Treatment of Two Cats with Advanced Nasal Lymphoma with Orthovoltage Radiation Therapy and Systemic Chemotherapy

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ABSTRACT

Background: Feline nasal lymphoma is generally a localized and radiosensitive tumor. Treatment options include radiation therapy, chemotherapy, or a combination of both treatments. Chemotherapy alone is generally not effective, leading to median survival times of 98 to 358 days, while RT alone or a combination of RT and chemotherapy lead to median survivals of 19 months and 955 days, respectively. Orthovoltage radiation therapy, the only radiation available in Brasil, has the disadvantage of being superficial, treating only tumors of 2 cm or less and causing marked skin side effects. The objective of this paper is to report two cases of advanced feline nasal lymphoma, with cribriform plate destruction and central nervous system invasion, successfully treated with orthovoltage radiation therapy and systemic chemotherapy.

Case: Two female mixed breed cats were presented with nasal discharge, sneezing and facial deformity. The second cat also had neurologic signalment. Definitive diagnosis in histopathology was lymphoma. Computed tomography revealed advanced disease in both cases, with intranasal mass, bone lysis, invasion of orbital space and central nervous system. Both cats were treated with radiation therapy combined with chemotherapy. The first case received radiation therapy for gross disease (12 daily fractions of 300 cGy, five times per week) and CCNU/prednisolone chemotherapy, while the second case received cytoreductive rhinotomy followed by radiation therapy (12 fractions of 300 cGy in a Monday-Wednesday-Friday schedule) and chemotherapy with COP protocol. Both cats had long term tumor control, superior to 1000 days. Radiation side effects were well tolerated and resolved with supportive treatment. Chemotherapy side effects was neutropenia, only observed in the first cat. One cat is still alive and in remission (1120 days after treatment), while the second cat died of unrelated cause (with no local tumor relapse) after 1011 days.

Discussion: Radiation therapy could be considered the mainstay of treatment for feline nasal lymphoma. However, given that lymphoma is generally a systemic disease, chemotherapy should also play a role in management of feline nasal lymphoma. In the current report, both radiation therapy and chemotherapy were prescribed as it was considered the most aggressive treatment option. All acute radiation therapy reactions (erythema, conjunctivitis and keratitis) resolved with supportive care in reported cats. The combination of therapies used in this case report resulted in extended progression free interval as well as survival times, of over 1000 days. This results exceeds survival times of cats with nasal lymphoma treated with chemotherapy alone or with prednisone alone. Megavoltage radiation has greater penetrability and is more effective in treating nasal tumors, particularly tumors located at greater depths from the skin surface. Orthovoltage radiation therapy has the disadvantage of being too superficial, treating tumors of 2 cm or less, with more skin side effects. As orthovoltage radiation is the only radiation therapy available in Brasil, it was used in both cats of this report and is efficient for appropriate long term tumor control. The presence of cribriform plate destruction at the time of diagnosis was considered to be a negative prognostic factor for both PFI and survival. However, in the reported cats, PFI and survival times were superior to 1000 days, even with cribriform plate destruction and central nervous system invasion. Feline nasal lymphoma should be aggressively treated by radiation therapy combined with systemic chemotherapy. These cats can benefit from long term tumor control and excellent quality of life after treatment.

Keywords: feline, nasal lymphoma, radiation therapy, chemotherapy, survival.
INTRODUCTION

Nasal tumours account for 1-8.4% of all tumours in cats [4,11,21]. In histopathological assessments, lymphomas account for 26-49% of nasal malignancies, followed by epithelial tumours such as adenocarcinoma and squamous cell carcinoma [2,15]. Nasal lymphoma is generally solitary and a radiosensitive tumor. The presenting clinical signs are mainly respiratory in nature, including nasal discharge, epistaxis, dyspnea and sneezing [10,21].

Treatment options include radiation therapy, chemotherapy, or a combination of both treatments [6,18]. Reports of treating feline nasal lymphoma with a chemotherapy alone are inconsistent, with median survival times of 98 days (3.1 months) in one study vs. a 75% 1-year survival in another [7,19]. Patients receiving no treatment or prednisone alone, have median survival time was only 22 days (0.7 months) [7,19]. When RT [17] or a combination of RT and chemotherapy [16] was used, the median survival was 19 months and 955 days, respectively.

