Greyhound “hyperfibrinolysis syndrome”: a breed-specific disorder

Marc Dhumeaux
DEDV MVSc DipACVIM DipECVIM-CA MRCVS
European and American Specialist in Small Animal Internal Medicine

Marc graduated from the National Veterinary School of Toulouse in 2007, and after completing a Small Animal rotating Internship in Ontario and a Small Animal Medicine Residency in Saskatchewan, Marc completed a Master of Veterinary Science in 2012 and became a Diplomate of the American and European Colleges of Veterinary Internal Medicine

Cécile Dor
DVM MRCVS
ECVIM-CA Small Animal Internal Medicine Resident

Cécile graduated in 2013 from the National Veterinary School of Alfort in France. She has completed a Rotating Internship and an Internal Medicine Internship, both in France. Cécile joined the Medicine team in September 2016.
**Introduction**

Greyhounds have many breed-specific particularities. Clinicians need to be aware of them as they can have a direct impact on medical and surgical management of these dogs. Recently, a breed-specific bleeding disorder affecting Greyhounds and sighthounds has been described, known as “hyperfibrinolysis syndrome”. Clinical signs can vary from minor localised bruising to life-threatening generalised haemorrhage after trauma or surgery. The underlying mechanism is not yet fully understood. Awareness of this bleeding disorder is crucial as its prevention/treatment can significantly improve post-trauma and postoperative outcomes. Below is an example of life-saving medical management of a severely affected sighthound after multiple dog bites.

**Case description**

A seven-year-old male entire Greyhound Saluki crossed dog was referred to Pride Veterinary Centre as a night emergency for management of severe subcutaneous haemorrhage following multiple dog bites.

The dog attack happened the day before, his first physical exam performed by his primary vet revealed seven puncture wounds on the head, under the chin and on the right shoulder. The dog deteriorated very quickly throughout the day. His owner reported lethargy, reluctance to walk, painful swelling on his multiple bite wounds, and red-tinged urine. Based on serial complete blood counts, the platelet count and haematocrit dropped significantly throughout the day, with persistently normal clotting times (PT, aPTT). The acute thrombocytopenia was interpreted as likely due to consumption from massive haemorrhage.

On admission, his physical exam revealed pink and moist mucous membranes, tachycardia (HR 160bpm), pyrexia (40°C) and lethargy. He had multiple painful and swollen subcutaneous haematomas mainly in his right axillary region, but also on his head and chin (Figure 1). Abdominal and sternal ecchymoses were better assessed after hair clipping. Those were rather far away from his multiple bite wounds, suggestive of a generalised bleeding disorder (Figure 2).

Imaging procedures were performed, including thoracic radiographs and abdominal ultrasound. No sign of internal bleeding was found.

A urinalysis revealed haemoglobinuria and marked proteinuria (UPCR = 7.68). Fortunately, this did not result in kidney injury based on serial measurement of serum creatinine.

Since thrombocytopenia was secondary to peripheral consumption and since repeated coagulation tests remained normal, this excessive post-traumatic bleeding was unlikely to be attributable to a primary or secondary haemostatic disorder. However, considering the extended subcutaneous haematomas, the breed and the history or trauma, a fibrinolysis disorder known as “hyperfibrinolysis syndrome” was strongly suspected.

Therefore, medical treatment with tranexamic acid (an antifibrinolytic drug) was immediately initiated at 10 mg/kg q8hours intravenously first and then orally, and continued for 7 days in total. Antibiotics (amoxicillin/clavulanic acid 20 mg/kg q8hours) and analgesia (initially methadone 0.2mg/kg q4hours and then buprenorphine 20 µg/kg q8hours) were also provided during his hospitalisation.

A significant improvement of cutaneous and subcutaneous haemorrhage was noticed 5 days after the initiation of tranexamic acid therapy (Fig 3). The platelet count and packed cell volume (PCV) were monitored daily. The PCV dropped initially dramatically (lowest at 20%) but this...
was rapidly followed by adequate regenerative response. The platelet count slowly improved throughout the hospitalisation and was back to normal three days after the initiation of tranexamic acid therapy.

The patient was discharged after seven days of hospitalisation. He was dispensed five more days of antibiotic cover in order to complete a 2-week course. His owner gave us an update one month and a half later. He was doing really well and back to his normal bouncy-self.

Discussion
Breed-related bleeding tendency in Greyhounds
Several major clinicopathologic differences are well described in this breed, including higher red blood cell mass, creatinine concentration, glomerular filtration rate, activities of hepatic enzymes, and concentration of cardiac troponin, as well as lower total white blood cell and neutrophil counts, and concentrations of serum haptoglobin, total globulins, and T4 [1].

Peri- and postoperative bleeding is also frequently reported. Twelve to 30% of these dogs develop delayed postoperative bleeding 36 to 48 hours after a surgical procedure (ovariohysterectomy, castration or limb amputation) [2,4,5], and a survey revealed that bleeding disorders account for up to 8% of all deaths in Greyhounds [4].

Suspected underlying mechanisms of this “Hyperfibrinolysis syndrome”
Slight and physiologic thrombocytopenia associated with faster platelet aggregation has been described in Greyhounds [3]. Nonetheless, studies revealed that the excessive postoperative/post-trauma bleeding reported in these dogs was not attributable to a primary or secondary haemostatic defect [2,3,7]. In fact, it may result from (a) the formation of weaker clots [6,7] and/or (b) enhanced fibrinolysis that leads to accelerated clot breakdown [2].

