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## **Concurrent physitis and portosystemic shunts in three dogs**

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### **Summary**

Hepatic disease is a known risk factor for the development of bone infection in humans. Three dogs with portosystemic shunting and concurrent physitis are presented here and an association is postulated between both disease processes. Portosystemic shunting may be a risk factor for the development of physitis in dogs. Skeletal structures should not be overlooked when reviewing diagnostic imaging studies of dogs with portosystemic shunts. Skeletal infections should be considered as a differential diagnosis in dogs with liver disease and concurrent skeletal abnormalities.

### **Introduction**

Infection of the physes (septic physitis) is infrequently seen in the dog. It has been linked to neonatal bacteraemia and haematogenous spread of infection from an infected focus, usually within the umbilicus (Nunamaker 1985). However, in the horse septic physitis is usually seen in older foals, typically those older than 10 days (Firth 1983). This is hypothesised to be as a consequence of age related changes in the physal vasculature and delayed haematogenous spread of bacteria, again usually secondary to omphalophlebitis (Firth 1983). Vertebral physitis has been described in the dog as a distinct disease entity from discospondylitis, and has been documented to be more common in animals less than 2 years of age (Jimenez & O'Callaghan, 1995).

Portosystemic shunts (PSS) are vascular anomalies that redirect blood from the portal circulation to the systemic circulation, bypassing the hepatic sinusoids and liver parenchyma (Berent & Tobias, 2009). The condition is one of the most common

congenital abnormalities in the dog, usually consisting of a single intra- or extra-hepatic shunting vessel, or may be acquired secondary to portal hypertension (Berent & Tobias, 2009). Acquired shunts usually consist of multiple tortuous extra-hepatic vessels communicating between the portal vasculature and the caudal vena cava or its tributaries.

Skeletal infection has been reported in conjunction with hepatic disease in humans and it has been shown that the presence of liver cirrhosis is a significant risk factor for the development of osteomyelitis (Akiyama et al., 2013). No such link has been made in animals. Here we present three dogs with phyllophagocytosis and concurrent PSS.

## **Case Presentation**

### *Case 1*

A 14-month-old female Rottweiler was presented with a two-week history of spinal pain, hyporexia, and intermittent pyrexia. She had been diagnosed ultrasonographically and histopathologically with primary hypoplasia of the portal vein and numerous extra-hepatic PSS, which were assumed to be secondary to portal hypertension 6 months previously. The dog was managed medically with a low protein diet, lactulose and spironolactone. The owners reported that the dog was behaving normally at the time of repeat examination, and that no signs consistent with hepatic encephalopathy had been seen recently.

### *Case 2.*

A 3-month-old male Labrador retriever was presented for assessment of altered mentation of 48 hours duration, lethargy and variable appetite over the previous 5 weeks. The referring veterinary surgeon had a high clinical suspicion of portosystemic shunting.

### *Case 3*

A one-year-old male Border collie was presented for with a history of ill-thrift, dullness and chronic intermittent diarrhoea, intermittent abdominal pain and intermittent pyrexia. Exploratory laparotomy and attempted portovenography by the referring vets had revealed a strong suspicion of PSS.

## **Investigation and treatment**

### *Case 1*

Clinical examination revealed a narrow based hindlimb stance, short pottery hindlimb gait and marked pain on palpation of the mid-lumbar spine. Abdominal palpation was also resented, but to a lesser extent. Radiographs of the lumbar vertebral column revealed moderate irregular lysis of the caudal vertebral endplate of the third lumbar vertebra (L3) with irregular periosteal reaction ventrally, consistent with physitis (**Figure 1A**). Repeat radiographs obtained 7 days later showed static caudal endplate lysis and progression of ventral periosteal reaction. Mild lytic changes were also seen in the cranial endplate of the fourth lumbar vertebra at this time (**Figure 1B**). Urinalysis revealed pyuria with significant numbers of gram-negative bacteria present, urine culture confirmed the presence of *E. coli* spp. Blood culture was negative. Antimicrobial treatment with marbofloxacin (2mg/kg PO q 24h) (Marbocyl P, Vetoquinol) and clindamycin (11mg/kg PO q12h) (Antirobe, Zoetis) was commenced, together with Tramadol (3mg/kg PO q 8h) and gabapentin (10mg/kg PO q 8h) for analgesia.

## Case 2

Blood samples obtained at the time of referral identified a marked elevation in serum bile acids post prandially, elevated from 29.8  $\mu\text{mol/l}$  fasting level (reference  $<7$ ) to 138.5  $\mu\text{mol/l}$  after feeding, consistent with impaired liver function or portosystemic vascular anomaly. Ultrasonographic examination and computed tomographic (CT) angiography were performed and revealed the presence of a large single right-divisional intrahepatic congenital PSS (**Figure 2A & B**). The shunt was positively identified on ultrasonography, however CT was requested for surgical planning. During hospitalisation the dog developed a right hindlimb lameness, which was localised to the distal tibia on orthopaedic examination. This region was subsequently included in the CT examination. Radiography and CT revealed an ill-defined T-shaped radiolucency within the medial aspect of the distal physis of the right tibia, consistent with physitis (**Figure 2C**). Blood culture was negative. Antimicrobial therapy with clavulanate-potentiated amoxicillin (125mg PO q 12h) (Synulox, Zoetis) and clindamycin (11mg/kg PO q 12h) (Antirobe, Zoetis) was commenced.

