

Thrombocytopenic purpura following envenomation by the nose-horned viper (*Vipera ammodytes ammodytes*)

Two case reports

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Abstract

Rationale: Two clinical cases are reported of envenomation by the nose-horned viper (*Vipera ammodytes ammodytes*) venom of a 9-year-old boy and of an 84-year-old woman.

Patient concerns: Both patients had been bitten on their extremities by such a snake in August near Split, a town in southern Croatia.

Diagnoses: Clinical manifestation of envenomation was severe in the case of the boy, being characterized by a severe coagulopathy. This was only just apparent in the case of the elderly woman, who suffered extensive local edema and hematoma at the site of the bite, together with a neurotoxic effect—bilateral ptosis. This was the first occasion of thrombocytopenic purpura being observed in patients envenomed by nose-horned viper venom. This unexpected clinical finding was characterized by an unusually profound thrombocytopenia of 5 and $10 \times 10^9/L$ platelets of the respective patients on their admission to the hospital, together with purpura, observed on the face and thorax of both individuals. In the most serious cases, such pathology can be life threatening if not promptly recognized and treated.

Interventions: The patients recovered quickly on receiving the specific antivenom along with all the usual supportive treatments.

Outcomes: No serious sequels were noticed at the moment of discharge.

Lessons: Our finding constitutes an important message to clinicians to consider the possibility of such complications in the case of nose-horned viper envenomation.

Abbreviations: aPTT = activated partial thromboplastin time, AT-III = antithrombin III, CNS = central nervous system, DIC = disseminated intravascular coagulation, ECG = electrocardiogram, FFP = fresh frozen plasma, GCS = Glasgow coma score, HR = heart rate, i.m. = intramuscularly, i.v. = intravenously, ITP = immune thrombocytopenic purpura, PICU UHS = Pediatric Intensive Care Unit in the University Hospital of Split, PT = prothrombin time, RR = respiratory rate, TP = thrombocytopenic purpura, TTP = thrombotic thrombocytopenic purpura, *Vaa* = *Vipera ammodytes ammodytes*.

Keywords: envenomation, petechiae, thrombocytopenia, thrombocytopenic purpura, *Vipera ammodytes ammodytes*

1. Introduction

The nose-horned viper, *Vipera ammodytes ammodytes* (*Vaa*), is the most venomous European viper.^[1] Local and/or systemic

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clinical manifestations of envenomation by its venom result from the pathophysiological effects caused by a mixture of enzymatic and nonenzymatic venom components acting, in particular on the blood and the cardiovascular system and on the nervous system.^[2–7] The hematotoxic effects are local, usually presenting as edema with erythema, hematoma and ecchymosis with or without hemorrhagic blister formation, together with thrombophlebitis at the site of the bite. Episodes of systemic bleeding vary from mild to life-threatening.^[8–10] The coagulopathy induced by this venom is reflected in the prolonged prothrombin time (PT) and/or the activated partial thromboplastin time (aPTT).^[5] About 3.1% of envenomed children experienced coagulopathy after *Vaa* envenomation.^[10] Blood clotting disorders have been observed more frequently in adult victims, 8.86% of such patients suffering bleeding manifestations. Thrombocytopenia, whose severity presumably correlates with the severity of envenomation, has been described in about 2% of patients envenomed by nose-horned viper venom, although the decrease of platelet count observed has never been critical.^[2] Purpura is a condition in which red or purple spots appear on the skin and these spots do not blanch by applying pressure. Thrombocytopenia or purpura is frequent manifestations of snake venom envenomation, although occurrence of both disorders in causal

connection, termed thrombocytopenic purpura (TP), is very rare. By tradition, TP can present as an immune-mediated condition—immune TP (ITP)—or as an endothelial defect in the vessels' walls leading to microvascular thrombosis—thrombotic TP (TTP). When its etiology is unknown, TP is regarded as idiopathic. TTP has been described as envenomation by the venom of a hump-nosed viper (*Hypnale hypnale*) that inhabits southern India and Sri Lanka.^[11] The pathology is characterized by platelet aggregation, microthrombi formation, and thrombotic microangiopathy, and can endanger life in the absence of prompt recognition and treatment. Here, we present the first 2 cases of envenomation by European vipers in which TP was observed. This constitutes an important message for clinicians to consider such a complication possible.

