



Acute and severe haemorrhage following pentosan polysulfate injection in a Cornish Rex

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Abstract

Case summary A 14-year-old male castrated Cornish Rex cat was referred for lethargy progressing rapidly to collapse in the hours following a subcutaneous injection of a product containing 100mg/ml pentosan polysulfate sodium and 168mg/ml glucosamine. Physical examination revealed the cat to be in hypotensive shock with swelling and interstitial oedema around the cranial thorax and caudal cervical regions without cutaneous haemorrhage. Initial diagnostics revealed a severe anaemia (packed cell volume 11%) which later deteriorated further, necessitating a blood transfusion and aggressive fluid therapy. Post-transfusion, the patient remained dyspnoeic and subsequent diagnostics found evidence of pre-existing cardiomyopathy and congestive heart failure. The cat was euthanased 24h following presentation due to increasing dyspnoea. Post-mortem findings were of severe subcutaneous and intermuscular haemorrhage over the neck and thorax, among other changes. There were no detectable levels of coumarin anticoagulants in the liver.

Relevance and novel information This is the first reported case of acute subcutaneous and intermuscular haemorrhage of this severity suspected to be related to the off-label use of an injectable product containing pentosan polysulfate in a cat. Given the popularity of its use for feline arthritis, there is a need for large-scale clinical trials to evaluate the safety and efficacy of products containing pentosan polysulfate for cats, and any side effects to be reported.

Keywords: Haemorrhage; pentosan polysulfate; adverse reaction; arthritis

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Introduction

Feline osteoarthritis is a common and important disease, affecting up to 90% of older cats.¹ Ideally, management should involve a combination of diet modification, environmental modification, medical therapy and physical rehabilitation.^{1,2} Medical options are limited to begin with, and the use of non-steroidal anti-inflammatory drugs chronically or at higher doses may be contraindicated by the presence of common comorbidities in older cats such as chronic renal disease and cardiac, liver or gastrointestinal disease.³

In dogs with osteoarthritis, a course of four injections of pentosan polysulfate at weekly intervals has been shown to have success in reducing lameness and pain, and increasing willingness to exercise.^{4,5} The use of this

medication in cats is extrapolated from its success in dogs and anecdotal evidence. There are currently no clinical trials evaluating its use in feline osteoarthritis, and its use is off-label. It is generally well tolerated, and most adverse effects (vomiting, lethargy, anorexia, depression) are mild and transient.⁶ It has recognised anticoagulant and

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fibrinolytic properties, and therefore its use with other drugs that affect coagulation are cautioned.^{6,7} We present the first report, to our knowledge, of a cat that developed widespread haemorrhage following, and likely associated with, an injection of pentosan polysulfate.

Case description

A 14-year-old male castrated Cornish Rex cat weighing 6.9 kg (15.2 lb) presented to a private referral and emergency clinic in a state of hypotensive and anaemic shock. The cat had presented to its primary veterinarian the prior afternoon for the second injection of pentosan polysulfate (Synovan; Ceva) of a four-weekly course, and was not on any other medications. The cat was previously clinically healthy apart from chronic mobility issues; haematology and biochemistry panels from 10 months prior were normal.

The injection was reportedly given at 3 mg/kg SC over the cervical region and the cat displayed a severe adverse and apparently painful reaction to this injection, which had not occurred at any previous injection (the cat had previously completed 4-week courses of pentosan polysulfate both 18 months and 10 months prior, which were temporarily effective for chronic elbow and stifle arthritis). Immediately after returning home the cat was noticed to be very restless, weak in the hindlimbs and a painful swelling was noted over the neck at the injection site. Over the next 5 h this progressed to lethargy, tachypnoea, vocalisation and eventually collapse with altered mentation.

The cat initially presented to a different after-hours veterinary clinic the day of the injection.

