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Thrombotic Microangiopathy in Snakebite Envenomation

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Introduction

Amongst the various causes of acute kidney Injury (AKI) in patients with snake bite envenomations, thrombotic microangiopathy (TMA) is an entity which may go unrecognized if not looked for. Anemia, thrombocytopenia, renal failure and hemolysis in the peripheral smear identifies the condition. Controversies regarding treatment with therapeutic plasma exchange exists. Early diagnosis and initiation of renal replacement therapy and therapeutic plasma exchange/plasma transfusions in refractory cases can improve the renal outcome.

We present 2 patients with snakebite envenomation who had TMA and were managed with fresh frozen plasma transfusions, without the need for therapeutic plasma exchange.

Case 1

5 yr old kid with history of snake bite was taken to local hospital, given first aid, 15 vials of anti-snake venom (ASV) and referred here for decreased urine output. She had local swelling at the bite site. She was hemodynamically stable at presentation and lab parameters, on arrival at our centre (Day 0), are given in **Table 1**.

One day after admission she was noted to have hypotension, drop in Hemoglobin and platelet counts. The PT and aPTT were within normal range. For hypotension she was managed with intravenous fluid infusions, and she improved within 24 hrs. Her renal functions deteriorated and CPK levels started rising, though she was nonoliguric. Hemodialysis was initiated. Evaluation revealed microangiopathic hemolytic anemia with raised LDH levels and she was managed with

fresh frozen plasma transfusions. She had an impending compartmental syndrome at the bite site, and she underwent fasciotomy. Causes of renal failure in this case were attributable to hypotension and shock, rhabdomyolysis and microangiopathic hemolytic anemia. She recovered. Therapeutic plasma exchange was not done in this patient.

Table 1: Serial Lab parameters, of case 1, from arrival to our center till recovery

	Day 0	DAY 1				DAY 7
Hb (g/dl)	12.3	9.2	7.5	6.2	9.1	
Total WBC counts (cells/cu.mm)	19700	14700	10600	9800	17300	13700
Platelets (10^3 cells/cu.mm)	161	65	95	80	155	117
Blood Urea (mg/dl)	53	61.7	72.5	84	59.2	31.5
Serum Creatinine(mg/dl)	0.68		1.47	1.88	1.82	0.86
Creatine Phosphokinase Total(U/L)	2758	5465	4346	2232	1370	111
Serum glutamic-oxaloacetic transaminase (U/L)	90		147	106		
Serum glutamic-pyruvic transaminase (U/L)	22		71	61		
Lactate Dehydrogenase (U/L)		1101		1348	1165	606
Sodium (mEq/L)		134	137	137	141	134
Potassium (mEq/L)		3.7	3.1	2.8	3	2.6
Chloride (mEq/L)		100.4	100.1	98.1		109
Bicarbonate (mEq/L)		20.1	24.4	34		25
APTT (sec)		21.8	20.6	20.6		22.7
PT (sec)		10.3	10.4			10.8
INR		0.9	0.95			0.9
Urine analysis						
albumin		4+	3+			
ketones		1+				
RBC		NUMEROUS	NUMEROUS			
Pus Cells		5--8	8--10			
Serum albumin(g/dl)			2.6			
Calcium (mg/dl)			7.3			8.3
Phosphorus (mg/dl)			5.8	6.8		2.6
Peripheral smear				Microangiopathic hemolytic anemia		

Case 2

13 yr old female with alleged history of snakebite initially received alternative medicine treatment for 2 days. She developed delirium and was taken to the hospital where she received anti snake venom. She had subconjunctival hemorrhage, local inflammation at the bite site, with stable vitals signs. Evaluation revealed AKI and rhabdomyolysis and she was referred to our centre. She underwent hemodialysis and FFP transfusions. She had microangiopathic hemolytic anemia in the peripheral smear along with deranged coagulation parameters. Lab parameters from the time of arrival to our centre is shown in **Table 2**.

She recovered with renal replacement therapy and plasma transfusions. Therapeutic plasma exchange was not done in this patient.

Table 2: Case 2 Lab parameters during hospitalisation.

