Name and credentials

Oncology

Case Log # 32

Signalment

"Buddy," an 8 yr old, 21.9kg, M/N Goldendoodle canine

Patient History

Buddy presented to his RDVM on 2/27/15 for lethargy, diarrhea, and a picky appetite. PE and abdominal radiographs (AXR) revealed foreign bodies (pebbles) in his rectum and stomach, which could explain the diarrhea. CBC and biochemical profile (Chem) revealed mild thrombocytopenia (127 K/µL; reference range [REF]: 148-484 K/µL) and hypercalcemia (HC) (total calcium=13.3mg/dL, REF: 8.6-11.8mg/dL). Due to the presence of HC, further blood analysis was submitted for parathyroid hormone (PTH=0.5pmol/L; REF: 0.5-5.8pmol/L), parathyroid hormone-related proteins (PTHrP=0pmol/L; REF: <0pmol/L), and ionized calcium (iCa=1.9mmol/L; REF: 1.24-1.43 mmol/L) to rule out thyroid disease. The presence of an elevated iCa in conjunction with a PTH>0 can point towards a parathyroid tumor as the cause of HC.

Buddy presented to the internal medicine service on 3/6/15 for further management. He weighed 21.9kg with a body condition score (BCS) of a 5/9. PE and 3-view thoracic radiographs (TXR) revealed no abnormalities. Peripheral lymph nodes palpated normal. An in-house Chem revealed HC (iCa=1.59mmol/L; REF: 1.15-1.34mmol/L) as expected and elevated lactate (3.0mg/dL; REF: 0.6-1.6mg/dL). A cervical ultrasound was performed to investigate the thyroid gland and revealed a parathyroid nodule measuring 5 x 6mm. A

parathyroidectomy was scheduled that same day. Histopathology of the mass confirmed a parathyroid adenoma. During post-operative hospitalization, iCa was checked daily and ranged between 15.6mmol/L and 1.7mmol/L. Theoretically, iCa levels would decrease post-op, but Buddy's values were increasing. Differentials include a delayed normalization of calcium levels, an undetected parathyroid adenoma, or another underlying cause driving the HC (i.e. neoplasia).

Buddy returned on 3/18/15 for blood analysis, revealing a decrease of iCa (1.58mmol/L) compared to previous values. He then re-presented 10d later for lethargy, diarrhea, occasional emesis, and persistent hyporexia/anorexia despite taking a tetracyclic antidepressant, mirtazapine, as an appetite stimulant. He was hospitalized for supportive care and fluid therapy for anorexia and persistent HC (iCa=1.66mmol/L). Ultrasound guided fine needle aspirates (FNA) of the liver and spleen were recommended to search for and rule out lymphoma (LSA). Cytology ultimately revealed lymphoid hyperplasia suggestive of LSA. Immunophenotyping of the hepatic aspirates revealed that the LSA was T cell in origin. With a diagnosis of LSA, an L-asparaginase trial was discussed with the owner to see if a favorable response occurs (i.e. resolution of clinical signs, iCa value decreases) which can further solidify the diagnosis of LSA. A baseline CBC was WNL other than a severe thrombocytopenia (23 K/µL; REF: 148-484 K/uL) which can result from occult neoplasia. L-asparaginase was dosed at 10,000iu/m^2 (7,200iu, 3.6mL, 2,000iu/mL), prepared using a class II laminar flow safety cabinet and personal protective equipment (PPE=chemo gown, chemo gloves, goggles), and administered SC on 3/30/15. A nasoesophageal tube was placed the following day to provide nutritional support during this period of anorexia. The iCa

values continuously decreased into the normal REF over the next wk from 1.66mmol/L to 1.2mmol/L, suggesting a favorable response to L-asparaginase. Prednisone 1mg/kg (20mg) SID PO was started on 4/2/15. A bone marrow aspirate was performed to determine if LSA was also present there. Cytology confirmed lymphoproliferative neoplasia. Buddy was discharged from the hospital on 4/6/15.

