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Hemolytic Uremic Syndrome- An unusual complication of snake envenomation

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Abstract :
Snake envenomation is an important and common cause of acute kidney injury (AKI) in India. The incidence of AKI following snake bite in India is 13-32 percent. It accounts for 1,50,000 deaths every year all over the world. AKI can occur following bites from snakes belonging to Elapidae, Viperidae and Colubridae families, due to multiple mechanisms such as hemodynamic disturbances, direct tubular toxicity, coagulopathy, hemoglobinuria and myoglobinuria. Hemolytic Uremic Syndrome (HUS) is an unusual cause of AKI following snake envenomation. We are reporting case series of two patients who developed HUS following snake envenomation and improved after treatment with therapeutic plasma exchange (TPE). HUS complicating snake bite has been reported earlier but those patients were not offered therapeutic plasma exchange.

Keyword :

HUS-Hemolytic Uremic Syndrome, AKI-Acute Kidney Injury, TPE- Therapeutic Plasma Exchange.

Introduction:
Snake envenomation is an important and common cause of Acute Kidney Injury (AKI) in tropical countries like India. There are more than 3million snake bites per year with more than 1,50,000 deaths all over the world[1]. Of 2700 species of the snakes, only 450 are recognized as poisonous due to presence of the front fangs. In rural India, snake envenomation is an occupational hazard with most of the bites occurring in farms while working barefoot or while walking in the fields during night time. There are four families of poisonous snakes: Elapidae, Viperidae, Hydrophidae, and Colubridae. Most often clinical effects of venom of elapids are neurotoxic whereas that of vipers are vasculotoxic and hydrophids or sea snakes are myotoxic. Colubrids have back fangs and are usually harmless but can cause fatal envenomation sometimes. In India viper bites are most common and incidence of AKI following Russell'sviper and E.carinatus bites is 13-32% [2,3]. AKI is one of the manifestations of snake envenomation and it occurs by numerous mechanisms such as hemodynamic disturbances, direct tubular toxicity,

hemoglobinuria, myoglobinuria, coagulopathy and thrombotic microangiopathy. Hemolytic Uremic Syndrome (HUS) is an unusual cause of AKI in snake envenomation. Here we are reporting case series of two patients with HUS following snake envenomation that are successfully treated with plasma exchange.

Case-1:

A 30 years old housewife, premorbidly well, not a hypertensive or diabetic, presented with history of bite by an unidentified snake, on left foot following which she developed swelling of the feet, bleeding per vagina and decrease in urine output followed by fever, facial puffiness and dyspnea. She was taken to primary health center next day and was treated with polyvalent anti-snake venom (ASV), tetanus toxoid and antibiotics. She was given a total of 12 vials of ASV over four days. On the seventh day after the bite, she was referred to our tertiary care referral center in view of renal dysfunction. She was hospitalized in medical intensive care unit. On examination she had tachycardia, blood pressure of 150/100mm Hg and respiratory rate of 22/min. Fang marks were seen on left foot with minimal swelling.She was pale, edematous and jugular venous pressure was elevated. Her investigation reports are given in table no.1. She was diagnosed to have acute kidney injury AKIN Stage-3 and was found to have evidence of thrombotic microangiopathy (TMA). She did not have clinical or laboratory features of sepsis. Her blood and urine cultures were sterile. The coagulation tests such as prothrombin time (PT) & activated partial thromboplastin time (aPTT) were normal. In view of evident microangiopathic hemolysis with thrombocytopenia and normal coagulation profile associated with acute kidney injury, a diagnosis of snake bite induced HUS was entertained. A renal biopsy to confirm HUS could not be performed in view of thrombocytopenia and the fact that platelet transfusions may be harmful in patients with possible HUS. She was treated with four sessions of therapeutic plasma exchange along with dialysis. Plasma exchange was given daily with removal of 2000ml of plasma with each session and replacement fluid was 1000ml fresh frozen plasma with 500ml of 5% Human Albumin and 500ml normal saline. She also required one unit of packed red cell transfusion for the anemia. Subsequent to these interventions, her urine output and renal function improved along with recovery of platelet count. She had renal function with creatinine of 1.0mg/dl and complete recovery of thrombocytopenia at discharge.

