Case Report

Potentially fatal coagulopathy secondary to yamakagashi (*Rhabdophis tigrinus*) bites that completely recovered with antivenom treatment

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Case: A healthy 40-year-old man was admitted with severe coagulopathy that developed after *Rhabdophis tigrinus* bites. On admission, he showed significantly elevated levels of thrombin–antithrombin III complex (60 ng/mL), plasmin–alpha 2-plasmin inhibitor complex (22.3 μg/mL), and fibrinogen degradation products (592 μg/mL). He subsequently developed severe hypofibrinogenemia (50 mg/dL).

Outcome: Antivenom was given 28 h after the patient was bitten, following which his hemorrhagic symptoms resolved. By day 3 of admission, scabs had formed over the bite wounds. Furthermore, his fibrinogen levels increased to >100 mg/dL, while his thrombin–antithrombin III complex, plasmin–alpha 2-plasmin inhibitor complex, and fibrinogen degradation product levels normalized. He was discharged on day 6 of admission.

Conclusion: *Rhabdophis tigrinus* bites induced disseminated intravascular coagulation with a fibrinolytic phenotype, which completely recovered with antivenom treatment.

Key words: Antivenom, disseminated intravascular coagulation with a fibrinolytic phenotype, hypofibrinogenemia, *Rhabdophis tigrinus* bites, thrombin–antithrombin III complex

INTRODUCTION

YAMAKAGASHI *(RHABDOPHIS TIGRINUS)*, mamushi (*Gloydius blomhoffii*), and habu (*Protobothrops flavoviridis*) are venomous snakes in Japan. *Rhabdophis tigrinus* is a rear-fanged venomous snake often found in paddy fields.[1] Its venom shows strong plasma coagulant activity, with prothrombin activating effects and weak thrombin-like effects that result in hemorrhagic symptoms.[2] Because this snake has no grooved fangs, envenomation does not occur in most bites; therefore, this snake has long been considered non-venomous.[1] Although *R. tigrinus* bites induces life-threatening injuries, their mechanism and treatment have not been examined because of the extremely rare incidence of severe cases (nine cases reported over the past 13 years), compared with that of bites from *G. blomhoffii* and *P. flavoviridis*.[1,3,4]

Our former survey indicated that the pathophysiology of *R. tigrinus* bites was considered disseminated intravascular coagulation (DIC) with a fibrinolytic phenotype; however, the details of coagulation markers remain unknown. Moreover, although antivenom therapy prepared from hyperimmunized horses (antivenin serum therapy) is established against *R. tigrinus* bites, sufficient information regarding antivenom therapy has not been provided in clinical practice.[3,5]

Here we describe the trends of coagulations markers in the case of *R. tigrinus* bites and highlight the antivenom therapy for *R. tigrinus*.

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CASE REPORT

A 40-YEAR-OLD MAN WITH no significant past medical history was bitten on his left hand by a snake

while fishing in a river in the afternoon. He went home and confirmed that the snake was *R. tigrinus* through an internet search. Nine hours after he was bitten, his left hand became tender and swollen, and another 3 h later, he began to bleed from the wound site. He visited the emergency center at a local hospital, where he was given first-aid treatment, including wound irrigation and suction. However, the bleeding persisted and petechiae developed; therefore, he visited the hospital again the following day.

On presentation, his Glasgow Coma Scale score was 15/15, and his vital signs were as follows: blood pressure, 122/66 mmHg; heart rate, 70 b.p.m.; and respiratory rate, 12 breaths/min. His oxygen saturation was 100% while breathing room air. Petechiae were observed on the tip of his nose and right cheek. Although his left hand was bleeding, no epistaxis or hematuria was observed.

The patient's laboratory data revealed severe coagulopathy (Table 1), particularly severe hypofibrinogenemia. On the basis of these findings and his clinical history, a final diagnosis of coagulopathy secondary to *R. tigrinus* bites was made. The patient was subsequently admitted to emergency hospital for treatment. On admission, his DIC diagnostic score as defined by the Japanese Association of Acute Medicine criteria[6] was 4. In addition, his thrombin–antithrombin III complex (TAT; normal range, <3–4 ng/mL), plasmin–alpha 2-plasmin inhibitor complex (PIC; normal range, <0.8 μg/mL), and fibrinogen degradation product (FDP) levels were significantly elevated at 60 ng/mL, 22.3 μg/mL, and 592 μg/mL, respectively. The patient's clinical course and trends of coagulation markers are shown in Figure 1.

