Intrahepatic cholangiocarcinoma and encephalomalacia in a budgerigar (*Melopsittacus undulatus*)

Nouri, M.*, Marjanmehr, S.H., Sasani, F.

Department of Pathology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.

Key words:
cholangiocarcinoma, encephalomalacia, Budgerigar, liver, brain.

Correspondence
Nouri, M.
Department of Pathology, Faculty of Veterinary Medicine, the University of Tehran, Tehran, Iran, P O. Box: 16558-46861.
Tel: +98(21) 88066331
Fax: +98(21) 66933222
Email: mnouri2@ut.ac.ir

Received: 21 September 2011
Accepted: 5 January 2012

Abstract:

Encephalomalacia is softening or loss of brain tissue following cerebral infarction; cerebral ischemia infection, craniocerebral trauma or other injuries. Cholangiocarcinomas are malignant neoplasms of biliary epithelium, which usually arise from the intrahepatic ducts. A budgerigar was presented with a history of ataxia, decreased activity, neck weakness and weight loss. Supportive care was attempted, but the bird did not improve and euthanasia was elected. At necropsy, the liver was pale and large. There were two symmetrical pale areas on the cortical surface of cerebrum. Representative specimens from all tissues were fixed in 10% buffered formalin, embedded in paraffin and stained with hematoxylin and eosin (HE). In gray matter of cerebral tissue, there were small clear vacuoles of varied size that formed in the cytoplasm of neuron cell bodies. Proliferation of capillaries was seen. The fluid-filled clear spaces were in the white matter especially in peduncles. There were a few thromboses in the vessels and neuronal necrosis of cerebrum. Neoplastic tissue was limited to the liver. There were numerous epithelial lined ducts with an associated dense fibrous stroma. Cholangiocarcinoma and encephalomalacia were confirmed based on the macroscopic and microscopic evidences. It seems that chronic exposure to a mycotoxin and vitamin E deficiency are probable causes of encephalpmalacia and cholangiocarcinoma in this bird.

Case history

Encephalomalacia is the softening or loss of brain tissue following cerebral infarction; cerebral ischemia infection, craniocerebral trauma, or other injury (Klein et al, 1994). This disease has the symptom of a common lesion in poultry and turkeys with vitamin E deficiency (Klein et al, 1994; Rendall, 1995). The occurrence of this disease in other birds is associated with some type of vitamin deficiency, especially vitamin E (Ryan, 1989; Huff, 1993; Rendall, 1995; Harcourt-Brown and Chity, 2005). Lesions are commonly observed in the cerebellum and peduncles, but may be seen in other parts of cerebrum.

Cholangiocarcinoma, also called bile duct carcinomas or cholangiocellular carcinomas, are malignant neoplasms of the biliary epithelium, which usually arise from the intrahepatic ducts, but extra hepatic bile ducts can be affected. A large single mass or multiple nodules may be present within the liver. Although rare, cholangiocarcinoma has been reported in several species of domestic and captive wild birds (Lombard and Witte, 1959; Webster et al., 1969; Wadsworth et al., 1978; Allen et al., 1985; Renner et al., 2001; Van Wetter et al., 2010). Prevalence of neoplasms appears to be considerably greater in psittacines than in other orders of birds (Lombard and Witte, 1959; McMillan, and Petrak, 1981; Elangbam and Panciera, 1988; Hillyer et al., 1991; Coleman, 1991; Leach, 1992; Kennedy et al., 1996; Degernes et al., 1998; Paul et al., 2002; Gibbons et al., 2002).

Internal papillomatosis is occasionally found in association with biliary, hepatic, intestinal, and/or pancreatic carcinomas in Amazon parrots (Amazona spp.) and macaws (Ara spp.) (Coleman, 1991; Hillyer et al., 1991; Kennedy et al., 1996; Gibbons et al., 2002). This association has not, however, been described in a Budgerigar. This report describes the ante mortem signs and the postmortem diagnosis of encephalomalacia and intrahepatic cholangiocarcinoma, in an adult male Budgerigar.

