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Congenital gallbladder agenesis in a 9-month-old Bull Terrier

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Abstract: Congenital gallbladder agenesis is an extremely rare disorder, which has, to the best of our knowledge, only been reported in seventeen dogs (mainly in Japan). In almost all of these cases, gallbladder agenesis or hypoplasia was detected in small dogs. In this report, we present a case of gallbladder agenesis in a 9-month-old intact female Bull Terrier. The clinical signs included diarrhoea, sporadic vomiting, apathy and decreased appetite. The serum biochemistry revealed an increased liver enzyme activity, an increased concentration of serum bile acids and mild hyperbilirubinaemia. A diagnostic laparotomy demonstrated the lack of a gallbladder and dilation of the common bile duct, which was misinterpreted as the gallbladder in the ultrasonographic examination. The histological examination of the liver revealed degenerative changes in the hepatocytes with glycogen accumulation and some necrotic hepatocytes. The therapy included a low protein diet, fluids, silymarin and ursodeoxycholic acid. After nine weeks of therapy, the dog was in good condition, the diarrhoea and vomiting ceased, and the liver function parameters, such as the AST and GLDH activities, and the concentration of bile acids had decreased to reference intervals.

Keywords: cholestasis; developmental disorder; liver; therapy; ursodeoxycholic acid

Canine congenital gallbladder agenesis is a rare developmental disorder. To the best of our knowledge, only three cases had been described up to 2010, two cases in Maltese dogs and one case in a Chihuahua (Liptak et al. 2000; Austin et al.2006; Kamishina et al. 2010). In 2018, Sato et al. (2018) described twelve cases of gallbladder agenesis and five cases of gallbladder hypoplasia in dogs from Japan. In that study most cases were detected in Chihuahuas. In 2019, Bugyiova et al. (2019) detected this anomaly in a Pug using ultrasonography and Kelly et al. (2019) diagnosed the disorder in another dog using computed tomography. Gallbladder agenesis is also rarely detected in humans, and clinical signs are observed only in about 25% of the cases (Serour et al. 1993).

The aetiology of this anomaly is still unknown; however, it is considered to be embryological and probably a hereditary disorder associated with a failure of the liver and gallbladder primordia development or a failure of the vacuolation of the gallbladder (Tang et al. 2015; Thornton et al. 2016).

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Case description

A 9-month-old, 25 kg, intact female Bull Terrier presented to the veterinary clinic with a three-month history of chronic diarrhoea, flatulence and sporadic vomiting. The owner of the dog described the stools as grey-green, abundant, unformed and pasty. At another clinic, during this 3-month period, the dog had received four therapies with Tylosin which resulted in an improvement for a few days. The referring veterinarian reported that an abdominal ultrasonography, a complete blood count and serum biochemical examination one month prior to referral did not reveal any abnormalities.

On presentation to the clinic, the dog was in good condition and, according to the dog's owner, it had a good appetite. A clinical examination did not reveal any abnormalities. An abdominal palpation did not reveal any pain or tension, with no abnormalities detected during the palpation examination. The mucosal membranes were pink without any yellow or yellowish colouration. The body temperature, hydration status and superficial lymph nodes were normal. The diagnostic tests included: an abdomi-

Table 1. Serum liver parameters in the 9-month-old Bull Terrier with gallbladder agenesis obtained between the 5th of April and the 1st of July, 2017

Parameter	Reference intervals	Examination No. 1 (5 Apr)	Examination No. 2 (6 May)	Examination No. 3 (20 May)	Examination No. 4 (3 Jun)	Examination No. 5 (1 Jul)
ALT (µkat/l)	0.02–1.33	2.98	6.98	2.4	3.6	–
AST (µkat/l)	0.02–1.26	1.32	4.62	1.28	1.55	0.78
ALP (µkat/l)	0.02–2.35	0.55	0.75	0.9	1.2	–
GLDH (µkat/l)	0.01–0.18	0.45	3.87	0.22	–	0.04
GGTP (µkat/l)	0.01–0.12	0.28	–	–	–	–
Cholesterol (mmol/l)	3.1–8.6	9.7	9.6	6.53	–	–
Total bilirubin (µmol/l)	0.01–3.4	5.4	6.31	8.5	6.8	–
Fasting bile acids (µmol/l)	0–18	30.7	65.4	99.4	22	1.79
Albumin (g/l)	25–44	37.9	37.2	–	–	–
Total protein (g/l)	54–75	70.1	66.3	–	–	–
Urea (mmol/l)	3.3–8.3	6.74	–	–	–	–
Glucose (mmol/l)	3.05–6.1	4.85	–	–	–	–
TLI (µg/l)	5–35	19	–	–	–	–
α-amylase (µkat/l)	0.17–27.51	8.74	–	–	–	–
Lipase (µkat/l)	0.02–2	0.6	–	–	–	–

