Idiopathic hepatic veno-occlusive disease causing Budd-Chiari-like syndrome in a cat

Budd-Chiari-like syndrome (BCLS) is a rare clinical entity characterised by portal hypertension and ascites. This report describes a case of BCLS in a cat due to obstruction at the level of the hepatic veins. The diagnosis was based on the clinical findings and a histopathological assessment of the liver demonstrating perivenular fibrosis around the central and sublobular veins. Although these lesions are similar to those observed in man with BCLS, the aetiology in this case remains unknown.

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INTRODUCTION

In veterinary medicine, the term Budd-Chiari-like syndrome (BCLS) is used to describe a rare clinical entity characterised by hepatic venous outflow obstruction. This results in postsinusoidal portal hypertension and generates a triad of clinical signs: abdominal pain, hepatomegaly and high protein modified transudate ascites (Grooters and Smeak 1995). BCLS is most commonly reported as a result of obstruction at the level of the right atrium or caudal vena cava (Table 1). There is only one previous report of BCLS due to obstruction at the level of the hepatic veins (Cohn and others 1991), and this occurred in a dog. In the cat, BCLS has been previously reported in only two cases, both of which had membranous obstruction of the caudal vena cava (Macintire and others 1995, Haskal and others 1999).

This report documents the first case of a cat with BCLS due to obstruction at the level of the hepatic veins. Perivenular lesions were histopathologically similar to hepatic veno-occlusive disease (VOD) in humans but their aetiology remains unknown.

CASE HISTORY

A three-year-old, male neutered domestic shorthaired cat presented with a seven-day history of progressive lethargy, reduced appetite, weight loss and abdominal swelling. There had been no response to antibiotics and diuretics. Feline leukaemia virus antigen and feline immunodeficiency virus antibody serology were negative. A feline coronavirus titre was 1/640.

Four weeks previously the cat had presented to the referring veterinary surgeon with right carpal swelling and lameness of acute onset. A five-day course of prednisolone (0·2 mg/kg orally once daily) was prescribed and the cat had made an uneventful recovery. The cat had re-presented to the referring veterinary surgeon four days previously with a three-day history of anorexia and abdominal swelling. The cat was hospitalised and amoxycillin and frusemide were administered subcutaneously. The cat ate well while hospitalised and was discharged the following day with a course of amoxycillin and frusemide tablets. The owners did not administer these medications and re-presented the cat to the referring veterinary surgeon two days later, at which point referral was arranged.

The cat was currently vaccinated against feline herpesvirus, feline calicivirus and feline parvovirus and there were no in-contact animals, although the cat was free-roaming. The cat was fed a combination of commercial feline diets.

On clinical examination, the cat was cachexic, with a body condition score of 3/10, and had an enlarged abdomen with a fluid thrill. Pyrexia (40·1°C), pale mucous membranes and tachycardia (200 bpm) with a grade I/VI systolic heart murmur were noted. Abdominal palpation revealed cranial abdominal pain, hepatomegaly and splenomegaly. Haematology confirmed anaemia (haematocrit 22·5 per cent [reference range 30 to 45 per cent]) which was microcytic (mean corpuscular volume 34·8 fl [39·0 to 55·0]), normochromic and non-regenerative. The only leucocyte abnormality was mild lymphopenia ($0{\cdot}732 \times 10^9$/litre [1·5 to 7·0]). An automated platelet count proved unreliable as a result of platelet agglutination. Examination of a fresh blood smear revealed normal platelet numbers. No abnormalities of red cell morphology were observed. Serum biochemistry detected mild elevations in alanine aminotransferase

Table 1. Previously reported cases of Budd-Chiari-like syndrome in the dog and cat

Species	Number of cases	Obstruction site	Aetiology	References
Dog	10	Right atrium	Cor triatrium dexter	Van der Linde-Sipman and Stokhof (1974) Miller and others (1989) Malik and others (1990) Otto and others (1990) Jevens and others (1993) Tobias and others (1993) Kaufmann and others (1994)
Dog	3	Right atrium	Neoplasia	Edwards and others (1978) Lombard and Goldschmidt (1980) Atkins and others (1982)
Dog	4	Caudal vena cava	Blunt trauma	Kolata and others (1982) Crowe and others (1984) Lisciandro and others (1995) Fine and others (1998)
Dog	1	Caudal vena cava	Extraluminal neoplasia	Cornelius and Mahaffey (1985)
Dog	2	Caudal vena cava	Intraluminal neoplasia	Schoeman and Stidworthy (2001) Beeso and others (1993)
Dog	2	Caudal vena cava	Idiopathic	Cornelius and Mahaffey (1985) Miller and others (1989)
Dog	1	Caudal vena cava	Fibrosis secondary to foreign body	Smith (1994)
Cat	2	Caudal vena cava	Intravascular fibrous web	Macintire and others (1995) Haskal and others (1999)
Dog	1	Hepatic veins	Perivenular fibrosis	Cohn and others (1991)

