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Hepatocellular Carcinoma in a Cocker Spaniel Dog with Hypoglycemia

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Abstract : A 5-year-old male Cocker spaniel was presented with an abrupt seizure episode. The dog was moderately dehydrated, hypersalivation and loss of consciousness at the presentation. Tentative diagnosis was made through history taking, clinical signs, physical examination, neurologic examination, basic laboratory examinations, radiological examination and cytologic examination. In addition, serum alpha-fetoprotein (AFP) value was measured to diagnose in this case. The serum AFP concentration was marked elevated (1513.5 ng/ml). The patient was suspected as HCC and medical therapy was initiated to control hypoglycemic-associated seizure. However, the dog was euthanized because of the owner's request. It was diagnosed as hepatocellular carcinoma (HCC) based on the histopathologic examination. This case indicates that AFP measurement might be valuable to diagnose HCC in dogs.

Key words **:** alpha fetoprotein, dog, hepatocellular carcinoma, hypoglycemia.

Introduction

Primary neoplasms of the liver and biliary tracts are rare in dogs, varying from 0.6% to 1.3% of all neoplasms (12). These hepatic tumors were including hepatocellular carcinoma (HCC), bile duct carcinoma, carcinoid, and sarcoma (12). Of them, HCC is the most common primary hepatic tumor (10, 12,13), particularly which is most common in dogs older than 10 years. Its occurrence is more often in males with no breed predominance (7,12,13).

In humans, the serum level of AFP has been used for the early diagnosis of HCC (1-3,5). As in humans, AFP concentrations are elevated in various canine hepatic disease, especially in HCC (4,8,15).

This case report describes that the value of serum AFP could be effective and acceptable diagnostic measurement in dogs with HCC.

Case

A 5-year-old male Cocker spaniel was admitted due to tonic-clonic seizures. Recently, the dog showed mild decreased appetite but no vomiting and diarrhea were noted.

When presented, the dog was depressed, laterally recumbent. Physical examination revealed a delayed skin turgor and hypersalivation. A palpable intraabdomminal mass was detected in the cranial abdominal cavity. There were no abnormal findings in neurological examinations except seizure episode.

A complete blood count (CBC) revealed moderate leukocytosis ($35.85 \pm 10^3/\mu l$; reference range, $6\text{-}17 \pm 10^3/\mu l$), mild erythrocytosis (HCT; 57%, reference range, 37-55%) and severe thrombocytosis ($966 \pm 10^3/\mu l$; reference range, $200\text{-}500 \pm 10^3/\mu l$). Serum chemistry profiles showed hypoglycemia (47 mg/dl; reference range, 75-128 mg/dl), hyperproteinemia (8.2 g/dl; reference range, 5.0-7.2 g/dl). Typically alanine aminotransferase (ALT) (1062 U/L, reference range; 17-78 U/L), aspartate transferase (AST) (126 U/L, reference range; 17-44 U/L), alkaline phosphatase (ALP) (> 3500 U/L, reference range; 0-142 U/L), gamma glutamyl transpeptidase (GGT) (60 mg/dl, reference range; 5-14 mg/dl), lactic dehydrogenase (LDH) (175 U/L, reference range; 20-109 U/L), creatine kinase (CK) (400 U/L, reference range; 49-166 U/L), and total serum bilirubin (0.8 U/L, reference range; 0.1-0.5 U/L) were all elevated.

On radiographic examination, hepatomegaly was observed in the cranial midline of abdomen (Fig 1A). Ultrasonography revealed an enlarged and hyperechoic hepatic mass (Fig 1B). Under the guidance of ultrasonography, fine needle aspiraton biopsy (FNAB) was performed. The results of FNAB revealed coarse chromatin, prominent nucleoli, anisokaryosis, increased N/C ratio, and clustered epithelia cells, which is indicative of hepatic carcinoma (Fig 3A). Thus, Serum AFP was measured in this dog and the result was markedly elevated (1513.5 ng/ml, reference range; less than 70 ng/ml). Based on the clinical signs and laboratory examination, ocurrence of the seizure episode were suspected of resulting from hypoglycemia which is induced by an intraabdominal mass.

