Adenoid Hepatocellular Carcinoma Accompanied by Uncharacterized Eosinophilic Intracytoplasmic Inclusions in a Green Iguana (*Iguana iguana*)

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Abstract: An adult, 2.9 kg, 4-year-old female green iguana, *Iguana iguana*, was examined for anorexia, weight loss, and lethargy. Physical examination revealed a dull integument, minimal pelvic and tailbase adipose deposits, and a distended coelom. Bilateral renal enlargement was identified on intracloacal digital palpation. Complete blood count and serum biochemistry results indicated hepatic and renal disease. Radiographs and ultrasound revealed severe liver enlargement and ascites. Exploratory coeliotomy revealed a massive and diffusely enlarged liver with rounded margins and a smooth capsular surface, indicative of an infiltrative process. Due to poor prognosis, the owner requested that the animal be euthanized. A diagnosis of acinar hepatocellular carcinoma was made on histopathological evaluation of liver tissue collected after euthanasia. Eosinophilic intracytoplasmic inclusion bodies, surrounded by clear halos, were seen in a few neoplastic cells. Several malignant hepatic tumors have been previously reported in reptiles; however, this case report documents the first reptilian adenoid hepatocellular carcinoma associated with intracytoplasmic eosinophilic inclusions in neoplastic hepatocytes.

Key Words: adenoid hepatocellular carcinoma, green iguana, *Iguana iguana*, inclusion bodies, liver, neoplasm.

A 2.9 kg, 4-year-old, female green iguana, *Iguana iguana*, was presented with a 2 month history of anorexia, weight loss, and sudden onset of lethargy. The iguana was captive born in Colombia and purchased when it was 3–4 months old from an exotic pet shop. The animal had no history of being dewormed. She was housed alone and had no history of egg laying. General husbandry, as outlined by the owner, was adequate. The iguana was housed at a daytime temperature range of 27–32°C (81–90°F) and a nighttime temperature range of 24–26°C (75–79°F). A general humidity of 80–90% was obtained by misting the plant foliage within the enclosure and the iguana. Lighting consisted of a circadian photoperiod of 10:14 h light:dark using correct full-spectrum light that produced artificial ultraviolet B radiation (290–320 nm). The iguana was offered an unsupplemented herbivorous diet with a proper calcium:phosphorus ratio (dandelion greens and flowers, green cabbage leaves, endive, beet greens, and commercial pellets containing alfalfa hay). A large water bowl on the bottom of the cage was available for drinking and bathing, and the enclosure was constructed to provide for an arboreal lifestyle (Roberts and Roberts, 1976; Frye, 1995; Jacobson, 2003).

Physical examination revealed a dull integument, no palpable adipose tissue present around the pelvis or tailbase, and a distended coelom (Frye *et al.*, 1994; Jacobson, 2003; Hernandez-Divers, 2006). The oral cavity was unremarkable, except for pallor of the gingival and lingual mucosa. Palpation of the internal organs was impeded because of the intracoelomic distension. Cardiac auscultation with a continuous crystal Doppler of 8 MHz revealed a normal heart rate and rhythm at 22°C (71.6°F) ambient temperature (Murray, 2006). Examination of the ocular adnexa revealed a mild-to-moderate hyperemia of the periocular conjunctiva. During intracloacal palpation, a mild bilateral enlargement of the kidneys was noted (Frye *et al.*, 1994; Jacobson, 2003; Hernandez-Divers, 2006).

Ventrodorsal and lateral survey radiographs of the coelomic cavity (Fig. 1A–B) showed a large amount of free fluid within the coelomic cavity and around the lungs, restricting visualization of the viscera (Lawson, 1979; McArthur *et al.*, 2004; Silverman, 2006). No evidence of egg stasis was identified (Cooper, 2000). An abundant amount of fecal material was visible within the cecum, which appeared distended (Rübel and Kuoni, 1991; Mitchell and Diaz-Figueroa, 2005;

