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DIAGNOSIS AND TREATMENT OF A DERMAL MALIGNANT MELANOMA IN AN AFRICAN LION (PANTHERA LEO)


Abstract: A 13-yr-old intact male African lion (Panthera leo) presented with a 4-mo history of left maxillary lip swelling. On physical examination, a 10-cm-diameter, ulcerated, round, firm, and pigmented mass at the level of the left maxillary canine tooth was noticed. All other organ systems examined were within normal limits. Multiple biopsies of the mass were collected and fixed in 10% neutral buffered formalin. Histopathologic evaluation of the biopsies revealed a malignant dermal melanoma. Hematologic and plasma biochemical parameters were within normal reference ranges. Thoracic radiographs taken 3 days following initial presentation showed no evidence of metastasis of the tumor. Computed tomography of the skull and neck was performed to evaluate local tumor invasion and to plan for hypofractionated radiation therapy. Therapy included four weekly treatments of 8 gray external-beam hypofractionated radiation and four bimonthly immunotherapy treatments. Following this treatment regime, the tumor size was reduced by 50%, and surgical excision was performed. No major side effects associated with radiation or immunotherapy were seen. Six months after diagnosis, hematologic and plasma biochemical parameters were within normal limits, thoracic radiographs showed no evidence of metastasis, and the lion showed no clinical signs of disease. The lion will continue to receive immunotherapy every 6 mo for the rest of its life. To the authors’ knowledge, this is the first report of a successful treatment of a malignant dermal melanoma with external-beam hypofractionated radiation, immunotherapy, and surgical excision in an African lion.

Key words: African lion, immunotherapy, melanoma, Panthera leo, radiation therapy.

INTRODUCTION

Melanomas are “round cell imposter”7 tumors of melanocytes or melanoblasts19 and have been reported in domestic animals to be either benign or malignant. In domestic animals, malignancy is determined by tissue site, mitotic index, tumor size, lymphatic invasion, and breed.19 In domestic cats, melanomas have been reported to affect ocular, dermal, or oral tissues.12,13,15 Whereas ocular and oral melanomas have been shown to be highly aggressive, dermal melanomas can be either malignant or benign.19 Reports in the literature of malignant melanomas in exotic felids are scant.4,17

The treatment of choice for patients with melanoma is surgical excision of the mass with at least 2-cm margins.20 Because of the aggressive nature of melanomas, thoracic radiographs, routine hematologic blood tests (complete blood count and chemistry panels), and aspiration of regional lymph nodes are recommended to determine if metastatic disease is present. External beam radiation therapy can be used successfully to control local disease as a primary or adjunctive treatment for malignant melanomas,5,6,16 but chemotherapy has been shown to be of little benefit.19 Recently, immunotherapy has been reported as an effective treatment of micrometastatic disease associated with malignant melanomas after surgical excision of the primary mass in dogs; it increased disease-free intervals and median survival times.3

CASE REPORT

A 13-yr-old, intact male African lion (Panthera leo) presented with a 4-mo history of facial swelling of the left maxillary lip at the level of the left upper canine tooth. Four months prior to evaluation, a tick was seen on the left lower eyelid, and the lion had severely scratched the left side of its face in attempts to remove the tick. During this time, the lion had been empirically treated with amoxicillin/clavulanic acid (Clavamox, Pfizer, New York, New York 10017, USA; 10 mg/kg p.o. b.i.d. for 14 days) for a suspected abscess because of the excoriation incident.
antibiotic therapy, the swelling continued to slowly enlarge until the time of examination.

The lion was immobilized with medetomidine (Wildlife Pharmaceuticals, Windsor, Colorado 80550, USA; 27 mcg/kg i.m.), midazolam (Nova-Plus, Hospira, Lake Forest, Illinois 60045, USA; 0.1 mg/kg i.m.), and ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA; 3 mg/kg i.m.). This protocol was used for all subsequent immobilizations. Physical examination revealed a 10-cm-diameter, ulcerated, round, firm, and darkly pigmented mass along the left maxillary cheek. The mass bled easily and was suspected to be a neoplastic mass of uncertain histologic type. The mass was infused with a 2% lidocaine solution (Hospira, 1 mg/kg) and three 6-mm punch biopsies were obtained from various areas of the mass. Biopsy specimens were fixed in 10% neutral buffered formalin, and biopsy sites were closed with polydioxanone (PDS, Ethicon, Somerville, New Jersey 08876, USA) in a simple interrupted pattern. All other physical examination findings were within normal limits. A blood sample was collected from the saphenous vein for determination of hematologic and plasma biochemical parameters. At the end of the procedure, the effects of medetomidine were reversed with atipamezole (Antisedan, Pfizer; 0.13 mg/kg i.m.).

