SIGNALMENT

Cooper, a 7-year old male neutered mixed breed dog, Weight 9.65kg. Case Log #30, Patient ID # 657176, Case Report #1

HISTORY

Cooper presented at the [redacted] on June 5, 2019 with a history of pale mucous membranes, lethargy, anorexia, polydipsia, polyuria and a grade IV/VI heart murmur was auscultated. Upon admission a complete blood count (CBC) was collected and revealed anemia with a packed red blood cell volume (PCV) of 25%, (ref: 35-45%), neutrophilic leukocytosis of 16.27 $x10^9$/L (ref) and white blood cell count (WBC) of 20.63 x 10^9/L (ref: 4.9-15.4$x10^9$/L). Biochemistry revealed hyperbilirubinemia at 27umol/L (ref: 0-4umol/L) and mild hypokalemia at 3.0mmol/L (ref: 3.8-5.4mmol/L). An in-house blood smear slide revealed agglutination. Cooper was suspected to have Immune Mediated Hemolytic Anemia (IMHA) and was admitted into the hospital for treatment. IMHA is characterized by a dysfunction within the immune system that causes the body to destroy red blood cells, leading to anemia[1]. Primary IMHA is idiopathic and accounts for sixty to seventy-five percent of IMHA cases[1]. Normal red blood cells are regenerated within three to five days, however failure to do so is indicative of an underlying immune mediated problem[2]. Cooper remained relatively stable during his six days in hospital, maintaining a PCV of 17-24% and did not need to receive blood products to resolve his anemia. He was, however started on immunosuppressants such as intravenous (IV) cyclosporine at a dose of 6 mg/kg and dexamethasone IV 0.25 mg/kg to prevent further hemolysis of his red blood cells (RBC) by suppressing his immune system. He also received oral (PO) clopidogrel 18.75 mg/day to reduce the chance of thromboembolism. IMHA patients are often also hypercoagulable due to a systemic inflammatory response as a result of acute RBC hemolysis[1]. Cooper's activated clotting time (ACT) on admission was 115 seconds (ref: 90-120 seconds), which is in normal range and is likely attributed to his previous use of the anticoagulant clopidogrel. Cooper was discharged home on June 11, 2019 to the care of his owners on Prednisone orally (PO) 25mg once a day and Cyclosporine PO 50 mg twice a day, clopidogrel PO 18.75 mg once a day, and maropitant PO 25 mg once a day. Antiemetics, such as maropitant are indicated for the nausea, vomiting and inappetence experienced by these patients.

The owners initially had difficulty administering the medications at home and noted intermittent blood in his stool as well as increased drinking and urination. On June 26, 2019 Cooper's stool progressed to diarrhea, he had decreased energy and appetite. He presented at his RDVM where blood work was performed and revealed a moderate normocytic normochromic non-regenerative anemia with polychromasia; poikilocytes, spherocytes and histiocytes on smear evaluation. He had marked leukocytosis, moderate mature neutrophilia, marked monocytosis and moderate thrombocytosis. His biochemistry results showed marked hyperglycemia, mildly low creatinine, and mild hypocalcemia, mild elevation in alanine transaminase and alkaline phosphatase, markedly increased amylase, lipase, mild hypokalemia, mild hypochloremia and abnormal canine pancreatic lipase immunoreactivity (cPl). He was subsequently referred to [redacted] for continued care. Cooper re-presented to the emergency service at [redacted] on June 29, 2019 for assessment of bloody diarrhea, vomiting and suspected relapse of immune medicated hemolytic anemia.