2. Case reports

2.1. Clinical case 1

An otherwise healthy 9-year-old boy was bitten by a snake, recognized after being killed as a nose-horned viper. This occurred in August, in the grounds of the family house on Hvar, an island near the town of Split in southern Croatia. At the time of being bitten, the boy felt a sharp pain in the dorsum of his left foot. He saw the snake and immediately ran to his mother, approximately 100 m away. He then lost consciousness and fell down. His mother promptly intervened to keep his airway open and provided basic layman's first aid. Ten minutes later, the boy was brought to the nearest outpatient medical center, where a general practitioner provided the first medical care. The oropharyngeal airway was put, 500 mL of crystalloids were administered intravenously (i.v.) and the first dose of Zagreb antivenom (Institute of Immunology, Zagreb, Croatia) administered as a dose of 10 mL intramuscularly (i.m.). Helicopter

transport was promptly organized to transfer the child to the Pediatric Intensive Care Unit in the University Hospital of Split (PICU, UHS). On the way to the hospital, the patient was unresponsive with occasional wince of the extremities and trismus. He had difficulties in breathing spontaneously and respiratory rate (RR) was 12 per minute. Blood pressure was not measurable with the noninvasive machine, but central pulse was palpable and counting gave 110 beats per minute. Heart rate (HR) was rhythmic and fast.

On arrival at the PICU UHS, 45 minutes after the bite, the child was in a state of shock, soporific with a Glasgow coma score (GCS) of 7. His body temperature was low (34.5°C), he was hypotensive (51/25 mm Hg after bolus of crystalloids), tachycardic (HR of 100 beats per minute), and bradypneic (RR of 8 per minute) with oxygen saturation of 88%. Peripheral pulses were not detectable, capillary reperfusion time was 8 seconds, and the skin was livid and cyanotic. Marks of the snakebite along with the local surrounding edema, erythema, and hematoma were present on the dorsum of the left foot (Fig. 1). Eye conjunctives were bilaterally hemorrhagic with periorbital edema. Purpura, specified as petechiae (reddish-purple hemorrhagic spots <2 mm in diameter), was presented on the face and thorax (Fig. 2). He exhibited hemorrhagic nasal bleeding and bleeding in the oral cavity. Breathing sounds were diminished. Cardiac action was rhythmic and fast, tones were silent without any pathological murmur. Clinical examination of the abdomen was normal. The patient was endotracheally intubated and mechanically ventilated (FiO₂ 40%, tidal volume 350 mL, frequency 25 per minute, inspiratory time 0.85 seconds, positive end-expiratory pressure 5 cm H₂O). Catheters were introduced into his central vein and artery. Boluses of crystalloids were provided continuously, along with inotropic support—norepinephrine (1 µg/kg per min) and dopamine (11–22 µg/kg per min), which was subsequently substituted by dobutamine (2.5 µg/kg



Figure 1. *Vipera ammodytes ammodytes* fang marks on the left foot of the 9-year-old boy. The local edema and hematoma developed 45 minutes after the snakebite. The child was in a state of shock and experienced severe coagulopathy.



Figure 2. Petechiae over the thorax of a child patient 45 minutes after envenomation with the *Vipera ammodytes ammodytes* venom. The 9-year-old boy was severely thrombocytopenic, displaying a platelet count of only $5 \times 10^9/L$.

per min), in continuous infusion under central venous pressure monitoring. The boy was under sedation with midazolam (2–4 $\mu\text{g}/\text{kg}$ per min) and fentanyl (2 to 4 $\mu\text{g}/\text{kg}/\text{hour}$). One dose of Zagreb antivenom (10 mL i.v.) was administered. Hydrocortisone was also given (100 mg i.v.), along with fresh frozen plasma (FFP) (560 mL), thrombocyte concentrate (200 mL), and transfusion of deplasmated erythrocytes (500 mL), recombinant factor VII (3 mg), antithrombin III (AT-III) (2000 U), and vitamin K (5 mg). Laboratory parameters were consistent with disseminated intravascular coagulation (DIC), prolongation of both PT and aPTT and of thrombin time (Table 1). Coagulopathy was also characterized by severe thrombocytopenia ($5 \times 10^9/L$), low levels of plasma fibrinogen and AT-III, and a slightly increased level of D-dimers (Table 1). The results of laboratory tests throughout the boy's hospitalization are collected in Table 1. As apparent from table, the initial electrolyte imbalance was adjusted promptly and coagulation parameters recovered within 2 hours and 45 minutes. Routine screens for autoimmune diseases—rheumatoid factor, antinuclear antibodies, and antibodies against extractable nuclear antigen—were all negative. Markers of HIV and viral hepatitis were not detectable, as were also antineutrophil and antiplatelet antibodies. Chest X-ray examination and transthoracic echocardiogram were found to be normal. An electrocardiogram (ECG) revealed sinus tachycardia but no other abnormalities. No adverse events were recorded after antivenom therapy. The therapy applied resulted in rapid clinical improvement. Sixteen hours later, the child was extubated and, the day after, central catheters were removed. The boy was transferred to an open pediatric ward for further care. No neurological disturbances were evident. He was discharged after 9 days of hospital care.