Hematology and plasma biochemistry panels were within normal limits. Histopathology of biopsy specimens of the mass showed that the deep dermal, subcutaneous, and muscular tissue architecture was variably disrupted to effaced by a highly pleomorphic population of heavily to minimally pigmented cells arranged in sheets, streams, and islands (Fig. 1A). These cells had marked anisocytosis and anisokaryosis. Mitotic figures averaged one per 10 high-power (×40) fields. Neoplastic cells were also present within multiple blood vessels (Fig. 1B). A diagnosis of a malignant melanoma was made based on the size of the mass and vascular invasion present on histopathology.

Three days after initial presentation, the lion was immobilized for further diagnostics, including computed tomography (CT) of the head and neck, thoracic radiographs, and possible surgical excision of the mass. At this time, the mass measured 4.5 cm (medial to lateral) × 10 cm (rostral to caudal) × 10 cm (dorsal to ventral). Anesthesia was induced with a combination of medetomidine, midazolam, and ketamine, as previously described. Following induction of anesthesia, the trachea was intubated with a 20-mm cuffed endotracheal tube, and anesthesia was maintained with isoflurane (IsoFlo, Abbott Animal Health, North Chicago, Illinois 60064, USA; 1–4%) in 100% oxygen for the remainder of the procedure. An 18-gauge, 1.25-in intravenous catheter was placed in the medial saphenous vein, and Normosol R (Hospira) was administered i.v. at 10 ml/kg/hr throughout the anesthetic event. Iodinated contrast was administered during the CT scan (Optiray, Covidien Pharmaceuticals, Hazelwood, Missouri 63042, USA; 100 ml i.v. once).

Thoracic radiographs showed moderate diffuse nonstructured interstitial opacities throughout the lung and mild bronchial mineralization consistent with age-related changes. No evidence of metastatic disease was present. CT was performed using a 40-slice helical CT scanner (Philips Brilliance-40, Philips International B.V., Amsterdam, The Netherlands) on the head and neck of the lion to evaluate tumor margins and regional lymph nodes and aid in radiation planning. Four-millimeter transverse images were acquired from the most rostral portion of the head to the cranial aspect of the second thoracic vertebra. There was a mixed hyper- and medium attenuating mass within the left labium extending from approxi-mately the level of the incisor teeth caudally to the level of the third maxillary premolar tooth (Fig. 2). The mass extended dorsally to the junction of the labium into the adherent maxillary soft tissues. There was no associated bone abnormality. On postcontrast images, there was heterogeneous enhancement of the left labial mass. CT assessment of regional lymph nodes was somewhat compromised by the animal’s relatively lean conformation, but no significant lymphadenopathy was identified. At the time, lymph node aspiration was not pursued given the findings on CT scan. Given the size and location of the mass, surgical removal and primary closure were determined to be impossible at that time. In an attempt to reduce tumor size and facilitate surgical excision, weekly external-beam hypofractionated radiation therapy was administered for four treatments. At the time, chemotherapy was discussed, but because of the short and minimal response of domestic animal melanomas to chemotherapy and the owners’ concern for adverse side effects to the drugs, this treatment modality was not pursued in this case. Radiation therapy was also accompanied twice by immunotherapy with a melanoma vaccine (Oncept, Merial, Duluth, Georgia 30096, USA; 1 ml administered
transdermally into the medial thigh every 2 wk for four treatments).

Hypofractioned radiation therapy consisted of 8 gray (Gy) once a week for 4 wk. The radiation protocol was chosen in part based on a report of the treatment of domestic cats with oral melanomas with 8 Gy weekly for three fractions. The total dose was increased to 32 Gy based on clinical experience of the radiation oncologist in treating canine and feline patients with oral melanoma, and with the goal of achieving a better local response with 32 versus 24 Gy. Regional lymph nodes were not irradiated because of normal appearance on the original CT scan.

Radiation therapy was administered using a Varian Clinac IX linear accelerator (Varian Medical Systems, Palo Alto, California 94304, USA).

Figure 1. Photomicrographs of a dermal melanoma in a 13-yr-old African lion (P. leo). A. Tissue architecture is variably disrupted to effaced by a highly pleomorphic population of heavily to minimally pigmented cells arranged in sheets, streams, and islands (×40, H&E). The cells have marked anisocytosis and anisokaryosis with single to multiple nuclei (white arrows). B. Neoplastic cells are seen within blood vessels (white arrows).

