Background

Rhabdophis tigrinus (Yamakagashi snake) is a rear-fanged venomous snake present throughout Russia and Asia [1]. Its venom induces life-threatening hemorrhagic symptoms and severe disseminated intravascular coagulation (DIC) with a fibrinolytic phenotype [2].

R. tigrinus antivenom manufactured by the immunization of horses to neutralize the venom has the risk of adverse events such as anaphylaxis and serum sickness disease [1,2]. It should be used when benefit is greater than the risk of adverse effects; however, its efficacy has not been well evaluated. Although our previous survey of nine cases demonstrated that seven of all cases treated with antivenom survived, the clinical characteristics and prognosis without antivenom administration remained unclear [3]. Further, theoretically, *R. tigrinus* antivenom only neutralizes the unbound venom and cannot restore organ function. Antivenom was administered after patients developed severe DIC in the study (the median interval between bite and antivenom administration was 35 h) [2]. We assume that the *R. tigrinus* antivenom administration overlaps self-recovery with supportive care.

The present study therefore aimed to determine the association between antivenom administration and outcome with further analyzed cases.

Methods

The institutional review board of the Japan Snake Institute approved the present study.

Patients and setting

The Japan Snake Institute was established in 1968 to research medical application of snakes.

In clinical practice, physicians managing patients with snake bites usually ask for the assistance of the Japan Snake Institute, where diagnosis is confirmed according to laboratory data and clinical symptoms. Clinical data was routinely collected, and all cases of *R. tigrinus* bites were recorded in this institute. The records of the Japan Snake Institute were retrospectively investigated between January 1, 1973 and December 31, 2013.

Diagnosis of *R. tigrinus* bites

R. tigrinus bites were diagnosed based on the detailed information of snakes that patients observed and hemorrhagic symptoms including severe hypofibrinogenemia, and final diagnosis was recorded in a file of the Japan Snake Institute.

We also applied DIC diagnostic criteria for critically ill patients, as outlined by the Japanese Association of Acute Medicine (JAAM criteria) [4]; DIC was defined as a total score of ≥4.

Treatment of *R. tigrinus* bites

The antivenom used against *R. tigrinus* bites was experimentally manufactured [1]. Severe adverse effects exclusively refer to anaphylactic shock in which the patient is at a risk of death because of antivenom administration.

Data collection

The following parameters were recorded: age, gender, date of injury, clinical symptoms, laboratory data, and DIC score as well as treatment-related factors and the outcomes including hospital mortality and renal failure requiring hemodialysis.

Outcome measures

The primary endpoint of the present study was to determine the association between antivenom administration and hospital mortality. The secondary outcome was to determine the association between antivenom administration and renal failure requiring hemodialysis after the acute phase of injury.

Primary data analysis

Statistical analysis was performed using JMP version 11 (SAS, Cary, NC, USA). Patient characteristics, treatment-related factors, and outcomes were compared between the antivenom group and the without antivenom group using Mann–Whitney U test and χ^2 test or, where appropriate, the Fisher exact test for categorical variables. P values of ≤0.05 alpha were considered statistically significant.

Results

Demographic data and clinical characteristics of all study patients

Over the 43-year study period, 34 patients were identified; the patient characteristics are summarized in Table 1. We further analyzed 25 cases from the previous study [3]. All patients, except for one, were male, with a median age of 37.5 years. On admission, the median levels of fibrinogen and fibrinogen degradation products (FDPs) were 35 mg/dL and 200 μg/mL, respectively, and platelet counts were 107,000/mm^3. The mean DIC score was 5.

Antivenom was administered to 19 patients, and the median interval between bite and antivenom administration was 32 h. No apparent adverse effects were observed. DIC was treated with heparin in 14 patients. Seven patients developed renal failure requiring hemodialysis after the acute phase of the injury, and the in-hospital mortality rate for all the patients was 11.8%.

Comparison of clinical characteristics between the antivenom and without antivenom groups

The comparison of clinical characteristics between the antivenom and without antivenom groups is summarized in Table 2. Baseline characteristics and laboratory

