

Case 3

Diarrhoea and vomiting in a Yorkshire Terrier

Eve Ramery¹, Manuel Pinilla², Hester McAllister², Hanne Jahns³, Barbara Gallagher⁴, Bernadette Legget⁵, Stratos Papakonstantinou¹, Peter J O'Brien¹

University College of Dublin, Veterinary Hospital, ¹Department of Clinical Pathology, ²Department of Diagnostic Imaging, ³Department of Pathology, ⁴Department of Small Animal Medicine, ⁵Department of Microbiology

Case Presentation

An entire female Yorkshire terrier, 9 years old was presented with a history of a 2 weeks episode of vomiting and diarrhoea. The report of the referring veterinarian revealed fever (39,8°C), anorexia, loss of weight and dullness at clinical examination.

Laboratory Results

The data from haematology and biochemistry are presented in Table 1 and Table 2 respectively. There were no abnormal findings on urinalysis. Clotting times were also normal (PT: 13, N:12-17; APTT: 89, N: 71-102).

Table 1: Haematology data for the patient

Parameter	Value	Unit	Reference range
Hct	0.45	L/L	(0.37 - 0.55)
Hgb	157	g/L	(120 - 180)
RBC	6.4	x10 ¹² /L	(5.5 - 8.5)
MCHC	348	g/L	(310 - 362)
MCV	71	fL	(60 - 77)
MCH	25	pg	(19.5 - 25)
Plt	300	x10 ⁹ /L	(150 - 500)
MPV	12	fL	(7 - 11)
WBC	20	x10⁹/L	(6 - 17)
Neut	13.5	x10⁹/L	(3 - 11.5)
Lym	2.9	x10 ⁹ /L	(1 - 3.6)
Mono	1.55	x10⁹/L	(0 - 1.35)
Eos	0.98	x10 ⁹ /L	(0 - 1.47)

Table 2: Biochemistry data for the patient

Parameter	Value	Unit	Reference range
Tot Protein	76	g/L	(54 - 71)
Albumin	30	g/L	(31 - 40)
Globulin	46	g/L	(28 - 42)
ALT	429	U/L	(0 - 50)
GLDH	94	U/L	(0 - 10)
ALP	4336	U/L	(0 - 140)
GGT	27	U/L	(0 - 8)

Bile Acids	37	umol/L	(0 - 15)
Post prandial bile acids	13.7	umol/L.	
Total Bili	10.6	umol/L	(0.9 - 10)
Amylase	876	U/L	(0 - 730)
LIPASE	51	U/L	(0 - 130)
CK	47	U/L	(0 - 50)
Cholesterol	5.8	mmol/L	(3.2 - 6.5)
Glucose	3.8	mmol/L	(3 - 6.5)
Urea	10	mmol/L	(3.6 - 8.6)
Creatinine	68	umol/L	(20 - 120)
Sodium	152	mmol/L	(137 - 151)
Chloride	113	mmol/L	(99 - 110)
Calcium	2.7	mmol/L	(2.3 - 3)
Phosphorus	1.8	mmol/L	(0.8 - 1.8)
Potassium	3.9	mmol/L	(3.7 - 5.8)

Ultrasonography



Figure 1: Ultrasonography of the gallbladder

Ultrasonography of the abdomen was performed in order to precise the suspected liver damages (Figure 1). Ultrasonography indicated severe thickening of the gallbladder wall measuring up to 4 mm in some areas, with normal reference range of 2-3 mm (Spaulding 1993). The common bile duct was marginally distended measuring up to 3 mm in the vicinity of the duodenal papilla. The liver was otherwise normal. There was a focal area of gastric wall thickening at the level of the lesser curvature of the pyloric canal measuring up to 1 cm. In the mucosal surface of this area there was a persistent gas accumulation generating multiple comet tail artefacts. These findings suggest distal gastric ulceration.

Cytology

Direct smears of bile obtained by gallbladder lumen aspiration were stained with Wright's-Giemsa for cytologic examination (Figures 2 and 3).

