Case Reports

A case of systemic envenomation by hump-nosed viper associated with coagulopathy, haemolytic uraemic syndrome and acute hepatic injury

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Introduction

Hump-nosed viper (HNV) bite usually causes a severe local reaction at the bite site. However, it can rarely lead to significant systemic envenomation in the form of coagulopathy, microangiopathic haemolysis and acute kidney injury with associated significant morbidity and even mortality[1]. We report an unusual case of an envenomed child presenting with coagulopathy, haemolytic uraemic syndrome (HUS) and acute hepatic injury, which has never been reported in the medical literature.

Case report

An 8-year–old previously healthy girl from the rural dry zone in Sri Lanka presented to the local hospital immediately following a snake bite on her left foot. The patient had pain and swelling over the bitten area. The snake was killed and brought in and it was identified by the healthcare staff as a HNV. On examination, she had swelling on the dorsum of the left foot with two fang marks on the lateral malleolus, but no evidence to suggest tissue necrosis. Her initial investigations done at the local hospital revealed coagulopathy, as evident by the delayed 20-minute whole blood clotting test (20min WBCT) and deranged clotting profile. She was transfused with fresh frozen plasma (FFP) 15ml/kg to reverse the coagulopathy.

The following day, she was transferred to the Nephrology Unit, Teaching Hospital, Peradeniya, as she became oliguric for 6 hours. On arrival in our unit, she was fully conscious and oriented. She had some facial puffiness and a high blood pressure at the 99th percentile. During the ward stay, she continued to be oliguric and hypertensive. She had no active bleeding or icterus. She was persistently afebrile and neurologically normal.

There was a rapidly rising serum creatinine (S Cr) and blood urea (BU). The platelet count which was initially 131,000/µl started to drop drastically during next few days. Blood film showed fragmented red cells consistent with the features of microangiopathic haemolytic anaemia (MAHA). The haemolytic screening was positive; lactate dehydrogenase (LDH) was 1431 IU/L (normal range 230-460), reticulocyte count was 9.8% (normal <1.5%) and unconjugated bilirubin was 67µmol/l (normal range 0-17). The direct and indirect Coombs tests were negative. The features of microangiopathy persisted for over 2 weeks.

The clotting parameters were altered from the outset but rapidly normalised by day 4; prothrombin time (PT) was 29 seconds (normal 9-13 seconds), international normalized ratio (INR) was >10 and activated partial thromboplastin time (APTT) was 69 seconds (normal 24-36). She was also noted to have significantly elevated liver enzymes by the 3rd day of the event. A summary of the laboratory investigations is shown in Table 1.

The patient developed 2 short lasting seizures on day 19 despite normal biochemical markers. Her blood pressure was also normal at the time and no neurological deficit was noted post-ictally. A non-contrast computerized tomography (CT) scan of the brain was performed and it revealed a symmetrical vasogenic white matter oedema in the para-median parietal lobes and evidence of subtle intra-cortical haemorrhage or cortical necrosis.

Acute peritoneal dialysis (PD) was initiated from the first day of admission and this was converted to haemodialysis one week later due to a non-functioning PD catheter. She continued to be afebrile and neurologically normal aside from the two seizures. As the overall picture was suggestive of haemolytic uraemic syndrome (HUS), she was started on therapeutic plasma exchange (TPE) with fresh frozen plasma (FFP) from day 3 onwards and she completed 7 sessions. She had a sustained

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improvement in platelet count from the third TPE onwards but microangiopathic haemolytic anaemia (MAHA) continued for 2 weeks. A course of N-acetylcysteine was given to treat the acute hepatic injury along with supportive management. The patient made a full recovery and was discharged on day 32, but she required a minimum dose of anti-hypertensive drugs for 3 months.

Table 1: Summary of investigations

Investigation	Reference range	D1	D3 1st TPE	D4	D5 2ND TPE	D8 3rd TPE	D13 5TH TPE	D17 7TH TPE	D32 On discharge
White blood cell count (×10³ µl)	4-12	19.8	18	12.1	18.7	16	10	10.8	9.8
Haemoglobin (g/dl)	11.5-14.5	10.4	8.6	8.0	7.6	7.9	7.5	9.2	12.3
Platelet count (×10³ µl)	150-400	131	101	89	74	89	112	148	267
Prothrombin time (s)	9-13	29	32	15				14	
International normalized ratio	0.8-1.1	3.5	3.9	1.1				0.9	
Activated partial thromboplastin time (s)	24-36	>60	>60	28		27		25	
Serum Creatinine (µmol/l)	20-52	221	310	287	291	176	161	101	61
Aspartate transaminase (u/l)	10-40		1846	433	156		78		34
Alanine transaminase (u/l)	10-40		778	221	123		61		22
Indirect bilirubin (µmol/l)	3.4-12								
Lactic dehydrogenase (IU/l)	230-460		1431		1341	834			
Blood picture (µmol/l)		MAHA	MAHA		MAHA		No haemolysis	No haemolysis	