Reported physical examination findings included hyperaesthesia, particularly over the neck and hindlimbs, pale mucous membranes, hypotension (Doppler blood pressure 74 mmHg) and hypothermia of 35.1°C (95.2°F). The cat was treated supportively overnight with intravenous fluid therapy, buprenorphine, dexamethasone and active warming. Haematology and serum biochemistry performed in house the following morning showed a severe non- or pre-regenerative anaemia with a haematocrit of 11.4% and absolute reticulocyte count of 26.2 K/ μ l (reference interval [RI] 3.0–50.0), a mature neutrophilia of $18.8 \times 10^9/l$ (RI 2.50–12.50), normal platelet count of 183 K/ μ l (RI 175–600), hyperglycaemia of 10.52 mmol/l (RI 3.95–8.84), mild panhypoproteinaemia of 47 g/l (RI 57–89) and mild hypophosphataemia of 0.89 mmol/l (RI 1.00–2.42). At this point, approximately 24 h post-injection, the cat was transferred to the tertiary referral clinic for further evaluation and care.

On arrival, the cat was dull but hyper-responsive to stimuli, and was painful around the injection site. Mucous membranes were pale and pulses were weak. A gallop sound was heard on cardiac auscultation. Packed cell volume (PCV) was 5% on presentation and adequate

blood to perform clotting times was not obtainable. Non-pitting interstitial oedema was noted on the shoulders, ventral thorax, neck and chin. A blood transfusion (50 ml whole blood over 4 h) was performed following blood typing (type A); however, a cross-match was not performed owing to the severity of the cat's clinical signs and lack of prior transfusion history. The cat's vital signs remained stable and 100% oxygenation measured via pulse oximetry was maintained throughout the transfusion. A post-transfusion PCV of 15% was achieved. Mentation initially improved following transfusion but subsequently deteriorated again. The cat was stabilised in an oxygen tent with intravenous fluid therapy, maropitant (1 mg/kg IV), dexamethasone (0.23 mg/kg IV) and subcutaneous vitamin B₁₂ injection (0.25 mg/cat) overnight, prior to further diagnostics.

An echocardiogram was performed by a board-certified cardiologist around 12 h after presentation, which documented severe left atrial enlargement, moderate right atrial enlargement and discrete upper septal thickening (DUST). There was small-volume pericardial and pleural effusion, which together with the cardiac changes was consistent with heart failure, a finding that complicated but did not explain the severe anaemia.

Abdominal ultrasound identified a mild peritoneal effusion, as well as mildly increased intestinal thickness and mildly altered layering. Thoracic radiographs interpreted by a board-certified radiologist reported a normal heart size with dilation of the pulmonary arteries and veins. A bronchointerstitial, but no alveolar, lung pattern was identified. Owing to the cat's normal respiratory rate and character at the time of these diagnostic tests and no evidence of pulmonary oedema on radiographs, the anaemia and subsequent blood transfusion and fluid therapy were considered as a possible cause of acute exacerbation of heart disease, so the initial recommendation was to discontinue fluid therapy before initiating diuretics or any cardiac medications. The cat was maintained in an oxygen tent.

The cat's condition deteriorated rapidly later that evening, despite oxygen therapy, becoming increasingly dyspnoeic. Venous blood gas analysis showed a severe respiratory acidosis (pH 7.074) and hypercapnia (PvCO₂ 73.3 mmHg). The owners were considering humane euthanasia, owing to a perceived poor prognosis, and elected for this at this time as a result of the cat's unstable condition, rather than attempting further therapeutics such as thoracocentesis.

The presence of widespread non-pitting interstitial oedema and anaemia prompted a suspicion for internal haemorrhage, and the body was sent to an external laboratory for post-mortem examination. The examination was performed by a board-certified anatomical pathologist, and significant post-mortem findings were as follows. (1) Large amounts of subcutaneous and intermuscular haemorrhage