Megavoltage radiation, with greater penetrability and more uniform absorption, would seem likely to be more effective in treating nasal tumors, particularly tumors located at greater depths from the skin surface [14]. However, reports of megavoltage radiation alone or in combination with surgical cytoreduction in dogs with nasal tumors show median survival times of 8.1 months (from completion of radiation therapy) [1], 12.8 months (from diagnosis) [12], 12.6 months (from completion of radiation therapy) [20] and 14.1 months (from hospitalization) [8]. Two studies reported better survival for dogs treated with orthovoltage than for those treated with megavoltage radiation therapy [1,9]. Orthovoltage radiation is the only radiation therapy available in Brazil until 2016.

The objective of this paper is to report two cases of advanced feline nasal lymphoma successfully treated with orthovoltage radiation therapy and systemic chemotherapy.

CASE

A 6-year-old female mixed breed cat was presented with nasal discharge, sneezing, nasal deformity and hyporexia. The clinical signs were present for one month and were getting worse. Several antibiotics had been used, with partial nasal discharge relief. Radiographs revealed bilateral nasal cavity opacification. An incisional biopsy had been performed ten days earlier and final diagnosis was nasal lymphoma. Thoracic radiographs and abdominal ultrasound revealed no evidence of other tumors, and blood results (hematology and biochemistry) were within normal limits.

A skull computed tomography was performed to determine tumor depth and invasion and radiation treatment planning. There were bilateral opacification of nasal cavity and a poorly defined intranasal mass originated on the left side, extending the turbinates and nasal choana, measuring about 2.3x1.3x3.3 cm (Figure 1). There was bone lysis of turbinates, nasal and maxillary bones and nasal septum. The mass was invading left orbital space. Additionally, tumor was causing cribriform plate lysis, with olfactory bulb invasion. Cervical lymph nodes had normal size and texture.

The source of radiation was an orthovoltage X-ray therapy machine (Stabilipan I) operated at 140 kV and 15 mA. The focal spot to skin distance was 30 cm. The half-value layer was 0.5 mm of Cu and the exposure rate was 60 cGy/min. Radiation was delivered via a single dorsal portal directed perpendicular to a line connecting the tip of the nose to the top of the head. Dose was calculated to the middle point of the tumor (at 1.5 cm depth) A 1-cm margin was added to the macroscopic tumor assessed in computed tomography. Left eye and brain were included in the radiation field.

Radiation was delivered in twelve 300 cGy daily fractions (Tuesday to saturday), to a total dose of 36 Gy. The cat was anesthetized with propofol (Propofol®), 4 mg kg⁻¹ intravenously in each fraction, in order to allow correct immobilization and positioning.

Tumor regression was observed in the first radiation fractions, with complete clinical response (of nasal discharge and deformity) in the second week of treatment. Side effects of radiation therapy started in the third week of treatment (in the 11th fraction), and included epilation, erythema, conjunctivitis, keratitis and rhinitis, that resolved within two weeks of supportive treatment (with topical antiinflammatory and antibiotic) and elisabethan e-collar (Figure 1). Epilation persisted for about three months, and hair coat started growing again with a different collar.

Chemotherapy was started one week after radiation therapy completion. Lomustine (Citostal®) was planned at a dose of 60 mg m⁻² every six weeks, for a total of four doses. Blood exams were performed after seven days of lomustine administration and two days
before the next chemotherapy. Prednisolone (Prelone®)^3 2 mg kg\(^{-1}\), SID, orally as given during six months. After one week of first lomustine dose, the animal had severe neutropenia (300 neutrophils/mm\(^3\)), and was treated with filgrasin (Filgrastim®)^3 5 µg kg\(^{-1}\), SID, subcutaneously for three days and amoxicillin with clavulanate (Synulox®)^4 12.5 mg kg\(^{-1}\), BID, orally for seven days. In the subsequent treatments, lomustine was given at a reduced dose of 50 mg/m\(^2\), with no more side effects observed. After 60 days of radiation therapy, the owner was asked to repeat skull computed tomography. However, due to financial constraints, only skull radiographs were performed, and revealed no abnormalities (Figure 1). The cat is still in complete remission and with absence of respiratory clinical signs, after 1120 days of treatment.

A 13-year-old female mixed breed cat was presented with exophthalmia, facial deformity, sneez-
ing, unilateral nasal discharge, hyporexia and neurologic signs. The animal was walking compulsively, sometimes in circles. Citology (fine needle aspiration) was suggestive of malignant neoplasia, but could not conclude its origin.

