INSIDE THE CASE
While previous studies report that hyperfibrinolysis is uncommon in dogs with pyometra, this case may represent an uncommon example in a Newfoundland.

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Abstract

Abnormalities of coagulation can be challenging to diagnose in small animal patients. Assessment of coagulation disorders in patients with clinical hemorrhage has focused on deficits of the traditional primary (platelets) or secondary (clotting factors) coagulation systems. However, as our understanding of the coagulation system has evolved, hyperfibrinolysis, or rapid clot breakdown, has been identified as an etiology of hemorrhage in some patients. Although previous evidence has supported that pyometra is not typically associated with hyperfibrinolysis, this case study involves a patient who was diagnosed with hyperfibrinolysis secondary to pyometra using a viscoelastic assay and was successfully treated with ε-aminocaproic acid. This may represent a novel complication of this disease.

CASE REPORT: EMERGENCY MEDICINE/CRITICAL CARE

Hyperfibrinolysis in a Dog With Pyometra

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Coagulopathies, when associated with potentially life-threatening disease processes, can be very complicated to diagnose and treat. Traditional evaluation of the coagulation system has focused on hypocoagulation. As understanding of the complex nature of coagulation has grown,[1] the ability of veterinarians to diagnose and treat disorders associated with hypercoagulation (patients at risk of blood clots) and hyperfibrinolysis (rapid clot breakdown) has improved, and knowledge of these disease processes is rapidly increasing.[2] When coagulation abnormalities are present, accurate diagnosis is essential to help direct treatment.

This case report describes a patient that developed moderate blood loss due to hyperfibrinolysis after surgery to treat pyometra. The dog was treated for hyperfibrinolysis, made a full recovery, and was reported to be normal 18 months later.

SIGNALMENT, HISTORY, AND INITIAL ASSESSMENT

A 4-year, 7-month-old intact female Newfoundland weighing 68 kg presented to the primary care veterinarian for evaluation of lethargy, hyporexia, increased thirst, and vaginal discharge of 2 days' duration. A complete blood count (CBC) demonstrated a moderate neutrophilia of 30.1 × 10^3/µL (reference range, 3 × 10^3/µL to 12 × 10^3/µL) and a mild thrombocytopenia of 124 × 10^3/µL (reference

Take-Home Points

- Differential diagnosis for patients with hemorrhage should include hyperfibrinolysis, or rapid clot breakdown, along with other congenital or acquired coagulopathies.
- A viscoelastic assay (global assessment of clot formation) is necessary to diagnose veterinary patients with hyperfibrinolysis; these may include a viscoelastic coagulation monitor, thromboelastograph (TEG 5000 or TEG 6s), or rotational thromboelastometry.
- Along with treating the underlying condition, treatment for hyperfibrinolysis includes administration of a lysine analog such as tranexamic acid or ε-aminocaproic acid, which bind to plasminogen and subsequently prevent cleaving of fibrin.
- Previous studies report that hyperfibrinolysis is uncommon in dogs with pyometra; however, this case may represent an uncommon complication of hyperfibrinolysis in pyometra.
- Hyperfibrinolysis has been demonstrated in a variety of other veterinary patients such as those with recent trauma, cavitary effusions, liver disease, or some parasitic infections, as well as greyhounds.

range, 165 × 10^3/µL to 500 × 10^3/µL). The patient was prescribed ciprofloxacin at 15 mg/kg PO q24h.

The patient presented again to the primary care veterinarian 2 days later with no improvement in clinical signs. A repeat CBC demonstrated a neutrophilia of 31.1 × 10^3/µL and thrombocytopenia of 124 × 10^3/µL. A serum biochemistry panel was performed and showed low blood urea nitrogen (6 mg/dL; reference range, 7 to 25 mg/dL) and mild hypoalbuminemia (2.1 g/dL; reference range, 2.5 to 4.4 g/dL). Abdominal radiographs were obtained and a large, tubular, soft-tissue opacity structure in the caudal abdomen, consistent with an enlarged uterus, was identified. The patient was transferred to a specialty facility for care.

