CASE REPORT

Neurological Involvement and Hepatocellular Injury Caused by a Snake With Hematotoxin Envenomation

Watchareewan Sontichai, MD; Sanit Reungrongrat, MD; Paitoon Narongchai, MD; Rungrote Natesirinilkul, MD

From the Department of Pediatrics (Drs Sontichai, Reungrongrat, and Natesirinilkul); and the Department of Forensic Medicine (Dr Narongchai), Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Venomous snakes with hematotoxin—Russell’s viper (*Daboia* spp), Malayan pit viper (*Calloselasma rhodostoma*), and green pit viper (*Cryptelytrops albolabris* and *C macrops*, previously named *Trimeresurus* spp) are commonly found in Thailand. Coagulation factor activation, thrombocytopenia, hyperfibrinolysis, and disseminated intravascular coagulation are the main mechanisms of hemorrhaging from these snake bites. The neurological involvement and hepatocellular injury after Russell’s viper bites were reported in Sri Lanka, but there is no report from Southeast Asia. This case was a 12-year-old hill tribe boy who had ptosis and exotropia of the left eye, respiratory distress, and prolonged venous clotting time, prothrombin time, and activated partial thromboplastin time; low fibrinogen and platelet count; and transaminitis after being bitten by a darkish-colored snake. He did not respond to antivenom for cobra, Malayan pit viper, or Russell’s viper. However, his neurological abnormalities, respiratory failure, and hepatocellular injury improved, and coagulopathy was finally corrected after receiving antivenom for green pit viper. The unidentified snake with hematotoxin was alleged for all manifestations in this patient.

Key words: neurological abnormality, ptosis, exotropia, hepatocellular injury, coagulopathy, snake bite

Introduction

Russell’s viper (*Daboia* spp), Malayan pit viper (*Calloselasma rhodostoma*), and green pit viper (*Cryptelytrops albolabris* and *C macrops*; previously named *Trimeresurus* spp) are known as venomous snakes with hematotoxicity.¹ All of them are classified in the family Viperidae and are called vipers. They are commonly found in every region of Thailand.^{1–9} Although their toxin, hematotoxin, cause bleeding disorders, the mechanisms of each hematotoxin are different. Russell’s viper toxin activates factor V and X and, moreover, can cause disseminated intravascular coagulation (DIC), whereas the Malayan and green pit viper toxins have thrombin-like effects that cause hypofibrinogenemia, thrombocytopenia, and hyperfibrinolysis.^{5–8} Bleeding disorders, local swelling, and pain of the affected areas are the common presentations of patients bitten by snakes with hematotoxin.^{1,5–9} The toxicity of a Russell’s viper bite has been reported to cause neurological symptoms^{10–12}

and liver injury.¹³ Neurological involvement without intracranial bleeding and liver injury as a result of the bite of a snake with hematotoxin has never been reported in Thailand.

We report the case of a boy who had ptosis, exotropia, respiratory failure, rhabdomyolysis, and transaminitis after being bitten by a darkish-colored snake, which was not captured. He did not respond to antivenom for cobra, Malayan pit viper, or Russell’s viper. His neurological and respiratory abnormalities, coagulopathy, and hepatocellular injury finally recovered after receiving antivenom for green pit viper.

Case Presentation

A 12-year-old hill tribe boy, previously healthy, presented with swelling and pain in his left leg after being bitten on his left ankle by a snake in the forest while he was playing with a friend 2 days before he came to Maharaj Nakorn Chiang Mai University Hospital (MNCMUH). The patient described the snake as a 1-foot-long, darkish-colored snake. After the snake bite, the patient had gradual and continuous oozing from the bite wound without bleeding from other sites. One day

Corresponding author: Rungrote Natesirinilkul, MD, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand (e-mail: rungrote.n@cmu.ac.th).

