

# Concurrent Heatstroke and Insulinoma in a Dog: A Case Report

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## ABSTRACT

An adult spayed female Boxer was presented with complaints of collapse, disorientation, and hyperthermia (rectal temperature 41 °C) following a prolonged exposure to an environmental heat stress. Clinicopathological abnormalities at presentation included increased creatine kinase activity, hypoglycemia (57.9 mg/dL, reference interval [RI] 64-123 mg/dL), mild prolongation of coagulation times, and rubricytosis. The dog was diagnosed with heatstroke, complicated by presence of hypoglycemia. The dog was hospitalized, treated, and improved over the following 48 hours, however the severe hypoglycemia persisted (34-51 mg/dL) despite therapy. Thoracic radiographs and abdominal ultrasound were unremarkable. Serum insulin concentration was high (31 µIU/mL, RI 5-20 µIU/mL), in the face of hypoglycemia (43 mg/dL). The dog was therefore tentatively diagnosed with an insulin-secreting tumor, which caused hypoglycemia. It was considered that this might have precipitated the heatstroke, possibly due to the persistent hypoglycemia, possible seizures, as a result of the heat stress. Alternatively, environmental heatstroke, known to induce hypoglycemia, may have aggravated the dog's insulinoma-induced hypoglycemia. The presence of heatstroke in this case is supported by the history of prolonged exposure to heat stress, presence of hyperthermia, prolonged coagulation times and peripheral rubricytosis. Insulinoma should be included as a differential diagnosis in dogs presenting with heatstroke and persistent, unresponsive hypoglycemia.

**Keywords:** hypoglycemia, hyperthermia, canine, insulin, heat-related illness.

## INTRODUCTION

Heatstroke is a severe clinical syndrome characterized by core temperatures > 40 °C in human patients, and > 41 °C in dogs, as well as by central nervous system (CNS) dysfunction (1-3). It results from the inability of the body to dissipate the accumulated heat, either because of heat overload, or thermoregulation derangement after exposure to hot, humid environments (classical heatstroke), strenuous physical exercise (exertional heatstroke) or prolonged uncontrolled muscular activity (e.g. seizures) (1-5). The direct thermal effects, along with physiological derangement can lead to acute activation of inflammation and coagulation, and consequently to a systemic inflammatory response syndrome (SIRS) and ultimately to multiple organ dysfunction syndrome (MODS)

(2, 4-8). Several factors are associated with high mortality in dogs with heatstroke, including delayed medical care, obesity, semicoma or coma at presentation, hypoglycemia (glucose < 47 mg/dL) at presentation, as well as occurrence of seizures, disseminated intravascular coagulation (DIC), and acute kidney injury (AKI) during the course of the disease (3). Hypoglycemia occurs in 63% of dogs with heatstroke (3); however, it may be associated with other, unrelated illnesses, and if so, this may complicate the diagnosis, and potentially may delay appropriate therapy. Hypoglycemia in adult dogs may occur due to decreased glucose production, excess glucose utilization and excess insulin or insulin-like factors secretion, most commonly due to β cell tumors (i.e., insulinoma) (9).

This report describes a novel case of heatstroke in a dog, which likely occurred as a complication of an insulinoma-induced hypoglycemic crisis.

## CASE HISTORY

An adult, spayed female Boxer of unknown age, suspected with heatstroke, was referred to the Hebrew University Veterinary Teaching Hospital (HUVTH). The dog lived in a rural area and was exposed to a hot, humid environment in a summer day for five hours. She was later found by its owner in a state of confusion, and was unable to stand. Rectal temperature, measured immediately by the owners following the referring veterinarian's advice, was 41 °C. The dog was cooled by whole body water irrigation, and was immediately referred to the HUVTH.

At presentation, approximately four hours after the episode, the dog was mentally obtunded, minimally responsive, recumbent and unable to stand. The rectal temperature was 36.3 °C, the pulse rate was 93 bpm and the respiratory rate was 36 breaths/min. Her hydration status was normal. Her body condition score was 3/9. The cranial nerves and spinal reflexes were normal. Blood samples were then obtained for complete blood count (CBC), serum chemistry and coagulation tests. Hematological and biochemistry tests results at presentation and in the following day are presented in Tables 1 and 2, respectively. The main clinicopathological abnormalities included mild thrombocytopenia ( $182 \times 10^3/L$ , ref-

erence interval [RI]  $200-500 \times 10^3/L$ ), hypoalbuminemia (2.6 g/dL, RI 3-4.4 g/dL), increased activities of creatine kinase (4589 U/L, RI 51-399 U/L) and aspartate aminotransferase (AST) (200 U/L, RI 19-42 U/L), hypoglycemia (57.9 mg/dL, RI 64-123 mg/dL) and mildly prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) (10.0 sec, RI 6.0-8.4 sec; 27.2 sec, RI 11.5-17.5 sec, respectively). Evaluation of a modified Wright's-stained blood smear revealed 3 metarubricytes per 100 white blood cells.

