Charlie's Tight Situation

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Introduction

Apocrine gland anal sac adenocarcinoma (AGASACA) is a malignant tumor that arises from the apocrine glands of the walls of the anal sacs (epithelium).[1] This type of tumor tends to be locally invasive and has a high metastatic rate (50-90%) to local lymph nodes (LN) such as the iliac, sacral, and sub-lumbar. Metastasis also occurs to distant sites in the body, most frequently the lungs, liver, and spleen. However, spread to the regional lymph nodes typically precedes this.[1,2] Paraneoplastic hypercalcemia occurs in up to 50% of dogs with AGASACA due to production of parathyroid hormone related protein (PTHrp).[1] Despite its ability to metastasize, this tumor has median survival times of 1-2 years with single or multimodal therapeutic modalities.[2]

History and Presentation

Charlie is a 10-year-old male neutered Border Collie mix who presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Emergency Services on January 23rd, 2020 for stranguria and tenesmus. He initially presented on April 10th, 2019 for a 4-day history of tenesmus and was then diagnosed with a retroperitoneal mass (10.5 x 3.4 x 4.0cm) that was causing ventral displacement and narrowing of the lumen of the descending colon and rectum. Cytology of the mass revealed epithelial proliferation likely to be of neuroendocrine origin. The Surgery Service was consulted and at that time, the mass was suspected to be a retroperitoneal sarcoma, which is an aggressive tumor with a high rate of local recurrence and metastasis, carrying a median survival time of 37.5 days.[3] Surgery was not recommended due to high risk of complications and little potential benefit. Charlie's owners medically managed his bowel obstruction with seven milliliters of lactulose three times a day. Over the holidays, he began to have trouble defecating and urinating and was treated with multiple enemas by his

referring veterinarian (rDVM). Since Charlie's condition did not improve, he was brought back to MSU-CVM on January 23rd, 2020 for further management and surgical reevaluation.

On physical exam, Charlie was bright, alert, and responsive. He weighed 16.6 kilograms (36.5 pounds) and had a body condition score of five out of nine. He had a temperature of 102.1°F, a heart rate of 128 beats per minute with strong synchronous pulses and was panting with normal respiratory effort. His mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. On cardiopulmonary evaluation, no murmurs, arrhythmias, crackles or wheezes were auscultated. Charlie had moderate to severe dental calculus and gingivitis. Two subcutaneous masses were palpated, one on his left inguinal region and one on his cranial sternum on the right. His peripheral lymph nodes were small, soft, and symmetrical. He had nuclear sclerosis bilaterally and mild debris in the external ear canals. On rectal exam, a firm bulge was palpated dorsally and a small round, firm mass on his right anal gland. The remainder of the physical exam was within normal limits.

Diagnostic approach

In dogs with AGASACA, clinical signs are dependent on the tumor size and presence of hypercalcemia. In some cases, AGASACA is an incidental finding, however many patients will present with a variety of clinical signs with the most common being tenesmus, constipation, change in stool consistency, polydipsia, polyuria, and perineal swelling.[4] In addition to a thorough physical exam, diagnostic work-up should include a complete blood count (CBC), a serum chemistry, thoracic radiographs or thoracic computer tomography (CT), and an abdominal ultrasonography or abdominal CT.[1] Additionally, measurement of serum ionized calcium, parathyroid hormone (PTH), and PTHrp levels can be helpful in confirming humoral hypercalcemia of malignancy (HHM).[5] Once diagnosis is suspected, confirmatory testing

includes fine needle aspirate cytology of the affected anal sac. Further diagnostics including abdominal CT or magnetic resonance imaging (MRI) and tumor biopsy for histopathology should be done to assist with staging and determine therapeutic options; including surgical resection, chemotherapy, and radiation.[1]

On April 7th, 2019, Charlie's initial work-up at his rDVM included a 3-day history of constipation. Following abdominal radiographs, he was diagnosed with a sub-lumbar mass causing ventral deviation and obstruction of the colon. He was then referred to MSU-CVM (4/10/2019) for further evaluation. Complete blood count was unremarkable with a mild neutrophilia of 14,609/uL (3,500-14,200/uL) and serum chemistry revealed a mild increase in anion gap (ANGAP) of 23 mMol/L (10-20 mMol/L), mild hyperglycemia of 190 mg/dL (75-125 mg/dL),and a mild increase in alanine aminotransferase (ALT) of 108 U/L (10-90 U/L). His urinalysis revealed proteinuria. While thoracic radiographs did not reveal metastasis, it revealed a bronchial pulmonary pattern thought to be secondary to age related changes or chronic bronchitis. Abdominal radiographs demonstrated a smoothly marginated, ovoid, soft tissue opaque mass (5.7 x 4.0 cm) ventral to L7-S1 vertebrae causing ventral deviation and compression of the descending colon and rectum. Other findings included caudal displacement of the gastric axis. An abdominal ultrasound showed hepatomegaly with rounded liver margins; mildly enlarged right medial iliac lymph node (0.87 cm in thickness); and a mass at the level of the aortic trifurcation measuring at least 9.78 cm in length and up to 3.52 cm in thickness with confirmed doppler flows. Fine needle aspirates of the liver and sub-lumbar mass were then performed. Results included hepatic congestion with moderate glycogen accumulation and epithelial proliferation, respectively. The latter likely of neuroendocrine origin. On CT, the same mass (10.5 x 3.4 x 4.0 cm) was described to be within the caudal retroperitoneal space and pelvic

