Case Report

Therapeutic Management of Diabetes mellitus with focal hepatic necrosis in dog

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Abstract

A 7-year-old female Labrador retriever was presented for weakness, anorexia, progressive weight loss (cachexia), polyuria and polydipsia. Physical examination revealed jaundice of mucus membranes and sclera, acholic feces, 5% dehydration, hepatomegaly, hepatodynia and sweet fruit smelling from oral cavity.Blood chemistry tests revealed hyperglycemia, hepatic dysfunction, cholestasis and inflammatory leukogram. Hematology revealed absolute neutrophilia with moderate left shift and marked toxic changes in many neutrophils, microcytic hypochromic anemia with some evidence of regeneration. Urinalysis revealed glucosuria, bilirubinuria, proteinuria, ketonuria and isosthenuria. Liver ultrasonography and fine needle aspiration biopsy (FNAB) of the liver were consistent with focal hepatic necrosis. The focal hepatic necrosis was successfully treated.

Keywords: diabetes mellitus; hepatic necrosis, management.

Introduction

Diabetes mellitus is a common condition in dogs with many concurrent complications such as cataract, urinary tract infection, metabolic acidosis, nephropathy, neuropathy, hepatic lipidosis and liver failure (Munana, 1995). Many times a treatment is directed towards maintaining the euoglycemia and ignoring other important conditions resulting from diabetes mellitus. Clinical signs are typically polyuria, polydipsia, and polyphagia. In the present study, proper diagnosis and management of a dog suffering from focal hepatic necrosis associated with diabetes mellitus was made using synergy of appropriate complementary examinations (including imaging and clinical pathology) and proper treatment.

Case discretion

A 7-year-old, intact female, Labrador retriever, was presented with a 5-day history of anorexia, weakness, polyuria and polydipsia. The report of the referring veterinarian revealed normal body temperature (102 F°), progressive weight-loss and dullness at physical examination. Hematology and biochemistry profiles are presented in Table 1 and 2, respectively. Remarkable results included subtle elevation of liver enzymes (subtle increased alanine aminotransferase and aspartate aminotransferase activities), decreased hepatic function (moderately increased fasting serum bile acids, mild hypoalbuminemia, and slightly perbilirubinemia) and cholestasis (markedly increased alkaline phosphatase and gamma-glutamyltransferase activities). Leukogram revealed inflammatory response (absolute neutrophilia with moderate left shift and marked toxic changes in many neutrophils).Urine analysis revealed bilirubinuria (+++), glucosuria (++), proteinuria (++), ketonuria (++++), isosthenuria and acidic urine pH. Coagulation profiles were within reference ranges. Microscopic examination of urine sediment revealed many coarsely to finely granular casts along with large number of intact RBCs and occasional pus cells (1-2 cells per HPF).

Table 1. Hematology data

Parameter	Value on presentation	Values post treatment	Reference range
Hematocrit (%)	22.5	35.7	37-55
Hemoglobin (g/dL)	8.0	10.9	12-18
Red blood cells ($x10^6$/µL)	3.53	5.31	5.5-8.5
MCHC (g/dL)	39.5	38	32-36
MCV (fL)	58.5	54	60-77
MCH (pg)	23.1	23.6	19.5-24.5
Platelets ($x10^5$/µL)	5.3	5.59	2-9
MPV (fL)	17.1	13	7-13
WBC ($x10^3$/µL)	15.6	9.56	6-17
Neutrophils ($x10^3$/µL)	86	82	60-70
Lymphocytes ($x10^3$/µL)	14	18	12-30

MCHC— mean corpuscular hemoglobin concentration, MCV— mean corpuscular volume
MCH — mean corpuscular hemoglobin, MPV— mean platelet volume, WBC— white blood cell count

Table 2. Serum biochemistry profile

Parameter	Value on presentation	Values post treatment	Reference range
Total protein (g/dL)	4.9	6.1	5.5-7.5
Albumin (g/L)	2.0	2.7	2.6-4
Globulin (g/L)	2.9	6.3	2.1-3.7
ALT (U/L)	90	62	8.2-57
AST (U/L)	90	83	8.9-49
ALP (U/L)	>1500	349	10.6-101
GGT (U/L)	40	13	1-9.7
Preprandial serum bile acids (µmol/L)	22.7	ND	0-15
Total bilirubin (mg/dL)	3.0	0.4	0.1-0.6
Cholesterol (mg/L)	160	278	116-254
Glucose (mg/dL)	672	290	62-108
Urea (mg/L)	9.0	9.0	8.8-26
Creatinine (mg/dL)	0.7	0.8	0.5-1.6
Sodium (mEq/L)	140	142	140-154
Chloride (mmol/L)	104	107	102-117
Calcium (mg/dL)	10.3	10.1	8.7-11.8
Phosphorus (mg/dL)	3.9	3.4	2.9-6.2
Potassium (mEq/L)	3.9	3.4	3.8-5.6

