Snakebite Envenoming by Sochurek's Saw-scaled Viper *Echis Carinatus Sochureki*

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Abstract: A snake breeder, 47-years-old man, was bitten by the saw-scaled viper (*Echis carinatus sochureki*). After admission to Toxinology Centre, within 1.5 h, laboratory evaluation showed clotting times prolonged to non-measurable values, afibrinogenaemia, significantly elevated D-dimers, haemolysis and myoglobin elevation. Currently unavailable antivenom was urgently imported and administered within 10 hours. In 24 hours, oligoanuric acute kidney injury (AKI) and mild acute respiratory distress syndrome (ARDS) developed. Despite administration of 10 vials of urgently imported Polyvalent Snake Antivenom Saudi Arabia, the venom-induced consumption coagulopathy (VICC) and AKI persisted. Another ten vials of antivenom were imported from abroad. VICC slowly subsided during the antivenom treatment and disappeared after administration of total 20 vials during 5 day period. No signs of haemorrhage were present during treatment. After resolving VICC, patient was transferred to Department of Nephrology for persisting AKI and requirement for haemodialysis. AKI completely resolved after 20 days. Despite rather timed administration of appropriate antivenom, VICC and AKI developed and the quantity of 20 vials was needed to cease acute symptoms of systemic envenoming. The course illustrates low immunogenicity of the venom haemocoagulation components and thus higher requirements of the antivenom in similar cases.

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Introduction

Saw-scaled or carpet vipers *Echis* sp. native in North Africa, Middle East and Central Asia (including India) are responsible for major part of snakebite morbidity and mortality in the places of occurrence (Warrell et al., 1977; Warrrell, 1995a, b). Sochurek's saw-scale viper *E. carinatus sochureki* (Figure 1) native in Arabian Peninsula, Iran, Afghanistan, Pakistan and India belongs to most venomous species of the genus. Saw-scale vipers are also rather popular among holders.

The main acting compounds of saw-scale venoms are toxic enzymes and toxins affecting haemocoagulation. Ecarin is one of the most clinically important components and it is direct activator of prothrombin to izoenzym meizothrombin, which is not inactivated by antithrombin-heparin complex and causes explosive thrombin activation (Gillissen et al., 1994; Lu et al., 2005). In contrary to disseminated intravascular coagulation (DIC), antithrombin, at least in the initial phase, remains intact or can be even elevated (Mba and Onyemelukwe, 1989). The uncontrolled thrombin generation produces fibrin formations, which are destructed by plasmin into large quantity of fibrin degradation products (FDP, D-dimer). Direct fibrino(geno)lytic enzymes also play some role in subsequent afibrinogenemia. The result is the consumption disorder – venom-induced consumption coagulopathy (VICC) (White, 2005; Brown et al., 2009).

Other venom components are desintegrins that inhibit the platelet (PLT) aggregation. Such activity can manifest inadequate participation of PLT in the consumptive coagulopathy (Warrell et al., 1977; Okuda et al., 2001). However, this does not eliminate the possibility of increased PLT agreggability by the other components and/or PLT consumption in fibrin formations.