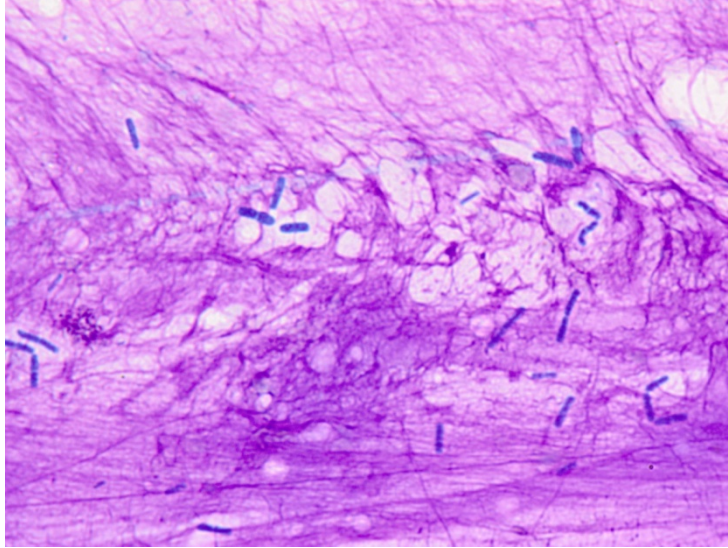


Figure 2: bile aspirate (Wright Giemsa, x1000 magnification)

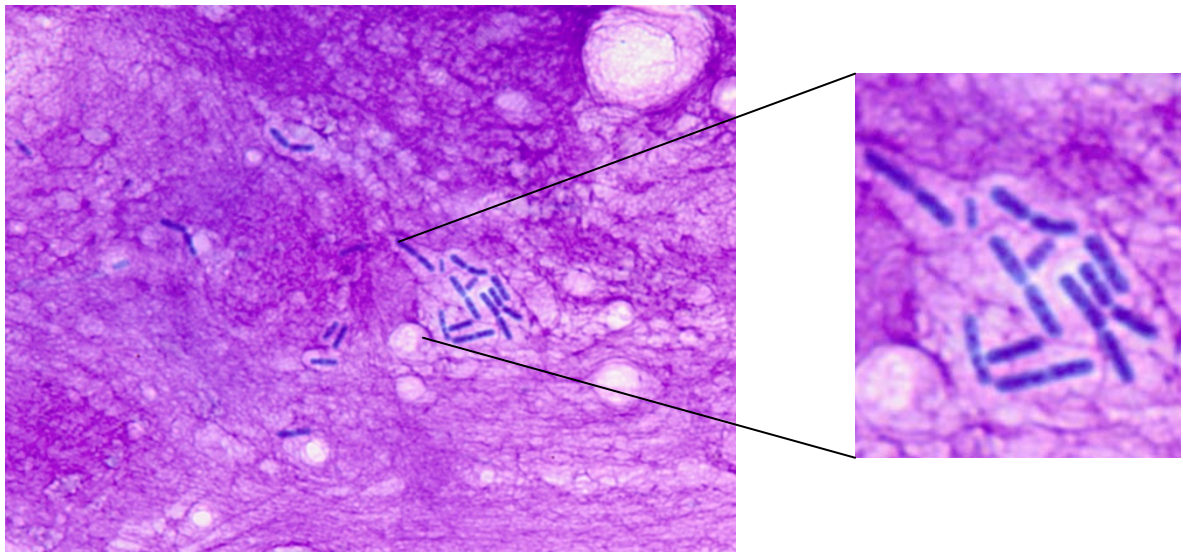


Figure 3: bile aspirate (Wright Giemsa, x1000 magnification)

Large numbers (up to 100 / 100 x objective field) of uniform, large bacterial rods in pairs and small chains typical of clostridial morphology were observed in an abundant bright-pink, fibrillar background (possibly degenerate nuclear material). No intact cells were retrieved.

Bacterial Culture

The bacterial culture resulted in a pure culture of *Clostridium* sp.