ALT — alanine aminotransferase, AST—aspartate aminotransferase, ALP — alkaline phosphatase, GGT — gamma-glutamyl transferase

Lateral abdominal radiograph revealed hepatomegaly with rounded liver margins. Abdominal ultrasound was conducted to investigate suspected liver damage and showed grossly enlarged liver with hyperechoic echotexture and had multiple hypoechoic nodules measuring 0.81 to 2.2cm in liver lobes suggestive of liver abscess/neoplasia or large focal hepatic necrosis (Figure 1). There was splenomegaly with normal echotexture. An ultrasound-guided, fine-needle aspiration of the nodules revealed hepatocellular degeneration, severe fatty changes and necrosis with loss of nuclei and in some places mild mononuclear cells infiltration, RBCs and neutrophils were also seen (Figure 2).

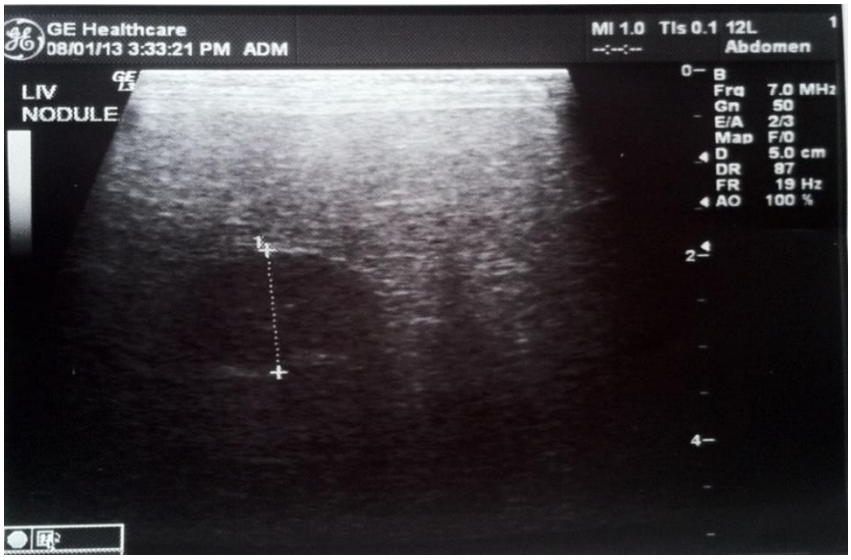

Figure 1. Ultrasonography of liver showing grossly enlarged liver with focal hypoechoic lesion (0.81x2.2cm) in the right liver lobe (focal hepatic necrosis) from a 7-year-old intact female Labrador retriever with diabetes mellitus.

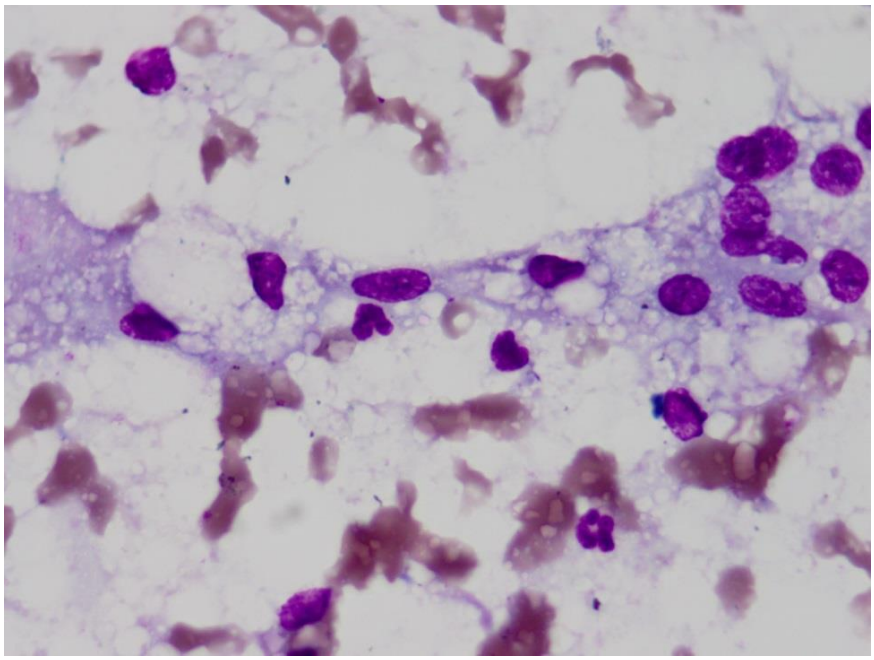

Figure 2.Fine needle aspiration biopsy of liver shows focal hepatic necrosis with severe fatty change in the liver.