Case-2:

A 49years old gentleman, plumber by occupation, was bitten by an unidentified snake on his right foot while working. He was hospitalized at our tertiary care referral hospital within 2 hours of bite and on examination was found to have swelling of the right leg and bilateral ptosis. He had stable vital parameters. There was no weakness in any of the extremities and no respiratory muscle weakness (single breath count was 35). He was treated with a total of 12 vials of polyvalent anti-snake venom (ASV) over 72 hours with which his ptosis improved. He had normal renal function with creatinine of 1.1mg/dl on admission but during his hospital stay he developed oliguria and AKI, AKIN stage-3, with rise in creatinine to 7.8mg/dl. He also found to have drop in Hb from 15.9gm% to 11.5gm% with thrombocytopenia with platelet count of 46,000cells/cumm. His PT and aPTT were within normal limits throughout this time period. His peripheral blood smear showed 2-4 schistocytes per high power

field. Blood and urine cultures were sterile, there was no hypotension or use of nephrotoxic drugs. So considering HUS, he was treated with therapeutic plasma exchange and hemodialysis. He received three sessions of plasma exchange with removal of 2500ml of plasma with each session and was replaced with 1250ml of fresh frozen plasma, 500ml of 5% Human Albumin and 750ml of normal saline. Following this treatment he improved in terms of urine output, platelet count and renal function. By 20 days after admission his renal function recovered near completely with creatinine of 1.4mg/dl.

Discussion:

Acute kidney injury following snake envenomation can occur due to multiple mechanisms. Hypotension and circulatory collapse occurs due to numerous mechanisms such as vasodilatation, increased capillary permeability, bleeding due to coagulation abnormalities and myocardial depression,ultimately culminating into ischemic AKI[4]. AKI can occur due to myoglobinuria due to myotoxins and hemoglobinuria resulting from intravascular hemolysis due to phospholipase A2 and direct lytic factor (found only in elapid venom), present in snake

Table-1: Lab investigation of two patients:

Lab Investigations	Case-1			Case-2		
	At admission	At time of TPE	At discharge	At admission	At time of TPE	At discharge
Creatinine (mg %)	9.3	11.2	1.0	1.1	7.8	1.4
Urea (mg %)	212	285	20.0	15	134	20
Hb (g/dl)	8.5	7.9	12.2	15.9	11.7	9.5
Platelet count (cells/cumm)	61,000	36,000	2,71,000	1,13,000	46,000	3,17,000
Schistocytes on peripheral smear (cells/hpf)	2-3	6-8	Nil	Nil	2-4	Nil
LDH	839	3948	650	407	1701	627
PT/INR (Normal range- 9.5-12.7)	10.1/0.94	12.3/1.12	12.2/1.11	11.9/1.08	12.1/1.10	12.3/1.12
aPTT (Normal range- 26.6-40.2)	20.1	24.0	28.0	27.0	26.0	26.3
Culture if any	No growth			No growth		

