severe thrombocytopenia (0–2 platelets/high-power field).

Fresh frozen plasma^f (FFP; 240 mL [18.6 mL/kg]) was administered over 8 hr, after which PT was 27 sec (reference range, 12–17 sec) and PTT was 167 sec (reference range, 71–102 sec). Broad-spectrum antibiotics (22 mg/kg ampicillin^g IV *q* 8 hr and 10 mg/kg enrofloxacin^h IV *q* 24 hr) and famotidineⁱ (0.5 mg/kg IV *q* 12 hr) were started. One episode of hematemesis was noted, and 1 mg/kg maropitant^j was given subcutaneously.

The dog remained comatose with ventral strabismus, and 0.5 g/kg mannitol^k was administered IV through an administration set with a filter over 20 min after the FFP. The strabismus resolved, but the menace response was absent, with minimal pupillary light reflexes bilaterally. The mannitol dose was administered twice more over the following 24 hr. The dog's head was kept elevated on a slant board. Overnight, the dog responded to handling by lifting its head. The heart rate, SAP, and body temperature (with the dog on a heat pad^l) remained normal.

During the first 24 hr of hospitalization, BUN and creatinine values increased (Table 1), and coarse granular casts were noted on urinalysis. The BUN and creatinine values gradually normalized, but the dog was polyuric throughout hospitalization (maximum urine production was 18 mL/kg/hr; reference range, 1–2 mL/kg/hr). Urine output was matched with equal volumes of IV electrolyte replacement fluid, which was gradually withdrawn when the dog showed interest in drinking 4 days later. The dog had polydipsia, which was presumed to be a direct response to the polyuria. Both the polyuria and the polydipsia resolved 1 wk after discharge.

Hypertension was noted 24 hr after admission. An arterial catheter was placed in the dorsal metatarsal artery without complication immediately following a second dose of FFP. Direct blood pressure measurement consistently showed mean arterial blood pressure (MAP) between 136 mm Hg and 181 mm Hg. At this stage (24 hr after admission), the dog's mentation was improving, and increased intracranial pressure was considered unlikely; therefore, a continuous rate infusion of sodium nitroprusside^m was started, and MAP was maintained between 115 mm Hg and 130 mm Hg, with infusion rates between 0.5 $\mu\text{g/kg/min}$ and 3.0 $\mu\text{g/kg/min}$. Frequent weaning attempts were made, but therapy was required for 3 days, until the dog's mentation allowed for oral medication. Amlodipineⁿ was prescribed (0.3 mg/kg *per os* *q* 12 hr). After two doses, the MAP remained consistently normal, and amlodipine was discontinued.

Intermittent premature ventricular contractions were evident on the continuous electrocardiogram for the first 24 hr when the dog's heart rate ranged from 92 beats/min to 100 beats/min.

The premature ventricular contractions resolved without treatment. Abdominal ultrasonography showed mild hepatomegaly and a low-volume peritoneal effusion. Thoracic radiographs revealed a small volume of pleural effusion.

One day after admission, the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase began to decrease, normalizing 1 wk after discharge (2 wk after being stung). Total bilirubin increased to 66.7 $\mu\text{mol/L}$ (reference range, 5.13–15.4 $\mu\text{mol/L}$) before gradually decreasing and becoming normal after discharge.

PT and PTT remained prolonged for 4 days, and 120 mL FFP was given *q* 8 hr for 48 hr, then *q* 24 hr for the following 48 hr. PT and PTT were then within normal range, and FFP was discontinued. D-dimers reduced gradually, but were still elevated (0.48 $\mu\text{g/mL}$) at discharge. Subcutaneous vitamin K₁^o (1 mg/kg *q* 24 hr for 3 days) was prescribed 24 hr after admission, given the elevation in liver enzyme activity and potential contribution of a hepatopathy to the coagulopathy. The thrombocytopenia worsened over the first 24 hr, but then improved slowly. Extensive ecchymoses resolved during hospitalization. At discharge, the platelet count was $36 \times 10^3/\mu\text{L}$ (reference range, $177\text{--}398 \times 10^3/\mu\text{L}$), and 1 wk after discharge, the platelet count was normal.

