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Thrombotic Microangiopathy Following Arabian Saw-Scaled Viper (*Echis coloratus*) Bite: Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 50-year-old
Final Diagnosis: Snake bite induce thromotic microangiopathy
Symptoms: Coagulopathy • hemolysis • renal failure • snake bite • thrombocytopenia
Medication: —
Clinical Procedure: Plasma exchange
Specialty: Hematology

Objective: Unusual clinical course

Background: Consumption coagulopathy post envenomation is one the most common complications after a snakebite. It occurs secondary to activation of a coagulation cascade by snake venom and could be followed by a syndrome consistent with thrombotic microangiopathy. The efficacy of plasma exchange for the treatment of thrombotic microangiopathy post envenomation is a matter of debate.

Case report: We reported the case of a 50-year-old male who had Arabian saw-scaled viper envenomation. He developed venom induced coagulopathy that improved within 24 hours of antivenom therapy. He subsequently developed micro-angiopathic hemolytic anemia, thrombocytopenia, and renal failure that was consistent with thrombotic microangiopathy. The patient was treated by plasma exchange and hemodialysis. He made a full recovery and was discharged after 4 weeks.

Conclusions: This case report supports plasmapheresis as an option for management of a patient who develops thrombotic microangiopathy secondary to snake bite, especially those who do not improve with antivenom and supportive therapy.

MeSH Keywords: Acute Kidney Injury • Disseminated Intravascular Coagulation • Plasmapheresis • Renal Dialysis • Snake Bites • Thrombotic Microangiopathies

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Background

Snakes produce some of the most lethal poisons in the world. It is estimated that more than 5 million people are affected by snakebites annually, resulting in more than 100 000 deaths [1]. The Arabian saw-scaled viper (*Echis coloratus*) is a venomous snake that belongs to the family Viperidae. It is a relatively small snake with a maximum length of 80 cm. This snake is abundant in parts of Sub-Saharan Africa, the Middle East, and vast regions of Asia [2]. In Jordan, it is found in the Jordan Valley, Wadi Araba, Petra, and Wadi Rum. It is a nocturnal animal that is active at night and in the early morning [3]. The family Viperidae is the most common genus that causes snakebite deaths worldwide. The mortality rate post envenomation exceeds 20%, even with supportive treatment and antivenom therapy [4]. There are no accurate statistics on the bite rate and mortality rate of this snake due to poor documentation in the developing countries where this snake lives. One of the most common and clinically significant complications of snakebites is venom-induced consumption coagulopathy (VICC). It occurs secondary to the activation of a coagulation cascade by procoagulant toxins in snake venom, which leads to a severe coagulation factor deficiency that ultimately causes hemorrhage [5]. VICC is linked to disseminated intravascular coagulopathy (DIC) because of elevated D-dimer levels, the prolongation of prothrombin time (PT), and low or undetectable fibrinogen levels. The rapidity of onset and the resolution of disarranged coagulopathy that typically lasts for 48 hours, as well as the absence of systemic microthrombi and end-organ damage in VICC, makes it a separate entity from DIC [6]. Thrombotic microangiopathy (TMA) is a clinical syndrome characterized by microangiopathic hemolytic anemia, acute renal failure, and thrombocytopenia. It has been reported in patients with VICC. Usually, it occurs after the resolution of VICC, or it may overlap it. The overlap between TMA and VICC is likely the reason for the mistaken idea that snake bites cause DIC [7]. We reported a case of TMA after Arabian saw-scaled viper envenomation. The patient experienced both laboratory and clinical improvement after undergoing hemodialysis and plasmapheresis.

