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Vet Record CaseReports

CASE REPORT

Companion or pet animals

Demonstration of hyperfibrinolysis on the VCM Vet in a dog with *Angiostrongylus vasorum*

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Abstract

This case report details the clinical investigation of an 11-month-old, entire, male Cockapoo, who presented with acute left forebrain signs associated with suspected intracranial haemorrhage due to *Angiostrongylus vasorum*. Initial investigations failed to identify a coagulopathy using traditional coagulation testing. Subsequent viscoelastic testing using the Viscoelastic Coagulation Monitor (VCM Vet, Entegrion) identified a hypocoagulable, hyperfibrinolytic trace. Anti-fibrinolytic treatment with tranexamic acid showed improvement of hypocoagulability and normalisation of hyperfibrinolysis. Subsequent canine fresh frozen plasma transfusion and treatment of the underlying *A. vasorum* led to resolution of the patient's coagulopathy. This case report demonstrates the ease of use and utility of viscoelastic monitoring in global assessment of coagulation, and is the first case to document hyperfibrinolysis using the VCM Vet in a patient with *Angiostrongylus vasorum*.

BACKGROUND

Haemostasis requires the complex interaction and balance of procoagulant, anticoagulant, profibrinolytic and antifibrinolytic mechanisms.[1,2]

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have both been used to document hyperfibrinolysis in naturally occurring *Angiostrongylus vasorum*.[3,4] Hyperfibrinolysis and hypofibrinogenaemia can contribute to coagulopathy in affected patients, which may result in acute neurological signs and fatal haemorrhage.[3,4] Rapid identification of hyperfibrinolysis may allow implementation of appropriate antifibrinolytic therapy[1]; however, both TEG and ROTEM require stringent laboratory settings, use of specific activators and regular quality control. Thromboelastography and ROTEM devices are prone to variation due to pre-analytical error such as movement artefact and the requirement for a variety of different activators.[5] The Viscoelastic Coagulation Monitor (VCM Vet) correlates well with ROTEM[6] and TEG,[7] providing an alternative bedside global assessment of haemostasis. The VCM Vet aims to eliminate the pre-analytical error noted in TEG and ROTEM by using whole blood without additional reagents,[8] and has been shown to perform well in the clinical setting.[9]

To date, hyperfibrinolysis has not been demonstrated using the VCM Vet in patients with naturally occurring *A. vasorum* infection. The aim of this communication was to describe hyperfibrinolysis in *A. vasorum* using the VCM Vet, and demonstrating its resolution following the use of a lysine analogue, tranexamic acid (500 mg/5 mL solution for injection; ADVANZ Pharma).

CASE PRESENTATION

An 11-month-old, entire, male Cockapoo was referred for evaluation of scleral haemorrhage and per-acute onset obtundation, left head turn, tetraparesis and a single seizure. The patient presented to the primary care practice with a 3-day history of progressive lethargy. Episcleral haemorrhage and possible cranial abdominal pain were documented on initial exam, and the patient was referred following a generalised tonic-clonic seizure. The patient was up to date with routine vaccinations for preventable diseases in the United Kingdom, and received a 3-monthly wormer containing febantel, praziquantel and pyrantel embonate (Drontal, Vetoquinol UK).

The patient presented obtunded in lateral recumbency. There was evidence of scleral haemorrhage bilaterally (Figure 1). There was no evidence of petechiation on the gingival mucosa or skin. Cardiovascular exam was within normal limits. The patient was tachypnoeic, with a respiratory rate of 60 breaths per minute, and thoracic auscultation documented harsh bronchovesicular sounds dorsally bilaterally. There was marked pain on ventroflexion of the neck. Neurological examination documented obtundation, non-ambulatory tetraparesis, a left head turn, slightly reduced conscious proprioception in the right forelimb and right pelvic limb, a miotic left pupil and reduced menace in the

right eye. Ophthalmic examination documented bilateral episcleral haemorrhage and focal retinal haemorrhage in the right eye. The rest of the physical examination was within normal limits.