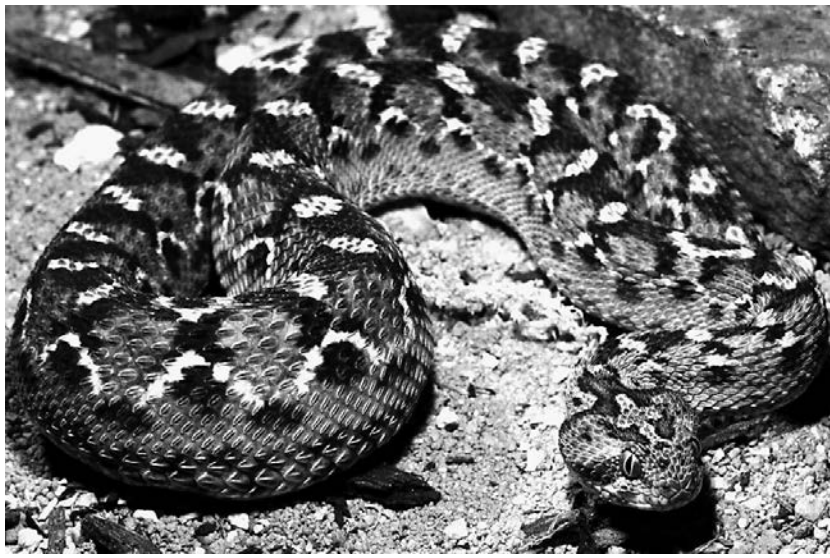

Figure 1 – Echis carinatus sochureki *(photo V. T. Jirousek).*

The venom of the *Echis* snakes, as the majority of vipers, contains haemorrhagins, which activate and disintegrate endothelium and its junctions, thus aggravating prothrombotic activation (White, 2005). In addition, there is a range of cytotoxic and destructive proteolytic enzymes causing local damage, including formation of necrosis (Annobil, 1993; Warrell, 1995a, b).

Clinical result of venom impact is then afibrinogenemia with possible haemorrhage and interstitial oedema with organ (i.e. respiratory) failure. Frequent AKI (acute kidney injury) results from multifactor action of above mentioned venom components (Merchant et al., 1989; Annobil, 1993; Top et al., 2006).

Case report

A snake breeder, 47-years-old man, was bitten into the thumb of left hand by the saw-scaled viper (*Echis pyramidum sochureki*). He attended a local hospital and subsequently was transported to Toxinology Centre of General University Hospital in Prague.

After admission, initial oedema of the thumb extended to the level of wrist. No other clinical signs of systemic envenoming were present. The laboratory examination, performed 1.5 hours after the bite, showed immeasurable values of clotting times, afibrinogenaemia, large quantity of fibrin degradation products, D-dimer, haemolysis, and myoglobin elevation up to 404 μg/l. Other laboratory results did not exceed the normal values. Count of platelets (PLT) decreased in 4 hours to 22.10^9/l (Table 1). Regarding these findings, which reflected serious systemic envenoming with venom-induced consumption coagulopathy (VICC), antivenom therapy was indicated. Because the adequate antivenom was unavailable at that moment, 10 vials of Polyvalent Snake Antivenom (Equine) Saudi Arabia was urgently ordered and transported from foreign Toxicology Centre. Fresh frozen plasma in quantity of 20 ml/kg was administered until antivenom became available to prevent development of potential serious haemorrhage. Simultaneously, crystalloid volume replacement therapy and furosemide IV was used for imminent acute kidney injury (AKI). Within 10 hours after the bite, three vials of antivenom were administered with no effect on coagulation parameters. Subsequently, another seven vials were used during that day. Following in total 10 vials of antivenom, the clotting times started to be measurable (Table 1). Despite this treatment, in 24 four hours oligoanuric AKI developed and ultrasound-guided central venous catheter for renal replacement therapy (RRT) had to be inserted. Continuous veno-venous haemodiafiltration (CVVHDF) with regional citrate anticoagulation was used. In the same time, mild respiratory failure with O_2 dependency developed. Chest X-ray showed a mild acute respiratory distress syndrome and echocardiographic examination excluded any cardiac failure. Ongoing hypoxemia required non-invasive ventilation support. In subsequent laboratory examination 24 hours after the bite, clotting times were found immeasurable again. Another ten vials of antivenom were ordered and the 2nd day five more vials were administered with positive effect in

Table 1 – Values of selected laboratory haemocoagulation parameters and antivenom administration

Day after bite	0	1					2			3	
Hours after bite	1.5	10	14	17	20	22	35	46	52		
Antivenom (vials)		3	2	2	3		3	2			
INR	>10	>10	>10	>10	>10	3.2	>10	3.23	2.09	2.39	1.40
APTT (s)	>180	>180	>180	>180	>180	149	>180	60.80	53.90	57.50	44.70
TT (s)	>180	>180	>180	>180	>180	93.7	>180	50.20	48.60	56.50	35.70
FBG (g/l)	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.10	0.19	0.12	0.21
AT (%)	97	81	74	70	64	63	77	66	68	68	76
D-dimer (μg/l)	>6400	>6400	>6400	>6400	>6400	>6400	>6400	>6400	>6400	>6400	>6400
PLT (10^9/l)	202	27	67	96	n/a	93	39	63	50	37	35

