Local tissue necrosis and thrombocytopenia following Bungarus multicinctus envenomation in a child

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ABSTRACT
Snakebite envenoming is a global public health problem. The pediatric population poisoned by snakebite envenoming has different features than adult patients. Bungarus multicinctus is a highly venomous species of the elapid snake. The documented clinical presentations following Bungarus multicinctus envenoming are minimal local reactions, respiratory failure, general pain, and life-threatening hyponatremia. We present an uncommon case of Bungarus multicinctus envenomation in a girl with unusual clinical findings, including severe tissue necrosis and thrombocytopenia with coagulopathy.

Key words: Bungarus multicinctus, necrosis, thrombocytopenia, blood coagulation disorder, child.

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INTRODUCTION
About 5 million snakebites occur each year around the world.1 Bungarus multicinctus is a highly venomous species of the elapid snake, which is wildly distributed in southern China. Bungarus multicinctus bites account for about 7.5 % of total snakebite records each year in China2 and the mortality rate reported is about 7-50 %.2,3 The documented clinical presentations caused by envenomation of Bungarus multicinctus are minimal local reactions,3 respiratory failure, general pain,2 and life-threatening hyponatremia.4,5 We present an uncommon case of Bungarus multicinctus envenomation in a girl with severe tissue necrosis and thrombocytopenia with coagulopathy.

CASE REPORT
A 7-year-old girl living in a mountainous area in southern China was bitten by a many-banded snake on her right index finger as she tried to pull a plastic ball out of a hole. Her father witnessed the event and kept the snake away. She immediately went to the pediatric surgery department without any specific treatment. It took her three hours to transfer to our institution. According to the process description from her father, the surgeon displayed a picture of the Bungarus multicinctus for him to witness. Her father quickly identified it as the snake that had bitten his daughter.

The girl was conscious and complained of right hand pain. Her vital signs included a heart rate of 100 beats per minutes, systolic blood pressure of 98 mmHg and diastolic blood pressure of 70 mmHg, respiratory rate of 28, oxygen saturation of 98 %, and body temperature of 36.8 ºC. On admission, there were fang marks on her right index finger. Superficial sensitivity and capillary refill of the bite site were normal.

In addition, there was no skin rash, redness, or swelling. The girl was hospitalized and positive findings of laboratory tests included a white blood cell count of 21.75×10^9/L and serum potassium concentration of 3.1 mmol/L. Her prothrombin time (PT) and International Normalized Ratio (INR) were 11.7 and 1.02 seconds, respectively (Table 1). Liver and kidney function were normal. Specific treatments with anti-venom against Viper, anti-tetanus toxin, and cephalexin were prescribed within one hour since the beginning of hospitalization. Surgical debridement was performed in the next thirty minutes. The wound was kept open and rinsed by saline injection thoroughly. The complete blood count and coagulation function were rechecked in the first 24 hours after debridement.

On day 2, her physical examinations were notable for skin redness, swelling, and erythema at the biting site. The count of platelets decreased...
from 369×10⁹/L to 32×10⁹/L with prolonged prothrombin time, a higher level of D-dimer (D-2) and fibrin degradation product (FDP) (Table 1). Diphenhydramine was added in addition to cephalexin. On day 3, the impaired hand developed pale fingers, reduced superficial sensitivity, and progressive swelling spreading from the bite site to the forearm. Her upper right limb was tender upon palpation (Figure 1A). Open decompression of the carpal canal and fascial compartment of the forearm was performed urgently. Twenty-four hours after the invasive procedures, superficial sensitivity and capillary refill were improved. However, the counts of platelets continued to decline. The lowest platelets count was 3×10⁹/L accompanied with prolonged prothrombin time of 44.8 s (Table 1). The patient required transfusion of allogeneic cryoprecipitate and platelets. No bleeding episodes occurred. On day 5, complete skin necrosis began originating at the sting site and spread to the wrist joint. Full-thickness skin loss reached about 1 % of the body surface area (Figure 1B). The motion of the right index finger was limited due to significant damage of the metacarpophalangeal joint. Repeated microbial cultures of the wound exudates had negative results. The progressive decline in platelet count stopped. Blood coagulation parameters returned to normal. On day 17, wound debridement and continuous vacuum sealing drainage (VSD) were conducted (Figure 1C).

On day 39, an attempt was made to repair the skin defect on the right hand with a crossed skin flap from the arm. On day 75, her wounds were healing well. A complete blood count showed a white blood cell count of 6.5×10⁹/L and a platelet count of 490×10⁹/L (Table 1). At a follow-up visit 60 days after the discharge, the normal function of the right index finger still depended on specific rehabilitation exercises for long-term recovery. (Figure 1D).