INITIAL PHYSICAL EXAMINATION

On presentation, Cooper was dull and quiet, he was estimated to be 8-10% dehydrated based on tacky mucous membranes and a prolonged skin tent. His mucous membranes were pale pink with a capillary refill time (CRT) of less than 2 seconds. He was normothermic, at 38.2°C (ref: 37.5-39.5°C). Heart rate was 132 beats per minute (ref: 70-140 bpm) with a grade 4/6 heart murmur on his left side. Pulses were strong and synchronous. Respiratory rate was 36 respirations per minute (rpm) (ref: 10-40 rpm) with normal lung sounds. Skin examination revealed no bruising or petechiation. Rectal examination revealed frank blood in his stool. Abdominal palpation revealed moderate to marked discomfort in the cranial abdomen. He was mildly cachexia with a low muscle condition score. Initial blood gas results showed hyperglycemia at 21.6 mmol/L (ref: 3.3-7.3 mmol/L), mild hypokalemia at 3.1 mmol/L (ref: 3.8-5.4 mmol/L) and a blood ketone level of 4.3 mmol/L (ref: 0-0.32 mmol/L). The remaining blood gas results were unremarkable. Cooper was admitted to [redacted] for treatment of diabetic ketoacidosis (DKA) and suspected pancreatitis, which is often affiliated with DKA. Symptoms of DKA included dehydration, vomiting, in appetence, polyuria, polydipsia, weakness, lethargy, muscle wasting, weight loss, poor fur coat and depressed mentation[3]. Blood work may include but it not limited to hyperglycemia, ketonemia, acidemia, leukocytosis, hypokalemia, hyponatremia, hypophosphatemia and azotemia[3].

INTIAL INTERVENTION

Cooper was admitted to the hospital with the intention of correcting his electrolyte imbalances, acidosis, dehydration, decreasing his ketonemia and ketonuria and increasing his absorption of glucose. A 22-gauge intravenous (IV) catheter placed in his right cephalic vein and he was placed on IV fluids at twice his maintenance level of fluids at 36 ml/hr on Plasmalyte-A™ (PLA) fluids. It is important to initially correct the patient's hydration status prior to initiation of insulin therapy, as rehydration alone can decrease blood glucose levels[5]. Cooper had already received a 4-hour dose of 6 mg/kg cyclosporine IV, 0.2 mg/kg IV dose of dexamethasone, 1 mg/kg IV dose of maropitant, 1 mg/kg IV of famotidine as well as 18.75 mg of clopidogrel PO before I began my shift. Once present, I prepared potassium chloride (KCL) for a continuous rate infusion (CRI) in order to increase Cooper's potassium level from the 3.1 mmol/L seen on presentation, I ran the CRI for 4 hours. The maximum level of potassium a patient is safety able to receive is 0.5 meq/kg/hr for a maximum of 4 hours[4]. Greater than ninety-five percent of the body's potassium is stored intracellularly[4]. Decreased potassium levels can occur due a decreased intake, such as in inappetent patients, gastrointestinal fluid loses seen in patients experiencing vomiting and diarrhea, and urinary loses due to polyuria[4]. A shift of potassium from the extracellular space to the intracellular space occurs in exchange of hydrogen ions (H+), and is associated with increased serum pH levels, known as alkalosis and results in hypokalemia[4,5,6]. An outward shift of potassium from the intracellular fluid to the extracellular fluid involving hydrogen ion exchange is often associated with decreased serum pH levels known as acidosis[3,5,6]. Cooper's blood pH level on admission was mildly acidotic at 7.218 (ref: 7.32-7.38), however acidemia does not invariably cause hyperkalemia and in Cooper's case his admission potassium level was mildly hypokalemic at 3.1 mmol/L (ref: 3.8 mmol/L-5.4 mmol/L) instead of the assumed hyperkalemia[4]. Potassium