canal extending from L6 to Cd4. This time showing severe ventral displacement and narrowing of the lumen of the descending colon and rectum as well as leftward displacement of the trifurcation of the abdominal aorta and origin of the caudal vena cava. Medial iliac lymph nodes were also bilaterally enlarged with the right being larger (1.4 x 0.9 x 2.0 cm).

The Surgery Service was consulted again on August 14th, 2019. As previously mentioned, the mass was thought to be a retroperitoneal sarcoma with a high rate of local recurrence and metastasis carrying a poor prognosis.[3] Again, surgery was not recommended due to perceived risks outweighing potential benefits. Medical management with laxatives and high fiber diet was recommended.

On January 23rd, 2020, Charlie returned to MSU-CVM to the Emergency Service with painful inability to urinate and defecate. The same diagnostics were repeated to reassess Charlie's mass and for surgical planning. His CBC and coagulation profile were within normal limits. Serum chemistry included mild hypoalbuminemia of 5.4 g/dL (5.5-8.0g/dL), mild hypercalcemia of 11.3mg/dL (8.8-11.2mg/dL), mild hypophosphatemia of 2.4 mg/dL (2.5-5.0 mg/dL) and mild hypomagnesemia of 1.6 mg/dL (1.7-2.4 mg/dL). Imaging studies showed a stable appearance of the chest, decrease in size of the liver, and enlargement of the previously described mass, now measuring 11.7 x 5.3 x 5.6 cm, causing severe ventral displacement and compression of the descending colon and rectum, as well as severe cranial and ventral displacement of the urinary bladder. The mass was also causing progressive ventral and leftward deviation of the caudal aorta and aortic trifurcation and severe narrowing of the caudal vena cava. Within the pelvic canal, it was also causing rightward displacement of the rectum and medial to lateral compression of the rectal lumen. The left and right medial iliac lymph nodes had demonstrated progressive enlargement and were now cranially displaced. The right medial

iliac lymph node was severely affected and measured 2.9 x 2.4 x1.3 cm. This study also described that within the right anal sac was an irregularly shaped contrast enhancing nodule.

Treatment and Prevention

Surgical excision is the treatment of choice for patients with AGASACA. Given the prevalence of local recurrence and metastasis, combination therapy with radiation, and chemotherapy is often necessary for prolonged disease control. Lymphadenectomy of metastatic lymph nodes at the time of primary tumor resection, has been reported as a positive prognostic factor.[6]

On January 27th, 2020, Charlie was taken into surgery for a ventral midline celiotomy to remove his abdominal lymphadenopathy and right anal sac. A celiotomy is a surgical incision into the abdominal cavity.[7] This is performed for various reasons; it may be indicated for diagnostic (e.g. biopsying an organ) and/or therapeutic reasons (e.g. mass removal).[7,8] Since Charlie's cytology did not confirm a diagnosis, histopathology of the mass and right anal gland was vital for appropriate diagnosis and for determining future treatment options. However, in Charlie's case, the main treatment goal was to relieve his obstruction and provide comfort. On surgical exploration Charlie's sublumbar lymphadenopathy had extended dorsal to the aortic trifurcation, extending deep into the pelvic canal. Sharp and blunt dissection were performed to carefully excise the mass and metastatic disease. No other abnormalities were noted on full abdominal exploration. After closing his abdomen, Charlie was placed on ventral recumbency to facilitate removal of his right anal sac (anal sacculectomy). A closed technique was performed on Charlie where the external anal sphincter muscle is not transected and the lumen of the anal sac remains closed, preventing contact between secretions and adjacent tissues.[9] Specimens

collected were placed in formalin and submitted for histopathology. Charlie recovered uneventfully from anesthesia and was placed in ICU for monitoring.

