Pituitary-dependent hyperadrenocorticism in a cockatoo

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Case Description—A 13-year-old female intact Moluccan cockatoo (Cacatua moluccensis) was evaluated because of coelomic distention, presumed to be secondary to an abdominal hernia. The patient also had a history of rapid weight gain and polyuria and polydipsia.

Clinical Findings—Ultrasoundography was used to confirm the existence of a pseudohernia that appeared to contain the small intestines, pancreas, and reproductive tract. Results of plasma biochemical analysis revealed hyperglycemia, hypophosphatemia, and high nonfasting bile acid concentrations and aspartate aminotransferase activity. A CBC revealed a relative lymphopenia with a concomitant lymphopenia and mild monocytosis. Histologic evaluation of a liver biopsy specimen indicated chronic hepatic lipidosis. Despite a strong clinical suspicion of hyperadrenocorticism, ACTH stimulation test results were equivocal.

Treatment and Outcome—The pseudohernia was strengthened with a prolene mesh. Despite ongoing medical and surgical care, the patient developed complications associated with the herniorrhaphy and was euthanatized. The clinical suspicion of hyperadrenocorticism was confirmed on the basis of histologic evaluation of the pituitary gland by use of special stains.

Clinical Relevance—To our knowledge pituitary-dependent hyperadrenocorticism has not been previously confirmed in Psittaciformes. The condition should be considered in birds with clinical signs consistent with those observed in mammals. For the cockatoo of this report, ACTH stimulation test results were equivocal and additional diagnostic tests should be developed for avian patients. (J Am Vet Med Assoc 2008;232:394–398)

A 13-year-old female Moluccan cockatoo (Cacatua moluccensis) was admitted to the Avian and Exotic animal service at the Cornell University Hospital for Animals for evaluation of a presumptive abdominal hernia. A hernia had been diagnosed by the referring veterinarian on the basis of physical examination and radiographic findings 10 days prior to admission. Historically, the owners reported sudden weight gain, dyspnea, polyuria, and polydipsia of approximately 2 months’ duration. Additionally, the bird had alopecia of the sternum and a sore on the keel of the sternum that were attributed to feather picking and self-mutilation, respectively. Dyspnea, polyuria, and polydipsia were temporally related to the abdominal distention, progressing conjointly in severity. At the time of hospital admission, the patient weighed 1,100 g (2.42 lb.), which is an increase from the typical adult weight of the bird of approximately 750 g (1.65 lb). Severe coelomic distention was observed with the duodenum and pancreas visible through the ventral midline skin. The liver was palpably enlarged with mild sternal lift, increased caudal extension of the liver, and rounded hepatic borders. No abnormalities were detected upon auscultation of the heart, lungs, or air sacs.

Results of physical examination, evaluation of whole body radiographic views by the referring veterinarian, and diagnostic testing supported a diagnosis of abdominol hernia, and the patient was admitted to the hospital for exploratory celiotomy and herniorrhaphy. Additional diagnostic tests performed included a CBC, plasma biochemical analysis, and ultrasonographic evaluation of the coelomic cavity. The total WBC count was within reference range limits (5.8 × 10^3 WBCs/µL; reference range, 5 to 11 × 10^3 WBCs/µL), with mildly low Hct (39%; reference range, 40% to 48%). A relative heterophilia (86%; reference range, 50% to 80%) was present with a relative concomitant lymphopenia (12%; reference range, 20% to 43%) and mild monocytosis (1.7%; reference range, 0% to 1%). Results of plasma biochemical analysis revealed mildly high aspartate aminotransferase activity (448 U/L; reference range, 145 to 355 U/L), high nonfasting bile acids concentration (209 µmol/L; reference range, 25 to 87 µmol/L), moderate hyperglycemia (502 mg/dl; reference range, 185 to 355 mg/dL), and hypophosphatemia (1.7 mg/dL; reference range, 2.5 to 5.5 mg/dL). The observed abnormalities in the WBC indices and the hyperglycemia were initially attributed to stress and excitement. High aspartate aminotransferase activity and plasma bile acids concentration were attributed to a hepatopathy with subsequent hepatomegaly. The etiology of the hypophosphatemia was not immediately apparent.

