Hypercoagulability and Adrenal Dysfunction in Critical Care

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Mabel, a 12-year-old, 15.8-kg, spayed wheaten terrier, presented in lateral recumbency with acute weakness and a history of two episodes of vomiting and one episode of diarrhea. Mabel was tachycardic, hypothermic, and hypotensive (Doppler ultrasound measured 30 mm Hg in the right pelvic limb; blood pressure [BP] could not be obtained in the left pelvic limb). The mucous membranes were pale and cold, with a capillary refill time of 3 seconds. Mabel had a 2/6 heart murmur of unknown etiology and lacked left femoral arterial pulses. The extremities were cool.

Mabel presented in early decompensated shock. A mixed acid–base disorder consisting of metabolic and respiratory acidoses was diagnosed. Brief ultrasonography showed no free abdominal or thoracic fluid. The initial packed cell volume (PCV) was 43%, and the total solids measurement was 7.6 g/dL. After administration of a 40-mL/kg bolus of a balanced isotonic crystalloid (Normosol-R, Abbott Laboratories), the BP was 60 mm Hg on Doppler ultrasonography, the PCV was 24%, and the total solids measurement was 4.0 g/dL. A 5-mL/kg artificial colloid (hetastarch) bolus was also given. Coagulation testing revealed a prothrombin time of 16 seconds (normal: 12 to 17 seconds) and an activated partial thromboplastin time (aPTT) of 121 seconds (normal: 70 to 102 seconds). A delayed aPTT may be a dilutional effect and/or a poorly understood effect of synthetic colloids.

After initial stabilization of the patient, plans were made to admit her to the intensive care unit. Although the BP continued to temporarily improve with administration of crystalloid and colloid boluses, it did not stabilize for several hours. The BP finally stabilized 8 hours after admission, with systolic BP holding at 90 mm Hg, according to Doppler ultrasonography. Broad-spectrum antimicrobials were initiated to treat a possible septic focus (based on severe hypotension and a left-shift neutrophilia on a complete blood count) and potential gastrointestinal (GI) bacterial translocation. (In patients with hypotension and decreased perfusion, the gut tissue fails to receive adequate nutrition, compromising the gut barrier, which can allow enteric bacteria to translocate into the systemic circulation.[1]) A central venous line was placed in a saphenous vein to administer additional fluids and to periodically draw blood. Packed red blood cells (RBCs) and fresh frozen plasma were transfused to treat anemia (because the PCV was 21% after volume resuscitation) and prevent dilutional coagulopathy after resuscitation with multiple infusions of crystalloids and colloids. Hematochezia was noted, and GI blood loss was added to Mabel's list of problems, further indicating potential GI translocation. Pain was managed with buprenorphine (0.015 mg/kg IV). GI protectants and antiemetics were administered to treat vomiting and GI hemorrhage. Enoxaparin, a low-molecular-weight heparin, was administered to prevent further clot formation.

On day 2, Mabel continued to be depressed and to lack a pulse in the left pelvic limb. Pancreatitis was confirmed using a canine pancreas-specific lipase test. Partial parenteral nutrition was initiated, and 25% human serum albumin was transfused to treat severe hypoalbuminemia (albumin level: 1.4 g/dL [normal: 2.7 to 4.4 g/dL]) and provide additional colloidal support. Abdominal ultrasonography revealed a highly inflamed GI tract (with thickening of the intestinal wall) and mesentery as well as ascites. Color-flow Doppler ultrasound of the distal aorta revealed no vis-

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ible thrombus. Because of the ultrasonographic findings, abdominal exploratory surgery was recommended, and the owners agreed to it. Surgery revealed a thickened GI tract, severely inflamed pancreas, and highly reactive mesentery. No foreign body or neoplasia was found. A gastrojejunostomy tube was placed to allow enteral feeding and gastric residual monitoring. A urinary catheter was placed. Urine output was measured at regular intervals, and fluid changes were made based on the patient's intake and output.

