Thymic haemorrhage due to ingestion of human anticoagulant medication in a puppy

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SUMMARY
A four-month-old male Shih-Tzu was presented with lethargy, mild dyspnoea and acute thoracic pain. Thoracic radiography revealed the presence of a mediastinal mass at the level of the thymus and ultrasound confirmed a thymic haemorrhage. Coagulation times were beyond the detection limit of the machine. After preprandial and postprandial bile acids excluded hepatic insufficiency, an anticoagulant intoxication was strongly suspected. Disappearance of multiple doses of phenprocoumon in the house and rapid response to vitamin K administration as a treatment and blood transfusion confirmed authors’ suspicion. The dog had clinically made a full recovery and was discharged after 36 hours. The following unique information has been provided: anticoagulant intoxication is commonly seen but the clinical presentation can be highly variable depending on the affected area. This report describes a rare thymic haemorrhage secondary to ingestion of human anticoagulant medication in a dog.

BACKGROUND
Rodenticides are some of the most common toxins encountered in small animals together with insecticides.1 The vast majority (90 per cent) of rodenticides are anticoagulants.2 The toxic effects of anticoagulant rodenticides (ARs) are initiated by an interaction with vitamin K1. Vitamin K1 is required for the synthesis of clotting factors II, VII, IX and X, which are involved in both intrinsic and extrinsic clotting pathways and eventually lead to fibrin formation. ARs inhibit the enzymes responsible for reduction of vitamin K1-epoxide to vitamin K1 causing a deficiency of the activated form of clotting factors II, VII, IX and X.2 Coagulation panels of intoxicated patients after depletion of these activated factors are characterised by a prolonged prothrombin time (PT), activated thromboplastin time (aPTT) and activated clotting time. Common clinical signs in case of anticoagulant intoxication are lethargy, dyspnoea, pallor and coughing/haemoptysis.3

CASE PRESENTATION
A four-month-old male Shih-Tzu weighing 3.8 kg was presented for anorexia, lethargy, mild mixed dyspnoea and a recent onset of chest pain. Trauma or access to toxic compounds was at first excluded by the owners. On presentation, physical examination revealed a respiratory rate of 44 breaths/min with mild mixed dyspnoea, a heart rate of 180 beats/min with bilaterally muffled heart sounds and acute pain upon application of pressure on the thoracic cavity. The remainder of the clinical examination was within normal limits.

As chest pain and dyspnoea could be secondary to rib fractures, intrathoracic masses, pneumonia or pleural effusion, thoracic radiographs (Fig 1) were performed. A large cranioventral mediastinal mass associated with moderate bilateral pleural effusion was observed. The differential diagnosis for this mediastinal mass included a haematomatoma, lymphadenopathy, mediastinal abscess or granuloma, mediastinal cyst or a neoplastic process (lymphoma, thymoma, ectopic thyroid or parathyroid tumour, malignant histiocytosis and other tumours (eg, lipoma and fibrosarcoma)).4 Thoracic ultrasound (Fig 2) was performed and confirmed the presence of a mediastinal, soft tissue mass located cranial to the heart.

Considering the heterogenous character of the mass, differential diagnoses at this stage were haematomata, abscess or granuloma and less likely neoplastic conditions of a mediastinal lymph node, thymus or ectopic thyroid/parathyroid gland. Thymoma, a neoplasm of thymic epithelial cells has, however, only been described in dogs from 2.5 years of age (median age 10 years), and was therefore considered very unlikely.5 6 Although lymphoma is the most common tumour of the cranial mediastinum, the lack of other clinical signs, the acute nature of the symptoms and the young age of the dog made this also implausible, just as the even more rare differential of thyroid or parathyroid neoplasia.

As haematomata and haemorrhage remained very high on authors’ list of differential diagnoses in this young dog, despite the lack of a history of trauma, a blood sample was taken to assess the clotting times in order to screen for (inherited) coagulopathies and perform a minimal database. A haematomatoma appeared at the site of venepuncture, despite prolonged compression, and the dog was placed in an oxygen cage after placement of a peripheral venous catheter. Clotting times were markedly increased (PT unmeasurable (reference: 11–17 s) and aPTT 204 s (reference: 72–102 s)) while haematology displayed a regenerative anaemia (haematocrit 29.4 per cent (reference: 30–45 per cent)) with mild leucocytosis at 20 980 cells/µl (reference: 5.500–19,500 cells/µl). The biochemical profile was unremarkable.

A rodenticide intoxication causing a thymic haemorrhage constituted the most likely hypothesis. In order to rule out hepatic insufficiency (potentially secondary to a congenital portosystemic shunt) as a...
potential cause of the coagulopathy, a bile acid stimulation test was performed and was within normal limits.

