

Kitty's Itty-Bitty Problem

A Case of Feline Gastrointestinal Lymphoma

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Introduction

Lymphoma (LSA) is considered one of the most common neoplasms in the cat, with GI LSA causing up to 70% of reported cases of feline lymphoma specifically.⁵ Older cats commonly tend to present, with a median age of 9-13 years old.⁶ The most common presenting complaints include gastrointestinal signs such as vomiting, diarrhea, anorexia, and weight loss. Gastrointestinal lymphoma can be classified as either low grade or high grade. Low grade is typically classified as a small cell (lymphocytic) GI lymphoma, whereas high grade is characterized as a large cell (lymphoblastic) GI lymphoma. The type of gastrointestinal lymphoma that is most commonly diagnosed among feline patients is low grade or small cell lymphoma. Histological cell type (small cell versus large cell) is a strong predictor of a patient's response to treatment and their estimated survival time. Small cell GI lymphoma tends to have a good prognosis while large cell GI lymphoma tends to have a poor prognosis. This report describes a case of gastrointestinal lymphoma in a feline patient who initially presented for weight loss and alopecia.

History and Presentation

Kitty, a 15-year-old male neutered domestic longhair cat, presented to the Mississippi State College of Veterinary Medicine (MSU-CVM) Internal Medicine Department on July 18, 2018 for weight loss and alopecia. Approximately 4 months prior to presentation, Kitty began scratching at his back and around his neck. A Seresto collar was being used for the prevention of fleas and ticks around the time that his dermatological issues began. At that time, the collar was removed and according to his owners, his clinical signs have only gotten worse. Kitty had previously been diagnosed by his referring veterinarian with a flea allergy dermatitis. His owners reported that they had not seen any fleas present; however, Kitty is an indoor/outdoor cat

who spends the majority of his time outside. Kitty had also been steadily losing weight since January 2018. He had lost approximately 4 pounds according to his previous medical records. According to his owners, Kitty also had a 2-week history of inappetence where he was not interested in eating dry food and was only licking at his wet food. His normal diet consisted of Hill's Sensitive Skin and Stomach. Kitty's owners also reported that he vomits 2-3 times per week as well as noted that recently he had been waking them up in the middle of the night to drink from the faucet. No changes in urination were described. Kitty had also been more vocal and lethargic as of recently. Kitty was not on any medications at the time.

On presentation, Kitty was bright, alert, and responsive. He weighed 5.12 kilograms (11.26 pounds) and was given a body condition score of 3/9. His vital parameters were within normal limits with a temperature of 101.7°F, a pulse of 192 beats per minute, and a respiratory rate of 40 breaths per minute. His mucous membranes were tacky and appeared pale pink. Due to his gum pallor, a capillary refill time could not be assessed. He had mildly increased skin turgor and was estimated to be about 8% dehydrated. On thoracic auscultation, normal bronchovesicular sounds were heard in all lung fields. On cardiac auscultation, no murmurs or arrhythmias were heard. Areas of alopecia with crusty lesions were present on his dorsum as well as the left side of his neck. A thyroid slip could not be appreciated. His abdomen was soft and non-painful with no other apparent abnormalities felt upon palpation. The remainder of his physical exam was within normal limits.

Diagnostic Approach/Considerations

Blood was collected for a CBC, chemistry panel, and send-out thyroid panel. The CBC revealed a moderate lymphocytosis (12789 /ul), a mild leukocytosis (26.1 K/ul) and a moderate eosinophilia (2871 /ul). Due to the increase in lymphocytes, a blood smear was performed. The