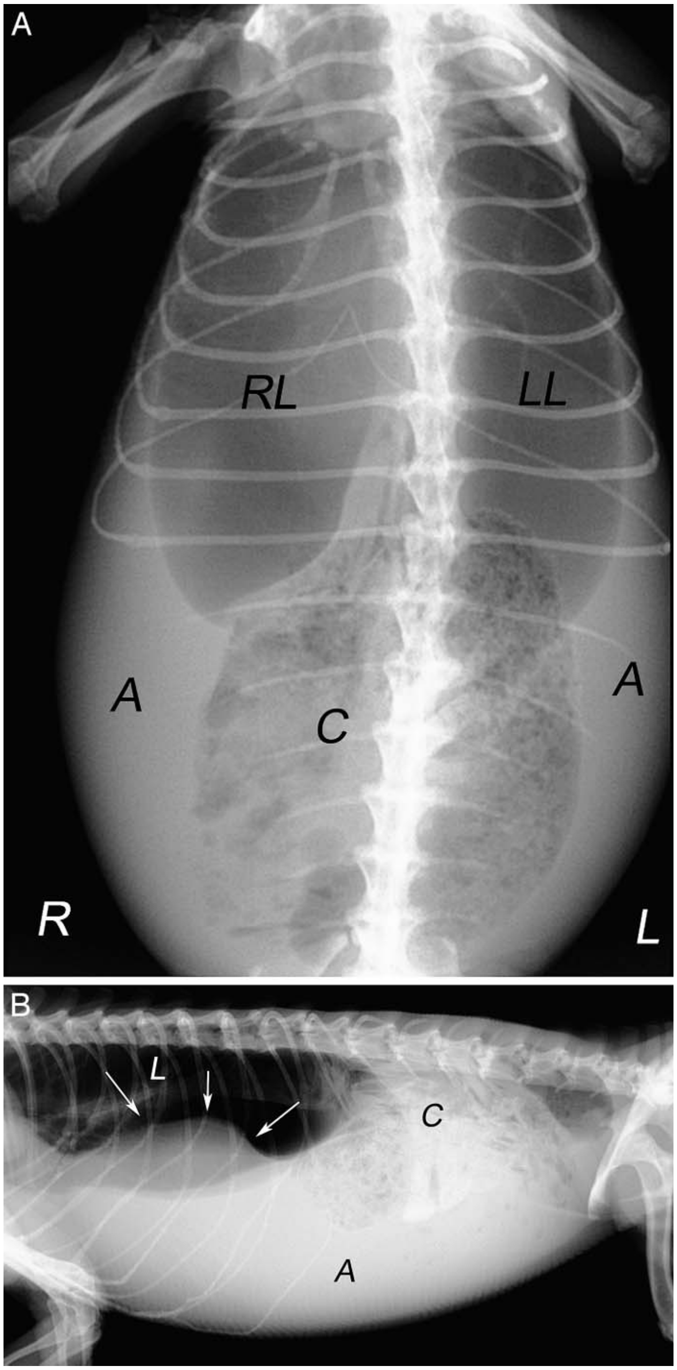

Figure 1. (A) Ventrodorsal radiographic image. Coelomic fluid opacity (ascites) around lungs restricts visualization of viscera: A = ascites, RL = right lung, LL = left lung, C = cecum (enlarged). (B) Lateral radiographic image showing soft tissue opacity (white arrows) and fluid density (A) in the coelomic cavity. A = ascites, L = lungs, C = cecum (enlarged).

Newell and Roberts, 2007). The cranial borders of the kidneys could not be identified at the entrance of the pelvic cavity (Silverman, 2006; Newell and Roberts, 2007).

Because the presence of ascites limited radiographic visualization of the coelomic viscera, ultrasonography was performed. Ultrasonography is a very specific and sensitive diagnostic tool for visualizing intracoelomic soft tissue masses, in particular in the presence of abdominal fluid, which enhances ultrasound wave penetration into the coelomic cavity. The ultrasound (MyLab®, Biosound Esaote, Genova, Italy) was performed with the animal in dorsal recumbency (Schildger *et al.*, 1996; Hochleitner and Hochleitner, 2004; Stetter, 2006; Newell and Roberts, 2007). The liver was enlarged, with caudal extension to the pelvis, and it blocked visualization of the gonads. The liver had an overall increase in echogenicity with areas of hypoechogenicity (Fig. 2A). Ultrasound confirmed the presence of abundant free coelomic fluid (Fig. 2B). The cecum and distal colon were distended with fecal material, and the fat bodies were smaller than expected for the size of the animal. Because conditions affecting the liver can lead to coagulation abnormalities (Schaffner, 1998), ultrasound-guided fine needle aspirates or biopsies were not taken due to the risk of hemorrhage.

Whole blood was collected from the ventral coccygeal vein into vacuum tubes containing either ethylenediaminetetraacetic acid or heparin for complete blood count

Figure 2. (A) Ultrasound image of the liver (short axis section). Hepatomegaly with areas of increased and decreased (white arrows) echogenicity. L = liver. (B) Ultrasound image of the liver (long axis section). Hepatomegaly with increased echogenicity and surrounding ascites. L = liver, A = ascites.

