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Intraocular osteosarcoma in an Umbrella Cockatoo (*Cacatua alba*)

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INTRODUCTION

Osteosarcoma can occur as a primary bone tumor, affecting the appendicular or axial skeleton, or as soft-tissue in origin (extra-skeletal osteosarcoma). Osteosarcoma has been described as a rare tumor in birds primarily occurring on the appendicular skeleton (1-4). Most reported cases of osteosarcoma in birds were left untreated and the patient euthanized (3,5-8), although amputation of the affected limb in cases of appendicular osteosarcoma has been described (2,4-6). In one case of axial osteosarcoma of the maxilla, a combination of surgical debulking and chemotherapy was used (8). While a few cases of osteosarcoma of the orbit have been reported in birds, they are described as arising from the axial skeleton (5-6,8-9). This is the first case of an intraocular osteosarcoma reported in a bird, and the first case of attempted treatment of osteosarcoma in a bird by a combination of surgery and radiation therapy.

CASE PRESENTATION

An adult, presumed intact female Umbrella Cockatoo (*Cacatua alba*) of unknown age was presented because of acute onset of hemorrhage from the right eye. The bird had been evaluated by a veterinary ophthalmologist 4 weeks earlier because the eye appeared to be protruding. Glaucoma was diagnosed with an intraocular pressure of 40 mmHg, and treatment was initiated with topical 2% dorzolamide HCl and 0.5% timolol maleate ophthalmic solutions. The clinical signs did not improve and a retrobulbar mass was suspected, but the owner declined further diagnostic workup at that time. The exophthalmos continued to progress and eventually hemorrhage was observed from the eye. On physical exam, the bird was bright and alert, with no signs of pain or discomfort. She was slightly thin based on the prominence of the keel, with a body weight of 0.444 kg and had pale pink mucous membranes. Ophthalmic examination revealed that the right cornea was ruptured with a solid, hemorrhaging mass emerging from the inside of the eye (Fig. 1). Her physical exam, including evaluation of the left eye, was otherwise unremarkable.

As part of the systemic evaluation and in preparation for general anesthesia, complete blood count (CBC) and biochemistry panel were analyzed and showed an elevated total white blood cell count (WBC) of 41,000 cells/ μ L (laboratory reference interval 10,000-14,000 cells/ μ L) with a mature heterophilia, as well as a moderate anemia with a hematocrit (HCT) of 23% (laboratory reference interval 42-55%). A reticulocyte count was not performed, so the cause of the anemia was not known, although both blood loss and anemia of chronic disease were possible. The biochemistry values were within normal limits except for mild elevations in the aspartate aminotransferase (AST) and creatine kinase (CK) consistent with

muscle inflammation associated with handling for physical exam, obtaining blood sample, or from the bleeding mass.

One day after admission, the bird was anesthetized for a more detailed diagnostic work-up. The bird was pre-medicated with buprenorphine (0.03 mg/kg IM), masked down with a 5% Isoflurane/O₂ gas mixture, intubated, and maintained on isoflurane gas anesthesia with intermittent positive pressure ventilation. Survey whole body and skull radiographs were performed which were unremarkable. A computed tomography (CT) scan of the head was performed which showed an intraorbital soft-tissue mass involving the right globe, invading other soft tissue structures and causing profound exophthalmos and lateral displacement of the globe (Fig. 2). The scleral ossicles were focally lysed. Cytology of the protruding mass was performed via impression smear. The presence of many spindle cells, moderate numbers of macrophages and plasma cells, rare multinucleated giant cells, and few lymphocytes was most consistent with a sarcoma (Figs. 3 and 4). An acid-fast stain was negative for mycobacteria. Treatment with enrofloxacin (20 mg/kg PO q24h) was initiated to treat or prevent a potential secondary infection of the ruptured right globe. Meloxicam (0.5 mg/kg PO q12h) was administered for the severe inflammation within and around the right eye.

Exenteration surgery was scheduled for the following week. Another CBC was performed prior to the surgery which showed a total WBC count now within normal limits (13,000 cells/ μ L) and an unchanged HCT (23%). Anesthesia was performed using the same protocol as previously described. The right globe was enucleated by transconjunctival approach. The lid margins and much of the intraorbital soft tissue content were removed and submitted together with the globe for histopathologic examination. Pieces of absorbable gelatin sterile compressed sponge (Gelfoam®, Pfizer Co., New York, NY USA) were placed into the orbit to control hemorrhage. Closure of the surgery site was done in two layers by use of 5-0 polydioxanone monofilament suture (PDS, Johnson & Johnson Co, New Brunswick, NJ, USA) in simple continuous (subcutaneous layer) and simple interrupted (skin) suture patterns. The bird recovered well from anesthesia. Post-operative treatment included continuation of the enrofloxacin and meloxicam at previous doses, as well as buprenorphine (0.03 mg/kg IM q12h) for post-surgical pain relief.

