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CASE REPORT
Treatment and long-term follow-up of extrahepatic biliary obstruction with bilirubin cholelithiasis in a Somali cat with pyruvate kinase deficiency

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A 2-year-old female neutered Somali cat was presented with vomiting and acute onset jaundice 1 year after diagnosis of pyruvate kinase (PK) deficiency. Diagnostic investigations revealed a moderate regenerative haemolytic anaemia, severe hyperbilirubinaemia and elevated liver enzymes. Ultrasonography revealed marked distension of the gall bladder and common bile duct (CBD), consistent with extrahepatic biliary obstruction (EHBO). At cholecystotomy, the gall bladder contained purulent material, and two obstructive choleliths were removed from the CBD by choledochotomy. The cat recovered from surgery uneventfully, and serum liver enzymes and bilirubin normalised within 10 days. Postoperative treatment consisted of cephalexin, metronidazole and ursodeoxycholic acid (UDCA). Bacterial culture of the gall bladder contents yielded a pure growth of an *Actinomyces* species. Cholelith analysis revealed that they consisted of 100% bilirubin. Antibiotic treatment was stopped 4 weeks after surgery but UDCA was continued indefinitely. The cat remains clinically well with no recurrence of cholelithiasis 20 months after initial presentation. This is the first report of successful treatment and long-term follow-up of a cat with EHBO due to bilirubin cholelithiasis in association with PK deficiency-induced chronic haemolysis.

Pyruvate kinase (PK) deficiency is a cause of haemolytic anaemia in Abyssinians and Somalis (Giger et al 1997). It is inherited as an autosomal recessive trait (Giger et al 1997) with homozygous cats being affected whilst heterozygote carriers are normal (Giger 2000). DNA screening tests exist that can identify both homozygous and heterozygous cats (Giger et al 1997). PK-deficient erythrocytes cannot sustain normal cell metabolism and are destroyed prematurely, manifesting as haemolytic anaemia (Ford et al 1992, Giger 2000).

Although bilirubin cholelithiasis is a frequent complication of chronic haemolysis in man (Wantanabe et al 2002, Tamary et al 2003), it has only been reported previously in one cat with haemolysis, and in this case cholelithiasis was identified only at post mortem (van Geffen et al 2005).

We report here the first documented case of feline PK deficiency in the UK. Additionally, this case comprises the first report of the successful treatment and long-term follow-up of a cat with extrahepatic biliary obstruction (EHBO) due to bilirubin cholelithiasis in association with PK deficiency-induced chronic haemolysis.

A 2-year-old neutered female Somali cat was referred to The University of Bristol Veterinary

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School (UOB) for investigation of acute onset jaundice and a 6-week history of vomiting, lethargy and inappetence. One year previously the cat had been extensively investigated by the referring veterinarians for intermittent vomiting and diarrhoea which had led to a diagnosis of lymphoplasmacytic inflammatory bowel disease (IBD). Additionally routine haematology and biochemistry had revealed a moderate regenerative anaemia and hyperbilirubinaemia, and PK deficiency was diagnosed (Dr Urs Giger, Josephine Deubler Genetic Disease Testing Laboratory, University of Pennsylvania, Philadelphia). A bland diet and intermittent prednisolone treatment successfully controlled the gastrointestinal signs and no clinical signs of anaemia were identified over the subsequent year.

On presentation at the UOB the cat was very dull and depressed with severely icteric mucous membranes. Routine haematology revealed a moderate regenerative anaemia (packed cell volume (PCV) 18%; reference range 24–45). Serum biochemistry revealed marked elevations in liver enzymes (alanine aminotransferase (ALT) 937 IU/l; reference range 15–45, alkaline phosphatase (ALP) 177 IU/l; reference range 15–60), severe hyperbilirubinaemia (899 µmol/l; reference range 0–10) and hypokalaemia (2.76 mmol/l; reference range 4–5). Although the icterus could have been due to haemolysis, the severity of the hyperbilirubinaemia in association with only a moderate anaemia made biliary stasis a major differential diagnosis. Abdominal ultrasound revealed distension of the gall bladder and common bile duct (CBD; >5 mm diameter), suggestive of EHBO. The gall bladder wall was thickened and the lumen was full of echogenic material. All other abdominal organs were ultrasonographically normal.