later, he had more swelling and pain in his left leg. He was taken to the local hospital 26 hours after the snake bite. His vital signs were assessed as follows: temperature 36.2°C, pulse rate 94 beats/min, respiratory rate 20 breaths/min, and blood pressure 140/90 mm Hg. His oxygen saturation was 90% at room air, which was corrected by oxygen supplementation. The physical examination showed blood oozing from the wound and swelling of the left leg. Mild ptosis of the left eye was also noted. Neurological examination was otherwise normal. The initial evaluation of blood tests revealed hemoglobin of 15 g/dL, white blood cell count of $16.05 \times 10^3/\text{mm}^3$, platelet count of $224 \times 10^3/\text{mm}^3$, creatinine 0.57 mg/dL, prothrombin time (PT) greater than 180 seconds, activated partial thromboplastin time (APTT) more than 180 seconds, and venous clotting time (VCT) more than 30 minutes. Because of the desaturation and prolonged coagulation tests, he was treated with 3 doses of antivenom for cobra and Malayan pit viper (Queen Saovabha Memorial Institute, Thai Red Cross Society, Bangkok, Thailand) and 1 dose of tetanus toxoid 0.5 mL and tetanus antitoxin 30,000 units. Despite the treatment, desaturation and prolonged coagulation time were not corrected. After receiving antivenoms, vitamin K, and 6 units fresh frozen plasma, he still had bleeding symptoms and prolonged VCT.

At 51 hours after the snake bite, his left leg became more swollen and inflamed. Ptosis, diplopia, respiratory distress, and red urine developed. He was intubated and then transferred to MNCMUH. Ceftriaxone and amoxicillin/clavulanic acid were given. The physical examination at MNCMUH showed 2 fang marks 0.1 cm in diameter, each with a fang mark distance of 0.8 cm on the left lateral malleolus (Figure 1). He had mild

Figure 1. Fang mark on left ankle, below to left lateral malleolus (arrows).

Figure 2. Exotropia and ptosis of the left eye on day 1 of admission.

tenderness and swelling of the left ankle without hemorrhagic bleb or ecchymosis. There was no more oozing from the bite wound and no other bleeding from other sites. He had normal consciousness but ptosis of the left eye with palpable fissure distance 0.9 cm of the left eye while his right eye had the palpebral fissure distance of 1.5 cm. He also had exotropia of the left eye (Figure 2). In addition to ophthalmoplegia, he had paradoxical breathing when he was accidentally extubated despite having normal breath sound on both sides on examination. The blood tests on day 2 after the snake bite were as follows: complete blood count with hemoglobin 10.8 g/dL, white blood cell count $10.2 \times 10^3/\text{mm}^3$, and platelets $153 \times 10^3/\text{mm}^3$; blood chemistry with creatinine 0.6 mg/dL, total creatine kinase 135,846 U/L, total protein 6.7 g/dL, albumin 3.4 g/L, alkaline phosphatase 209 U/L, aspartate aminotransferase 3,897 U/L, alanine aminotransferase 1,268 U/L, total bilirubin 0.57 mg/dL, and direct bilirubin 0.07 mg/dL; arterial blood gas showed pH 7.47, pO_2 157 mm Hg and pCO_2 39.8 mm Hg with FiO_2 of 0.4 on ventilator setting; urine analysis showed heme 3+, red blood cell count 2 to 3/high-power field, white blood cell count 20 to 30/high-power field; coagulation tests found PT greater than 200 seconds, APTT more than 200 seconds, VCT greater than 30 minutes, D-dimer 8.5 mg/L, factor X clotting assay 71%, and factor V clotting assay 105%; his chest radiograph was unremarkable. The boy was diagnosed with snake bite and coagulopathy, respiratory failure, and myoglobinuria. He was treated with 5 doses of antivenom for Russell's viper and 1 dose of fresh frozen plasma in 48 hours without any improvement of the clinical symptoms and coagulopathy. Moreover, his platelet count was gradually decreasing to the lowest number, at $125 \times 10^3/\text{mm}^3$ on day 5 after the snake bite. His blood chemistry gradually improved, however.

