The Blue Merle Bonnie Blues

Brandie R. Amos

4/17/2020

Advisor: Dr. Taya Marquardt

Introduction:

The kidney is one of the filtration systems for the body; it filters waste, provides water for urine, and keeps your body's salts and minerals balanced. Many filtering units make up a kidney. Each unit is called a nephron, and each nephron contains a glomerulus, loop of Henle, proximal tubule, and distal tubule. The glomerulus filters out the bigger particles such as proteins and cells, while allowing water and other small molecules to pass through. The set of tubules then absorb the minerals and water your body needs at any given time while sending the waste away to make urine.

The kidneys at times can be a very delicate yet important organ; luckily renal cancers, primary or metastatic, in small animals are an uncommon occurrence (Knapp, 2007). These tumors can arise from renal epithelium, renal mesenchyme, or from embryonal tissue of mixed origin (Bryan, 2006). The main types of neoplasia that can arise from the kidney are: renal cell carcinoma, transitional cell carcinoma, anaplastic carcinoma, lymphoma, hemangiosarcoma, a variety of sarcomas, and nephroblastoma (Locke, 2006). In dogs, the most commonly diagnosed renal neoplasia is renal cell carcinoma, accounting for less than 2% of cancer in all dogs (LeFebre, 2013); in cats the most commonly diagnosed is lymphoma. Benign forms, such as fibromas or papillomas, can be seen but they are more uncommon than the neoplastic conditions. Primary, metastatic, or benign neoplasms can be unilateral or bilateral. The common presentation is middle aged to older animals, although renal lymphoma and nephroblastomas can be seen in younger patients. The mean age for carcinomas and sarcomas is 7-8 years and there is no strong sex predilection (Bryan, 2006), although some studies show androgens may play a role (LeFebre, 2013).

History and Presentation:

Bonnie is a 4 year old female spayed Shetland Sheepdog who presented to Mississippi State College of Veterinary Medicine (MSU CVM) Oncology service on 5/7/2019 for referral from Animal Emergency and Referral Center (AERC). Bonnie presented to AERC on 5/7/2019 for a four week history of decreased appetite, two week history of weight loss (reported 8lbs), and a one day history of vomiting. AERC performed abdominal radiographs and an abdominal ultrasound which revealed a large mass in the area of the right kidney. There was no evidence of metastasis at that time.

When Bonnie presented to MSU CVM she seemed quiet, alert, and responsive. She weighed 10.5kg (23 lbs) and had a body condition score of 5/9. She had a temperature of 101.9 F, a pulse of 140 beats per minute, and was panting. No murmurs or arrhythmias were auscultated on cardiac examination. No crackles, wheezes or rales were heard on pulmonary auscultation. Abdominal palpation revealed a large firm mass in the area of the right kidney. A small animal anesthesia profile was performed preoperatively, all values were normal. On ultrasound there was a mild amount of sludge in the gravity dependent portion of the gallbladder, the left renal pelvis was mildly dilated measuring 3.3mm, and the right kidney was enlarged measuring 6.84cm x 8.57cm x 6.53cm and had effacement of the corticomedullary distinction. Normal renal parenchyma was not identifiable and there were multifocal ill-defined regions within the parenchyma. The right pelvis was markedly dilated measuring 1.37cm. There was a small amount of hyperechoic debris in suspension on the urinary bladder and the jejunal lymph nodes were mildly hypoechoic and measured 8.0mm in thickness. A fine needle aspirate was

obtained on the right kidney. The changes in the right renal parenchyma were expected to be neoplasia and the hydronephrosis was likely due to a partial obstruction of the right ureter. Metastatic neoplasia or reactive lymphadenopathy was considered for the hypoechoic jejunal lymph node. Fine needle aspirate showed a highly suspected neoplastic population of cells, most likely renal cell carcinoma but nephroblastoma or other tumors could not be ruled out.

She had a right nephrectomy on 5/9/19. She was given acepromazine 0.1mg and methadone 2mg intramuscularly for premedication and catheter placement and then sedated with Alfaxalone 30mg intravenously. Bonnie did well under anesthesia and recovered uneventfully. Her renal mass was sent off for histopathological examination. The results showed a renal cell carcinoma with a high mitotic index of 26 per ten high powered fields. The cells were forming papillary projections and irregular tubular structures making this a tubular/papillary renal cell carcinoma. There was evidence of capsular invasion and it is possible that the tumor expanded into the retroperitoneal space. She did well post operatively and the owner had no concerns during this time. She was sent home on Tylenol 4, 15mg by mouth every 8 hours for 14 days.