ALT = alanine transaminase; ALP = alkaline phosphatase; AST = aspartate transaminase; GGTP = gamma-glutamyltranspeptidase; GLDH = glutamate dehydrogenase; TLI = trypsin-like immunoreactivity

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nal ultrasonography, faecal examinations (using flotation techniques with oversaturated NaCl and 33% $ZnSO_4$ solutions), a urine examination, a complete blood count and determination of the serum biochemical parameters (Tables 1 and 2).

The abdominal ultrasonography revealed the inhomogeneous hyperechoic structure of the liver. According to the ultrasonographic description, the lumen of the gallbladder was subtly filled with bile without any calculi or changes in its wall. The results of the faecal examinations were negative; however, a microscopic examination revealed the presence of fat in the stool. The urine examination did not reveal any abnormalities. The complete blood count did not reveal any pathological changes; however, the serum biochemical examination revealed increased concentrations of the liver parameters (Table 1: examination No. 1). When repeated the next day, the concentration of the fasting serum bile acids was within the reference interval (6.1 μmol/l). The reason for the increased serum bile acid concentration during the initial examination was considered to be because the blood sample was probably collected after a meal. The hepatoprotective drug Zentonil 400 (Vetoquinol), a commercial diet supporting liver function (Hepatic Royal Canine) and a probiotic supplement FortiFlora (Purina PRO PLAN Veterinary Diets) were prescribed for 4 weeks.

Table 2. Results of the complete blood count performed on the 9-month-old Bull Terrier with gallbladder agenesis on the 5th of April, 2017

Parameter	Reference interval	Result of examination
RBC count (T/l)	5.5–8.5	6.32
Haemoglobin concentration (mmol/l)	9.31–11.79	9.99
Haematocrit (l/l)	44–55	47.6
MCV (fl)	60–77	75.3
MCHC (mmol/l)	19.86–22.34	20.98
WBC count (g/l)	6–12	11.2
Neutrophils (%)	55–75	70
Lymphocytes (%)	13–30	22
Monocytes (%)	1–10	5
Eosinophils (%)	0–6	3
Basophils (%)	0–1	0
Platelet count (g/l)	150–500	320

MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; WBC = white blood cell count

After 3 weeks, the dog presented to the clinic again owing to a decreased appetite and apathy. The diarrhoea had ceased; however, the stools were pale and yellow. A clinical examination did not reveal any abnormalities except apathy. Cholestasis was considered as a probable cause of the current state of the animal. However, an abdominal ultrasonography showed no obstruction in the bile ducts, and, according to the ultrasonographic description, the gallbladder was unchanged and subtly filled with bile. An ultrasound examination of the liver did not show a portosystemic shunt. Fluid therapy [alternately Solutio Ringeri and 0.9% NaCl; 500 ml, subcutaneously (s.c.) twice daily], ursodeoxycholic acid [5 mg/kg, perorally (p.o.) twice daily] and Zentonil 400 were administered.

After 10 days of therapy, the state of the dog was unchanged, and the stools were still pale and yellow. Increased liver function indicator values were still observed (Table 1: examination No. 2). The owner of the dog agreed to a diagnostic laparotomy and the collection of material for liver histological examinations. The surgery revealed a lack of a gallbladder on the visceral surface of the liver and dilation of the common bile duct (Figure 1). A histological examination revealed diffuse, moderate hepatocellular cytoplasmic vacuolar degeneration (Figure 2), and a periodic acid-Schiff staining showed glycogen accumulation in the hepatocytes (Figure 3).