Intervention

Buddy presented to the oncology service on 4/8/15 with hypercalcemic T cell LSA and was classified as a stage Vb due to LSA being present in the liver, spleen, and bone marrow as well as a symptomatic presentation. PE revealed Buddy to be bright, alert, and responsive with normal vital signs (T=99.9^{o}F, P=110 bpm, R=24/min), MM=pk/moist, CRT<2s. His wt was 18.9kg, a 3kg loss since original presentation to RBVH on 3/6/15. His BCS was a 3/9 on the Nestle Purina Pet Care Center model. A CBC revealed monocytosis (1.57 K/µL; REF: 0.16-1.12 K/µL) and continued thrombocytopenia (38 K/µL). The prognosis and therapy options were discussed with the owners. They elected to pursue chemotherapy involving a 19-week multi-agent CHOP protocol in conjunction with a T cell canine LSA monoclonal antibody (T-MAb) therapy. A CHOP protocol is an acronym for the following medications: C=cyclophosphamide (CTX), H=hydroxydaunorubicin (doxorubicin [DOXO]), O=Oncovin® (vincristine [VCR]), and P=prednisone. Treatments (tx) are typically administered weekly with the exception of a wk off after doxorubicin due to potential of a nadir in blood values, typically WBCs. Aratana Therapeutics® is currently conducting clinical trials on T-MAb at select hospitals. T-MAb is generally dosed at 2.5mg/kg, rounded up to the whole vial(s). T-MAb is administered IV over 20min twice a wk for the first 4 wks, then once every other

wk for 4 txs, totaling 12 txs.

At this initial visit, Buddy was enrolled in the T-MAb trial, but only VCR was Rx'd for that day. VCR was dosed at 0.5mg/m^2 (0.35mg, 0.35mL, 1mg/mL) and prepared using a class II laminar flow safety cabinet, closed system transfer device (CSTD), and PPE. An administration system was assembled, containing a 25 gauge (ga) winged infusion set and CSTD components, and primed with 0.9% sodium chloride (NaCl). The skin was aseptically prepped with 70% isopropyl alcohol and VCR was administered IV in the right saphenous vein, flushing pre- and post-VCR administration with approximately 3mL 0.9% NaCl, respectively. The prednisone dose was increased to 2mg/kg (40mg) SID PO according to the protocol. Buddy was prescribed maropitant citrate 2mg/kg (40mg) SID PO and metronidazole 13mg/kg (250mg) BID PO for nausea/emesis and diarrhea, respectively. Buddy returned for his first T-MAb tx 2d later. The right cephalic vein area was shaved and aseptically prepped for a 22ga IV catheter placement. T-MAb was dosed at 2.5mg/kg (47.3mg) but rounded up to 75mg (two 37.5mg vials) and was administered IV over 20min via an extension set primed with 0.9% NaCl. After the infusion concluded, the IV catheter was removed, a bandage was placed, and the patient was discharged to the owners.

Buddy's appetite improved over the course of a month and the nasoesophageal tube was removed on 5/4/15. Buddy continued to respond favorably to the chemotherapy and T-MAb txs, aside from a brief 2d hospitalization on 8/3/15 for hyporexia, diarrhea, vomiting, and lethargy. During this time, a CBC and Chem revealed normal iCa (1.28mmol/L) and a mildly elevated blood urea nitrogen (BUN=43mg/dL, REF: 7-27mg/dL), which may have been a result of dehydration and/or gastrointestinal (GI) bleeding. This was the first time that the iCa

was measured since starting chemotherapy, displaying a response to the chemotherapy txs. The patient was placed on Plasma-Lyte A fluids IV to correct dehydration. To treat nausea, a neurokinin receptor antagonist, maropitant citrate, was administered SC and a proton pump inhibitor, pantoprazole, IV. An AUS was rechecked, revealing no evidence of lymphoma recurrence. Buddy completed the T-MAb on 7/2/15 and the CHOP protocol on 8/13/15.

Final Outcome

Buddy continues to do well and iCa levels remain WNL. He returns monthly for reassessment.

Case Discussion

Buddy's LSA presented symptomatically and with HC, a paraneoplastic syndrome. Although the thyroid was of initial concern, surgical intervention to remove the mass did not result in a reduction in calcium levels. A search for LSA was initiated in organs that would be a typical place for LSA, such as the spleen, liver, and bone marrow. A continued search for the reason behind the HC was crucial in this patient's outcome. Buddy's prognosis improved due to implementation of multi-agent chemotherapy and immunotherapy, as well as placing a nasoesophageal tube to minimize cancer cachexia. When a tx protocol is completed, frequent monitoring of the disease with PE, TXR/AUS, blood and urine analysis, and owner vigilance is imperative in order to address any relapses in a timely fashion.as

Lymphoma is one of the most commonly diagnosed cancers in dogs and cats, accounting for about 20% of all canine cancers. Golden retrievers and boxers have shown a predilection for LSA indicating that a genetic link may be present. LSA develops from lymphatic cells, specifically the lymphocytes. LSA can present in various organs, including lymph nodes,

spleen, liver, kidneys, eyes, GI tract, mediastinum, bone marrow, central nervous system, and skin. Initially, a patient is staged with a thorough PE, CBC, Chem, 3-view thoracic radiographs, and AUS to provide a complete diagnostic picture of the extent of disease. The stage of LSA is then determined via the World Health Organization staging system.