slide showed numerous small, normal appearing lymphocytes. The chemistry panel was unremarkable, and the thyroid panel was within normal limits. Urine was collected via a voided sample. The urinalysis revealed a mild proteinuria (1+), mild hematuria (1-5), and mild leukocyturia (1-5). However, these results were attributed to the voided nature of the sample due to Kitty's lack of clinical signs. At this point, Kitty's most significant problems included a moderate lymphocytosis, weight loss, vomiting, inappetence, dehydration, and lethargy. Based on Kitty's history and physical exam, our top differentials consisted of lymphoma and inflammatory bowel disease (IBD). In order to make a definitive diagnosis, further diagnostics were warranted. Kitty was sedated with butorphanol and dexmedetomidine in order to perform radiographs and ultrasound. The abdominal radiographs revealed multiple segments of small bowel containing a moderate volume of gas and splenomegaly. Incidental findings included a left nephrolithiasis and bilateral coxofemoral degenerative osteoarthritis. The thoracic radiographs revealed an enlarged cardiac silhouette and a rightward mediastinal shift with an ovoid, sharply marginated soft tissue opaque structure within the cranial mediastinum. This structure was most likely due to the effects of sedation and prolonged lateral recumbency. A mild interstitial pulmonary pattern was also observed. Incidental findings included multiple degenerative changes such as chronic intervertebral disc disease and spondylosis deformans. The abdominal ultrasound revealed multiple enlarged jejunal, aortic, lumbar, mesenteric, and sacral lymph nodes. The small intestines were of normal thickness but had a diffusely thickened muscularis layer. Ultrasound-guided fine needle aspirates of the mesenteric lymph nodes were performed and revealed mostly normal appearing small lymphocytes; however, no definitive diagnosis could be confirmed based on this cytological evidence alone. As Kitty's problem list now included enlarged gastrointestinal lymph nodes and a diffusely thickened muscularis layer

of the small intestine, a biopsy procedure was discussed with Kitty's owner in order to obtain a definitive diagnosis with histopathology. Two options were explained to Kitty's owners. These included a surgical biopsy and an endoscopy procedure. After reviewing the pros and cons of each procedure, Kitty's owners opted for the less invasive and cheaper option of an endoscopy procedure, knowing that the partial thickness biopsy samples may not yield a definitive diagnosis. Kitty was sent home for the night with instructions to return the following morning for his biopsy procedure.

The following morning, Kitty was sedated with butorphanol and dexmedetomidine in order to place an IV catheter. Intravenous fluids were started to rehydrate Kitty, as he was previously estimated to be moderately dehydrated (~ 8%). A gastroduodenoscopy procedure was performed under general anesthesia. During the procedure, Kitty became bradycardic but was treated with glycopyrrolate and Vetstarch after which his heartrate normalized. There were no complications throughout the remainder of the procedure. During the gastroduodenoscopy, the stomach appeared normal; however, the duodenum did have a "cobblestone" appearance. Sixteen biopsy samples were taken from the duodenum and twelve biopsy samples were taken from the stomach. These samples were submitted for histopathology. Two biopsy samples were also taken from the duodenum and impression smears were made and submitted for cytology. The results of the cytology revealed lymphocytic, neutrophilic, and mildly macrophagic inflammation. Kitty recovered from anesthesia without any complications and was discharged. His owners were instructed to monitor him for any worsening in his clinical signs until the biopsy results became available.

The following week, the histopathology results revealed that the lamina propria were infiltrated and expanded by a monotonous population of neoplastic lymphocytes. The

lymphocytes had scant cytoplasm and small hyperchromatic nuclei with condensed chromatin and multiple prominent nucleoli. Mitotic figures were less than one per high power field. Neoplastic lymphocytes were present in clusters within the mucosal epithelium. These results confirmed that Kitty had gastrointestinal lymphoma. The neoplastic cells were described as small and well differentiated correlating with a small cell lymphoma. An immunohistochemistry for immunophenotyping was also performed and revealed that the neoplastic lymphocytes were CD3+, indicating a uniform population of T-cells consistent with small cell GI lymphoma.