Day after bite	4		5		6	8	10	12
Hours after bite								
Antivenom (vials)		1	4					
INR	1.21	1.72	1.18	1.16	1.24	1.36	1.13	1.07
APTT (s)	40.40	43.00	33.30	33.20	31.70	37.70	33.30	28.60
TT (s)	46.50	54.90	30.30	31.10	25.40	19.90	17.10	16.60
FBG (g/l)	0.21	0.20	0.23	0.21	0.23	0.45	1.88	2.74
AT (%)	95	102	103	107	115	94	n/a	100
D-dimer (μg/l)	>6400	>6400	>6400	>6400	>6400	>6400	>6400	3031
PLT (10^9/l)	40	9	48	49	33	57	120	201

n/a – not available

shortening clotting times and slight elevation of FBG (fibrinogen) (Table 1). On day 4 and 5, dropped PLT count (pseudothrombocytopenia was excluded); no increase in FBG values and free haemoglobin > 700 mg/l signalized persisting influence of non-neutralised part of venom. Following this, another five vials of antivenom were used (Table 1).

The whole time of VICC lasting, no clinical signs of haemorrhage were present. Subsequently, the 6th to 7th day after the bite, the laboratory findings and clinical status normalised, except for D-dimer values and persisting AKI. The 10th day, the prophylactic mini-heparinization was initiated; uroinfection, confirmed in residual urine, was treated by antibiotics (Ciprofloxacin). The patient was transferred to Department of Nephrology at the 12th day for persisting AKI and the need of haemodialysis. AKI resolved in 20 days.

Discussion

The serious haemocoagulation disorder presents one of the most difficult problems for treatment. As VICC represents non-characteristic infliction of coagulation system, supplementary therapy like FBG or FFP (fresh frozen plasma) application does not improve the scenario, until the acting venom components are neutralised (White, 2005). However, in a case, when formed afibrinogenaemia brings a risk of serious haemorrhage and antivenom is not immediately available, administration of FFP can be a way to reinforce, at least temporarily, the ability of blood clotting. The second reason for clotting factors substitution could be slow onset of clotting equilibration after the venom neutralisation (Brown et al., 2009), particularly in higher risk of haemorrhage from other reasons, e.g. trauma, gastric ulcer, hepatopathy and others. This case demonstrates, that afibrinogenaemia lasting 48 hours, may not bring any haemorrhage. On that fact, substitution of FFP can participate as well as early antivenom treatment, even if it was titrated to laboratory findings and the time of neutralization was prolonged.

Another problem of VICC treatment is irregular antigenicity of haemocoagulation components, thus occasionally a need high and/or repeated doses of antivenom to neutralise this venom impact (Weis et al., 1991). That increases the time required to full restitution, when the total antivenom dose is titrated by haemocoagulation examination findings. The second approach to antivenom treatment is primary administration of high number of antivenom vials; but the total need of antivenom is not easy to estimate and high dosage of antivenom brings the risk of complications, e.g. serum sickness.

The use of heparin during the venom impact is controversial and not generally recommended (White, 2005). Nevertheless, according to Paul et al. (2003), heparin bolus of 5,000 units and further application of 2,500 units every 8 hours, in parallel with antivenom administration, can reduce mortality of persons envenomed by the saw-scaled viper *Echis carinatus* and the Russell's viper *Daboia russelli* from 26% to 19%. However these results are not highly significant. Heparin does not terminate

ongoing VICC and increases the risk of serious haemorrhage. But, after resolving of acute VICC with persisting activation of haemocoagulation and endothelial damage, prophylactic mini-heparinisation can prevent further possibility of thrombotic complications.

In this case adequately diagnosed respiratory failure of ARDS-type shows possibility of developing pulmonary affection, which was already registered by authors three times in other cases (Valenta et al., 2014). Unfortunately, this type of venom induced disability is not sufficiently evidenced in literature. The reasons may be short, mild and transitory course of respiratory failure and usually unsatisfactory blood gases monitoring and chest X-ray examination.

AKI developed rapidly despite of early antivenom treatment and provided volume replacement and absence of most reliable reasons: significant myoglobinuria (low level of serum myoglobin), haemoglobinuria, haemorrhage and hypotension. Developing AKI clinically confirmed influence of venom compounds, which can significantly affect the functional renal tissue.

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