Coelomic ultrasonography was performed to characterize further the hernial contents. A true hernia could not be characterized further the hernial contents. A true hernia could...
not be identified; however, generalized atrophy of the abdominal musculature was observed. The duodenum, pancreas, and ventriculus, as well as a large, mildly hyperechoic liver, were readily viewed within the coelom. In addition, the ovary and oviduct were also identified dorsal to these structures. These findings were corroborated by surgical exploration of the area that revealed a diffusely thin, transparent abdominal musculature underlying the coelomic contents. Owing to the large size of the liver, its rounded margins, and fatty appearance, as well as the abnormal plasma aspartate aminotransferase activity and bile acids concentration, a biopsy specimen of the liver was obtained for histologic evaluation. Detailed exploration of the coelomic cavity during surgery was limited by extensive coelomic fat accumulation. Because of the diffuse and severe atrophy of the abdominal muscles, an 8 × 6-cm ovoid piece of prolene mesh was used to replace the abdominal wall. The repair yielded a reduction in the size of the abdominal distention by approximately 15%. Anesthetic recovery was uneventful. The patient was discharged from the hospital the following day and was administered a 7-day course of enrofloxacin (15 mg/kg [6.8 mg/lb], PO, q 24 h) and a 5-day course of meloxicam (0.3 mg/kg [1.4 mg/lb], PO, q 24 h). A postoperative examination within 7 days was recommended.

Histologic evaluation of the liver biopsy specimen indicated severe, diffuse hepatic lipidosis with biliary hyperplasia and extramedullary hematopoiesis. Hepatic portal areas and central veins were indistinct, and multifocal areas of parenchymal collapse were identified within the examined sections, changes indicative of chronic hepatic lipidosis. The patient was reevaluated 17 and 24 days after surgery. The bird was bright, alert, and responsive, and by the second visit was approaching an ideal body weight. The droppings continued to be voluminous; however, the owners perceived that the frequency and total volume had decreased slightly over time. On initial reexamination, evidence of delayed wound healing of the skin was observed, particularly along the most dependent two thirds of the incision.

During the first postoperative visit, CBC and plasma biochemical analyses were repeated. The Hct had decreased to 32%, and mild leukocytosis (11.8 × 10³ WBCs/µL) was observed. When considering the WBC differential, the proportion of heterophils was toward the upper end of the reference range (72%), whereas the proportion of lymphocytes was toward the lower end (24%). Mild monocytosis (1.7%) was also present. Plasma biochemical parameters were within reference limits except for a mild to moderate hypouricemia (1.4 mg/dL; reference range, 3.5 to 10.5 mg/dL). By the second visit, the cranial-most third of the skin incision had healed; the caudal two thirds continued to be covered by a dark-brown scab. However, owing to a lack of evidence of disseminated systemic disease, odor, or discharge, medical management consisting of enrofloxacin (15 mg/kg, PO, q 24 h) and nonadherent dressings was elected.

Review of clinical signs and history after the second postoperative examination suggested that these features were consistent with those seen in mammalian hyperadrenocorticism.1 Thus, an ACTH stimulation test was recommended to evaluate the hypothalamic-pituitary-adrenal axis.

An ACTH stimulation test based on a previously published protocol in Moluccan cockatoos2 was performed 41 days after surgery. As per the published protocol, the patient received 0.15 mg (0.2 mg/kg [0.09 mg/lb]) of cosyntropin via IM injection into the pectoral musculature. Baseline serum corticosterone concentration was measured, as were concentrations at 1 and 3 hours after stimulation, with the aim of comparing the degree of stimulation to that found in the work of Walsh et al.2 The patient had a baseline serum corticosterone concentration of 13 ng/mL, with concentrations of 87 and 92 ng/mL, at 1 and 3 hours after stimulation, respectively. Given that the patient had a similar degree of stimulation to that observed in the work of Walsh et al,2 it was decided that the patient did not over stimulate; thus, a diagnosis of hyperadrenocorticism was not achieved via this test.