Histology

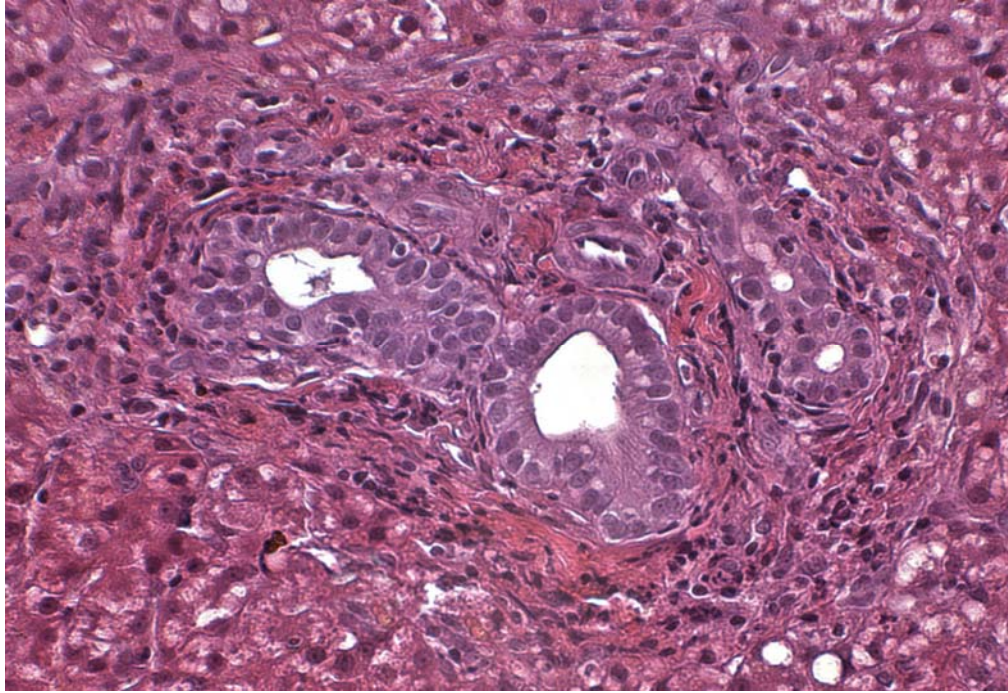


Figure 4: Liver biopsy

The microscopic examination of a core biopsy from the liver (Figure 4) revealed an expansion of the periportal areas by macrophages, plasma cells, neutrophils and occasional lymphocytes. The bile ducts were very prominent and there was low grade bile duct hyperplasia present. The hepatocytes were mildly swollen and contained occasionally dark yellow granules (bile). There were multifocal small foci of macrophages containing dark brown granular pigment (haemosiderin). The Kupffer cells were prominent and the sinusoids contain moderate numbers of neutrophils. Mild multifocal hepatocyte necrosis with neutrophilic and histiocytic infiltration was present.

The above histology findings are characteristic of a mild to moderate subacute hepatopericholangitis.

Description of Results

Cytological examination of bile obtained from gallbladder lumen aspiration, showed bacterial contamination and infectious agents were further identified as *Clostridium sp.* Reports of bacterial infections that are confined to the hepatobiliary system include diffuse cholangitis/cholangiohepatitis, cholecystitis, choledochitis, focal suppurative lesions and multiple hepatic microabscesses (Center, 1998). Along with the laboratory results indicating cholestasis, severe hepatocellular injury, decreased hepatic function, inflammation and with the gallbladder wall thickening observed on ultrasonography, a diagnosis of cholangiohepatitis was made. Moreover, a distal gastric ulceration was observed on ultrasonography. Concurrent subacute hepatopericholangitis was noticed on histopathology.

Outcome

The dog was successfully treated with clindamycin (40 mg p.o BID) and amoxicillin clavulanate (50 mg p.o BID). It also received sucralfate (0.5 g p.o TID) and ursodeoxycholic acid (50 mg p.o SID) and lansoprazole (3.75 mg p.o SID). After 2 months, all haematology and biochemistry parameters were returned to normal.

Discussion

Cholangitis is the inflammation of the intrahepatic biliary ducts and leads to cholangiohepatitis when it is associated with secondary inflammation of the surrounding hepatic parenchyma (O'Neill et al., 2006). It is a rare disorder not only in dogs (O'Neill et al., 2006) but also in cattle (Coombs et al., 2002; Whitlock and Brown, 1969) and humans (Helmberger et al., 2000). In humans, it occurs mainly in Asia (oriental cholangiohepatitis) and usually results from hepatolithiasis (Mori et al, 2006). Rare other human-cases report cholangiohepatitis as a consequence of the congenital Caroli's disease (Madjov et al, 2005) or of cholangiocarcinoma (Suzuki et al, 2006). Cholangiohepatitis is more commonly documented in the cat (Day, 1995; Zawie and Garvey, 1984). The difference between species has been suggested to result from differences in pancreatic and bile duct anatomy (Center, 1996; Zawie and Garvey, 1984).