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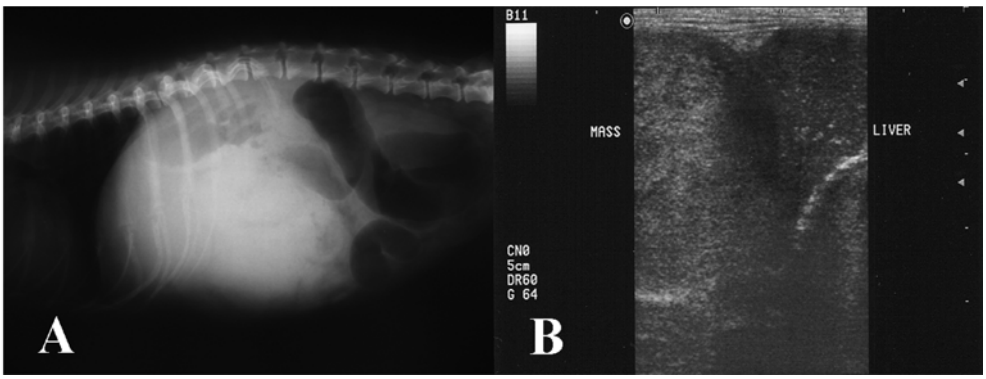

Fig 1. A photograph of lateral radiography. Note severe hepatomegaly with soft tissue density and displaced stomach (A). A photograph of ultrasonography. Note hyperehoicc hepatic mass in left lateral hepatic lobe (B).

Fig 2. A photograph of liver. Note large nodular masses in left lateral and medial liver lobes (a open arrow) and enlarged gall bladder (a black arrow).

The treatment was initiated with 20% glucose solution. The blood glucose level increased to 117 mg/dl after injection of 20% glucose solution (1 mg/kg, slowly IV). The patient recovered from the seizure episode and returned to normal consciousness. Within two hours, the blood glucose level decreased to 50 mg/dl. However, the patient was alert and favorable appetite. Thus, dietary therapy (Hill's Prescription Diet a/d) was prescribed with intravenous 10% glucose solution for hypoglycemia, but blood glucose level was decreased after 2 hours. The dog was euthanized with the owner's consent and the necropsy was performed. On gross examination, discrete nodules of various sizes in left lateral and medial liver lobes were found. However, no abnormalities were observed in other visceral organs, including pancreas and lung (Fig 2). On histopathological examination, the liver mass consisted of sheets of hepatocytes. The cells showed moderate variation in nuclear size and occasional binucleated tumor cells (Fig 3B).

Based on the histopathological results, HCC was definitely diagnosed and the hypoglycemia was paraneoplastic syndrome of HCC in this case.

Discussion

Although the primary hepatic tumors are rarely reported in dogs, HCC is the most common hepatic neoplasia (13). The gross morphologic features of HCC have been described as massive, nodular and diffuse (13). Massive HCC, especially which is involved in the left lateral liver lobe, was most common and was potentially respectable (7,13). However, involvement of multiple liver lobes has been usually unresect-

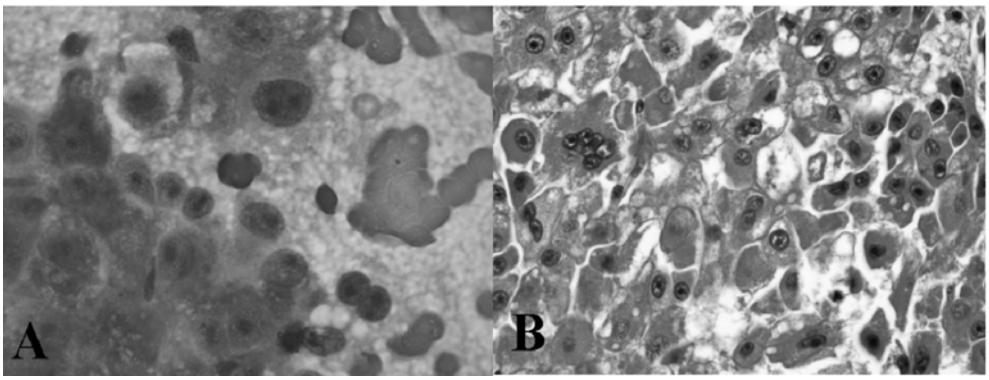

Fig 3. A microphotograph of FNAB. Note that coarse chromatin, prominent nucleoli, anisokaryosis, increased N/C ratio, and clustered epithelia cells, which is indicative of hepatic carcinoma. Diff-Quik stain (× 1000). (A). A microphotograph of histopathology. Note the mass consisted of sheets of hepatocytes. The cells showed pleomorphism and occasional multinucleated cells. H&E, × 400 (B).

able (7,13).