We requested the assistance of the Japan Snake Institute (Gumma, Japan), where the diagnosis of *R. tigrinus* bites was confirmed by laboratory data and clinical symptoms. Antivenom from the Chemo-Sero-Therapeutic Research Institute (Kaketsuken; Kumamoto, Japan; Fig. 2) was delivered to the hospital 27 h after the *R. tigrinus* bites. One hour later, one vial of antivenom was administered to the patient following premedication with antihistaminics and steroids. No anaphylactic reaction was observed.

On day 2 of admission (16 h after antivenom treatment), the bleeding from the wound site subsided. Complete hemostasis was achieved 24 h after treatment. By day 3 of admission, scabs had formed over the wounds (Fig. 3). His fibrinogen level increased to >100 mg/dL, while his TAT, PIC, and FDP levels normalized. Clotting factor replacement with fresh frozen plasma or protease inhibitors were not required for DIC treatment, and no serious hemorrhagic complication was observed. The patient was discharged on day 6 of admission and was followed-up for 1 month, during which no clinical symptoms representing serum sickness were observed.

Table 1. Laboratory data on admission of a 40-year-old man with severe coagulopathy that developed after *Rhabdophis tigrinus* bites

Blood cell count	
WBC	9840/μL
RBC	447 × 104/μL
Hb	14.4 g/dL
Ht	42.4%
Plt	19.6 × 104/μL
Biochemistry	
TP	6.6 g/dL
TB	0.8 mg/dL
BUN	17 mg/dL
Cr	1 mg/dL
AST	26 U/L
ALT	18 U/L
LDH	347 U/L
AMY	87 U/L
CK	484 U/L
Na	141 mEq/L
K	3.5 mEq/L
Cl	105 mEq/L
Ca	8.9 mEq/L
CRP	0.3 mg/dL
GLU	98 mg/dL
Coagulation system	
PT	ODL
APTT	ODL
Fibrinogen	50 mg/dL
PIC	22.3 μg/mL
TAT	60 ng/mL
FDP	592 μg/mL
AT-III	79%

AMY, amylase; APTT, activated partial thromboplastin time; AT-III, antithrombin-III; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; Cr, creatinine; FDP, fibrinogen degradation products; GLU, glucose; K, potassium; Na, sodium; ODL, over detection limit; Plt, platelet; PT, prothrombin time; TB, total bilirubin; TP, total protein.

DISCUSSION

WE DESCRIBED A case of *R. tigrinus* bites that completely recovered following antivenom treatment in a 40-year-old patient who developed DIC accompanied by bleeding manifestations secondary to the bites.

Our current case developed markedly elevated TAT, PIC, and FDP levels on admission. Asakura reported that severely elevated makers indicate DIC, particularly DIC with enhanced fibrinolysis (fibrinolytic phenotype),[7] which is observed in patients with severe blunt trauma in the acute phase[8] or acute leukemia, particularly acute promyelocytic