Only 4 published papers have previously reported suppurative cholangiohepatitis in dogs (Forrester et al., 1992; Rivers et al., 1997; Neel et al., 2006; O'Neill et al., 2006), although occasional, very limited descriptions do exist within articles on other topics (Uno et al, 2009; Morrison et al, 2008). Culture of liver tissue and bile from these cases yielded 4 dogs with *Escherichia coli* (Neel et al., 2006; O'Neill et al., 2006), 3 dogs with *Clostridium sp.* (Rivers et al., 1997; O'Neill et al., 2006) and one dog with *Klebsiella sp.* (Forrester et al., 1992).

Commonly associated clinical signs are fever, anorexia, vomiting, weight loss, dullness and icterus. Laboratory abnormalities usually include neutrophilia with left shift; non-regenerative anemia; hyperbilirubinemia; moderate to marked increases in ALT, AST, and ALP; and a mild to moderate increase in GGT. Serum bile acids are usually increased, especially postprandially. Histopathologic changes include neutrophilic inflammatory infiltrates in the hepatic parenchyma and bile ducts, periportal necrosis, bile duct hyperplasia, and fibrosis. Biopsy samples should be cultured for both aerobic and anaerobic bacteria. (Kearns, 2009, O'Neill et al., 2006)

Acute cholangiohepatitis can progress into chronic cholangiohepatitis. In that case, ascites and icterus are the most frequently reported clinical signs, and lymphadenopathy may be present. In advanced disease, hypergammaglobulinemia, hypoalbuminemia, low BUN, and coagulopathies due to vitamin K deficiency can be seen. Histopathologic changes include portal and biliary infiltration with lymphocytes and neutrophils; marked bile duct proliferation, degeneration, and fibrosis; and periportal necrosis and fibrosis. Progression to cirrhosis or end-stage liver disease is possible. If the disease has progressed to cirrhosis, clinical signs of hepatic encephalopathy may also be seen (Fuentabala et al., 1997).

In the present case the neutrophilia with a slight left shift was indicative of an acute process. However, hypoalbuminemia and hyperglobulinemia can be interpreted as being caused by the inflammatory process or as a progression towards a more chronic

form. Along with the histological findings, these results indicated that a subacute process was more likely. Marginal hyperbilirubinemia was in agreement with previous reports stating that bilirubin increase is not a constant finding in biliary system disorders (Center, 2009). Mild GGT increase together with marked ALP increase were in accordance with previous results reporting ALP increase up to 100 fold higher than GGT increase (Center, 2007). Lack of inflammatory cells in bile cytology was in agreement with reports from human literature according to which inflammatory cells were not always observed in bile from patients with clinically significant cholecystitis (Neel et al., 2006). Preprandial serum bile acids exceeding postprandial serum bile acids have been previously reported in 30 out of 170 (~20%) dogs (Center et al., 1991) and in 6 out of 108 (~6%) cats (Center, 1995) with suspected liver disease. Similar findings were attributed to differences in the optimal time of post-prandial sample collection in humans (Beckett et al., 1981) and to spontaneous gallbladder contraction in humans (Shaffer et al., 1980; Shaffer, 2000) and in dogs (Keane et al., 1980).

It is suspected that, in cholangiohepatitis, bacteria originate from the gut and ascend via the bile duct due to some predisposing condition, such as inflammatory bowel disease, cholestasis, choleliths, chronic pancreatitis, immunosuppression, altered gut motility or anatomic abnormalities of the gallbladder (Kearns, 2009). Accordingly, *Clostridium sp.* is normal component of the flora of the intestines and the gallbladder infection thus likely originates from the gut.

In the present case, cholangiohepatitis was concurrent with distal gastric ulceration. Concurrent gastric ulceration was previously reported with cholangiohepatitis in a dog (Neel et al., 2006) and in a horse (Buote et al., 2003). It is hypothesised that it might be linked to the liver dysfunction.

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