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Multiple Thrombotic Occlusions of Vessels after Russell's Viper Envenoming

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Abstract: Systemic bleeding due to consumption coagulopathy and thrombocytopenia due to activation of procoagulants is the leading manifestation and cause of death in Russell's viper systemic envenoming. Thrombotic occlusion of the blood vessels is rare in cases of snakebite. In this report, two adult patients with Russell's viper systemic envenoming presented multiple cerebral infarctions, digital gangrenes and ischaemic organs in addition to typical clinical manifestations of bleeding diathesis and renal involvement. Our findings in these two special cases suggest that the venom-induced coagulopathy and endothelium damage, predisposed by toxin-induced vasoconstriction, might be the possible mechanism of multiple thrombotic vascular occlusions in systemic envenoming of Formosan Russell's viper.

The Formosan Russell's Viper (*Daboia russelli formosensis*) is a subspecies found exclusively in Taiwan. Epidemiologically, it is the sixth most important poisonous snake in Taiwan (Chen *et al.* 1997; Hung *et al.* 1997). Snakebites from this viper are very rare, accounting for only 0.4 % of poisonous snakebites in Taiwan (Sawai 1969). Haemorrhagic complications and acute renal failure are the main manifestations and causes of death from Russell's viper systemic envenoming in the South and East Asia area (Myint-Lwin *et al.* 1985; Than-Than *et al.* 1988). The toxic principles, including procoagulant factors V and X, protease and phospholipase A2 are responsible for the toxic manifestations of systemic envenoming (Warrell 1989). Thrombotic occlusions of blood vessels have rarely been described in cases of Russell's viper snakebite (Ameratunga 1972). Here, we report two cases of Russell's viper systemic envenoming with multiple thrombotic occlusions in the vital organs and digitals and discuss the possible mechanisms of the occurrence of thrombosis instead of haemorrhage.

Materials and Methods

Two cases of Russell's viper snake bites. Case 1. A 67-year-old male was admitted due to mild swelling of the right palm, multiple bruising and change of consciousness after snakebite. He was a healthy farmer and was bitten by a snake on the dorsal side of the right palm while working in a field at 7 a.m. on April 25, 1991. He reported to a local clinic 90 min. later with the offending snake, which he had caught. Two vials of "haemorrhagic" snake antivenin (specific for *Trimeresurus mucrosqamatous* & *T. stejnegeri*, produced by the Vaccine Center, Center for Disease Control, Taiwan) were incorrectly administered. About 6 hr after the snakebite, ecchymosis, decreased urine excretion, and delirium developed. He was admitted to a regional medical center 12 hr after the snakebite with haemolysis, rhabdomyolysis, acute renal failure, thrombocytopenia, coagulopathy and bleeding from the genitourinary and gastrointestinal tracts. He was then referred to the National Poison Center due to deterioration in his condition even after transfusion with fresh frozen plasma and 2 more vials of haemorrhagic snake antivenin. After admission, drowsy consciousness, left upper limb flaccid paralysis and multiple ecchymosis patches over the trunk were noted. Scanty and dark-red urine from the urinary catheter and coffee-ground material from the nasogastric and endotracheal tube were also noted. The results of serial laboratory examinations are summarized in tables 1 and 2. Acute renal failure, haemolysis, thrombocytopenia and positive disseminated intravascular coagulation test were noted. Non-contrast computed tomogram of the brain showed multiple low densities over the right side in the fronto-temporal and bilateral parieto-occipital area (fig. 1). Blood transfusion with fresh frozen plasma, platelets and packed red blood cells was performed to replace the lost blood components and correct the bleeding tendency. Two days later, a herpetologist identified the snake to be *D.r.formosensis.* Two vials of antivenin specific to *D.r.formosensis* (Vaccine center, CDC, Taiwan) were administered on the 4th day after the systemic envenoming. The renal function continued to worsen and reached a peak (BUN: 170 mg/dl, Cr: 12 mg/dl) on the 7th day of systemic envenoming. During that period he received dialysis treatment several times to remove waste. A polyuric phase developed and renal function began to improve 13 days later and returned to normal 34 days after systemic envenoming. The platelet count began to be restored 5 days after antivenin and was normal 3 days later. Gangrenous change in the toes was noted on the second day after admission (fig. 2). Amputation of the diseased toes was performed about one month after the systemic envenoming. He was discharged with neurological sequelae after 61 days of hospitalization.

Case 2. A 52-year-old healthy woman was bitten by a snake on the dorsal side of the left foot at 2:30 p.m. on March 24, 1999, while she was working in a field. She was sent to a local hospital where 2 vials of "haemorrhagic" antivenin were administered immediately. The dead snake was identified as *D. r. formosensis.* About 2 hr later, she was transferred to a regional medical center due to change in consciousness, high blood pressure, haematuria and bloody vomits. Due to her deteriorated condition, despite blood transfusion, and

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Table 1.