Pathophysiology

Lymphoma affects the lymphatic system and involves multiple organs and tissues, including the lymph nodes, bone marrow, spleen, thymus, and gut-associated lymphoid tissue (GALT). The gastrointestinal tract harbors the largest population of lymphoid and accessory immune cells in the body.⁵ Gastrointestinal lymphoma in cats is characterized by infiltration of neoplastic lymphocytes particularly in the wall of the GI tract where they can cause significant damage to the mucosal epithelium. These lymphocytes can sometimes extend into the nearby draining lymph nodes as well. GI lymphoma can be classified as either low grade or high grade. Low grade GI lymphoma is often considered to be a disorder affecting T-cell lineage, whereas high grade GI lymphoma is usually characterized by a uniform population of B-cells. Cats are most commonly diagnosed with low grade gastrointestinal lymphoma. This is because the diffuse, mucosal associated lymphoid tissue (MALT) of the small intestine, which consists of lamina propria compartments (LPC) and intraepithelial compartments (IEC), is populated largely by CD3 T-cells in normal cats.^{1,5} There are many risk factors thought to be associated with gastrointestinal lymphoma. It has been proposed that inflammatory bowel disease may be a precursor to lymphoid malignancy.⁴ This is due to the fact that cats are highly sensitive to

inflammatory processes such as IBD. This chronic inflammation causes them to become susceptible to multiple neoplastic diseases including GI lymphoma. Other studies have shown that feline leukemia virus (FeLV) and cigarette smoke in the environment may also play a role in contributing to the development of lymphoma. In one study, cats with cigarette smoke exposure had a 2.4-fold increased risk of developing lymphoma.⁸ Cats with more than 5 years of environmental tobacco smoke exposure had a 3.2-fold relative risk.⁸ FeLV is a directly oncogenic retrovirus. Another study showed that cats who test positive will have a 60-fold increased risk of lymphoma development compared with negative status cats.¹ While these cats have an increased risk, the number of FeLV positive cats with gastrointestinal lymphoma specifically is actually quite low.

The most common presenting clinical signs of gastrointestinal lymphoma include vomiting, diarrhea, weight loss, and anorexia. These signs however, are often indistinguishable from inflammatory bowel disease, and a number of diagnostic tests must be performed in order to make a definitive diagnosis. In one study, ultrasonographic thickening of the muscularis layer of the small intestine was significantly associated with gastrointestinal lymphoma, especially T-cell in cats.⁹ While abdominal ultrasound and cytology are beneficial diagnostic tools, they are often non-diagnostic as generalized intestinal thickening as well as enlarged mesenteric lymph nodes are common in both gastrointestinal lymphoma and inflammatory bowel disease.⁴ Histopathology is the gold standard for determining a definitive diagnosis. Biopsies can be taken from the alimentary system by way of two different techniques. Either an endoscopy procedure or surgery can be performed to retrieve the biopsy samples. While endoscopy may be cheaper and less invasive, the samples may not always yield the best results as these are only partial thickness biopsy samples. Surgery to retrieve full thickness biopsy samples is often performed

in the cases where endoscopy is either not available or the results of the samples were inconclusive. Immunophenotyping is also a useful adjunctive technique to routine H&E for diagnosis of GI lymphoma.² This technique is often used to determine whether the lymphoma is either of T-cell or B-cell lineage. If a population appears to be uniform with either mostly T-cell or mostly B-cell, this would support a diagnosis of lymphoma. If a population appears to contain a mixture of these two cell types, this would however, support a diagnosis of IBD. Immunophenotyping can be determined by performing immunohistochemistry to detect the expression of CD3 (T-cell) and/or CD79a (B-cell) within the GI tract.⁵

Treatment and Management

The mainstay of treatment for feline low grade gastrointestinal lymphoma is oral chemotherapy and glucocorticoids. The chemotherapeutic agent used is chlorambucil, which can be given at a lower dose orally once every two days or at a higher dose orally once every two weeks. Due to Kitty's temperament, his owners elected for the higher dose once every two weeks. While there are obvious benefits to the high-dose pulse chlorambucil therapy, there can be some negative side effects to monitor for such as myelosuppression. It is important to monitor the white and red blood cell lines before administering any chemotherapy drugs. In this specific protocol, prednisolone is also given orally initially on a daily basis with the intent to taper the dose throughout the treatment. In one study, the use of chlorambucil and glucocorticoids were associated with a longer duration of remission (786 days) for cats with GI small cell lymphoma.⁷ Adverse effects are usually uncommon with this type of chemotherapy treatment and are easily treated with prompt supportive therapy.

