Long-term Management of Ovarian Neoplasia in Two Cockatiels (*Nymphicus hollandicus*)

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Abstract: Cockatiels (Nymphicus hollandicus) are commonly diagnosed with ovarian neoplasia. However, there is very little information regarding medical management of this disease condition and subsequent patient response. Long-term medical therapy of 2 cockatiels eventually diagnosed with ovarian neoplasia is described along with responses to the treatment regimens. Each bird had initial signs consistent with reproductive disease (chronic egg laying, ascites, and lethargy) and respiratory distress. The diagnosis of ovarian adenocarcinoma was confirmed on postmortem examination of both birds. The birds were conservatively managed by periodic coelomocentesis and gonadotropin-releasing hormone (GnRH) agonist administration for 9 and 25 months, respectively. A positive response to GnRH agonist therapy was documented in 1 of the 2 birds. These 2 cases demonstrate that periodic coelomocentesis with or without GnRH agonist therapy may be a viable option for the long-term management of ovarian neoplasia and reproductive-organ-associated ascites in cockatiels.

Key words: ovarian neoplasia, ovarian adenocarcinoma, ovarian adenoma, ascites, leuprolide acetate, deslorelin, gonadotropin-releasing hormone agonist, avian, cockatiel, Nymphicus hollandicus

Clinical Report

Case 1

An 8-year-old female wild-phenotype cockatiel (Nymphicus hollandicus) was presented to the Louisiana State University Veterinary Medical Teaching Hospital (LSU VMTH) for emergency evaluation of a 1-day history of tail bobbing and dyspnea. The bird had a history of chronic egg laying and follicular damage to primary feathers on the left wing, which rendered it flightless. The bird was housed with 2 other cockatiels in a home with other birds and was fed a diet of primarily seeds with intermittent offerings of commercial pellets.

On presentation, the bird exhibited tail bobbing and open-mouth breathing. The coelom was distended, and the pubic bones were palpably spread apart. The cockatiel was immediately placed in a warmed intensive care unit (Nursery Hospital Brooder NH 3A, Freed Enterprise, Wichita, KS, USA) and supplemented with 35%–40% oxygen for 2 hours. Once the bird was stable, general anesthesia was induced and maintained with 2%–3% isoflurane delivered in oxygen at a flow rate of 0.8 L/min, and lateral and ventrodorsal whole-body radiographs were taken. Coelomic effusion, loss of intracoelomic detail, and polyostotic hyperostosis of the long bones were evident radiographically. Polyostotic hyperostosis was consistent with chronic egg laying and ovarian activity. Coelomocentesis was performed while the bird was anesthetized, and 3 mL of clear yellowish fluid was retrieved and submitted for fluid analysis,
cytologic evaluation, and aerobic bacterial culture. The bird recovered uneventfully from anesthesia, was treated with long-acting doxycycline (50 mg/kg IM; Vibramycin, Pfizer, Capelle a/d IJssele, Netherlands), and continued to be supplemented with 35%–40% oxygen overnight. Results of cytologic evaluation and fluid analysis revealed mild acute hemorrhage within a modified transudate. The bacterial culture was negative for growth.

The following morning, the bird’s previous clinical signs had improved, but it exhibited open-mouth breathing when stressed. The bird was anesthetized as described above for coelomic ultrasound examination with a 4- to 12-MHz phased-array transducer probe. Multiple cystic structures with anechoic to mildly hypoechoic content were observed throughout the caudodorsal coelom and ventrally displaced the ventricular cardiac ultrasound findings were within normal limits. The presumptive diagnosis was cystic or neoplastic changes of the oviduct or ovary.

Because of suspected ovarian pathology and chronic hormonal stimulation, the bird was treated with leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist (1500 µg/kg IM; Lupron, TAP Pharmaceuticals Inc, Lake Forest, IL, USA). In order to decrease fluid retention and reduce inflammation of coelomic membranes, the bird was also treated with furosemide (4 mg/kg IM q12h) and dexamethasone sodium phosphate (0.25 mg/kg IM q12h tapered to 0.1 mg/kg IM q24h over a week), respectively. The bird showed moderate improvement after 48 hours of hospitalization and treatment and was subsequently discharged to its owner.