INVESTIGATIONS

Venous blood gas and electrolyte analysis (radiometer ABL800 FLEX; Radiometer), haematology (haematology analyser Advia 2120i; Siemens Healthcare) and biochemistry (Clinical Chemistry Analyzer AU680; Beckman Coulter) and coagulation screening tests (canine and feline PT and aPTT; Coag Dx Analyser; IDEXX) were performed on presentation. Venous blood gas and electrolyte analysis was unremarkable. Haematology documented a mild neutrophilia (13.95×10^{10}; 3–11.5), monocytosis (2.69×10^{10}; 0.15–1.5) and a normal platelet count (230×10^{10}; 150–900). Biochemistry was unremarkable. Prothrombin and activated partial thromboplastin time were within normal limits (PT: 17 seconds; 11–17; aPTT: 98 seconds; 72–102). Faecal smear analysis documented presence of *A. vasorum* stage 1 larvae (Figure 2), and a commercial *A. vasorum* antigen test (Angio Detect; IDEXX Laboratories) was positive for *A. vasorum*. Point-of-care ultrasound (POCUS) of the thorax and abdomen were within normal limits. Non-invasive systolic Doppler blood pressure was 150 mmHg.

A blood sample was taken for viscoelastic testing (VCM Vet), which documented a hypocoagulable and hyperfibrinolytic trace (Figure 3; T0, Table 1).

DIFFERENTIAL DIAGNOSIS

A. vasorum infection.

TREATMENT

Given concerns over hyperfibrinolysis in patients affected by *A. vasorum*,[3] the patient received an infusion of tranexamic acid (20 mg/kg intravenously) over 30 minutes. Repeat viscoelastic testing (VCM Vet) performed 1 hour following completion of the tranexamic acid infusion showed a marked reduction in lysis percentage (Figure 3; T1, Table 1), but persistent hypocoagulability. Following repeat viscoelastic testing, the patient was treated with an imidacloprid/moxidectin spot-on (Advocate spot-on solution for dogs, Elanco UK) and received a fresh frozen plasma (FFP) transfusion (12.2 mL/kg) over 4 hours. Repeat viscoelastic testing (VCM Vet) performed immediately after finishing the FFP transfusion documented normalised lysis index and persistent hypocoagulability (Figure 3; T2, Table 1). A further unit of FFP (11.2 mL/kg) was transfused.

LEARNING POINTS/TAKE-HOME MESSAGES

- Patients presenting with peracute or acute forebrain signs should be assessed for possible intracranial haemorrhage.
- Patients with *Angiostrongylus vasorum* can present with an array of coagulopathic disturbances, including hypocoagulability and hyperfibrinolysis.
- The VCM Vet provides a rapid, bed-side global assessment of coagulation, and can detect hyperfibrinolysis like other traditional viscoelastic testing.
- Tranexamic acid resulted in attenuation of the hyperfibrinolytic state in this case and may have reduced the risk of ongoing intracranial haemorrhage.

OUTCOME AND FOLLOW-UP

The patient's mentation improved and normalised over the following 24 hours. The following day, the patient developed worsening tachypnoea, and repeated thoracic point-of-care ultrasound documented diffuse B lines. The patient received dexamethasone (0.15 mg/kg intravenously; Dexadreson 2 mg/mL solution for injection, MSD Animal Health UK) due to suspected pneumonitis related to *A. vasorum* death post imidacloprid/moxidectin. Tranexamic acid was continued (20 mg/kg intravenously every 8 hours for 3 days), and a 14-day course of oral fenbendazole (50 mg/kg; Panacur 10% oral suspension, MSD Animal Health UK) was started. The patient's tachypnoea, neck pain and neurological signs resolved during hospitalisation and was therefore discharged