The most common clinical signs are hepatomegaly, lethargy, weakness, anorexia and vomiting (13). However, the dog was presented with seizure episode associated with hypoglycemia in this case. Hypoglycemia is rare paraneoplastic syndrome of HCC, which is caused by increased utilization of glucose by the tumor. Its mechanism includes release of an insulin, insulin-like peptides or growth factors (6). Recent study showed that this type of hypoglycemia is associated with hypersecretion of insulin like growth factor II synthesized in the liver of humans and dogs (14).

Although serum enzyme activities related liver functions are typically high in dogs with HCC, The early diagnosis of HCC is difficult due to the absence of remarkable clinical signs and laboratory examination (7,12,13). In addition, no characteristic signs are associated with HCC in humans (5). Thus, the serum level of AFP has been used for the early diagnosis of HCC (1-3,5). As in humans, concentrations of AFP are elevated especially in canine HCC (15). In a veterinary literature, a recent study (15) showed that serum AFP values in clinically healthy dogs were under 70 ng/ml. Serum AFP values in HCC dogs, 77% were remarkably high, more than 1,400 ng/ml. However, serum AFP values in hepatic diseased dogs without tumors were under 500 ng/ml in 90%. Non-hepatic tumor bearing dogs showed variable serum AFP values, and 92%, it was under 1,000 ng/ml. In this case, the serum AFP value was 1513.5 ng/ml, which is markedly elevated value.

The definite diagnosis of HCC is made based on the histopathologic examination. However, the remarkably high AFP value in serum is very useful diagnostic method in early detection of HCC. In this present case, we could confirm that the seizure associated with hypoglycemia resulted from HCC, since it was diagnosed by histopathology and AFP measurement in serum.

Hypoglycemia associated with massive HCC is improved generally by resection of the tumor (7,14). However, new approach for the treatment of unresectable hepatic tumor with transcatheter hepatic arterial embolization (TAE) was tried in a recent study (9,11).

In conclusion, this case demonstrates that the serum AFP value could be effective and acceptable diagnostic measurement in hypoglycemic dogs with nonislet cell tumor, HCC.

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저혈당증을 동반한 코커스파니엘견에서의 간선암종 증례

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요 약 : 5년령의 수컷 코커스파니엘견이 갑작스런 발작증상으로 내원하였다. 내원당시 중등도의 탈수, 과다유연이 관찰되었고, 의식이 소실된 상태였다. 신체검사상 상복부에서 복강내 종괴가 촉진되었고, 실험실 검사에서 저혈당증과 간효소 수치의 상승이 관찰되었다. 진단으로는 병력, 임상증상, 신체검사, 신경검사, 기본적 실험실 검사와 방사선 검사 및 세포검사가 이용되었다. 특히 원발성 간 선암종이 의심되어 혈청 중 alpha-fetoprotein (AFP)을 측정하였다. 혈청 중 AFP 수치는 특이적으로 정상견에 비해 매우 높은 수준이었다(1513.5 ng/ml). 이 환축은 원발성 간 선암종이 의심이 되었으며 이로 인한 저혈당으로 발작증상을 관리하기 위해 포도당투여를 포함한 약물치료가 시작되었다. 하지만, 보호자의 요청에 의해 안락사가 실시되었고 부검 후 조직 검사를 통하여 원발성 간 선암종으로 확진되었다. 결론적으로 본 증례의 경우 개에서 원발성 간암의 진단에 혈청 중 AFP 측정이 진단에 유용할 수 있음을 보여주는 증례다.

주요어 : alpha fetoprotein, 개, 간선암종, 저혈당증.