	Day 0	DAY 1	Day 5	Day 24
Hb (g/dl)	8.1	7.7	10.5	9.7
Total WBC counts (cells/cu.mm)	19300	13800	8000	4600
Platelets (10^3 cells/cu.mm)	30	45	105	129
Blood Urea (mg/dl)	124	108.2	156	44.1
Serum Creatinine (mg/dl)	3.6	3.6	3.9	2.4
Creatine Phosphokinase (U/L)	17439	11056	288	
Total Bilirubin (mg/dl)	0.57	0.6		
Direct Bilirubin (mg/dl)	0.14	0.17		
Serum glutamic-oxaloacetic transaminase (U/L)	437	307		
Serum glutamic-pyruvic transaminase (U/L)	156	131		
Serum alkaline Phosphatase (U/L)	135			
Total Protein(g/dl)	5.4			
Serum Albumin(g/dl)	2.9			
Lactate Dehydrogenase (U/L)	1078		788	329
Sodium (mEq/L)	136	137		136
Potassium(mEq/L)	4.8	3.9		4.2
CHLORIDE (mEq/L)	102.2			101
BICARB (mEq/L)	19.1			23.4
APTT (Sec)	33	29.1	30.5	29.9
PT(Sec)	16.5	15.6	13.2	13.6
INR	1.54	1.46	1.22	1.26
D dimer (mic.gm/litre)	>10	>10		
Fibrinogen (mg/dl)		654		
Calcium		8.2	9.4	
Phosphorus		5.6		
Peripheral smear		Microangiopathic hemolytic anemia		
Urine routine				
albumin		4+		
ketones		Neg		
RBC (cells/hpf)		numerous		
Pus cells (cells//hpf)		1--2		

Discussion

Acute kidney injury (AKI), a life-threatening systemic effect of snake envenomation commonly happens from the enzymatic toxins, in turn causing systemic bleeding, vascular leakage and renal hypoperfusion, other mechanisms include proteolytic degradation of the glomerular basement membrane by snake venom metalloproteinases (SVMPs), deposition of microthrombi in the kidney microvasculature (thrombotic microangiopathy), direct cytotoxic action of venom, systemic myotoxicity (rhabdomyolysis) and accumulation of large amounts of myoglobin in kidney tubules [1].

Snake venoms have toxins which can act as anti-coagulant toxins which inhibit the clotting cascade, or as pro-coagulant toxins which activate the clotting cascade and consume clotting factors. Venom-Induced Consumption Coagulopathy (VICC) distinct from DIC has been identified because it better describes the clinical features and lack of other features of the DIC. VICC is marked by prolonged

clotting times, prolongation of the PT and aPTT, and clotting factor deficiencies (i.e., hypofibrinogenaemia, low factor V, low factor VIII) and an elevated D- dimer. Low level of protein C can also be observed via coagulation testing. VICC is characterized by bleeding without evident fibrin deposition, microvascular thrombotic obstruction, or non-renal end organ failure and is due to the action of snake toxin in the coagulation pathway, not to the tissue factor/factor VIIa pathway. The extended clotting period in VICC is due to the activation of the coagulation cascade by thrombin like enzymes, prothrombin, and factor X activator in the venom.

Thrombotic microangiopathy (TMA) is seen in a group of individuals who have been bitten by a snake and have either VICC or TMA. Venom or its vascular endothelial toxins act either as von Willebrand factor activators or vascular endothelial growth factor-like factors and cause TMA by causing endothelial damage. VICC has a rapid onset and resolves with neutralization or inactivation of the toxins and synthesis of new clotting factors [2]. The pathological hallmarks of TMA include small vessel micro-thrombosis and endothelial damage.The main risk in TMA is vaso-occlusive organ damage. In TMA following snakebite, the major end organ injury appears to be renal [2].

Antivenom is the mainstay of therapy for snake envenoming and should always be given in this setting. Dialysis is the mainstay of therapy for AKI in snakebite.

According to Noustos, there is no evidence to support a beneficial effect of intervention with therapeutic plasma exchange for renal outcomes in dialysis-dependent AKI complicating snakebite associated TMA. Plasma exchange can be considered in patients who are refractory to traditional ASV treatment. In addition to toxin removal, mediators of inflammatory and coagulopathic pathways produced by snake toxins may be removed [3].

While immune complexes and toxins were removed during plasma exchange, studies showed no difference in timing of renal recovery, anaemia, and platelet count between treatment with or without plasmapheresis [4].

In a 1999 study Small G et al. concluded that renal function needs to be properly evaluated at one year after HUS. Longer term follow-up should generally be limited to individuals having proteinuria, hypertension, abnormal ultrasonography, and/or impaired Glomerular Filtration Rate (GFR) at one year, according to the research [5].

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