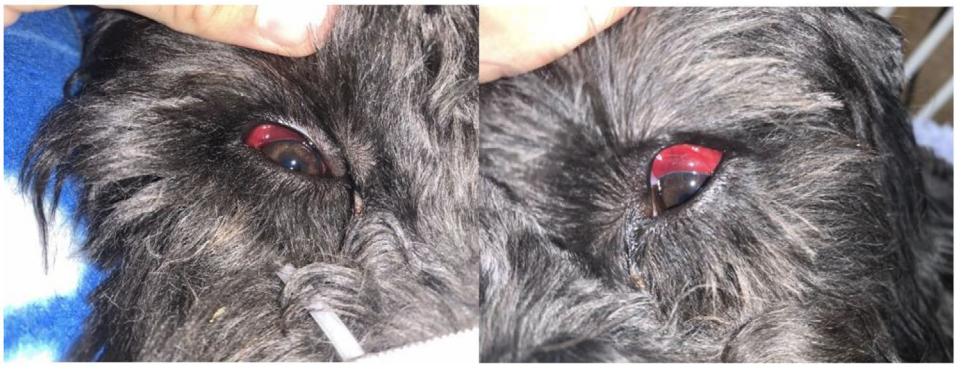

FIGURE 1 Bilateral episcleral haemorrhage and miosis of the left pupil (right image).

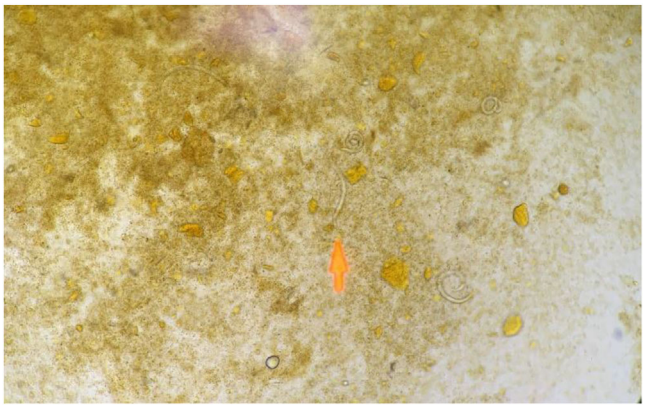

FIGURE 2 Faecal smear performed by placing sample of faeces to microscope slide and adding saline. Image viewed at 100× magnification.

after 3 days. Repeat viscoelastic testing (VCM Vet) before discharge documented almost complete normalisation of all parameters (Figure 3; T3, Table 1).

DISCUSSION

In the dog reported here, hyperfibrinolysis was diagnosed based on the marked improvement in lysis index at 30 and 45 minutes, documented by a bedside viscoelastic monitor (VCM Vet). Multiple coagulation abnormalities were documented on initial and subsequent viscoelastic tracings; however, further discussion aims to focus on the assessment of fibrinolysis. To date, the VCM Vet has not specifically been reported in the assessment of hyperfibrinolysis due to *A. vasorum*, although changes in the lysis index have been noted in healthy dogs during the perianaesthetic period,[10] and a recent retrospective study extensively evaluated fibrinolysis demonstrated by the VCM Vet in a variety of diseased patients.[11] It should be noted, however, that a fibrinolysis artefact of unknown origin has been noted with the VCM Vet, suggesting that concern over hyperfibrinolysis should be re-confirmed with a repeated sample.[7]

The lysis index, measured at 30 (LI30) and 45 (LI45) minutes following maximum clot firmness, is a calculated value derived from the relationship between amplitude and maximum clot firmness, demonstrating the percentage of remaining clot firmness.[8] The lysis index, therefore, is used to evaluate plasmin-mediated fibrinolysis.[10] A full review of the fibrinolytic cascade is beyond the scope of this brief communication, and is discussed elsewhere.[1] In the dog reported here, the LI30 and LI45 were most severely decreased at T0, documenting marked clot lysis when compared to normal viscoelastic tracings. Tranexamic acid and aminocaproic acid are lysine analogues that competitively bind C-terminal lysine sites on plasminogen, preventing the binding of plasminogen to fibrin and the subsequent production of plasmin.[1]