Three days after surgery, Charlie was found panting, restless, and uncomfortable. Soon after initial physical exam he developed seizures, characterized by lateral recumbency, hyperextension of neck and forelimbs, tachycardia (198 bpm), hyperthermia (105.7 °F), and hypertension (systolic 203 mmHg). After initial supportive care, a neurological assessment proved no new neurological deficits. Caudal aorta and vena cava obstruction were also ruled out. However, his ionized calcium levels revealed a hypocalcemia of 0.9 mmol/L (1.25-1.50 mmol/L). He was started on intravenous (IV) calcium gluconate and calcitriol (0.03 mg/kg/day; 0.1 µg/ml) orally while undergoing continuous EKG monitoring. Once his calcium levels normalized, IV calcium gluconate was discontinued. He was also started on clopidogrel (2mg/kg/day; ~ 75 mg) orally and enoxaparin (0.8mg/kg/day; 100mg/ml) subcutaneously in case the seizures had been caused by a thromboembolic event. Given appropriate response to calcium supplementation and resolution of seizures, these were attributed to hypocalcemia and enoxaparin was discontinued.

Pathophysiology

Humoral hypercalcemia of malignancy (HHM) is a common cause of hypercalcemia in dogs.[5,10] This is known as a paraneoplastic syndrome where tumor-cells produce parathyroid hormone-related peptide, a promoter of osteoclastic activity and osteolysis secondary to bone metastasis.[5,6,10] Thus, mimicking parathyroid hormone activity. It has been reported in 27-53% of canine patients with AGASACA.[6,8] Return to normal levels of calcium is generally seen after

successful tumor excision, and recurrence of hypercalcemia is generally associated with tumor recurrence or metastasis.[6,10]

Normally, PTH acts to raise extracellular calcium levels by increasing bone resorption, renal reabsorption of calcium and phosphorus, and formation of the active metabolite of vitamin D (calcitriol).[6,10] The ionized form of calcium (iCa) is the biologically active form. Its level is tightly regulated by PTH and calcitonin. When iCa levels are elevated PTH production is inhibited and when levels are low production is stimulated. This tight regulation is extremely important to prevent clinical signs and adverse effects of calcium imbalances. Chronic hypercalcemia can be detrimental to the kidneys leading to nephrocalcinosis and ischemic injury.[6] Clinical signs of hypercalcemia include polyuria, polydipsia, weakness, vomiting, constipation, and muscle twitching.[5] Hypocalcemia, on the other hand, is associated with facial rubbing, panting, nervousness, inappetence, vomiting, diarrhea, lethargy, and in severe cases, neurological and neuromuscular disturbances (i.e. seizure, tremors, muscle cramping).[6,10,11]

As previously mentioned, following removal of PTHrp secreting tumor iCa levels drop, return of normocalcemia is considered a marker of successful management of AGASACA. However, in rare instances, hypocalcemia can be seen following removal of AGASACA and its metastasis. The presumed mechanism of calcium dysregulation in these patients is secondary hypoparathyroidism.[6,10] Saba and collaborators suggested that chronic suppression of the parathyroid glands by high circulating calcium levels in HHM can lead to glandular atrophy and inability to adequately secrete PTH and regulate iCa levels.[6,10] In other words, Parathyroid hormone-related peptide production by the tumor leads to high circulating calcium levels and hence, down regulation of PTH production by the parathyroid glands.[10] Similarly, rebound

hypocalcemia and hypoparathyroidism has been reported following induction chemotherapy in patients with HHM related to lymphosarcoma.[6,12]

Case Outcome

Charlie was discharged on February 4th, 2020 once regulation of his calcium levels were achieved. He was sent home with an Elizabethan collar, acetaminophen/codeine (1.63mg/kg PO Q8H for 7 days) for pain; trazodone (5.46 mg/kg PO Q8H for 2 weeks) for anxiety; amoxicillin/clavulanate (13.66 mg/kg PO Q12H); calcitriol (0.027µg/ml PO Q24H for 30 days) for management of hypocalcemia; and clopidogrel (2mg/kg PO Q24 H for 2 weeks) for prevention of blood clot formation. His owners were instructed to monitor him for signs of hypocalcemia (e.g. facial rubbing, pawing at the face, ear twitching, excessive panting etc.), limit his activity, provide passive range of motion, and apply warm compresses to his surgical incision site.

Charlie came back on February 12th, 2020 for an oncology consult and staple removal. After careful consideration and being presented with all the treatment options (radiation, chemotherapy, palliative management, his owners elected for palliative treatment and he was prescribed piroxicam (0.27mg/kg PO Q24H). His calcitriol supplementation was reduced to 0.0135 µg/kg PO Q24H and was later discontinued (February 24th, 2020) as his ionized calcium levels maintained within normal limits at 1.27mmol/L (1.25-1.50 mmol/L).

Today, approximately 300 days after surgery, Charlie is doing well. He is a testament of how dogs with AGASACA can experience long-term survival after surgical excision of the metastatic lesion[13]. His quality of life drastically improved with surgical removal and, so far, has provided him with ten additional months with his family.

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