(Laboratoire Hernandez-Morin®, Longjumeau, France) and biochemical analyses (Vettest-Idexx®, Eragny sur Oise, France), respectively (Hernandez-Divers, 2006). The complete blood count and white blood cell differential revealed that the animal was anemic with concurrent increases in lymphocyte and basophil counts (Table 1) (Frye, 1991c, 1995; Carpenter *et al.*, 2001; Jacobson, 2003; Diethelm and Stein, 2006). Biochemical analyses revealed hyperphosphatemia, hyperuricemia, hyperglycemia, and increased aspartate aminotransferase catalytic activity (Table 2) (Frye, 1991b, 1995; Carpenter *et al.*, 2001; Jacobson, 2003; Diethelm and Stein, 2006).

A direct fecal smear (Laboratoire Hernandez-Morin) performed on feces collected after spontaneous defecation revealed a mild intestinal infection with a low pathogenic flagellated protozoan *Tritrichomonas* sp.

Exploratory coeliotomy was performed to assess the coelomic organs. Tiletamine-zolazepam (Zoletil 20®, 20 mg/ml; Virbac France®, Carros, France) was administered intramuscularly at 7.5 mg/kg (Carpenter *et al.*, 2001; Funk and Diethelm, 2006). A paramedian incision was made extending from the sternum to the pelvis. The coeliotomy confirmed the presence of a large volume (nearly 100 ml) of clear and viscous ascitic fluid in the coelomic cavity that could explain the distended coelom and the difficulties encountered interpreting the radiographs. After aspiration of the free abdominal fluid, the liver was inspected and found to be pale and enlarged with rounded edges, and it had a loss of normal lobar division (Fig. 3). Macroscopically, this condition was highly suggestive of a widespread intrahepatic neoplasm. The ovaries contained a few, grossly normal, 4–5 mm follicles and were surrounded by a hyperemic serous membrane, suggestive of coelomitis (DeNardo, 2006). The kidneys were visualized at the entrance of the pelvic canal and considered to be moderately enlarged with urate stasis identifiable through the fibrous renal capsule.

Due to a poor prognosis and suspected infiltrative process concerning the liver, the iguana was euthanized at the owner's request. Immediately preceding euthanasia, two liver biopsies and one kidney biopsy were collected and fixed in 10% neutral buffered formalin; processed routinely; embedded in paraffin; sectioned at 3–5 μm; mounted on glass slides; and stained with Harris hematoxylin, eosin, and safranin.

Histopathology revealed that most of the liver architecture was diffusely replaced and expanded by abnormal hepatocytes that formed tightly packed tubules, acini, or duct-like structures and cords containing intraluminal eosinophilic (proteinaceous) amorphous material, and they were supported by moderate amounts of vascularized collagenous stroma (Fig. 4). The neoplastic cells contained a fine granular eosinophilic cytoplasm with a single, often vesicular nucleus bearing one to (rarely) two prominent nucleoli. Bile stasis was observed within the bile canaliculi due to the obstructive tumor mass. Mitoses were rare, with fewer than one per × 400 field. Small intracytoplasmic eosinophilic inclusions surrounded by clear halos were identified within several neoplastic hepatocytes (Fig. 5). In this instance, the histology of the mass was characterized by round-to-oval formations of acini-like groups of malignant neoplastic liver cells with bile secretion. Thus, this hepatic

Table 1. Complete blood count and white blood cell differential results for a green iguana, *Iguana iguana*, with adenoid hepatocellular carcinoma.

	Results	Reference range
Erythrocytes (10^6/μl)	0.51	0.8–2[a]
		1.48 ± 0.19[b]
		1–1.9[c]
Hemoglobin (g/dl)	4.1	7.1[d]
		10.7 ± 1.5[b]
		6–10[c]
Packed cell volume (%)	19	30[d]
		24–37[a]
		38.2 ± 4.4[b]
		25–38[c]
Leukocytes (10^3/μl)	40	4.5–10[a]
		13.3 ± 5.7[b]
		3–10[c]
Heterophils (%)	9	30–45[a]
		19 ± 11[b]
Heterophil absolute value (10^3/μl)	3.6	1.2–4[a]
		0.35–5.2[c]
Eosinophils (%)	0	0–2[a]
		1 ± 1[b]
Eosinophil absolute value (10^3/μl)	0	0–0.25[a]
		0–0.3[c]
Basophils (%)	6	1–4[a]
		4 ± 3[b]
Basophil absolute value (10^3/μl)	2.4	<0.5[a]
		0–0.5[c]
Lymphocytes (%)	81	40–65[a]
		69 ± 16[b]
Lymphocyte absolute value (10^3/μl)	32.4	1.6–8[a]
		0.5–5.5[c]
Monocytes (%)	2	1–4[a]
		5 ± 4[b]
Monocyte absolute value (10^3/μl)	0.8	<0.5[a]
		0–0.1[c]
Azurophils (%)	2	15–25[a]
		2 ± 2[b]
Azurophil absolute value (10^3/μl)	0.8	<0.5[a]
		0–0.1[c]