(75 µ/litre [0 to 35]) and aspartate aminotransferase (37 µ/litre [0 to 30]). Pre- and postprandial bile acids were within reference ranges. Mild hyponatraemia (142 mmol/litre [145 to 160]) and azotaemia (urea 26·2 mmol/litre [2·7 to 9·2], creatinine 197 µmol/litre [91 to 180]) were also present. Urine specific gravity was 1·025 suggesting that renal insufficiency was at least partly responsible for the azotaemia. Urinalysis was otherwise unremarkable.

Thoracic radiographs revealed no abnormalities. Abdominal radiographs demonstrated hepatomegaly with rounded margins and splenomegaly. There was a ground-glass appearance and reduced contrast throughout the abdomen consistent with the presence of free abdominal fluid. The left kidney was not identified but radiographically the right kidney appeared normal. Echocardiography was unremarkable and the heart murmur was ascribed to a flow murmur as a result of anaemia and tachycardia.

Abdominal ultrasonography revealed a moderate amount of anechoic free abdominal fluid localised in the cranial abdomen around the liver. There was splenomegaly but splenic vessels were not engorged. The left kidney could not be identified. The right kidney appeared ultrasonographically normal. The liver was large with rounded margins and was of similar echogenicity to the renal cortex. The common bile duct was distended and imaged as a coiled, tubular, anechoic structure running from the gallbladder towards the hilus. The intrahepatic section of the caudal vena cava measured 0·45 cm in diameter, the portal vein measured 0·62 cm in diameter at the porta hepatis, and the hepatic veins were not clearly visualised. The portal vein demonstrated a maximum flow rate of 21 cm/second (normal 10 to 12 cm/second), which was non-pulsatile (Lamb 1998). A vessel demonstrating retrograde venous flow of 24 cm/second was identified in close proximity to the portal vein just before it entered the liver, and was thought to represent an extrahepatic shunting vessel. The branches of the portal vein within the liver were prominent but no abnormal intrahepatic blood vessels were identified.

Abdominal fluid analysis was consistent with a modified transudate: total protein was 40 g/litre and there was a nucleated cell count of $0{\cdot}40 \times 10^9$/litre, consisting of a mixed population of non-degenerate neutrophils, a few lymphocytes, several macrophages, occasional mast cells and several reactive mesothelial cells; a few large/giant cells were also seen. The most common causes of modified transudate abdominal effusions in small animals are right-sided congestive heart failure, cardiac tamponade, primary hepatic disease and postsinusoidal venous outflow obstruction. A high protein (>25 g/litre), low cellular fluid is characteristic of chronic postsinusoidal venous obstruction (Johnston 1987a,b). In this case, echocardiography and thoracic radiography excluded right-sided congestive heart failure and cardiac tamponade. Primary hepatic disease remained a differential diagnosis. However, high protein modified transudate ascites is uncommon in primary liver disease. A tentative diagnosis of postsinusoidal venous outflow obstruction was made. Splenomegaly remained unexplained.

An exploratory laparotomy was performed and hepatic and splenic biopsies obtained. The left kidney was identified but was hypoplastic ($2 \times 1{\cdot}5 \times 1$ cm) and a mesh of extrahepatic vessels was observed which was thought to represent extrahepatic portosystemic shunts. Histopathologically, the biopsies showed the liver to be congested with distinct perivenular fibrosis around the central (Fig 1) and sublobular veins. The splenomegaly was largely due to the presence of histiocytes in the red pulp (Fig 2); the white pulp was also expanded, but to a lesser degree. The histiocytic cells had ovoid or slightly indented open nuclei with prominent nucleoli. Their cytoplasm was abundant with poorly defined borders and mitotic figures were plentiful. The cells were negative for iron by the Perl's reaction but stained positively using a monoclonal mouse