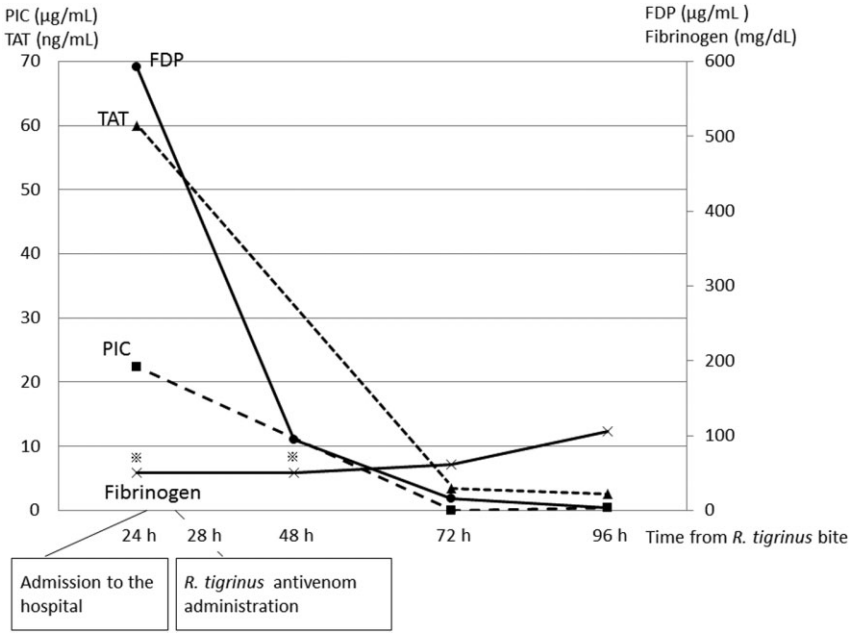

Fig. 1. Trends of coagulation markers in a 40-year-old man admitted with severe coagulopathy that developed after *Rhabdophis tigrinus* bites. Thrombin–antithrombin III complex (TAT), plasmin–alpha 2-plasmin inhibitor complex (PIC), and fibrinogen degradation product (FDP) levels were markedly elevated on admission and normalized following treatment with antivenom.

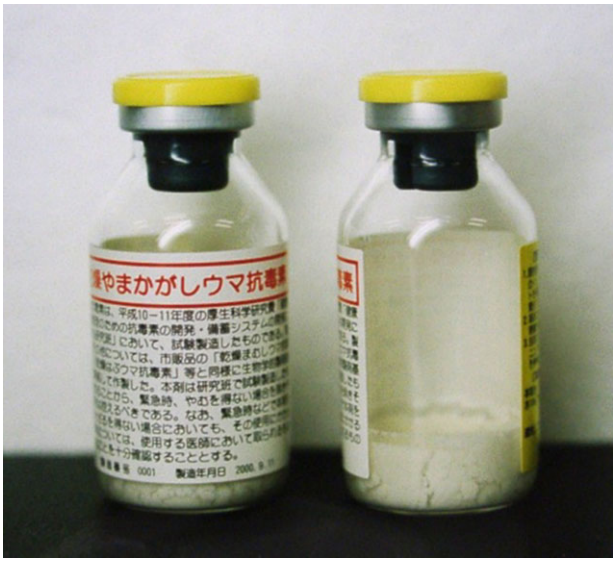

Fig. 2. Antivenom against yamakagashi (*Rhabdophis tigrinus*) was manufactured from hyperimmunized horses with support from Health Science Grants (1998–1999) by the Ministry of Health, Labour and Welfare, in 2000. It was freeze-dried to maintain its initial potency for longer periods.

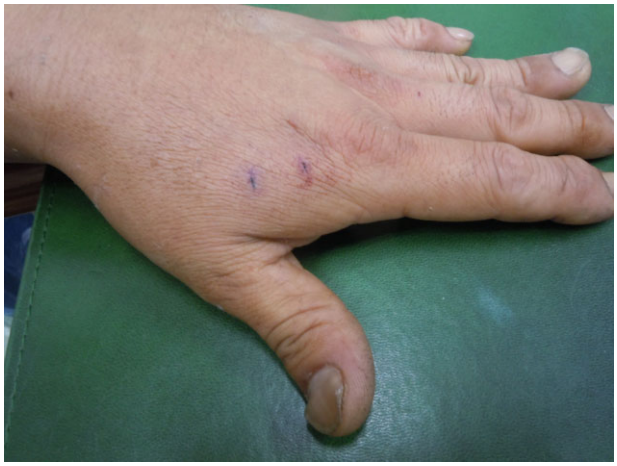

Fig. 3. Photograph of the patient's left hand on the third day of admission following *Rhabdophis tigrinus* bites, showing rhagades and scabs.

leukemia.[9] We realized that the pathophysiology of *R. tigrinus* bites in acute phase is DIC with enhanced fibrinolysis (fibrinolytic phenotype) by the examination of coagulation markers, such as TAT, PIC, and FDP. However, because primary fibrinogenolysis activation and fibrinolysis suppression were not followed, the change of DIC with enhanced fibrinolysis after the acute phase of injury remains unknown.