After consultation with the institutional toxicologist and Ramathibodi Poison Center at Mahidol University in Bangkok, the patient was treated with antivenom for green pit viper on day 5 after the snake bite. He subsequently had clinical improvement of left ptosis, exotropia, and respiratory weakness within 12 hours after the first dose of antivenom. The coagulation tests also became normal within 6 hours and the platelet count within 24 hours after antivenom treatment. On day 10 of

the snake bite, however, his VCT, PT, and APTT were prolonged again. He was given a second dose of antivenom for green pit viper, and again, his coagulopathy was rapidly corrected, and blood testing remained in the normal range until he was discharged from the hospital. He was admitted to the hospital for 12 days and was discharged uneventfully on day 14 after the snake bite.

Discussion

The presentation of this patient was similar to the syndrome caused by the bite of a snake with hematoxin because he had pain and swelling of the affected part and abnormal coagulation tests, including prolonged VCT, PT, and APTT, and low fibrinogen and platelet count. These findings were compatible with Russell's, Malayan, or green pit viper toxicity.^{1,5-14} However, he also had ptosis, exotropia, and respiratory distress, which were compatible with the syndrome caused by the bite of a snake with neurotoxin, such as a cobra or king cobra. Therefore, he had indications for antivenoms for both hematoxin and neurotoxin.¹ Because of his description of the snake, the geographic range, and the severity of his clinical manifestations, he was treated with antivenoms for Malayan pit viper and cobra, 2 of the most likely snakes, although the chance of 2 snake bites at the same time was low. After 3 doses of antivenoms, however, he did not have any clinical and laboratory improvement but, rather, worsening respiratory symptoms.

In general, identification of snake bite is based on the examination of the snake by experienced medical personnel. If the snake is not available to be examined, as in our case, the details of the snake and circumstances of its bite obtained from the patient and a witness, combined with a clinical syndrome of symptoms and signs and incidence of common snake bites in each area can be used to infer the species of snake.¹ According to a report by the World Health Organization, the Malayan pit viper (40%), green pit viper (37%), and cobra (16%) are 3 of the most common causes of venomous snake bites in Thailand.¹ These findings were similar to a local report written in Chiang Mai.² The epidemiology of snake bite was quite different in Bangkok, where green pit viper was much more prevalent (77% to more than 90%) than the other types of venomous snakes.^{4,14} Although serologic testing to identify the species of snakes is the reliable method for diagnosing definite type of snake bite,^{15,16} these tests are not available in most general hospitals, and the interpretation of blood tests of patients who received antivenom is still problematic.

Russell's viper bite was the most likely diagnosis as it could explain most symptoms of this patient, according to a report by Kularatne.¹¹ That case series of 336 patients in Sri Lanka who were bitten by Russell's viper (*Daboia russelii russelii*) showed that neurological involvement was found in approximately 80%.¹¹ Ptosis and external ophthalmoplegia were the common neurological symptoms, which were the same as in another case series from Sri Lanka.¹⁰ The pathophysiology of neurological involvement was explained by 3 mechanisms: presynaptic inhibition of neurotransmission by phospholipase A₂ in Russell's viper venom,¹ intracranial hemorrhage, or acute brain infarction. Most patients who had acute brain infarction would display muscle weakness or seizure.¹² Neurological abnormalities usually resolve in 5 days regardless of the effect of antivenom.¹¹ In our case, however, the patient still had neurological symptoms on day 5 after the snake bite. Furthermore, there has been no report of neurological involvement by *Daboia russelii siamensis*, the species of Russell's viper found in Thailand.^{1,11} Respiratory distress was also found in patients with Russell's viper bites, but the cause of dyspnea could be from pulmonary edema (36%)¹⁰ or respiratory muscle weakness, which was uncommon.¹¹ Nonetheless, regarding normal chest radiograph and arterial blood gas, the latter was more likely the cause in this patient.

The patient in this case had red urine with positive urine heme by urine dipstick, but no significant red blood cells or red blood cell cast in the urine, and markedly elevated total creatine kinase, so he was suspected of having rhabdomyolysis and myoglobinuria rather than hematuria or hemoglobinuria. Rhabdomyolysis has a wide range of prevalence, from 14% to 73% of patients bitten by Russell's viper.¹⁰ The depletion of platelet count, fibrinogen, and factors V and X were commonly found in patients with Russell's viper bites.⁵ However, the results of factors V and X clotting assay in this patient should be carefully interpreted because he received fresh frozen plasma before blood testing.