After surgery, the dog was treated with a low protein diet, ursodeoxycholic acid (5 mg/kg, p.o. twice daily) and fluids (alternately Solutio Ringeri and 0.9 % NaCl; 250 ml, s.c. twice daily). Maropitant at a dosage of 1 mg/kg s.c. once a day for 5 days was also administered owing to the vomiting. Ten days after surgery, the dog presented to the clinic for a control visit. The owner of the dog described it as having increased vitality. The vomiting had ceased, the dog had a good appetite, and stools

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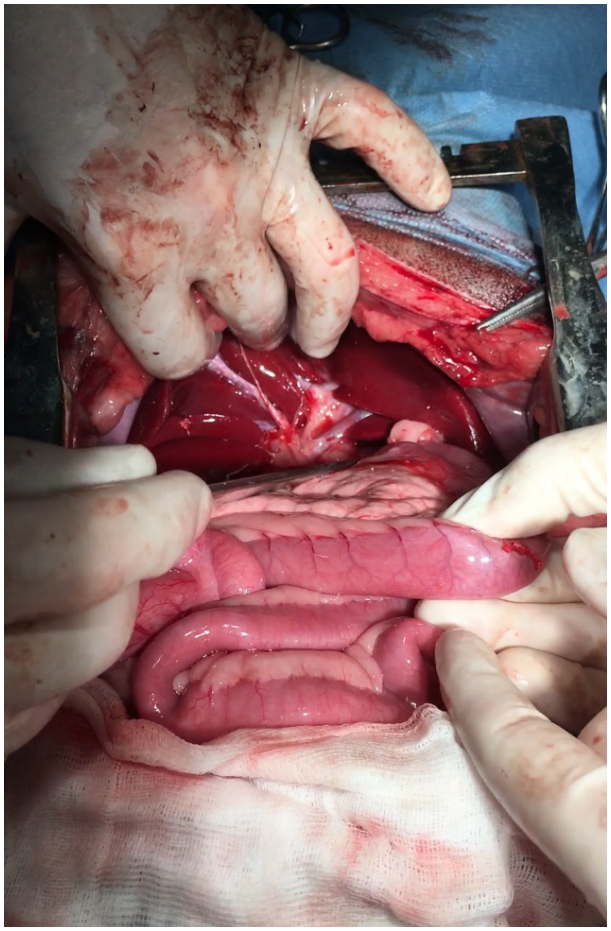

Figure 1. View of the porta hepatis during the diagnostic laparotomy in the 9-month-old Bull Terrier. Visible lack of a gallbladder and dilation of the common bile duct

were light brown and formed. A clinical examination revealed a lack of fever, abdominal pain, or yellow or pale mucosal membranes. A serum biochemical examination showed increased concentrations of the liver parameters; however, they were lower than in the previous examinations, with the exception of the total bilirubin and bile acid concentrations. The glutamate dehydrogenase (GLDH) activity was mildly increased, while the cholesterol concentration was within the reference interval (Table 1: examination No. 3). An increased dosage of ursodeoxycholic acid to 7.5 mg/kg twice daily was recommended, and, additionally, silymarin at 70 mg *in toto* orally 3 times a day after a meal was administered. A fluid therapy, the same as previously, was continued for the next 14 days.

After 2 weeks of therapy, a serum biochemical examination revealed an increased alanine transaminase (ALT) and aspartate transaminase (AST) activity, but the concentrations of bilirubin and

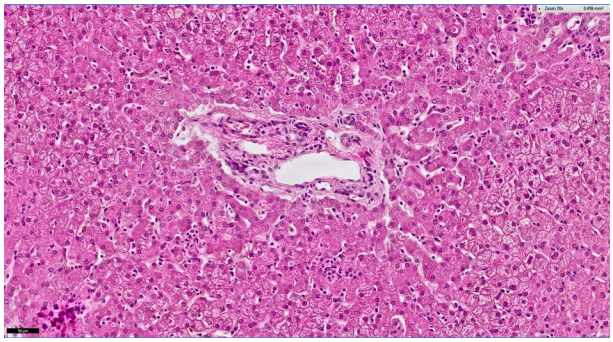

Figure 2. Cytoplasmic vacuolar degeneration of the hepatocytes in the 9-month-old Bull Terrier with gallbladder agenesis; magnification × 20, haematoxylin-eosin staining