2.2. Clinical case 2

In August, in the rural part of Dalmatia near Split in southern Croatia, an 84-year-old woman was bitten by a snake recognized

as the nose-horned viper. The woman did not seek medical assistance immediately but was brought to the Clinical Department of Infectious Diseases in the University Hospital of Split 16 hours after the bite, when neighbors noticed edema and hematoma spreading along her left arm.

Immediately after admission, 10 mL of Zagreb antivenom was administered i.m., along with human tetanus IgG (250 IU i.m.), vaccinum tetani adsorbatum (0.5 mL i.m.), dexamethasone (4 mg i.v.), and chloropyramine (20 mg i.m.). She also received single doses of FFP (230 mL) and thrombocyte concentrate (200 mL) together with infusions of crystalloids. No allergic reaction was observed on antivenom therapy. On physical examination, the patient was afebrile (36.4°C), eupneic, cardiorespiratory sufficient with GCS counting 15 and in relatively good physical condition, considering her age. The woman was without a significant medical history and was taking no medications. An extensive edema, skin discoloration and ecchymosis were present on the entire upper left limb with extension to the left side of the thorax (Fig. 3). Fang marks were visible on the left-hand forefinger, where a hemorrhagic blister was forming. Cardiac action was rhythmic and fast (92 per minute), tones were clear, no pathological heart murmurs were heard and arterial blood pressure was 105/65 mm Hg. The sound of breathing was normal, as well as RR (14 per minute). Oxygen saturation was 99%. Hepatomegaly, splenomegaly, and lumbar tenderness were not detected. Neurological examination revealed bilateral eyelid ptosis. Purpura, manifested as petechiae, was detected on the face and thorax (Fig. 4). Laboratory findings at admission showed profound thrombocytopenia ($10 \times 10^9/L$) but no other clinically significant coagulation abnormalities (Table 2). No clinical evidence of DIC was found in her case. Tests for markers of autoimmune and viral diseases, as declared under Clinical case 1, were all negative. Analysis of the chest X-ray revealed normal cardiopulmonary status. Sinus tachycardia was diagnosed by ECG. The patient was hemodynamically stable during hospitali-

Table 1**Laboratory blood parameters of a 9-year-old boy envenomed by *Vipera ammodytes ammodytes* venom.**