Clinical presentation

In mid-May 2009, an adult male budgerigar was presented with a 1 month history of decreased activity and weight loss, despite good food intake. Also, the owner reported observing ataxia over that time period. Physical examination revealed a weak bird with signs of neck weakness, dysmetria and star gazing (Figure 1a). The bird's diet was composed largely of a commercial parrot mix (commercial name was not recorded), fresh fruit and an equal proportion of a mixture of seeds purchased from bulk bins at a local retail pet store. The budgerigar was referred by the clinician to the Veterinary Pathology Department, University of Tehran, for more routine pathological studies.

At necropsy, the liver was diffusely pale and large. The gastrointestinal tract was congestive. A section of the skull revealed well-circumscribed symmetrical pale areas meas uring 7 mm in diameter, located at the caudal part of the cortical surface of cerebrum and the volume of CSF fluid was increased from that which would have been expected in a normally healthy adult budgerigar. The cerebellum appeared edematous (Figure 2a). Other organs appeared normal in size and shape. Icterus was not present.

Upon microscopic examination, in the gray matter of the cerebral tissue, there were small clear vacuoles of varied size that formed into the cytoplasm of the neuron cell bodies (spongiform change). The perivascular spaces were wide as a result of fluid leakage and similar changes were seen around neurons. Neuronal cell bodies of the cerebral cortical laminae were red, angular and shrunken, and their nuclei were dense (neuronal necrosis). Proliferation was observed in the capillaries. The fluid filled clear spaces (status spongiosus) were in the white matter, especially in the peduncles (Figure 2b). There were a few thromboses in the vessels and there was neuronal necrosis of the cerebrum.

Histopathologic examination of the liver revealed marked alteration of hepatic architecture due to the widespread infiltration by neoplastic biliary tissue. There were numerous epithelial lined ducts with associated dense fibrous stroma (Figure 1b). The remaining hepatic architecture was almost totally disrupted by chronic inflammatory cell infiltration and fibrosis. There were multiple sites of hepatic necrosis in the adjacent parenchyma and occasional mitotic figures. Neoplastic tissue was not recognized in other organs and tissues.

Diagnostic Testing

Supportive care was attempted, but the bird did not improve and euthanasia was elected. Representative specimens from all organ tissues were fixed in a 10% buffered formalin, embedded in paraffin and stained with HE.

Assessments

Avian tumors are common (Petrak and Gilmore, 1982; Leach, 1992; Rendall, 1995; Harcourt-Brown and Chity, 2005). Lombard and Witte 1959 reviewed the frequency and type of tumors found at post-mortem examination of 10,240 birds at the Philadelphia Zoo. Only 17 tumors out of a total of 136 avian tumors were reported to be of hepatic, biliary or pancreatic origin. Neoplastic disease of exotic and caged birds appears to be especially prevalent in the kidneys, gonads, and adrenals (Montali, 1985), and is very common in birds of the Psittaciformes order (Lombard and Witte, 1959). Cholangiocarcinoma is the most common avian hepatic tumor, and it has been reported in a variety of species (Lombard and Witte, 1959; Webster 1969; Wadsworth et al., 1978; Allen et al., 1985; Renner et al., 2001, Van Wetter et al., 2010). No environmental or nutritional etiologies for avian cholangiocarcinomas have been documented. Cholangiocarcinoma have been associated with bile duct parasites in mammals (Popp, 1990), and with a variety of chemical compounds found in all species (Popp, 1990; Ling et al, 1993), and bile duct hyperplasia has been associated with mycotoxicosis

