Traumatic Coagulopathy

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Introduction:

In the last decade, management of coagulopathy in severely injured trauma patients has changed dramatically. It was originally believed that the main causative factor for traumatic coagulopathy was the iatrogenic hemodilution, which is now disproven since hemorrhaging patients have an established coagulopathy prior the dilutional effects of fluid resuscitation[1]. Currently, the new terminology is either trauma-induced coagulopathy (TIC) or acute traumatic coagulopathy (ATC), recognizing that this is a complex, multifactorial process that results in depletion, dilution, or inactivation of normal clotting factors[2]. Contributing factors that influence ATC include hypothermia, acidosis, hypoperfusion and hemodilution[3,4]. Clinically, ATC can be identified by a significant prolongation of activated partial thromboplastin time (aPTT) and prothrombin time (PT) [5,6,]. The etiology is still unclear; however, injury severity and hemorrhagic shock are both implicated as etiological factors [5,7,8]. It is important to note ATC can look similar to disseminated intravascular coagulopathy; however, there is no evidence supporting inappropriate disseminated clots histologically [9,10,11].

History/ Presentation:

Cyborg is a 5 month old neutered male domestic shorthair cat that presented to MSU-CVM Small Animal Internal Medicine on August 31, 2017, for a non-regenerative anemia after he was rescued (3 days ago) from being wedged in a tree trunk. His pelvic area was entrapped at the narrowest part of the tree trunk. The owner reported that the duration of being trapped in the tree was unknown, but on the day he was rescued he had pale mucous membranes and cold extremities. He was brought in as an emergency to his primary veterinarian.

At Cyborg's primary veterinarian, he was medically managed on Lactated Ringers Solution and (initially a shock dose and then 2x maintenance after) was given cefazolin, SoluMedrol, buprenorphine, and prazosin. The prazosin was initiated to improve urination via urethral relaxation, as a large bladder was noted since he was not urinating on his own. Thoracic and abdominal radiographs were unremarkable. His limited neurological exam revealed deep pain with no superficial pain in the hind limbs with a minimal withdrawal reflex and anal tone present. A cystocentesis revealed hematuria. Since he was not urinating on his own, a urinary catheter was placed. His neurological deficits in the right hind limbs improved and the withdrawal reflexes were bilaterally normal. Oral prednisolone was added (8/29) to the treatment plan. Throughout this time, he had a decreased appetite and normal defecation habits. On 8/31, his mentation changed to depressed. His CBC revealed a normocytic, hyperchromic non-regenerative anemia and a moderate thrombocytopenia. The biochemistry revealed a mild hyperglycemia, mild hypoalbuminemia, mild hypoglobulineamia, mild hypocalcemia, mild hypocholesteremia, an elevated ALT, and elevated blood urea nitrogen and creatinine. At this time, he was transferred to MSU-SAIM.

On presentation Cyborg was depressed, laterally recumbent, and minimally responsive. He had an intravenous catheter in his right cephalic vein and a urinary catheter. His vital parameters were as follows: tachycardic at 270 bpm, respiratory rate of 28 brpm, and temperature of 99.0° F. He had pale mucous membranes, pinnae, and sclera with an undetectable capillary refill time (due to the pale mucous membranes). Upon abdominal palpation, he had a firm, enlarged palpable bladder. On FAST scan, he had a small amount of free abdominal fluid and bilateral hydroureternephrosis. His bladder was intact but contained a large ovoid, soft tissue opacity mass suspected to be a hematoma. On his limited neurological exam, he was ambulatory

