Oncology
Case log #3
Initial treatment date: 11/4/22
Ryuu #150571

Ryuu was a 7 year 11-month-old, neutered male, Alaskan Malamute canine that presented to oncology for an incompletely excised high grade 3 cutaneous mast cell tumor. He initially presented to his rDVM on 10/6/22 for a mass that had been present for 2 months on his mid-dorsal tail. He had been licking at the mass, and it became ulcerated and painful. A punch biopsy of the mass was performed that day. The histopathology returned as an incompletely excised round cell neoplasia with a mitotic count of 34 per 10 high-power fields (HPF) with no angiolymphatic invasion. Giemsa and toluidine blue stains were performed and confirmed that many of the neoplastic cells had low to-moderate number of fine, metachromatic granules – diagnosing the mass as a cutaneous mast cell tumor, Kiupel high grade, Patnaik grade 3. The patient was not started on any medications prior to presentation to the oncology department.

The patient was presented to the oncology department on 11/4/22. Ryuu's vitals were within normal limits (WNL) and were as follows: 100.5 °F temperature (normal: 99.5 °F – 102.5 °F), 84 beats per minute (bpm) heart rate (normal (large dog): 60 – 90 bpm), and 24 breaths per minute (brpm) respiratory rate (normal: 16-24 brpm) with normal effort. Mucous membranes were pink and moist (normal: pink and moist) with a capillary refill time (CRT) of less than 2 seconds (normal: less than 2 seconds), and at a weight of 56 kg. Ryuu was bright, alert, and responsive. A physical examination by the clinician found a large, oozing, erythematous mass measuring 8.4 cm x 4.8 cm near the midline dorsal aspect of his tail in the same area of the previously biopsied mass. Dental calculus was noted on his teeth, and the remainder of the physical examination was unremarkable. His diagnosis was likely a recurrent mast cell tumor of the midline dorsal tail. The initial prognosis was good to poor dependent on stage, treatment choice, and response to treatment.

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For staging, thoracic radiographs could have been performed to check for metastasis in the thoracic cavity, and an abdominal ultrasound could have been performed to check for metastasis in the abdominal cavity. A CT is the better alternative to an abdominal ultrasound when looking for intraabdominal lymph nodes in the pelvic area. Ultrasonic waves cannot pass through the pelvic bone, decreasing the visualization likelihood of the intrapelvic lymph nodes. In cases such as Ryuu, evaluation of the pelvic lymph nodes is the area of interest for staging, as the cluster of lymph nodes are the closest to the primary tumor site. There is a 55 % to 96 % chance with high-grade/grade 3 mast cell tumors metastasizing to the local lymph nodes. A buffy coat smear for mast cells also could have been run for evaluation of peripheral mastocytosis, but there was no suspicion for systemic disease because the patient was not experiencing symptoms of mastocytosis. These symptoms include vomiting, diarrhea, urticaria, and anaphylaxis. According to Vail et al. (2020), a CBC, chemistry panel, buffy coat smear, regional lymph node aspirate, abdominal ultrasound, splenic and/or liver aspirates (if indicated on abdominal ultrasound), thoracic radiographs, and bone marrow aspirate were the previous minimum required database. With current research, it is unlikely that a full, extensive work up is required as a minimum database unless the patient has negative prognostic indicators which include a high histologic grade, a high clinical stage, high cell proliferation rate, fast growth rate, local recurrence, systemic signs, large tumor, and some locations like subungual, oral, prepuce, and scrotum (Vail et al., 2020). Although Ryuu did have many negative prognostic factors, his staging consisted of a CT scan and liver and splenic aspirates.

The owners elected to be aggressive and stage the patient with a CT and possibly elect tail amputation. Baseline lab work consisted of a CBC and chemistry profile, and all values were