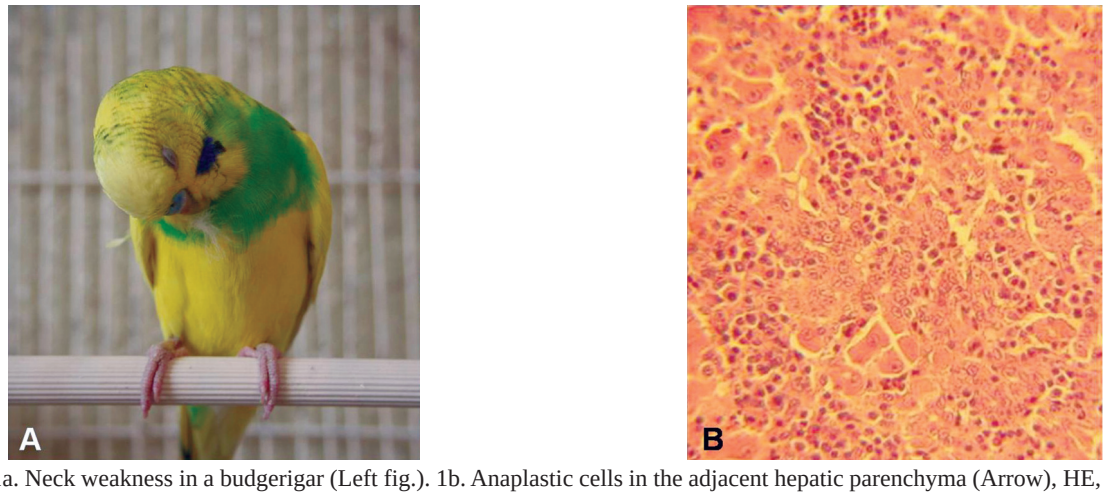

Figure 1a. Neck weakness in a budgerigar (Left fig.). 1b. Anaplastic cells in the adjacent hepatic parenchyma (Arrow), HE, Original magnification 40× (Right fig.).

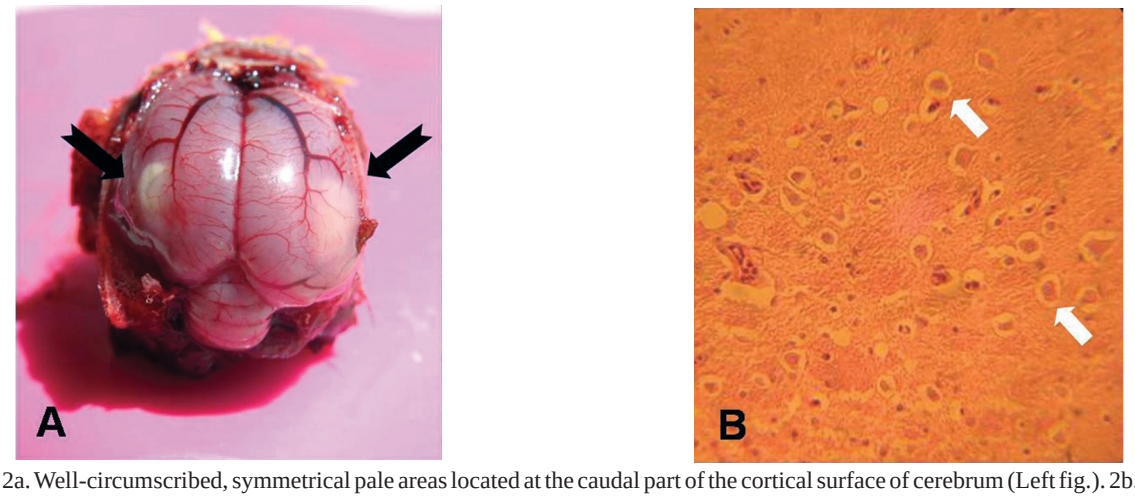

Figure 2a. Well-circumscribed, symmetrical pale areas located at the caudal part of the cortical surface of cerebrum (Left fig.). 2b. Status spongiosus and edema in white matter of peduncle, HE, Original magnification 40× (Right fig.).

in fowl (Latimer, 1994; Clyde et al., 1996). No evidence of parasitism was noted in this bird. Bile duct hyperplasia has been reported to occur in psittacine birds with hepatotoxic diseases, including aflatoxicosis (Latimer, 1994; Clyde et al., 1996). Aflatoxins may, also, be carcinogenic, and bile duct hyperplasia may precede hepatic neoplasia, although controlled studies on psittacine birds are lackig (Campbell, 1986; Clyde et al., 1996). The diet of the presently reported budgerigar contained a very small complement of peanuts, and the owner provided a seed mix purchased in small quantities from bulk bins at a local pet retailer, so chronic exposure to a mycotoxin is possible. Cholangiocarcinoma have been associated with cloacal papillomas in Amazon parrots (Amazona spp.) (Hillyer et al., 1991; Gibbons et al., 2002), and may have been associated with cloacal prolapse in an orange-winged Amazon parrot (Coleman, 1991). Oropharyngeal and cloacal papillomas with neoplasia and hepatic metastasis has been reported in macaws (Ara spp.) (Kennedy et al., 1996). We could not trace any such disease in the medical record of this bird.

