The Trouble with Sugar Bear

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Introduction

Glomerular disease is becoming a more commonly recognized cause of kidney disease in veterinary medicine. Etiologies for glomerulonephritis can be broken down into infectious diseases, non-infectious inflammatory diseases, neoplasia, and idiopathic. The most common underlying infectious, inflammatory, and neoplastic diseases include, but are not limited to, babesiosis, ehrlichiosis, hepatozoonosis, leptospirosis, heartworm disease, pyelonephritis, pyometra, chronic bacterial infections, pancreatitis, periodontal disease, polyarthritis, inflammatory bowel disease, hemangiosarcoma, hepatocellular carcinoma, lymphoma, and transitional cell carcinoma. Additional etiologies include chronic corticosteroid use, hypertension, familial disease, diabetes mellitus, and hyperadrenocorticism. In idiopathic glomerulonephritis, no antigen source can be identified [1].

Primary glomerular diseases must be differentiated from secondary glomerular changes which resulted due to renal tubular damage. Presence of proteinuria, while suggestive, is not specific for glomerular disease. Localization, persistence, and magnitude of proteinuria must be determined. Basic diagnostics required for glomerulonephritis include a comprehensive history, physical exam, and a minimum database including complete blood count (CBC), serum chemistry, urinalysis, urine protein creatinine ratio (UPC), and urine culture. History must include breed predilections, travel associated infectious diseases such as Lyme, heartworm disease, and ehrlichiosis, and any drugs/diet that may result in hypertension or glomerular disease such as phenylpropanolamine, steroids, tyrosine kinase inhibitors, or a raw food diet. A physical exam should be performed including body condition score, retinal exam, rectal exam, and blood pressure measurement [2].

Bloodwork and urine tests should be analyzed for signs of systemic disease, and any concurrent diseases should be investigated with the appropriate diagnostics. Common abnormalities seen with glomerulonephritis include azotemia, hyperphosphatemia, metabolic acidosis, hypoalbuminemia, and anemia. Proteinuria seen on urinalysis is highly suggestive of glomerular disease, but it must be confirmed with two UPC ratios. UPC ratio measures the magnitude of proteinuria, with a high magnitude of proteinuria being more suggestive of glomerular disease. When UPC ratios are persistently greater than 0.5 (2-3 values over 0.5, at least 2-3 weeks apart), additional diagnostics are required. Imaging such as abdominal ultrasound and thoracic radiographs should be performed to evaluate renal architecture, presence of pleural or peritoneal effusion, organomegaly, and lung infiltration [2].

Infectious diseases must be ruled out, and determining which tests are performed is guided by clinical judgement based on the animal's environment and travel history. Tests which can be performed include a SNAP 4DX to rule out heartworm disease, Lyme, anaplasma, and ehrlichia, leptospirosis PCR or antibody testing, and PCR for various flea and tick-borne diseases such as bartonellosis, babesiosis, and Rocky Mountain Spotted Fever. If hypertensive, non-renal causes such as hyperadrenocorticism, pheochromocytoma, hyperaldosteronism, drugs, and fluid/salt overload should be ruled out. Additionally, liver disease, gastrointestinal loss, and malnutrition should be ruled out as other causes of hypoalbuminemia. Azotemia, if present, should be characterized as pre-renal, renal, or post-renal, and renal causes should be classified as acute kidney injury, chronic kidney disease, or acute on chronic kidney disease. Kidney disease should be staged with the appropriate IRIS classification scheme [2].

A renal biopsy is indicated if any of the following criteria are met: substantial proteinuria with a UPC ratio greater than 3.5, no response to treatment, or progressive disease despite

therapy. A renal biopsy will provide a definitive diagnosis and differentiates between different types of glomerulonephritis. However, a renal biopsy should not be performed should there be end stage kidney disease or if the patient is clinically unstable [2, 3]. Hemorrhage is a major complication of renal biopsy, and there is an increased risk in small patients. Hemostatic abnormalities such as thrombocytopenia or prolonged bleeding times and uncontrolled hypertension are also associated with an increased risk of hemorrhage; therefore, renal biopsy is contraindicated when these abnormalities are present. [3]

Treatment of glomerulonephritis focuses on the treatment of the underlying cause of disease and supportive therapy, such as reducing proteinuria, preserving renal function, and management of chronic renal failure (if present). Supportive therapy can also include angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers, protein and salt restricted diets, anti-hypertensive therapy, anti-thrombotic therapy, fluid therapy, diuretic therapy if pulmonary edema or hyperkalemia are present, and potentially immunosuppressive therapy if no underlying infectious, inflammatory, or neoplastic cause may be identified [1, 4].