REFERRAL ASSESSMENT

Abnormalities noted on physical examination in the emergency department included an elevated rectal temperature of 40.3 °C, 5% dehydration, and bloody, purulent vaginal discharge. Preoperative diagnostic tests included a venous blood gas and electrolyte panel that showed a mixed pattern characteristic of metabolic acidosis and respiratory alkalosis: pH, 7.47 (reference range, 7.31 to 7.42); HCO_3-, 17.2 mmol/L (reference range, 20 to 29 mmol/L); and Pco_2, 25 mm Hg (reference range, 32 to 49 mm Hg). Mild hypernatremia (167 mmol/L; reference range, 144 to 160 mmol/L) and hyperchloremia (126 mmol/L; reference range, 109 to 122 mmol/L) were also present. Packed cell volume (PCV), total solids (TS) by refractometer, anion gap, potassium, glucose, lactate, and ionized calcium were within reference intervals. The patient was hemodynamically stable with a normal heart rate and normal perfusion parameters.

TREATMENT

With findings consistent with an open pyometra, the patient was taken for exploratory laparotomy. An IV catheter was placed in the cephalic vein, and she was started on a balanced, isotonic crystalloid at a rehydration rate of 54 mL/kg/d over 8 hours. She was also administered 10 mg/kg enrofloxacin IV. She was premedicated with 0.07 mg/kg hydromorphone, and anesthesia was induced with 5.5 mg/kg of ketamine and 0.28 mg/kg of midazolam IV. She was intubated and maintained on oxygen and isoflurane. Anesthesia was monitored with electrocardiography, end-tidal CO_2, blood pressure, and pulse oximetry; values remained normal during the procedure.

Abdominal exploratory revealed an enlarged, engorged, and fluid-dilated uterus. An ovariohysterectomy was performed in a standard fashion, using ligatures for the major ovarian and uterine vessels, along with a bipolar vessel sealing device (LigaSure; Covidien, medtronic.com/covidien) for hemostasis and monopolar cautery for the subcutaneous tissues and falciform removal. The remainder of the abdominal viscera were unremarkable. A preventive incisional gastropexy was performed, the abdomen was lavaged with sterile saline and suctioned, and a standard 3-layer abdominal closure using skin staples completed the surgery. Mild oozing of the subcutaneous tissues was noted prior to closure, but hemostasis otherwise appeared adequate at the time of closure.

Recovery was uneventful and the patient was hospitalized with the following treatments: isotonic crystalloids (35 mL/kg/d IV), enrofloxacin (10 mg/kg IV q24h), gabapentin (5.8 mg/kg PO q8h), hydromorphone (0.05 mg/kg IV q6h as needed based on modified Glasgow Pain Scale scores), and carprofen (2.2 mg/kg SC, initial dose; subsequently 2.2 mg/kg PO q12h). She also received a single dose of acepromazine (0.04 mg/kg IV) during recovery. A nonadherent pad and adhesive dressing were placed over the incision. Uterine fluid was submitted for aerobic culture. The patient continued to have normal vital parameters for the duration of hospitalization.

FIGURE 1. Laparotomy pads and an adherent skin bandage covering the abdomen of the patient, soaked with serosanguinous fluid post-ovariohysterectomy.

Eight hours postoperatively, the incisional bandage had become saturated with a sanguineous fluid (**FIGURE 1**). Inspection of the incision site showed 2 staples that were not engaging both edges of the skin; they were replaced. An AFAST (abdominal focused assessment with sonography for trauma) ultrasound scan exhibited free peritoneal fluid in the splenorenal view. The fluid collected had a PCV of 18% and TS of 4.6 g/dL, while a peripheral blood sample had a PCV of 33% and TS of 6 g/dL. The abdominal fluid was presumed to be mild hemorrhage, diluted with a small amount of remaining saline that had been used to lavage the abdomen. Two laparotomy pads were placed over the incision, both of which needed to be changed twice within 4 hours as they became saturated, resulting in an estimated fluid (blood) loss of about 3.6 mL/kg.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for ongoing hemorrhage after surgery included bleeding from the surgical procedure; a congenital coagulopathy, such as factor VIII deficiency (hemophilia A), factor IX deficiency (hemophilia B), von Willebrand disease, or less common factor deficiencies or congenital platelet disorders; or an acquired coagulopathy, including thrombocytopenia or coagulation factor deficiency due to consumption (from ongoing hemorrhage), hyperfibrinolysis, disseminated intravascular coagulation (DIC), or liver failure. Anticoagulant administration or anticoagulant rodenticide intoxication were considered less likely as there was no known exposure.

