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Case report

Thromboelastometry analysis of severe North American pit viper-induced coagulopathy: A case report

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ABSTRACT

Case details: A 51-year-old man presented with rapid onset encephalopathy and respiratory failure after a suspected intravascular envenomation from a North American pit viper. The patient received antivenom and was transferred to a tertiary care facility where he had cardiovascular collapse and persistent coagulopathy requiring 28 vials of Crotalidae polyvalent immune Fab antivenom for initial control and six vials for maintenance. The patient's coagulopathy was monitored using "traditional" measures (platelets, fibrinogen, and prothrombin time/international normalized ratio) and rotational thromboelastometry (ROTEM®). The patient also subsequently developed intestinal necrosis requiring exploratory laparotomy with ileum and colonic resections, and anuric renal failure requiring continuous renal replacement therapy. After coordinated multidisciplinary management, he was discharged to an acute inpatient rehabilitation on hospital day 25 and has since made a full recovery.

Discussion: In the setting of a severe intravascular pit viper envenomation, thromboelastometry correlated well with "traditional" measures. During recovery, ROTEM® demonstrated measurable improvements in the extrinsic coagulation pathway while the INR remained between 1.5 and 1.6. Patient's intestinal necrosis may have resulted from microvascular thrombosis due to *Crotalinae* venom. The patient's ultimate recovery necessitated a coordinated multidisciplinary effort. ROTEM® abnormalities after North American pit viper envenomation may be more sensitive than "traditional" measures and may have prognostic value to determine the severity of envenomation, but further research to define its utility is required.

1. Introduction

North American pit viper envenomations commonly cause local tissue injury and coagulopathy, but severe and intravascular envenomations are rare (Gummin et al., 2017). We describe a case of a severe intravascular envenomation by a suspected pit viper.

2. Case report

A 51-year-old man with unknown medical history was bitten on the left leg by a snake in Northeast Texas, United States and became unresponsive en route to the hospital. The incident occurred at night in a poorly lit wooded area. The patient reported to his brother that he saw a "large black snake" without further details. Upon presentation to the emergency department, the patient was intubated and received three vials of Crotalidae polyvalent immune Fab antivenom (CroFab®, FabAV), epinephrine, and steroids for a presumed anaphylactic reaction to a pit viper envenomation. Three hours after envenomation, the patient arrived at a referral hospital with blood pressure of 140/114 mmHg and heart rate of 157 beats/min. Physical examination was remarkable for mottled extremities and two puncture wounds (approximately 2 cm interfang distance) with minimal surrounding ecchymosis proximal to the left medial malleolus (Fig. 1). Bradycardia developed, followed by pulseless electrical activity requiring two rounds of advanced cardiac life support before return of spontaneous circulation. Initial laboratory results were remarkable for international

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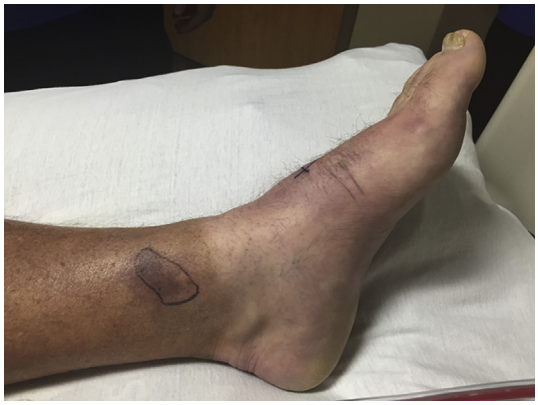

Fig. 1. Puncture wound visualized on the left medial malleolus.

normalized ratio (INR) 6.8, prothrombin time (PT) 70.2 sec, fibrinogen < 60 mg/dL, d-dimer > 32 mg/L, lactate 5.5 mmol/L, and platelet count 339 × 10^9/L. Seven additional vials of FabAV were administered.

Computed tomography of the abdomen due to increasing abdominal rigidity demonstrated ischemic bowel (Fig. 2). Following stabilization with 28 vials of FabAV, he was taken for exploratory laparotomy, revealing transmural necrosis of the ileum and right/transverse colon. Total colectomy with temporary abdominal closure was performed. Two units of cryoprecipitate and one unit of fresh frozen plasma (FFP) were given intraoperatively. Resected specimens of the ascending colon contained microvascular thrombi on histopathology.

Rotational thromboelastometry (ROTEM®) performed on whole blood evaluated the dynamics of clot development, stabilization, and dissolution during treatment with FabAV. ROTEM® uses a rotating pin in the developing clot to create TEMograms—reaction curves showing clot elasticity over time. ROTEM® is composed of five distinct specifications (Fig. 3A and Table 1) (Calatzis et al., 2016).

Seven ROTEM® samples were obtained during the hospitalization (Table 2). The first sample showed marked increase in clotting time (CT) and clot formation time (CFT) despite 16 vials of antivenom. A20 and alpha angle were also decreased in both specificities, indicating decreased clot firmness and clot formation rate, respectively (Fig. 3B and C). HEPTEM and APTEM also showed prolonged CT and did not fully form a clot. FIBTEM was unmeasurable. Similarly, PT/INR exceeded measurable parameters and fibrinogen was undetectable.