She slowly became more alert at home, regained her appetite, and had no more episodes of vomiting. On 5/23/2019 Bonnie's CBC, SDMA and renal panel revealed adequate blood cell lines and normal renal function to receive chemotherapy for prophylactic treatment of metastasis. Her ionized calcium level was within normal limits. Her urinalysis was suspicious of a urinary tract infection; she was initiated on Clavamox pending urine culture results for further antibiotic recommendation. She received Carboplatin (112 mg; 10 mg/kg) in her left saphenous vein without immediate complications. She was sent home on Clavamox 375mg, given ½ tablet every 12 hours pending urinary culture results. Metronidazole 100mg orally every 12 hours for

treatment of loose stool, Ondansetron 4mg by mouth every 12 hours for decreased appetite and nausea, and Tylenol 4 15mg by mouth for pain, were sent home for prophylactic treatment of adverse chemotherapy effects. On 5/25/2019 the culture results showed Proteus mirabilis growth and her enrofloxacin was initiated.

On 6/12/2019 CBC showed a sufficient white cell count for chemotherapy and Bonnie was given 240mg/m2 of Carboplatin because of an unremarkable nadir following her first dose. Enrofloxacin was finished on 7/2/2019. Metronidazole 100mg, Ondansetron 4mg, and Tylenol 4 15mg were sent home for prophylactic treatment of adverse chemotherapy effects.

On 7/10/2019 a CBC was performed and was sufficient for chemotherapy. Thoracic radiographs revealed no evidence of metastatic pulmonary disease and her abdominal ultrasound revealed persistent and mildly progressive changes to her gallbladder and the previously identified jejunal lymph node was not identified. Bonnie was administered Carboplatin (240 mg/m2) in her left lateral saphenous vein without immediate complications. Urine was collected for culture and sensitivity to ensure that the past urinary tract infection had resolved. Prophylactic treatment of adverse chemotherapy effects was sent home.

On 7/31/2019 the CBC revealed a mild neutropenia. A blood gas analysis was run to evaluate ionized calcium, which was borderline elevated. Carboplatin (240 mg/m2) was given intravenously in Bonnie's left lateral saphenous vein. Because she has a grade 3 neutropenia with a nadir at day 15 post-Carboplatin treatment, Clavamox was prophylactically prescribed for days 13-18 post-Carboplatin treatment. Prophylactic treatment of adverse chemotherapy effects was sent home.

On 8/21/2019 a renal panel revealed a mild hyperphosphatemia. The complete blood count revealed a mildly decreased hematocrit and a mild eosinopenia. Carboplatin (240 mg/m2) was given intravenously in Bonnie's left lateral saphenous vein. She was sent home with the same supportive meds, as well as antibiotics in anticipation of her neutrophil nadir.

On 9/11/2019 CBC and renal blood panel were adequate for Bonnie's last dose of chemotherapy. Carboplatin (240 mg/m2) was given intravenously in Bonnie's left lateral saphenous vein. Thoracic radiographs revealed no evidence of nodular pulmonary metastatic neoplasia. The abdominal ultrasound revealed resolution of the previously described abnormalities of the gallbladder mucosa. Resolved left renal pelvic dilation. The same prophylactic medication was sent home following chemotherapy administration.

On 1/4/2020 On thoracic radiographs, no evidence of metastasis was visualized. Abdominal ultrasound also had no evidence of neoplasia. There was a moderate amount of gallbladder sludge visualized. A renal panel was performed to ensure her only kidney is maintaining proper function. Her ionized calcium was slightly elevated, but consistent with what it has been in the past. Bonnie was sent home on Ursodiol 78mg, given 1 capsule orally every 12 hours. Bonnie was scheduled for a recheck and restaging around April.

Pathophysiology:

Renal cell carcinomas are the most common primary renal tumor in dogs; the prevalence is 1.5 per 100-100,00 canines (LeFebre, 2013). In the kidney, renal cell carcinomas generally start from the epithelial cells of the convoluted tubules. Studies show they are malignant, highly invasive, and there is a 17% chance of metastasis at the time of diagnosis (Edmondson, 2015).

When they are invasive they will generally invade the renal pelvis, the ureters, or the blood vessels of this region (LeFebre, 2013). This type of renal neoplasia does not have a major breed predilection but generally presents in 8-9 year old canines. Some studies show that androgens do play a role and so it is possible that males are more prone to developing this type of renal neoplasia (Bryan, 2006).