The cat was blood type A (Rapid Vet H blood tying cards; Agrolabo). It was stabilised with intravenous (IV) 0.9% saline (Vetivex NaCl 0.9%; Ivex Pharmaceuticals) supplemented with potassium chloride (sterile KCl 15%; Antigen Pharmaceuticals), subcutaneous (SC) vitamin K_1 (Konakion MM ampoules; Roche products) (0.5 mg/kg bid) due to prolonged coagulation times (activated partial thromboplastin time 30.4 s; control 14.6, prothrombin time 39 s; control 9.2), and 50 ml of fresh type A whole blood. Coagulation times and serum potassium concentration had normalised 24 h later. At exploratory surgery the gall bladder wall was grossly thickened and the CBD very dilated. Cholecystocentesis yielded 3 ml of purulent fluid which was submitted for cytology and culture. Choledochotomy revealed

two obstructing choleliths, each approximately 5 mm in diameter, which were removed (Fig 1). Duodenotomy was also performed and the gall bladder, cystic duct and CBD catheterised and flushed with 0.9% saline.

The cat recovered from surgery uneventfully. Whilst awaiting culture results, postoperative treatment with amoxycillin-clavulanate (Augmentin; SmithKline Beecham) (20 mg/kg IV tid) and metronidazole (Metronidazole; Phoenix Pharma) (10 mg/kg IV bid) was started. Buprenorphine (Temgesic; Schering Plough) 30 µg/kg IM tid and vitamin K_1 (0.5 mg/kg SC bid) were also administered for 3 days. After 3 days, antibiotics were continued orally for 4 weeks using cephalexin (Ceporex Vet 50; Schering Plough) (15 mg/kg bid) and metronidazole (Metronidazole; Approved Prescription Services) (10 mg/kg bid), and ursodeoxycholic acid (UDCA, Destolit; Norgine) (10 mg/kg PO sid) was started. Within 10 days serum liver enzymes had normalised and bilirubin had significantly reduced (51.5 µmol/l). The cat was discharged 12 days postoperatively.

Cytology of the gall bladder contents revealed neutrophilic inflammation whilst culture yielded a pure growth of an *Actinomyces* species, sensitive to amoxycillin-clavulanate, penicillin and cephalexin. Cholelith analysis (Algemeen Medisch Laboratorium, Veterinary Department, Desguinlei, Antwerp, Belgium) showed them to be 100% bilirubin.

Repeat haematology and serum biochemistry every few weeks revealed mild to moderate regenerative anaemia (PCV varying from 12% to 20%) and mild hyperbilirubinaemia (varying from 8.6

Fig 1. Bilirubin choleliths that were removed from the CBD.

to 36.4 µmol/l) with normal ALT and ALP. No clinical signs of anaemia were ever apparent. Initial ultrasonographic re-evaluations of the biliary tract revealed persistently thickened gall bladder and CBD walls with 'sludge' in the gall bladder, but 5 months following surgery, serum biochemistry was unremarkable and the gall bladder, bile ducts and intestines were ultrasonographically normal. However, intermittent vomiting continued, thought most likely to be due to the IBD previously diagnosed, so metronidazole (10 mg/kg bid PO) was initiated. The vomiting stopped during metronidazole treatment, and following a 2 month period without vomiting metronidazole treatment was stopped. UDCA was continued. The cat remains clinically well, 20 months since initial presentation with jaundice, with no recurrence of cholelithiasis evident on ultrasonography.

Metronidazole was initiated for its immunomodulatory and anti-inflammatory properties (Tanga et al 1975, Grove et al 1977). Although there are no published data confirming the efficacy of this treatment for IBD, the authors and others (Jergens 1994, Willard 1999) have noted clinical improvement when some IBD cases have been treated with metronidazole. UDCA is recommended for feline inflammatory liver disease due to its anti-inflammatory, immunomodulatory and antifibrotic properties, and its ability to increase fluidity of biliary secretions (Maddison 2001, Center, 2002, Marks 2003). Although inflammatory liver disease was not confirmed by biopsy in this case, it is highly likely that secondary inflammatory liver disease was present due to the biliary obstruction and bacterial infection. The role of UDCA in contributing to the successful outcome of this case is uncertain. As the bilirubin cholelithiasis was a likely consequence of chronic haemolysis, the benefit of continuing UDCA was questionable. But as the cat had remained well on UDCA with no further evidence of biliary stasis, it was decided to continue it indefinitely.