After 22 vials of antivenom, cryoprecipitate, and FFP, the second sample showed improvement of EXTEM, but both CT and CFT remained prolonged. The A20 and maximum clot firmness (MCF) normalized on EXTEM but remained low on FIBTEM. After 28 vials of FabAV, initial

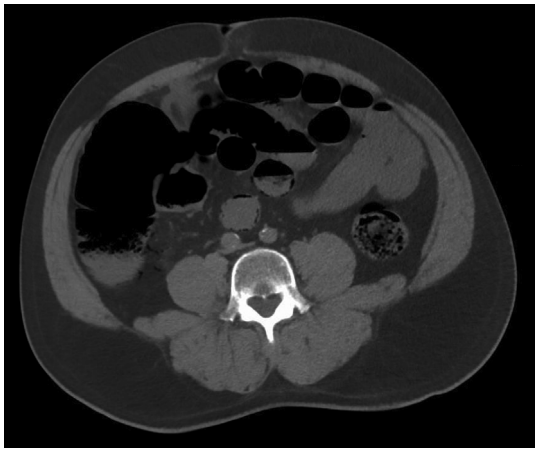

Fig. 2. Computed tomography image demonstrated intestinal ischemia.

control of coagulopathy was achieved by ROTEM® parameters. Further samples drawn after completion of scheduled maintenance antivenom doses remained within normal limits despite asymptomatic thrombocytopenia.

The patient required two additional operations for terminal ileum resection, end ileostomy, and delayed abdominal closure. Despite complications of anuric renal failure requiring renal replacement therapy and abdominal abscess requiring percutaneous drainage, he was discharged to acute inpatient rehabilitation on hospital day 25 and has since made a full recovery.

3. Discussion

North American *Crotalinae* venom contains a complex mixture of proteins, peptides, and non-peptide toxins that cause local tissue destruction, injure vascular endothelial layers, and interfere with coagulation, thrombus formation, fibrinolysis, and platelet adhesion (Gold et al., 2002; Warrell, 2010; White, 2005). Although venom composition varies by species, snake age, and location, most North American pit viper envenomations produce similar clinical effects with the exception of the neurotoxic components of *Crotalus scutulatus* venom (White, 2005). The exact species and venom in this case was not identified. Possible species of venomous pit viper in the geographic area that could cause severe envenomations include *Crotalus atrox*, *Crotalus horridus*, and *Agkistrodon piscivorus*. *Crotalus horridus* is more common in the area than *C. atrox*, and both *Crotalus* species cause are more likely to cause severe envenomations than *A. piscivorus*.

Severe pit viper envenomations may present with coagulopathy, respiratory distress, altered mental status, and hemodynamic instability (Gold et al., 2002). Venom-induced consumptive coagulopathy resembles disseminated intravascular coagulation (DIC) and can lead to severe hemorrhage and hypovolemic shock (Maduwage et al., 2015; White, 2005). Additionally, venom metalloproteinases cleave cell-cell junctions which weakens vascular walls and increases vascular permeability (Gutierrez et al., 2017). Some *Crotalinae* venom, such as from *Bothrops jararaca*, have bradykinin-potentiating peptides that induce vasodilatory shock (Hayashi and Camargo, 2005). Central nervous system effects are typically secondary to multisystem derangements such as hypoperfusion since snake venom components are restricted by the blood brain barrier with very few exceptions (Warrell, 2010). Fortunately, severe envenomations are rare in the United States, occurring in 2.3% of pit viper envenomations in 2016 (Gummin et al., 2017).

Our case represented a severe envenomation with ischemic bowel likely due to thrombotic complication given the presence of microvascular thrombi found in the ischemic bowel vascular and persistent venom-induced coagulopathy. Only two reported cases of non-North American *Viperidae* envenomations—*Vipera aspis* and *Lachesis muta*—were complicated by right-sided colonic necrosis from severe thrombotic vessel occlusion (Beer and Musiani, 1998; Rosenthal et al., 2002). Some *Crotalinae* venom activates formation of fibrin clots through thrombin-like components and activation of factor X (Beer and Musiani, 1998; Thomas et al., 1995). These fibrin clots are highly susceptible to fibrinolysis from the endogenous plasmin fibrinolytic system leading to ineffective fibrin degradation products and cross-linked d-dimer. Although anticoagulant effects and defibrination predominate in clinical presentations, viper envenomation-induced cerebral, coronary, and pulmonary thromboemboli, and in-situ arterial thrombosis have occurred, especially with *Bothrops lanceolatus* and *Bothrops caribbaeus* (Beer and Musiani, 1998; Numeric et al., 2002; Thomas et al., 1995). Alternatively, hypoperfusion from our patient's shock state may have contributed to the intestinal ischemia; however, ischemic colitis most commonly occurs in a watershed distribution in the left colon, whereas right-sided ischemic colitis, as seen in this patient, is more commonly associated with superior mesenteric artery occlusion (Longstreth and Hye, 2015).

The role of thromboelastography in directing antivenom and blood