WNL. The patient was sedated with 5 mcg/kg of dexmedetomidine (5 mcg/kg x 56 kg = 280 mcg/500 mcg/mL = 0.56 mL) and 0.25 mg/kg of butorphanol (0.25 mg/kg x 56 kg = 14 mg / 10 mg/mL = 1.4mL) IV. Butorphanol was chosen as a sedation drug because of the short duration of analgesia effects, and dexmedetomidine was chosen because it is a reversable drug that has great sedative effects. A CT scan of the chest, abdomen, pelvis, and tail both pre- and post-contrast (600 mg/kg of iohexol was used for contrast (600 mg/kg x 56 kg = 33600 mg / 300 mg/mL = 112 mL) was performed for staging and surgical planning. The CT did not show changes of the liver or spleen, although, there is a high rate of metastasis for high-grade/grade 3 mast cell tumors (Vail et al., 2020). A fine needle aspirate of the liver was attempted, and a fine needle aspirate of the spleen was performed. The liver was unreachable for needle sampling due to the large size of the patient. Cytology of the spleen was negative for metastasis. This result was expected because the spleen had a normal appearance on the CT. A regional lymph node aspirate was not attempted due to location within the pelvis; however, all intra-pelvic lymph nodes were of a normal size and appearance. The patient's dexmedetomidine was reversed with 0.05 mg/kg of atipamezole (0.05 mg/kg x 56 kg = 2.8 mg / 5 mg /mL = 0.56 mL) IM. The patient was started on 1.8 mg/kg of diphenhydramine (1.8 mg/kg x 56 kg = 100 mg) PO BID to reduce the effects of local mast cell tumor histamine release and 1.07 mg/kg prednisone (1.07 mg/kg x 56 kg = 60 mg) PO SID for 7 days, then reduce to 0.71 mg/kg prednisone (0.71 mg/kg x 56 kg = 40 mg) PO SID until surgery to inhibit mast cell tumor proliferation. This patient was not started on famotidine, a histamine-2 blocker to prevent and treat gastric ulcers that can be caused by mast cell tumors. Ryuu had his tail amputated 11/17/22 at a different specialty hospital. Histopathology returned as a complely excise (11 cm from proximal margin of the mass grossly,

and not present in the section of proximal margin examined histologically) Kiupel low grade, Patnaik grade 2 mast cell per 10 HPF and no angiolymphatic invasion. Histopathology returned with a lower grade (low grade, grade two) than what it was when it was initially biopsied. This result was expected because the patient had been treated with steroids prior to surgeryor high-grade mast cell tumors, histologic margins of 3 cm laterally and one fascial plane deep is recommended. In one study, patients with a mitotic index of less than 5 per 10 HPF had a median survival time of 80 months compared to patients that had a mitotic index of greater than 5 per 10 HPF that had a median survival time of 3 months (Vail et al., 2020).

The patient returned on 12/21/22 to start weekly vinblastine chemotherapy. The patient's vitals were within normal limits and weighed 58.3 kg. However, a new, approximately 1 cm, erythematous and ulcerated mass just ventral to the anus, was noted on physical examination by the clinician. In-house fine-needle aspirate (FNA) and cytology of the mass, performed by the clinician, found sheets of round cells with many purple granules, diagnosing a new mast cell tumor. Ryuu was sedated with 5 mcg/kg dexmedetomidine (5 mcg/kg x 58.3 kg = 291.5 mcg / 500 mcg/mL = 0.58 mL) and 0.25 mg/kg butorphanol (0.25 mg/kg x 58.3 kg = 14.5 mg / 10 mg/mL = 1.4 mL) IV, and the mass was removed with an 8 mm punch biopsy tool by the clinician. While closing the incision from the punch biopsy, a new mass was noted along the scar. In-house FNA and cytology of the mass also found it to be a mast cell tumor. The owners declined mass removal along the scar and elected to treat him with weekly vinblastine chemotherapy. A CBC was performed to ensure his neutrophils and platelets were adequate for chemotherapy treatment. To receive chemotherapy treatment in the applicant's hospital, the neutrophils must be greater than 1.5 thousand (K)/microliter (uL) and platelets greater than 50

K/uL. At the applicant's hospital, there are not any specific guidelines for hematocrit, and it is at the discretion of the clinician. However, the clinician is notified if there is a significant drop in hematocrit. He was treated with 2.1 mg/squared meters (m2) of vinblastine (2.1 mg/m2 x 1.518 m2 = 3.18 mg / 1 mg/mL = 3.18 mL) IV as a bolus, without complication in the left cephalic vein. The patient's dexmedetomidine was reversed with 0.05 mg/kg of atipamezole (5 mg/mL) (2.9 mg; 0.58 mL) The patient was to continue 40 mg of prednisone (0.71 mg/kg) PO SID until otherwise directed and 100 mg of diphenhydramine (1.71 mg/kg) PO BID, and was sent home with 2.7 mg/kg maropitant (2.7 mg/kg x 58.3 kg = 160 mg) PO SID for 5 days to prevent nausea post chemotherapy. The goal of therapy for this patient was to slow the disease progression so the patient could have a good quality of life. The owners knew that the patient had a guarded to poor prognosis depending on how he responded to treatments.