The dog was treated with an IV bolus of Lactated Ringer's solution (LRS, Teva Medical, Ashdod, Israel; 30 mL/kg) and 25% dextrose (Cure Medical, Emek-Hefer, Israel; 10 mL/kg), followed by constant rate infusion of intravenous LRS (5 mL/kg/hr) with 2.5% dextrose and metoclopramide (Pramin, Rafa Laboratories, Jerusalem, Israel, 0.04 mg/kg/hr IV). Additional treatment included amoxicillin-clavulonate (Augmentin, SmithKline, Brentford, UK; 15 mg/kg IV q12hr), metronidazole (Braun, Melsungen, Germany; 15 mg/kg IV q12hr), mannitol (Osmitol 20%, Baxter, Deerfield, IL, USA; 0.5 g/kg IV q8hr), low molecular-weight heparin (Clexan, Sonofi-Aventis, 2 mg/kg SQ, q8hr), and fresh-frozen plasma (10 mL/kg IV).

The next day, the dog was ambulatory, alert, responsive, and showed appetite. Serum electrolytes, creatinine, and urea

**Table 1:** Selected hematologic test results at presentation and after 24 hours in a dog with concurrent heatstroke and insulinoma

Parameter	Day 0	Day 1	Reference interval
Total Leukocytes ( $\times 10^3/\mu L$ )	11.4	9.2	5.2-13.9
Eythocytes ( $\times 10^6/\mu L$ )	6.0	4.7	5.7-8.8
Hemoglobin (g/dL)	12.9	10.1	12.9-18.4
Hematocrit (%)	37.0	29.2	37.1-57.0
Mean corpuscular volume (fL)	61.0	62.0	58.8-71.2
MCHC <sup>1</sup> (g/dL)	34.9	34.6	31.0-36.2
Red blood cell distribution width (%)	18.3	18.3	11.9-14.5
Platelets ( $\times 10^3/\mu L$ )	250.0	109.0	143-400
Mean platelet volume (fL)	10.4	9.6	7.0-11.0
Packed cell volume (%)	37.0	30.0	37-55
Total solids	6.8	5.8	5.5-7.5
Prothrombin time (sec)	10.0	8.5	6.0-8.4
Activated partial thromboplastin time (sec)	27.2	26.3	11.0-17.4

<sup>1</sup> Mean Corpuscular Hemoglobin Concentration.

**Table 2:** Serum biochemistry parameters at presentation and after 24 hours in a dog with concurrent heatstroke and insulinoma

Parameter	Day 0	Day 1	Reference interval
Glucose (mg/dL)	57.8	43	64-123
Urea (mg/dL)	37.8	13.3	10.7-53.5
Albumin (g/dL)	2.6		3.0-4.4
Alkaline phosphatase (U/L)	37.8		21-170
Alanine aminotransferase (U/L)	75.4		19-67
Aspartate aminotransferase (U/L)	199.8		19-42
Amylase (U/L)	1091.5		103-1510
Total calcium (mg/dL)	7.4		9.7-11.5
Creatine kinase (U/L)	4589		51-399
Creatinine (mg/dL)	0.7	0.5	0.3-1.2
Phosphorus (mg/dL)	6		3.0-6.2
Triglycerides (mg/dL)	47.1		19-133
Protein (g/dL)	5.4		5.4-7.6
Total bilirubin (mg/dL)	0.1		0.0-0.2
$\gamma$ -glutamyltransferase (U/L)	1		0-6
Chloride (mmol/L)	115.9	118.8	108-118
Potassium (mmol/L)	4.12	3.5	3.6-5.3
Sodium (mmol/L)	144.4	146.9	145-154

concentrations were within RI, and coagulation tests results improved. However, despite this clinical improvement, blood glucose concentrations remained below RI (34 mg/dL), and the dog was uncharacteristically aggressive when handled. At this time, a blood sample was obtained for insulin measurement. Dextrose dose was then increased (5% in the IV fluids), and over the next 24 hours blood glucose concentration was monitored every 4 to 6 hours, and ranged between 34 to 51 mg/dL, while the clinical status remained unchanged. Dextrose supplementation was gradually decreased, and it was withdrawn at 48 hours post-presentation, with no apparent change in blood glucose concentration.

Abdominal ultrasound and thoracic radiographs were unremarkable. While results of blood insulin concentration were pending, the dog was discharged, and treatment recommendations included prednisone (Rekah, Holon, Israel, 0.75 mg/kg PO q12hr). Serum insulin concentration, available later on, was high (31.0  $\mu$ IU/ml, RI 5-20  $\mu$ IU/ml), consistent with a diagnosis of insulinoma. Further diagnostic tests and surgical intervention were suggested, but were declined by the owners.