The patient continued to have delayed surgical wound healing and was admitted twice over the next 2 weeks for management of the incisions. The prolene mesh was found to be infected, and an abscess was removed, but unfortunately, the patient’s condition worsened after the second surgery; the bird had 2 episodes of cardiorespiratory arrest and was subsequently euthanatized. Gross necropsy examination performed 24 hours after death revealed extensive fibrous adhesions between the coelomic visera and the prolene mesh as well as multiple fibrous and fibrinous adhesions between caudally located coelomic visera. Additionally, fibrin was present in the cranial portion of the coelomic cavity. In contrast to the normal anatomical situation in birds in which the adrenal glands are flat and closely opposed to the cranial poles of the kidneys, adrenal glands in this bird were prominent, rounded, and bulged over the ventral aspect of the renal surfaces.3 The adrenal glands were roughly bilaterally symmetrical, measuring 5 mm in diameter. The pituitary gland measured 3 mm in diameter, had caused mild compression of the surrounding CNS structures, and was therefore considered enlarged. Thyroid glands were pale tan, smooth, and bilaterally symmetrical and measured 2 mm in diameter each. Because of the small size, symmetry, and contour of the thyroid glands, they were judged to be within reference limits. Representative sections of tissues were fixed in neutral-buffered 10% formalin, processed routinely, and stained with H&E for histologic examination. Histologic sections from the CNS, including the pituitary gland, measured 5 µm thick; all remaining tissues were sectioned at 4-µm thickness. In addition to routine staining, sections of the pituitary gland were examined for ACTH immunoreactivity via a streptavidin-biotin immunoperoxidase technique by use of a rabbit anti-ACTH antibody4 and an automated immunohistochemistry stainer in accordance with the instructions of the manufacturer.5 An additional section of pituitary gland was incubated with normal rabbit IgG rather than rabbit anti-ACTH antibody to serve as a negative control sample.

Histologically, diffuse bilateral hyperplasia of the adrenal glands was found. Adrenal glands were com-
posed of approximately 85% inter-renal (cortical type) cells, recognized by abundant foamy eosinophilic cytoplasm. Fifteen percent of the adrenal gland was composed of chromaffin (medullary type) cells. The normal structure of the pituitary gland was replaced by a mass of largely agranular epithelial cells arranged in chords and acini supported by a fine fibrovascular stroma. Neoplastic cells had abundant pale, basophilic, foamy cytoplasm and round nuclei containing coarsely stippled chromatin. Moderate anisocytosis and anisokaryosis were observed. Rare, widely scattered cells contained small numbers of eosinophilic cytoplasmic granules. Scattered acini were filled by small amounts of homogeneous eosinophilic material. Small numbers of the neoplastic cells were immunoreactive for ACTH. Immunoreactive cells were either solitary or present in small clusters.

These findings were consistent with a pituitary adenoma. Given the necropsy findings of a pituitary tumor with bilateral adrenal hyperplasia as well as the clinical signs at admission, a diagnosis of PDH was made.

Discussion

To our knowledge, a confirmed case of PDH has not been previously reported for birds. The patient in this report presented with several clinical signs and clinicopathologic features common to dogs with hyperadrenocorticism, such as polyuria and polydipsia, pendulous abdomen, abdominal muscle weakness, hepatomegaly, hepatic lipidosis, increased intra-abdominal fat, weight gain, delayed wound healing, a relative heterophilia, lymphopenia, concurrent monocytosis, high liver enzyme activities, hyperglycemia, and hypophosphatemia. It was these clinical signs and clinicopathologic findings that directed us toward the consideration of hyperadrenocorticism as a potential diagnosis.

Despite a high index of clinical suspicion and an attempt to confirm the diagnosis with antemortem testing, a definitive diagnosis was not achieved in this bird until a necropsy examination had been performed. An ACTH stimulation test was performed on the basis of the published protocol of Walsh et al. The original study of 28 clinically normal adult Moluccan cockatoos revealed a mean basal serum corticosterone concentration among females of 18 ng/mL and a mean post-stimulation concentration of 110 ng/mL at 2.5 hours. Therefore, the typical degree of stimulation achieved was 6 times the baseline concentration. The patient in this report achieved a 7-fold increase in serum corticosterone concentrations in response to ACTH (13 ng/mL at baseline and 92 ng/mL at 3 hours after stimulation). Such a degree of stimulation was not considered appreciably greater than that reported by Walsh et al; thus, a diagnosis of hyperadrenocorticism was not obtained via this test.