The initial treatment for most dogs with proteinuria is an ACE-I such as enalapril or benazepril. ACE-I reduce proteinuria by decreasing efferent glomerular arteriolar resistance to reduce glomerular hydrostatic pressure. In fact, enalapril has been shown to reduce proteinuria and delay onset and progression of azotemia in glomerulonephritis. An initial dose for enalapril is 0.5mg/kg PO q24h. However, many animals will require a dosage increase with twice daily administration. The dosage can be increased by 0.5mg/kg/day to a maximum of 2mg/kg/day. Angiotensin receptor blockers such as losartan and telmisartan have been studied in humans to reduce proteinuria similar to ACE-I. Further study is required due to limited data in dogs;

however, there is good anecdotal evidence that angiotensin receptor blockers can be beneficial, especially in combination with ACE-I. [5].

Decreased dietary protein and dietary sodium can help to minimize further proteinuria and effusions/hypertension, respectively. Additionally, it has been showed that supplementation of omega-3 polyunsaturated fatty acids (PUFA) alters the long-term course of renal injury by lowering glomerular pressure, decreasing renal eicosanoid excretions, and long-term renal protection. Therefore, it is recommended to reduce the omega-6:omega-3 PUFA by supplementing omega-3 PUFA [5].

Loss of antithrombin III in glomerulonephritis leads to an increased risk of thromboembolism; therefore, daily administration of low dose aspirin (1-5mg/kg/day) is recommended. Hypertension can result in organ damage particularly in the kidney, eye, brain and heart. In order to minimize or prevent further injury to the kidney, hypertension must be controlled. Treatment is indicated when systolic blood pressure is greater than 160 mmHg, when diastolic blood pressure is greater than 100 mmHg, or both. Unless there is ocular or CNS organ damage, blood pressure should be lowered gradually over several weeks until systolic blood pressure is less than 150 mmHg, diastolic blood pressure is less than 95 mmHg, or both. Many different drugs can be used and include the following: ACE-I, angiotensin receptor blockers, calcium channel blockers (amlodipine), beta blockers (atenolol), alpha1 blockers (prazosin, phenoxybenzamine), direct vasodilators (hydralazine, acepromazine), or diuretics [5].

Fluid therapy should be considered after careful assessment of the patient's hydration status. Animals with glomerulonephritis are at risk for fluid overload, so fluid therapy is only indicated when dehydration or poor tissue perfusion exists. Colloids or plasma must be used

judiciously when crystalloid fluid support has failed to correct hemodynamic abnormalities. If edema or effusion results, treatment is correction of underlying etiology and reduction in proteinuria. Diuretic use should be limited to situations when effusion seriously impairs organ function, such as pleural effusion resulting in respiratory distress. Drainage of effusions via thoracocentesis or abdominocentesis is reserved for supportive care of those animals in respiratory distress or abdominal discomfort from pleural or peritoneal effusion respectively [5].

Stable patients are assessed 1-2 weeks after start of therapy and every 2 weeks for the first 4-6 weeks. Assessments are then performed once monthly for the next 3 months and every 3 months thereafter until resolution of disease. If patients are hospitalized, then monitoring should be performed daily and includes the following: physical exam, hydration status, body weight, UPC, urinalysis, systemic arterial blood pressure, serum albumin, creatinine, and electrolyte concentrations [5]. Serial UPC ratios, creatinine, and albumin are the most reliable indicators of response to therapy. Successful therapy can be defined as the following: reduction of UPC to less than 0.5, reduction of creatinine to less than 1.4 mg/dL, and increase in serum albumin to greater than 2.5g/dL. Partial response to therapy can be defined as a reduction of UPC by 50% or more, reduction in creatinine by 25% of baseline, or an increase in albumin to 2-2.5g/dl or 50% increase [6]. Additional monitoring includes monitoring for fluid overload with serial body weights and lung auscultation, worsening of hypertension or azotemia, and side effects of medications given [5].