The patient returned on 12/28/22 for his second dose of vinblastine, he tolerated the first dose well, with no reported side effects from his treatment. His CBC and vitals were within normal limits, and he weighed 56.8 kg. On physical examination, it was noted that there were several new, less than 1 cm nodules around the anus. His disease was progressive. His prognosis was changed to guarded/poor. Since he tolerated the first vinblastine well, the owners agreed to a dose escalation and did not want to switch treatments at this time. A dosage of 2.4 mg/m2 of vinblastine was administered (2.4 mg/m2 x 1.492 m2 = 3.58 mg / 1 mg/mL = 3.58 mL) IV as a bolus in the right cephalic vein without complication. He was sent home with 160 mg of maropitant (2.81 mg/kg) PO SID for 5 days post chemotherapy, and he was to continue both 40 mg of prednisone (0.7 mg/kg) PO SID until directed otherwise and 100 mg of diphenhydramine (1.76 mg/kg) PO BID.

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The patient returned on 1/4/23 for his third dose of vinblastine, and he was reportedly doing great with no side effects from treatment. His CBC and vitals were within normal limits, and he weighed 58 kg. The patient's masses were stable, all measuring less than 1 cm. The patient tolerated the vinblastine dose increase well, and he was dose escalated again. He received a dosage of 2.6 mg/m2 vinblastine (2.6 mg/m2 x 1.514 m2 = 3.93 mg / 1 mg/mL = 3.93 mL) IV as a bolus in the right saphenous vein without complication. He was sent home with 160 mg of maropitant (2.76 mg/kg) PO SID to prevent nausea for 5 days post chemotherapy and was to continue 40 mg of prednisone (0.69 mg/kg) PO SID until directed otherwise and 100 mg of diphenhydramine (1.72~~6~~ mg/kg) PO BID.

The patient returned on 1/11/23 for his fourth dose of vinblastine, he was doing well aside from some reported side effects from the prednisone (voracious appetite and urinary accidents in the house). His CBC and vitals were within normal limits except for a mild decrease in red blood cells likely due to his disease progressing (4.72 million per microliter (M/uL) normal: 5.1 - 8.5 M/uL), and he weighed 57 kg. The patient's masses were larger (one mass measured 2.5 cm and another measured 2 cm) than they were previously on physical examination. The patient's vinblastine dosage increased again to 2.8 mg/m2 (2.8 mg/m2 x 1.495 m2 = 4.19 mg / 1 mg/mL = 4.19 mL) IV as a bolus in the left saphenous vein without complication. He was sent home with 160 mg of maropitant (2.8 mg/kg) PO SID to for 5 days post chemotherapy, and he was to reduce his prednisone down to 10 mg (0.35 mg/kg) PO SID until directed otherwise and 100 mg of diphenhydramine (1.75 mg/kg) PO BID. The plan was to switch his chemotherapy to toceranib phosphate the next week instead of continuing vinblastine

if his masses were still progressing. Toceranib phosphate is indicated for treatment of grade 2 or 3, recurrent, or cutaneous mast cell tumors, and it is well tolerated.

The patient returned on 1/18/23 and weighed 57.9 kg. Physical examination noted that his masses were even larger (2.8 cm and 2.1 cm) and inflamed, and he switched to toceranib phosphate. A CBC, chemistry panel, urinalysis, and blood pressure were performed for a baseline prior to starting toceranib phosphate. Toceranib phosphate can cause proteinuria and elevated systolic blood pressure which is why a urinalysis and blood pressure are routinely performed. His ALT was noted to be mildly elevated (130 international units per liter (IU/L) (normal: 12 – 188 IU/L) which was suspected to be due to prednisone usage. His CBC, urinalysis, and blood pressure were within normal limits. He started on 160 mg of maropitant (2.76 mg/kg) PO on Mondays, Wednesdays, and Fridays to prevent nausea from the toceranib phosphate and 150 mg of toceranib phosphate (2.6 mg/kg x 57.9 kg = 150 mg) PO on Mondays, Wednesdays, and Fridays. He continued his previously prescribed doses of prednisone and diphenhydramine.

The patient returned on 2/1/23 for a two-week toceranib phosphate recheck and weighed 57 kg. The owners reported that the patient had been doing well and the masses were less inflamed and had gotten smaller. On physical examination, the masses were slightly smaller (2.6 cm and 2.0 cm) and much less inflamed. The patient's CBC was within normal limits, and he was to continue the previously prescribed doses of maropitant, toceranib phosphate, prednisone and diphenhydramine.