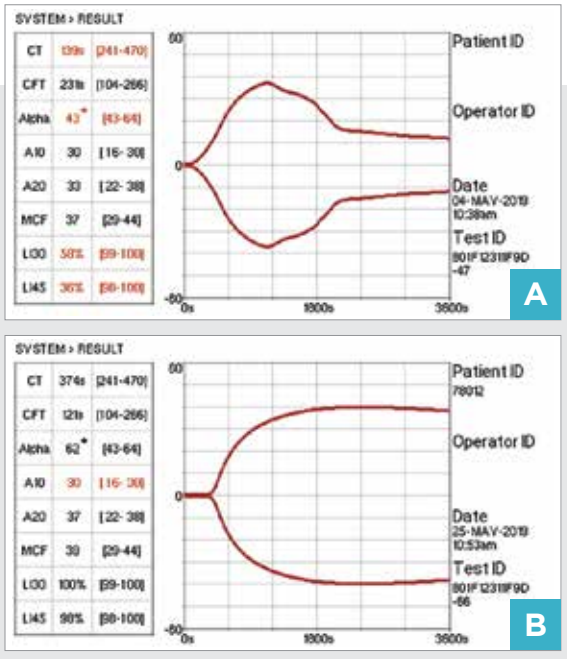

FIGURE 2. (A) Entegrion VCM viscoelastic tracing of blood from the patient. The following abnormalities were noted: LI30 of 58% (normal, 99%–100%), LI45 of 36% (normal, 98%–100%), and clotting time of 139 sec (normal, 241–470 secs). Normal clot formation and strength were present as assessed by the other test variables. This tracing is most consistent with normal clot formation and hyperfibrinolysis. **(B)** Entegrion VCM viscoelastic tracing of blood from a normal patient provided for reference. Alpha, alpha angle; A10 and A20, amplitude at 10 and 20 minutes, respectively; CT, clot time; CFT, clot formation time; LI30 and LI45, lysis index at 30 and 45 minutes, respectively, expressed as a percentage of MCF (maximal clot formation).

DIAGNOSTIC TESTING AND THERAPY

Since platelets were only mildly decreased prior to surgery, viscoelastic coagulation testing was performed using a VCM analyzer (Entegrion, entegrion.com). Results are shown in **FIGURE 2**. The tracing was most consistent with hyperfibrinolysis, or rapid clot breakdown. A disorder of platelets or clotting factors was considered less likely because the tracing demonstrated normal to rapid clot formation and normal clot strength.

An antifibrinolytic medication, ε-aminocaproic acid (EACA), was initiated at a dose of 50 mg/kg IV q8h for a total of 5 doses. The patient had no changes in vital parameters to indicate significant blood loss, and serial PCV/TS measurements remained stable at 33% and 6 g/dL, respectively. Within 12 hours of instituting EACA, the discharge from the incisional site decreased dramatically and no further bandage changes were required.

Culture and susceptibility results from a uterine fluid sample demonstrated an *Escherichia coli* strain that was susceptible to all antimicrobials tested.

OUTCOME

The patient clinically improved and was discharged from the hospital 48 hours after surgery. During follow-up at suture removal 13 days postsurgery and a telephone call 18 months postsurgery, the owner reported a healthy dog with no ongoing medical issues.

DISCUSSION

Coagulation is a complex series of events that results in

formation of a clot at the site of vessel injury; formed blood clots are eventually broken down through natural fibrinolysis.[1,3] During fibrinolysis, plasminogen activators such as tissue plasminogen activator (tPA) convert plasminogen to plasmin; plasmin is an enzyme that cleaves fibrin, an important part of the clot structure. Other factors play an important role in minimizing clot breakdown, such as thrombin activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitors (PAIs). A complex system of feedback loops ensures that both clot formation and clot breakdown occur in a controlled and balanced manner.

Hyperfibrinolysis, or excessive clot breakdown, occurs when the balance of clot formation and clot breakdown is not well controlled; this may occur when plasmin breaks down the fibrin clot in an unregulated fashion and can result in clinically important hemorrhage.[4] Hyperfibrinolysis is suspected to be a congenital disease in greyhounds[5] and has been demonstrated as an acquired consequence of a variety of pathologies in veterinary patients, including trauma, cavitary effusion, liver disease, and certain parasitic infections (e.g., *Angiostrongylus vasorum*).[4]

It can be very challenging to clinically differentiate a patient that is bleeding from hypocoagulation (clotting factor or platelet disorder) versus one that is bleeding from hyperfibrinolysis. Diagnosis of hyperfibrinolysis remains challenging in veterinary medicine and requires specific laboratory machines that perform a global evaluation of clot development, strength, and breakdown by performing viscoelastic blood tests. Briefly, these tests monitor the speed of formation, strength, and fibrinolysis of a clot as blood moves from a liquid to a semi-solid (clot) and back into a liquid state. This clot formation is portrayed as a viscoelastic tracing, from which numerical data are derived.[4]

Therapy for hyperfibrinolysis relies on specific antifibrinolytic medications such as EACA or tranexamic acid (TXA).