Gando *et al*.[10] reported that 24–48 h after severe traumatic injury, DIC with a fibrinolytic phenotype converts to DIC with a thrombotic phenotype, which causes fatal multiple organ dysfunction syndrome (MODS). In the current patient, although the levels of coagulation markers were markedly elevated on admission, they normalized promptly following antivenom treatment. It appears that *R. tigrinus* antivenom

can result in normalization of coagulation markers as well as clinical recovery without the development of multiple organ dysfunction syndrome, even in the presence of severe DIC.

Therefore, antivenom therapy should be considered for patients with *R. tigrinus* bites. In the current case, antivenom was given 28 h after the *R. tigrinus* bites with completely recovery. The median time from *R. tigrinus* bites to antivenom treatment in our previous survey was 35 h due to both the inconvenient supply of antivenom and the delays in diagnosis.[3] Compared with the more common *G. blomhoffii* bites, which are typically rapidly progressive, there appears to be a longer therapeutic window for administering *R. tigrinus* antivenom. However, because *R. tigrinus* antivenom only neutralizes the unbound venom, and cannot restore organ function, antivenom should be given as early as possible.

Although *R. tigrinus* antivenom is considered a definitive and effective treatment, it was not approved for clinical use and was only experimentally manufactured by a regional health laboratory in 2000. In total, 1369 vials were produced and they were stored at two institutes, the Japan Snake Institute and the Chemo-Sero-Therapeutic Research Institute.[1] Because *R. tigrinus* antivenom is manufactured by immunizing horses, we should remain vigilant to the risk of adverse events such as anaphylaxis and serum sickness disease. We carried out an *in vitro* examination regarding the effectiveness and safety of antivenom, and confirmed that the quality of antivenom has not been changed for the past 13 years.

Although the safety is examined, we recommend that premedication with antihistaminics and steroids should be considered for anaphylaxis.

There are some limitations to the current case report. First, because tissue plasminogen activator was not evaluated, the modes of primary fibrinogenolysis activation remain unclear. Moreover, plasminogen activator inhibitor-1, which induces fibrinolysis suppression, was not evaluated. Further study is required to clarify the pathophysiology of *R. tigrinus* bites.

CONCLUSION

Rhabdophis tigrinus bites induced DIC with a fibrinolytic phenotype, which completely recovered with antivenom treatment.

CONFLICT OF INTEREST

NONE.

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REFERENCES

1 Morokuma K, Kobori N, Fukuda T *et al*. Experimental manufacture of equine antivenom against yamakagashi (*Rhabdophis tigrinus*). Jpn J. Infect. Dis. 2011; 64: 397–402.
2 Komori K, Konishi M, Maruta Y *et al*. Characterization of a novel metalloproteinase in Duvernoy's gland of *Rhabdophis tigrinus tigrinus*. J. Toxicol. Sci. 2006; 31: 157–68.
3 Hifumi T, Sakai A, Yamamoto A *et al*. Clinical characteristics of Yamakagashi (*Rhabdophis tigrinus*) bites: a national survey in Japan, 2000–2013. Journal of Intensive Care. 2014; 2: 19.
4 Hifumi T, Yamamoto A, Morokuma K *et al*. Surveillance of the clinical use of mamushi (*Gloydius blomhoffii*) antivenom in tertiary care centers in Japan. Jpn J. Infect. Dis. 2011; 64: 373–6.
5 Sakai A. Diagnosis and treatment of snakebite by Mamushi and Yamakagashi. Chudoku kenkyu. Chudoku Kenkyu. 2013; 26: 193–9.
6 Gando S, Iba T, Eguchi Y *et al*. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit. Care Med. 2006; 34: 625–31.
7 Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. J. Intensive Care 2014; 2: 20.
8 Gando S, Tedo I, Kubota M. Posttrauma coagulation and fibrinolysis. Crit. Care Med. 1992; 20: 594–600.
9 Barbui T, Falanga A. Disseminated intravascular coagulation in acute leukemia. Semin. Thromb. Hemost. 2001; 27: 593–604.
10 Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. Ann. Surg. 2011; 254: 10–9.