Adora the Renal Explorer

Caitlin C. Light

Mississippi State University

College of Veterinary Medicine

Class of 2021

Clinicopathological Conference

December 11, 2020

Advisor:

Alyssa Sullivant, DVM, MS, ACVIM

Introduction:

Idiopathic primary renal hematuria (IRH), also known as benign essential renal hematuria, is a diagnosis of exclusion. It is a rare condition characterized by chronic, mild to severe upper urinary tract bleeding. Previously, a nephrectomy with or without a cystotomy was the treatment of choice. However, due to the disease having the potential to be bilateral, it is no longer recommended. Sclerotherapy with povidone iodine, silver nitrate, or a combination of the two is now the recommended treatment. The pathophysiology of IRH is not fully understood, but a few theories derived from human medicine are being examined as potential causes.

History and Presentation:

Adora is an approximately 4-year old, female spayed Chihuahua. She presented to Mississippi State University College of Veterinary Medicine's Emergency Service on May 4, 2020 for complaints of anemia, stranguria, and hematuria. Adora initially presented to her referring veterinarian on April 14, 2020 for an episode of vomiting blood and straining to urinate. At that time, a complete blood count was performed and revealed a thrombocytopenia. A tick panel was submitted. She was begun on amoxicillin, prednisone, and Pepcid AC. Approximately 6 days later, the tick panel results returned and revealed a negative diagnosis for all diseases tested. At this time, the amoxicillin antibiotic was discontinued. On April 22nd, a second complete blood count was performed, as well as a serum biochemistry. At that time, Adora's platelet count was normal so the prednisone dose was decreased. However, the complete blood count revealed a leukocytosis and amoxicillin was started again. On April 30th, Adora presented to a second referring veterinarian who performed an abdominal ultrasound revealing a mass within the urinary bladder which was believed to be a blood clot at that time. A urinalysis

was not performed at that time. Adora's owner reported a slight improvement in the hematuria when the prednisone was begun but it worsened again upon tapering the dose.

On presentation, Adora was bright, alert, and responsive. She weighed 6.6 kilograms with a body condition score of 7 out of 9. She had a heart rate of 160 beats per minute, respiratory rate of 44 breaths per minute, and temperature of 103 degrees Fahrenheit. Her mucous membranes were pale pink and tacky with a capillary refill time of approximately 1.5 seconds. Her eyes and ears were clear, and no ocular or nasal discharge was noted. She had mild to moderate dental tartar with no oral masses or lesions. Cardiopulmonary auscultation revealed no abnormalities. She had strong and synchronous femoral pulses. She was tense on abdominal palpation but did not seem painful. Rectal examination revealed smooth mucosa with no masses or lymphadenopathy palpated. Her stool was of normal appearance. The remainder of her physical examination was within normal limits.

Diagnostic Approach:

On presentation, a complete blood count, serum biochemistry, and abdominal radiographs were performed. The complete blood count revealed a severe leukocytosis with a white blood cell count of 50.99 (5.0-14.2), severe neutrophilia of 46911.0 (3100-11800), and a moderate to severe elevation of banded neutrophil count of 1020 (0-400). It also revealed anemia characterized with a low red blood count of 3.04 10^6/ul (5.6-7.9), low hematocrit of 21.9 (35.2-55.7), and low packed cell volume of 24% (34-60). Her platelet estimate appeared adequate. The serum biochemistry revealed a mildly elevated glucose of 134 (75-125), mildly elevated blood urea nitrogen of 26 (8-24), moderately to severely elevated alanine transaminase of 493 (10-90), moderately to severely elevated alkaline phosphatase of 432 (11-140), and mildly elevated phosphorus of 6.2 (2.5-5.0).

Abdominal radiographs showed mildly rounded liver margins which was attributed to being a normal variant with less consideration given to neoplasia, abscess/granuloma, or nodular regeneration. A large amount of tissue opaque and mineral opaque material was seen within the stomach which is likely normal ingesta with chronic partial outflow obstruction or foreign material. The remainder of the study was within normal limits.