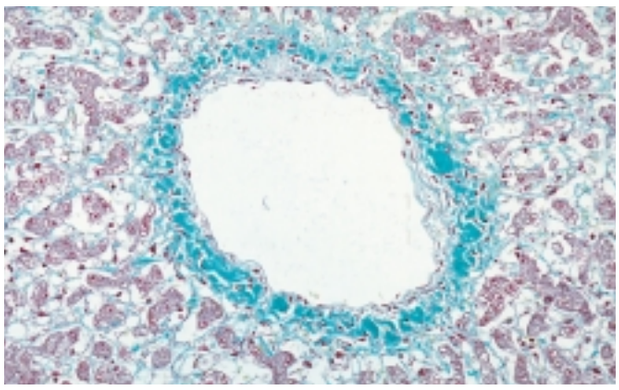

FIG 1. Histological section of liver from a cat with hepatic veno-occlusive disease showing a central vein displaying subendothelial fibrosis with extension into the sinusoids. Masson's trichrome stain ×250

antibody, Mac 387 (Dako, A/S, Denmark), which is known to react with macrophages.

The histopathological findings in the liver, together with a modified transudate in the abdomen, were consistent with a diagnosis of a BCLS, but the appearance of the spleen and the microcytic anaemia were confusing. The histiocytic reaction in the spleen raised the possibility of a malignant histiocytosis, which in some way could have caused pressure on the hepatic vein or induced hepatic fibrosis through inflammatory mediator release (Center 1999). This complex and provisional diagnosis was discussed in full with the owner who declined further treatment for the cat but requested a full postmortem examination. The cat was subsequently euthanased.

At postmortem examination the abdominal cavity was taut and distended. The liver appeared enlarged with a pale mottled granular surface and all lobules were swollen with rounded edges. The cut surface was firm but did not ooze blood. The spleen was expanded and more turgid than normal, with scant fibrin strands on the capsular surface. Sectioning revealed the substance to have a dense meaty texture with a tacky feel. There were prominent acquired portosystemic anastomoses within the mesentery, indicating portal hypertension. Fifty millilitres of straw-coloured fluid were recovered from the abdominal cavity. A detailed dissection of the heart, posterior vena cava and major hepatic vessels eliminated the possibility of any posthepatic cause of the portal hypertension.

Samples for histopathology were taken from a wide range of tissues, fixed in 10 per cent neutral buffered formalin, processed and embedded in paraffin blocks. Special stains were Masson's trichrome technique for collagen fibres, Gordon and Sweet's method for reticulin fibres and immunocytochemistry using a peroxidase stain to identify T and B lymphocytes and macrophages.

In all lobes of the liver the normal architectural skeleton was clear, with demarcation of hepatic lobules by the portal triads. There was some duplication of bile ducts in the portal areas but the major pathological finding in all lobes was centred on the hepatic and sublobular veins. Most veins had varying degrees of perivenular fibrosis that then radiated out towards the portal triads within the sinusoids (Fig 1). There was concurrent loss of hepatocytes in the centilobular areas. Staining with Masson's trichrome technique highlighted the increase in collagen fibres found both subendothelially in the central veins and in the tunica media of the larger sublobular veins. Occasionally, strands of fibrous tissue spanned the lumen of some vessels to reduce the functional diameter. This increased resistance resulted in a serpentine tortuosity of the veins within the collagen matrix (Fig 3). The outer capsule of the liver was thickened due to fibrosis and the mesothelial cells were plump and active. In some areas, the single layer of cells was folded back to form pseudoacini and tuft-like projections from the liver surface.

The histiocytic reaction was confirmed in the spleen and active histiocytes were also noted in the bone marrow. The lymph nodes were not affected in this way. A final diagnosis of hepatic veno-occlusive disease with reactive histiocytosis was made.

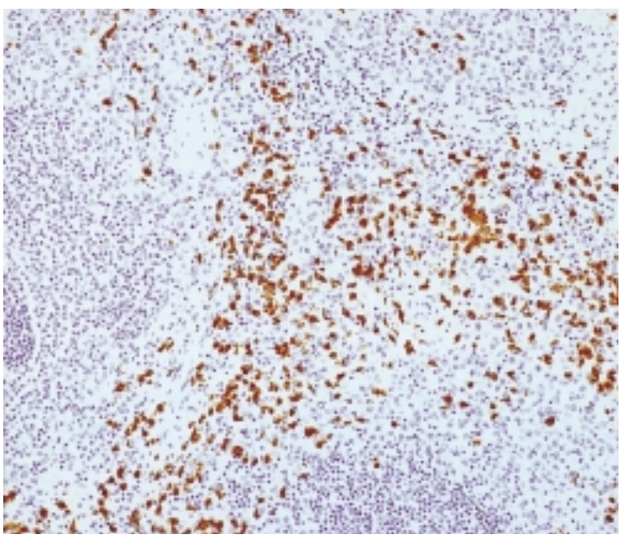

FIG 2. Histological section of spleen from a cat with hepatic veno-occlusive disease showing increased numbers of brown-stained histiocytes in the red pulp. Immunoperoxidase stain ×125

