

“Lymph Nodes, Liver, and Spleen, Oh My!”

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Introduction:

Lymphosarcoma (lymphoma) is not only the most common hematopoietic neoplasia seen in dogs, but also the most commonly diagnosed of all canine neoplasias.^{2, 11} About 80% of lymphomas are multicentric, high-grade, and originate in the lymph nodes, however, lymphoma can affect any organ in the body.^{2, 11} Middle aged to older dogs are more commonly affected and breeds that are predisposed include, but are not limited to, boxers, bulldogs, golden retrievers, Scottish terriers, pitbulls, and St. Bernards.^{7,9, 11} Since lymphoma is a systemic neoplasia, chemotherapy is the best treatment option.³ The goal of chemotherapy in veterinary oncology is to induce remission, not cure. 60-90% of multicentric lymphomas achieve remission through chemotherapy and the median survival time ranges from 6-12 months.³

History and Presentation:

Rags, an 8-year-old female spayed golden retriever, presented to Mississippi State College of Veterinary Medicine on July 30, 2021 for an oncology consultation. A few days prior to presentation, Rags' owner noticed large, firm masses under her jaw and took Rags to her primary veterinarian for evaluation. The owner noted that Rags also had a decreased appetite at the time of presentation, but otherwise seemed normal. Fine needle aspiration was performed on her enlarged submandibular lymph nodes by her primary vet, and lymphoma was diagnosed by the pathologist. Rags was then referred to MSU-CVM Oncology Department.

Upon presentation, Rags was bright, alert, and responsive. She weighed 33 kilograms and had a body condition score of 7/9. All vital parameters were within normal limits with a rectal temperature of 103.4 degrees Fahrenheit, a pulse of 70 beats per minute, and she was panting with normal respiratory effort. Mucus membranes were pink and moist with a capillary refill

time of less than 2 seconds and there was no nasal, ocular, or aural discharge. A small uveal cyst was present in the anterior chamber of her right eye. On cardiothoracic auscultation, no murmurs or arrhythmias were heard, and all lung quadrants were free of crackles and wheezes. Strong, synchronous femoral pulses were appreciated. Her abdomen was soft with no evidence of pain or distension on palpation. Rags' submandibular, prescapular, popliteal, and inguinal lymph nodes were firm and markedly enlarged bilaterally.

Diagnostic Approach:

A thorough physical examination was performed on presentation and diagnostic options were discussed with the owner, along with treatment and prognosis. The owner elected to pursue staging diagnostics, including a complete blood count (CBC), thoracic radiographs, abdominal radiographs, abdominal ultrasound with liver, spleen, and lymph node aspirates, and flow cytometry.¹⁰

Lymphoma is categorized into 5 stages depending on extent and location of the cancer. Stage I involves a single lymph node, stage II involves lymph nodes on one side of the diaphragm, stage III has a general lymphadenopathy, stage IV involves the liver and spleen, and stage V involves any other organ such as the bone marrow, eye, or nervous system.^{5,10}

Lymphoma can then be further substaged as "A" or "B" depending on how the dog feels at time of diagnosis. "A" means the dog is not exhibiting clinical signs consistent with disease and "B" means there are clinical signs indicating disease.^{5,10,11} Most dogs present at a minimum of stage III as this is typically when owners notice the enlarged peripheral lymph nodes.⁷

Thoracic radiographs for Rags were unremarkable and showed no evidence of pulmonary metastasis, and abdominal radiographs revealed hepatomegaly and splenomegaly. Differentials