The hematochezia resolved over 48 hr after hospital admission. Another episode of hematemesis after 24 hr was treated with ondansetron^p (0.2 mg/kg IV *q* 12 hr) and a continuous rate infusion of metoclopramide^q (1 mg/kg/day).

There was slow improvement in neurologic status. Twenty-four hr after admission, the dog could raise his head and briefly respond to stimuli, such as the owner's voice. Otherwise, the dog was recumbent and severely obtunded with periods of stupor. The blood ammonia level was 8.0 $\mu\text{mol/L}$ (reference range, 11–35 $\mu\text{mol/L}$). Forty-eight hr after admission, the dog had a brief seizure and ventral strabismus with mild anisocoria were noted. Another dose of mannitol (0.5 g/kg) was administered, as well as an IV loading dose of levetiracetam^r (50 mg/kg), followed by a maintenance dose (15 mg/kg IV *q* 8 hr). The strabismus and anisocoria resolved after mannitol administration, and there were no further seizures. Mentation continued to improve slowly, and by day 4, the dog could stand and walk with marked ataxia and circling to the left. By discharge, the dog's gait was normal. The dog was discharged with oral levetiracetam^s (2.2 mg/kg *q* 8 hr). The owner discontinued this shortly after discharge, and there were no further seizures.

Marked behavioral changes were noted both during hospitalization and after discharge, including random episodes of vocalization, lack of response to humans, and failure to recognize commands. The dog was reported to have been affectionate and

obedient before this incident. Obedience and behavior exercises were recommended; however, the owner reported that over the following 6 wk, the dog's behavior and demeanor gradually returned to normal without recourse to the exercises.

An epinephrine autoinjector[†] was prescribed (to deliver 0.15 mg [0.02 mg/kg] epinephrine), with instructions to inject the entire contents IM in the quadriceps in the event of a bee sting, before seeking urgent veterinary attention.

Discussion

This is the first report of anaphylaxis following a bumblebee sting in a dog. Bumblebees are members of the genus *Bombus* (family Apidae, order Hymenoptera) and are docile, stinging only when provoked. Anaphylaxis following bumblebee stings is rare in humans, but is increasing in prevalence due to commercial use of bumblebees for greenhouse plant pollination.¹⁹ Bumblebees build small nests underground, and the owner in this case subsequently found a nest in the dog's run. Unlike honeybees, bumblebees can retract their stinger from the victim's skin, which explains the absence of a stinger on examination of the dog.²⁰ Bumblebee venom is similar to honeybee venom, containing numerous allergenic proteins.²¹ Whereas honeybee venom contains mellitin, bumblebee venom contains polypeptides, called bombolitins, with similar function to mellitin.²²

The clinical signs and progression in the dog described in this report were consistent with anaphylactic shock. Signs typically associated with anaphylaxis in humans (e.g., vomiting, cardiovascular collapse) were observed immediately after antigen exposure.² Onset usually occurs within 15 min, as observed in this case, and severity of reaction is thought to correlate with rapidity of onset and with parenteral exposure.^{2,3} Clinically apparent cutaneous involvement and respiratory compromise were not seen in this dog; however, those signs may occur less frequently than is commonly assumed, and dexamethasone and diphenhydramine were administered prior to referral.¹³ Canine models of anaphylaxis show that hemodynamic deterioration with hypotension occurs shortly after allergen challenge, resulting from a combination of vasodilation and increased vascular permeability, leading to hypovolemia and eventual distributive shock.²³ In the dog in this report, hepatic and gastrointestinal abnormalities were evident before cardiac arrest, and were consistent with a period of hypoperfusion, although cardiac arrest likely exacerbated the severity of both the hepatic and gastrointestinal abnormalities.