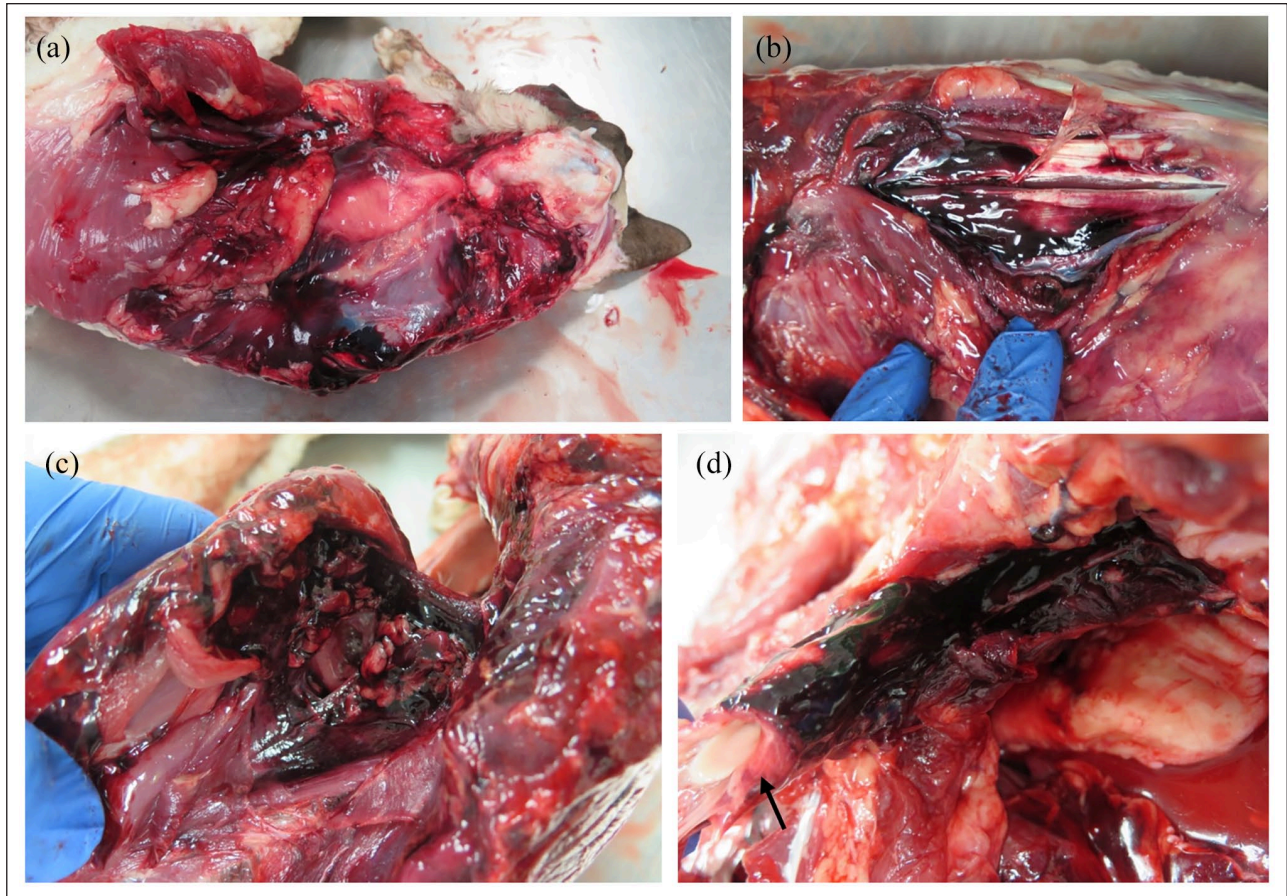


Figure 1 Post-mortem images showing severe haemorrhage in the dorsal (a) subcutaneous and (b) intermuscular spaces, (c) the left forelimb suspensory muscles, and (d) between the hypaxial muscles and the oesophagus and trachea, which have been partially dissected away (black arrow) in the ventral neck

circumferentially around the neck (particularly ventrally), caudal head and mandibular skin and over the dorsal thorax. The haemorrhage extended between dorsal and left lateral thoracic muscle layers, and between the left scapula and the body wall, as well as over both proximal forelimbs (Figure 1a–c). (2) Retropharyngeal haemorrhage with extension between hypaxial muscles and the oesophagus into the mediastinum and pericardium (Figure 1d). (3) Retropharyngeal haemorrhage with extension between hypaxial muscles and the oesophagus into the mediastinum and pericardium (Figure 1d). (4) Subcutaneous oedema without haemorrhage in the distal left forelimb. (5) Red serous fluid (100–200 ml) within the pleural cavity, and 1–2 ml of red serous fluid within the pericardial cavity (Figure 2). (6) The lung parenchyma ranged from light to dark red and oedematous (Figure 2). (7) Two small liver nodules (5 mm and 10 mm, respectively). No other gross abnormalities were identified, including no cutaneous petechiae or ecchymoses, and no evidence of haemorrhage from recent blood sampling and catheter sites.