Blood biochemical data showing the changes in renal and hepatic function of *D. r. formosensis* snakebite patients.

	Time after envenoming	BUN/Cr mg/dl	CK U/l	LDH U/l	ALT/AST U/l	I/T bilirubin mg/dl
Case 1	12 hr	41/2.7	1249	1173	36/64	
	26 hr	48/4.5	4319		59/297	1.37/1.72
	48 hr	51/5.0	2377	1957	112/360	1.5/2.0
	7th day	170/12				
	10th day	91/8.6	96			
	26th day	49/2.3	53	327	7/37	0/0.1
Case 2	24 hr	48/4.1	3009		124/735	/1.5
	48 hr	61/6.2	2596			
	3rd day	58/6.2	2734	4490	276/947	0.8/1.2
	7th day	97/7.8	66	1424	40/42	2.0/4.8
	23rd day	57/6.6	82	608	60/71	0.9/2.2
	41st day	112/6.9	29	519	23/37	1.1/2.2

BUN: blood urea nitrogen; Cr: creatinine; CK: creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase, ALT: alanine aminotransferase I/T: indirect/total.

lack of antivenin, she was transferred to the National Poison Center 24 hr after the snakebite. After admission, irritated mood, shortness of breath, muscle weakness of the four limbs with positive Barbinski's sign bilaterally, haematuria, fresh blood from the nasogastric tube, multiple ecchymotic lesions of both lower limbs and cold extremities with weak pulsation of the right pedis dorsalis were noted. Laboratory data (table 1 and 2) indicated that she suffered from deterioration of renal function, disseminated intravascular coagulation and bleeding tendency. The brain computerized tomogram examination revealed multiple low densities in the bilateral parieto-occipital, left insula, left lentiform nucleus, posterior limb of left internal capsule, right thalamus, bilateral high frontal, parietal and centrum semiovale area and high densities in the bilateral high frontal area (fig. 3a and b). One vial of antivenin specific to *D.r. formosensis* and transfusion with fresh frozen plasma, platelets and packed red blood cells were administered in the emergency room. She was admitted to intensive care unit 48 hr after the systemic envenoming. In the 3rd day, pulmonary oedema or infarction was suspected due to pink to bloody sputum and X-ray of the chest. Diffused myocardial ischaemia with significant left ventricle dysfunction was also suggested based on a cardiac echocardiogram. Two more doses of specific antivenin were administered under the impression of systemic arterial thrombosis. The haematological condition improved after the third dose of antivenin, but her vital function deteriorated to deep coma, low blood pressure and worsened renal function. Ultrafiltration was performed to remove possible fluid overload due to oligouric renal failure. Inotropic agents, such as dopamine, were used in order to restore adequate tissue perfusion. The patient's condition improved with normal coagulopathy, no more bleeding tendency, and more clear consciousness during the first week of hospitalization. Unfortunately, multiple septic conditions complicated the hospital course and the patient died after 49 days of hospitalization.

Results and Discussion

Several distinct and debilitating clinical effects caused by Russell's viper snake bites, such as coagulopathy, haemolysis, renal failure, generalized increase in capillary permeability, rhabdomyolysis and neurotoxicity, have been described previously (Warrell 1989) as serious health hazards across the entire geographical area of this species. The toxic components of Russell's viper venom including two major procoagulant enzymes, factor V and X activators, protease inhibitor, haemorrhagins, several enzymes and phospholipase A2 are abundant, which contribute to the distinct clinical pictures described in this paper. Incoagulable blood

Table 2.

Blood biochemical data showing the coagulability and blood cell counts of *D. r. formosensis* snakebite patients.

	Time after envenoming	PT/APTT sec./sec.	Fibrinogen mg/dl	FDP ug/ml	D-dimer ug/ml	Platelet $\times 10^3/\mu l$	Hb %	WBC/μl
Case 1	12 hr	46/35.8	<54	640	>3.0	53	16	15020
	26 hr					27	10.6	18100
	48 hr					40	9.1	10900
	7th day					71	9.1	
	10th day					177	9.4	14500
Case 2	24 hr	1.43(INR)		320	1.0–2.0	44	13.5	19800
	48 hr	1.04(INR)	20	640				
	3rd day	1.15(INR)	482	320	0.5–1.0	46	11.7	16400
	7th day	1.23(INR)	680	10		116	11.9	13300
	23rd day						8.8	8700
	41st day						9.6	13700

PT: prothrombin time; APTT: activated partial thromboplastin time; FDP: fibrinogen degradation products; Hb: hemoglobin; INR: international normalized ratio.