paraparetic with the right hind limb being more affected. There was superficial and deep pain present bilaterally. He had delayed right and left hind limb conscious proprioception deficits. All his cranial nerves were normal. He had a SPO2 on room air of 99%. His PCV was 9% with a total solids of 4.2 g/dL. A lactate was 4.2 g/dL. He had a prolonged PT (at 26.8 seconds) and PTT at the high end of normal (17.8 seconds). He came with a urinary catheter from his primary veterinarian, but he was leaking around the catheter so a Foley urinary catheter (3.5 Fr) was placed, and 73 ml of bloody urine was aspirated upon placement. A shock bolus of Lactated Ringers Solution as well as hetastarch and methadone were given intravenously. The abdominal radiographs revealed gas bubbles within the small intestine, a large urinary bladder, and a catheter that terminated in the bladder. The abdominal ultrasound revealed bilateral pyelectasis, and hydroureteronephrosis. There was a small amount of anechoic free fluid within the retroperitoneal space. There was a small amount of subcapsular anechoic fluid around the left kidney. The left renal pelvis measured 2.5 mm in width, and the right renal pelvis measured 1.6 mm. The right and left ureters were both significantly dilated and tortuous with the left being more affected. The left ureter was measured at 5.3 mm in thickness and the right measured 3.5 mm in thickness. The hematoma was a large, mixed, echogenicity undulating in margin, ovoid mass not attached to the mucosal bladder. It measured 4.06 cm x 2.42 cm with regions of anechoic fluid and regions with dirty distal acoustic shadowing within the urinary bladder. A hyperechoic linear to tubular structure was also seen within the urinary bladder and extending from the urethra, consistent with a urinary catheter placement. Due to the hematoma in the bladder, the urinary catheter was not flowing, and this lower urinary obstruction ledto the hydroureternephrosis. Upon completion of the ultrasound the right ureter decreased to 1.2 mm in thickness due to the new placement of the urinary catheter as well as aspiration of the bladder.

Cyborg's mentation changed from depressed to comatose, and he became hypothermic at 92.0° F, by the time diagnostics were completed. These signs were attributed to his severe anemia. Cyborg was blood typed as A, and he was given 60 mL of whole blood over 5 hours. No complications were noted during his transfusion. During his transfusion his temperature normalized. He became bright, alert and responsive about halfway through his blood transfusion.

Differential Diagnoses:

Due to Cyborg's recent traumatic experience of being wedged in a tree, the cause of his bladder hematoma and severe non-regenerative anemia was likely acute traumatic coagulopathy. However, ATC, is a diagnosis of exclusion. To diagnose ATC is challenging. Especially in young patients like Cyborg, who was <1 years old, inherited congenital coagulopathy must be considered. In cats, the most common inherited congenital coagulopathy is an autosomal recessive disorder, Hageman's deficiency (Factor XII)[12]. It is important to remember Hageman's deficiency does not typically cause clinical bleeding unless it is associated with factor IX deficiency. Additionally, in male cats Haemophilia A (factor VIII deficiency) and Haemophilia B (Factor IX deficiency) are sex-linked autosomal recessive traits that occur most commonly in domestic shorthaired cats and could result in similar signs observed in Cyborg's case[12]. It is important to rule out these inherited congenital coagulopathies especially since it could be coinciding with acute traumatic coagulopathy and potentially exacerbating the clinical signs. It is critical to rule out the inherited coagulopathies especially since it would change the medical treatment and would require supplemention of the deficient factor. A deficiency in vitamin K-dependent factors due to the consumption of rodenticide, severe malabsorption or dysbiosis, a warfarin type drug, or a congenital abnormality (Vitamin K deficiency), would lead to a deficiency in Factors II, VII, IX, and X[6]. Additionally, immune-mediated hemolytic anemia and

hepatic failure are differential diagnoses. Primary immune-mediated hemolytic anemia is less common in cats but still necessary to rule out[5]. Plasma coagulation factors are produced in the liver; so, when the liver function is compromised greater than 70%, it can cause a coagulopathy [13]. Hepatocellular necrosis and end stage chronic hepatic disease can commonly cause a coagulopathy as well [13].