Among dogs, ACTH stimulation tests have been reported to have a sensitivity of approximately 85% for the diagnosis of PDH; therefore, 13% of truly affected dogs are falsely declared negative for PDH by this test. The sensitivity of this test in birds is currently unknown, and despite a high degree of conservation between the avian and mammalian endocrine system, it is unclear whether an exaggerated response should be expected. One possible explanation of the lack of aberrant ACTH stimulation could be that the bird had a cyclic form of hyperadrenocorticism (ie, Cushing’s disease). This condition occurs rarely in humans and is associated with intermittent secretion of ACTH hormone via functional pituitary adenomas. Clinical signs and clinicopathologic features may vary with this condition and wax and wane depending upon the degree of secretion of ACTH. Such a condition might explain the resolution in the biochemical parameters observed between the initial profile and that performed at the first recheck appointment of the patient in this report. As an alternative hypothesis, it is possible that ACTH responsiveness varies diurnally among cockatoos. Among rats, it has been shown that ACTH stimulation is greatest during the diurnal nadir of corticosterone concentrations. If such a phenomenon were to occur among cockatoos, then failing to perform an ACTH stimulation during the corticosterone nadir may lead to a spurious decrease in the degree of stimulation. Although this theory remains possible, it is somewhat less likely given previous work indicating that no evidence exists for diurnal responsiveness to ACTH stimulation in pigeons (Columba livia domestica).

We considered the use of a dexamethasone suppression test to confirm the suspected diagnosis in vivo. However, although baseline data on the degree of suppression achieved by various doses of dexamethasone exist for pigeons, no published data exist for psittacines. We also considered advanced imaging modalities in the diagnostic process; however, the patient had developed complications associated with the herniorrhaphy prior to any such testing.

Necropsy findings of a pituitary adenoma along with bilateral adrenal gland hyperplasia are consistent with PDH. Additionally, the presence of ACTH immunoreactive cells within tumor indicates that the neoplasm may have been hormonally active. Despite certain structural and functional differences between birds and mammals, the avian hypothalamic-pituitary-adrenal axis shares many similarities with the mammalian axis. In their report on the microscopic and functional anatomy of the hypothalamic-pituitary-adrenal axis of the budgerigar (Melopsittacus undulatus), Kobayashi et al confirmed findings of earlier reports that the avian pituitary gland consists of an adenohypophysis and a neurohypophysis. However, unlike the situation in mammals, the adenohypophysis consists only of the pars distalis and the pars tuberalis; no functional pars intermedia exists. The pars distalis represents the largest portion of the adenohypophysis and is situated ventral to the neurohypophysis. The pars distalis consists of the cephalic lobe and the caudal lobe, which consist of 2 cytologically distinct cell types. The ACTH-secreting cells are located in the cephalic lobe and are under the positive influence of corticotrophin-releasing factor, produced by the hypothalamus. Corticotrophin-releasing factor is itself negatively regulated by corticosterone, the primary adrenal glucocorticoid of birds.