At this point, congenital coagulopathies such as a deficiency in factor VIII (haemophilia A) which is reported in German shepherd dog, German Shorthaired Pointer, golden retriever and labrador retriever and a depletion in factor IX (haemophilia B) as seen in Airedale, Cairn terrier and labrador retriever or a deficiency in factor XI could be ruled out as they would not cause a prolonged PT. Similarly, a depletion in factor VII would only cause a prolonged PT, a normal aPTT and could hence also be excluded. Other uncommon congenital coagulopathies such as hypofibrinogenaemia or dysfibrinogenaemia and a deficiency in factors II or X could however not be completely excluded as they do cause prolonged PT and aPTT times. However, these rare conditions would also benefit from the initial stabilisation that was planned for this patient.

Initial treatment for the suspected rodenticide intoxication consisted of 5 mg/kg of Vitamin K1 twice a day and a blood transfusion after blood typing. After initial stabilisation, the dog received intravenous fluids and vitamin K1 was continued at 2.5 mg/kg orally twice daily. More extended questioning of the owners after stabilisation revealed that the inliving grandfather had a vitamin K antagonist (phenprocoumon) prescription and had been missing some pills.

On day 2, clotting times had normalised and besides a mild mixed dyspnoea the dog’s general condition had improved rapidly. The dog was discharged after 36 hours with no remaining abnormalities on clinical examination, and treatment with vitamin K1 at 2.5 mg/kg twice daily was continued for four weeks.

OUTCOME AND FOLLOW-UP
A control visit was performed after one week, and no abnormalities were detected on clinical examination; however, thoracic radiographs showed only a mild improvement (Fig 3). One month later, at the final follow-up visit, which occurred 48 hours after cessation of vitamin K1 treatment the dog had fully recovered. Physical examination and haematological examination were unremarkable. The PT was also found to be within normal limits, excluding the remaining rare congenital coagulopathies (hypofibrinogenaemia, dysfibrinogenaemia and factors II or X). Finally, thoracic radiographs showed resolution of mediastinal enlargement and tracheal displacement (Fig 4).

DISCUSSION
Anticoagulant intoxications induce a variety of clinical findings depending on the site and the extent of the haemorrhage and can be categorised as either classic or atypical. Clinical signs are due to the depletion of vitamin K-dependent clotting factors (II, VII, IX and X), VII being the limiting factor with a half-life of four to six hours. Consequently, the first clinical signs appear two to five days after the ingestion of the anticoagulant.

Diagnosis and implementation of treatment can be delayed in case of atypical clinical presentation such as haematemesis and acute mediastinal haemorrhage, often resulting in a less
a possible cause of haemothorax in a three-year-old WHWT. As duration of vitamin K treatment depends on the type and amount of ingested anticoagulant and a definitive diagnosis was not made in this case, treatment was installed for four weeks and PT was reassessed 48 hours after discontinuation of treatment. Normalisation of the coagulation panel at this time ruled out the remaining congenital coagulopathies and a definitive diagnosis of thymic haemorrhage secondary to an anticoagulant intoxication was made.

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9 Littlewood JD. Disorders of secondary haemostasis. 5 12 15–17. The thymus and anterior mediastinum have indeed been described as sites of predilection for spontaneous haemorrhage in rodenticide intoxication. 16 The thymus is large in young dogs and is continuously subjected to cardiac and respiratory movements while located in a region with negative pressure, factors which may all contribute to this predilection. In addition, mild trauma could be a cofactor in seemingly spontaneous or idiopathic thymic bleeding in young animals, as physiological thymic involution between 6 and 12 months of age is associated with a lack of counterpressure from loose surrounding tissues. 14 This involution without counterpressure might cause vessels to rupture more easily, especially in case of a sudden rise in blood pressure, resulting in haemorrhage. A retrospective study of postmortem histopathological findings on cases of thymic haemorrhage secondary to anticoagulant intoxication found animals to be often younger than six months of age and did not consistently identify signs of thymic involution. These authors also did not find any evidence of vascular fragility of thymic vessels or sudden increase in blood pressure.

In a recent study evaluating the use of AR screening in dogs, brodifacoum was the most commonly detected. Other frequently used ARs include warfarin, bromadiolone, chlorophacinone, diphacinone and difenacoum.

Phenprocoumon is a vitamin K1 antagonist used for thromboembolic prophylaxis in human beings and is the most important described complication of this anticoagulant therapy is bleeding. Chronic ingestion or intake of a single large amount might cause spontaneous bleeding. Only one case report has described it as