Paradoxically, severe portal hypertension can also occur in dogs due to histamine release into the portal vein, causing increased blood flow and concurrent constriction of the hepatic venous sphincters.²⁴ Resultant ischemia and hypoxia cause

hepatocellular damage and ALT leakage.¹³ Rapid ALT elevation (< 12 hr) is a sensitive biomarker of anaphylaxis in dogs, and ALT is expected to remain elevated for > 24 hr.¹³ One potential mechanism of vomiting shortly after exposure may have been portal hypertension. Other possible causes of ongoing gastrointestinal signs include either prolonged gastrointestinal hypoperfusion or renal dysfunction.

Renal failure is common after Hymenoptera stings and is usually due to acute tubular necrosis resulting from hemolysis, rhabdomyolysis, or direct venom nephrotoxicity in cases of massive envenomation.²⁵ In the case described herein, there was no evidence of hemolysis, and the sting was solitary. Rhabdomyolysis cannot be ruled out because creatine kinase was not measured, although pigmenturia and hyperkalemia were not noted. Acute tubular insult secondary to ischemia during prolonged hypotension was considered most likely.

Coagulopathies consistent with DIC have been described after experimental and clinical envenomations.^{7,8,26} The administration of bee venom or individual components of bee venom has been associated with significant elevations in serum cytokine levels.²⁶ Bee venom has also been shown to both induce and inhibit platelet aggregation *in vitro*; however, the detailed pathophysiology of DIC secondary to envenomation has not yet been fully elucidated.²⁶

The severe neurologic signs and prolonged behavior recovery noted in this case differ from previously reported cases. Peripheral neuropathy causing ataxia and facial paralysis has been reported in dogs after massive bee envenomation, which was attributed to direct venom neurotoxicity.¹¹ In this case, neurotoxicity was unlikely given the solitary sting. Potential causes of the initial seizure and ongoing neurologic signs include neuronal damage from persistent hypoglycemia and global brain ischemia after prolonged hypotension and cardiac arrest. Peripheral and central nervous demyelination causing delayed neurologic effects after bee stings have been described in humans, possibly due to an immune-mediated reaction, and a similar mechanism may have contributed to neuronal dysfunction in this case.²⁷ Given the lateralizing signs that were noted as the dog started to recover, focal lesions could not be ruled out, such as either intracranial hemorrhage or infarction (secondary to either DIC or hypertension). Further diagnostics were not pursued because the dog improved. Hypoglycemia has not been reported after anaphylaxis, but its presence has been shown to worsen the severity of anaphylactic shock in rodents.²⁸ Common causes of hypoglycemia, such as toxins, neoplasia, and sepsis, were ruled out.

To the authors' knowledge, hypertension following an episode of anaphylaxis is not reported in the veterinary literature,

and is rare in humans.²⁹ Increased intracranial pressure may cause hypertension, but was considered unlikely in this dog because his mentation was improving by the time the hypertension developed. Had increased intracranial pressure been suspected, treatment with mannitol, rather than sodium nitroprusside, would have been indicated. Common causes of secondary hypertension, such as chronic renal disease, hyperadrenocorticism, diabetes mellitus, and pheochromocytoma, were considered unlikely. The hypertension was hypothesized to be secondary to ongoing release of catecholamines and vasoconstriction following the initial insult.

Diagnosis of anaphylaxis in this case was presumptive given the history and clinical signs. It was unknown whether the dog had previously been exposed to, and become sensitized to, the bumblebee venom antigen. It is therefore unclear whether this reaction was Ig- or nonIg-mediated. Specific human or veterinary tests for anaphylaxis are lacking. Rapid ALT elevation and gallbladder wall thickening on ultrasound were shown to be sensitive biomarkers of anaphylaxis in dogs, but are nonspecific.¹³ Although the dog in this report had elevated ALT, gallbladder changes were not found. Serum tryptase and plasma histamine, as well as urinary histamine and *N*-methylhistamine are considered biomarkers of anaphylaxis in humans, but are also nonspecific. Such tests have not been evaluated in dogs and are not routinely available.² Under-diagnosis and frequent misdiagnosis of anaphylaxis are reported in humans.² Biphasic reactions with recrudescence of signs several hr after the initial episode are reported, which may confound diagnosis and treatment.² Careful monitoring of suspected cases is strongly recommended.