Case Report

A 50-year-old male patient presented to his local hospital a few minutes after a saw-scaled viper bit the tip of his right index finger. The dead snake was identified as a saw-scaled viper (Figure 1). On admission, the patient complained of pain and swelling at the bite site. Upon examination, he had stable vital signs: his blood pressure was 135/80 mmHg, his pulse was 98 beats per minute and a systems examination was unremarkable. A 20-minute whole blood clotting test (WBCT20) was not done. Investigation revealed an elevated white blood cell count (WBC) of 13×10^3/μL with 64% neutrophils, hemoglobin (Hb) level of 15 g/dL, platelet count of 157×10^3/μL, an elevated PT of 21.5 seconds, international normalized ratio (INR) 1.7, normal activated partial thromboplastin time (APTT), normal creatinine level (0.80 mg/dL), and a slightly elevated total bilirubin level (1.92 mg/dL). He was admitted to the hospital, and treatment was started with the intravenous administration of 3 vials of 10 mL snake antivenom (lyophilized, polyvalent, enzyme-refined, equine immunoglobulin). Three hours after admission, he started to vomit blood and hematuria. Repeated laboratory investigations showed a rising PT >60 seconds and INR >6, a drop in Hb to 9.8 g/dL and platelets 104×10^3/μL, and a normal creatinine level at 0.91 mg/dL. His total bilirubin was elevated at 3.92 mg/dL (normal, 0.2–1 mg/dL). A diagnosis of VICC was made. Then, supportive treatment was administered with 3 packs of fresh frozen plasma (FFP) and 1 unit of packed red blood cells (pRBC). The coagulation profile improved back to a normal range within 24 hours. Thereafter (day 3 after the snakebite), the patient developed acute renal failure (creatinine 3.7 mg/dL), thrombocytopenia (platelet count 56×10^3/μL), and a drop in Hb level to 8 g/dL). PT was 15 seconds, INR was 1.4, T. bilirubin was 7.9 mg/dL, lactate dehydrogenase was (LDH) 23 510 U/L (normal, 140–280 U/L). He was referred to King Hussein Medical Center, which is a tertiary hospital in Amman, Jordan. The patient's general condition was stable with no neurological or respiratory compromise. On examination, he was jaundiced and had a swollen right hand extending from the index finger (the site of the bite) to the elbow. The laboratory results were: Hb 7.7 g/dL, platelets 32×10^3/μL, WBC 9.7×10^3/μL, creatinine 4 mg/dL, INR 1.4, total bilirubin 9.2 mg/dL, LDH 3110 U/L. His blood film showed normochromic normocytic anemia, marked thrombocytopenia, and many schistocytes, which suggested microangiopathic hemolytic anemia. As the patient developed acute renal failure, thrombocytopenia and intravascular hemolysis with a normal clotting profile, the diagnosis of TMA was made. He was then treated with 3 additional vials of antivenom. Nephrologists were consulted and hemodialysis was started. After reviewing similar cases published in medical journals, we decided to start plasma exchange. The treatment plan was plasmapheresis alternating with hemodialysis until the complete recovery

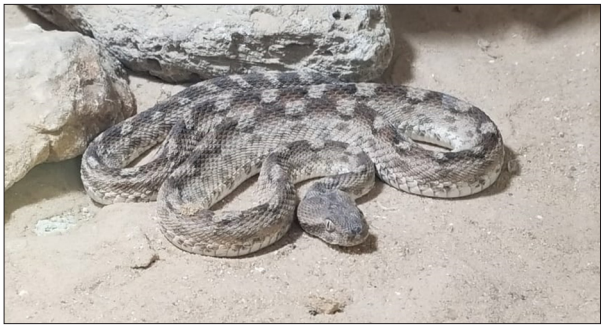

Figure 1. Arabian saw-scaled viper.

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Table 1. Detailed laboratory results during patient stay at King Hussein Medical Center.

Investigation	Reference range	D1	D2	D3	D4	D5	D6	D7	D14	D21	D28
WBC (10^3/μL)	4–11	9.7	8.7	8.6	8.8	9.5	9.2	9.2	8.7	7.5	7.6
Platelets (10^3/μL)	140–450	32	25	30	60	95	120	129	190	214	215
Hb (g/dL)	11–16	7.7	6.5	8.5	8.8	7.5	6.5	9.5	8.5	10.1	11
PCV (%)	37–54	23	20	25	26	22	20	30	25	33	34
PT (s)	10–15	14	13					12	13	11	13
INR	1.0–1.4	1.4	1.3					1.2	1.2	1.0	1.0
APTT (s)	25–30	28	27					25	24	23	25
Creatinine (mg/dL)	0.4–1.4	4	5	5.5	7.5	8.5	7.5	8.7	9.4	5.5	1.5
SGOT (AST) (U/L)	0–35	19	21					23	25	26	
SGPT (ALT) (U/L)	0–45	21	23					24	28	23	
T. bilirubin (mg/dL)	0.1–1.2	9.2	11.2	14.7	13.5	9.2	5.7	3.7	1.6	1.2	1.2
D. bilirubin (mg/dL)	<0.3	0.2	0.4								
LDH (U/L)	140–280	3110	3560	4215	4158	3982	3254	2785	950	325	199
Blood Film		MAHA	MAHA	MAHA	MAHA	MAHA	MAHA	MAHA	NR	NR	NR