Gross diagnoses were: (1) severe cervical and thoracic subcutaneous, intermuscular, mediastinal and pericardial

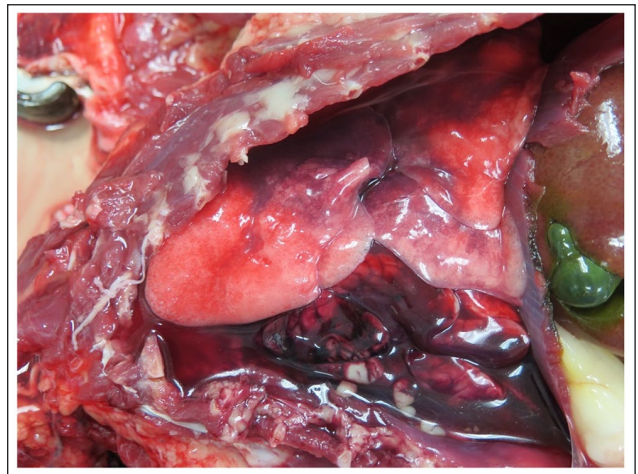


Figure 2 Post-mortem image of the opened thorax showing pulmonary oedema and congestion, pleural effusion and mediastinal haemorrhage

haemorrhage, and forelimb oedema; (2) pleural and pericardial effusion; (3) pulmonary oedema, congestion and

possible haemorrhage; and (4) hepatic nodular hyperplasia or neoplasia.

Testing was also carried out on a post-mortem liver sample for coumarin anticoagulants using the liquid chromatography–mass spectrometry method to rule out rat bait poisoning as a cause of the haemorrhage. There were no levels of brodifacoum, bromadiolone, coumatetralyl or flocoumafen detected, with a limit of detection of 0.005 µg/g using this method.

Histopathology was performed on tissue samples taken as part of the necropsy. This confirmed the presence of interstitial haemorrhage between muscle fibres and adipose tissue with a mild mixed inflammatory infiltrate, and evidence of myofibre regeneration in a sample from the typical site for an injection. This was presumed to be related to the first injection of pentosan polysulfate administered 1 week prior. Sections of the heart, particularly in the basal interventricular septum and left ventricular free wall, were characterised by large areas of interstitial fibrosis and small areas of neutrophilic and lymphocytic subendocardial and interstitial inflammation, which was considered to be consistent with the DUST finding on echocardiography and confirmed a pre-existing cardiomyopathy and endomyocarditis. The liver also had small-to-large areas of centrilobular hepatocellular necrosis and vacuolation; one large area of necrosis was related to a liver nodule, but an underlying neoplastic cause of nodule formation was not obvious. The necrosis and vacuolation were felt by the histopathologist to be most likely attributable to tissue hypoxia related to the hypotension and anaemia. The lungs were congested, and contained interstitial oedema, with no evidence of microthrombi. There were no other significant microscopic findings.

Discussion

We report a suspected adverse reaction (SAR) to a product containing pentosan polysulfate and glucosamine, which resulted in severe widespread haemorrhage in a cat. Owing to a lack of data of similar reported incidents, the link between the haemorrhage and the use of this medication can only be made based on clinical suspicion and judgement. The haemorrhage is thought most likely to be secondary to the injection owing to its temporal relation with the onset of clinical signs, the location of the haemorrhage, and lack of evidence for anticoagulant ingestion or other coagulopathy. An inherited coagulopathy is also considered unlikely given the lack of previous history of abnormal bleeding in a cat of this age. The cat had no history of trauma and had been kept indoors and monitored following the injection. A thrombocytopenia was unlikely to be the cause of the haemorrhage, as the platelet count was normal. Although an acquired thrombocytopathia could not be ruled out given its diagnostic difficulty, there was not continuous bleeding from

catheter or blood sample sites suggestive of this. Feline von Willebrand's disease has been reported very rarely,⁸ and any platelet dysfunction would most likely be attributed to a drug reaction.