The dog described herein was treated with supportive care, which is the mainstay of treatment of anaphylaxis. IM epinephrine at the time of presentation is recommended in humans based on consensus, rather than evidence.²⁰ Experimental studies in dogs showed that epinephrine is more effective for hemodynamic recovery in the laboratory setting as a constant rate infusion than in bolus doses.²³ In the current case, hypotension was treated with IV fluids, and vasopressors were not required. Glucocorticoids and antihistamines were administered prior to referral. Those drugs are routinely used in human and veterinary medicine, and are theoretically of benefit, but clinical evidence is lacking to either support or refute their use.^{30,31}

Humans with insect sting anaphylaxis have a 30–60% recurrence rate after being stung again, and prevention of future episodes is considered paramount.²⁰ Exposure avoidance strategies were discussed with the dog's owner, and an epinephrine autoinjector was prescribed. Unfortunately, human autoinjectors are limited to fixed total doses of either 0.15 mg or 0.3 mg of

epinephrine, which is inappropriate for many veterinary patients. It is essential to train owners to properly use the autoinjector considering there is an increasing number of reports of accidental injections.²⁰ In humans, preventative venom immunotherapy may be used with excellent results (80–90% efficacy).²⁰ This has not been evaluated in animals.

Conclusion

Anaphylaxis can cause multiorgan failure and is potentially fatal, requiring prompt diagnosis and aggressive treatment. In the authors' clinical experience, anaphylaxis is an infrequent presentation. There is little veterinary data regarding therapeutics other than supportive care. The mechanism of anaphylaxis is an active area in human research, with the potential to improve the diagnostic and therapeutic approach in future. ■

FOOTNOTES

- ^a Ultrasonic Doppler flow detector model 811-BL; Parks Medical Electronics Inc., Aloha, OR
- ^b 50% dextrose; Hospira Inc., Lake Forest, IL
- ^c 0.9% sodium chloride injection USP; Hospira Inc., Lake Forest, IL
- ^d 6% hetastarch in 0.9% sodium chloride; Hospira Inc., Lake Forest, IL
- ^e Normosol-R; Hospira Inc., Lake Forest, IL
- ^f Fresh frozen plasma; Penn Animal Blood Bank, Philadelphia, PA
- ^g Ampicillin injection USP; Sandoz Inc., Princeton, NJ
- ^h Baytril; Bayer HealthCare, Shawnee Mission, KS
- ⁱ Famotidine injection USP; Baxter Healthcare Corporation, Deerfield, IL
- ^j Cerenia; Pfizer Animal Health, New York, NY
- ^k 25% mannitol injection USP; Hospira Inc., Lake Forest, IL
- ^l T/Pump; Gaymar Industries Inc., Orchard Park, NY
- ^m Nitropress; Hospira Inc., Lake Forest, IL
- ⁿ Amlodipine besylate; Greenstone LLC, Peapack, NJ
- ^o K-ject; Butler Animal Health Supply, Dublin, OH
- ^p Ondansetron injection USP; West-Ward Pharmaceuticals, Eatontown, NJ
- ^q Reglan injection; Baxter Healthcare Corp., Deerfield, IL
- ^r Levetiracetam injection; Nexus Pharmaceuticals Inc., Vernon Hills, IL
- ^s Levetiracetam oral solution; Sandoz Inc., Princeton, NJ
- ^t EpiPen Jr; Dey Pharma, Napa, CA

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