The mass was determined via histopathology to be an osteosarcoma with chondroid and osseous differentiation involving both the eye and orbit. The globe was filled with a neoplastic cell proliferation, which extended into the scleral veins, and there was a large perforation in the central cornea filled with inflammatory cells and fibrin. The neoplastic cells were highly pleomorphic and in some areas formed sheets of basophilic, round to polyhedral to spindle shaped cells with numerous mitotic figures (mitotic index for the cellular areas: 12 per 10 40X high magnification fields) and occasional small wispy areas of eosinophilic material consistent with osteoid (Figs. 5 and 6). A guarded prognosis was given as neoplastic cells were present within the orbit, extending beyond the surgical margins.

At one week post-op, the patient was doing well but the medial half of the surgical wound had dehisced, resulting in a draining tract with dried hemorrhagic discharge covering part of the incision. The bird was anesthetized using the same anesthesia protocol as previously described, the surgical site explored, and the partially opened orbit was sampled for aerobic and anaerobic bacterial cultures. Cytologic examination of the exudate showed no evidence of tumor growth or infection. The PDS skin sutures were replaced by 5-0 nylon monofilament suture (Ethilon, Johnson & Johnson Co., New Brunswick, NJ, USA) placed in a horizontal mattress pattern as a suture reaction was suspected. Meloxicam and enrofloxacin was continued but the oral antibiotic was later changed to chloramphenicol (50mg/kg PO q12h) as *Staphylococcus aureus* was grown in culture which was sensitive to

chloramphenicol but resistant to enrofloxacin. The bird was administered meloxicam and chloramphenicol for two weeks following surgery.

Since there was evidence of neoplastic cells at the surgical margins and a lack of visible metastasis, a recommendation was made for radiation therapy (RT) of the orbit as a more definitive treatment of the primary tumor site. Computed tomography was performed again under general anesthesia prior to starting RT to establish accurate measurements for treatment. There was no visible evidence of regrowth or extension of the mass into the brain.

Radiation was performed using a Stabilipan orthovoltage unit (Siemens Co, New York, NY, USA). A total dose of 68 Gray was given divided over 17 treatments in a six week time period on a Monday-Wednesday-Friday schedule. The animal was anesthetized for each treatment using the same protocol as previously described. The bird was positioned in sternal recumbency and the right orbit was treated through a single dorsal portal. The patient recovered well from each anesthetic event although the 12th treatment was aborted as the bird was not breathing well under anesthesia. The bird recovered well from this and all other anesthetic episodes.

Within the first three weeks of the course of radiation, the incision appeared to heal although a draining tract opened intermittently from the medial aspect of the incision. Cytology of the discharge was performed periodically during the course of treatment and indicated no markers of inflammation or infection. There were no signs of acute radiation side effects such as dermatitis or feather loss in the area of treatment. Five weeks after starting RT, a CBC and biochemistry panel were performed. Total WBC was 12,000 cells/ μ L and the HCT had normalized to 43%. Biochemistry results were within normal limits. Whole-body survey radiographs were taken under isoflurane gas anesthesia as previously described and showed no evidence of metastasis or local regrowth of the tumor, and there was no destruction of the bones of the skull. An ultrasound guided fine needle aspirate of the orbit was performed and cytology revealed no signs of infection or recurrence of neoplasia. Computed tomography scan was recommended but declined by the owners.

At one month and two month post- RT rechecks, the bird was reported by the owners to be doing well in terms of appetite and activity. She was bright and alert on physical exams and had gained weight (0.480 and 0.490 kg at one and two months respectively). The affected area appeared healed except for occasional clear yellow discharge from the draining tract as had been previously seen. Cytology of the discharge was evaluated at both visits and was found to be mostly acellular, with no markers of inflammation, infection, or neoplasia.