Prognosis of glomerulonephritis depends upon the underlying cause of disease and the severity of proteinuria and azotemia [7]. Blood urea nitrogen (BUN), creatinine, and hematocrit levels are prognostic indicators, with high BUN and creatinine and low hematocrit being associated with a worse clinical outcome. If an underlying disease is identified and treated

appropriately with response to treatment, prognosis is better. In fact, animals that survive for longer than 6 months have a fair to good prognosis [8]. However, most cases of glomerulonephritis are progressive, and prognosis is poor [7]. One study with 40 dogs with glomerulonephritis reported an average median survival time of 173 days [8]. This report describes the management of a severe case of glomerulonephritis and its associated sequela. As the case progressed, the patient developed several complications and did not show consistent improvements. The owner was advised of the lack of progress and poor to guarded prognosis but chose to continue treatment despite all of the complications experienced.

History and Presentation

Sugar Bear, an 8-year-old male neutered Yorkshire Terrier, presented to MSU-CVM Emergency Service on May 2, 2018 for vomiting and diarrhea. He began vomiting and having bloody diarrhea on April 30, 2018. He presented to his regular veterinarian, where he received metronidazole and sucralfate. He continued to vomit and have diarrhea, and he was not interested in eating his food. He represented to his veterinarian on May 2, 2018, where bloodwork was performed and showed severe azotemia, hyperphosphatemia, and an elevated ALP. Sugar Bear was then referred to MSU-CVM for management of acute kidney injury. He had been urinating and drinking water normally prior to presentation but had a history of being polyuric/polydipsic for years. He also had a history of intermittent diarrhea episodes when he received table scraps, which typically cleared with metronidazole. He was maintained on Low Fat I/D, lived with one other dog in the house, and received Bravecto and Proheart for parasite prevention. Sugar Bear had no history of exposure to toxins, had limited access to outside, and was not fed food such as grapes or raisins to the owner's knowledge. There were no pesticides around the house. He was two months overdue for his leptospirosis vaccination.

On presentation Sugar Bear was quiet, alert and responsive. Initial physical exam was unremarkable except for pain elicited upon abdominal palpation. Abdominal FAST scan and thoracic FAST scan showed no significant findings. Abdominal radiographs were taken and revealed hepatomegaly, splenomegaly, and bilateral renomegaly. A urinary catheter was placed so that ins and outs could be measured. Initial bloodwork on May 2, 2018 included a snap PLI, complete blood count (CBC), serum chemistry, urinalysis, and NOVA. The snap PLI test was abnormal, indicating pancreatitis. CBC and chemistry showed that Sugar Bear had a mild leukopenia (6.3 K/ul), stress leukogram, severe azotemia (BUN 135 mg/dl, Creatinine 5.75 mg/dl), severe hyperkalemia (6.32 mmol/L), severe hyperphosphatemia (25.8 mg/dl), moderate hyperglycemia (134 mg/dl), moderate hypocalcemia (7.9 mg/dl), mild hypoalbuminemia (2.3 g/dl), and a severely elevated ALP (887 U/L). Urinalysis revealed isosthenuria with 3+ protein, 4+ SSA, 1-3 finely granular casts and rare bacteria. Due to an active sediment seen on urinalysis, a urinary tract infection needed to be ruled out as a source of proteinuria versus a form of protein losing nephropathy, so a urine protein creatinine ratio was not performed upon initial presentation. Urine culture was negative after 48 hours. Overnight, Sugar Bear did well. He had no vomiting or diarrhea, and he remained on fluids throughout the night at twice maintenance. Initial therapy included aggressive fluid diuresis with LRS, Unasyn, Cerenia, pantoprazole, methadone, and metronidazole.