When these canines present with renal cell carcinoma, the signs are generally nonspecific but can include; anorexia, depression, weight loss, palpable mass, pain on palpation, emesis, dysuria, pollakiuria, and hematuria (Edmondson, 2015). Blood work (complete blood count, chemistry, and urinalysis) should be performed on a complete work up. In renal cell carcinomas the blood work may be unremarkable or you may see some secondary anemia, secondary polycythemia, neutrophilia, hypocalcemia, azotemia, proteinuria, and rarely ALP and ALT elevations (Chung, 2014).

There has also been immunohistochemical characterization of canine renal cell carcinomas in order to create correlations of immunohistochemical profiles and histologic classification. In up to 90 % of human renal cell carcinoma cases, CD10 is expressed which is used as a prognostic indicator but also a potential therapy target (Gil da Costa, 2011). In canines they have found that vimentin, CEA and c-KIT are more commonly expressed by confirmed renal cell carcinoma cases (Gil da Costa, 2011).

Differential Diagnoses

As discussed previously there are several other types of renal neoplasm, both of the benign, primary, or metastatic versions. We will discuss the major ones now. Renal papillomas

and fibromas are the benign version and if surgically resected the animal can be cured. On the other hand, renal lymphoma is rarely cured and is uncommon in canines. In addition to renal cell carcinomas you can also have adenocarcinomas, transitional cell carcinomas (TCC), and cystadenocarcinoma. TCC of the renal pelvis will generally be multilobulated and locally aggressive (vsso). It is possible for TCC to begin in the bladder and invade up a ureter and into a renal pelvis or simply begin at any spot along this path. Cystadenocarcinoma is associated with an autosomal dominant condition in German Shepherds and is a slowly progressive neoplasia that is generally bilateral (Locke, 2006). Mesenchymal tumors are rare and make up only 11% of renal neoplasms but they are often aggressive and highly metastatic; they include; hemangiosarcomas, fibrosarcomas, and leiomyosarcomas (Locke, 2006). Nephroblastomas are the congenital renal tumors and are normally seen in young animals less than 12 months of age (Montinaro, 2013). Many types of metastasis to the kidney are also common because of the rich blood flow and microvasculature (Chung, 2014).

Diagnostic Approaches:

Diagnosis of renal tumors is generally done by advanced imaging. As discussed earlier, if unilateral neoplasia is present, an abnormal kidney on imaging may be the only sign. For advanced imaging, an abdominal ultrasound is recommended with an accompanying CT or MRI for surgical planning, as these can be highly invasive tumors (Edmondson, 2015). An excretory urogram can also be useful in differentiating normal renal tissue from neoplastic tissue for surgical planning (Knapp, 2007). Thoracic radiographs are also recommended because pulmonary metastasis was found in 11% of canines prior to nephrectomy in one study

(Edmondson, 2014). Though advanced imaging is helpful a definitive diagnosis can only be made by histopathological examination. From histopathological examination we can not only get a diagnosis, but also diagnose a cellular subtype and gain mitotic index. There are nine subtypes recorded in human medicine, the three main subtypes are clear cell, papillary, and chromophobe. These subtypes represent different biological behavior and prognostic indicators in both human and canine medicine (Edmondson, 2014). Because surgery is a mainstay of treatment, a complete blood count, chemistry panel, and urinalysis is recommended to ensure good anesthetic candidacy.

Treatment and management:

Surgical removal of the neoplastic tissue, including associated ureter (i.e. ureteronephrectomy) is the gold standard of treatment of unilateral renal cell carcinomas. Renal scintigraphy can be used to observe the glomerular filtration rate of both kidneys before surgery to better assess kidney function (Knapp, 2007). Bilateral renal cell carcinomas often result in end stage kidney failure, which carries a grave prognosis. There is limited research on renal cell carcinoma chemotherapy in small animals though some studies show that it has an apparent resistance (Parekh, 2015). Although in human medicine surgery with a combination of radiation, chemotherapy, and biological therapy is used to treat renal cell carcinoma. Cisplatin or Sutent are usually one of the agents of choice in human urogenital cancers, but have shown to have no improvement to survival in canine patients (Bryan, 2006).

Expected outcomes and Prognosis:

There are a few uniform characterizations that can be used to determine prognosis when looking at histopathologic sections of renal cell carcinomas. Mitotic index has been shown to be highly predictive of survival rates and was the only factor with independent prognostic value (Edmondson, 2014). Recognition of clear cell subtypes on histological examination can have implications on survival and biological behavior. Clear cell subtypes correlate with decreased survival times and have higher likelihood of being malignant in human renal cell carcinoma (Edmondson, 2014). In a small study, multilocular cystic variants have been described to be associated with prolonged survival times (Edmondson, 2014).