In histological appearance, the cholangiocellular carcinoma found in this bird was essentially similar to the liver tumors encountered in other avian species (Hillyer et al., 1991; Degernes et al., 1998; Gibbons et al., 2002; Paul et al., 2002) with the histology varying according to the degree of malignancy.

Cholangiocarcinomas needs to be differentiated from chronic hepatotoxin induced bile duct proliferation that is often accompanied by fibrosis and distortion of the hepatic architecture. In domestic mammals (Popp, 1990), cholangiocarcinomas may be confused with metastatic adenocarcinomas, especially those arising within the gastrointestinal tract. In the

present case, the digestive tract lacked macroscopic and microscopic evidence of a primary neoplastic process.

Vitamin E and selenium deficiencies have been frequently described in the avian species (Ryan, 1989; Huff, 1993). Encephalomalacia is commonly reported in chicks and associated with a high dietary content of polyunsaturated fatty acids and Vitamin E deficiency (Klein et al, 1994; Rendall, 1995). Vitamin E deficiency is unusual with adequate amounts of seed based diets (Harper, 1998). However, with an excessive supplementation of the diet with cod liver oil, a deficiency can occur through oxidation of Vitamin E because of the presence of unsaturated fatty acids (Tollefson, 1982). Vitamin E is very unstable and prone to oxidation; therefore, it may be important as a deficiency problem in birds maintained on formulated diets, particularly those without preservatives. Because of the slow turnover of many of these products, storage times may become excessive in retail outlets. It is important to instruct clients to check the expiration dates carefully and/or look for protective (gas barrier) packaging (Bauck, 1995). In young birds, Vitamin E deficiency causes signs of myopathy due to encephalomalacia, but adult birds are not affected in this manner (Harcourt-Brown and Chity, 2005). Vitamin E deficiency is a probable cause of encephalpmalacia in this bird.

This case appeared to be the first reported case of encephalomalacia associated with intrahepatic cholangiocarcinoma in a budgerigar.

Acknowledgments

We particularly thank Dr. Hasti Azarabad for assistance with photomicroscopy.

References

1. Allen, J.L., Martin, H.D., Crowley, A.M. (1985) Metastatic cholangiocarcinoma in a florida sandhill crane. J. Am. Vet. Med. Assoc. 187: 1215.
2. Bauck, L. (1995) Nutritional problems in pet birds. Sem. Avian. Exot. Pet. Med. 4: 3-8
3. Campbell, T.W. (1986) Mycotic diseases. In: Clinical Avian Medicine and Surgery. Harrison G.J., Harrison, L.R. (eds.). W.B. Saunders Co., Philadelphia, PA, USA. p. 464-471.
4. Clyde, V.L., Orosz, S.E., Munson, L.M. (1996) Severe hepatic fibrosis and bile duct hyperplasia in four amazon parrots (Amazona spp.). J. Avian. Med. Surg. 10: 252-257.
5. Coleman, C.W. (1991) Bile duct carcinoma and cloacal prolapse in an orange-winged amazon parrot (*Amazona amazonica amazonica*). J. Assoc. Avian. Vet. 5: 87-89.
6. Degernes, L.A., Trasti, S., Healy, L., Spaulding, K.A., Flammer, K., Romagnano, A. (1998) Multi-cystic biliary adenocarcinoma in a blue-and-gold macaw (*Ara ararauna*). J. Avian. Med. Surg. 12:100-107.
7. Elangbam, Ch.S., Panciera, R.J. (1988) Cholangiocarcinoma in a blue-fronted amazon parrot (*Amazona estiva*). Avian Dis. 32:594-596.
8. Gibbons, P.M., Busch, M.D., Tell, L.A., Graham, J. E., Lowenstine, L.J. (2002) Internal papillomatosis with intrahepatic cholangiocarcinoma and gastrointestinal adenocarcinoma in a peach- fronted conure (*Aratinga aurea*). Avian Dis. 46:1062-1069.
9. Harper, E.J., Skinner, N.D. (1998) Clinical nutrition of small psittacines and passerines. Sem. Avian. Exot. Pet. Med. 7: 116-127.
10. Harcourt-Brown, N., Chity, J. (2005) BSAVA Manual of Psittacine Birds, British Small Animal Veterinary Association. (2nd ed.). London, UK.
11. Hillyer, E.V., Moroff, S., Hoefer, H., Quesenberry, K.E. (1991) Bile duct carcinoma in two out of ten amazon parrots with cloacal papillomas. J. Assoc. Avian. Vet. 5: 91-95.
12. Huff, D. (1993) Avian fluid therapy and nutritional therapeutics. Sem. Avian. Exot. Pet. Med. 2:13-16.
13. Kennedy, F.A., Sattler, A.S., Mahler, J.R., Jansson, P.C. (1996) Oropharyngeal and cloacal papillomas in two macaws (Ara spp.) with neoplasia with hepatic metastasis. J. Avian. Med. Surg. 10:89-95.
14. Klein, D.R., Novilla, M.N., Watkins, K.L. (1994)