Parameters	Reference range	t1	t2	t3	t4
White cell count	4.4–11.6 × 10 ⁹ /L	8.1	21.2	18.3	6.2
Neutrophils	34–65%	43	50	65	71
Lymphocytes	19–52%	51	42	29	19
Monocytes	5–13%	1	2	1	6
Eosinophils	0–9%	5	4	4	3
Basophils	0–3%	0	1	1	1
Reticulocytes	0.4–1.9%	0.9	1	1.1	1.1
Erythrocytes	4.34–5.47 × 10 ¹² /L	4.29	5.14	5.07	3.86
Hemoglobin	121–145 g/L	118	144	142	108
Hematocrit	0.366–0.452 L/L	0.350	0.422	0.414	0.311
Platelets	178–420 × 10 ⁹ /L	5	236	220	182
Glucose	3.9–5.9 mmol/L	7.9	16.0	6.1	7.0
Blood urea nitrogen	2.7–6.8 mmol/L	3.9	7.2	9.2	10.0
Serum creatinine	30–48 μmol/L	37	62	50	48
Sodium	135–144 mmol/L	147	141	143	144
Potassium	3.6–5.0 mmol/L	2.0	4.4	3.7	4.0
Chloride	97–108 mmol/L	121	105	107	110
Total calcium	2.16–2.63 mmol/L	1.8	1.9	2.08	2.18
Phosphate	1.11–1.73 mmol/L	1.23	1.27	1.46	0.91
Total magnesium	0.74–0.97 mmol/L	0.73	0.73	0.72	0.82
Total bilirubin	6–24 μmol/L	8	6	8	10
Aspartate aminotransferase	14–39 U/L	14	30	53	52
Alanine aminotransferase	11–37 U/L	<6	8	21	20
γ-Glutamyl transferase	10–27 U/L	<4.0	10	15	14
Lactate dehydrogenase	164–299 U/L	127	250	352	316
Alkaline phosphatase	179–472 U/L	108	110	115	111
Creatine kinase	70–285 U/L	194	250	926	815
Creatine kinase MB fraction	<24 U/L	28	30	60	44
High sensitive-troponin I	<0.033 ng/mL	0.588	0.646	1.064	0.590
Lactic acid (lactate)	0.5–1.7 mmol/L	5.4	4.2	1.0	0.7
Erythrocyte sedimentation rate	2–21 mm/h	2	n.d.	n.d.	n.d.
C-reactive protein	0.1–2.8 mg/L	<0.10	37.9	15.6	17.4
Total proteins	66–81 g/L	26	68	57	52
Albumins	41.6–50.8 g/L	14.0	39.0	35.0	31.0
Globulins	25–30 g/L	12	29	22	21
Prothrombin time	>0.70	0.07	1.14	1.04	1.25
Activated partial thromboplastin time (aPTT)	22–33 s	103.8	26.0	23.2	26.1
aPTT ratio	0.8–1.2	3.58	0.89	0.80	0.90
Thrombin time	14–21 s	62.9	33.1	21.6	23.4
Plasma fibrinogen	1.6–4.0 g/L	0.6	2.2	2.2	2.3
D-dimers	<0.50 mg/L	1.60	3.29	1.65	1.46
Antithrombin III	0.75–1.25	0.28	1.31	1.08	0.98

The parameters were evaluated 45 minutes (t1), 2 hours and 45 minutes (t2), 7 hours (t3), and 13 hours (t4) after the snakebite. For comparison, normal values of the parameters for children are listed (reference range).

U = unit, n.d. = not defined.

zation, laboratory parameters registered anemia 24 and 48 hours following the bite (Table 2), probably the consequence of extensive edema and hematoma on the left arm, but the recovery was quick. There were, however, no signs of the compartment syndrome, and hemorrhagic blister was not indicated to require the incision. Bilateral ptosis disappeared within 72 hours. The local manifestations of hematotoxicity disappeared gradually. The patient was discharged after 7 days of medical treatment.

3. Discussion

Clinical pictures are reported of 2 patients, a 9-year-old boy and an 84-year-old woman, both envenomed by the venom of a *Vaa* snake. Impairment in the first case was severe and, in the second, moderate. Symptoms typical of *Vaa* venom envenomation were observed in both patients.^[2,10] The boy in particular suffered

from severe coagulopathy, while the woman did not. Apart from extensive signs of local hematotoxicity, she developed no significant coagulopathy but was, in contrast to the boy, anemic. In her case, neuropathy was also manifested clinically. In the state of shock, the child very likely suffered from depression of the central nervous system (CNS). Before arriving at the hospital, he experienced an epileptic seizure, so venom-induced CNS neurotoxicity cannot be excluded in his case also. Both patients were, however, exceptional in the occurrence of a profound thrombocytopenia of 5 and 10 × 10⁹/L (reference range between 150 and 450 × 10⁹/L), and, at the same time, of purpura in the form of petechiae. In spite of an extensive clinical record consisting of several hundred clinical cases, these are the first 2 descriptions of such a condition in patients envenomed by the nose-horned viper venom or by the venom of any other European viperid.^[2,10] Analysis of 542 snakebite envenomation cases in



Figure 3. An 84-year-old woman 16 hours post *Vipera ammodytes ammodytes* envenomation. The woman was bitten by the snake in the forefinger of the left hand. Extensive edema and hematoma spread over the entire upper left limb and left side thorax of the patient.