The 18.5 kg dog was treated for 6 weeks with NPH insulin (Human-Mixact) 9 Units BID and ampicillin (Roscillin; Ranbaxy India) 250 mg, IM, twice daily for 2 weeks, liver extract (Belamyl), silymarin syrup 10 mg, BID, ursodeoxycholic acid (Udiliv; Solvay Pharma India) tablets, 300 mg, PO, SID and *N*- Acetylcysteine (Mucinac 600; Cipla) tablets 300 mg, PO, SID. In addition, owner was advised to give low carbohydrate, high fiber and high protein diet. A careful glucose monitoring and frequent dose adjustment of insulin was carried out for 2 weeks. Hematologic and serum biochemical results obtained 2 months after diagnosis showed rapid and satisfactory improvement in animal condition (Tables 1 and 2). Ultrasonographic scanning of the liver after 60days showed hyperechoic echotexture of the liver which could be attributed to the chronicity of the disease/ secondary hepatic lipidosis but the large focal areas of hepatic necrosis were disappeared.

Discussion

Diabetes mellitus is commonly seen in dogs presented for the treatment, but thorough investigation of other organ systems involved is rarely done, therefore, treatment is always directed toward maintaining blood glucose and ignoring the other complications which could be life threatening as well. We report a case of a dog suffering from diabetes mellitus complicated with focal liver necrosis. Many hepatic lesions are frequently associated with diabetes mellitus and ultrasonographic-guided FNAB for pathological examination of hepatocytes help to determine the diagnosis of hepatic lesions (Vignoli and Saunders, 2011). Microscopic examination of the FNAB confirmed focal hepatic necrosis. Patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes (Tolman*et al.,* 2007). The mechanism of hepatic necrosis in this case is unclear. Many factors such as shock, sepsis, anaesthesia, biliary disease and diabetic ketoacidosis may result in hepatic necrosis. Deng*et al* (2006) reported a case of diabetes mellitus in a man who developed multiple hepatic infarctions. However, hepatic disease is often treatable and has a predictable prognosis when a definitive diagnosis is made. The treatment is often non-specific,

empirical and symptomatic (Watson, 2004; Bexfield and Watson, 2006).

The management of diabetes in patients with liver disease is theoretically complicated by liver-related alterations in drug metabolism, potential interactions between the drugs, and a low, albeit real, incidence of hepatotoxicity. There are few clinical trials that specifically target patients with coexistent diabetes and liver disease, and all are limited by small numbers of patients. In this report, we share our experience in the management of patients with concurrent diabetes and liver disease. The massive hepatic necrosis was managed by administration of *N*-acetylcysteine and silymarin along with ursodeoxycholic acid and liver extract. Following treatment, focal hepatic lesion were found to decrease significantly and totally disappeared after 3 months based on ultrasonographic examination, though the liver remained hyperechoic in echotexture due to hepatic lipidosis. It seems that *N*-acetylcysteine and silymarin were able to counteract lipid peroxidation and enzyme leakage. Effectiveness of *N*-acetylcysteine was attributed to its membrane stabilizing ability, antioxidant, anti-inflammatory and hepatoprotective properties (De Flora *et al.*, 2001, Kerksick and Willoughby, 2005). Silymarin possesses an antioxidant activity (Bexfield and Watson, 2009). Ursodeoxycholic acid was also included in the treatment regimen as it reduces cell damage and oxidative stress resulting from the retention of bile acids in the liver (Meyer*et al.*, 1997) as well as is potentially indicated in most cases of liver disease, particularly those associated with biliary stasis (Bexfield and Watson, 2009). In summary, we suggest that dogs with diabetes mellitus should be investigated for liver functions and other conditions. This will allow early detection of occult complications and successful medical treatment. This study also suggests that antioxidants such as *N*-acetylcysteine administration should be considered in patients with hepatic insufficiency.

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