Nutritional encephalomalacia in turkeys: diagnosis and growth performance. Avian Dis. 38:653-659.

15. Latimer, K.S. (1994) Oncology. In: Avian Medicine, Principles and Application. Ritchie, B. W., Harrison, G.J., Harrison, L.R. (eds.).Wingers Publishing Inc., Lake Worth, Florida, USA. p. 640-672.
16. Leach, M.W. (1992) A survey of neoplasia in pet birds. Sem. Avian. Exot. Pet. Med. 1:52-64.
17. Ling, Y.S., Guo, Y.J., Yang, L.K. (1993) Pathological observations of hepatic tumors in ducks. Avian Pathol. 22:131-140.
18. Lombard, L.S., Witte, E.J. (1959) Frequency and types of tumors in mammals and birds of the philadelphia zoological garden.Cancer. Res. 19: 127-141.
19. McMillan, M.C., Petrak, M.L. (1981) The clinical significance of abdominal enlargement in the budgerigar (*Melopsittacus undulatus*). Compend. Contin. Educ. Pract. Vet. 3: 898-904.
20. Montali, R.J. (1985) An overview of tumors in zoo animals.In: Comparative Pathology of Zoo Animals. Montali, R.J., Migaki, G. (eds.). Smithsonian Institution Press, Washington, D.C, USA. p. 531-542.
21. Montali, R.J. (1985) An overview of tumors in zoo animals. In: Comparative Pathology of Zoo Animals. Montali R. J., Migaki, G. (eds.). Smithsonian Institution Press, Washington, D.C., USA. p. 531-542.
22. Gibbons, P.M., Busch, M.D., Tell, L.A., Graham, J.E., Lowenstine, L.J. (2002) Internal papillomatosis with intrahepatic cholangiocarcinoma and gastrointestinal adenocarcinoma in a peach-fronted conure (*Aratinga aurea*). Avian Dis. 46: 1062-1069.
23. Petrak, M.L., Gilmore, C.E. (1982) Neoplasms. In: Diseases of Cage and Aviary Birds. Petrak, M.L. (ed.). Lea & Febiger, Philadelphia, USA. p. 479.
24. Popp, J.A. (1990) Tumors of the liver, gall bladder, and pancreas. In: Tumors in Domestic Animals,
25. Moulton, J.E. (ed.). (3rd ed.). Berkeley, University of California Press, USA. p. 436-457.
26. Ryan, T. (1989) Hypovitaminosis E in a cockatoo. Companion. Anim. Pract. 19:31-32.
27. Rendall, C.J. (1995) A Colour Atlas of Diseases and Disorders of the Domestic Fowl and Turkey. (2thed.). London, UK.
28. Renner, M.S., Zaias, J., Bossart, G.D. (2001) Cholangiocarcinoma with metastasis in a captive adelie penguin (*Pygoscelis adeliae*). J. Zoo. Wild. Med. 32:384-6.
29. Tollefson, C.I. (1982) Nutrition. In: Diseases of Cage and Aviary Birds (2thed.). Petrak, M.L. (ed.). Philadelphia, PA, Lea and Febigex. p. 220-249.
30. Wadsworth, P.F., Majeed, S.K., Brancker, W.M., Jones, D.M. (1978) Some hepatic neoplasm in non-domesticated birds. Avian. Pathol. 7: 551-555.
31. Webster, W.S., Bullock, B.C., Prichard, R.W. (1969) A report of three bile duct carcinomas occurring in pigeons. J. Am. Vet. Med. Assoc. 155:1200-5.
32. VanWettere, A.J., Degernes, L.A., Barnes, H. John. (2010) Combined hepatocellularcholangiocarcinoma in a lesser flamingo (*Phoenicopterus minor*). Avian. Pathol. 39: 275 - 278.