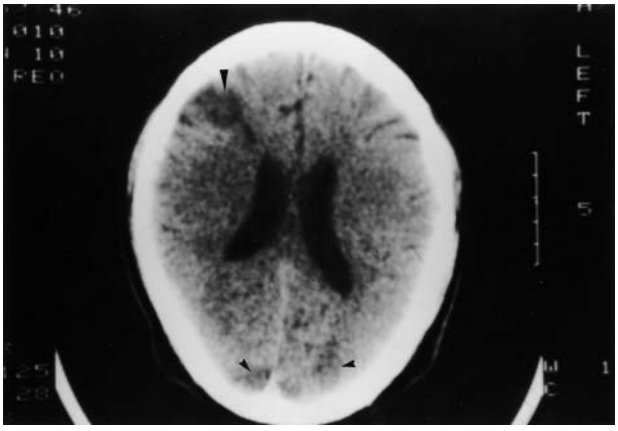

Fig. 1. Non-contrast computerized tomogram of the brain of case 1. Low density areas over bilateral fronto-temporal and right parieto-occipital regions (arrow heads indicate lesions).

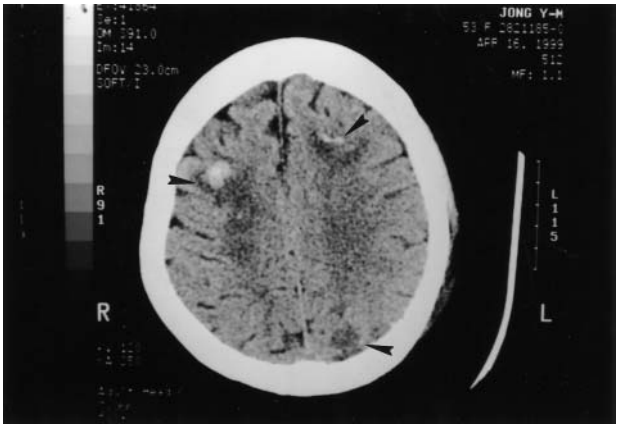

Fig. 3. Non-contrast computerized tomogram of the brain of case 2. Multiple low densities in the left occipital cortex, bilateral high fronto-parietal subcortical white matter and centrum semiovale area. High densities in the bilateral high frontal area (arrow heads indicate lesions).

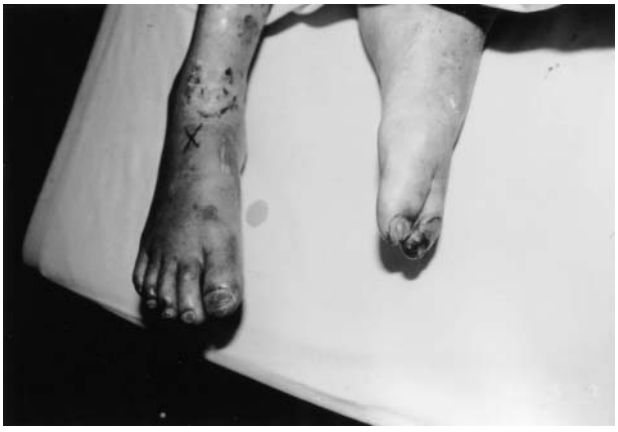

Fig. 2. Gangrenous change over multiple toes of both lower legs, X: indicate absence of pulsation of pedis dorsalis.

and spontaneous bleeding caused by consumption of haemostatic factors, including coagulation proteins and thrombocytes, are the most prominent manifestations and the leading cause of death from Russell's viper systemic envenoming. Although paralysis and neurological blockade might occur in cases of systemic envenoming of Sri Lanka Russell's viper (*D. r. pulchella*) (Phillips *et al.* 1988), intracranial haemorrhage, pituitary or intracerebral, and other systemic haemorrhages are the most frequent neurological features of Russell's viper bite (Tun-Pe *et al.* 1987). These two cases show the typical clinical manifestations of Russell's viper envenoming except for the multiple vascular occlusions.

Cerebral infarction, instead of haemorrhage, is rarely reported in cases of snakebite. *Bothrops lanceolatus* snake in Martinique may be the only snake in the world that induces systemic thrombosis in approximately 30% of snakebites (Thomas *et al.* 1995). In the literature, only one case of middle cerebral artery occlusion after a Russell's viper bite has been previously reported in an 18-year-old Sri Lankan woman shortly after snakebite (Ameratunga 1972). There have been few case reports of other snakebites with multiple thrombotic vascular occlusions away from the site of envenoming. They occur in systemic envenoming of saw-scaled viper (Bashir & Jinkins 1985; Murthy *et al.* 1997) and other European or Asian vipers (Aravanis *et al.* 1982; Iwakiri *et al.* 1995; Blondheim *et al.* 1996; Beer & Musiani 1998). The thrombotic occlusions occurred in vessels of vitals organs, such as brain, heart, lung and intestine, and led to significant morbidity or even mortality. Most cases of cerebral infarcts or other major vessel occlusions following snake envenoming developed in young people (5 in 13–28 years old, 2 in 57–58 years old). It is thought that venom-induced disseminated intravascular coagulation and vessel-damaging toxins in the venom, such as haemorrhagin, damage the vascular endothelium leading a definite thrombotic process. If the venom acts on the endocardium, the thrombosis may lead to a different presentation. Singh *et al.* (1998) described a mortality case (a 23-year-old person) of viper snakebite and autopsy due to non-bacterial thrombotic endocarditis complicated with multiple embolic infarcts in the kidneys, spleen and brain.