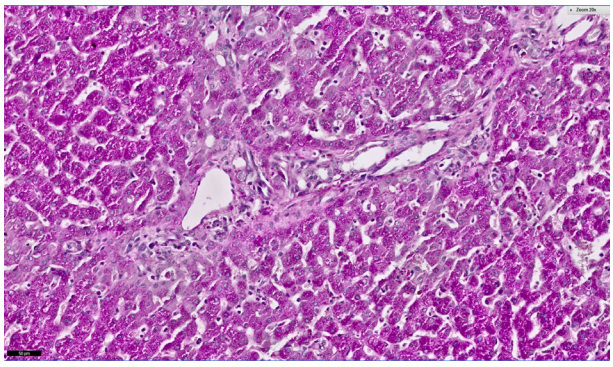

Figure 3. Glycogen accumulation in the hepatocytes in the 9-month-old Bull Terrier with gallbladder agenesis; magnification × 20, periodic acid-Schiff staining

the fasting bile acids had decreased in comparison to the previous tests (Table 1: examination No. 4). The dog was in good condition, had a good appetite, and the stools were brown and formed. A clinical examination did not reveal any abnormalities. The therapy (ursodeoxycholic acid, silymarin, low protein diet and fluids) was continued for the next 4 weeks. After this time, a serum biochemical examination revealed the AST, GLDH and bile acids were within reference intervals (Table 1: examination No. 5). The dog was in good condition; however, urticaria appeared on both hind legs; this symptom disappeared after a single intramuscular injection with 0.2 mg/kg of dexamethasone.

A further therapy was based on a low protein diet and ursodeoxycholic acid. Control examinations of the serum liver parameters, urine examination and liver ultrasonography were recommended every 2 months.

Over the next 17 months, the complete blood counts and serum biochemical examinations were performed every 2 months; no abnormalities were revealed, except sporadic, mildly increased ALT and

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AST activities. The concentrations of bilirubin, bile acids, and the alkaline phosphatase (ALP) and GLDH activities were within reference intervals (Table 3). The ultrasonographic examinations of the liver every

Table 3. Monitored serum liver parameters and complete blood count from the 9-month-old Bull Terrier with gallbladder agenesis over a period of 17 months between the 30th of August 2017 and the 28th of November 2018

Parameter	Reference interval	30/08/17	25/10/17	03/01/18	07/03/18	09/05/18	11/07/18	19/09/18	28/11/18
RBC (T/l)	5.5–8.5	6.68	6.44	6.36	7.29	6.31	6.40	6.12	6.97
Hb (mmol/l)	9.31–11.79	9.74	9.87	10.18	10.67	9.99	10.12	9.68	10.61
Ht (l/l)	44–55	45.9	45	47.1	52	46.7	46.9	44.7	48.2
MCV (fl)	60–77	69	69.1	74.1	71.3	74	73.3	73	69.2
MCHC (mmol/l)	19.86–22.34	21.29	21.97	21.6	20.54	21.41	21.53	21.72	22.09
WBC (g/l)	6–12	12.7	11.5	10.8	12.3	10.7	11.2	12.2	11.9
Segmented neutrophils (%)	55–75	77	67	71	73	69	74	73	70
Band neutrophils (%)	0–4	3	0	2	1	0	2	2	3
Lymphocytes (%)	13–30	17	28	21	24	25	20	21	23
Monocytes (%)	1–10	2	2	2	1	2	1	2	1
Eosinophils (%)	0–6	1	3	4	1	4	3	1	3
Basophils (%)	0–1	0	0	0	0	0	0	1	0
Platelet count (g/l)	150–500	270	277	267	239	242	287	291	236
ALT (µkat/l)	0.02–1.33	0.52	1.57	1.43	0.63	0.77	1.02	1.72	1.2
AST (µkat/l)	0.02–1.26	0.55	1.12	1.2	0.6	0.65	0.83	1.4	1.1
ALP (µkat/l)	0.02–2.35	0.65	0.73	1.02	0.88	0.78	0.9	1.02	0.87
GLDH (µkat/l)	0.01–0.18	0.16	0.15	–	0.14	–	0.15	0.16	0.15
Tot. bil. (µmol/l)	0.01–3.4	3.2	3.34	3.23	3.12	–	3.04	3.4	3.1
Fast. BA (µmol/l)	0–18	12.9	9.1	11.8	14.3	10.8	13.7	16.4	15