مجله طب دامی ایران، ۱۳۹۱، دوره ۶، شماره ۱، ۵۵-۵۱

کولانژیوکارسینوما داخل کبدی و آنسفالومالاسی در یک طوطی استرالیایی کوچک (*Melopsittacus Undulatus*)

محسن نوری* سید حسین مرجانمهر فرهنگ ساسانی

گروه پاتوبیولوژی، دانشکده دامپزشکی دانشگاه تهران، تهران، ایران.

(دریافت مقاله: ۳۰ شهریور ماه ۱۳۹۰ ، پذیرش نهایی: ۱۵ دی ماه ۱۳۹۰)

چکیده

آنسفالومالاسی نرم‌شدگی و از بین رفتن نسج مغز است که در پی انفارکتوس مغز (عفونت و تروما و سایر عوامل) روی می‌دهد. کولانژیوکارسینوما داخل کبدی تومور بدخیم پارانشیم صفراوی است که معمولاً از داخل کبد رشد می‌نماید. طوطی مبتلا تاریخچه‌ای از عدم تعادل، کاهش فعالیت، ضعف در نگهداشتن گردن و افت وزن داشت. علی‌رغم انجام مداخلات درمانی، پرنده نشانه‌ای از بهبودی را نشان نداد و کالبدگشایی صورت پذیرفت. در مطالعه ماکروسکوپیک، کبد رنگ پریده و بزرگ بود. در مغز دو ناحیه رنگ پریده متقارن بر روی سطح قشری هر دو لوب مغز خودنمایی می‌نمود. به منظور تثبیت نسوج، نمونه‌ها در فرمالین ۱۰٪ نگهداری شد و با استفاده از رنگ‌آمیزی هماتوکسیلین و ائوزین اسلایدهای تشخیصی تهیه گردید. در مطالعه ریزبینی، در ماده خاکستری مغز، واکوئل‌های کوچکی با اندازه‌های مختلف در سیتوپلاسم سلول‌های عصبی وجود داشت. فضای اطراف عروقی وسیع و بزرگ بود و تزاید عروقی هم مشاهده گردید. در ناحیه سفید، فضایی پر از مایعات دیده می‌شد. ترومبوزهای عروقی و نکروز نورون‌ها هم دیده می‌شد. نسوج سرطانی به کبد محدود می‌شد و در پارانشیم‌های کبدی، ارتشاح سلول‌های توموری دیده می‌شد. شمار زیادی از اپیتلیال‌ها با استرومایی فیبروزی خشن در مجاری دیده شد. با توجه به تاریخچه، یافته‌های بالینی و پاتولوژی، احتمالاً مواجه طولانی مدت با مایکوتوکسین و کمبود ویتامین E به ترتیب در بروز تومور کولانژیوکارسینوما داخل کبدی و آنسفالومالاسی نقش داشته‌اند.

واژه‌های کلیدی: کولانژیوکارسینوما، آنسفالومالاسی، کبد، مغز، طوطی استرالیایی کوچک.

*)نویسنده مسؤول: تلفن: ۸۸۰۶۶۳۳۱ (۲۱)۹۸+ نمابر: ۶۶۹۳۳۲۲۲ (۲۱)۹۸+ *Email: mnouri2@ut.ac.ir*