Pathophysiology

The glomerulus is a capillary bed within the kidney that sits between two arterioles, an afferent arteriole and an efferent arteriole. There are three layers of the glomerulus: capillary endothelium, glomerular basement membrane, and the epithelial cells (podocytes) surrounding the outer surface of the capillary basement membrane (known as Bowman's capsule). The

purpose of the glomerulus is filtering of plasma. It is size and charge selective and does not allow macromolecules with a radius larger than 35 angstroms or with a negative charge to pass into the urine. Because albumin is negatively charged and has a radius of 36 angstroms, it is not readily filtered in a normal glomerulus [Nelson].

In glomerular disease, the glomerulus is injured via immune-mediated disease or non-immune mediated diseases such as infectious, inflammatory, or neoplastic etiologies. Once there is glomerular destruction, the corresponding nephron becomes non-functional, and the remaining nephrons compensate by increasing their glomerular filtration rate (GFR). Progressive glomerular destruction results in decreased GFR, azotemia, and eventual renal failure. There are several types of glomerular diseases including glomerulonephritis, glomerular amyloidosis, familial glomerular basement membranes disorders, and glomerular sclerosis [Nelson].

Glomerulonephritis typically results from antigen-antibody complexes lodging within the glomerulus, resulting in inflammation and cellular damage. Damage to the glomerulus will activate the renin-angiotensin-aldosterone system (RAAS), which will vasoconstrict the efferent glomerular arteriole. This leads to hypertension within the glomerulus. Increased hydrostatic pressure in the glomerular capillaries results in protein loss and subsequent damage to the renal tubular cells [Nelson].

Nephrotic syndrome is a common sequela to glomerulonephritis and consists of proteinuria, hypoalbuminemia, hypercholesterolemia, and edema or ascites. Additional sequela includes hypercoagulability and thromboembolism due to loss of antithrombin III; hypertension due to sodium retention, RAAS activation, and decreased release of renal vasodilators; and hypoalbuminemia due to loss through the urine. Hypertension, if not managed, contributes to

further proteinuria and nephron loss as well as target organ damage in the kidney, eye, brain, and heart [Nelson 4].

Diagnostics, Treatment, and Management

Throughout Sugar Bear's hospitalization, many diagnostics were performed depending upon clinical status and to monitor progression of disease and effectiveness of therapies. Supportive care and fluid diuresis were the mainstay of therapy. His fluid rate was adjusted depending upon his urine production to avoid fluid overload. This was determined by measuring ins and outs after placement of an indwelling urinary catheter. Cerenia (1 mg/kg IV q24h), pantoprazole (1 mg/kg IV q24h), metronidazole (10.8 mg/kg PO q12h), and methadone (0.2 mg/kg IV q8h) were initiated upon presentation. Following initial diagnostics, an abdominal ultrasound was performed and showed the following: hyperechoic material within the gallbladder consistent with gallbladder sludge; a hyperechoic nodule within the right liver lobe; several hyperechoic, well-defined nodules within the spleen; bilaterally enlarged kidneys with hyperechoic renal cortices and outer medulla, cortical cysts, numerous pinpoint hyperechoic foci within the renal cortices, decreased distinction of the renal corticomedullar junction bilaterally, and mild dilation of the renal pelves most likely due to fluid diuresis; hyperechoic pancreas and surrounding mesentery consistent with a mild pancreatitis; and a few hypoechoic colic lymph nodes that were normal in size. Ultrasound findings were convincing of chronic renal disease; therefore, his recent azotemia was suspected to be due to an acute-on-chronic renal insult. Aluminum hydroxide (15 mg/kg PO q12h), mirtazapine (1.25 mg/kg PO q24h), ursodiol (7.5 mg/kg PO q12h), and Unasyn (30 mg/kg IV q8h) were added to bind phosphate, stimulate his appetite, prevent a gallbladder mucocele, and treat a potential urinary tract infection respectively. Due to his renal disease, Sugar Bear's diet was changed to Hill's k/d. However, due to lack of

interest in the prescription diet, he was given some chicken, which he did consume most days while in hospital. His appetite seemed to be responsive to mirtazapine administration until the last few days of hospitalization.

