

Cholangiocarcinoma in a Bitch - Multimodal Diagnosis

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ABSTRACT

Background: Hepatic tumors of primary origin account for 0.6% to 2.9% of cases in canine species, less common than hepatic metastases. The hepatic tumors are divided into hepatocellular tumors, neuroendocrine tumors, bile duct tumors or cholangiocarcinomas, and mesenchymal tumors. Cholangiocarcinomas, are classified according to their origin, being intrahepatic, extrahepatic, or gallbladder type. Cholangiocarcinomas are considered rare in dogs and cats with a ratio of 29% to 71% compared to hepatocellular carcinomas, accounting for 9% of the hepatic tumors. The present study aims to describe a case of cholangiocarcinoma in a bitch, focusing on the diagnostic approach.

Case: A 10-year-old castrated bitch Poodle was attended presenting hypoglycemia and seizure crisis. The patient had previous exams of hemogram and serum biochemical profile, showing a discrete increase of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), besides hypoglycemia. Previous ultrasound exam revealed the presence of a hepatic mass located between the right and square lobes, immeasurable, and significant splenomegaly. Abdominal palpation revealed the presence of immeasurable abdominal formation of undetermined origin. Abdominal computerized tomography (CT), glycemic curve, and insulin dosage were requested. Tomography exam showed an increase in hepatic volume with the presence of a heterogeneous formation in the right lateral lobe topography; increase in spleen dimensions and the presence of multiple nodules; and the presence of a nodule in the right lung, at the caudal thoracic region. The glycemic curve showed acute variations, and insulin dosage was between normal values. The animal was referred for surgery, as in abdominocentesis, it was observed the presence of hemorrhagic fluid, confirming active bleeding by ultrasonography. The owners chose for euthanasia. In the post-mortem evaluation the main lesion was confirmed of hepatic origin, with a massive, irregular, cavitory presentation, involving multiple hepatic lobes, and a single nodule was observed in the right caudal lobe of the right lung. Histopathological evaluation was considered inconclusive. Immunohistochemistry was performed and the association of the immunohistochemical profile with the morphological characteristics indicated diagnosis of cholangiocarcinoma.

Discussion: The related symptomatology, in hepatic neoplasms, is generally considered non-specific, with reports of lethargy, vomiting, dyspnea, anorexia and weight loss, however, the dog in this study presented a unique manifestation of hypoglycemia and one episode of convulsive crisis resulting from it. The clinical manifestation observed was extremely unspecific making initial diagnosis difficult. The ultrasonographic examination was effective in evidencing the abdominal mass. In addition, abdominal CT was also performed, which confirmed the hepatic origin, detailing the macroscopic aspect. Biochemical analyses of ALT and AST showed a discrete increase. Biochemical changes may occur in dogs with hepatic neoplasms, although they are not specific. Functional pancreatic beta-cell tumors producing insulin are the most common cause of paraneoplastic hypoglycemia, although in the case the insulin dosage was within normal limits. In cases of non-islet cell tumor the mechanism is frequently associated with the production of insulin-like growth factor (IGF). In most cases the definitive diagnosis of cholangiocarcinoma can be obtained by histopathological examination, although in the present report the result obtained was inconclusive, requiring an immunohistochemical examination. Due to the aggressive and metastatic character of this neoplastic type, early detection becomes extremely important in order to maximize therapeutic chances, however, diagnosis may be difficult.

Keywords: hepatic neoplasm, dog, biliary carcinoma, immunohistochemistry.

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INTRODUCTION

Hepatic tumors of primary origin account for 0.6% to 2.9% of cases in canine species, less common than hepatic metastases, and malignant neoplasms are more frequent than benign [2,16]. Hepatic tumors are divided into hepatocellular tumors, neuroendocrine tumors, bile duct tumors or cholangiocarcinomas, and mesenchymal tumors [5,11,17,18]. The morphological presentation may occur in nodular form, characterized by the presence of multiple nodules in hepatic lobes; massive form, corresponding to a solitary mass restricted to one of the hepatic lobes; and diffuse form, defined by multifocal to coalescing nodules disseminated in all hepatic lobes [12,16].

Cholangiocarcinomas, also called cholangiocellular carcinomas or bile duct carcinomas, are classified according to their origin, being intrahepatic, extrahepatic, or gallbladder type [6,17]. These tumors are considered rare in dogs and cats with a ratio of 29% to 71% compared to hepatocellular carcinomas [9], accounting for 9% of the hepatic tumors [17]. The present study aims to describe a case of cholangiocarcinoma, focusing on the diagnostic approach.