Tranexamic acid has previously been used in patients with naturally occurring *A. vasorum* and was shown to normalise ROTEM parameters of hyperfibrinolysis, with hypofibrinogenaemia subsequently being treated with FFP transfusion.[3] It should be noted, however, that not all patients with *A. vasorum* infection present with coagulopathy, and not all patients that present with bleeding have hyperfibrinolysis.[3] Currently, the mechanism of coagulopathy in *A. vasorum* patients is not entirely known; however, hyperfibrinolysis and hypofibrinogenaemia remain a consistent finding.[3,4,12,13]

Emesis is a known side effect of tranexamic acid usage,[14] and may represent a contraindication to patients with the potential for intracranial bleeding and/or vasculitis due to risk of increasing intracranial pressure with vomiting; however, previous studies have shown that 1 mg/kg maropitant intravenously can completely abolish emetic events at up to 50 mg/kg of tranexamic acid.[15] Fortunately, the largest scale study to date documented a low rate of adverse events, occurring in only 1.7% of dogs and 3% of cats.[11] Appropriate use of tranexamic acid relies on the identification of patients at risk for ongoing bleeding due to hyperfibrinolysis to avoid polypharmacy, potential side effects and unnecessary cost to the client.

The dose of tranexamic acid used in this case report was based on previous pharmacokinetic and pharmacodynamic data in healthy dogs.[14] While a variety of tranexamic acid dosages have been suggested, given the risk of fatal intracranial haemorrhage, the authors chose to use the highest dose reported in veterinary patients.[14] As noted at T1, an hour following administration of tranexamic acid, there was a marked improvement in fibrinolysis parameters on the VCM Vet; a further improvement was noted at T2, although it is not possible to know whether this was a residual effect of the tranexamic acid or as a result of the administered FFP.

The VCM Vet is a reagent-free, cartridge-based system that uses less than 300 μL of fresh whole blood, and provides results in a maximum of 60 minutes. Reference ranges have been established in healthy dogs[8] and cats,[16] and a recent study documented marked improvement in the fibrinolytic parameters for three dogs after administering tranexamic acid.[11] Unfortunately, the VCM Vet remains inferior as a screening test when compared to gold-standard testing, such as ROTEM, as it lacks diagnostic sensitivity for fibrinolysis.[6] However, given the usability and potential for increased access to the device when compared to traditional testing, further studies comparing diagnostic accuracy of the VCM Vet to ROTEM and TEG are warranted.

This case report had several limitations. Most importantly, traditional viscoelastic testing with TEG or ROTEM was not performed, and additional coagulation assays such as measurement of fibrinogen or D-dimers were not performed. Ideally, repeat viscoelastic testing at several time points after administration of tranexamic acid alone would have been performed to establish a duration of effect; however, due to concern over hypofibrinogenaemia also contributing the coagulopathy associated with *A. vasorum*, the authors did not feel it was appropriate to delay treatment with FFP. Additionally, the authors' institute uses reference values provided by the manufacturer of VCM Vet, and it has been noted that the VCM Vet is prone to inter-device variability.[8] It is currently recommended for each institution to establish their own reference values for their device, raising caution to extrapolation and interpretation of the values in this case report.[8]

In conclusion, this case report documents the utility of the VCM Vet in demonstrating hyperfibrinolysis and provides a more readily accessible and possibly more cost-effective global measure of coagulation when compared to traditional viscoelastic testing. Future prospective studies assessing the VCM Vet and traditional viscoelastic testing (TEG/ROTEM)

