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Envenoming after a Snakebite from the Northeast African Saw-scaled Viper *Echis Pyramidum*: Prolonged Therapy upon Failed Treatment by Antivenom

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Abstract: A reptile holder based in the Czech Republic was bitten into his hand and foot by the Northeast saw-scaled viper (*Echis pyramidum*). The person arrived at the health institution after twenty hours for anuria. Despite the antivenom against the Asian *Echis carinatum* – the *Echis pyramidum*'s close relative – was readily available and administered repeatedly, the envenoming continued to develop with subsequent coagulopathy, hepatopathy and respiratory failure. The effects of plasmapheresis and symptomatic therapy were positive, but only temporary. Continual renal replacement therapy and plasmapheresis were complicated by thrombotic occlusions of the device tubing set. A turning point arrived following repeated application of imported antivenom containing antigens against venom components of another African saw-scaled viper species, *Echis leucogaster* (the antivenom containing *E. pyramidum* antigens was not available). The clinical status, including complications, resolved following 30 days of hospitalization. The case further validates the geographical specifics of immunogenicity of venom components with similar clinical action in snakes of the same genus.

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Introduction

Saw-scaled or carpet vipers *Echis* sp. reside in West, North and Northeast Africa, Middle East and Central Asia as far as Central and East India, and are largely responsible for morbidity and mortality of population in the places of occurrence (Warrell et al., 1977; Warrell, 1995; Hasson et al., 2003; Casewell et al., 2010), this including *E. pyramidum*, the species ranging over Northeast Africa (Warrell, 1995).

As *Echis* vipers are much in favour amongst holders, envenomings can be encountered even outside the genus range. Descriptions of envenoming by *Echis* sp. vipers are quite frequent in literature, which however does not apply to those of cases of holders envenomed outside places of occurrence that are rather rare, with more detailed description of envenoming by *E. pyramidum* found just in a single case (Gillissen et al., 1994), while in the other the species involvement was only assumed based on symptoms and site (Seignot et al., 1992). Reasons for the above might include the former classification of the species as *E. carinatus* subspecies.

Echis pyramidum (Northeast, Egyptian, Geoffroy's, Kenya saw-scaled or carpet viper) (Figure 1) ranges in the wild over Northeast Africa from Algeria across Egypt to North Somalia and Kenya. Adult snakes can grow up to 50–85 cm. When in danger, the saw-scaled viper will coil, rubbing its lateral keel-like scales and producing a typical loud and crispy sound that resembles that of a saw cutting wood, hence its name.

The venom components are very similar throughout the *Echis* genus members in that the venom largely consists of enzymes and toxins affecting hemocoagulation, with the envenoming effect chiefly determined by ecarin enzyme that is responsible for a direct activation of prothrombin to a different type of thrombin – meizothrombin that cannot be inhibited by AT-heparin complex. Although this substance does not seem to possess its own coagulation activity, ecarin is a potent prothrombin activator that is subsequently converted to alpha-thrombin (Merchant et al., 1989; Gillissen et al., 1994; Warrell, 1995; Hasson et al., 2003). Even small quantities of ecarin cause thrombin to activate explosively, allowing meizothrombin

Figure 1 – Northeast saw-scaled viper Echis pyramidum *(photo: Jiroušek).*

that cannot be inhibited to freely propagate within circulation. During the process, the activity of the person examined remains AT-intact, or is even increasing (Mba and Onyemelukwe, 1989; Valenta, 2010). The influence of thrombin produces fibrin formations. These are destructed by activated plasmin to a large quantity of fibrin degradation products (FDP) with resulting consumptive disorder of the disseminated intravascular coagulation (DIC) type. Substances responsible for resulting fibrino(geno)lysis and afibrinogenemia include fibrino(geno)lytic proteinases that are present in the venom.

Other venom components are desintegrins (echistatin, leucogastrin, ocellatin, and pyramidin) that inhibit the platelet (PLT) aggregation (Okuda et al., 2001). Such an activity can in some cases manifest via inadequate PLT participation in the consumptive coagulopathy in progress (Warrell et al., 1977; Seignot et al., 1992). However, this does not eliminate the effect of venom components conversely causing increased PLT aggregability and consumption in parallel with formation of fibrin microthrombi produced as a result of a thrombin activity at a systemic level.

Components that participate in damage of vascular walls, basal membranes and extracellular structures include hemorrhaging-like substances in that they aggravate prothrombotic activation, intima disintegration, hemorrhaging, and formation of fibrin deposits (Warrell, 1995; Valenta, 2010).