supplementation is important as decreased levels can cause muscle weakness, lethargy, confusion, vomiting, polyuria or urine retention, polydipsia, decreased gastrointestinal motility, weight loss, to ventroflexion of the neck and can to progress more serious complications such as cardiac arrhythmias and respiratory failure[4,7]. Severe hypokalemia is a serum potassium level of less than 3.0 mmol/L[4]. After the KCL CRI, I administered a 0.4 mg/kg dose of butorphanol IV for sedation for the placement of a double lumen central venous catheter. Jugular catheters are generally favored in patients suffering from DKA as multiple blood samples are needed to monitor blood glucose (BG) and potassium (K+) levels[5]. I clipped the fur and aseptically prepared the jugular site for my placement of a 15 cm MILA double lumen central venous catheter, which I placed in Cooper's right jugular vein. Central venous catheters last much longer then peripheral catheters and it is important to ensure sterile technique during placement[7]. Upon successfully placement, I obtained a blood gas sample, which showed a BG level of 13.5 mmol/L (ref: 3.3-7.3 mmol/L) and a K+ level of 3.5 mmol/L (ref: 3.8-5.4 mmol/L), the remaining values where within normal range. I then prepared a second sodium chloride (NaCl) 0.9% bag, IV drip set, line and buretrol in order to administer the prescribed insulin CRI. Insulin is a complicated pancreatic hormone and has many uses, such as activating glucose absorption for energy expenditure, lipolysis repression, free fatty acid release and is used in the anabolic reaction to convert glycogen to glucose (gluconeogenesis) and it also causes the breakdown of glucose to pyruvate (glycolysis) for energy in a catabolic reaction, to name a few[8]. The use of NaCl is supported due to its ability to expand volume and maintain serum osmolality when BG is reduced, while supporting any sodium deficits[2]. I calculated the insulin CRI at 0.1 U/kg/hr and set up the CRI to last for 10 hours. I primed the adjoining lines with the saline/insulin solution and let it sit for one hour; this is a necessary step, as insulin molecules are known to bind to plastic, waiting one hour allows for this process to occur[2]. The absorption of insulin by the plastic can lead to a decreased potency of 20-30% of insulin[5]. I also administered a dose of 0.1 U/kg of regular Toronto insulin IV, a conservative starting dose to prevent an accelerate drop in osmolality[5]. IV administration of regular Toronto Insulin can last between one to four hours and is ideal for a fast onset of action(am782). Once the hour had past, I proceeded to drain the IV lines and buretrol, then re-administered the insulin into the buretrol and filled the line with the new insulin solution of 0.1 U/kg/hr before attaching this line to Cooper's right cephalic peripheral catheter. Cooper's maintenance fluids were then attached to his central line, allowing the second distal port to be used for repeated blood sampling. I chose this set up, presuming Dextrose would eventually be added to his maintenance fluids to maintain a target BG level. Higher concentrations of dextrose can aggravate the vascular endothelium leading to thrombophlebitis[8]. Supplementation through a larger vein, such as the jugular vein can reduce this occurrence and is superior to using a peripheral catheter for high levels of dextrose supplementation[8]. I also added metoclopramide to his maintenance fluids at a dose of 2 mg/kg/day. Metoclopramide is a prokinetic with antiemetic properties, that stimulates upper gastro intestinal (GI) motility and can assists in the control of one of Cooper's presenting complaints, such as vomiting and it may also improve food tolerance[5,6]. Cooper's maintenance fluid rate was adjusted to reflect his rate on his insulin CRI, so that total fluids were being maintained at 36 ml/hr. According to the prescribed fluctuating insulin CRI chart created by his clinician, changes to his insulin CRI rate were made every two hours in accordance

with his blood glucose levels. Copper was initially started at 5 mls/hr on his insulin CRI. At three am, his BG value was 10.5 mmol/L and his insulin CRI rate was adjusted to 3 ml/hr. In order to cautiously prevent the clotting of his peripheral catheter due to low fluid rate, I added an additional PLA IV fluid line to his insulin line. I ran this line at 15ml/hr, halving his fluid maintenance rate between his two IV lines.