Abdominal ultrasound revealed a mesenteric lymph node enlargement (1.5 x 1.1 cm). Blood results revealed mild azotemia (creatinine 1.9 mg/dL; ref 0.5-1.8 mg/dL and BUN 88 mg/dL; ref 5-60 mg/dL) and leukopenia (leukocytes 4,300 cels/μL). Echodoppler revealed hypertrophic cardiomyopathy, and diltiazem (Cardizem®) 0.5 mg kg⁻¹, SID, and benazepril (Fortekor®) 0.5 mg kg⁻¹, SID, orally were prescribed continuously.

A skull computed tomography was performed, which revealed an heterogeneous mass, measuring about 4.1x3.0x3.5 cm, blocking the entire right nasal cavity, with bone lysis in turbinate and maxillary bones, invasion of nasal choana and right orbital space (Figure 2). There was invasion of nasal choana and right orbital space, displacing laterally and rostrally the eyeball. There was brain invasion, with an area of low attenuation in the right cerebral hemisphere, causing deviation from the midline to the left. There was secondary sinusitis. Retropharingeal lymph nodes were slightly enlarged, with normal texture.

Due to the extensive size of the intranasal mass, a rhinotomy was performed before radiation therapy, with the objective of cytoreduction and his-

Figure 2. Treatment of cat with advanced nasal lymphoma with cytoreductive rhinotomy, radiation therapy and chemotherapy. A- Skull computed tomography revealing a mass in the right nasal cavity (red arrow), with bone lysis in turbinate and maxillary bones, invasion of nasal choana and right orbital space (blue arrow). B- Facial deformity before treatment. C and D- Cytoreductive rhinotomy. E- Cat after two years of treatment. F- Computed tomography after two months after radiation therapy completion.
topathologic examination of the tumor (Figure 2). A midline incision was made from caudal to the nasal planum to frontal bone. An unilateral bone flap was created using an osteotome. The mass was removed. The nasal cavity was flushed before closure. Bleeding occurred after surgery and lasted for three days. An irreparable corneal injury was present in the right eye and it was enucleated. An esophageal tube was placed for medication and feeding. Post surgery analgesia included meloxicam (Maxicam®) 0.1 mg kg⁻¹, SID, subcutaneously for four days, tramadol (Cronidor®) 2 mg kg⁻¹, BID, subcutaneously for seven days and dipirone (Novalgina®) 25 mg kg⁻¹, BID, subcutaneously for five days. Histopathology revealed diffuse lymphoma of intermediate grade.

Radiation therapy was started after five days of cytoreductive surgery. The source of radiation was an orthovoltage X-ray therapy machine (Stabilipan I) operated at 140 kV and 15 mA. The focal spot to skin distance was 30 cm. The half-value layer was 0.5 mm of Cu and the exposure rate was 60 cGy/min. Radiation was delivered via a single dorsal portal directed perpendicular to a line connecting the tip of the nose to the top of the head. Dose was calculated to 1.0 cm depth. A 1-cm margin was added to the macroscopic tumor assessed in computed tomography before surgery.

Radiation was delivered in twelve 300 cGy fractions (on a Monday-Wednesday-Friday schedule), to a total dose of 36 Gy. The animal was anesthetized with propofol (4 mg/kg intravenously) in each fraction, in order to allow correct immobilization and positioning. Side effects of radiation therapy started in the fourth week of treatment, and included only epilation and mild erythema. Esophageal tube was removed in the completion of radiation therapy, as the cat was eating normally.

Chemotherapy (with COP protocol – vincristine, cyclophosphamide and prednisolone) was started two weeks after radiation therapy. Vincristine (Tecnoris®) 0.75 mg m² intravenously was administered weekly in the first month and every three weeks during one year. Cyclophosphamide (Genuxal®) 50 mg m² orally for four consecutive days (starting after two days of vincristine) was administered every three weeks during one year. Prednisolone 2 mg kg⁻¹, SID, orally was administered during the whole protocol. Subcutaneous fluid therapy (150 mL subcutaneously once a week) was prescribed together with chemotherapy. Ondansetron (Vonau®) 0.5 mg kg⁻¹, BID, orally was administered always in the first seven days after each chemotherapy session. The treatment was well tolerated, with minimal toxicity.