Figure 4. Purpura over the face of the patient 16 hours after envenomation with the *Vipera ammodytes ammodytes* venom. At this time, the patient, an 84-year-old woman, was profoundly thrombocytopenic, with a platelet count of only $10 \times 10^9/L$.

southern Croatia, mostly inflicted by *Vaa*, showed that purpura, clinically displayed as ecchymosis at the site of the bite, with or without local progression, was recorded in 92.2% of patients.^[2] By contrast, only 2% of patients suffered from mainly moderate thrombocytopenia (platelet count around $100 \times 10^9/L$). Interestingly, these 2 pathologies have never before been observed together (Lukšić B, personal communication) implying that they were not causally connected. Further support for such a view is the large difference between their incidence (92.2% against 2% in adults, and 97.5% against 3.1% in children), which, moreover, suggests that the disorders are mutually exclusive. The complete segregation of thrombocytopenia and purpura at the *Vaa* venom envenomation recorded so far strongly supports the hypothesis that, in the 2 cases described here, thrombocytopenia and purpura are causally connected, meaning that, here, we observed TP. Such a phenomenon is very like that of viper venom envenomation. In actual fact, it has been documented so far only for poisoning with the venom of *H hypnale*, a hump-nosed viper from Asia.^[11] The venom of this snake induces TP that can be lethal if not promptly recognized and treated. On analysis of the mechanism of the pathology induced by *H hypnale* venom, the authors observed platelet aggregation, microthrombi formation, thrombotic microangiopathy, and the main characteristics of the TTP. DIC that was diagnosed in the case of our young patient is suggestive of TTP, even more so because the negative results for the presence of immune diseases—antineutrophil and antiplatelet antibodies—did not support the possibility of immune-mediated

thrombocytopenia. Because neither fragmented red blood cells (schistocytes) nor other signs of hemolytic anemia were observed in the peripheral blood of the boy (e.g., values for bilirubin and lactate dehydrogenase were normal), his profound thrombocytopenia was probably the result of an extensive secondary coagulation disorder induced by the venom (Table 1). The bleeding episodes observed in the boy patient are consistent with DIC, and the petechiae represent a skin reflection of the severe coagulopathy. In the case of the elderly woman, however, DIC was not detected, so in her case the thrombotic type of TP cannot be confirmed. Further, ITP was not indicated by laboratory testing. In contrast to the boy, the old patient was profoundly anemic (Table 1), although lacking signs of hemolysis. Without evidence for immune, coagulation or hereditary factor for TP, the way in which she developed petechiae can only be speculated. It appears that the only hematotoxic manifestation of the *Vaa* envenomation in her case was the presence of local hematoma and petechiae. Purpura over her face and thorax likely developed as a result of thrombocytopenia induced by attachment of platelets to the venom-affected capillary endothelium.

Besides the specific antivenom therapy, these patients also received corticosteroids and blood derivatives. They both recovered quickly, although we cannot specify whether the antivenom or the supportive treatment was more important for the rapid improvement in health.

Table 2**Laboratory blood tests during hospitalization of an 84-year-old woman envenomed by *Vipera ammodytes ammodytes* venom.**

Laboratory parameters	Reference range	t1	t2	t3	t4
White cell count	3.4–9.7 × 10 ⁹ /L	16.5	15.7	12.6	9.9
Neutrophils	44–72%	93	89	79	72
Lymphocytes	20–46%	4	5	17	21
Monocytes	2–12%	3	6	2	5
Eosinophils	0–7%	0	0	1	1
Basophils	0–1%	0	0	1	1
Reticulocytes	0.5–1.5%	1	1	1	1
Erythrocytes	3.86–5.08 × 10 ¹² /L	4.59	3.08	3.12	4.29
Hemoglobin	119–157 g/L	125	104	111	120
Hematocrit	0.356–0.470 L/L	0.370	0.310	0.321	0.359
Platelets	158–424 × 10 ⁹ /L	10	399	201	253
Glucose	4.4–6.4 mmol/L	12.6	8.9	7.2	5.1
Blood urea nitrogen	2.8–8.3 mmol/L	14.5	11.2	9.7	8.1
Serum creatinine	49–107 μmol/L	111	110	108	106
Sodium	137–146 mmol/L	138	137	140	141
Potassium	3.9–5.1 mmol/L	4.4	4.2	4.1	4.0
Chloride	97–108 mmol/L	104	103	102	100
Total calcium	2.14–2.53 mmol/L	2.21	2.21	2.18	2.31
Phosphate	0.79–1.42 mmol/L	1.03	1.05	1.10	1.15
Total magnesium	0.85–1.05 mmol/L	0.89	0.93	0.94	0.99
Total bilirubin	3–20 μmol/L	8.1	7.9	13.4	14.1
Aspartate aminotransferase	8–30 U/L	29	17	23	26
Alanine aminotransferase	10–36 U/L	17	19	25	27
γ-Glutamyl transferase	9–35 U/L	39	38	37	33
Lactate dehydrogenase	25–241 U/L	214	235	240	195
Alkaline phosphatase	69–153 U/L	70	81	88	84
Creatine kinase	<153 U/L	61	80	96	100
Creatine kinase MB fraction	<25 U/L	11	13	16	17
High sensitive-troponin I	<15.6 ng/mL	0.124	1.584	1.776	1.923
Lactic acid (lactate)	0.5–2.3 mmol/L	0.9	0.8	0.7	0.7
Erythrocyte sedimentation rate	4–12 mm/h	8	n.d.	n.d.	n.d.
C-reactive protein	<5.0 mg/L	14.2	16.7	10.3	4.6
Total proteins	56–81 g/L	58	58	56	56
Albumins	40.6–51.4 g/L	42	42	41	41
Globulins	25–30 g/L	25	25	25	26
Prothrombin time	>0.70	0.56	0.96	0.98	0.98
Activated partial thromboplastin time (aPTT)	26–38 s	25.2	26.5	27.3	28.1
aPTT ratio	0.8–1.2	1.81	1.12	0.93	0.93
Thrombin time	14–21 s	16.4	17.2	17.6	17.8
Plasma fibrinogen	1.8–3.5 g/L	2.1	3.2	3.2	3.3
D-dimers	<0.50 mg/L	0.69	0.71	0.70	0.47
Antithrombin III	0.75–1.25	0.89	0.91	0.92	0.99