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; Fast. BA - concentration of fasting bile acids; GLDH = glutamate dehydrogenase; Hb = haemoglobin concentration; Ht = haematocrit; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; Tot. bil. = total bilirubin concentration; WBC = white blood cell count

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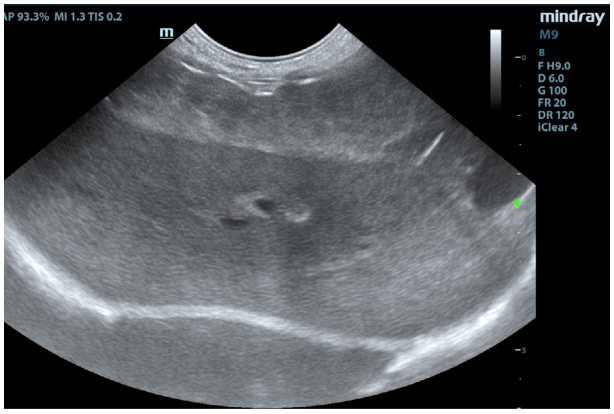

Figure 4. Ultrasound picture of the liver of the 9-month-old Bull Terrier with gallbladder agenesis showing its non-homogeneous and hyperechoic structure

two months showed the same non-homogeneous and hyperechoic structure of the organ (Figure 4). Yet, the ultrasonography did not reveal a hepatomegaly. During this time, the dog was in good condition, no vomiting was observed, and the stools were brown and formed.

Currently, over two years after surgery, the dog is still under the care of the first author of this case report. The dog is still treated with ursodeoxycholic acid and fed a low protein diet. Occasionally, allergic skin reactions are observed; these are probably caused by the pharmaceutical products containing ursodeoxycholic acid. The dog was castrated 17 months after the laparotomy that was complicated by severe bleeding, which may have been caused by the improper functioning of the liver.

DISCUSSION

Congenital gallbladder agenesis occurs, or is detected, extremely rarely in dogs. This anomaly is observed in small and miniature breeds of dogs. So far, the lack of a gallbladder has been detected only once in a larger dog. In that case, the gallbladder agenesis was recognised in a German Shepherd from Japan (Liptak et al. 2000; Austin et al. 2006; Kamishina et al. 2010; Sato et al. 2018). To our knowledge, the presented case report is the first description of congenital gallbladder agenesis in a Bull Terrier, and, so far, the second case of this anomaly in a dog other than a small or miniature dog. In this case, the clinical signs, such as vomiting, diarrhoea, decreased appetite and apathy, were similar to other reported cases, and, like most of the other cases, appeared at a young age. However, as opposed to most of the other cases, diarrhoea, but not vomiting, was the main clinical sign. Ascites, anorexia and seizures were also reported in the other dogs with congenital gallbladder agenesis. However, in eight out of the seventeen dogs with agenesis or hypoplasia of the gallbladder, like in many humans with this anomaly, no clinical signs were observed (Austin et al. 2006; Kamishina et al. 2010; Scobie and Bramhall 2016; Sato et al. 2018).

In all the cases of the dogs with gallbladder agenesis, including this report, the laboratory liver parameters were elevated. In these cases, the ALT and AST activities were increased, probably resulting from the action of the hydrophobic bile acids (Liptak et al. 2000; Austin et al. 2006; Kamishina et al. 2010; Sato et al. 2018). In few cases, the ALP activity was also increased; however, it was not observed in the present case. Interestingly, a mild increase in the bilirubin concentration was observed in this case, but not in the other cases of the dogs with this anomaly (Sato et al. 2018). However, hyperbilirubinaemia has also been observed in humans with this defect (Tjaden et al. 2015). In the present report, the increased concentrations of the total bilirubin and bile acids might be associated with cholestasis (Berk and Javitt 1978). This may result from the compensatory dilation of the common bile duct, with the role of the gallbladder probably taken over by the common bile duct (Liptak et al. 2000). Moreover, it should be mentioned that a dilated common bile duct may be misinterpreted as a gallbladder by an ultrasonographic examination, this is also observed in humans with this anomaly (Serour et al. 1993; Liptak et al. 2000; Sato et al. 2018). Thus, it is possible that cases like the one described here are not so extremely rare; the under-reporting may result from the subclinical course of the disease in some cases and the low sensitivity of an ultrasonographic examination for the diagnosis. Currently, in human medicine, computed tomography or magnetic resonance imaging are recommended for the diagnosis of this anomaly (Kelly et al. 2019).