for the enlarged liver include neoplasia, endocrinopathy, inflammation, and nodular regeneration; differentials for splenomegaly include neoplasia, lymphoid hyperplasia, and extramedullary hematopoiesis. On ultrasound of the abdomen, the liver appeared normal, and the spleen was diffusely enlarged with hypoechoic nodules measuring less than 5mm throughout the parenchyma. Multiple enlarged lymph nodes were appreciated on ultrasound, and aspirates were taken of the left medial iliac lymph node along with the spleen and liver. Cytology results of the liver and spleen aspirates were consistent with lymphoma and showed large numbers of medium to large lymphocytes. The aspirate of the left medial iliac lymph node was nondiagnostic. Her complete blood count was within normal limits aside from a mild lymphocytosis of 7,329.9 μ /L (normal range: 1,110-4,800 μ /L). Flow cytometry showed a cell population primarily consisting of B-lymphocytes consistent with B-cell lymphoma. Rags' diagnostics proved she had lymphoma in her lymph nodes, liver, and spleen, and her initial lymphocytosis suggested bone marrow involvement. Rags was diagnosed with multicentric B-cell lymphoma, suspect stage VB. While staging is important in knowing if the cancer has spread, B-cell versus T-cell, and prognosis, it does not change how the cancer is treated or give us information on remission or survival rate.⁵ For Rags to have received complete staging, a bone marrow biopsy would have been done, however, there was already a strong suspicion of bone marrow involvement due to her initial lymphocytosis.⁵ Since Rags already had a definitive diagnosis of lymphoma and was starting the CHOP chemotherapy protocol, there was no need to pursue the bone marrow biopsy.^{5,9}

Pathophysiology:

Lymphoma is a neoplasia of lymphocytes that can be categorized as B-cell or T-cell in origin. This neoplasia can originate in any organ of the body but most commonly arises from the

lymph nodes or other lymphoid tissue.¹⁰ B-cell lymphoma is much more common accounting for approximately 70% while T-cell constitutes 30%.¹¹ Immunophenotyping through flow cytometry is helpful in distinguishing between the two types. Flow cytometry is a tool that tags specific cell molecules such as receptors or proteins with fluorescent markers.⁸ Cells are then transmitted single file through a laser beam where information can be taken about the cell type based on the fluoresced cell marker.⁸

Several common negative prognostic factors associated with lymphoma include hypercalcemia, mediastinal lymphadenopathy, and advanced stage (IV or V, substage b) at the time of diagnosis.⁹ Hypercalcemia is more common in T-cell lymphoma when the CD4 T-cells produce parathyroid hormone related peptide (PTH-rP).¹¹ This increase in calcium decreases the effect of antidiuretic hormone on the collecting ducts and causes vasoconstriction of the afferent glomerular artery which can result in acute renal failure.¹¹ Patients with mediastinal lymphadenopathy or a mediastinal mass can present in respiratory distress and typically have a poorer prognosis due to the common association between mediastinal lymphoma and T-cell lymphoma.^{9,11} Advanced disease including bone marrow involvement and the patient showing signs of disease at the time of diagnosis negatively impacts prognosis.^{9,11} Bone marrow involvement has been reported in 55% of dogs presenting for lymphoma, however, bone marrow biopsy is needed to confirm this and is rarely done due to the invasiveness of the procedure and because it has little effect on treatment.^{5,11}

Prognosis and Treatment:

Prognosis for lymphoma can vary depending on location of disease, B-cell versus T-cell, and treatment options. Multicentric lymphoma is treated with a multi-agent chemotherapy approach.³ CHOP is the gold standard and consists of vincristine, cyclophosphamide,

doxorubicin, and prednisone.³ The chemotherapy agents are rotated through cycles being given once a week with prednisone being given over the first 4 weeks on a tapering dose.³ This protocol can be administered over 15, 19, or 25 weeks.³ There is no evidence supporting that length of the protocol influences efficacy of the treatment; length is more tailored to client finances and logistics.³ Complete blood counts are checked prior to chemotherapy administration and one week post chemotherapy to ensure adequate neutrophil levels. When neutrophils fall below 2,000 μL , chemotherapy is stopped. If neutrophils are below 1,000 μL , prophylactic antibiotics are started to prevent infection.³ B-cell lymphoma treated with CHOP has a median survival time of 12 months and T-cell lymphoma treated with CHOP has a median survival time of 6-9 months.³ About 80-95% of dogs will go into remission on the CHOP protocol, however they will eventually relapse.³ If the first CHOP treatment induces remission and relapse occurs, a second CHOP cycle can be started.⁹ After 2 CHOP cycles, a different chemotherapy protocol is typically required as drug resistance can occur due to the overexpression of MDR1 (ABCB1) genes.⁹ These genes are responsible for removing cytotoxic drugs from cells and overexpression can decrease chemotherapy efficacy.⁹