A treatment depth of 5.0 cm was selected based on the size of the tumor and in order to spare the underlying maxillary gingiva. Manual planning of an electron field using 16 MeV electrons at 100-cm skin-to-surface distance was formulated. The gross tumor volume was determined to be the measurable disease seen on the pretreatment CT scan. A clinical target volume (CTV) of 1 cm was established to include any potential microscopic disease. A patient target volume (PTV) of 1 cm around the CTV was established, and the treatment was planned to include the PTV within the 90% isodose line.

A custom Cerrobend electron mold was made on the first treatment day in order to contour the 15-cm electron cone opening to adequately treat the tumor and spare the surrounding normal tissues. The lion was positioned in right lateral recumbency with its head toward the gantry. An angled Styrofoam wedge was used to level the patient’s muzzle. The gantry of the linear accelerator was set to 0°, and the central axis was positioned in the center of the visible tumor. Bolus material was placed around the tumor area to establish a flat treatment surface, and to protect the underlying normal tissues on the periphery of the tumor area.

After two radiation treatments, the treatment depth was changed to 4 cm because the tumor had...
responded to treatment and was reduced in size. The subsequent radiation plan was identical to the first two treatments, with the exception of an additional 1-cm bolus over the top of the tumor, to once again limit the dose to the underlying maxillary gingiva. Even though the tumor mass had decreased both in length and width, the treatment area was not changed in order to treat any microscopic residual disease.

Throughout radiation and immunotherapy, the melanoma continued to decrease in size (Table 1). Complete blood counts and plasma biochemistries were performed at each treatment interval, and no significant clinical abnormalities were identified. A venous blood sample was also collected for determination of anti-human tyrosinase titers at each immobilization. Acute radiation side effects detected were grade I alopecia and pigmentation at the radiation site.

Approximately 2 mo after the diagnosis of melanoma was made and following completion of external-beam radiation, it was elected to surgically excise the mass because of the reduction in size by approximately 50%. The lion was anesthetized with the protocol described previously, and prior to surgical excision, a CT scan was performed to reevaluate tumor margins and possible invasion of regional lymph nodes. At the time of immobilization, it was noted that the lion had developed left submandibular lymphadenopathy. A CT scan showed a decrease in size of the melanoma and mild ipsilateral mandibular lymphadenopathy that was most consistent with metastatic disease.

It was elected to surgically excise the melanoma along with the left submandibular lymph node. The left side of the head and neck was clipped and prepped from the nose to the fifth cervical vertebra. In order to provide intraoperative local anesthesia, an infraorbital nerve block was performed within the left maxillary infraorbital foramen with 2 ml bupivacaine HCl (Hospira). An incision was made over the enlarged submandibular lymph node, and blunt dissection was performed to isolate the lymph node. The lymph node and surrounding tissue were dark, and enlarged consistent with metastatic disease. An elliptical incision was made around the primary mass, and the mass was dissected from the surrounding subcutaneous and muscular tissues. Streams of neoplastic tissue could be observed following the paths of various blood vessels and nerves of the left maxilla. Macroscopic excision was deemed the best procedure for this lion. The mass was removed en bloc, and both the primary mass and the submandibular lymph node were submitted for histopathology. Histopathology found perinodal metastasis but no intranodal metastasis present in the lymph node and incomplete excision of the primary melanoma.

The lion recovered from anesthesia and surgery without complications and was administered meloxicam (Metacam, Boehringer Ingelheim, St. Joseph, Missouri 64506, USA; 0.2 mg/kg s.c.) and tramadol (Pfizer; 2 mg/kg p.o. b.i.d. for 3 days) for postoperative analgesia. Following surgery, the animal was eating and acting normally and showed no signs of disease or postoperative complications.

Six months after surgical excision of the melanoma, the lion was immobilized for recheck thoracic radiographs and melanoma vaccine administration. At that time, no physical evidence of regional or distant metastatic disease was present, and a small 3-cm round surgical dehiscence was present at the primary surgical site. The dehiscence site was clean, and no additional masses could be palpated in the area of the original melanoma. A small raised area on the gum line of the first left maxillary premolar was aspirated, and cytology revealed low-grade inflammation with no signs of metastatic disease. Thoracic radiographs showed previously noted age-related lung changes but no evidence of metastatic disease. Hematologic and plasma biochemical values were within normal limits. At the time of writing, the lion is doing well and there is no evidence of disease recurrence. The plan is to continue vaccine administration and thoracic radiographs every 6 mo for the rest of its life.