MAHA: microangiopathic haemolytic anaemia

Discussion

Hump-nose pit vipers of the genus *Hypnale* are the commonest cause of venomous snakebites in Sri Lanka[2]. The taxonomic classification recently introduced 3 species of Hypnale: H hypnale, H zara and H nepa and their bites usually resulted in features of local envenomation such as pain, swelling and blistering of the bitten site[3]. The possible effects of systemic envenomation are coagulopathy, acute and chronic kidney injury, thrombotic microangiopathy, myocardial infarction, ischaemic stroke and even death[1,3,4]. Recent studies demonstrate that 20% of cases were reported to have acute kidney injury due to systemic envenoming[1] with glomerulosclerosis the commonest finding on renal histology[5]. Another study conducted in 2008 revealed that about 40% had coagulopathy (delayed 20min WBCT) following HNV bite[4].

H. hypnale venom contains strong procoagulants like phospholipase A2, hyaluronidase, L-amino acid oxidase, thrombin-like enzymes, arginine esterase and various proteases[6]. Vascular occlusion is caused by the micro-thrombi and fibrin deposits in the vasculature due to the activation of intrinsic and common pathway of the clotting cascade by these substances[6]. *H hypnale* is now considered to be highly venomous requiring antivenom administration; however, the currently available polyspecific antivenom is not effective here as it does not contain hump-nosed viper antivenom.

Coagulopathy associated with snake venom, including HNV, is often due to venom induced consumptive coagulopathy (VICC)[1]. Rapid onset coagulopathy with deranged clotting profile and occasional thrombocytopenia are characteristically seen in VICC[7]. It tends to reverse within 24 to 48 hours[7]. It is not associated with micro-thrombi and end organ damage[7,8]. The occurrence of VICC and end organ damage are therefore likely to be mutually exclusive and have different pathophysiological mechanisms. They however can co-exist in the same patient[8]. Our patient had both coagulopathy and end organ damage (liver and renal failure) but the coagulopathy was reversed by day 4, while renal impairment persisted well into the 3rd week following envenomation.

The exact aetiology for end organ damage, which is renal failure in most occasions, is not clearly identified[8]. Venom induced thrombotic microangiopathy (TMA) is thought to be one of the mechanisms for this[8,9]. TMA includes the clinical spectrum of haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) and denotes the triad of thrombocytopenia, microangiopathic haemolytic anaemia and acute renal failure. When VICC and TMA coexist in the same patient, VICC precedes TMA in most instances[7]. This pattern was seen in our patient as well. It is thought that the pathology is driven by the same toxin[7], with micro-thrombi formation blocking the vessels causing ischaemia and organ failure[3,8]. During this process, platelet aggregation occurs causing thrombocytopenia[3]. Red cells are damaged as they traverse through these vessels resulting in intravascular haemolysis[3,8]. Direct nephrotoxicity caused by proximal tubular cell damage and acute tubular necrosis have also been suggested as a mechanism for acute kidney injury following HNV envenomation[10].

In our patient, the diagnosis of HUS is favoured since the renal impairment was more prominent while in TTP, neurological involvement predominates. It could be suggested that VICC alone could explain the deranged haematological parameters in our patient, but the persistent thrombocytopenia accompanied by haemolytic anaemia and acute renal impairment, well beyond the resolution of the coagulopathy (>2 weeks vs 4 days), favours the diagnosis of TMA and HUS. The fact that the resolution of renal impairment

coincided with the resolution of thrombocytopenia further substantiates this.

Hump-nosed viper bite related hepatic injury is not described in the literature. In our opinion, the acute hepatic injury seen in this case was probably due to microangiopathic changes in the hepatic vessels and subsequent ischaemia. Similar hepatic injury is known to occur in HUS. Hump-nosed viper induced direct neurotoxicity or effects on the neuromuscular junction are again not described apart from a case report of ischaemic stroke due to the potent pro-coagulant induced vaso-occlusive crisis[7]. HUS related neurological changes are typically seen in basal ganglia[11]. White matter changes including infarction or haemorrhage are also described[11]. Our patient's CT findings were compatible with these, and therefore would most likely be explained by the HUS.

Treatment of HNV envenomation is primarily supportive. Acute renal impairment requires renal replacement therapy which may need to be continued if chronic renal failure ensues. Haematological derangements are optimized by correcting the coagulopathy and plasma exchange[1,3]. However, there is no clinical trial based evidence confirming their effectiveness.

This case report draws further attention to HNV associated TMA and HUS which can be treated effectively with early institution of TPE. The acute hepatic injury, which we believe was due to the TMA, is also an unusual finding which clinicians should be alert to, in patients presenting with HNV envenomation.

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