Three months after the last RT treatment, the patient presented with a one week history of lethargy, decreased appetite and progressive ataxia. On physical exam, she appeared dull in mentation, and blind in the left eye. She had trouble stepping up and was ataxic when perching. An ophthalmic exam confirmed the blindness on the left with a negative menace response and the inability of tracking objects such as cotton balls. In addition, pupillary light and dazzle reflexes were negative. These findings were suggestive of retinal disease or a lesion along the central visual pathways. In addition, a focal posterior capsular cataract was found.

Electroretinography was recommended to exclude retina dysfunction as the cause for vision loss, but the owners declined further work-up. Bloodwork revealed a normal total WBC count (11,000 cells/ μ L) and a slightly decreased HCT of 39%. Biochemistry values were within normal limits. The bird was prescribed meloxicam (0.5 mg/kg PO q12h) for possible central nervous system inflammation and trimethoprim/sulfamethoxazole (30 mg/kg PO q12) for a potential infection of the central nervous system. Eight days later, the bird presented dead on arrival. She had become progressively more lethargic, inappetent, and less

responsive and had started regurgitating frequently. Her neurologic signs had progressed to pronounced mental dullness, severe ataxia, a head twitch and nystagmus. Seizures had started to occur within the 24 hours prior to presentation and had increased in frequency until death occurred during a seizure. The owners declined necropsy.

DISCUSSION

Intraocular tumors have been reported infrequently in birds. Most commonly reported tumors include medulloepitheliomas and lymphoreticular tumors (10-12), although there are too few reports of ocular neoplasias in birds to predict tumor type based on the location within the eye. Treatment of intraocular tumors, when attempted, has been surgical (enucleation or exenteration) with variable results. Several retrobulbar or periorbital soft-tissue tumors have been reported: a retrobulbar adenocarcinoma (11), two rhabdomyosarcomas (11), one glioma (13), one round cell sarcoma (13), two lymphosarcomas (14,16), one liposarcoma (15), and one squamous cell carcinoma (1). Treatments, when attempted and described, include surgical removal (16), radiation therapy (14), as well as debulking and *beta*-radiation with Strontium-90 (1) with variable results.

Concerns for performing ocular surgery in birds include hemorrhage of the ophthalmic vascular plexus (16-18), bradycardia associated with traction applied to the extraocular muscles or compression of the globe (oculocardiac reflex) (16,19-20) as well as blindness in both eyes due to traction on the optic nerves and chiasm (21,22). None of these complications were seen in this animal. The cause of inflammation and discharge associated with the incision was initially thought to be secondary to a suture reaction or infection but may have been due to continued drainage from orbital glandular material that could have remained after exenteration, especially as the discharge persisted after the infection had resolved. The draining tract was believed not to be associated with regrowth of the tumor based on repeated cytology of the draining fluid, ultrasound of the orbit, and fine needle aspirate of the fluid within the orbit.

Osteosarcoma has been reported in birds and is thought to be primarily skeletal, most often occurring in the long bones (appendicular osteosarcoma) (1-4,7). Axial osteosarcoma has been described in birds as well, reported in one blue and gold macaw (9), one robin (5), and four budgerigars (6-8). In many cases, treatment is not attempted and diagnosis is made at necropsy (3,5-7). Treatment of skeletal osteosarcoma in birds include amputation of the affected limb in cases of appendicular osteosarcoma (2), amputation and chemotherapy in one case of appendicular osteosarcoma (4), and surgical debulking and chemotherapy in one case of axial osteosarcoma (9). Osteosarcoma in birds has been described as having a low metastatic potential (3-4,6).

To our knowledge, there are no previous reports of intraocular osteosarcoma in a bird. There are also no reports of extraskkeletal osteosarcoma in birds. Given the presence of scleral ossicles in the avian eye, it is difficult to categorize ocular osteosarcoma in birds as soft-tissue in origin or arising from the axial skeleton, namely the scleral ossicles, unless the entire globe was sectioned and examined histologically. The entire globe was not available for histopathology in this case.

Radiation therapy has been used in birds with variable results (14,24,26-28). We chose radiation in our case because the finding of neoplasia beyond the surgical margins made local recurrence a major concern, and the fact that osteosarcoma in birds has been previously described as having low metastatic potential (3-4,6). While our initial plan in this case was to give a total radiation dose of 72 Gray over 18 treatments, the 12th treatment was aborted as the bird was not breathing well under anesthesia. The dose of radiation for this patient

was chosen based on findings from a study by Wilson et al. in which Indian ring-necked parakeets were radiated with doses up to 72 Gray divided into 4 Gray fractions given on an alternate day protocol (23). In this study, the esophagus/crop, trachea, and part of the cervical spine were radiated; results showed no acute or late effects of radiation on mucosal or cutaneous tissue, and no neurological abnormalities were noted. Other reports also suggest that birds may tolerate a significantly higher dose of radiation than mammals and that avian neoplasia may require a higher dose of radiation than mammals to be effective (23-26).