The parameters were evaluated 16 hours (t1), 24 hours (t2), 48 hours (t3), and 72 hours (t4) postsnakebite. For comparison, the normal values of parameters are listed (reference range). U = unit, n.d. = not defined.

4. Conclusion

For the first time, 2 clinical cases of nose-horned viper venom envenomation are described in which a profound thrombocytopenia accompanied by petechiae was detected. Such a pathology of snake venom envenomation is very rare, so far being described only for Asian hump-nosed viper venom. It can even be life threatening if not properly treated. In one of our cases, DIC suggested microvascular thrombosis characteristic of TTP. In the other, the TP could not be mechanistically specified but was definitely not of TTP or ITP type.

4.1. Patient consent statement

Patients have provided informed consent for publication of the case.

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References

- [1] Chippaux JP. Epidemiology of snakebites in Europe: a systematic review of the literature. *Toxicon* 2012;59:86–99.
- [2] Lukšić B, Bradarić N, Prgomet S. Venomous snakebites in southern Croatia. *Coll Antropol* 2006;30:191–7.
- [3] Georgieva D, Risch M, Kardas A, et al. Comparative analysis of the venom proteomes of *Vipera ammodytes ammodytes* and *Vipera ammodytes meridionalis*. *J Proteome Res* 2008;7:866–86.
- [4] Križaj I. Ammodytoxin: a window into understanding presynaptic toxicity of secreted phospholipases A2 and more. *Toxicon* 2011;58: 219–29.
- [5] Sajevic T, Leonardi A, Križaj I. An overview of hemostatically active components of *Vipera ammodytes ammodytes* venom. *Toxin Rev* 2014;33:33–6.
- [6] Latinović Z, Leonardi A, Šribar J, et al. Venomics of *Vipera berus berus* to explain differences in pathology elicited by *Vipera ammodytes ammodytes* envenomation: therapeutic implications. *J Proteomics* 2016; 146:34–47.
- [7] Karabuva S, Lukšić B, Brzić I, et al. Ammodytin L is the main cardiotoxic component of the *Vipera ammodytes ammodytes* venom. *Toxicon* 2017;139:94–100.
- [8] De Haro L, Glaizal M, Tichadou L, et al. Asp viper (*Vipera aspis*) envenomation: experience of the Marseille Poison Centre from 1996 to 2008. *Toxins (Basel)* 2009;1:100–12.
- [9] Lukšić B, Culić V, Stričević L, et al. Infant death after nose-horned viper (*Vipera ammodytes ammodytes*) bite in Croatia: a case report. *Toxicon* 2010;56:1506–9.
- [10] Karabuva S, Vrkić I, Brzić I, et al. Venomous snakebites in children in southern Croatia. *Toxicon* 2016;112:8–15.
- [11] Withana M, Rodrigo C, Gnanathanan A, et al. Presumptive thrombotic thrombocytopenic purpura following a hump-nosed viper (*Hypnale hypnale*) bite: a case report. *J Venom Anim Toxins Incl Trop Dis* 2014;20:26.