The patient returned on 2/15/23 for a one-month toceranib phosphate recheck and weighed 58.3 kg. The owners reported that the patient had a great appetite recently, but his

activity level had decreased. He was also having pain when defecating, and the owners noted that the masses were getting larger and had started bleeding the day prior. The patient's vitals were normal. Physical examination found all the masses to be larger (3 cm and 2.6 cm) and some bleeding. The owner's elected to discontinue toceranib phosphate therapy and to pursue palliative care at home. The patient was to continue 20 mg of prednisone (0.34 mg/kg) PO SID and 100 mg of diphenhydramine (1.71 mg/kg) PO BID. He was started on 600 mg of gabapentin (10.29 mg/kg x 58.3 kg = 600 mg) PO BID – TID for pain relief from the bleeding masses.

The patient was euthanized on 3/16/23 due to progressive disease and quality of life concerns. The patient was not necropsied.

Canine mast cell tumors are one of the most common skin tumors in dogs, and their behavior within the body varies greatly (Sabattini et al., 2014). Their purple-staining cytoplasmic granules within and around round cells are characteristic for canine mast cells (Vail et al., 2020). Mast cells can be found throughout the body, but all mast cell precursors are made in the bone marrow (Vail et al., 2020). Mast cells are a part of the inflammatory response in the body, mostly allergic reactions. In Ryuu's case, the mast cell tumor was high grade according to the Kiupel system and a grade 3 according to the Patnaik system. Ryuu's mast cell tumor was histologically high grade and was expected to act aggressively and metastasize if there was no intervention. Although there was no evidence of metastatic disease found within the body, the tumors acted locally aggressive which was to be expected for his tumor. Despite complete excision of the mass, high grade/grade 3 mast cell tumors have a 40% chance of recurring (Meuten, 2017). Ryuu had recurrence along the scar and a new location (ventral to the anus) just 5 weeks after his tail amputation surgery. The patient's quality of life was affected by the gross mast cell

tumors because of pain and bleeding that occurred from degranulation of the mast cell tumors. The symptoms of nausea and vomiting develops due to the histamine release from the mast cell tumors stimulating gastric histamine-2 receptors that causes overproduction of hydrochloric acid which ultimately causes ulceration and bleeding of the gastric wall (Meuten, 2017).

The etiology of most cancers is unknown. Previously, dogs with chronically inflamed skin were thought to be predisposed to developing mast cell tumors (Vail et al., 2020). However, it is now thought that there is an underlying genetic change that predisposes certain breeds (Golden Retrievers, Labrador Retrievers, Boxers, Boston Terriers, and Pugs) to mast cell tumors (Garrett, 2014). A mast cell tumor can be found anywhere on the body. This includes both cutaneous (more common) and subcutaneous lesions. They can also vary in appearance (Garrett, 2014). For Ryuu, his mast cell tumors were erythematous and ulcerated. Ryuu did not have a breed predilection as he was an Alaskan Malamute. High grade and grade three mast cell tumors typically grow very quickly and become ulcerated and irritated (Vail et al., 2020). Small nodules, called satellite nodules, may develop in the area surrounding the mass (Vail et al., 2020). In the case of this patient, the mass grew quickly, became ulcerated, and satellite masses grew as well. Mast cell tumors are most likely to metastasize to the regional lymph nodes, liver, and spleen, however, this patient did not have any evidence of lymph node or distant metastasis (Meuten, 2017).

The applicant's advanced skills influenced the patient's course of treatment and outcome by being able to identify changes (examples: increase in appetite, decrease in activity level, pain while defecating) at home from taking a detailed history and monitoring his quality of life. The applicant also monitored the patient’s masses throughout the course of treatment by taking

measurements at each appointment and monitoring his lab work. Things the applicant watched for were anemia, thrombocytopenia, neutropenia, proteinuria, and hypertension.

The applicant's advanced knowledge influenced the patient's course of treatment and outcome because the applicant was able to talk to the owners about the patient's quality of life. When Ryuu's masses started breaking open and bleeding, the owners knew it was time to move on to another treatment. Due to finances, radiation treatment was not an option for them. Ryuu was in pain and having trouble defecating caused by the intrusive masses surrounding the anus. The applicant told the owners that without further treatment, the masses would continue to grow, bleed, and ultimately rupture. This would cause significant pain for Ryuu. This influenced their decision to humanely euthanize when they thought the time was right instead of waiting until Ryuu had unmanageable pain and the masses were bleeding uncontrollably.

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