**DISCUSSION**

Melanomas are uncommonly diagnosed in domestic cats and have been reported to

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*a Radiation therapy performed.  
*b Melanoma vaccine administered.
Feline melanomas have a variable degree of malignancy, with oral and ocular forms being the most aggressive. At present, malignancy is most accurately determined by histopathologic evaluation of the tumor. Surgery is the treatment of choice for resectable tumors and wide surgical margins, and adjunctive treatment is suggested if margins cannot be achieved. Adjunctive treatment consists of radiation therapy, chemotherapy, and/or immunotherapy. Survival rate in domestic cats with melanomas has been reported to be dependent on both malignancy and tissue site. This report showed that the mean survival time of cats after a diagnosis of malignant melanoma varied: oral, 61 days; ocular, 156 days, with four cats living past 255 days; and palpebral melanoma, 409 days.

This case report describes surgical excision, external-beam hypofractionated radiation, and immunotherapy for the treatment of a dermal melanoma in an African lion. Because of the size and location of the tumor, surgical resection could not be pursued as an initial step because of the concern for the inability to close the wound created after the mass removal. As a result, external-beam hypofractionated radiation therapy in conjunction with immunotherapy was performed with the goal to reduce tumor size for surgical excision. In nondomestic felids, there are few reports of patients with melanomas, and information regarding treatment is scant.

Radiation therapy is considered an effective modality for the treatment of patients with non-resectable or incompletely excised melanoma tumors. Radiation planning for the lion reported here consisted of a CT scan, including administration of contrast. A standard external-beam hypofractionated radiation plan for the treatment of malignant melanomas in cats was used for the lion in this report. One study demonstrated no difference in the median survival rate in dogs with oral melanoma treated with weekly-dose radiation versus daily radiation. Acute radiation side effects are commonly seen in rapidly dividing tissues such as skin, oropharyngeal mucosa, intestinal mucosa, urinary bladder, and vaginal mucosa. Common side effects observed in the skin are erythema, dry or moist desquamation, and dermal destruction. In the lion reported here, acute side effects occurred at the site of radiation therapy and included grade I alopecia and pigmentation of the tissue surrounding the tumor. Eleven months after the conclusion of radiation therapy, no signs of late side effects have been detected. Radiation therapy in domestic cats is not commonly used for the treatment of malignant melanomas, probably because of the low incidence of this type of tumor in cats. One study showed that 60% of cats had a partial or complete response when treated with hypofractionated radiation therapy for oral melanomas. The median survival time of all cats in that study was 146 days. Currently, the lion in this report has survived for 390 days from the time of diagnosis, and there is no evidence of disease recurrence for 336 days from surgical excision.

Because of the aggressive nature of melanomas and the known minimal and short-lived response to conventional chemotherapy, additional adjunctive treatments were applied for this case. Immunotherapy is a novel treatment currently marketed for the management of canine melanomas. Two different types of melanoma vaccines have been developed, but only one is commercially available. For canine malignant melanomas, the human tyrosinase enzyme has been used in the development of a xenogeneic vaccine because of the high amount of tyrosinase present within melanoma cells. A xenogeneic human tyrosinase vaccine has been developed that results in inducing antibody and cytotoxic T-cell antitumor responses in canine patients with melanoma that receive it. The vaccine is most efficacious and labeled for patients who have complete local disease control. Occasionally, patients with gross disease do have a response to the vaccine, but this is not the norm. The homology of African lion tyrosinase versus human tyrosinase is unknown; however, it can be surmised that it is close to that of the domestic cat, which is similar to that of the domestic dog. Antibody responses to the human tyrosinase melanoma vaccine have been shown to coincide with long-term survival in dogs. The rationale for the use of a human tyrosinase vaccine in this lion was to slow or prevent future metastatic disease. Currently at the authors' institution, studies are being performed evaluating the human tyrosinase antibody response of nondomestic felids with melanoma to the melanoma vaccine. No adverse vaccine reactions such as pain, redness, or swelling at the injection site were observed in the lion in this report. Treatment with human tyrosinase vaccine improved long-term survival in dogs that had their primary tumor excised even in the presence of advanced metastatic disease. It is unknown what the long-term outcome will be for the lion in this report, but currently there is no physical evidence of disease in the lion.
In conclusion, dermal melanomas in exotic felids are infrequently reported. Diagnostic and treatment modalities for this type of tumor include biopsy, fine-needle aspiration of regional lymph nodes for cytology, complete blood count, chemistry panel, thoracic radiographs, surgical excision, external-beam hypofractionated radiation, chemotherapy, and immunotherapy. In the case presented here, external-beam radiation and/or immunotherapy was effective in reducing tumor size to facilitate surgical excision. Currently, immunotherapy with a melanoma vaccine is approved only for domestic dogs, and its use in nondomestic animals is considered off label. The effectiveness of immunotherapy in developing an immune response in this lion is under investigation. Further studies need to be performed to determine if there are any side effects to either external-beam hypofractionated radiation or immunotherapy with a melanoma vaccine in exotic felids.

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LITERATURE CITED


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