D – day after admission; WBC – white blood cells; Hb – hemoglobin; PCV – packed cell volume; SGOT – serum glutamic-oxaloacetic transaminase; AST – aspartate aminotransferase; SGPT – serum glutamic-pyruvic transaminase; ALT – alanine aminotransferase; T. bilirubin – total bilirubin; D. bilirubin – direct bilirubin; LDH – lactate dehydrogenase; MAHA – microangiopathic hemolytic anemia; NR – normal.

of kidney function and the platelet count. The patient underwent 5 cycles of plasmapheresis and 6 cycles of hemodialysis. His kidney function gradually recovered, and repeated laboratory tests revealed no evidence of hemolysis. A follow-up blood film showed no evidence of schistocytes. He made a full recovery and was discharged after 4 weeks. At his last outpatient follow-up appointment, he had no residual renal impairment and showed a normal blood film and blood count. Detailed laboratory results during patient admission at King Hussein Medical Center are shown in Table 1.

Discussion

Our patient developed VICC that settled within 24 hours with supportive and antivenom treatment. The WBCT not done in this case because the patient had elevated PT and INR so emergency administration of antivenom was mandatory.Then he subsequently developed TMA, which was characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. TMA is caused by disseminated microthrombi composed of agglutinated platelets, which results in the occlusion of small arteries, arterioles, and capillaries. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are the 2 main subcategories of TMA. TTP is characterized by the pentad of fever, thrombocytopenia, hemolytic anemia, renal dysfunction, and neurologic dysfunction [6]. The pathogenesis of TTP is thought to be from either a congenital or acquired decrease or absence of the enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). This enzyme degrades ultra-large Von Willebrand factor (ULVWF) multimers which are large proteins involved in the clotting of blood; thus, it leads to a decrease in their activity. In turn, this inhibits spontaneous platelet aggregation within blood vessels. HUS is commonly caused by infection with *Escherichia coli*, which produces Shiga-like toxins and mainly affects the kidneys, causing renal failure. It is also associated with diarrhea. Other types of TMA occur secondary to organ transplantation, disseminated malignancy, chemotherapy, antiphospholipid syndrome, sepsis, drugs, and snake envenomation [8]. The pathology of TMA following snake envenomation is still unknown. One explanation is that a toxin (venom) causes an endothelial injury that initiates thrombotic microangiopathy [9]. For diagnosis, the laboratory tests must show anemia

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and thrombocytopenia along with proof of active hemolysis, such as the presence of schistocytes, increased unconjugated bilirubin, an increased reticulocyte count, and increased LDH. PT and PTT will be normal, which differentiates TMA from DIC. Following the diagnosis of TTP, all patients should immediately be started on plasma exchange. It is thought that this procedure removes the autoantibodies against the ADAMTS13 and ULVWF multimers. Plasma exchange in other forms of TMA has no clear benefit, while it is useful for the treatment of atypical HUS associated with alterations of the complement system and drug-induced TMA. On the other hand, it is less helpful in *E. coli*-associated HUS where supportive therapy, including renal dialysis, is required [10]. TMA following a snakebite has been described for many years. Reported cases involve snakes including the hump-nosed viper (*Hypnale hypnale*), lowland viper (*Proatheris superciliaris*), Australian brown snake (genus *Pseudonaja*), coastal taipan snake (*Oxyuranus scutellatus*), rough-scaled snake (*Tropidechis carinatus*), Saharan horned viper (*Cerastes cerastes*), Russell's viper (*Daboia russelii*) and the common tiger snake (*Notechis scutatus*) [11–18]. Persistent renal impairment with thrombocytopenia in the absence of clotting abnormalities should raise the suspicion of TMA, and a blood film to look for evidence of hemolysis should be sought. An early blood film may alert the physician as to whether patients will progress to TMA or not. Plasma exchange has been used in snakebite-associated TMA. It is beneficial in removing venom toxins from the bloodstream to decrease the incidence of further endothelial injury, leading to the normalization of the coagulation cascade and platelet aggregation [19].

In 1990, Kornalik and Vorlova [20] was the first to report the use of plasmapheresis in the management of snakebite envenomation. In the literature, there are many case reports about adding plasmapheresis in the management of thrombotic microangiopathy post envenomation. These reports have documented great responses with minimal side effects of this procedure, which could provide proof of the benefits and safety of adding plasma exchange in the management of these patients [21–24]. But there are still no clinical trials assessing the effectiveness of adding plasma exchange in the management of TMA secondary to snakebite.

Conclusions

We reported the management of a patient who developed classical features of TMA after Arabian saw-scaled viper envenomation. This case management supports that plasmapheresis could be one of the options for management in a patient who develops TMA after a snakebite.

Department and Institution where work was done

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Conflict of interest

None.

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