## Case 3

Multiple extra-hepatic portosystemic shunt vessels were seen on ultrasonography and CT angiography (Figure 3A). Radiographs revealed widening of the physis of the caudal vertebral endplate of L3 with mild periosteal new bone formation over the ventral portion of the vertebral body of L3. Lytic changes surrounding the caudal vertebral endplate were similarly seen on CT (Figure 3B). Blood culture was negative. Antibiotic treatment with cephalexin (15mg/kg PO q 12h) (Rilexine, Virbac) and enrofloxacin (5mg/kg PO q 24h) (Baytril, Bayer) was commenced. The PSS was successfully managed medically as described for case 1.

## Differential Diagnosis

## Cases 1 & 3

The primary differential diagnosis in these cases is discospondylitis. Jiminez et al. (1995) discussed the difference between vertebral physitis and discospondylitis. The key features of vertebral physitis are that it begins in one vertebral body, and is centred on the caudal vertebral physis, sparing the vertebral end plate. As disease progresses there may be collapse of the vertebral end plate and ventral new bone arising from the caudal vertebral end plate only. This remains asymmetric, as seen in cases 1 & 3. Discospondylitis involves symmetrical destruction and new bone formation involving the vertebral bodies on either side of the affected intervertebral disc. Although a small lesion was seen in the cranial endplate of L4 in case 1, the majority of bony reaction was confined to the caudal vertebral physis and end plate of L3, therefore physitis was considered most likely in this case. Definitive diagnosis of the extent of vertebral body and intervertebral disc involvement would require MRI examination of the lumbar vertebral column, which was not available in this case.

## Case 2

Metaphyseal osteopathy is a differential diagnosis in case 2. It was excluded in this case on the basis that the lesion is unilateral and does not encompass the entire metaphyseal region. The appearance of metaphyseal osteopathy is that of bilaterally symmetrical polyostotic lesions which involve the metaphyses of long bones, particularly distal radius, ulna and tibia. There are usually transversely oriented lucent zones within the metaphysis that are parallel and adjacent to the physes and there is usually widening and remodeling of the physis. The lesion described in this case was monostotic and confined to the metaphyseal region. The 'double physeal sign' seen with metaphyseal osteopathy was not present and there was minimal surrounding sclerosis. On balance it was considered that an atypical presentation of metaphyseal osteopathy was less likely than physitis.

## **Outcome and follow-up**

### *Case 1*

Antimicrobial treatment was continued for 12 weeks and radiographic monitoring performed at four-week intervals. The dog became more comfortable and no further episodes of pain were noted following cessation of treatment. Radiographically the L3 vertebra appeared more sclerotic and the ventral periosteal reaction was reduced.

### *Case 2*

Antimicrobial therapy for 4 weeks resulted in resolution of the lameness. The PSS was initially managed medically. The dog was surgically treated for PSS at another institution and was lost to further follow-up.

### *Case 3*

Antimicrobial therapy for 8 weeks resulted in resolution of pain and pyrexia. Radiographs taken at this time revealed resolution of the lytic changes of the L3 caudal endplate with ventral new bone formation.

## **Discussion**

All three cases presented here had concurrent physitis and PSS. Simultaneous occurrence of these conditions has previously been reported once in a dog, however

this was regarded as coincidental and no association between the conditions was postulated (Walker et al., 1999). The link between liver disease and orthopaedic infection is well established in humans and this report describes the first case series linking portosystemic disease and phyllophagitis in dogs.

The presence of liver cirrhosis in humans has been shown to be associated with development of osteomyelitis (Morrison & Naktin, 2009; Akiyama et al., 2013; Jeong et al., 2014; Kusuyama et al., 2013;). One epidemiological study showed that the presence of liver cirrhosis resulted in an increased risk of development of vertebral osteomyelitis (odds ratio of 2.6) (Akiyama et al., 2013). It is hypothesised that this is due to inefficient clearance of bacteria from the bloodstream by the reticuloendothelial system, as demonstrated in rats with PSS, resulting in bacteraemia (Katz et al. 1991; Hung et al. 1997). Although liver cirrhosis and PSS are different disease processes, the failure of bacterial and toxin clearance from the blood stream by the reticuloendothelial system may be common to both conditions. If so, it is possible that bacteraemia occurs in cases of PSS, and thus these animals may be predisposed to the development of opportunistic skeletal infections, such as phyllophagitis in the cases described above.