Splenectomy has been reported to reduce haemolysis in humans with PK deficiency (Coon 1985, Wantanabe et al 2002) and has been helpful in some affected cats (Ford et al 1992, Giger 2000). An elective splenectomy was a considered treatment option for this cat at a later stage, but was not performed as the cat remained clinically well with only mild asymptomatic anaemia and no recurrence of cholelithiasis.

Unfortunately, due to surgery time concerns due to instability of the patient, biopsies were not taken from the liver, gall bladder or bile ducts so the presence of cholangiohepatitis and/or cholecystitis cannot be confirmed. However, they were likely to be present given the purulent septic material and the thickened gall bladder and bile duct walls. Although cholangiohepatitis and/or cholecystitis can give rise to choleliths, cholangiohepatitis is also known to arise secondary to damage caused by bile duct obstruction (Center et al 1986, Mayhew et al 2002). In the current case, if cholelithiasis had occurred secondarily to cholangiohepatitis and/or cholecystitis, it is unlikely that cholelith composition would have been 100% bilirubin. Although choleliths have not been extensively analysed in cats, in the 28 cholelithiasis feline cases previously reported, mostly attributed to cholangiohepatitis and/or cholecystitis, cholelith composition was only described in 15 and mostly consisted of varying proportions of calcium salts and cholesterol (see Table 1). Given that the choleliths identified in the current report were 100% bilirubin, they were considered most likely to be a consequence of PK deficiency-induced chronic haemolysis. One case report does describe bilirubin cholelithiasis in association with cholangitis in a DSH cat (Morrison 1985) but detailed haematology and follow-up was not provided, although a blood count was described as being normal. The only other feline bilirubin cholelithiasis case reported is that of the Somali cat with PK deficiency-induced chronic haemolysis, where diagnosis was only made post mortem (van Geffen et al 2005).

Interestingly, one Abyssinian cat with immune-mediated haemolytic anaemia was included in a case series of feline cholelithiasis, but the composition of the cholelith was not described and no link was made between the haemolysis and cholelithiasis (Eich and Ludwig 2002). It is possible that haemolysis may have contributed to the cholelithiasis in that case. In humans bilirubin cholelithiasis is frequently reported as a complication of chronic haemolysis (Wantanabe et al 2002, Tamary et al 2003) and the authors feel that it is important that cholelithiasis, and possible subsequent EHBO, is recognised as a potential complication of chronic haemolysis in cats. Otherwise it may be wrongly assumed that jaundice in a cat with haemolytic anaemia is due to haemolysis alone.

Cholelithiasis rarely causes EHBO in cats (see Table 1; Gibson 1952, Wigderson 1955, O'Brien and Mitchum 1970, Naus and Jones 1978, Hirsch and Doige 1983, Wolf 1984, Heidner and Campbell 1985, Morrison 1985, Jorgenson et al 1987, Elwood et al 2001, Mayhew et al 2002, Eich and

Table 1. Previously reported cases of feline cholelithiasis

Number	Reference	Details of cats	Underlying disease	EHBO present	Reported cholelith composition	Treatment	Outcome
1	Gibson 1952	6 year old M DSH	ND	Yes	Calcium salts of bilirubin	None	Died before diagnosis reached
2	Wigderson 1955	3 yearr old MN unknown breed	ND	Yes	ND	None	Euthanased at presentation
3	O'Brien and Mitchum 1970	Adult M DSH	ND	Yes	Mainly cholesterol with some bile and calcium salts	None	Died 6 days after presentation
4	Naus and Jones 1978	14 year old MN DSH	Cholecystitis	Yes	Bilirubin and calcium	Cholecystectomy and choledochotomy	Normal 9 months post surgery
5	Hirsch and Doige 1983	13 year old FN American Shorthair	Suppurative cholangitis	Yes	ND	Unknown	Unknown
6		16 year old American Shorthair	Suppurative cholangitis	Yes	Cholesterol and bile	Unknown	Unknown
7	Wolf 1984	7 year old MN DLH	Cholecystitis	Yes	Bilirubin, calcium and cholesterol	Choledochotomy	Normal 6 weeks postoperatively
8	Heidner and Campbell 1985	4 year old MN DSH	ND	Yes	Contained calcium	None	Euthanased prior to diagnosis
9	Morrison 1985	2 year old M DSH	Cholangitis (NB complete blood count reported as normal)	Yes	100% bilirubin	Cholecystoduoenostomy	Recovered from surgery, follow-up not reported
10	Jorgenson et al 1987	8 year old MN DSH	Suppurative cholangitis and pancreatitis	Yes	86% cholesterol, 5% calcium bilirubinate, 4% calcium carbonate, 3% mixed bile pigment, 2% blood	Cholecystotomy, choledochotomy, cholecystojejunostomy	Recurrence 14 months postoperatively, normal 4 months following 2nd surgery
11	Elwood et al 2001	14 year old FN DSH	Hyperthyroidism, cholangitis, pancreatitis	No	50% calcium carbonate and 50% calcium bilirubinate	Cholecystectomy	Recovered from surgery, follow-up not reported