Pathophysiology:

Acute traumatic coagulopathy occurs due to multiple independent, but interacting, mechanisms[14]. The main components are hypocoagulation and hyperfibrinolysis[14]. There are key initiators of ATC that influence and prolong the coagulopathic state. These physiological derangements are metabolic acidosis, hypothermia, and hemodilution [14,15,16]. It has been shown that patients with only tissue damage and no concurrent physiological derangements have a lower mortality and do not suffer with ATC [14].

ATC is thought to occur by a major cascade of events that stimulate thrombin generation, fibrinogen, platelet consumption, and fibrinolysis by damaged tissues, which result in a consumptive coagulopathy [17]. Once tissue injury occurs, the body is exposed to tissue factor, which leads to thrombin and fibrin generation[18]. During this time, platelet activation is also triggered due to the exposure of sub-endothelial matrix to platelet glycoprotein VI and von Willebrand Factor (vWF) to glycoprotein Ib[18]. Thrombin generation is amplified due to the activated platelets adhering to the damaged tissues[18]. The increase in thrombin, which is an essential effector molecule in hemostasis, increases secondary fibrinolysis by stimulating tissue plasminogen activator (t-PA) [18,19]. When t-PA is released by the endothelium, primary fibrinolysis occurs due to factors such as hypoxia, epinephrine, and vasopressin[19].

Activated protein C is important in the multifactorial pathophysiology of ATC [20]. In physiological hemostasis, the function of fibrinolysis is important in maintaining local endothelium hemostasis [20]. However, if an overabundance is formed in the body this causes excess bleeding in the patient[20]. Protein C is a complement protein that is increased during post trauma. In many studies, during the state of ATC, protein C produced an anti-coagulable state by either reducing the thrombin formation by inactivation of factor Va and factor VIIIa, or by increasing fibrinolysis through inhibition of plasminogen activator inhibitor 1 (PAI1) [7,20]. According to human studies, injured patients with shock have high levels of protein C, and coagulation factors including V and VIII were decreased [21].

Hypoperfusion is another contributing factor to ATC. During normal physiological events, a prothrombic environment is formed during tissue injury, which includes endothelial cell activation thrombin and various cytokines, as well as hypoxia and hypoperfusion[22]. Hypoperfusion promotes an anticoagulant and hyperfibrinolytic environment [22]. This creates an issue since hypoperfusion allows thrombin to stay in the body longer, making it available for a longer period of time, allowing more thrombin to bind to thrombomodulin [22]. This unravels a sequence of events, with activation of protein C, which then continues to promote systemic anticoagulation and hyperfibrinolysis. If hypoxia and acidosis are occurring at the same time, endothelial cell activation will predominate [7,23]. Due to the prothrombic environment, there will be an increase in production of PAI-1 over t-PA[23] which will shut down fibrinolysis [18,23].

In human literature, when ATC patients were given platelet transfusions, they had a better prognosis [20,23]. In primary hemostasis, platelets act as the main "scaffold of clots"[24] and "serve as the catalysts of coagulation"[24]. But in the trauma patient, platelets become

dysfunctional and do not respond to collagen, ADP or arachidonic acid[24], even when there is a sufficient amount of platelets. The reason behind this platelet dysfunction is unknown.

ATC may resemble disseminated intravascular coagulation (DIC); however, patients with ATC show no evidence of inappropriate disseminated clot formation on histological examination[10].

Diagnostic Approach/Considerations

Early diagnosis of acute traumatic coagulopathy is important since uncontrolled hemorrhage is responsible for 50% of deaths in human medicine[25]. There is no definitive test that confirms ATC [26]. The traditional key diagnostics for hemostatic testing are prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration, and platelet count. The adopted marker for ATC is the prolongation of PT[26]. It is also important to note, the traditional coagulopathy tests only evaluate active hemorrhage. Therefore, PT, PTT, and platelet count would be the test of choice initially on presentation to diagnose a coagulopathy and then again post treatment in order to monitor the progress of the coagulopathy[26].