In this case, the recognition of cholestasis may also be confirmed through a microscopic faecal examination via the detection of fatty drops in the stool before treatment, and improvement of the condition of the dog after treatment with ursodeoxycholic acid which increases the bile flow. The hepatoprotective action of this hydrophilic bile acid also results from its anti-inflammatory

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properties and inhibition of cellular apoptosis and necrosis. Moreover, the competitive displacement of endogenous hepatotoxic hydrophobic bile acids by the ursodeoxycholic acid in the enterohepatic circulation prevents the liver fibrosis and cirrhosis induced by the hydrophobic bile acids (Lazaridis et al. 2001; Roma et al. 2011).

In the presented report, the degenerative hepatocellular changes were probably caused by the increased concentrations of hydrophobic endogenous bile acids, such as taurochenodeoxycholic and taurolithocholic acids, as a result of the cholestasis. The pro-inflammatory action of these acids results from the activation of Kupffer cells, stimulating secretion of pro-inflammatory cytokines such as TNF-α and IL-1β. Moreover, the lipid peroxidation of the hepatocellular membranes, induced by the hydrophobic bile acids, leads to injury of the hepatocytes and further cellular apoptosis and necrosis, and the long-term exposure of hepatocytes to these acids may lead to liver fibrosis and cirrhosis (Lazaridis et al. 2001; Copple et al. 2010; Chiang 2013). The excessive glycogen accumulation in hepatocytes observed in this case might also result from the prolonged exposure of hepatocytes to bile acids which activate the liver enzyme glycogen synthase (Fang et al. 2007; Chiang 2013).

Silymarin, a mixture of flavonoids and polyphenols with antioxidative and hepatoprotective properties, was used in the therapy for 6 weeks, owing to the observation of the hepatocellular changes in the dog under the histological examination (Feher and Lengyel 2012). We propose that ursodeoxycholic acid must be administered to the dog for the reminder of its life. The purpose of such a therapy is to limit the progress of liver disease. The liver in this dog will probably never function properly. This supposition may be confirmed by the severe bleeding observed after the dog's castration. Although the dog has allergies, and pharmaceutical products with ursodeoxycholic acid may contribute to the development of urticaria and other skin allergic reactions, the authors concluded that ursodeoxycholic acid should be used permanently in this dog (Hempfling et al. 2003). In case of allergic reactions stemming from products containing ursodeoxycholic acid, glucocorticosteroids should be used if antihistamine drugs are not available despite their influence on the stimulation of glycogen and lipid accumulation in the hepatocytes and increasing the serum ALT and gamma-glutamyltranspeptidase (GGTP) activity and the pharmaceutical product with ursodeoxycholic acid should be changed to another with the same active substance (Plumb 2008). However, it should be emphasised that glucocorticosteroids should be used carefully in dogs with cholestasis and increased bile acids concentrations. Out et al. (2014) showed that the use of prednisolone in mice caused an increase in the serum bile acid concentration. On the other hand, two weeks of using dexamethasone in rats limited the liver injury caused by cholestasis (Eken et al. 2006). Similar conclusions were drawn by Tiao et al. (2011). Those authors observed a decrease in the serum ALT, AST and ALP activity, and the bilirubin concentration in rats with cholestasis after a single dose of dexamethasone. Moreover, Gabbia et al. (2018) showed that dexamethasone counteracts a hepatic inflammation and the oxidative stress in cholestatic rats. Thus, it is possible that in the presented case report, the single dose of dexamethasone had no negative influence on the course of the liver disease or even contributed to limiting its progress.

Gallbladder agenesis is recognised extremely rarely in veterinary practice. To the best of our knowledge, the presented report is the first description of this anomaly in a Bull Terrier, and the second report from Europe. It cannot be excluded that such cases may occur more frequently, yet remain undiagnosed, due to the subclinical course of the disease in some cases and the low sensitivity of the ultrasonographic examinations in the diagnosis of this defect.

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Conflict of interest

The authors declare no conflict of interest.

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