Thromboelastography in Greyhounds showed that clotting kinetics are slower and clot strength is weaker in Greyhounds than in non-Greyhound dogs. Thus, these dogs fail to reach a physiologic reactive hypercoagulable postsurgical state [6,7].

Besides, antiplasmin has been found to be significantly lower in Greyhounds that will develop post-operative bleeding, compared to “non-bleeder” ones. Low antiplasmin is suspected to result in higher levels of activated plasmin, which breaks down the fibrin clot, resulting in haemorrhagic diathesis [2]. Once again, these dogs fail to reach an appropriate reactive hypercoagulable postsurgical/post-trauma state.

The above mechanisms support the increased tendency to bleed observed after trauma (sometimes even minor) or surgical procedures in this breed. This breed-specific bleeding condition is called “hyperfibrinolysis syndrome”. Some authors suggest that this could be an adaptive mechanism to high-speed running or an evolutionary trait designed to prevent excessive clotting of circulating high viscosity blood (Greyhounds have high red blood cell mass and whole blood viscosity), as it has been reported in human athletes [2].

How do we diagnose this bleeding disorder?
The diagnosis of “hyperfibrinolysis syndrome” is an exclusion diagnosis. It is based on epidemiologic and clinical criteria, lack of evidence of primary and secondary haemostasis disorder and positive response to antifibrinolytic therapy. The typical presentation is a Greyhound or sighthound, with or without previous history of bleeding, developing extensive cutaneous and subcutaneous haemorrhage after surgery or trauma. Coagulation times (aPTT, PT) are expected to be normal and the platelet count is usually normal at least initially (keeping in mind that normal platelet count in Greyhounds is lower than in other dog breeds [1]). However, the platelet count may drop within 12-24 hours due to consumption from profuse haemorrhage.

In this context, an important differential diagnosis remaining is Von Willebrand disease as a cause of thrombocytopathy. Some authors suggest that the reference range of Von Willebrand factor in Greyhounds may be lower than in other dog breeds [1]. Hence, we recommend interpreting cautiously mild decrease in Von Willebrand factor in Greyhounds, as it may not necessarily explain clinical signs of bleeding.
The next question clinicians may have is how to recognize “at risk” asymptomatic Greyhounds? Unfortunately, conventional coagulation tests (PT, aPTT), platelet count and fibrinogen concentration are not predictors of bleeding in Greyhounds undergoing surgery. Thromboelastography is the only diagnostic test that may bring out the “at risk” animals, but is still largely unavailable [6]. Hence, this still leaves most clinicians in the dark regarding at risk animals.

How to prevent postoperative haemostasis disorder?
The risk of delayed post-operative bleeding can be significantly decreased with the administration of antifibrinolytic drugs such as tranexamic acid (TEA) or epsilon-aminocaproic acid (EACA). These drugs are both analogues of the amino acid lysine. They competitively inhibit the activation of plasminogen to plasmin on the surface of the fibrin clot, by binding to specific sites of both plasminogen and plasmin (which is responsible for the degradation of fibrin). To a lesser extent, they also increase anti-plasmin activity resulting in decreased fibrinolysis and improved fibrin clot stability.

Overall, dogs have been found to be hyperfibrinolytic compared to humans. Therefore, higher doses of EACA and TEA are required to adequately inhibit fibrinolysis in dogs [9].

Is it safe to treat dogs preventively with antifibrinolytic drugs, without knowing if they are “at risk” of bleeding?
According to the literature, EACA and TEA have a wide therapeutic index. No relevant adverse effects were reported in toxicologic studies in dogs, rabbits and rats with doses of EACA as high as 0.5 g/kg (25 times higher than the recommended doses in dogs) [10]. TEA is safe to use at 10mg/kg IV q8hours in dogs [11].

Moreover, postoperative administration of EACA has been shown to decrease significantly the incidence of postoperative bleeding in Greyhounds (from 30 to 10%), by increasing clot strength. In this study, dogs were administered 500 mg orally every 8 hours (15 to 20mg/kg q8h) for 5 days starting the night of surgery [5].

A more recent study conducted in healthy dogs, showed that a 100 mg/kg intravenous dose of EACA inhibited fibrinolysis “in vitro” more effectively than a 20 mg/kg dose [8]. Further studies are required to determine if this higher dose can further decrease the risk of postoperative bleeding in Greyhounds undergoing surgery. So far, no study has assessed the efficacy of TEA in reducing the prevalence of postoperative bleeding in Greyhounds but we could expect similar results.

Conclusion
Based on these results and our clinical experience, we recommend to treat Greyhounds and sighthounds with antifibrinolytic drugs perioperatively to any minor or major surgery. A typical recommendation is to start treatment one to two days prior to elective surgery and to treat for 5 to 7 days following any surgery. A similar recommendation would be reasonable for management of bruising/bleeding secondary to any trauma. Tranexamic acid is readily available as oral or injectable forms in the UK. A 10 to 20 mg/kg dose every 8 hours (IV or PO) is currently recommended. This drug appeared to be greatly effective in the patient described above and possibly avoided the use of blood products in this case. Nevertheless, further studies are needed to determine the clinical effectiveness of the recommended dose of TEA for this indication.