Kularatne¹¹ reported the manifestations of hematotoxicity from Russell's viper usually improved within 48 hours in most patients (94%) after antivenom administration.¹¹ Unlike the previous report, our patient did not have any response to antivenom for Russell's viper, even though he received 5 doses of antivenom within 48 hours. Severe liver injury was found in only 1 report of a patient who was bitten by Russell's viper.¹⁵ Renal failure, which was a common complication (in 5 of 7 patients) in the case series of Russell's viper bites in Thailand, was not found in our patient. Therefore, a Russell's viper bite was less likely in our patient.

Many types of green pit viper are found in all parts of Thailand, but 3 of the most common species are *Cryptelytrops albolabris*, *C. macrops*, and *C. popeorum*.^{3,7,14,17} The color of the latter 2 species is darker than the former.^{3,7} The toxin of green pit viper acts like thrombin that can cleave fibrinogen but has no effect on fibrinopeptide B of fibrinogen. This phenomenon causes the depletion of fibrinogen but no formation of fibrin clot.⁶ The toxin also activates platelets to aggregate and cause thrombocytopenia.^{3,18} Moreover, hyperfibrinolysis can be found after a green pit viper bite.¹⁷ Bleeding, local swelling, and pain are some of the most common presentations in these patients, but usually they are mild to moderate.^{5,6} However, patients bitten by *C. albolabris* would have more severely affected parts, with blisters and skin necrosis, than the other 2 species.³

Rojnuckarin et al¹⁷ reported that, owing to the large molecule of green pit viper venom, the clearance of its venom antigen could be more delayed than cobra or Russell's viper venom antigen. Moreover, symptoms can recur in patients bitten by vipers because of slow absorption of the venom from the wound, as seen in this patient.^{3,17} In addition, this patient had severely prolonged coagulation tests while his platelet count was relatively normal. These results were compatible with the kinetic study of venom antigen of green pit viper that showed early prolongation of coagulation test but delayed thrombocytopenia.¹⁷ The proposed mechanism was because of different components in green pit viper venom, with longer half-life that could stimulate platelets and cause thrombocytopenia.

The only report regarding neurological involvement after a green pit viper bite was from Thailand, but that patient's course was complicated by tetanus.¹⁹ Our patient, however, received tetanus toxoid, tetanus antitoxin, and antibiotics that could cover anaerobic bacteria since admission to the local hospital; thus, the possibility for tetanus for this patient was low. To our knowledge, the mechanism of neurological involvement in this case is still unclear. Also, there is no explanation for the hepatocellular injury. Myoglobinuria might be a result of a local muscle injury from proteolytic enzymes in the snake venom.¹ Although Coca-Cola urine was found in a patient who had acute tubular necrosis after a green pit viper bite,⁵ no laboratory test of myoglobinuria was available to confirm the etiology of the brown-colored urine.

STUDY LIMITATIONS

There are several limitations to this report. Firstly, no blood testing confirmed the exact type of snake. Serological testing for confirmation of green pit viper bite is

still not available for routine service in Thailand, and interpretation of the test in a patient who received antivenom is still doubtful. Secondly, although no bleeding was detected on a computed tomography brain scan of this patient, magnetic resonance imaging would have been more sensitive to detect brain parenchyma lesion, especially infarction, than computed tomography. Thirdly, all symptoms might have resolved spontaneously, not by the effect of antivenom, because this patient had been admitted for a week when he recovered. Fourthly, the explanation for liver injury and rhabdomyolysis in this patient was unclear.

Even though the specific species of snake could not be identified, this patient was likely bitten by a snake with hematotoxin, as supported by the markedly abnormal coagulation tests.

Acknowledgments

We would like to thank Ramathibodi Poison Center at Mahidol University, Bangkok, for the excellent consulting service. We also would like to thank Mr Ken Dolen and Dr Pimlak Charoenkwan for English language editing of the manuscript.