Although a number of birds with pituitary adenomas and adenocarcinomas have been reported in the literature, these reports lack the clinical, clinicopatho-
logic, and histopathologic features necessary for a definitive diagnosis of PDH.\textsuperscript{15-17} Previously reported pituitary pathologic changes of birds include adenomas and adenocarcinomas with variable frequency, particularly in budgerigars.\textsuperscript{15,16} In 1999, Suchy et al\textsuperscript{17} reported on the occurrence of 6 pituitary gland tumors among 286 necropsy examinations of birds obtained over a 10-year period in which the brain was examined histologically.\textsuperscript{17} Two of the lesions were classified as chromophobic pituitary adenomas, 2 as chromophobic adenocarcinomas, and 2 as acidophilic carcinomas. Although the 2 acidophilic carcinomas had immunoreactivity to anti-growth hormone antibodies, no other pituitary gland neoplasms were immunoreactive to anti-ACTH, anti-growth hormone, anti-melanocyte-stimulating hormone, or anti-prolactin antibodies. Thus, no immunohistochemical support of PDH was found among the members of that study population.\textsuperscript{17} Although clinical signs consistent with PDH, such as polyuria, polydipsia, hyperglycemia, and obesity, have been observed in a number of birds, the authors of these reports\textsuperscript{15,16,18,19} were unable to determine the exact etiology of these clinical signs and thus could not confirm PDH. It has been suggested that the clinical signs observed among affected birds may be the result of growth hormone excess, decreased arginine vasotocin production, cerebral compression, or excess production of ACTH.\textsuperscript{19}

The microanatomy of the avian adrenal gland is distinct from the mammalian adrenal gland. It is not divided into an outer cortex and an inner medulla; rather catecholamine-producing cells (chromaffin cells) and corticoid-producing cells (cortical [inter-renal] cells) are interspersed within the adrenal glands. Cortical cells are the major cell type and form cords that generate a subcapsular zone and an extensive inner zone within the gland.\textsuperscript{20,21} As reviewed by Lumeij,\textsuperscript{22} various forms of primary adrenal pathologic findings have been reported for a number of avian species. Reported adrenal gland lesions include bilateral adenoma and cortical hyperplasia, unilateral adenoma, and unilateral adrenocortical carcinoma.\textsuperscript{22} However, in none of these affected birds was functional hyperadrenocorticism described clinically. To our knowledge, only 1 clinical report\textsuperscript{15,16} of hyperadrenocorticism in a bird exists in the veterinary literature. This brief communication describes a scarlet macaw (Ara macao) found to have unilateral adrenal gland carcinoma on necropsy examination. The patient was affected with PDH on the basis of the observed clinical and clinicopathologic findings, in conjunction with the histologic findings. A small number of the neoplastic cells in the pituitary gland were immunoreactive for ACTH. The presence of immunoreactivity in the atypical cell population, as well as the bilateral hyperplasia in the adrenal glands, suggests that the pituitary gland tumor was endocrinologically active. Findings of a study,\textsuperscript{19} in domestic birds indicate that ACTH-secreting cells are normally present only in the cephalic lobe of the avian pituitary gland. In the bird of this report, the neoplastic process had profoundly altered the anatomy of the gland such that anatomic origin of the tumor could not be determined. Detailed descriptions of the normal number and distribution of ACTH-secreting cells in pituitary gland of cockatoos are lacking, and normal pituitary glands from an age-matched bird were not available for comparison in this study. However, specific knowledge of the normal anatomy of the pituitary gland for this species might be useful in interpreting the anatomic origin of neoplasms in the future. It is, however, recommended that the diagnosis of hyperadrenocorticism be considered among psittacines with clinical signs and laboratory findings analogous to those observed in dogs with hyperadrenocorticism. Given the inability of the ACTH stimulation test to obtain a definitive diagnosis in the bird of this report, it would seem prudent to perform advanced imaging techniques to quantify gross pituitary gland lesions in suspect birds. It is also recommended that additional studies be performed to determine the viability of low-dose dexamethasone suppression testing in the diagnosis of this condition among psittacines.

\begin{itemize}
  \item[a.] Bard mesh, CR Bard Inc, Murray Hill, NJ.
  \item[b.] Cortrosyn, Amphastar Pharmaceuticals Inc, Rancho Cucamonga, Calif.
  \item[c.] ImmunoChem double antibody corticosterone—\textsuperscript{125I} RIA kit (Rats & Mice), MP Biomedical, Diagnostics Division, Orangeburg, NY.
  \item[d.] Polyclonal rabbit anti-human adrenocorticotropic, DakoCytomation Inc, Carpinteria, Calif.
  \item[e.] Dako Autostainer Plus, DakoCytomation Inc, Carpinteria, Calif.
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\textbf{References}