SECOND INTERVENTION

The next day on Cooper's morning blood gas and electrolytes, his potassium level was 2.6 mmol/L. He received a second KCl CRI of 0.5 meq/kg/hr for 4 hours, which increased his K+ level to 3.5 mmol/L. Potassium levels must be consistently monitored during insulin therapy as insulin will cause a shift of serum potassium into cells due to the sodium (Na) -potassium pump, which utilizes the enzyme Na+/K+ -ATPase, leading to a decreased amount of serum potassium levels[9]. Cooper was then started on a KCl CRI at a rate of 0.1 meq/kg/hr in order to maintain a normal range of his K+ levels while remaining on the insulin CRI. I continued to adjust the rate of his insulin CRI every 2 hours depending on his BG levels, in order to maintain the optimal range of his BG levels falling between 8-12 mmol/L as prescribed by his team of internal medicine clinicians. Cooper's KCl CRI was also subsequently adjusted according to his K+ levels, which were checked every 4-6hrs. His 8pm blood ketone level was 2.9 mmol/L. Cooper also received additional doses of cyclosporine, dexamethasone, maropitant, famotidine, oral clopidogrel and oral potassium gluconate. The oral potassium gluconate was administered due to a hospital shortage of injectable KCL. Seventeen hours post admission, Cooper's HR began to elevate to 170bpm, I placed Cooper on a Lead II electrocardiogram to monitor his cardiac rhythm, complexes and rate. I orchestrated and assisted with an abdominal focused assessment with sonography for trauma (AFAST), which lead to the discovery of a distended stomach full of fluid. I placed a naso-gastric tube in order to measure his residual stomach volume. The initial residual volumes obtained from his NG tube were 125 mls and upon removal his heart rate subsequently decreased to 140 bpm. On Day 3 of hospitalization Cooper's phosphate level was 0.54 mmol/L (ref: 0.9-1.85 mmol/L) and I started him on potassium phosphate (KPO_4) supplementation at a dose of 0.06 mmol/kg/hr at a rate of 0.19 ml/hr. Hypophosphatemia is known to cause neurological signs, such as weakness and hemolysis, which in Cooper's particular case is of great concern due to his previous anemia associated with his previous diagnosis of $IMHA_5$. In addition, I considered his total potassium supplementation, as Cooper had already received additional potassium from a KCl CRI and was now also receiving KPO_4. I calculated the total potassium supplementation he was receiving at 0.3 meq/kg/hr, well below the recommend maximum dose of 0.5 meq/kg/hr of potassium.

DISCUSSION

Diabetes mellitus (DM) is an endocrine disorder characterized by a deficiency or loss in the pancreas' Beta cells ability to release the insulin hormone or an insulin resistance, which subsequently leads to an inability to digest sugars[6]. Insulin resistance can be due to a decreased amount of insulin receptors in response to exaggerated or long-term insulin production[6]. This results in an increased blood glucose level referred to as hyperglycemia. DKA is differentiated from DM as an emergent status due to insulin deficiency,

hyperglycemia, and ketonemia; it also is likely to include severe symptoms such as metabolic acidosis, dehydration and electrolytes depletion, as previously discussed[2]. Insulin resistance or deficiency terminates the body's ability to utilize ingested glucose for energy and thus the body instead utilizes fat stores resulting in the production of ketone bodies[6]. When ketone bodies are produced from the metabolism of fat cells they are released into the bloodstream causing ketosis and ketoacidosis, resulting in devastating electrolyte disturbances and suppression of nervous functions, which can be life threatening[6]. In Cooper's case, he was a newly undiagnosed diabetic, who remained untreated for an unknown amount of time, resulting in the further development of DKA. Glucocorticoids such a Prednisone can have inadvertent metabolic effects such as DM also known as steroid induced DM[10]. Cooper's symptoms such as hyperglycemia in a patient with prior history of DM, along with his regular use of glucocorticoids to suppress his IMHA condition is believed to have lead to his further development of DM and subsequently lead to DKA. Adverse side effects of glucocorticoid use include, but are not limited to PU/PD and polyphagia, which are similar to the early symptoms of DM and are theorized to have masked theses early indicators in his disease process.

Often, animals much like Cooper who are experiencing diabetic ketoacidosis present with abdominal pain or distention due to concurrent pancreatitis[4].. The pancreas is involved in the regulation of endocrine hormones such as insulin and glucagon, which are used in carbohydrate metabolism and blood glucose levels[11]. The pancreas can be a complicating factor in the management of DM, as inflammation of the pancreas known as pancreatitis may further damage the pancreatic B-cells needed for insulin production[11].

OUTCOME:

Cooper remained in hospital for 10 days. Due to the rigorous management of his BG and K+ levels on the insulin CRI, he was slowly weaned off the insulin CRI after three days and started on subcutaneous long acting insulin administered postprandial twice a day. He remained in hospital to monitor his BG levels and for insulin dose adjustments prior to being discharged home. Cooper was discharged on prednisone (10 mg/day), long acting insulin (6U/12hrs), clopidrogrel (75 mg/day) and cyclosporin (50 mg/12hrs).

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