Cancer is the leading cause of HC, with lymphoma being the most common cause of hypercalcemia of malignancy (HM) (10-35% occurrence).[3] Approximately 10-40% of dogs with lymphoma have concurrent HC which can also be the first abnormality found.[1] Other tumor types associated with HC are anal sac apocrine gland adenocarcinoma, thyroid carcinoma, multiple myeloma, and parathyroid gland tumors. Other differentials for HC are hyperparathyroidism, hypoadrenocorticism, chronic renal failure, Vitamin D toxicosis, and certain granulomatous diseases.[1] Ionized calcium is a more accurate assessment of the concentration of calcium in the body than total calcium levels. Symptoms of HC can include polydipsia, polyuria, anorexia, vomiting, constipation, and muscle tremors. These patients may require fluid therapy, diuretics, glucocorticoids (after a diagnosis is made), and/or chemotherapy (for neoplasia) to help the body excrete the excessive calcium from the body.

FNA's can be a minimally invasive way of sampling sites suspicious for LSA. Submission of those samples for cytology can provide a diagnosis of LSA. A biopsy is recommended when cytology is not diagnostic, grading (low, intermediate, or high) of tumor is needed, and/or the tumor is inaccessible for FNA. Further information about the lymphoid cell differentiation (B cell, T cell, NK cell, plasmacytoid dendritic cells) can be obtained by performing immunophenotyping. Immunophenotyping is the analysis of heterogeneous populations of cells in order to identify specific antigens/cell markers. It is commonly

performed via flow cytometry, immunocytochemical/histochemical staining, or polymerase chain reaction (PCR). In Buddy's case, this step was a requirement to determine cell differentiation and assess eligibility for the T-MAb therapy.

The cytotoxic drugs used in the CHOP protocol can be myelosuppressive. Side effects, such as nausea/vomiting, diarrhea, lethargy, anorexia, and alopecia, are generally mild/moderate and can be managed with medications. Patients with more serious side effects may require hospitalization and supportive care. VCR, a vinca alkaloid derived from the Madagascar periwinkle plant, inhibits mitosis leading to apoptosis. It is a vesicant and can cause peripheral neuropathy. CTX, a nitrogen mustard alkylating agent, attaches an alkyl group to DNA which disrupts its replication. It is supplied in injectable and oral forms and is known to cause sterile hemorrhagic cystitis in some patients. DOXO, an anthracycline antibiotic, interferes with DNA replication by intercalation. It is a significant vesicant, cardiotoxic, and can cause anaphylactoid reactions. The oxidative properties of DOXO can cause severe tissue necrosis with extravasation as well as a potential to cause cardiomyopathy in some patients. Dexrazoxane, a free radical scavenger and cardioprotectant, can frequently mitigate these processes. Surgical debridement of a DOXO extravasation may be necessary. Prednisone is a glucocorticoid that has cytotoxic effects on lymphocytes and can reduce inflammatory processes. L-asparaginase, an enzyme derived from e. Coli, catalyzes the hydrolysis of asparagine to aspartic acid. Lymphatic tumor cells are typically unable to produce their own asparagine (a non-essential amino acid) unlike normal healthy cells. They require a large, external supply of asparagine in order to fuel their rapid growth. L-asparaginase helps deprive the tumor cells of asparagine, leading to apoptosis.

On 1/2/15, Aratana Therapeutics received full product license from the U.S. Department of Agriculture (USDA) to release the first biological, targeted cancer immunotherapy, B cell canine LSA monoclonal antibody (B-MAb), into clinical trials in the veterinary oncology community. Shortly thereafter, T-MAb was introduced into clinical trials and received conditional licensing from the USDA. In dogs with LSA, B-MAb recognizes CD-20 (an antigen that is expressed on B cells), whereas T-MAb recognizes CD-52 (an antigen that is expressed on T cells). When a MAb binds to its antigen target, the immune system is able to identify that target more easily, helping to eliminate the malignant B or T cells. MAbs have been used in human medicine since 1986 when the FDA approved the first human MAb, a CD3 specific transplant rejection drug named muromonab. Since the MAb data is incomplete in veterinary medicine, we can refer to human medicine to direct the trajectory of the future of oncology in veterinary medicine.

The median survival time of LSA is about 1 yr, with some patients living much longer. A study conducted by Valli et al[5] stated that dogs with low grade T-cell LSA had a MST of 622d, whereas high grade T-cell LSA had a MST of 162d. Therapy with a CHOP-based protocol is standard for LSA. Most dogs respond favorably to CHOP with 70-90% achieving a complete or partial remission. A remission is still achievable with a relapse, but is usually of shorter duration than the 1st remission. About 15% of dogs with LSA are cured of disease with chemotherapy.

References

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