Three weeks after initial examination, the cockatiel again became dyspneic and was presented to the LSU VMTH. Coelomocentesis yielded 20 mL of dark yellow fluid, and the bird was hospitalized for fluid therapy and treatment with meloxicam (0.5 mg/kg IM q12h; Metacam, Boehringer Ingelheim Vetmedica, St Joseph, MO, USA). The bird’s condition did not improve over the following 24 hours, and the owners elected euthanasia.

On postmortem examination, the bird had adequate body condition, and the coelom was distended with approximately 15 mL of clear yellow fluid. Membranes of both the hepatic and intestinal peritoneal cavities were thickened. The caudal coelom contained a multilobular, 1.5 × 1.5 × 2-cm, irregular soft tissue mass. Histopathology examination revealed an infiltrative and expansile, poorly demarcated, highly cellular, unencapsulated neoplasm composed of tall columnar to occasionally pleomorphic epithelial cells, which were arranged in tubules, acini, and papillary forms contained within a thin fibrovascular stroma. In some areas, lumina of the neoplastic tubules and acini contained variable amounts of eosinophilic proteinaceous material (glandular secretions) (Fig 1). Mitotic figures averaged approximately 1 per ×40 field. The findings were most consistent with a low-grade adenocarcinoma. Severe atherosclerotic lesions were also found in the ascending aorta and brachiocephalic arteries, consistent with type VI lesions based on the psittacine classification.
Case 2

A 13-year-old female wild-phenotype cockatiel was presented as an emergency to the LSU VMTH for a 2-day history of dyspnea. The bird had a 10-year history of chronic egg laying and a previous episode of egg binding, which was successfully treated. The bird was housed with a male cockatiel and was fed a diet including seeds and pellets supplemented with fruits and vegetables.

On presentation, the bird was moderately dyspneic with tail bobbing, coelomic distention, and spreading of the pubic bones. The bird was placed in a warm intensive care unit and supplemented with 35%–40% oxygen for 2 hours before evaluation. After stabilization, the bird was mask-induced with 5% isoflurane, then intubated with a 2-mm-diameter uncuffed endotracheal tube and maintained under general anesthesia with 2%–3% isoflurane delivered in oxygen at a flow rate of 0.8 L/min. Whole-body radiographs were taken, which demonstrated moderate coelomic distention, loss of coelomic detail, and polyostotic hyperostosis of the long bones. Coelomocentesis subsequently yielded 5 mL of serosanguineous fluid, which was submitted for fluid analysis, cytologic evaluation, and aerobic bacterial culture. A blood sample was collected from the right jugular vein and submitted for a complete blood count (CBC) and plasma biochemical analysis.

The bird recovered uneventfully from anesthesia and demonstrated an improved respiratory pattern. Results of fluid analysis and cytologic evaluation revealed a protein level of 1.5 g/L with small numbers of red blood cells, consistent with a modified transudate and acute hemorrhage likely secondary to the sampling procedure. The bacterial culture was negative for growth. Results of the CBC showed a moderate nonregenerative anemia (packed cell volume [PCV] 23%; reference interval, 45%–54%),2 which was attributed to the chronicity of the disease and recent fluid administration resulting in dilution; however, intracoelomic or intratumoral hemorrhage could not be ruled out. A mild increase was seen in plasma levels of both bile acids (114 μmol/L; reference interval, <109 μmol/L)3 and creatine kinase (668 U/L; reference interval, 30–245 U/L).2

Based on the chronic history of reproductive stimulation, physical examination findings, and diagnostic test results, a presumptive diagnosis of hyperestrogenism and reproductive-organ–associated ascites was made. The bird was hospitalized for 3 days and treated with fluids (lactated Ringer’s