As stated previously, Kitty was treated with oral chlorambucil and prednisolone. Oral Cerenia was given as well for additional supportive therapy. This anti-emetic medication was

prescribed for Kitty to prevent any nausea or vomiting that may be associated with either lymphoma and/or his chemotherapy treatment. Dietary modifications should also be considered as part of the treatment protocol for cats with lymphoma.³ In the wild, cats are intended to eat up to 8-10 multiple small meals a day in order to thrive. This is because the stomachs of cats are less distensible than dogs and they are not adapted to holding large amounts of food at any one time. With this, Kitty's owners were advised to feed him multiple small meals throughout the day to decrease any chance of vomiting and/or gastrointestinal upset. Due to the damage caused in the GI tract, cats with GI lymphoma are often not able to appropriately absorb vitamin B in their gut. Although we did not do this with Kitty, many cats are often supplemented with B12 injections for the first few weeks of treatment to decrease the risk of possible deficiencies.

Case Outcome

Kitty returned to the Mississippi State University College of Veterinary Medicine Oncology Department on June 26, 2018 for an oncology consult for his recently diagnosed small cell gastrointestinal lymphoma. A CBC was performed revealing a similar increase in lymphocyte numbers within his blood, as well as adequate numbers of red blood cells, white blood cells, and platelets for him to receive chemotherapy. Oral administration of medication is difficult for Kitty's owners and therefore a pulse dosing regimen for chlorambucil was started. A chemotherapy schedule was initiated, involving weekly rechecks for the first three weeks with two week rechecks thereafter at either MSU-CVM or Kitty's referring veterinarian. At this first recheck, Kitty was administered his first dose of chlorambucil and was started on prednisolone daily.

Kitty's most recent recheck at MSU-CVM took place on September 21, 2018. At this time, Kitty's owners report that he is doing very well at home and has an improved energy level.

He is now eating up to 3 cans of food spread out in multiple small meals throughout the day. He has been having normal stool and has had no recent episodes of vomiting. Previously, Kitty's owners had described that Kitty had developed an issue with urinating outside of the litterbox. This was however contributed to a behavioral problem as there were no indications of an infection seen on urinalysis via cystocentesis at a previous recheck appointment. A urine culture was also performed at this time which revealed no bacterial growth. Currently, Kitty is no longer eliminating inappropriately. However, Kitty's owners report that he has recently become polyuric and polydipsic since starting on prednisolone. His most recent weight was measured at 6.53 kilograms (14.36 pounds), indicating that he had a 28% weight gain since his initial visit in July 2018. Diagnostics were repeated at this time to reevaluate Kitty's current health. A CBC was performed and showed an improvement in the number of circulating lymphocytes as well as indicated adequate blood cell lines to receive his chemotherapy. A recheck abdominal ultrasound was also performed in which the results remained largely unchanged with no apparent worsening detected. Kitty's prednisolone dose has since been tapered and he is continuing to tolerate the high-dose pulse chlorambucil therapy.

The vast majority of cats affected with small cell gastrointestinal lymphoma respond very well to chemotherapy and can have a good quality of life during treatment. The prognosis for low grade gastrointestinal lymphoma is good in cats with the average survival time measuring approximately 2 years. In one study, Cats that had low grade GI lymphoma had a more favorable outcome when treated with oral prednisolone and high-dose pulse chlorambucil as compared to cats that had high grade GI lymphoma treated with multiagent injectable chemotherapy.⁴

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