Ideally, we would have been able to assess the efficacy of the radiation therapy in this case with a post-treatment CT scan or necropsy but the owners declined both. Without this information it is impossible to comment on the efficacy of the dose except to say that the bird appeared to recover well from treatment and had no signs of acute radiation reaction, such as dermatitis or feather loss.

A focal cataract was diagnosed in the contralateral eye three months after the last RT treatment. In mammals, cataracts can occur as a late side effect of radiation and the latency for cataract formation is dose-dependent (29-31). The specific effects of radiation on the bird lens are unknown. In this case, because of the small size of the bird's skull, the contralateral eye and lens probably received a modest dose of scattered radiation. It is therefore possible that the cataract in this bird was induced by the radiation despite the short latency. Based on its location at the posterior pole of the lens, the cataract also could have been caused by advanced retinal degeneration (32). Based on our examination, this option does not seem likely, although we were not able to record an electroretinogram to rule out retinal disease. Retinal disease could also be a complication of radiation therapy (29). The death of this bird was due to neurologic signs that progressed from lethargy and ataxia to central nervous system blindness, nystagmus, mental dullness and seizures. Neurologic signs could be due to recurrence of the tumor and extension into the brain or an "early late" side effect of RT. Transient demyelination can occur within weeks to a few months after RT in mammals and is responsive to corticosteroids (33). A late-delayed side effect due to brain necrosis can occur years after RT in mammals and is not responsive to corticosteroids (33). Corticosteroids were not used in this bird due to concern for immunosuppression; neurologic signs did not resolve nor abate with nonsteroidal anti-inflammatory medication (meloxicam). Without necropsy, we do not know if the cause of death was recurrent or metastatic osteosarcoma or radiation-induced CNS damage. Either could have been responsible for the neurologic signs in and death of this bird.

To the best of our knowledge, this is the first case of an intraocular osteosarcoma reported in a bird. It is hoped that with more reported cases of neoplasia in birds, refinement of treatment and more frequent successful outcomes of treatment of neoplasia in birds will occur.

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Figure 1. Illustration (A) and photograph (B) of the mass taken from the laterocaudal aspect of the head. The mass can be seen protruding laterally from the right orbit with a dark red, irregular surface (*), with upper eyelid (a) and lower eyelid (b) indicated. Lubricant has been placed on the surface of the mass.

Figure 2.

Computed tomography image of the patient's head demonstrating intraorbital soft-tissue mass involving the globe and invading other soft-tissue structures, causing profound exophthalmos with proptosis and displacement of the globe laterally. Bony involvement was not evident.

Figure 3. Cytology of the mass. Evident are many neoplastic spindle cells (osteoblasts) (open arrowheads) and many erythrocytes (filled arrowheads) amid abundant bright pink, smooth to lacy material (possibly osteoid) (arrows). Wright–Giemsa stain, length of calibration bar 100 μ m

Figure 4.

Cytology of the mass. Neoplastic osteoblasts are fusiform or oval or stellate with oval to occasionally elongate nuclei, stippled chromatin, single to multiple, oval, basophilic nucleoli (examples indicated with arrows), and a moderate amount of lightly basophilic cytoplasm that forms indistinct cell borders and occasional wispy projections. Wright–Giemsa stain, length of calibration bar 50 μm .

Figure 5. Photomicrograph of the densely cellular portion of the neoplasm demonstrating wispy eosinophilic osteoid (*) embedded in a sheet of pleomorphic cells with round to oval basophilic nuclei and amphophilic cytoplasm with indistinct cell borders. Numerous mitotic figures are noted with arrows. Length of calibration bar 50 μ m.

Figure 6. Photomicrograph of the eye and mass with (from top to bottom) the sclera (a), scleral ossicle with area of mineralization (b), cells containing melanin (remnants of the uvea) (c), neoplasm with densely cellular areas and areas of hemorrhage (d), and islands of chondroid differentiation (e). Length of calibration bar 200 μ m.