[a] DeNardo (2006).
[b] Frye (1991b).
[c] Frye *et al.* (1994).
[d] Jacobson (1981).

Table 2. Plasma chemistry results for a green iguana, *Iguana iguana*, with adenoid hepatocellular carcinoma.

	Results	Reference range
Calcium (mg/dl)	12.5	10.5–13.6[a]
		12 ± 0.7[b]
		8.8–14[c]
Phosphorus (mg/dl)	12	5.3–6.8[a]
		7.3 ± 1.5[b]
		4–6[c]
Aspartate aminotransferase (IU/L)	766	24–45[a]
		50.1 ± 39.5[b]
		5–52[c]
Creatine kinase (IU/L)	178	<100[a]
		73–666[c]
Uric acid (mg/dl)	9.2	5[d]
		0.5–3.2[a]
		4.3 ± 2.3[b]
		1.2–2.4[a]
Glucose (mg/dl)	180	155[d]
		65–155[a]
		152.6 ± 31.6[b]
		169–288[c]

[a] DeNardo (2006).
[b] Frye (1991b).
[c] Frye *et al.* (1994).
[d] Jacobson (1981).

Figure 3. Coeliotomy. Note the large size, rounded margins and severe pallor of the externalized liver.

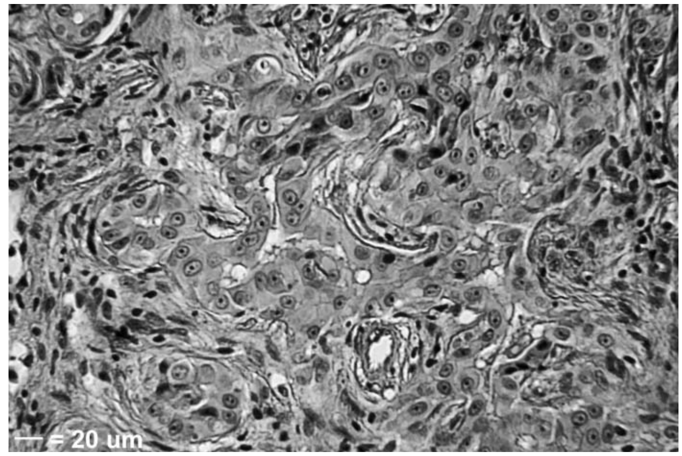

Figure 4. Photomicrograph of the hepatic tumor. Note the closely packed neoplastic hepatocytes that form branching cords and tubular structures. Hematoxylin and eosin stain, × 640 original magnification, bar = 20 μm.

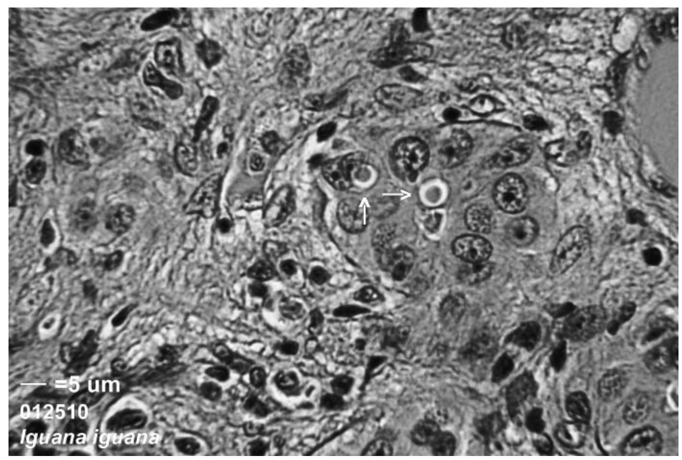

Figure 5. Photomicrograph of the adenoid hepatocellular carcinoma. Few malignant cells contain eosinophilic intracytoplasmic inclusions (white arrows) reminiscent of viral inclusions. Hematoxylin and eosin stain, × 640 original magnification, bar = 5 μm.

tumor met the criteria of an adenoid hepatocellular carcinoma (Meuten, 2002). The sole notable renal histopathological lesion consisted of mild pigment deposition within a few of the glomerular tufts.