ATC is diagnosed by diagnosis of exclusion. Knowing the history of the patient and doing a thorough physical examination can help determine the next most likely diseases to rule out. It is important to cast a wide net of diagnostics to narrow down the initiating cause of coagulopathy. However, ATC is a high differential when the patient's history suggests a traumatic situation such as in Cyborg's case (being trapped in a tree). A complete blood count will quantify the platelet count, access the anemia, and help support a coagulopathy. If platelets are less than <30,000 to 40,000/μL this is suggestive of a hemostatic disorder [27]. To verify the blood machines are correctly numbering the platelets, a manual platelet count should be performed. A serum chemistry will rule out any suspected underlying diseases such as hepatic

failure, or extrahepatic biliary obstruction. It will also reveal any electrolyte abnormalities that need to be corrected either due to the disease process or sequelae of the disease. A packed cell volume (PCV), total protein (TP) and lactate are also used to monitor the patient especially on initial presentation.

Thromboelastography and rotational thromboelastometry are also helpful. In human literature thromboelastography and rotational thromboelastometry are still being investigated as a better modality for identifying and guiding therapy for ATC [3,28].

Imaging modalities such as radiographs and ultrasound are helpful diagnostics since they can access a target organ or body cavity that has hemorrhage. At the same time, it serves to evaluate the all abdominal organs[3,28]. For instance in a hepatic or extrahepatic case the echogenicity and structure of the liver could be evaluated and help diagnose hepatic failure. In Cyborg's case, he initially received a full abdominal ultrasound to access the hemorrhage and then once our target organ was found which was a bladder hematoma. An aFAST was performed on Cyborg daily to access the progression of the bladder hematoma.

To rule out single factor deficiencies due to an inherited coagulopathy a plasma coagulation factor activity analysis should be performed[5]. A rodenticide screening is important to include, especially in Cyborg's case since he was found outdoors. To further rule out hepatic diseases, an ammonia tolerance test oror bile acid tests are helpful. Additionally, D-dimers and FDPs are performed to rule out disseminated intravascular coagulopathy.

Treatment and Management

There is no specific treatment to cure acute traumatic coagulopathy. The appropriate blood product is dictated by what is lost in conjunction with clinical signs of the patient. The various blood products offered in veterinary medicine for ATC are fresh whole blood, frozen

plasma, cryoprecipitate and platelets[31,34]. There are also limited studies on red cells and tranexamic acid [31,34]. Whole blood is indicated if the patient is showing signs of tachycardia, abnormal pulses, or weakness after fluid resuscitation with a PCV <20% along with a history of acute bleeding. Fresh frozen plasma is indicated for hemophilia, vWD , and anticoagulant rodenticide ingestion since it rapidly supplies the loss of clotting factors such as XII, XI, X, IX, VIII, VII, V, II and vWF. Cryoprecipitate is necessary for a patient deficient in vWD or fibrinogen. When a patient is in acute traumatic coagulopathy they are in a hyperfibrinolytic state, so theoretically using an antifibrinolytic such as tranexamic acid can potentially be part of the treatment [32,33]. Most of the studies that use tranexamic acid are extrapolated from human literature, particularly in hemorrhaging cardiovascular surgery [33,34]. However, there are two studies in veterinary medicine that test tranexamic acid for therapy [32,33,34]. A retrospective study was performed where tranexamic acid was administered to various bleeding disorder dogs [33,34]. They concluded that it was clinically safe to use in dogs but it did not reduce the transfusion requirements. Another study by Blackstock et al concluded dogs had no improvement; potentially, they need a higher dose to be effective. The main treatment that will help improve the survival times for ATC are transfusions. The use of intravenous fluids such as colloids or crystalloids were originally the mainstay of treatment for a coagulopathy. However, recent studies prove a limited use of colloid or crystalloid infusions are preferred during acute traumatic coagulopathies [30,34]. The result of a primary endpoint meta-analyses study failed to support colloids are better than crystalloids [35,36].