Adora was started on Plasmalyte intravenous fluids and she was continued on prednisone, but the dose was decreased to once daily. She was transferred to the Internal Medicine Department on May 5, 2020. An urinalysis, urine culture, packed cell volume and total protein, blood typing, cross-matching, buccal mucosal bleeding time, coagulation profile, and abdominal ultrasound were performed.

Urine was collected and found to have a red and cloudy appearance. Urinalysis revealed isosthenuria with a specific gravity of 1.012. The pH was 6.0 and she had a mild proteinuria of 2+ protein. Urobilinogen measured 0.2 and large amounts of bilirubin were present. This was most likely due to anemia, potential hemolysis and subsequent hemoglobinuria, and/or mild liver damage. The white blood cell count was 1-5 per high powered field. The red blood cell count was too numerous to count. Urine culture was submitted, and no growth was present at both 24 and 48 hours.

Packed cell volume and total protein, whole blood typing, and cross-matching were performed. Adora had a packed cell volume of 17% and total protein of 5 g/dL. Adora was determined to be DEA 1.1 negative blood type and cross-matched compatible with blood donor Noreen. Buccal mucosal bleeding time was within normal limits at 2 minutes and 7 seconds. A coagulation profile was found to be within normal limits. A 150-milliliter whole blood

transfusion was performed due to Adora's anemia and continuing hematuria which occasionally consisted of frank blood.

An abdominal ultrasound was performed to further investigate Adora's clinical signs of hematuria and stranguria. There was a small amount of hyperechoic debris within the gallbladder which was attributed to possible cholestasis or gallbladder sludge. Bilateral chronic renal infarcts were present characterized by a 0.91 cm wide concave defect in the left kidney wall and a 1.0 cm wide concave defect in the right kidney wall. The left kidney and ureter were otherwise within normal limits. A large, heterogenous, ovoid mass was present within the lumen of the bladder and had an onion-like appearance when viewed in cross section. There was no blood flow detected on Doppler. The right renal pelvis was moderately to severely dilated with the renal pelvis thickness measuring 1.43 cm. A smoothly marginated, irregularly shaped, heterogenous structure measuring 1.54 by 1.88 cm was located within the right renal pelvis. There was no blood flow detected on Doppler. The right ureter was moderately dilated with hypoechoic fluid and measured 0.55 cm proximally, 0.42 cm mid-ureter, and 0.24 cm distally. The ureter could be traced from the right kidney to its entrance in the bladder at the level of the trigone. The structures within the right kidney and urinary bladder were diagnosed as likely hematomas with primary or secondary hematuria with right hydronephrosis and right ureteral dilation (hydroureter).

Due to Adora's clinical signs and other causes being ruled out, a presumptive diagnosis of idiopathic primary renal hematuria was made.

Pathophysiology:

Idiopathic primary renal hematuria (IRH) is a very uncommon disorder in dogs and cats. It is typically seen in otherwise healthy, young large-breed dogs.[1] While it has been described in dogs ages 2 months to 11 years, it is mostly seen in dogs less than 2 years of age.[4] The disease is described as chronic intermittent to persistent hematuria. Other lower urinary tract signs can also be present such as stranguria and pollakiuria.[7] However, occasional cases will cause vomiting, lethargy, and abdominal pain.[7] If IRH becomes severe enough in a patient, it can result in anemia, iron deficiency, and ureteral or urethral obstruction from blood clots.