Serial CBCs and serum chemistries/renal profiles were performed to monitor the progression of Sugar Bear's severe azotemia, electrolyte abnormalities, total protein, and albumin levels. His azotemia initially responded to fluid therapy until he developed peritoneal effusion on May 5, 2018, with the following lowest values: BUN 91 mg/dl, creatinine 2.19 mg/dl and hyperphosphatemia 8.9 mg/dl. After a few days in hospital, fluids were unable to be pushed aggressively due to development of pleural effusion and ascites, presumably due to uremic vasculitis, pancreatitis, and/or leptospirosis. Furthermore, hypoalbuminemia never improved and actually worsened throughout hospitalization with 1.6 g/dL being the lowest value. After his urine culture results came back negative, a urine protein:creatinine ratio was elevated, indicating a likely glomerular component to his renal disease. Blood pressures were also monitored closely because he was hypertensive. A blood pressure on May 4, 2018 showed a systolic pressure of 170 mmHg. His pressures fluctuated but remained high throughout hospitalization. A baseline cortisol was elevated, which ruled out Addison's disease. Urine culture was negative after 48 hours.

Due to development of peritoneal effusion on May 5, 2018, serial abdominal FAST scans were performed once or twice daily, and the fluid rate was decreased as needed based on body weight and amount of effusion, which seemed to worsen with aggressive diuresis. Sugar Bear developed abdominal distension and an increased amount of abdominal pain upon palpation; therefore, methadone was discontinued, and a fentanyl CRI was begun at 3mcg/kg/hr for better pain control secondary to pancreatitis and/or discomfort from abdominal distension from ascites.

CBC and chemistry were run on May 5, 2017, with the most significant findings being a decrease in PCV from 39% to 26%, a persistent and worsened hypoalbuminemia (1.8 g/dl), and an improved but persistent azotemia (BUN 99 mg/dl, Creatinine 3.9 mg/dl). Corresponding urine dipstick showed 3+ protein in the urine with a urine specific gravity of 1.013. Due to the development of a mild anemia, a coagulation profile was run. PT and PTT were within normal limits, and a manual platelet count revealed an adequate number of platelets. Enalapril (0.35 mg/kg PO q12h) and aspirin (1mg/kg PO q24h) were initiated due to proteinuria, hypertension, and risk of thromboembolism. Baytril (10mg/kg IV q24h) administration was begun to treat potential pyelonephritis, and Unasyn was continued for possible leptospirosis. Additional therapies overnight included weight monitoring every 4 hours, lung auscultation every 4 hours, and abdominal FAST scans every 6 hours to monitor for fluid overload. Despite clear lung sounds with no crackles heard, Sugar Bear developed a mild to moderate pleural effusion overnight which was evident on thoracic FAST scan. This was suspected to be due to fluid overload. Therefore, Lasix (1mg/kg IV) was given as needed throughout the day, and his fluid rate was decreased. Due to development of tachypnea despite Lasix, thoracocentesis was performed bilaterally, which revealed a serous fluid characteristic of a pure/modified transudate suspected to be secondary to hypoalbuminemia and/or fluid overload. Fluid analysis was not performed at this time.

On May 6, 2018, Sugar Bear appeared brighter than the day before. Abdominal effusion was reduced, but pleural effusion persisted. However, there was not enough fluid to indicate additional thoracocentesis that morning. Sugar Bear's abdomen was still mildly distended; however, he was not as tense upon abdominal palpation. Sugar Bear was not interested in chicken that morning, but he did eat some canned Metabolic Mobility. His urine had a red tinge