DISCUSSION

In human medicine, the term Budd-Chiari syndrome was originally used to describe postsinusoidal hypertension associated with a specific lesion – inflammation of the intima of small hepatic veins (McDermott and others 1984). VOD is a major differential diagnosis for Budd-Chiari syndrome in humans and results in similar clinical signs but distinct histopathological findings. Histopathology reveals variable disruption of blood flow in the terminal hepatic venules (central veins), ultimately resulting in damage to the zone 3 (centrilobular) hepatocytes. The process initially presents with subendothelial oedema resulting in concentric narrowing of the terminal and central veins, often progressing to collagen deposition with sclerosis of the venules (Rappeport 1996). The pathophysiology of VOD in humans remains obscure. A

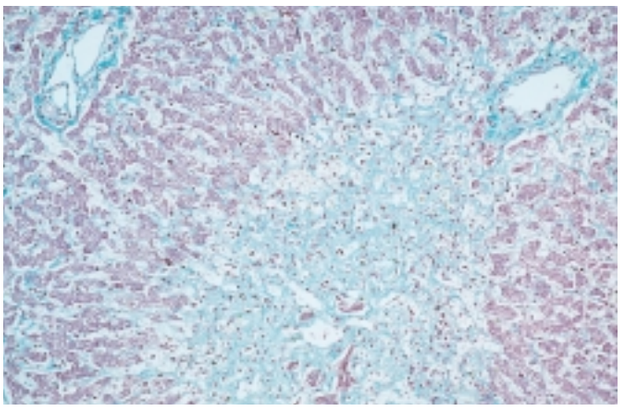

FIG 3. Histological section of liver from a cat with hepatic veno-occlusive disease showing distortion of a central vein in a collagen matrix with extension towards surrounding portal triads. Masson's trichrome stain ×125

hypercoagulable state has been associated with VOD. Elevations of tumour necrosis factor-alpha and interleukin-1-beta could represent either an initiating factor or an inflammatory response to VOD (Rappeport 1996).

In veterinary medicine, it has been proposed that the term BCLS should be used more broadly to describe the clinical manifestations of hepatic venous outflow obstruction caused by a mechanical obstruction between the hepatic sinusoids and the right atrium (Grooters and Smeak 1995). The clinical signs include the triad of hepatomegaly, abdominal pain and high protein modified transudate abdominal effusion (Fine and others 1998). Hepatic veins lack valves and so an increase in postsinusoidal venous pressure causes a direct increase in sinusoidal pressure. Hepatic sinusoids have large fenestrations compared to other capillaries and increased sinusoidal pressure causes leakage of high protein fluid into the space of Disse. If the capacity of hepatic lymphatic drainage is exceeded, this high protein fluid contributes to ascites (Johnston 1987a,b).

BCLS has been reported in 24 dogs and two cats (Table 1). A hepatic venous site of obstruction has only been reported before in one dog (Cohn and others 1991). Histopathological findings in this dog included distended subcapsular lymphatics, marked centrilobular congestion and slight narrowing of the central veins. Central and sublobular veins were surrounded by fibroblasts and collagen deposits and zone 3 hepatocytes were atrophied. These lesions were considered to be similar in location to VOD in humans. However, the histopathological findings were too dissimilar to confirm this diagnosis and a diagnosis of idiopathic intrahepatic postsinusoidal venous obstruction was made. This is the first report of BCLS in a cat with a hepatic venous site of obstruction. The authors believe that the histopathological findings in this cat are sufficiently similar to those in humans with VOD to make the first reported diagnosis of VOD in a domestic cat.

In humans, VOD has been associated with pyrrolizidine alkaloid ingestion, chemotherapy, radiotherapy and bone marrow transplantation (Epstein and others 1992, Rappeport 1996). VOD develops frequently in dogs treated experimentally with the pyrrolizidine alkaloid monocrotaline and infrequently in dogs treated with irradiation or busulphan (Shulman and others 1987, Epstein and others 1992). VOD has been reported in captive cheetahs fed a commercial feline diet containing large amounts of phytoestrogens (Setchell and others 1987). The aetiology of VOD in this cat remains obscure. Of the known inciting factors in other species only dietary ingestion of pyrrolizidine alkaloids seems possible. However, further questioning of the owner failed to suggest any compatible dietary history in this case.