However, haemorrhagin was absent in the venom of *D.r. formosensis* (Lee 1948). The clinical and radiological findings of our patients strongly indicate that multiple thrombosis was the major pathogenesis of their problems. These clinical features caused by Russell's viper are unique in medical literature. Despite the absence of haemorrhagin, other major components in the venom of *D.r. formosensis* or other possible mechanisms may contribute to these unique clinical features. Russell's viper venom has been noted to exhibit both anticoagulant and coagulant effects (Than-Than *et al.* 1988). Arginine esterase of Russell's viper venom is similar to thrombin in its action and has a coagulant effect. Disseminated intravascular coagulation induced by these procoagulants and toxic components might play a decisive role. These procoagulants, once in the blood stream

in a sufficiently large dose, activate thrombin formation and lead to widespread intravascular deposition of fibrin and vascular occlusion. In small animals, which are the snake's natural prey, death ensues within a minute of the bite through massive blood coagulation within the heart and great vessels (Aung-khin *et al.* 1977). But in human victims, the dose of venom relative to body weight is insufficient to cause clot formation in the heart. The formation of thrombi in the microcirculation activates the fibrinolytic process (Spero *et al.* 1980) to lyse the clot. Systemic bleeding, instead of thrombotic occlusion, ensues due to depletion of coagulation factors and thrombocytopenia resulting from disseminated intravascular coagulation.

Systemic coagulation induced by disseminated intravascular coagulation can also result in intravascular formation of fibrin or platelet-like thrombi and ultimately thrombotic occlusion of small and midsize vessels (Margaretten 1967; Levi & Cate 1999). In India and Burma (Jayanthi & Gowda 1988; Than-Than *et al.* 1989), fibrin disposition in the renal microvasculature and parenchyma ischaemia was noted in cases of systemic envenoming of Russell's viper with rapid deterioration of renal function. Russell's viper venom has also been used to trigger arterial thrombosis in a model using atherosclerotic rabbits to study the mechanism of arterial thrombosis (Constantinides & Whyman 1962; Abela *et al.* 1995; Nakamura *et al.* 1997 & 2000). Russell's viper venom in a dose of only 150 μg/kg of body weight combined with histamine, an arterial vasoconstrictor in rabbits, can induce significant arterial thrombosis in rabbits with damaged/atherosclerotic arteries. In these studies, the Russell's viper venom was used as a procoagulant and endothelial toxin, and endothelial injury plays a central role in these processes (Picon *et al.* 1997). According to a study by Liau (1991), the average venom amount of a *D.r. formosensis* snake is 18.4±10.3 mg. If 40% of the venom in the venom glands is injected into a victim in each bite, the average dosage administered to a patient of 50 kg body-weight is close to 150 μg/kg. Thrombotic occlusion of atherosclerotic vessels might develop in a bite victim if vasoconstriction occurs during systemic envenoming. The history of arteriosclerosis was not clear in our patients, but varying degrees of atherosclerotic change must have existed in these patients, aged 52 and 67. The young age of previously reported cases, however, is in conflict with this speculation. The role of atherosclerotic vessels in Russell's viper venom-induced thrombotic occlusion needs further investigation.

Russell's viper snakebites are relatively rare in Taiwan as compared with other Southeast Asian countries. We encountered another case of severe Russell's viper venom systemic envenoming with suspected multiple vascular occlusions over vital organs. This old farmer (72 years old) was not radiologically examined due to unstable vital signs during hospitalization. These cases of systemic vascular occlusion after Formosan Russell's viper bite indicate that Formosan Russell's viper venom might play a decisive role in initiating the thrombotic process. The possibility of some intersubspecies or intraspecific variability might explain this unique clinical symptom (Chippaux *et al.* 1991).

We conclude that systemic thrombotic occlusion of blood vessels, in addition to bleeding diathesis and renal function impairment is a major feature of Formosan Russell's viper snakebite. Vasocontriction in atherosclerotic or damaged vessels might play a predisposing role in the mechanism of Russell's viper venom-induced thrombotic occlusion of vessels. Further studies are required to establish the true mechanism and the proper treatment of Russell's viper envenoming beyond specific antivenin.

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