These results in afibrinogenemia, and in some cases also in thrombocytopenia, damaged endothelium and endothelial junctions, and increased capillary permeability with symptoms of hemorrhage and interstitial edema (Warrell et al., 1976, 1977; Weis et al., 1991). Clinical results namely involve increased bleeding incl. serious organ hemorrhaging, impending (micro) thromboses, interstitial edema and potential development of organ failure (Warrell et al., 1977; Seignot et al., 1992; Gillissen et al., 1994; Kochar et al., 2007).

Frequent renal failure as well as rather rare cases of pulmonary failure, hepatopathy and pancreatic irritation occurs as a result of multifactor action of venom components, with significant rate of affecting hemocoagulation and systemic action of toxic enzymes (Merchant et al., 1989; Annobil, 1993; Warrell, 1995; Sagheb et al., 2011).

Presence of presynaptic enzymatic neurotoxins is possible in the event of *E. pyramidum*, but with no clinical importance (Gillissen et al., 1994).

In addition, the venoms of the *Echis* snakes, as with the majority of vipers, contain a range of cytotoxic and destructive proteolytic enzymes causing local damage to tissues including formation of necrosis (Warrell et al., 1977; Annobil, 1993; Warrell, 1995).

Case report

A Czech-based snake breeding enthusiast, 41-year-old man, suffered bites to the right antebrachium and subsequently above the left ankle while handling an adult *Echis pyramidum*, this immediately developing swelling of the right arm and left shin.

Anuria occurred within several hours after the bite. Twenty hours later, the affected person arrived at the local hospital, from which he was transferred to the general intensive care unit of the General University Hospital.

After the reception (day 2 of envenoming), oligoanuric renal failure and laboratory evidence of consumptive coagulopathy of DIC type was found in

Table 1 – Values of selected parameters of laboratory examinations

Day	1	2	3	4	5	6	7	8	9	10	15	20	25	28
PT (INR)	>10	2.3	3.2	>10	>10	1.5	1.26	1.07	0.9	1	0.9	0.9	1	1.1
APTT (s)	>180	57.6	46.5	>180	>180	54.5	28	27.9	37.4	56.9	35	26.7	35.7	38.9
FBG (g/l)	0.01	0.3	0.1	0.05	0	0.5	1.15	5.4	6.2	6.3	6.1	5.8	5.6	5.9
D-dim (µg/dl)	>640	>640	>640	>640	>640	>640	>640	>640	638	367	270	56.8	60.4	40.6
PLT × 10^9	22	39	64	82	74	37	30	68	75	50	111	194	315	351
BR total (µmol/l)	21.7	24.5	n/a	41.7	81.2	84.5	91	235	297	295	147	35.6	29.4	30.8
BR conj. (µmol/l)	8.1	8	n/a	12.6	n/a	35.2	47.1	164	189	278	94.7	14.9	10.6	11.5
ALT (µkat/l)	2.82	2.08	n/a	0.42	n/a	0.44	0.56	0.48	0.59	0.58	0.73	1	1.03	0.97
AST (µkat/l)	5.32	4.51	n/a	1.46	n/a	1.4	2.24	1.85	0.94	0.54	0.65	0.5	0.47	0.47
GGT (µkat/l)	1.57	1.29	n/a	0.66	n/a	1.07	1.06	2.02	2.74	1.88	1.93	4.56	4.27	3.08

BR – bilirubin; n/a – not available

addition to local findings: INR > 10.0; APTT > 180.0 s; FBG < 0.01 g/l; D-dim > 6500 μg/l; PLT 22 × 10^9/l (Table 1, Figure 2). The patient was lacking any visible signs of bleeding. 2 vials of Snake Antivenin I.P. (Polyvalent) Haffkin India were administered, including a component against *Echis carinatum*, the relative of *Echis pyramidum* within the same genus. In parallel, fresh frozen plasma (FFP) and antithrombin (AT) were applied.

To make use of improved coagulation parameters after the first wave of therapy, venous dialysis catheter was implemented on day 3 via *v. jugularis int.* Continual renal replacement therapy (CRRT) for renal failure was launched and additional FFP administered the same day; blood transfusions were also applied due to symptoms of hemolytic anemia. As the progression of laboratory evidence of DIC repeated in the course of several more hours, additional 4 vials of antivenom were administered. The hemocoagulation parameters improved for several hours.

The day after, i.e. the day 4 of envenoming, the progression of coagulopathy revived. For the low efficiency of the antivenom and the momentary unavailability of another type of the substance, plasmapheresis was carried out to eliminate the venom components. This action controlled coagulation for a mere several hours. Plasmapheresis was further repeated every 12 hours; the result was similar at all times.