Blood culture was negative in all cases described. Urine culture in case 1 was positive for *Escherichia coli* spp. It should be noted that a negative blood culture is not necessarily indicative of absence of bacteraemia; as few as 36% of cases of acute haematogenous osteomyelitis in children have a positive blood culture (Weichert & Sharland, 2008). This may reflect the difficulties in ex-vivo culture of some bacterial species or differences in the trophic factors present in the blood that are absent when in-vitro culture is attempted. Attempts have been made to compare bacterial isolates from the blood of normal dogs, dogs with single, congenital PSS and dogs with experimentally induced extra-hepatic PSS (Tobias & Besser, 1997; Howe et al., 1999). Whilst no difference in the frequency of bacteraemia was identified, there



was variation in the type of bacteria isolated (Tobias & Besser, 1997; Howe et al., 1999). PSS dogs had a significantly higher percentage of gram-positive bacteria isolated (42% compared to 16% in normal dogs) and a significantly lower percentage of gram negative bacteria isolated (58% compared to 84% in normal dogs) (Howe et al., 1999). Gram-positive bacteria are commonly associated with osteomyelitis. *Staphylococcus aureus* is the most common isolate in children with acute haematogenous osteomyelitis, although this is not the case in adults (Weichert & Sharland, 2008). Similarly canine osteomyelitis and physitis have been associated with *Streptococcus* and *Staphylococcus* isolates, but gram-negative species are seen also (Walker et al., 1999; Rabillard et al., 2011). The absence of positive blood culture results makes comparison between these results and our cases difficult. It is possible that case 1 had a primarily *E. Coli* infection, owing to the positive urine culture but in the other cases speciation is impossible.

The vascular anatomy of the physis is hypothesised to predispose this location to infection. The presence of vascular loops between the metaphyseal capillaries and venules is thought to produce sluggish blood flow, allowing bacteria to settle out in this highly vascular region and establish infection (Firth 1983; Firth & Poulos 1983; Rabillard et al., 2011). The capillary beds have been shown to have porous endothelium, facilitating the extravasation of red blood cells and bacteria and predisposing to infection (Rabillard et al., 2011). Cases 1 and 3, both of whom were less than two years of age had vertebral physitis of the caudal vertebral endplate, which correlates to a previous study where vertebral physitis is most common in animals of this age (Jimenez & O'Callaghan, 1995). Case 2, aged 3 months had physitis of the distal tibial physis. Both the distal tibial and caudal vertebral physes close at similar time points, approximately 12 months of age (Thrall and Robertson 2011), making the differing locations of the physitis difficult to explain. There may be age related changes in the microvasculature resulting in vertebral physitis being more common than limb changes in older animals, however further cases are required to confirm or refute this.

The demonstration of physitis in several dogs with portosystemic shunting has a number of potential clinical implications. Firstly, images obtained from dogs with suspected liver disease should be carefully screened for the presence of skeletal infections. Radiography adequately revealed these changes in all three cases. In many patients, it is feasible to assess a significant proportion of the skeleton for the presence of infection during an abdominal CT examination, which is increasingly undertaken to assess dogs for the presence of PSS. Secondly, there is a growing body of work linking inflammation and the development of hepatic encephalopathy (HE), which is a major cause of morbidity and mortality in dogs with liver disease (Gow et al., 2012; Kilpatrick et al., 2014; Tivers et al., 2014; Tivers et al., 2015). Our report suggests it is necessary to consider skeletal infections as a potential differential diagnosis in dogs with HE and concurrent inflammation.

#### Learning points

- Physitis should be considered as a potential complication in dogs with PSS and HE.
- There is potential for concurrent inflammatory bone disease processes in patients with PSS, especially in those presenting with atypical signs such as lameness or pyrexia.
- Thorough evaluation of the skeletal system in all images acquired is necessary in cases of PSS to distinguish potential bone involvement

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#### Figure Legends

Figure 1: Lateral radiographs of the lumbar spine of case 1 at the time of presentation (A) and 7 days later (B). A – There is an ill-defined widening of the caudal vertebral physis of L3 extending from the ventral margin of the vertebral body to floor of the vertebral canal (arrowhead). There is ill-defined new bone formation ventrally extending from the mid-point of the ventral surface of the vertebral body of L3 caudally to the intervertebral disc space (arrows). B – The widening of the caudal vertebral physis is similar and the ventral new bone formation is increased in size and opacity. There is also a mild, well-defined lucent lesion within the cranial vertebral endplate of L4 (arrowhead).

Figure 2: A & B - Transverse portal-phase vascular CT images from case 2. A large tortuous shunt vessel (S) can be seen extending between the portal vein (P) and the caudal vena cava (C). The aorta is labelled Ao. C – Dorsally reconstructed CT image of the distal hindlimbs. There is irregular widening of the medial aspect of the distal tibial physis of the right hindlimb with a residual bone fragment within the area of osteolysis (arrow).

Figure 3: A – Transverse portal-phase vascular CT image from case 3. The caudal vena cava (C) and the aorta (Ao) can be seen dorsally. There is a myriad of small tortuous shunting vessels between the kidneys, the ventral extent is marked by arrows. B – Lateral radiograph of the lumbar spine showing a well-defined radiolucent region within the caudal vertebral physis of L3 (arrowhead) and mild irregularity of the

vertebral endplate. C- Sagittally reconstructed CT image showing similar pattern of physeal lysis (arrowhead).