Figure 1. Photomicrograph of a low-grade ovarian adenocarcinoma in a cockatiel composed of an infiltrative and expansile, highly cellular, unencapsulated neoplasm. Tall cuboidal neoplastic cells with frequent brush borders are arranged in tubules, acini, and papillary forms within a thin fibrovascular stroma. The tubular lumina contain an eosinophilic proteinaceous material presumed to be glandular secretions (hematoxylin and eosin; ×20).
solution, 30 mL/kg SC q12h), long-acting doxycycline (50 mg/kg IM once), meloxicam (0.5 mg/kg IM once followed by PO q12h), vitamin A (10 000 IU/kg IM; Injacom ADE, Northwest Pharmacy Compounding Center, Houston, TX, USA), gavage feeding (6 mL PO q12h; Emeraid Omnivore-Avian, Lafeber, Cornell, IL, USA), and calcium glubionate (50 mg/kg PO q12h; Rugby Laboratories, Duluth, GA, USA). The bird was discharged with oral meloxicam and oral calcium supplementation. Despite medical recommendations, the owner elected to delay hormonal treatment. At the 4-week recheck examination, the bird was less dyspneic and was reported to be in good general condition, and a second injection of long-acting doxycycline was administered.

One month after initial examination, the bird was again presented with severe dyspnea and coelomic distention and was placed in a warm critical care unit supplemented with 35%–40% oxygen. After stabilization, the bird was anesthetized with isoflurane as described above, and coelomic and cardiac ultrasound examinations were performed. Ultrasound confirmed the presence of fluid in the intestinal peritoneal cavity as well as hyperechoic material in the ovarian/oviductal area, which was interpreted as evidence of inflammation of the reproductive organs. Results of the cardiac ultrasound examination were within normal limits. A blood sample was collected and submitted for a CBC and plasma biochemical analysis, the results of which were unremarkable. The bird was hospitalized for 2 days and placed on a treatment regimen similar to that used during the initial hospitalization, with the addition of leuprolide acetate (1500 µg/kg IM). The bird was discharged with oral meloxicam for 5 days.

During the following 5 months, the bird was treated with leuprolide acetate injections (1500 µg/kg IM) once every 2–4 weeks for a total of 8 injections. During this period, the cockatiel did not display evidence of reproductive activity, egg laying, dyspnea, or ascites, which was considered to be a favorable response to the hormonal therapy. After 5 months, a 4.6-mg deslorelin implant was placed subcutaneously in the interscapular region. The bird’s response to deslorelin was favorable for 4 months until reproductive-organ–associated ascites and dyspnea. The clinical signs were thought to be associated with ovarian neoplasia, which was later confirmed by postmortem examination. These 2 cases demonstrate that periodic coelomocentesis

Discussion

This clinical report documents the long-term conservative management of 2 female cockatiels affected by reproductive-organ–associated ascites and dyspnea. The clinical signs were thought to be associated with ovarian neoplasia, which was later confirmed by postmortem examination. These 2 cases demonstrate that periodic coelomocentesis
and/or GnRH agonist therapy can be a viable option for management of this presentation. The survival time after initial presentation for the birds presented in case 1 and case 2 was 9 and 25 months, respectively.

Epithelial ovarian tumors have been reported in several mammalian species. In the avian literature, ovarian tumors, including adenocarcinomas, are common and have been reported in turkeys, chickens, guinea fowl, pigeons (Columba livia), canaries (Serinus canaria), budgerigars, cockatiels (Melopsittacus undulatus), macaws, cockatoos, Amazon parrots, African grey parrots (Psittacus erithacus), Eastern rosella (Platycercus eximius), and other psittacine species. Ovarian adenocarcinomas are also relatively common in laying hens. These two birds with ovarian neoplasia initially presented for respiratory distress and ascites. Ascites is a common clinical sign observed in psittacine birds with ovarian diseases, including neoplasia. Respiratory distress was presumably caused by the large quantities of fluid in the coelom pressing against the air sacs and lung parenchyma, which reduced the available respiratory volume and prevented normal air flow.

Hind limb paresis or paralysis is a typical presenting complaint in birds with ovarian tumors, because such tumors can press on the ischiatic nerve or result in lumbar pain. The cockatiel in case 1 ultimately presented with pelvic limb paresis. The significant atherosclerotic lesions subsequently found in the bird’s arteries may also have contributed to the paresis. Other common findings associated with ovarian neoplasia in parrots are egg binding, oviductal impaction, and hernias. Both of the patients we describe exhibited prolonged histories of chronic reproductive problems and egg laying.