Computed tomography was repeated after two and twelve months after treatment, with no evidence of tumor relapse (Figure 2). Abdominal ultrasounds, performed every three months, revealed slight mesenteric lymph node enlargement (0.8 x 0.6 cm). Blood results, performed every three months, revealed mild azotemia.

Complete clinical remission of the tumor was observed in the following 1011 days. However, dyspnea was observed due to pleural effusion, which was attributed to a possible mediastinal lymphoma or cardiomyopathy descompensation. Citology of pleural effusion revealed no malignant cells, but the animal was euthanized due to poor clinical conditions.

**DISCUSSION**

Nasal lymphoma clinical signs are initially similar to a chronic rhinitis, including nasal discharge, epistaxis, dyspnea and sneezing [10]. However, in this study, in addition to the above signs, both cats had facial deformity, exophtalmy and central nervous system invasion. These latter signs are related to advanced stage of disease and late diagnosis.

Radiation therapy could be considered the mainstay of treatment for feline nasal lymphoma. Lymphoma is very sensitive to radiation and most cats diagnosed with nasal lymphoma have localized disease at the time of presentation [13]. However, given that lymphoma is generally a systemic disease, chemotherapy should also play a role in management of feline nasal lymphoma [13,16,18]. Even though most cats with nasal lymphoma appear to have localized disease at the time of diagnosis, chemotherapy for at least six months is recommended due to possible target residual local tumor cells as well as undetected systemic disease [13,16]. Although radiation therapy alone may lead to long-term remission, systemic relapse has been reported. Chemotherapy alone is not an effective treatment for cats with nasal lymphoma [5,7]. In the current report, both radiation and chemotherapy were prescribed as it was considered the most aggressive treatment option.

According to the literature, radiation acute reactions include erythema, dry or moist desquamation, epilation, rhinitis, conjunctivitis and keratitis [3]. The
late reactions can occur months or years after radiation therapy, and include depigmentation, irreversible alopecia, fibrosis, necrosis, fistulas formation, chronic conjunctivitis, keratoconjunctivitis sicca and cataracts [3]. Acute and late radiation side effects were well tolerated by both cats. All acute radiation therapy reactions (erythema, conjunctivitis and keratitis) resolved with supportive care and in an acceptable period of time. Late side effects, such as chronic nasal discharge, did not occur in the reported cats. The only late side effect observed was hair regrowth of different color in the treatment Field that not interfere with quality of life.

The combination of therapies used in this case report resulted in extended progression free interval (PFI) as well as survival times of over 1000 days. This exceeds survival times of cats with nasal lymphoma treated with chemotherapy alone or with prednisone alone. Chemotherapy alone with COP-based protocol alone lead to median survival times of 98-358 days, while patients receiving no treatment or prednisone alone have median survival time of only 22 days [7,19].

Megavoltage radiation has greater penetrability and more uniform absorption, and is more effective in treating nasal tumors, particularly tumors located at greater depths from the skin surface [1,12,14]. Orthovoltage radiation therapy has the disadvantage of being too superficial, treating tumors of 2 cm or less, with more skin side effects. Two studies reported better survival for dogs with nasal tumors treated with orthovoltage than for those treated with megavoltage radiation therapy [1,9]. As orthovoltage radiation is the only radiation therapy available in Brazil, it was used in both cats of this report. In the first case, tumor measured about 2.3x1.3x3.3 in computed tomography, which allowed orthovoltage treatment, as dose was calculated to 1.5 cm depth. However, in the second case, the mass was at a higher depth, measuring about 4.1x3.0x3.5 cm. For this reason, a cytoreductive rhinotomy was performed before treatment, and radiation started five days after surgery to avoid tumor regrowth. Radiation dose was calculated to 1.0 cm depth, which was sufficient for appropriate long term tumor control.

The presence of cribriform plate destruction at the time of diagnosis was found to be a negative prognostic factor for both PFI and survival. Patients with cribriform plate destruction had a median survival time of 76 days vs. 1296 days for those without cribriform plate involvement [16]. However, in the reported cats, PFI and survival times were superior to 1000 days, even with cribriform plate destruction and central nervous system invasion.

In conclusion, feline nasal lymphoma should be aggressively treated by radiation therapy combined with systemic chemotherapy. These cats can benefit from long term tumor control and excellent quality of life after treatment.

**REFERENCES**