Discussion

Several different hepatic tumors (hepatocellular carcinoma, cholangiocarcinoma, cholangioma, cholangiocarcinoma, biliary adenomas, cholangiosarcomas, hemangioendothelioma) have already been described in various species of reptiles, primarily in ophidians but also in green iguanas (Stolk, 1964; Harschbarger, 1974; Effron *et al.*, 1977; Jacobson, 1981; Hruban and Maschgan, 1982; Machotka, 1984; Majeed *et al.*, 1985; Frye, 1991c, 1994; Well and Rodiger, 1992; Cooper, 2000; Garner *et al.*, 2004; Reavill, 2004; Schilliger *et al.*, 2011). Two separate cases of hepatocellular carcinomas have been reported in green iguanas, and they consisted of multifocal hepatic nodules containing a disorganized matrix of hepatocytes and areas of multinucleated giant cells (Stolk, 1964). Bile duct adenomas also have been reported in iguanas and some species of snakes, especially colubrids. They are typically small, well differentiated, often cystic, and may be symptomatic (Garner *et al.*, 2004). A case of biliary adenocarcinoma was found in a green iguana that was asymptomatic before death (Frye, 1991a). The diagnosis was made post-mortem, with the histopathology revealing severe bile duct hyperplasia and periportal invasion with neoplastic cells. One case of a cholangioma of the gallbladder of a green iguana also has been described (Well and Rodiger, 1992).

Many factors can contribute to the development and growth of neoplastic tissue, including genetic, parasitic, environmental, and viral causes (Reavill, 2004; Mauldin and Done, 2006). Even though only a few eosinophilic intracytoplasmic inclusion bodies were identified in this case, the findings outlined remain noteworthy. This type of eosinophilic inclusion surrounded by a clear halo is commonly found in boids suffering from inclusion body disease (IBD) (Schumacher *et al.*, 1994; Wozniak *et al.*, 2000; Jacobson *et al.*, 2001; Schumacher, 2006; Chang and Jacobson, 2010; Schilliger *et al.*, 2011). This fatal disease, which has been associated with the loss of entire animal collections, has long been considered a multisystemic viral infection caused by a 90–120 nm retrovirus affecting boid snakes worldwide and has sometimes been associated with neoplasms (Ippen *et al.*, 1978; Schumacher *et al.*, 1994; Wozniak *et al.*, 2000; Jacobson *et al.*, 2001; Schumacher, 2006; Chang and Jacobson, 2010; Schilliger *et al.*, 2011). It is rarely documented in other reptile species (including snakes) and has never been reported in lizards (Raymond *et al.*, 2001). Recently, viruses with a typical arenavirus genome organization belonging to a lineage separate from that of the Old and New World arenaviruses and more similar to those of filoviruses have been recognized as candidate etiologic agents of IBD (Stenglein *et al.*, 2012).

The most commonly identified viruses in reptilian livers are the adenoviruses, and these viruses have been well studied in herpetological virology (Jacobson and Kollias, 1986; Frye *et al.*, 1994; Ramis *et al.*, 2000; Moorman *et al.*, 2009). Members of the *Adenoviridae* are non-enveloped linear double-stranded DNA viruses with an icosahedral nucleocapsid measuring between 80 and 110 nm in diameter. Replication occurs within the host cell nucleus, and new viral particles are released at cell lysis. When examining tissue sections with hematoxylin and eosin stain, typical basophilic intranuclear inclusions can be distinguished, which is not consistent with the findings in the present report. Moreover, adenoviral infections have never been reported in iguanas. Intrahepatic inclusion bodies have been found in a juvenile male green iguana that died from herpesvirus infection; however, as is the case with adenovirus infection and contrary to the present case, the inclusion bodies were intranuclear (Wilkinson *et al.*, 2005).

Antibodies against reptilian reoviruses and against one reptilian paramyxovirus were detected in wild-caught iguanids (*Ctenosaura bakeri*, *Ctenosaura similis*, and *Iguana iguana rhinolopha*), but no histological investigations were performed on the positive animals (Gravendyck *et al.*, 1998).

Unfortunately, without further ultrastructural investigation, such as electron microscopy, it was not possible to determine whether the inclusion bodies observed in this green iguana were the consequence of a viral infection.

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