to it. Due to a low ionized calcium (0.8mmol/L) seen on iSTAT, treatment with calcium gluconate (1mg/kg IV PRN) was indicated. The calcium gluconate was diluted 1:2 with saline and administered over 30 minutes while Sugar Bear was monitored with an ECG for bradyarrhythmias. Due to development of an increased amount of fluid within the thoracic cavity seen on thoracic FAST scan as the day progressed, Vetstarch was added at 7 ml/hr, and the rate of Plasmalyte was decreased. This was initiated due to limited ability for aggressive diuresis with crystalloids and hope that colloidal support would allow for better renal perfusion. A fentanyl bolus of 3 mcg/kg was given, and thoracocentesis was performed bilaterally, which yielded a more hemorrhagic fluid than previously, suspected to be due to iatrogenic vessel injury. Sugar Bear developed tachypnea and mild tachycardia in the evening, so thoracocentesis was performed again bilaterally yielding a serosanguinous fluid. Lidocaine was given intradermally to numb the site of thoracocentesis, and a fentanyl bolus of 3mcg/kg was given prior to tapping. Sugar Bear's respiratory rate returned to a more normal rate after thoracocentesis. The site of lidocaine injection developed urticaria bilaterally with the right side being more severe and was treated with diphenhydramine (2 mg/kg). Overnight, Sugar Bear developed a grade 5/6 systolic right and left sided heart murmur. He had bilaterally serous nasal discharge, and his weight had increased 0.1 kg. There were no crackles heard on lung auscultation, but lung sounds were decreased due to pleural effusion which was moderate at this time. Furosemide (2 mg/kg IV) was given, and Vetstarch and Plasmalyte were discontinued. It was suspected that the Vetstarch worsened the cavitary effusions. Diagnostic results that were also received that day included a GI panel, which revealed a hypocobalaminemia likely due to dysbiosis from small intestine bacterial overgrowth (which was supplemented), and a severely elevated PLI at over 2,000. This indicated a more severe pancreatitis than initially suspected.

The next day, on May 7, 2018, Sugar Bear was mildly depressed and not interested in food. He developed a minimal amount of diarrhea characterized by loose, yellow-brown fecal material. Thoracic and abdominal FAST scans revealed persistent abdominal and thoracic effusion. Sugar Bear became oxygen dependent and was tachypneic and dyspneic with cyanotic mucous membranes outside of oxygen due to pleural effusion and suspect atelectasis of the left cranial lung lobe based on thoracic radiographs. Therefore, at this point, Baytril was continued for possible pneumonia. He developed ventral edema on his abdomen which worsened throughout the day. Plasmalyte was begun again at 12.8 ml/hr based on non-improving azotemia and pancreatitis, but this rate was adjusted to match urine output and try to avoid fluid overload. In fact, a rate lower than what had previously led to fluid overload was chosen. Therapeutic thoracocentesis was performed for the remainder of Sugar Bear's hospitalization as needed depending upon the amount of fluid accumulation seen on thoracic FAST scan and respiratory rate and effort. The amount of pleural effusion fluctuated daily with some days being small enough not to warrant thoracocentesis. A urine protein/creatinine (UPC) ratio was 14 on May 7, 2018 but increased to 28 by May 14, 2018. This finding indicated severe glomerular damage, which was causing progression of his renal disease and azotemia, and likely, the fluid intolerance.

Sugar Bear's lungs were auscultated frequently to assess the impact of the persistent pleural effusion on his lung function. On May 8, 2018, Sugar Bear developed decreased bronchovesicular sounds on the left side of the chest, but no crackles or wheezes were heard. His heart murmur was persistent but decreased from a grade 5/6 murmur to a grade 2/6 murmur bilaterally throughout hospitalization. An echocardiogram was performed, but no abnormalities

were found. The pleural fluid obtained from thoracocentesis was submitted for fluid analysis, which revealed an acute hemorrhagic effusion.

On May 9, 2018, Sugar Bear seemed interested in food but did not eat much on his own. He was syringe fed 10mL of an i/d slurry in the evening. Entyce administration was begun to help stimulate his appetite. He exhibited mild diarrhea in the morning, and he did not exhibit any normal bowel movements while hospitalized. Sugar Bear was oxygen tested and removed from the oxygen box. Thirty minutes out of oxygen, he had an SpO2 of 100%. However, later in the day, SpO2 was measured at 90%, so Sugar Bear was placed back into oxygen. There was a hole in the urinary catheter line, so it was removed. To administer the proper rate of fluids, his urine output for the last 5 days was analyzed. His fluid rate was adjusted accordingly to match his average urine output.