In both of these cases, the birds had radiographic evidence of hyperostosis of the long bones. Polyostotic hyperostosis is thought to be caused by hyperestrogenism, although it is also associated with other pathologic conditions, including ovarian neoplasia. Hyperestrogenism has been diagnosed in normal preovulatory hens, budgerigars with hyperestrogen syndrome, and birds with oviductal or ovarian conditions including cystic, degenerative, or neoplastic changes. In one study of psittacine birds with polyostotic hyperostosis, 23% of hens had a tumor of reproductive tissue origin and an additional 20% had inflammatory lesions (cysts, inflammation, or nodular hyperplasia) originating from reproductive tissues. Radiography did not highlight a caudodorsal mass in the birds presented here, likely because the large quantities of intracoelomic fluid obscured radiographic detail. In cases without ascites, radiography is still not as sensitive at discerning the origin of a caudodorsal soft tissue mass as...
other modalities such as ultrasound.\textsuperscript{18} Coelomic ultrasound has been used for the diagnosis of ovarian pathology in birds and is capable of imaging active ovaries in birds as small as 70 g.\textsuperscript{18} Sonographic examination is more sensitive for diagnosing specific organ pathology than radiography alone.\textsuperscript{18} Ascites improves the ultrasound visualization of reproductive and other coelomic organs, as was the case in the 2 birds presented here. Specific sonographic findings reported for birds with ovarian neoplasms include massive enlargement of the ovary with well-defined structures appearing as large rounded masses of mixed echogenicity.\textsuperscript{18} In the birds presented in this report, ultrasound identified abnormal tissue of reproductive origin but failed to further characterize these abnormalities as neoplastic or inflammatory.

The ascites typically encountered in ovarian disease conditions has not been given much attention in the avian medical literature despite its effect on respiration and other clinical signs. Ascites related to ovarian neoplasia is a recognized paraneoplastic disorder in humans\textsuperscript{4,5} and has been reported in dogs\textsuperscript{8} and goats\textsuperscript{11} with ovarian adenocarcinoma. Typical clinical signs observed in humans with ascites of malignancy include abdominal distension, dyspnea, fever, and pain.\textsuperscript{4} In avian medicine, ascites of malignancy has been reported in a pigeon diagnosed with a seminoma\textsuperscript{29} and in female parrots and chickens with ovarian and oviductal neoplasias.\textsuperscript{20,24,26,30} In humans, several other neoplasms, some nonreproductive, can be associated with ascites, and the presence and progression of malignant ascites is associated with poor quality of life and a poor prognosis.\textsuperscript{4,5}

The pathogenesis of ascites of malignancy is complex and has been adequately described in human medicine. Proposed etiologies of this disease process include tumor cell accumulation in lymphatic vessels leading to decreased lymphatic drainage of the abdominal cavity and tumor cell production of vascular endothelial growth factor, which increases capillary permeability. These changes induce altered Starling’s equilibrium forces leading to fluid extravasation from the vasculature.\textsuperscript{4,5} In chickens, ascites associated with ovarian carcinoma is thought to be caused by obstruction of lymph drainage.\textsuperscript{30} In human medicine, the gold standard for diagnosis of ascites of malignancy is the presence of tumor cells in the ascitic fluid.\textsuperscript{5} In the birds described in this report, no neoplastic cells were noted during repeated cytologic evaluations of the aspirated coelomic fluid; however, acute hemorrhage within a pure to modified transudate was identified, suggesting a potential pathogenesis related to altered Starling’s forces.

Several therapeutic modalities have been evaluated in the treatment of ascites of malignancy in humans. Although diuretics have been used with variable success in humans,\textsuperscript{4,5} furosemide therapy in the bird in case 1 did not result in a noticeable reduction in fluid production. Frequent and recurrent large-volume paracentesis has been documented to be the most efficacious procedure in treating ascites of malignancy in human medicine.\textsuperscript{4,5} This treatment modality used alone was considered effective for long-term management of the cockatiel in case 1 and in conjunction with hormonal therapy in the cockatiel in case 2. Coelomocentesis did not have any noticeable adverse effects except for mild local hemorrhage detectable on cytologic examination of the coelomic fluid. Therefore, periodic coelomic drainage can be recommended for birds with ovarian neoplasia when surgical intervention is not possible.