On physical examination, the most common clinical finding is hematuria. Differential diagnosis lists usually include pyelonephritis, neoplasia, trauma, coagulopathies, urinary calculi, and hypertension.[1,3,7] Because IRH is a diagnosis of exclusion, all other differentials should be ruled out via history, physical examination, and diagnostic testing. Due to the amount of blood lost, a complete blood count, serum biochemistry, and coagulation profile should be performed. Other diagnostics should typically include a urinalysis, urine culture and sensitivity, blood pressure, abdominal radiographs, and abdominal ultrasound.[4]

On complete blood count and serum biochemistry, anemia is the most common abnormality found. In some cases, thrombocytopenia, leukopenia, and azotemia are also noted.[7] The coagulation panel is performed to rule out any underlying coagulopathy, and if found to be within normal limits can rule out coagulopathy from the differential list. Urinalysis shows moderate to severe hematuria with occasional proteinuria.[7] This is also used to assist in ruling out urinary calculi as an underlying cause of hematuria. Urine culture is used to rule out infection. Radiography is helpful in ruling out urinary calculi and neoplasia. Abdominal ultrasound also assists in ruling out neoplasia and urinary calculi. In IRH, some typical

ultrasonographic changes include hydronephrosis, hydroureter, obstruction, and hyperechoic material consistent with blood clots.[3,4,7]

Cystoscopy is another diagnostic tool used but is also employed in the recommended treatment modality at this time. Spontaneous hemorrhage from one or both ureters entering the bladder occurring multiple times during observation is considered a positive diagnosis of renal hematuria.[7]

Once all other causes of hematuria are excluded and bleeding from one or both kidneys is confirmed, a diagnosis of IRH can be made. The disease can be unilateral or bilateral. While IRH is not a completely understood disease in both human and veterinary medicine, some theories have been reported in human medicine.[1,4] In people, IRH is thought to be a result of renal vascular abnormalities such as hemangiomas and papillary angiomas which lead to spontaneous hemorrhage. In humans, these lesions have been diagnosed via cystoscopy.[4] While no such lesions have been found in canine patients, a similar mechanism is thought to occur.[4]

Treatment and Management Options:

Because IRH can be a unilateral or bilateral disease, sclerotherapy using povidone iodine, silver nitrate, or both is the current treatment of choice. Other treatment options include but are not limited to ureteroscopy with electrocautery, selective renal arterial embolization, nephrectomy with or without cystotomy in unilateral disease, and medical management with Yunnan Baiyau, ACE inhibitors such as benazepril, and aminocaproic acid.[3]

Cystoscopy is performed under general anesthesia. A 2.7 mm, 30-degree angle, 18-cm long rigid cystoscope is used. The scope is advanced into the urinary bladder and is used to evaluate the bladder and ureterovesicular junctions (UVJ).[1,4] Both the left and right UVJ are

monitored for a minimum of 30 seconds to see 2 or more urine jets exiting.[1,4] Once one or both sides have been assessed for hematuria, the affected side(s) can be treated using sclerotherapy. Instead of using 0.9% saline as irrigation fluids, 5% dextrose fluids are employed.[1,4] This prevents red blood cell hemolysis and improves vision during the procedure.[1,4] On the affected side, a 0.035-inch angled tipped guidewire is inserted via the UVJ and advanced through the ureter. A 5F open-ended urethral catheter is advanced over the guidewire and a retrograde utereopyelogram is performed using 76% meglumine diatrizoate.[1,4] The guidewire is removed and replaced with a J-tipped stiffened wire and the cystoscope is removed. A ureteropelvic junction (UPJ) balloon catheter is advanced over the wire and the wire is then removed.[1,4] Air is used to occlude the proximal ureteral opening. Filling volume of the renal pelvis is determined with 76% meglumine diatrizoate and 5% dextrose solution in a 1:1 dilution.[1,4] It is allowed to passively drain. Within the renal pelvis, 2 rounds (10-20 minutes each) of a 1:1:3 dilution of 5% povidone iodine, 76% meglumine diatrizoate, and 5% dextrose solution are inserted then passively drained.[1,4] It is optional to follow with 2 rounds (15-20 minutes each) of a sterilized 0.5-1% silver nitrate solution.[4] The solution is again allowed to passively drain. The guidewire is reinserted, the balloon catheter is removed, and the cystoscope is reintroduced. A double pigtail ureteral stent is placed with 1 loop curled inside the renal pelvis and the other looped curled inside the urinary bladder.[1,4] Most dogs can be sent home post-procedure in as little as 6 to 24 hours with 1 to 3 days of a non-steroidal anti-inflammatory medication and antibiotics.[1,4] A complete blood count, serum biochemistry, urinalysis, urine culture, and abdominal ultrasound are recommended at 2 weeks and 2 months post-procedure and then every 3 to 6 months for up to 1 year.[4] It is also recommended to remove the pigtail stent approximately 4 to 6 weeks post-sclerotherapy if clinical signs of hematuria have resolved.[1,4] In a study of 6 dogs, 5 of the