On May 10, 2018, Sugar Bear became acutely lethargic and continued to be inappetant, so he was syringe fed 20mL of an i/d slurry twice. Sugar Bear did not have an increased respiratory effort, and his abdomen did not feel tense upon palpation. Sugar Bear also had a large bowel movement with a fecal score 5-6/7. It was semi-formed and orange in color. At 2PM Sugar Bear's SpO2 was 85 off of oxygen and 91 on oxygen. Because of this, thoracocentesis was performed, and 100mL of hemorrhagic fluid was pulled from the left side of the chest. This fluid had a PCV of 14. Recheck thoracic radiographs were taken which showed persistent pleural and peritoneal effusion; however, there was improved aeration of multiple lung lobes. Blood was pulled for a renal panel, PCV, coagulation profile, and blood gas analysis. His PCV had worsened from 26% to 17%. Therefore, a hemothorax was likely. This was suspected to be due to aspirin administration, which inhibited proper clotting of a vessel hit during a prior thoracocentesis. PT and PTT times were once again within normal limits. A whole blood

transfusion was performed without any complications, and aspirin was discontinued. Sugar Bear was blood typed before the transfusion, and he was DEA 1 positive. After a blood transfusion, Sugar Bear's PCV increased to 24% and was monitored for the next few days. Sugar Bear's PCV plateaued at 28% over the next few days; however, a BMBT performed on May 11, 2018 was prolonged with no clot formed at 15 minutes. Due to the development of metabolic alkalosis and hypokalemia seen on blood gas analysis, Sugar Bear was started on saline and 20 mEq of KCl for fluid therapy.

On May 12, 2018 118mL of serosanguineous fluid was pulled off the left side of the chest. This fluid was less hemorrhagic than previous thoracocentesis. A PCV and iSTAT were run in the morning and in the evening to monitor his anemia and metabolic alkalosis. Due to improving pH on the iSTAT and persistent hypokalemia, Sugar Bear was switched from saline to Plasmalyte with 20 mEq of KCl that evening.

On May 13, 2018, Sugar Bear had a great appetite. While outside, his respiratory effort increased, and he had increased bronchovesicular sounds from the night before. Hetastarch was started at 5 ml/hr and Plasmalyte was decreased from 28 ml/hr to 17 ml/hr. Thoracocentesis was performed on the right side of the chest, and 20 mL of serosanguinous fluid was pulled off. This fluid had a PCV of 5% and a TP of 1.2 g/dl confirming a decrease in hemorrhagic effusion. That afternoon, Sugar Bear had an increased respiratory effort and rate with an expiratory component and wheezes. The Hetastarch was discontinued at this time, and Lasix (1 mg/kg IV) was administered. Sugar Bear then developed mild effusion within the abdomen seen on abdominal FAST scan. He developed harsh lung sounds throughout the day and had wheezes heard over the left cranial lung lobe. That evening, diltiazem (0.3 mg/kg IV) was given over 15 minutes, and he was started on a 1mcg/kg/min CRI to promote diuresis and address systemic hypertension;

however, due to hypocalcemia, diltiazem was later discontinued. Pentoxifylline (15 mg/kg PO q8h) was also begun to treat vasculitis and the effusions.

On May 14, 2018, his lung sounds improved, and there was a decrease in the wheezes heard on auscultation. There was a mild amount of fluid within the abdomen seen on abdominal FAST which was persistent for the next few days. Throughout the day, there was a progressive amount of fluid within the chest, and 75 mL of serosanguinous fluid was pulled from the right side of the chest. His enalapril dosage was increased from 0.5 mg/kg PO q12h day to 1 mg/kg PO q12h due to worsening proteinuria. He had a large pile of red-orange diarrhea with a fecal score of 6/7. He had persistent expiratory wheezes throughout the night, but these decreased throughout the night.

On May 15, 2018, Sugar Bear became inappetant again. He persistently had increased respiratory rate and effort while not in the oxygen cage. A single dose of Lasix was given due to an increased expiratory effort and increased lung sounds. The fluid rate of Plasmalyte was decreased to 18 mL/hr (~3 ml/kg/hr). Expiratory wheezes were persistent on auscultation. Due to frequent replacement of peripheral catheters, a jugular catheter was placed.