CASE

A 10-year-old castrated bitch Poodle was attended presenting hypoglycemia and seizure crisis. The patient had previous exams of hemogram and serum biochemical profile, showing a discrete increase of the hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), besides hypoglycemia, reported in 37.0 mg/dL. Previous ultrasound exam revealed the presence of a hepatic mass located between the right and square lobes, immeasurable, and significant splenomegaly.

The owners referred that the animal presented normorexia, with the maintenance of stable weight, normodipsia, normouria, and normoquesia. Abdominal palpation revealed the presence of immeasurable abdominal formation of undetermined origin. In view of the observed condition it was recommended food management with diet fractioning and support prescription with silymarin¹ [Compounded - 40 mg/kg, oral administration, every 24 h, 30 days] and prednisolone² [Prediderm® - 1.0 mg/kg, oral administration, every 24 h, 14 days]. Abdominal computerized tomography (CT), glycemic curve, and insulin dosage were requested.

The tomography exam showed an increase in hepatic volume with the presence of a heterogeneous formation in the right lateral lobe topography, measuring 12.6 x 9.0 x 6.3cm; increase in spleen dimensions and the presence of multiple nodules measuring 0.5 to 0.7cm; without significant changes in other structures. When the caudal thoracic region was scanned the presence of a nodule measuring about 0.7 x 0.6cm was observed in the right lung. The glycemic curve was performed for 3 consecutive days, with a maximum glycemic of 71 mg/dL and a minimum of 37 mg/dL on Day 1; 79 mg/dL and 41mg/dL on Day 2; and 75 mg/dL and 43 mg/dL on Day 3. The insulin dosage was 4.0 mcU/mL.

The animal was referred for surgery objetiving the mass excision with palliative purposes, but manifested a severe worsenem on its clinical condition with acute abdomen, distention and increase of local sensibility. On abdominocentesis, it was observed the presence of hemorrhagic fluid, confirming active bleeding by ultrasonography. Due to the severity of the condition and unfavorable prognosis, the owners chose for euthanasia.

In the *post mortem* evaluation the spleen, pancreas, and mesenteric lymph nodes were enlarged, with no apparent morphological changes. The main lesion was confirmed of hepatic origin, with a massive, irregular, cavitary presentation, involving multiple hepatic lobes (Figure 1). A single nodule was observed in the right caudal lobe of the right lung. The histopathological evaluation of the hepatic and pulmonary lesions showed a proliferation of neoplastic cells arranged in strips, forming a moderate amount of tubules and rosettes, with cuboid to columnar cell morphology and distinct cell limits. Pleomorphism, anisocytosis, and anisocariosis alterations were considered pronounced, with 16 figures of mitosis in 10 fields of greatest

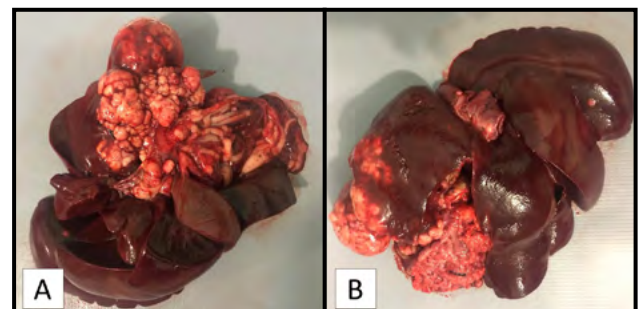


Figure 1. Liver with irregular, multilobulated mass showing multiple lobes affected. A- Visceral view. B- Parietal view.

magnification (obj. 40x). The diagnosis was considered inconclusive in both samples.

Immunohistochemistry was performed for definitive diagnosis and a positive immunoexpression panel was observed for markers AE1/AE3³, CK8/18³ (Figure 2) and CK19³; and negative for markers Chromogranin⁴, Synaptophysin³, HepPar⁵, Estrogen receptor (RE)⁵, CEA⁶, CK7⁵, and CDX2⁵. The association of the immunohistochemical profile with the morphological characteristics indicated diagnosis of cholangiocarcinoma.

DISCUSSION

The hepatic neoplasms mainly affects elderly dogs, with ages ranging from 10 to 12 years [5,7,10,14,15], with no breed or sexual predisposition established [4]. The animal described fit the epidemiological profile. The related symptomatology is generally considered non-specific, with reports of lethargy, vomiting, dyspnea, anorexia and weight loss [10,14,16,], however, the dog in this study did not present such alterations, with a unique manifestation of hypoglycemia and one episode of convulsive crisis resulting from it, with a report of this symptomatology already described [12]. Paraneoplastic hypercalcemia syndrome has also been described in the literature [8], but it was not observed in the patient. The clinical manifestation observed was extremely unspecific making initial diagnosis difficult.