**DISCUSSION**

Neuromuscular symptoms are known outstanding complications of *B. multicinctus*

**TABLE 1. Evolution of platelets count and coagulation function**

| Test value         | Day 1  | Day 2  | Day 3  | Day 4  | Day 5  | Day 74 |
|--------------------|--------|--------|--------|--------|--------|--------|
| Platelets count (×10⁹/L) | 369    | 32     | 3      | 64     | 68     | 490    |
| PT (s)             | 11.7   | 20.9   | 44.8   | 11.5   | 12.4   | 12.2   |
| PT-INR (s)         | 1.02   | 1.88   | 4.23   | 1      | 0.93   | 1.06   |
| APTT (s)           | 23.6   | 33.4   | 32.2   | 22.7   | 25.1   | 23.1   |
| TT (s)             | 18.7   | 19.1   | 18.3   | 14.8   | 15     | 19.2   |
| D-2 (μg/mL)        | 0.77   | 2.73   | 3.17   | 1.24   | 0.35   | 0.28   |
| FDP* (μg/mL)       | 3.6    | 16.6   | 12.27  | 5.08   | 3.2    | 2.5    |

**PT**, prothrombin time; **PT-INR**, ratio of thrombin time international; **APTT**, activated partial thromboplastin time; **TT**, thrombin time; **D-2**, D-dimer; **FDP**, fibrin degradation product; ***, the normal value of the FDP is less than 5 μg/mL.
envenomation. The existing literature also documented mild local reactions. Severe local reactions and significant thrombocytopenia with coagulopathy in the present case have not been previously reported.

The degree of envenoming injury of venomous snakebites is relevant to the categories of snake toxins. The well-studied venoms of B. multicinctus are α, β, and γ-bungarotoxin. The α-bungarotoxin destroys binding of acetylcholine and acetylcholine receptors; β and γ-bungarotoxin inhibit the release of acetylcholine from the nerve terminal. Reduced depolarization in the postsynaptic membrane leads to neuromuscular blockade. Its common symptoms are ptosis, ophthalmoplegia, mydriasis, pharyngeal pain, palatal palsy, limb paralysis, and even breathing muscles paralysis, which is the main factor causing patients’ respiratory failure. However, the outstanding symptoms of this case were severe tissue necrosis and thrombocytopenia, rather than neuromuscular symptoms. This shows that the victim suffered from a different kind of venomous destruction. In fact, a total of 136 proteins have been identified in Bungarus multicinctus. About 5.9% of proteins are venomous proteins. In addition to the 17 toxic families discovered previously, new protein families such as phospholipases A2 (PLA2), metalloproteinase, hyaluronidase, and vascular endothelial growth factor have been found in B. multicinctus toxins. Their biological reactions and clinical effects are still unclear.

Snake venom-related tissue destruction can lead to long-term pathophysiological, social and psychological effects on victims. Among the intricate pathological changes, toxin-induced damage targeting cells and extracellular matrixes (ECMs) is an important factor for tissue destruction. PLA2 homologues are the principal mycotoxins destroying the integrity of the plasma membrane. Snake venom metalloproteinases (SVMPs) are able to lead to the degradation of ECMs. Both PLA2 and SVMPs are found in the venom of B. multicinctus. They may be responsible for the severe tissue necrosis in this case.

Coagulopathy and hemorrhage are potential effects on victims following snake envenoming. Defibrination and anticoagulation are two principal patterns of snake venom-induced coagulopathy. Defibrination coagulopathy manifests as prolonged PT/PT-INR and APTT with low to absent FDP. Prolonged PT/PT-INR and APTT with elevated FDP occurring in this case conformed to the features of defibrinogenating coagulopathy.

Platelets play an important role in human hemostatic processes. There are two dramatic effects, including inhibition or promotion of platelet activity, on platelet function following snake envenoming. Excessive promotion of platelet activity increases the consumption of available platelets, resulting in lower circulating numbers of platelets. It also increases the bleeding risk. Two venom components, PLA2 and α-fibrinogenase, can promote platelet activity. PLA2-induced platelet activity may be responsible for thrombocytopenia occurring in this case.

Unlike common coagulopathies, rapid development and spontaneous resolution are characteristics of snakebite-related coagulopathy. However, the speed of development and resolution of coagulopathy is highly variable. Time from the bite to coagulopathy can be less than 15 minutes for some Australian elapid snakes, while complete resolution may take several hours or days. By contrast, the present case had initial coagulopathy at 24 hours post-bite but severe coagulopathy with thrombocytopenia occurred 48 hours post-bite. The time to complete resolution of coagulopathy was 72 hours post-bite. The emergence of marked coagulopathy was relatively late, whereas the consumption of coagulation factors commenced by early activation of the coagulation system caused by snake envenoming.

It needs to mention that we identified the B. multicinctus based on identification of witness rather than capturing it. There was a possibility that the atypical clinical evolution for Bungarus bites may due to another species.

Here we have presented a rare case of local tissue necrosis and coagulopathy with thrombocytopenia from a B. multicinctus envenomation. Regional reactions are worse than in previous reports. B. multicinctus venom contains multiple toxins that could contribute to these local effects as well as to coagulopathy with thrombocytopenia. Administration of antivenom against B. multicinctus is the mainstay therapy when victims confront B. multicinctus envenomation. If specific antivenom is unavailable, correction of coagulopathy and application of surgical intervention are supportive measures to reduce venom-related complications.
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