On May 16, 2018, Sugar Bear had a persistent increased respiratory rate and effort while outside. He has stertorous breathing likely due to his jugular neck wrap, and wheezes were heard over the left cranial lung lobe. His abdomen was mildly tense upon palpation. His fentanyl CRI was decreased from 3 mcg/kg/hr to 2 mcg/kg/hr in an attempt to wean him off pain control. Due to persistent wheezes heard in the left cranial lung lobe, an ultrasound guided fine needle aspirate (FNA) was performed. These samples were submitted for cytology and revealed neutrophilic inflammation with no etiologic agents present. Prior to FNA, thoracocentesis was performed bilaterally to remove the majority of the fluid within the chest, leaving only a scant amount.

On May 17, 2018, due to decreased abdominal pain, he was weaned off his fentanyl CRI. Throughout the day, there was a mild increase in fluid accumulation within the chest with the left being more severe than the right. Overnight, Sugar Bear had two seizure like episodes characterized by muscle fasciculations, vocalization, urination, and defecation. During these episodes he was still aware of his surroundings and able to ambulate. He was given a rescue dose of midazolam (0.5 mg/kg IV). A venous blood gas was run and due to hypocalcemia (0.72mmol/L), calcium gluconate was administered IV slowly over 30 minutes. The morning of May 18, 2017, it was attempted to transition him to a calcium gluconate CRI at 0.3 ml/kg/hr; but he became bradycardic and severely hypertensive (280mmHg), so this was discontinued. He developed chemosis bilaterally and was lethargic. Blood was collected for a CBC and chemistry which showed neutrophilia, progressive azotemia (BUN 91 mg/dl, creatinine 3.5 mg/dl), and worsening hyperphosphatemia (12.4 mg/dl). Sugar Bear then went into respiratory distress, stopped breathing, and became rigid. He still had pulses and a heartbeat; however, his blood pressure was over 300mmHg. He was intubated and maintained on oxygen. Humane euthanasia was elected at this time due to grave prognosis.

Case Outcome

Necropsy results confirmed a diagnosis of severe, chronic glomerulonephritis which contributed significantly to clinical signs of refractory azotemia, fluid overload, and hypertension. Vascular endothelial damage likely occurred due to uremic toxins from severe renal disease. This uremic vasculitis is suspected to have contributed to the development of pleural and peritoneal effusions. The inciting cause of kidney disease could not be determined; however, a leptospirosis PCR was negative. At the time of presentation, he was not a candidate for renal biopsy to determine the cause of his proteinuria due to renal failure and persistent

hypertension, which was presumed to be due to glomerulonephritis. It is unknown how long Sugar Bear had been proteinuric, as a UPC had never been recorded. His renal disease may have been incited by or exacerbated by the proteinuria. Sugar Bear was hypercoagulable likely to due to loss of antithrombin III which resulted in thrombi present in many organs, such as the lung and liver, and subsequent multi-organ dysfunction. Hypoalbuminemia can be attributed to loss from the kidney and intestine which had chronic inflammation and crypt abscesses, suggestive of protein loss.

There was compromised cardiopulmonary function which was evidenced by changes seen in the lung and the heart. The left cranial lung lobe was atelectatic and sank in formalin, and there was fibrinous material adhered to the left side of the heart. Histologically, there was moderate diffuse alveolar damage with alveolar siderophages within the lung, and there was multifocal myocardial fibrosis within the heart. These changes are usually seen when there is impaired circulation, and this was seen clinically as Sugar Bear never became non-oxygen dependent. There were partially organized thrombi within the liver which suggests chronicity.

Retrospectively, this case is typical of glomerulonephritis and exhibited all the signs of nephrotic syndrome except hypercholesterolemia—proteinuria, hypoalbuminemia, and ascites. Additionally, Sugar Bear exhibited hypertension and hypercoagulability which are common sequela to glomerulonephritis. The persistent pleural and abdominal effusion was likely due to the glomerular disease, which is associated with fluid intolerance for a variety of reasons, as well as uremic vasculitis.

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