The prognosis of renal cell carcinomas can be guarded to poor depending on presentation; animals that present with hematuria and cachexia have a decreased survival rate (Edmondson, 2014). If the patient has bilateral renal cell carcinoma the prognosis is grave because of the amount of functional kidney left. If the patient has unilateral renal cell carcinoma the malignancy, invasion of surrounding tissue, and metastasis will play a larger role in prognosis (Seaman, 2003). At the time of diagnosis approximately 16% of canines will have metastasis which is considerably greater at post mortem examination (approximately 77%) (LeFebre, 2013). Metastatic sites include lungs, liver, ipsilateral adrenal gland, regional lymph node, contralateral kidney, omentum, peritoneum, diaphragm, skin, heart, brain, and appendicular and axial skeleton (Parekh, 2015). Survival times have a mean of 6-8 months but survival terms of up to 4 years have been reported (Knapp, 2007).

Conclusion:

Bonnie was diagnosed with renal cell carcinoma. Renal neoplasia is uncommon in dogs, but Bonnie was diagnosed with the most common of the neoplasms. When canines present with renal cell carcinoma their signs can be very vague which makes advanced imaging and histopathology the mainstays of diagnosis. Surgical resection of the affected kidney is the gold standard for treatment because renal cell carcinoma has been shown to be resistant to chemotherapy in small animal studies. Before going to surgery CT, MRI, or urinary scintigraphy is recommended for surgical planning because of the invasiveness of the tumor. Because of a high likelihood of metastasis, thoracic radiographs or other thoracic imaging is also recommended. There is a guarded to poor prognosis for this type of neoplasm, and the median survival time is 6-8 months with surgical resection.

References:

Bryan, J. N., Henry, C. J., Turnquist, S. E., Tyler, J. W., Liptak, J. M., Rizzo, S. A.,Sfiligoi, G., Steinberg, S. J., Smith, A. N. and Jackson, T. (2006). Primary RenalNeoplasia of Dogs. *Journal of Veterinary Internal Medicine*, 20:1155–1160.doi:10.1111/j.1939-1676.2006.tb00715.x

Chung, J. Y., Kim, J. I., Jang, H.S. (2014). Unilateral renal cell carcinoma in a dog. *Pakistan Veterinary Journal*, 34(1): 146-148.

Edmondson E. F., Hess A. M., Powers B. E. (2015). Prognostic significance of histologic features in canine renal cell carcinomas: 70 nephrectomies. *Veterinary Pathology*. 52(2):260-8. http://vet.sagepub.com/content/52/2/260.short

Gil da Costa, R. M., et al. (2011). "Immunohistochemical characterization of 13 canine renal cell carcinomas." *Veterinary Pathology* 48(2): 427-432. https://journals.sagepub.com/doi/pdf/10.1177/0300985810381909

Knapp, Deborah W. (2007). "Tumors of the Urinary System." *Withrow and MacEwen's SmallAnimal Clinical Oncology*. By Stephen J. Withrow and E. Gregory. MacEwan. St. Louis: W.B.Saunders. 655-657

LeFebre L. R., Rhoades, L. (2013). Renal Cell Carcinoma. *Veterinary Medical and Surgical Group.* https://www.vmsg.com/wp-content/uploads/2017/01/case-report-renal-cell-carcinoma.pdf

Locke J. E., Barber L. G. (2006). Comparative aspects and clinical outcomes of canine renal hemangiosarcoma. *J Vet Intern Med*; 20:962-967. http://onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2006.tb01812.x/abstract

Montinaro V., Boston S. E., Stevens B. (2013). Renal nephroblastoma in a 3-month-old golden retriever. *Can Vet J* 2013;54(7):683-6. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3685002/

Seaman R. L., Patton C.S. (2003). Treatment of renal nephroblastoma in an adult dog. *J Am Anim Hosp Assoc* 2003;39:76-79. http://www.jaaha.org/doi/abs/10.5326/0390076

Parekh H, Rini B. I. (2015). Emerging therapeutic approaches in renal cell carcinoma. *Expert Rev Anticancer Ther* 2015;17:1-10. [Epub ahead of print]. http://www.tandfonline.com/doi/abs/10.1586/14737140.2015.1090315 – .Vj3ybYS5eFI