On day 3, jejunal feeding was initiated using Clinicare (Abbott Laboratories) at a constant-rate infusion of one-eighth of the daily resting energy requirement (RER). Mabel began to regurgitate after the rate was increased to one-third of the RER, so the rate was returned to one-eighth of the RER. Because of Mabel's catabolic state and persistent regurgitation, enteral nutrition had to be discontinued. Total parenteral nutrition (TPN) was scheduled because Mabel could not tolerate full enteral nutrition in the presence of severe critical illness and hypoalbuminemia. Despite the 25% human serum albumin transfusion, Mabel's albumin level was only 1.6 g/dL (normal: 2.7 to 4.4 g/dL). TPN was initiated to provide total caloric requirements along with amino acids, lipids, dextrose, trace minerals, and B vitamins. To provide TPN, a triple-lumen, 5.5-French central venous catheter was placed in Mabel's right jugular vein using the Seldinger technique. In this technique, an initial short catheter is placed aseptically into the jugular vein. A wire is fed into the catheter and seated deep in the jugular vein. A venous dilator is fed over the wire to facilitate placement of a larger catheter. This dilator stretches the skin hole and vein size to accommodate the large triple-lumen catheter. The dilator is removed, the catheter is fed over the wire, and the wire is removed. A 5.5-French polyurethane catheter was selected for Mabel. This catheter size was small for this patient; however, using a smaller catheter can help minimize thrombogenic tendencies, helping to prevent further thromboembolic episodes. Before this, venipuncture or catheterization of the jugular veins had been avoided to minimize endothelial activation. TPN was initiated at half of the RER, and an increase to full RER in 24 hours was planned. Central venous pressure (CVP) was measured using a water manometer to help guide fluid therapy. The average measurements every 4 hours were 2, 6, and 4 cm H_2O. (A patient's CVP can vary: a range of 0 to 10 cm H_2O is typically considered normal. When monitoring CVP, it is important to watch for trends. Steadily increasing or decreasing CVP values [even within the normal range] can indicate fluid overload or hypovolemia.)

On day 4, Mabel's TPN was increased to full RER. The BP, obtained via Doppler, was 62 mm Hg, revealing hypotension. Because the CVP was 6 cm H_2O, Mabel's preload and, therefore, volume status were determined to be adequate. Dopamine (5 µg/kg/min) was initiated, and increased as needed, to address possible cardiac contractility deficits and systemic vascular resistance. Dopamine is usually titrated to effect with a dose range of 5 to 20 µg/kg/min. A corticotropin stimulation test performed the night before revealed a resting cortisol level of 2.2 mg/dL (normal: 1.0 to 5.0 mg/dL); after administration of adrenocorticotropic hormone (ACTH), the cortisol level was only 4.2 mg/dL (normal: 8 to 17 mg/dL). This was not a classic addisonian response: Mabel's resting cortisol was normal, but not enough cortisol was released in response to ACTH secretion. Therefore, Addison's disease was considered to be low on the list of differentials. Mabel's change in cortisol level (i.e., the difference between the resting and post-ACTH cortisol levels) was <4 µg/dL, indicating an inadequate response to ACTH stimulation. This increased the likelihood of relative adrenal insufficiency (now known as *critical illness–related corticosteroid insufficiency*[a,2]), which was considered a diagnostic differential because of Mabel's refractory hypotension; the possibility of sepsis or systemic inflammatory response syndrome (SIRS), which was never confirmed but was highly suspected; and the adequate baseline cortisol level (2.2 mg/dL [normal: 1.0 to 5.0 mg/dL]) but insufficient response to corticotropin stimulation. (Patients with potentially limited adrenal reserve may have a normal resting cortisol level but cannot effectively mount a response to corticotropin stimulation, such as administration of ACTH or physiologic stress. Lack of adequate cortisol secretion in response to stress, especially during sepsis, can manifest as hypotension that is refractory to inotropic or vasopressor therapy. The change in the cortisol level between resting and stimulation levels is measured, and the difference is examined. Typically, administration of ACTH causes a large release of cortisol, so the cortisol values before and after stimulation are widely different [e.g., >4 µg/dL]). Methylprednisolone was initiated at a physiologic dose to replace endogenous steroids. Overnight, Mabel required an additional packed RBC transfusion because her PCV had dropped to 19%. Mabel began to show vestibular signs (vertical nystagmus). Shortly thereafter, decompensation occurred, and Mabel vocalized and then experienced cardiopulmonary arrest. Cardiopulmonary–cerebral resuscitation was unsuccessful. Mabel may have had thromboembolic brain disease, but necropsy was not performed to confirm this.