The ultrasonographic examination was effective in evidencing the abdominal mass, suggesting it hepatic origin, being considered an efficient method for this evaluation [1,2,16,18]. In addition, abdominal CT was also performed, which confirmed the hepatic origin, detailing the macroscopic aspect. The CT exam is considered efficient in aiding the diagnosis of neoplasms of the abdominal cavity, in addition to its importance in surgical planning [16], although the surgery was not performed in this case. In laboratorial biochemical analyses of ALT and AST it was observed and discrete increase, as result of hepatic injury. Hematologic and biochemical changes may occur in dogs with hepatic neoplasms, although they are not specific [12].

Functional pancreatic beta-cell tumors producing excess amounts of insulin are the most common cause of paraneoplastic hypoglycemia [16], although in the present case the insulin dosage was within normal limits. In cases of non-islet cell tumor the mechanism

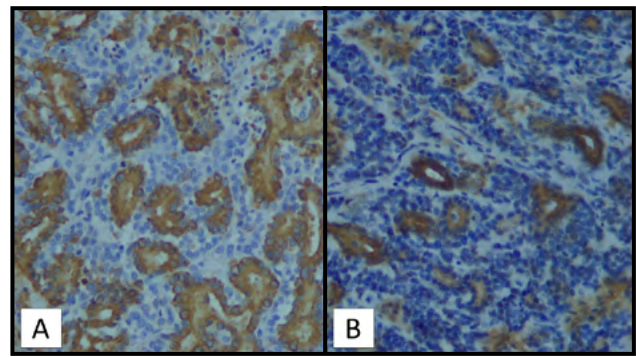


Figure 2. Immunohistochemistry exam. A- AE1/AE3 positive immunoexpression. B- CK8/18 positive immunoexpression [40x].

is frequently associated with the production of insulin-like growth factor (IGF) [13,16]. The most common form is the IGF-2 that can be produced both by neoplasias of mesenchymal and epithelial origin [3], and is characterized by persistent and severe hypoglycemia [13]. As the evaluating of the glucose curve, showed acute variation values, with persistent hypoglycemia, the mechanism was associated with the IGF-2 production. The specific IGF-2 production associated with a cholangiocarcinoma has not yet been reported.

In most cases the definitive diagnosis of cholangiocarcinoma can be obtained by histopathological examination [2,17,18], although in the present report the result obtained was inconclusive, requiring an immunohistochemical examination. Positive results were obtained for CK8/18 and CK19 markers, in agreement with the results in similar studies that reported positive markers for CK7, CK8, CK18, and CK19 for cholangiocarcinomas [11,17]. The negative result for the CK7 marker is explained by the low sensitivity of this antigen, positive in only 67% to 77% cholangiocarcinomas [11]. Other negative markers were Chromogranin, Synaptophysin, RE, CEA, HepPar, and CDX2, adding to the diagnosis exclusion of other neoplasms [16].

Cholangiocarcinomas have no aggressive behaviour and high metastatic potential, affecting more frequently lungs, lymph nodes, and peritoneum [8,9,16], although some authors also consider intrahepatic metastases, with dissemination among other hepatic lobes [10]. In the present report, a single metastatic focus in the lung and dissemination throughout the hepatic parenchyma was observed, but it is impossible to delimit which was the lobe of the initial manifestation. The development of hemoperitoneum or hemothorax due to rupture was observed in about 28%

of the cases of cholangiocarcinoma [4], in accordance with the reported case.

Surgical excision is considered the treatment of choice for hepatic tumors in early stages, although in advanced cases it may have palliative purpose [7,14,16], as indicated for the patient. The life expectancy of patients with diffuse hepatic neoplasms is lower than in massive or nodular neoplasms [12]. The presence of distant metastases is also considered a negative prognostic factor [16]. The animal had a poor prognosis, with a low survival expectancy.

Due to the aggressive and metastatic character of this neoplastic type, early detection becomes extremely important in order to maximize therapeutic chances. However, the non-specific symptomatology make diagnosis difficult. The manifestation of persistent hypoglycemia represents an important paraneoplastic syndrome, being the only early manifestation

in this case. The multimodal diagnosis, through the association of different techniques, was extremely important in the case described, and can help early detection of the neoplasm and greatly increases the chances for successful treatment.

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