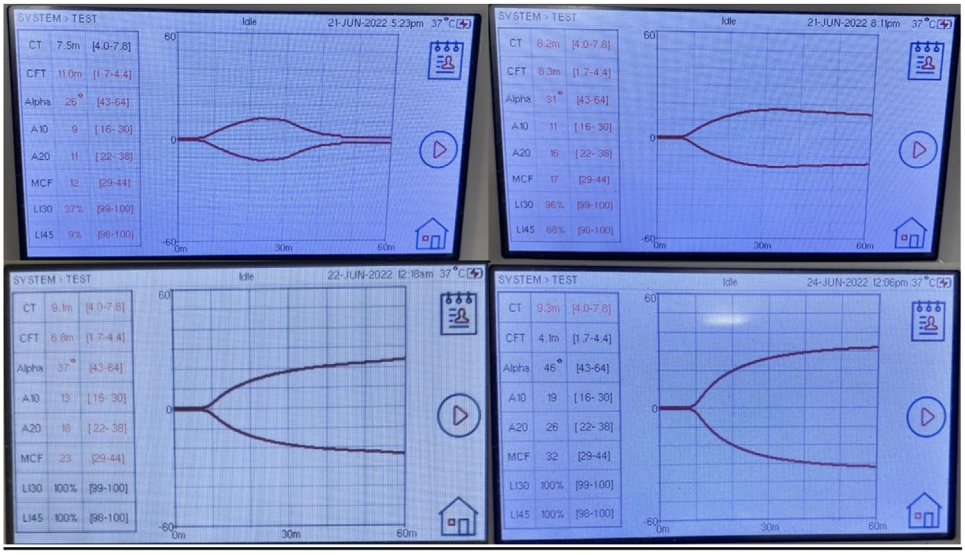

FIGURE 3 Viscoelastic testing performed on the Viscoelastic Coagulation Monitor Vet. Top left: T0; top right: T1; bottom left: T3; bottom right: T4.

TABLE 1 Viscoelastic Coagulation Monitor parameters pre-TXA (T0), post-TXA (T1), post-FFP (T2) and at discharge (T3).

Parameter	Pre-TXA (T0)	Post-TXA (T1)	Post-FFP (T2)	Discharge (T3)	Reference interval
Clotting time	7.5 m	**8.2 m**	**9.1 m**	**9.3 m**	4.0–7.8
Clot formation time	**11.0 m**	**8.3 m**	**6.8 m**	4.1 m	1.7–4.4
Alpha angle	**26°**	**31°**	**37°**	46°	43–64
Amplitude at 10 minutes (A10)	**9**	**11**	**13**	19	16–30
Amplitude at 20 minutes (A20)	**11**	**16**	**18**	26	22–38
Maximum clot firmness	**12**	**17**	**23**	32	29–44
Lysis index at 30 minutes (LI30)	**37%**	**96%**	100%	100%	99–100
Lysis index at 45 minutes (LI45)	**9%**	**88%**	100%	100%	98–100

Note: Abnormal parameters are highlighted in bold.
Abbreviations: FFP, fresh frozen plasma; TXA, tranexamic acid.

in a larger population of patients naturally infected with *A. vasorum*, with and without clinical bleeding, are needed to further categorise the coagulopathy and provide targets for treatment.

AUTHOR CONTRIBUTIONS

Dave Beeston and Stefano Cortellini conceived and designed the project. Dave Beeston acquired the data. Dave Beeston and Stefano Cortellini analysed and interpreted the data and wrote the paper.

CONFLICT OF INTEREST STATEMENT

The VCM Vet used in this study was donated to the authors' institute following product release.

FUNDING INFORMATION

The authors received no specific funding for this work.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this was a retrospective, observational case report, with no original research data.

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IMAGE QUIZ

Figure 3 Which of the following viscoelastic parameters are used to assess hyperfibrinolysis on the VCM Vet.

a) Clotting time
b) Clot formation time
c) Alpha angle
d) Maximum clot firmness
e) LI30

CORRECT ANSWER

e) LI30

The lysis index, measured at 30 (LI30) and 45 (LI45) minutes following maximum clot firmness, is a calculated value derived from the relationship between amplitude and maximum clot firmness, demonstrating the percentage of remaining clot firmness.[8] The lysis index, therefore, is used to evaluate plasmin-mediated fibrinolysis.[10]