Table 1 (*continued*)

Number	Reference	Details of cats	Underlying disease	EHBO present	Reported cholelith composition	Treatment	Outcome
12	Eich and Ludwig 2002	7 DSH, 1 Maine Coon, 1 Abyssinian, 6 MN, 3 FN, 5−18 years (mean 12 years), NB one cat was anaemic (Hct 17.5%) but not specified which cat	Cholecystitis, cholangiohepatitis, hepatic lipidosis	Yes	Only determined in 3/9 cases (specific cases not specified). 100% calcium carbonate in 2 cats, 40% calcium carbonate, 55% calcium bilirubinate and 5 % cholesterol in one cat	Cholecystectomy	Euthanased 2 days post-operatively
13			Hepatic lipidosis	Yes		Cholecystoduodenostomy	Died postoperatively
14			cholecystitis, cholangiohepatitis	Yes		Cholecystectomy	Alive 15 months postoperatively
15			Cholecystitis, cholangiohepatitis	Yes		Cholecystotomy, PEG tube	Euthanased 13 months postoperatively
16			Cholecystitis, cholangiohepatitis	Yes		Cholecystectomy, PEG tube	Alive 24 months posoperatively
17			Cholecystitis	Yes		Cholecystectomy	Alive 24 months postoperatively
18			Cholecystitis, cholangiohepatitis	Yes		Cholecystectomy	Alive 26 months postoperatively
19			Cholangiohepatitis, IBD	Yes		Cholecystoduodenostomy	Euthanased 18 months postoperatively due to renal failure
20			Cholangiohepatitis	Yes		Cholecystojejunostomy	Euthanased 27 months postoperatively for laryngeal neoplasia
21	Mayhew et al 2002	2 year old FN DSH	Cholangiohepatitis	Yes	Only determined in 1/6 cases (specific case not specified), in which case it was 100% calcium carbonate	Cholecystojejunostomy	Died 19 months postoperatively (cause unknown)

22		11 year old MN DLH	Cholecystitis	Yes		Cholecystectomy, choledochotomy	Alive 6 years postoperatively
23		8.5 year old MN DSH	Cholangiohepatitis, cholecystitis, pancreatitis	Yes		Cholecystoduodenostomy (and revision 20 months later due to recurrent cholelithiasis)	Alive 4 years postoperatively
24		8.5 year old FN DSH	ND	Yes		Cholecystojejunostomy	Died immediately postoperatively
25		18 year old FN DSH	ND	Yes		None	Euthanased at presentation
26		10 year old FN Himalayan	Cholangiohepatitis, cholecystitis	Yes		Cholecystectomy	Died immediately postoperatively
27	Lecoindre and Chevallier 2004	12 year old European cat	ND	No	Calcium bilirubinate and calcium carbonate	Cholecystectomy	Alive 3 months postoperatively
28	van Geffen et al 2005	2.5 year old FN Somali	Chronic haemolysis associated with PK deficiency	Yes	100% bilirubin	None	Euthanased at presentation

ND = not determined, FN = female neutered, MN = male neutered, ND = not diagnosed, DSH = domestic shorthair, PEG = percutaneous endoscopically placed gastrostomy tube.

Ludwig 2002, Lecoindre and Chevallier 2004, van Geffen et al 2005). EHBO per se is also uncommon in cats and in the veterinary literature surgical treatment of feline EHBO is associated with high mortality and morbidity (Martin et al 1986, Buote et al 2006, Mayhew et al 2002), although one study reported a low mortality rate with cholecystectomy (Eich and Ludwig 2002).

This is the first report of successful treatment and long-term follow-up of a cat with EHBO due to bilirubin cholelithiasis in association with PK deficiency-induced chronic haemolysis, and the first documented case of feline PK deficiency in the UK. Bilirubin cholelithiasis should be considered a potential complication of chronic haemolysis and the possibility of EHBO should be investigated if such cats present with jaundice.

Acknowledgements

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