Pentosan polysulfate has been licensed for use in dogs in multiple countries, including New Zealand, for many years, with several clinical trials documenting its efficacy in reducing clinical signs of osteoarthritis.^{4,5,9} To date, no clinical trials have been performed for the use of pentosan polysulfate for osteoarthritis in cats, although studies have evaluated its use in feline idiopathic cystitis.^{10,11} However, it is still used widely as an off-label treatment for osteoarthritis in cats with similar anecdotal benefits to dogs. SARs to pentosan polysulfate in dogs were investigated in a systematic review in the UK by Hannon et al¹² in 2003, with data from 1991 to 1999. Haemorrhage and death were reported at 18% and 16.8% of the total SARs, respectively. Although none of the reports of death could be attributed to a 'probable' relationship with pentosan polysulfate injection, 41.4% were considered 'possibly' related, based on definitions of causality provided by the Veterinary Medicines Directorate in 1996. We believe this case to be 'probably' related to the off-label drug administered based on the 'ABON' system used in the European Union.¹³

Pentosan polysulfate has several pharmacological actions that aid in the management of osteoarthritis. It modulates cytokine action, preserves proteoglycan content and in human models has been shown to stimulate hyaluronan synthesis.⁹ In people, it was originally used as an antithrombotic/antilipidaemic agent with known profound effects on the blood coagulation, fibrinolytic and lipid/cholesterol systems.¹⁴ These properties are also thought to aid in its use as a disease-modifying osteoarthritis drug by improving subchondral and synovial membrane blood flow in arthritic joints.^{9,14} Although bleeding is listed as a possible side effect in people, there have been no similar reports of widespread haemorrhage relating to its use in people, to our knowledge. The product's other ingredient, glucosamine, is used in the management of osteoarthritis as it is a component of cartilage and joint fluid, and has anti-inflammatory effects.¹⁵ It has also been shown to have antithrombotic effects *in vitro* in humans¹⁶ and *in vivo* in guinea pigs;¹⁷ however, the significance of these effects is currently unknown.

The mechanism of the haemorrhage in this case is not completely clear, and is likely to be complex. A full coagulation panel, including prothrombin time, activated partial thromboplastin time (aPTT) and thrombin time, may have given valuable additional information in this case, but an adequate sample could not be obtained without further destabilising the cat. Human studies have demonstrated that pentosan polysulfate is able to inhibit formation of several clotting factors.¹⁸ Clinical trial data of another pentosan polysulfate product (Cartrophen Vet; Bipharm Australia) showed prolongation of aPTT in

dogs following subcutaneous injections at 3 mg/kg on 12 occasions at weekly intervals. The prolongation was transient, returning to normal by 8 h, but marked: aPTT was increased to almost twice the RI.¹⁹ The other significant effect it has on blood coagulation is fibrinolysis through the stimulation of tissue plasminogen activator from the vessel wall, resulting in the formation of active plasmin, which is the main enzyme in fibrinolysis.²⁰ In the light of this, fibrinogen and viscoelastic testing, had it been available for this cat ante-mortem, would also have added valuable information for the mechanism of the haemorrhage. Development of disseminated intravascular coagulation (DIC) is theorised as another acquired disorder of haemostasis that may have contributed to the case outcome in the later stages; however, the platelet count was normal at the time the anaemia was first identified so it was unlikely to be the initial cause of the haemorrhage. If present, DIC may have been secondary to an injection site reaction to pentosan polysulfate, or hepatocellular necrosis, the latter of which would be related to the severe anaemia with resultant hypoxaemia and possibly the subsequent cardiac decompensation given the previously normal alanine aminotransferase and other liver values.

It is important to note that the cat, although previously perceived as healthy by the owner, had several comorbidities, which were revealed through both ante- and post-mortem diagnostic testing. The finding of pre-existing heart disease is particularly significant, and likely contributed to the cat's decline, as many of the clinical findings could be explained by congestive heart failure (CHF) – lethargy, gallop sound, tachypnoea and dyspnoea, collapse, pleural and pericardial effusion, as well as the left forelimb peripheral oedema noted at the post-mortem examination. In cats with endomyocarditis, decompensation and manifestation of clinical signs often occurs within 3 months after a stressful event²¹ – such as a painful injection – followed by acute blood loss, hospitalisation and multiple interventions.