Portal hypertension usually causes reduced portal venous blood flow (Lamb 1998) but, in this cat, portal flow was elevated at the time of examination. Increased portal venous flow is commonly associated with a congenital intrahepatic portosystemic shunt due to the creation of a low resistance path for blood to bypass the liver (Lamb 1998). However, congenital intrahepatic portosystemic shunts are readily identifiable within the liver using ultrasound and demonstrate pulsatile flow due to exposure to pressure changes within the caudal vena cava. There were no findings suggestive of an intrahepatic portosystemic shunt in this cat.

Identification of extrahepatic shunts using ultrasound can be difficult due to the complex abdominal vascular anatomy and interference from intestinal gas. Congenital and acquired extrahepatic shunts are both associated with reduced portal flow. The hepatomegaly with prominent portal vein branches detected in this case makes a congenital extrahepatic shunt unlikely. Acquired portosystemic shunts can develop as a result of portal hypertension, which also promotes the formation of ascites. The vessel demonstrating retrograde venous flow identified in this cat is likely to represent one of the numerous extrahepatic shunts identified at postmortem examination.

Normal hepatic blood vessel diameters have not been established in the cat. In dogs, the portal and hepatic venous systems are generally considered to be of similar diameter (Lamb 1998). The finding of prominent portal veins in the absence of clearly visualised hepatic veins in this case would be consistent with a reduction in hepatic vein diameter. In a dog with BCLS as a result of obstruction at the level of the hepatic veins, the diameter of the intrahepatic caudal vena cava and hepatic veins was also reported to be small when compared to that of the portal vein (Cohn and others 1991).

Ultrasonographic diagnosis of VOD in humans has proved difficult. McCarville and others (2001) observed a slight trend of decreasing portal blood velocity in a group of children developing VOD following bone marrow transplantation. However, this measure proved highly variable on a day-to-day basis in any single patient and portal blood velocity was elevated on some occasions. These authors conclude that gray scale and Doppler ultrasound findings cannot reliably diagnose VOD in pediatric bone marrow transplant recipients and that ultrasound does not currently replace clinical criteria as the gold standard for the diagnosis of VOD. Thus, the findings of raised portal blood velocity on a single occasion in this individual case may not be at odds with a diagnosis of VOD. Repeated measurements over time may have proved more informative.

Mesenteric portography may have been of diagnostic benefit antemortem in this case. It may have allowed better evaluation

of portosystemic shunting and exclusion of vena caval obstruction than was possible with plain radiography and ultrasonography.

The cause of the histiocytosis involving the spleen and bone marrow remains obscure. Malignant histiocytosis in the cat is reported to produce similar clinical signs of anorexia, lethargy, hepatomegaly and splenomegaly with anaemia (Kraje and others 2001). Grossly, tan nodules are present in the affected organs, which may include spleen, bone marrow, lung, liver and brain. Cytologically, haemophagocytosis is common and the invading histiocytes can appear in clusters that destroy the normal architecture of the affected organ. In dogs, evaluation of haemophagocytic disorders by cytology highlights the difficulty of differentiating between benign and malignant conditions, due to a lack of consistent parameters attributable to either condition (Weiss 2001). There is no mention of a reactive histocytosis without haemophagocytosis in the literature. In this case, neither the location nor the phagocytic properties of the histiocytes are consistent with a diagnosis of malignant histiocytosis, suggesting a reactive rather than a neoplastic source of the histiocytes. Whatever the cause, it is unlikely that these two concurrent rare disorders are unrelated. The fact that splenic vessels drain entirely into the hepatic portal system supports the possibility that inflammatory mediator release from the histiocytes could be responsible for the fibrosis in the liver.

Unfortunately, the owner did not wish the cat to be treated as the outcome following the hepatic and splenic biopsies was clearly uncertain. However, in humans, treatment of established VOD is difficult. Diuretics may be beneficial but no evidence supports the use of corticosteroids, heparin or pentoxifylline. Some patients have been treated with prostaglandin E_1 or recombinant tissue plasminogen activator, but evidence of efficacy is limited (Rappeport 1996). In veterinary medicine, reports of the treatment of established VOD are limited to removal of the inciting cause (Setchell and others 1987) which remained undetermined in this case.

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