References

1. Warrell DA. *Guideline for the Management of Snake-Bites*. New Delhi, India: World Health Organization; 2010.
2. Nantachit N, Chaimongkol B, Nawarawong W. Poisonous snake bite patients treated at the Chiang Mai University Hospital. *Chiang Mai Med Bull*. 1983;3:219–224.
3. Hutton RA, Looareesuwan S, Ho M, et al. Arboreal green pit vipers (genus *Trimeresurus*) of South-East Asia: bites by *T. albolabris* and *T. macrops* in Thailand and a review of the literature. *Trans R Soc Trop Med Hyg*. 1990;84: 866–874.
4. Dumavibhat B. A study of epidemiology, risk factors and preventive measures against snake bites. *J Med Assoc Thai*. 1997;80:547–556.
5. Mahasandana S, Rungruxsirivorn Y, Chantarangkul V. Clinical manifestations of bleeding following Russell's viper and green pit viper bites in adults. *Southeast Asian J Trop Med Public Health*. 1980;11:285–293.
6. Dumavibhat B, Visudhiphan S, Malasit P. Severe cases of green pit viper snake venom poisoning. *J Med Assoc Thai*. 1989;72:593–596.
7. Visudhiphan S, Tonmukayakul A, Tumliang S, Dumavibhat B, Piankijagum A. Dark green pit viper (*Trimeresurus popeorum*) bite: clinical and serial coagulation profiles in 51 cases. *Am J Trop Med Hyg*. 1989;41:570–575.
8. Rojnuckarin P, Mahasandana S, Intragumthornchai T, Sutcharitchan P, Swasdikul D. Prognostic factors of green pit viper bites. *Am J Trop Med Hyg*. 1998;58:22–25.

9. Wongtongkam N, Wilde H, Sitthi-Amorn C, Ratanabanangkoon K. A study of 225 Malayan pit viper bites in Thailand. *Mil Med*. 2005;170:342–348.
10. Jeyarajah R. Russell's viper bite in Sri Lanka. A study of 22 cases. *Am J Trop Med Hyg*. 1984;33:506–510.
11. Kularatne SA. Epidemiology and clinical picture of the Russell's viper (*Daboia russelii russelii*) bite in Anuradhapura, Sri Lanka: a prospective study of 336 patients. *Southeast Asian J Trop Med Public Health*. 2003;34:855–862.
12. Gawarammana I, Mendis S, Jeganathan K. Acute ischemic strokes due to bites by *Daboia russelii* in Sri Lanka—first authenticated case series. *Toxicon*. 2009;54:421–428.
13. de Silva HJ, Ratnatunga N, de Silva U, Kularatne WN, Wijewickrema R. Severe fatty change with hepatocellular necrosis following bite by a Russell's viper. *Trans R Soc Trop Med Hyg*. 1992;86:565.
14. Rojnuckarin P, Intragumtornchai T, Sattapiboon R, et al. The effects of green pit viper (*Trimeresurus albolabris* and *Trimeresurus macrops*) venom on the fibrinolytic system in human. *Toxicon*. 1999;37:743–755.
15. Kittigul L, Ratanabanangkoon K. Reverse passive hemagglutination tests for rapid diagnosis of snake envenomation. *J Immunoassay*. 1993;14:105–127.
16. Chinonavanig L, Karnchanachetanee C, Pongsettakul P, Ratanabanangkoon K. Diagnosis of snake venoms by a reverse latex agglutination test. *J Toxicol Clin Toxicol*. 1991;29:493–503.
17. Rojnuckarin P, Banjongkit S, Chantawibun W, et al. Green pit viper (*Trimeresurus albolabris* and *T. macrops*) venom antigenaemia and kinetics in humans. *Trop Doct*. 2007;37:207–210.
18. Soogarun S, Choewbamrunangkit M, Wiwanitkit V, et al. The effect of green pit viper (*Trimeresurus albolabris*) venom on platelet morphology by electron microscopy. *Southeast Asian J Trop Med Public Health*. 2006;37:937–939.
19. Suankratay C, Wilde H, Nunthapisud P, Khantipong M. Tetanus after white-lipped green pit viper (*Trimeresurus albolabris*) bite. *Wilderness Environ Med*. 2002;13:256–261.