Other therapies employed for the treatment of ascites of malignancy in humans include lowering dietary sodium; peritoneovenous shunting; intraperitoneal infusion of chemotherapy interferon, tumor necrosis factor, or radiolabeled monoclonal antibodies; and surgical debulking of tumors.\textsuperscript{4,5,31–33} Surgical options were declined in both of the birds presented here, and few of the ancillary treatments used in humans have been investigated in birds. In chickens, supplementation with omega-3 fatty acids by addition of 10% flax seed or dietary aspirin supplementation results in significant reduction in the severity of ovarian neoplasia, although it does not decrease the incidence of the neoplasia.\textsuperscript{34,35} To our knowledge, no studies have evaluated the use of chemotherapy or ancillary therapeutics in psittacine species diagnosed with ovarian carcinomas.

Leuprolide acetate and deslorelin acetate are synthetic GnRH analogues, which act on the hypothalamic-pituitary-gonadal axis. In this pathway, endogenous GnRH is released from the hypothalamus and acts on receptors in the anterior pituitary gland to cause release of the gonadotropin hormones, follicle-stimulating hormone and luteinizing hormone. The gonadotropins, in turn, act on receptors of the gonads to cause steroidogenesis.\textsuperscript{36} The use of synthetic GnRH agonists in many species has been shown to initially cause hyperstimulation, followed by suppression of the hypothalamic-pituitary-gonadal axis by causing down-regulation of GnRH receptors in the pitui-
tary gland. This leads to decreased gonadotropin production and decreased steroidogenesis.37,38

GnRH analogues have been used in human and veterinary medicine in the treatment of several reproductive disorders and to achieve ovarian suppression.38–45 In birds, the use of leuprolide acetate to regulate reproductive cycles has been reported, especially during attempts to stop egg laying in small psittacine pets46–48; however, only limited studies are available on the use of GnRH agonists in other psittacine birds.49,50 In one study, Hispaniolan Amazon parrots (Amazona ventralis) given a single intramuscular injection of leuprolide acetate at a dose of 800 µg/kg had significantly decreased plasma concentrations of 17 beta-estradiol and androstenedione, but no change in testosterone concentration was noted to inhibit the hypothalamic-pituitary-gonadal axis in avian species.51 Hormonal suppression lasted for approximately 2 weeks.49 The length of action of deslorelin has been evaluated in Japanese quail ( Coturnix coturnix japonica) after implantation of a 4.7-mg deslorelin implant. In 60% of the birds implanted, egg production was decreased for approximately 70 days.50 These findings and clinical experience indicate that deslorelin may have a longer lasting effect than leuprolide in avian species. Studies have also evaluated the use of other GnRH agonists, such as buserelin, in a laboratory setting in order to evaluate testosterone secretory capacity in the initial hyperstimulatory stage.51

In the cases presented here, the use of a GnRH agonist seemed beneficial only for the bird in case 2, and the effects were suspected to last about 2 weeks and 4 months for leuprolide acetate and deslorelin, respectively. The initial leuprolide doses used in this report were taken from reports in the literature52,53 and personal experience of the authors. Further increases in the dose as well as frequency of administration were performed based on clinical response. Deslorelin implants were also considered more cost effective and reduced the frequency of hospital visits for the cockatiel in case 2. On the contrary, the bird in the first case was unresponsive to both leuprolide and deslorelin, which may have been because of an inadequate dose or frequency of dosing, unresponsive ovarian tumor cells, or a lack of additional environmental changes necessary to inhibit the hypothalamic-pituitary-gonadal axis.54 GnRH agonists may aid in long-term treatment of ovarian neoplasia in cockatiels, but as shown here, variable responses may be encountered.

These 2 cases illustrate the clinical signs, available diagnostic tests, variation in treatment responses, and long-term management options for ovarian adenocarcinoma in cockatiels. In birds with recurrent ascites, intermittent coelomocentesis can both increase the quality of life and survival time. The study also showed that response to treatment with GnRH agonists may or may not be beneficial in cockatiels and, perhaps, other psittacine birds with ovarian neoplasia.

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References


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