patients had resolved all gross hematuria within a week of the procedure. All 6 dogs' packed cell volume improved; at the last follow up visit, one dog had gross hematuria and only 1 of the remaining 5 dogs had microscopic hematuria.[4]

Ureteroscopy with electrocautery is the next therapeutic option. However, it is only recommended in patients >20 kilograms and those in which sclerotherapy with ureteral stenting did not resolve clinical signs.[3] A cystoscope is used to evaluate the renal pelvis and each calix very carefully.[3] Once bleeding lesions are identified, a Bugbee cautery electrode probe is inserted, and the lesion is cauterized.[3] This process is continued for all bleeding lesions that are identified.

Selective renal arterial embolization is the final renal-sparing procedure that can be performed. It is achieved via angiography and cystoscopy where the branch of the renal artery contributing to the bleeding is occluded.[3] Typically, femoral or carotid arterial access is used. Each of the 6 main branches of the renal artery (3 dorsal, 3 ventral) is occluded individually and is monitored for bleeding to cease.[3] Once bleeding stops for approximately 30-60 seconds, a microcoil is placed into the correct branch.[3] This is continued until all branches contributing to bleeding has been occluded with a microcoil. Due to the difficulty of this procedure and its potential complications, it is rarely performed.

Nephrectomy with or without cystotomy is the next option. A cystotomy is performed to remove any clots present within the urinary bladder as well as to take samples of the bladder mucosa. The affected kidney and ureter are then removed. The abdomen is flushed with warm saline and is closed. This surgical technique was once the treatment of choice. However, some cases are bilateral at the time of presentation and >20% of cases become bilateral over time.[1,4,7] Due to the chances of bilateral disease, nephrectomy is no longer recommended. It is still

performed in certain cases when other treatment modalities are not available, unaffordable, or are unsuccessful.

Medical management is the final option and is sometimes performed first based on owner and clinician preference. This varies by clinician but Yunnan Baiyau, ACE inhibitors such as benazepril, and aminocaproic acid are used. Yunnan Baiyau is a Chinese herb, and its mechanisms are not completely understood. However, it has been shown to improve coagulation abilities and platelet function. It has improved bleeding in 10-15% of cases in which it was employed.[3] Benazepril has shown a great improvement in gross hematuria in patients in which it was prescribed.[2] In one study, it also improved microscopic hematuria in 2 of 4 dogs studied.[2] Benazepril causes reduction in intraglomerular blood pressure and glomerular filtration pressure while also decreasing the porous properties of the glomerular membrane.[2] It is thought that these properties led to a good clinical outcome especially with the reduction of intraglomerular blood pressure.[2] Aminocaproic acid has been used in human medicine in the treatment of IRH, and it has recently been started in veterinary medicine cases of IRH.[4] It is a derivative of lysine which inhibits proteolytic enzymes such as plasmin.[4] This works to increase clot strength and decrease fibrinolysis. It has been efficacious in other cases of bleeding disorders.[4] These medical modalities can also be used in conjunction with one of the previously listed treatments.

Case Outcome:

Treatment options were discussed with Adora's owner. Due to financial constraints and the COVID-19 pandemic, Adora underwent a right nephrectomy and cystotomy on May 6, 2020. A large blood clot was removed from the urinary bladder and bladder wall mucosa was submitted for histopathology and culture and sensitivity. The right kidney and ureter were removed. Adora recovered well from surgery. She was continued on the previously prescribed

omeprazole, prednisone, and Plasmalyte fluids. She was started on benazepril and hydromorphone.