Correcting the hemorrhage in an acute traumatic coagulopathy is extremely important and should be attended to immediately since it can ultimately lead to hemorrhagic shock[39]. Contributing factors of ATC such as hypothermia, metabolic acidosis, and hemodilution need to

be monitored and managed accordingly[40]. It is shown in human and veterinary literature that surgical intervention to control hemorrhage may be necessary if medical treatment is not effective [10].

In human literature, hemorrhage accounts for 40% of human trauma related deaths. However, this information is lacking in veterinary medicine;it is currently unknown. In human medicine, there are only ten to twenty five percent of human trauma patients that will experience ATC. When ATC does occur, there is a four-fold increase in mortality rate since ATC will prolong hemorrhage, deter resuscitative effort and promote sepsis [2,41]. The prognosis depends 'upon achieving rapid definitive hemostasis, early attenuation of posttraumatic coagulopathy, and timely restoration of effective circulating volume'[2,41]. Being able to control the hemorrhage, metabolic acidosis and hypothermia will all significantly improve survival time.

Case Outcome

Even prior to Cyborg's diagnosis, he was given a whole blood transfusion on presentation due to his prolonged PT (at 26.8 seconds) and PTT at the high end of normal (17.8 seconds). He was treated with and was maintained on intravenous fluids lactated ringers solution (2x maintenance), Buprenex (buprenorphine), Cerenia (maropitant), Vitamin K (phytonadione) subcutaneous injections and prazosin. The vitamin K was given subcutaneously to supplement for potential rodenticide toxicity or deficiency in vitamin K dependent factors. Cerenia was added intravenously since he was inappetent post transfusion, which was suspected to be because of nausea. The buprenorphine was for pain control due to the bladder hematoma. Cyborg's mentation changed post transfusion to bright, alert and responsive. However, overnight he became dull and tachycardic with a PCV of 13%; Cyborg was given a whole blood transfusion

which increased his PCV to 25%. However, the following morning he was dull, with pale mucous membranes and had a PCV of 13%. Cyborg was administered another whole blood cell transfusion. Following this transfusion, his PCV significantly improved to 25%. His PTT time was within normal limits with his PT still mildly prolonged.

Frequent aFAST scans were performed of the bladder hematoma, which was static in size and at first was in the apex of the bladder. After 4 days (Sunday, 9/3/17) the hematoma moved causing an obstruction in the ureters. Cyborg became pyrexic that night and Clavamox was added to his oral medications. Cyborg was still able to urinate but was pooling urine in front of the hematoma. His mentation changed dramatically from playful to dull overnight. At this point, since his ureters were obstructed and his kidneys were showing signs of hydronephrosis, it was elected to perform a cystotomy to remove the hematoma. A central line was placed prior to surgery. Cyborg underwent the cystotomy on Sunday (9/3/17). Another whole blood transfusion was administered immediately prior to the cystotomy. The only complications peri-operatively that were noted were that Cyborg became hypertensive and bradycardic and was treated with glycopyrrolate and hetastarch.

A urinary catheter was placed post operatively and his pain was controlled with a fentanyl CRI. A post-transfusion PCV was 32%. A chemistry performed on 9/5/17 was unremarkable, and his PCV was 30%. His behavior and appetite were substantially improved, and he was transitioned to oral medication and moved into the wards. On discharge, Cyborg was bright, alert, and responsive, and urinating on his own, although he occasionally had trouble completely voiding his bladder. He remained on Clavamox, Buprenex, prazosin, and phytonadione for the remainder of his hospitalization and seven days after he was home. At time of discharge, he continued to have urethral spasms; however, it eventually resolved. Due to his

urtheral spasm, it was recommended a diet of Hill's prescription C/D and a water fountain to entice him to drink. Even though hydronephrosis had resolved, it was recommended to recheck a renal panel in seven days along with a packed cell volume/total protein. This was performed at his primary veterinarian and were all within normal limits. Currently, seven months later, Cyborg is doing well.

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