Machines used to generate viscoelastic tracings include the TEG 5000 and TEG 6S (Haemonetics, teg.haemonetics.com), the ROTEM (Werfen, werfen.com), and the Entegrion VCM. Each uses different technology to generate similar information about clot dynamics, and each has its own reference ranges. Some of these machines can run several variations of a viscoelastic tracing concurrently to aid in diagnosis of complex or occult disease; for example, a tPA-TEG tracing may uncover a hyperfibrinolytic state or aid in more complex diagnoses. However, even with these machines, diagnosis of hyperfibrinolysis may be a challenge. The VCM technology provides an easy-to-use, cartridge-based system that is becoming more common in larger veterinary hospitals.

Therapy for hyperfibrinolysis relies on specific antifibrinolytic medications such as EACA or tranexamic acid (TXA). These are lysine analogues that bind to the kringle domain of plasminogen, preventing its ability to bind with and cleave fibrin and result in a more stable clot.[5,6] Several veterinary studies have demonstrated the successful use of antifibrinolytic medications.[4,5] However, dosing regimens for EACA and TXA have yet to be standardized in veterinary patients. Some literature indicates that higher doses may be required in dogs compared with humans to fully inhibit fibrinolysis.[7] Current recommendations in dogs include 50 to 100 mg/kg PO or IV q6h to q8h for EACA and 10 to 15 mg/kg IV q3h to q4h for TXA.[8] Single doses may be followed by a continuous infusion; there is limited information on duration of use and use in other species.[9]

The patient in the present report exhibited clinical manifestations of hyperfibrinolysis, noted by the new oozing at the end of surgery and ongoing blood loss following ovariohysterectomy for pyometra. When hyperfibrinolysis was confirmed via viscoelastic testing in the postoperative period, the patient responded rapidly to treatment with EACA.

It is possible that other disease processes could have accounted for the ongoing bleeding in this patient. Mild thrombocytopenia was present; however, it was not severe enough to be commonly associated with clinical bleeding, there was no evidence of petechiae, and the VCM tracing did not support a disorder of platelets or coagulation factors (normal maximal clot formation, clot formation time, and alpha angle).[10,11] Poor surgical technique could have accounted for hemorrhage; however, no bleeding from the surgical

site was noted, 2 modalities of electrocautery were used, and the veterinarian was experienced with this type of surgery. Other disorders of hypocoagulation may have been present, such as a hemophilia or other factor deficiency; however, the other VCM tracing parameters and clinical resolution of bleeding with administration of EACA without further intervention do not support this. DIC was a diagnostic differential; however, the VCM coagulation tracing does not show characteristics typically found in patients with DIC, including an abnormal maximal clot formation and hypercoagulation.[12,13] Further investigation of alternative coagulation disorders did not appear to be warranted as the patient's clinical signs resolved.

The etiology of this patient's clinically transient hyperfibrinolysis is not definitively known. It has been demonstrated that *E coli* bacteria can manufacture and express a pro-urokinase enzyme.[14] Urokinase is a plasminogen activator and, if present in sufficient quantities, could theoretically result in a hyperfibrinolytic state, as it may increase the activation of plasminogen to plasmin.[14] However, this has not been clinically investigated. Activation of the fibrinolytic system has also been identified in experimentally induced *E coli* sepsis in pigs.[15] However, clinical hyperfibrinolysis has not been reported with *E coli* infections in veterinary or human medicine. In fact, many patients with sepsis have been shown to develop a procoagulant state with a reduction in fibrinolysis,[16,17] believed to be due primarily to elevated levels of PAI-1, even when plasminogen activators are present. Thromboelastography of bitches with pyometra has been reported in 1 veterinary study,[18] in which 18 dogs with pyometra were compared with 8 healthy spayed animals. Bitches with pyometra were demonstrated to have evidence of hypercoagulation. TVP

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