The echocardiogram documented biatrial enlargement and the presence of heart failure, with only mild pleural and pericardial effusion (and did not warrant thoracocentesis or pericardiocentesis at the time), which was thought to be attributed to the prior aggressive fluid therapy, or transfusion-associated circulatory overload (TACO). An underlying cause could not be identified as DUST is usually a benign finding in older cats,²² although focal hypertrophic cardiomyopathy could not be ruled out. Other transfusion-related reactions such as transfusion-related acute lung injury (TRALI) or transfusion-associated dyspnoea (TAD) may also have caused similar signs of respiratory distress in a cat with recent transfusion, but evidence of pulmonary oedema was not present on thoracic radiographs taken more than 6 h after the end of the transfusion,

making TRALI less likely,²³ and TAD is less suspected given the evidence of existing heart disease and the possibility of TACO being more likely explanations.²³ Pulmonary oedema was found at post-mortem examination, which may have developed closer to the time of euthanasia, either as a result of the cat's acute decompensation during its final moments, or – in conjunction with the pleural effusion (which had increased based on post-mortem findings compared with earlier echocardiographic findings) – as a manifestation of decompensated heart failure. The histological findings documented endocardial inflammation in the region of the DUST, which can be found in cats with endomyocarditis, a cardiomyopathy unique to cats;²¹ the relative significance of this is unclear as the clinical findings were more consistent with hypertrophic rather than restrictive cardiomyopathy. This case demonstrated the challenges of diagnostics and treatment in unstable patients with comorbidities, and highlights some interesting differences between the impression of echocardiographic, post-mortem examination and histological findings with regard to this form of cardiomyopathy. However, the presence and severity of the haemorrhage remains unexplained by a diagnosis of CHF alone, and the cardiac decompensation is more likely the cause of death, rather than the initial trigger for the clinical signs. It is unknown whether in the absence of concurrent heart disease, the cat would have shown improvement following the initial blood transfusion, or whether the haematological abnormalities would have persisted and the PCV dropped again.

This case was an unusual presentation of acute haemorrhage given that the bleeding was largely subcutaneous and intermuscular. This was only evident externally by swelling, without bruising, of the shoulders, neck, ventral thorax and chin, which was initially suspected to be oedema caused by either an unusual anaphylactic reaction or lymphatic obstruction, leading to the use of dexamethasone. B₁₂ was given subcutaneously for a possible previously undiagnosed cobalamin deficiency leading to anaemia, and the suspicion of a possible bleeding diathesis was low at the time. The use of corticosteroids may have had some benefit in this case via the inhibition of fibrinolysis, which has been studied in other species,^{24,25} but may have equally put the cat at risk of pulmonary thromboembolism or further haemorrhage via the gastrointestinal tract, although neither of these were evident on post-mortem and histological examination. In future cases that present similarly, the presence of internal haemorrhage may be recognised earlier, and considerations for the use of antifibrinolytic drugs should be given in the light of the fibrinolytic property of pentosan polysulfate, although this would ideally be investigated in further clinical trials involving fibrinogen measurements and viscoelastic testing in cats treated with pentosan polysulfate.

The cat also had a history of multiple doses of pentosan polysulfate in the 2 years prior. Repeat courses of pentosan polysulfate are off-label in both dogs and cats, with no clinical trials evaluating the safety and pharmacokinetics of repeat dosing or long-term use. A safe window for repeat dosing has not been established, although a 1-year interval has been suggested by one manufacturer.²⁶ Considerations for potential overdose, inadvertent intramuscular administration or product expiration should also be given, although this was not documented. Ultimately, even if a relationship with the use of pentosan polysulfate could be definitively proven, this is clearly a very unusual, perhaps idiosyncratic, adverse reaction and does not necessarily preclude the use of this drug in arthritic animals that may benefit from the pain relief and increased mobility it provides. Further clinical trials and a more recent review of reported SARs will help clinicians to better understand and educate clients on the full effects of this drug.

Conclusions

This is the first report of an SAR to multiple doses of pentosan polysulfate in a cat resulting in severe haemorrhage. A blood transfusion was initially able to improve the anaemia; however, the cat ultimately succumbed to what we believe was a combination of severe haemorrhage and concurrent congestive heart failure. Clinicians utilising this medication should be aware of possible haemostatic adverse reactions, and further testing would be ideal to further delineate the relationship, if, in fact, one is present.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken

(prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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