From day 5 on, respiratory distress was developing. At the beginning, this was possible to control using oxygenotherapy, with subsequent intubation of the patient and ventilatory lung support due to continued respiratory failure (p_aO_2/FiO_2 = 185). There were intermittent symptoms of increased bleeding from the stitches and the oral cavity and treatment of hemolytic anemia was necessary through blood transfusions. Signs of hepatopathy appeared: foetor hepaticus, minor ascites and hepatomegaly. Levels of liver enzymes and bilirubin could not be currently provided due to hemolysis of samples; any sampling following

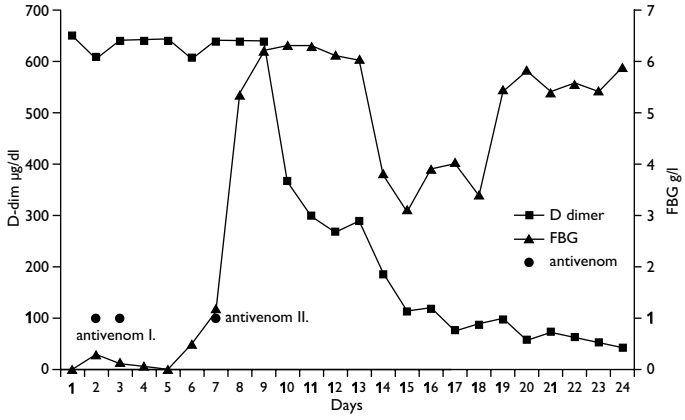

Figure 2 – Relationship among FBG, D-dim and administration of antivenoms.

plasmapheresis would also not be objective. Prolonged coagulation times have now been gradually reducing.

On day 6, there is a continued minor bleeding from the oral cavity and nasopharynx. Packed RBC and PLT administered due to hemolytic anemization and thrombocytopenia. Despite plasmapheresis improving the results of hemocoagulation tests, both continual renal replacement therapy (CRRT) and plasmapheresis cause in the regional citrate anticoagulation recurrent blood coagulation within the device tubing set and in the cannula. Due to thrombophilia, impending microthromboses and thromboembolic complications, the patient was heparinized using UFH 5,000 IU/24 hours continually IV upon the laboratory finding of normal coagulation times. A slighter degree of hepatopathy was confirmed via increased values within the liver function test (LFT) with maximum values as follows: bili 296.7 μmol/l (N 17 μmol/l), bili conj. 189.3 μmol/l (N 5.1 μmol/l), ALT 1.41 μkat/l (N 0.78 μkat/l), AST 1.85 μkat/l (N 0.72 μkat/l), GGT 4.98 μkat/l (N 0.84 μkat/l) (Table 1). Ammonia values have remained on the upper limit of normal range, probably also due to the CRRT. There is a short-term increase in serum amylase to 2.42 μkat/l (N 0.88 μkat/l), with a correlate of pancreatic hyperechogenicity in the ultrasonographic findings.

Due to the low efficiency of the antivenom used and the unavailability of a specific antivenom, an order was placed for a type containing a component against the closely related Africa-dwelling *Echis leucogaster*.

The next day, i.e. day 7, a total of 7 doses of Favirept Sanofi Pasteur France were administered, after which there has been initially only a slight improvement. Over the subsequent days, however, the levels of fibrinogen (FBG) and coagulation times have gradually normalized and stabilized, with persistent high levels of D dimers (D-dim), and borderline low PLT. Replacement of erythrocytes and PLT is necessary.

From day 10 to day 15, the condition becomes complicated due to bronchopneumonia and septic symptoms with mild circulatory destabilization. Both mechanical ventilation and oligoanuria persist, with the need for CRRT. Laboratory findings have shown a decrease in D-dim, LFT (Table 1) and serum amylase levels return to normal. For persistent hypercoagulation and thrombotic occlusions of the device circuit and IV cannulae for CRRT produced intermittently, UFH temporarily increased to 40,000 UI/24 hours IV continuously. Formation of blood clots in the CRRT device circuit and cannulae has now stopped.

With time, the condition has improved, with the regression of bronchopneumonia and the possibility of spontaneous ventilation. Oliguria persists with intermittent need for CRRT. UFH replaced with LMWH (Clexan) from day 22 on, preventive dose, and the patient extubated; from day 26 on there is a recovery of sufficient diuresis with supportive treatment using furosemide. The patient transferred to the internal medicine department for after-treatment in good clinical condition on day of envenoming 29.