Tanovea is a new chemotherapy agent, conditionally approved by the FDA, that has been shown to induce remission in 74% of dogs with B-cell lymphoma that have previously come out of remission.² Tanovea is administered every 3 weeks for 5 doses.⁴ Glucocorticoids such as prednisone induce apoptosis and cell cycle arrest.^{6,9} Administration of prednisone can reduce lymphoma burden and lymph node size; however, it is imperative to remember that chemotherapy will be less effective if the patient is already on prednisone.⁶ If lymphoma is treated solely with prednisone, median survival time is about 50 days.⁶

Chemotherapy in veterinary patients is relatively safe and most owners report no decrease in quality of life after receiving treatment.² In one study assessing adverse effects in chemotherapy patients, 50.5% showed no adverse effects while 49.5% did.² Of the patients with side effects, most were consistent with gastrointestinal upset or neutropenia.² Specific side effects associated with the chemotherapy used in the CHOP vary based on species. In dogs, vincristine is relatively safe but can cause GI upset and is a vesicant.¹⁰ If extravasation occurs, 10mL saline should be administered at the site and a warm compress should be applied.¹⁰ Cyclophosphamide can cause a sterile hemorrhagic cystitis and it is important that dogs being given this medication are able to urinate frequently throughout the day and no blood is observed in the urine.¹⁰ Doxorubicin has been linked to anaphylaxis and has cumulative cardiotoxic effects resembling dilated cardiomyopathy.¹⁰ It is important to monitor cardiac function while on this medication especially when more than 6 doses have been given.¹⁰ Doxorubicin is also a severe vesicant.¹⁰ If any extravasation occurs, immediate intervention is required to control and minimize tissue damage caused from the chemotherapy.¹⁰

Case Outcome and Conclusion:

After Rags completed her staging diagnostics, she was started on the 15-week CHOP chemotherapy protocol. She completed her first cycle and was determined to be in remission once her lymph nodes decreased to normal size. After her first dose of doxorubicin, Rags developed a hepatopathy that was most likely related to a trazadone sensitivity. Although trazadone induced hepatotoxicity is rare, one study showed a dog maintained progressively elevated liver enzymes until the trazadone was discontinued.¹ During her second cycle, premature ventricular contractions were seen on her electrocardiogram, and she was switched from doxorubicin to mitoxantrone to avoid the cumulative cardiotoxic effects. One week after

mitoxantrone was administered Rags developed a grade IV neutropenia and was started on antibiotics. When Rags presented for her fourth cycle of CHOP, she was out of remission and different chemotherapy protocols were discussed with the owner. It is likely Rags developed a chemotherapy resistance to the drugs she was taking with CHOP, and a new protocol would induce remission again. Rags' owner elected to continue treatment with Tanovea. After her first dose, Rags became inappetent and icteric. She had an increased alanine transaminase (ALT) and alkaline phosphatase (ALP). She was hospitalized at her primary vet and treated for her hepatopathy with little improvement. Based on her rapid decline in health and quality of life, her owner elected humane euthanasia. At this time, Rags' lymph nodes were normal in size and she appeared to be in remission. A postmortem liver cytology was done to determine if her hepatopathy was related to the Tanovea or if she had underlying liver disease that could have contributed to her previous hepatopathy. Cytology showed diffuse lymphoma infiltration with no underlying disease.

Canine lymphoma has been treated and researched in the veterinary field for decades. The number of cases diagnosed and treated with successful remission and prolonged life through chemotherapy continue to grow. Unfortunately, Rags did not surpass her estimated median survival time, but the few extra months she got with her owner were cherished and her quality of life was maintained for the majority of her treatment.

Citations:

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