venom[3,5].Renal injury can also be induced directly by the action of toxin enzymes, especially phospholipases and metalloproteases[6]. A number of proinflammatory cytokines and mediators such as tumor necrotic factor (TNF), interleukins 1,6,10, interferon- and nitric oxide are released following exposure to toxin enzymes[7,8]. HUS has been described as a complication of snake envenomation. There are very few case reports of HUS following snake bite. Anand Date et al.[9] had reported case series of 22 patients having HUS after snake envenomation and HUS like features were also described in some of the 45 patients with acute kidney injury following snake bite in Northern India[3]. Stéphane M.et al had reported autopsy finding of thrombotic microangiopathy leading to multiple cerebral, myocardial and mesenteric infarction in a patient who succumbed to pit viper envenomation and had features suggestive of HUS[10].HUS is characterized by presence of thrombocytopenia, microangiopathic hemolytic anemia with normal prothrombin time and activated partial thromboplastin time and renal dysfunction. Microangiopathic hemolytic anemia is suggested by drop in hemoglobin, high lactate dehydrogenase (LDH), reduced serum haptoglobin levels, indirect hyperbilirubinemia and presence of schistocytes in peripheral blood smear. Microangiopathic hemolytic anemia is also seen in other conditions such as disseminated intravascular coagulation (DIC), malignant hypertension, scleroderma renal crisis, preeclampsia etc. Different causes of HUS are listed in table-2. The diagnosis of HUS is mainly indirect as there are no definite tests to prove and renal biopsy is not always feasible due to presence of thrombocytopenia. In addition, platelet transfusions could be potentially harmful in patients with HUS.

Table-2: Causes of HUS:

Infections:
E.coli (O157:H7)
Shigella dysentery
Streptococcus pneumoniae
HIV
Drugs:
• Anti-cancer drugs- Mitomycin-C, Vinblastin, Cisplatin, Bleomycin, Daunorubicin, Cytosine arabinoside
• Antiplatelets- Ticlopidine, Clopidogrel
• Immunosuppressants- Cyclosporin, Tacrolimus, OKT3 antibodies, Interferon
• Quinine
• Oral contraceptives
Complement abnormalities:
• Factor H deficiency- genetic or immune mediated
• Membrane cofactor protein deficiency
ADAMTS 13 abnormality:
• Genetically determined (Upshaw Schulman syndrome)
• Immune mediated
Malignancy:
• CA stomach
Pregnancy:
• Pregnancy associated TTP
• Post-partal HUS
Associations:
• Systemic lupus erythematosus
• Scleroderma
• Vasculitis
• Malignant hypertension
Idiopathic

Figure 1a— Trend of creatinine and platelet count in Case 1

Figure 1b: Trend of creatinine and platelet count in case—2

Both of our patients had evidence of thrombotic microangiopathy in the absence of disseminated intravascular coagulation (DIC) as PT & aPTT were within normal limits, malignant hypertension and without any use of drugs known to cause HUS. Table-1 gives blood investigations of both patients. We could not do the renal biopsy in any of our patients due to thrombotcytopenia. There was no hypotension, rhabdomyolysis or clinical and laboratory evidence of sepsis in both of our patients. So the diagnosis of AKI secondary to snake envenomation induced HUS was made. We treated both our patients with therapeutic plasma exchange and supported with hemodialysis. Figure 1a & 1b shows trend in creatinine and platelet count of both patients. Following treatment there was near complete recovery of renal function in both of our patients. One of the major determinants of prognosis of renal failure is the nature of underlying lesion. Acute cortical necrosis was shown in 27% of the patients of snake bite in a study from North India and it was associated with fatal outcome in 80% of snake bite patients[3]. Surviving patients with patchy cortical necrosis progress to end stage renal failure over several months or years. HUS causing microangiopthy is one of the known mechanisms to produce cortical necrosis. So the presence of HUS in snake envenomation should be sought as timely intervention in the form of therapeutic plasma exchange can aid in recovery of renal function as well as increase the survival probability. Although snake envenomation induced HUS has been described in literature, to the best of our knowledge, there is only one reported case of HUS following taipan snake envenomation treated with therapeutic plasma exchange but without any renal recovery[11].

Conclusion:

Snake bite is an important cause of AKI in tropical countries. Among the numerous mechanisms by which snake envenomation can cause AKI, development of HUS is one of them, although uncommon. Snake envenomation induced HUS responds well to treatment with therapeutic plasma exchange. So there should be high index of suspicion to diagnose HUS in this setting.

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