Adora was swapped to subcutaneous buprenorphine and maintained on benazepril, omeprazole, and prednisone. Renal panels were submitted daily post-operatively to monitor renal values and her packed cell volume and total protein levels were monitored daily as well.

	May 6, 2020	May 7, 2020	May 8, 2020	May 9, 2020	May 10, 2020
PCV/TP		34%/ 6	30%/ - 31%/ 6.8	37%/ 8.4	34%/ 8
Sodium	148.8	146.3		145.6	
Potassium	4.61	4.33		5.54	
Chloride	112.5	113.5		111.1	
CO2	23.5	21.9		17.5 (low)	
Anion Gap	17	15		23 (high)	
BUN	10	8		13	
Creatinine	0.94	0.72		0.62	
Calcium	9.1	9.0		9.6	
Phosphorus	5.5 (high)	5.3 (high)		5.3 (high)	
Albumin	2.6	2.6		3.0	

Adora was discharged on May 10, 2020 with instructions to continue Tylenol 3, prednisolone, and benazepril. She was started on Yunnan Baiyao upon discharge. A recheck appointment was scheduled for 7 days later.

On May 19, 2020, Adora returned for her recheck examination. Her owner reported a complete improvement in gross hematuria. Her complete blood count revealed a stress leukogram and renal profile revealed a mild to moderate elevation in blood urea nitrogen of 39 (8-24). A SDMA was performed and found to be within normal limits. Reticulocyte count was mildly elevated at 1.4% (0-1.0). Urinalysis revealed moderate amounts of microscopic blood, trace protein, small amounts of bilirubin, and a specific gravity of 1.041. No gross hematuria was

noted. Her blood pressure was within normal limits. She was discharged with instructions to continue benazepril and return in 1-2 weeks for a second recheck.

On July 11, 2020, Adora presented on emergency to MSU-CVM for hematuria with blood clots present. A complete blood count, serum biochemistry, urinalysis, and urine culture were suggested but declined by the owner. She was discharged with instructions to begin Yunnan Baiyao. Adora was lost to follow-up after this visit.

Conclusion:

Idiopathic primary renal hematuria is a rare, chronic disease characterized by intermittent to persistent hematuria. All other potential differential diagnoses should be ruled out before IRH can be presumptively diagnosed as it is a diagnosis of exclusion. It is mainly seen in young, large breed dogs but can affect all breeds and cats. While IRH is not completely understood, some theories have been derived from human medicine. Because of the disease having the potential to be bilateral, sclerotherapy is currently the recommended treatment.

References

1. Adelman L, Bartges J, Whittemore J. Povidone iodine sclerotherapy for treatment of idiopathic renal hematuria in two dogs. Journal of American Veterinary Medical Assocation 2017 Jan; 250 (2); 205-210.
2. Bazelle J, Foale R. The Successful Treatment of Idiopathic Renal Haemorrhage with Benazepril in Four Dogs. British Small Animal Veterinary Congress 2011. Access through VIN.
3. Berent, Allyson. Interventional Treatment of Idiopathic Renal Hematuria. *Veterinary Image-Guided Interventions*, First Edition. John Wiley & Sons, Inc. 2015.
4. Berent A, Weisse C, Branter E, et al. Endoscopic-guided sclerotherapy for renal-sparing treatment of idiopathic renal hematuria in dogs: 6 cases (2010-2012). Journal of American Veterinary Medical Association 2013 June; 242 (11); 1556-1563.
5. Biezus G, Withoeft J, Grima de Cristo T, et al. Unilateral idiopathic renal hematuria in a dog. Acta Veterinaria Brasilica 2019 Sept; 105-109.
6. Di Cicco M, Fetzer T, Secoura P, et al. Management of bilateral idiopathic renal hematuria in a dog with silver nitrate. The Canadian Veterinary Journal 2013 Aug; 54 (8); 761-764.
7. Shell, Linda. Idiopathic Renal Hematuria. VINCyclopedia of Diseases 2016 Feb. VIN.