[a]Unlike patients with classic hypoadrenocorticism, those with this condition usually have a normal to elevated basal serum cortisol concentration but a blunted cortisol response to an ACTH stimulation test.

Discussion

Mabel's disease progression illustrates the complex issues surrounding hypercoagulability in critical care. This case presented a unique experience for a veterinary technician. Often, a technician can pinpoint specific interventions for minimizing disease progression. In this case, hypercoagulability became a factor to consider in a critically ill patient.

The triad of endothelial damage, stasis, and factors that predispose a patient to hypercoagulability are determinants of a patient's risk for thromboembolic disease. In endothelial damage, endothelial cells are activated and induce the coagulation cascade, starting with platelet adhesion. Platelets, in turn, recruit additional coagulation factors, and the endothelial cells release chemical mediators that interact to form thrombi. Antithrombotic substances may not be produced once the cascade moves toward a prothrombotic model. In the case of stasis, decreased flow can cause blood pooling and red cell clumping. The most common example is heart chamber enlargement,[3] in which blood flow velocity is decreased and turbulence is increased. This favors blood cell clumping, which, in turn, can cause adhesion and thrombi formation. In recumbent patients, blood flow is decreased due to lack of muscle movement, which is important for venous blood flow. As with chamber enlargement, velocity is decreased and turbulence is increased. A tendency toward hypercoagulability has been documented in patients with pancreatitis. These patients can have α-macroglobulin deficiency, which can result in deficient fibrinolysis.[3] This imbalance can shift the normal hemostatic conditions of coagulation toward a prothrombotic state.[3]

Mabel's risk factors included acute pancreatic necrosis, recumbency, likely decreased antithrombin, surgery, placement of intravenous catheters, transfusions (packed RBCs), administration of TPN, and SIRS. Hypercoagulability is a result of the relationship between endothelial damage, blood stasis, and factors that predispose a patient to hypercoagulability.[4] Pancreatitis, surgery, placement of intravenous catheters, and SIRS damage endothelium and can activate the coagulation cascade. Recumbency predisposed Mabel to thrombosis due to decreased blood flow. TPN, packed RBC transfusions, and antithrombin loss may have contributed to a hypercoagulable state. In Mabel's case, nursing care included avoiding use of the jugular vein and unnecessary venipuncture, minimizing thrombogenicity with appropriate catheter selection, and changing the patient's position to reduce blood stasis. Mabel's hemostatic disorder might have been caused by disseminated intravascular coagulation (DIC) resulting from SIRS due to acute pancreatic necrosis. Although some signs of DIC were present (e.g., thrombocytopenia, elevated aPTT), other diagnostic criteria, including the antithrombin III level, fibrin degradation products, and the D-dimer level, were not obtained. DIC has two stages. The early hypercoagulable stage is usually subclinical but represents a shift toward procoagulation and involves microthrombi formation in the vascular beds. Progression to the second stage involves consumption of coagulation factors, leading to spontaneous hemorrhage. Mabel might have developed vascular thrombi due to SIRS, and then medical interventions, such as plasma and heparin therapy, halted progression of the disease.[5]

Conclusion

This case strongly demonstrates how hypercoagulability can become a complication that must be addressed in critically ill patients. As we learn more about the hemostatic system and improve identification of risk factors for thromboembolic events in patients (through bedside coagulation testing [thromboelastography] or early recognition), recognition and preemptive management of possible risk factors may help improve the prognosis and reduce the morbidity and mortality of critically ill patients. In this case, all efforts were made to aggressively treat Mabel's illness. Mabel required skilled, around-the-clock care. Unfortunately, this case did not end well. When the patient presented to the hospital, she was already in a prothrombotic state. I hope this case will educate others about hypercoagulability in critically ill patients.

References

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