## DISCUSSION

Dogs with heatstroke typically present with neurological abnormalities of varying severity, and clinicopathological abnormalities which include increased serum muscle enzymes activity, hypoglycemia and rubricytosis, as was observed in the present case, supporting the clinical diagnosis of heatstroke (3, 10, 11). In both dogs and humans with heatstroke, hypoglycemia at presentation is common (3, 12, 13), and has been shown to be a risk factor for death in dogs when blood glucose concentration is below 47 mg/dL (3). In heatstroke, hypoglycemia may result from decreased production, due to hepatic failure or increased utilization, due to increased ATP demand, seizures, respiratory effort and sepsis (3, 13, 14). Therefore, persistent hypoglycemia in heatstroke may be a sign of severe systemic complications. However, in this case, persistent hypoglycemia was documented in spite of an ongoing clinical and clinicopathological improvement (e.g. normalization of serum liver and muscle enzyme activities and coagulation times), warranting additional investigation for other possible causes.

The causes of hypoglycemia may be broadly classified into four groups: diseases associated with increased production of

insulin or insulin-analogues (e.g. exogenous insulin overdose, insulinoma, paraneoplastic syndrome, toxins and medications), decreased glucose production (e.g. in neonates, toy breeds, hepatic dysfunction and hypocortisolism), excess glucose utilization (e.g. infection, exercise-induced, paraneoplastic and polycythemia), and laboratory errors (e.g. hand-held glucometers) (9, 15-18). In this case, lack of clinicopathological or imaging abnormalities suggestive of liver insufficiency and sepsis, with persistent hypoglycemia despite parenteral glucose supplementation and with subsequent clinical improvement, raised the suspicion of increased secretion of insulin or insulin-like factors.

Insulinoma is the most common islet-cell neoplasia in dogs (9, 18). Clinical signs are secondary to hypoglycemia, and commonly include generalized weakness, exercise intolerance, hind limb weakness behavioral changes, collapse and seizures (9, 18-22). Insulinoma may be suspected clinically based on compatible clinical signs, and concurrent hypoglycemia and hyperinsulinemia (9, 17-19). Abdominal ultrasonography may show evidence of neoplasia; however, it has relatively low sensitivity and specificity (9, 17-19). A definitive diagnosis of insulinoma requires histopathological evidence of a tumor in tissue samples (9, 18, 24). In this case, a definitive diagnosis of insulinoma could not be made as the owner declined an exploratory laparotomy in order to obtain tissue biopsies. Nevertheless, in light of the high serum insulin concentration, and in face of a concurrent hypoglycemia, insulinoma is highly likely (9, 17-19).

Our assessment is that this dog had an insulin-secreting tumor, which led to a hypoglycemic episode on the day of presentation. The resulting neuroglycopenia, resulted in weakness, disorientation, depression and confusion. In this state, the dog might have had difficulties seeking water and shade, thereby exposing herself to extreme heat stress and eventually to heatstroke. The fact that the dog is a brachycephalic breed further predisposed it to heatstroke, because of its poor ineffective evaporation ability and their tendency to develop laryngeal edema during heat stress (3). Another possible scenario is that insulin-induced hypoglycemia may have led to seizures and to heat accumulation, exacerbated by the environmental heat stress. We cannot rule out the possibilities that hypoglycemia induced by heatstroke was exacerbated by the presence of insulinoma, or that insulinoma was only an incidental finding in this dog which was presented due to an environmental heatstroke. The increased

body temperature, along with hypoglycemia, increased muscle enzymes activities and other clinicopathological characteristic of heatstroke (e.g., prolonged coagulation times and rubricytosis) do not allow discrimination between the above scenarios. However, prolonged clotting times and rubricytosis at presentation are not characteristic of insulinoma *per se*, and therefore in support of 'true' heatstroke in this case (3, 11). Interestingly, a retrospective study of dogs with insulinoma showed that the vast majority presented during the summer months (24), similarly to this case, and this may emphasize the increased susceptibility of such dogs to heat stress, due to the aforementioned scenarios.

This dog showed uncharacteristic aggressive behavior, previously unobserved by the owners, and the reason for this phenomenon remains unclear. Hypoglycemia may cause behavioral abnormalities; however, aggressiveness was not reported as a clinical manifestation of insulinoma in dogs (9, 18). Naturally-occurring chronic hypoglycemia in humans and dogs has been shown to cause cerebrocortical and hippocampal neuronal death and myelin damage (25, 26). These same anatomic areas are also infiltrated by the rabies virus (27-29), often leading to aggressive behavior (30).

In conclusion, this case of concurrent heatstroke and insulinoma exemplifies that hypoglycemia, commonly present in dogs with heatstroke, may occur due to other, unrelated conditions, such as insulinoma. Therefore, such differential diagnoses should not be neglected in the investigation of hypoglycemia in cases of heatstroke, especially if hypoglycemia persists despite clinical improvement.

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