Discussion

Although descriptions of envenoming by *Echis* sp. vipers being quite frequent, they mainly concern the Asia-dwelling species, *Echis carinatus*, while those involving species from Africa and Middle East refer to *E. coloratus* (de Vries et al., 1966; Fainaru et al., 1970; Schulchynska-Castel et al., 1986; Gilon et al., 1989; Porath et al., 1992; Benbassat and Shalev, 1993) and *E. ocellatus* that ranges in Central and West Africa (Einterz and Bates, 2003). Cases of envenoming by *E. pyramidum* from northeast Africa have been collectively described only in the literature of older dates (Corkill, 1949). Any self-contained descriptions detailing envenoming by *E. pyramidum* are sporadic (Gillissen et al., 1994); Seignot et al. (1992) describe a case of envenoming with fatal development, one that might have occurred according to the region and the course of actions as a result of snakebite from that species.

The classic symptoms of envenoming by *Echis* sp. vipers virtually do not differ amongst the species. The symptoms of coagulopathy with significant consumptive component and hemorrhaging are caused by a complex of venom components that affects hemocoagulation, with namely ecarin – prothrombin activator, and fibrino(geno)lytic enzymes being the responsible substances amongst others (Forbes et al., 1966; Seignot et al., 1992; Gillissen et al., 1994; Warrell, 1995; Hantson et al., 2003).

D-dim levels in the described case suggest formation of stabilized fibrin and its subsequent destruction, i.e. prothrombin activation, and a significant role of consumption in causing the afibrinogenemia. The gravity of the consumption failure reaches the form of overt DIC, which through replacement therapy and plasmapheresis temporarily turns into a form of non overt DIC. AT activity levels were not significantly outside the normal due to ongoing substitution of FFP and AT. The positiveness of the ethanol gelification test resolved after administering the second type of antivenom.

The microthromboses emerging in the process are involved in organ disorders of kidney, lung, liver and pancreas, probably with the participation of systemic functional hemorrhagins and destruction enzymes (Valenta et al., 2010; Sagheb et al., 2011). The hepatopathy developed in the described case and documented through elevated LFT levels was not fully supported by higher levels of ammonia, probably due to the elimination of the latter during CRRT. Relatively frequent oligoanuric renal failure can be made more intense by hypovolemia during extravasation, hemorrhage, and inadequate volume replacement (Merchant et al., 1989).

The course of action of the protracted envenoming is indicative, with respect to the clinical symptoms of organ inflictions, with the likely involvement of microthrombotizations and repeated thrombotization of cannulae and tubing sets, of the clinically important component of hemocoagulation system activation symptoms in the case of resulting consumptive coagulopathy of the DIC type, even

in the period of extended coagulation times and slight expressions of increased bleeding.

The effect of neurotoxins as described by Gillissen et al. (1994) was not recorded in this event. In the beginning of envenoming, none was observed, while later on the patient was sedated.

The clinically clear interspecific differences in the effect of venom of *Echis* sp. vipers are only indistinctive; there is probably lower venom toxicity in *E. coloratus* (Gilon et al., 1989) and potential slight neurotoxic symptoms in *E. pyramidum* (Gillissen et al., 1994). In terms of immunology, however, venom components differ per species and region, which has been repeatedly confirmed by both laboratory results and clinically through low effectiveness or even ineffectiveness of antivenoms that differed geographically or per species (Kornalík and Táborská, 1973; Schaeffer, 1987; Weis et al., 1991; Gillissen et al., 1994; Casewell et al., 2010).

In the case described by the authors, the readily available Haffkin polyvalent antivenom containing a component against the venom of *E. carinatus* of Indian origin was administered in the first place. The result testified to its low antigenicity against the venom components of *E. pyramidum*. Similarly, the repeated use of plasmapheresis showed the lack of effectiveness, this resulting only in a temporary improvement in coagulation and patient's condition. The antivenom containing *E. pyramidum* antigens was not available. The situation started getting better only with the administration of the Favirept Sanofi Pasteur France antivenom containing components against the venom of the African *E. leucogaster*.

Conclusion

Plasmapheresis, symptomatic and replacement therapy in the case of serious envenoming by *E. pyramidum* upon failure of the available antivenom had insufficient effects; nonetheless, the procedures employed allowed for spanning the time to obtaining the effective antivenom without any grave symptoms of bleeding and systemic thromboembolisms.

This again confirmed the need for early use of antivenom containing components that are identical in terms of species or at least geographically, if the former is not available. The effectiveness of the second antivenom applied, though different in terms of species but geographically similar, proved to be sufficient. This suggests a certain antigenic similarity between the venom components of African vipers *E. pyramidum* and *E. leucogaster* and possibilities of switching antivenoms if no specific antivenom is available.

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