Table 1 Population characteristics, *n* = 34

Population characteristics	Values
Age (years)	37.5 (43.8)
Gender, male, *n* (%)	33 (97.1)
Date of getting injury (year)	
1973–1999	25 (73.5)
2000–2013	9 (26.5)
Clinical symptoms	
Nasal bleeding, *n* (%)	4 (11.8)
Gum bleeding, *n* (%)	15 (44.1)
Bleeding from the bite sites, *n* (%)	27 (79.4)
Headache, *n* (%)	6 (17.6)
Laboratory data	
Platelet counts ($\times 10^4/mm^3$)	10.7 (10.4)
Fibrinogen (mg/dL)	35 (30)
PT-INR	5 (4.38)
FDP (μg/mL)	200 (180)
DIC score	5(3)
Treatment	
Heparin, n (%)	14 (41.2)
FFP, n (%)	8 (25.0)
PE, n (%)	4 (11.8)
Antivenom, n (%)	19 (55.9)
Time interval between getting Yamakagashi bites and antivenom administration (h)	32 (31)
Severe adverse effects related to antivenom	0 (0)
Outcome	
Mortality, *n* (%)	4 (11.8)
Hospital stay	9.5 (9.5)
Renal failure requiring hemodialysis, *n* (%)	7 (20.6)

Data are presented as median (interquartile, IQR) for continuous variables and *n* (percentage) for categorical variables. *PT-INR* prothrombin time international ratio, *FDP* fibrinogen degradation products, *DIC* disseminated intravascular coagulation, *FFP* fresh frozen plasma, *PE* plasma exchange, *SD* standard deviation.

data were not significantly different between the two groups.

Heparin use in the antivenom group was significantly lower than that in the without antivenom group (21.1% vs. 66.7%, $P = 0.01$).

Correlations between antivenom administration and outcomes

Hospital mortality in the antivenom group was significantly better than that in the without antivenom group (0% vs. 26.7%, $P = 0.03$) (Figure 1). Moreover, the number of patients developing renal failure requiring hemodialysis was significantly lower in the antivenom group (5.3% vs. 40.0%, $P = 0.03$) (Figure 2).

Table 2 Comparison between the antivenom and the without antivenom groups

Characteristics	Antivenom group (*n* = 19)	Without antivenom group (*n* = 15)	*P* value
Age (years)	37 (40)	43 (50)	0.93
Gender, male, *n* (%)	18 (94.7)	15 (100)	1.00
Date of injury, year (2000–2013), *n* (%)	7 (36.8)	2 (13.3)	0.24
Clinical symptoms			
Nasal bleeding, *n* (%)	1 (5.3)	3 (20.0)	0.07
Gum bleeding, *n* (%)	8 (42.1)	7 (46.7)	1.00
Bleeding from the bite sites, *n* (%)	16 (84.2)	11 (73.3)	0.67
Headache, *n* (%)	3 (15.8)	3 (20.0)	1.00
Laboratory data			
Platelet counts ($\times 10^4/mm^3$)	12.5 (10.1)	7.9 (11.6)	0.21
Fibrinogen (mg/dL)	42.5 (20)	31 (43)	0.34
PT-INR	5.84 (4.24)	2.81 (4.11)	0.1
FDP (μg/mL)	236 (185)	160 (214)	0.06
DIC score	5 (4)	4.5 (3)	0.6
Treatment			
Heparin, *n* (%)	4 (21.1)	10 (66.7)	0.01
FFP, *n* (%)	3 (15.8)	5 (38.5)	0.22
PE	1 (5.3)	3 (20.0)	0.30

Data are presented as median (interquartile, IQR) for continuous variables and *n* (percentage) for categorical variables. *PT-INR* prothrombin time international ratio, *FDP* fibrinogen degradation products, *DIC* disseminated intravascular coagulation, *FFP* fresh frozen plasma, *PE* plasma exchange, *SD* standard deviation.

Discussion

In the present study, we demonstrated that hospital mortality and the number of renal failure requiring hemodialysis following the acute phase of *R. tigrinus* bites were significantly better in patients receiving antivenom than in those not receiving antivenom. Previously, we demonstrated that the pathophysiology of *R. tigrinus* bites involves DIC with the fibrinolytic phenotype [3]. However, it seems that this DIC with fibrinolysis phenomenon does not persist throughout hospitalization and may be limited to the acute injury phase. The present survey revealed that in the acute phase, patients developed DIC with the fibrinolytic phenotype; however, 40% of patients without antivenom developed renal failure requiring hemodialysis in the later phase of the injury. Renal pathology has revealed that glomerular fibrin thrombi and tubular necrosis are responsible for renal failure associated with *R. tigrinus* bites [5]. Indeed, Gando et al. reported that 24 to 48 h after severe traumatic injury, DIC with the fibrinolytic phenotype changes to DIC with the thrombotic phenotype, which can result in the fatal multiple organ dysfunction syndromes (MODS) [6,7].

	Dead	Survival	Total
Antivenom group	0	19	19
Without-antivenom group	4	11	15
Total	4	30	34

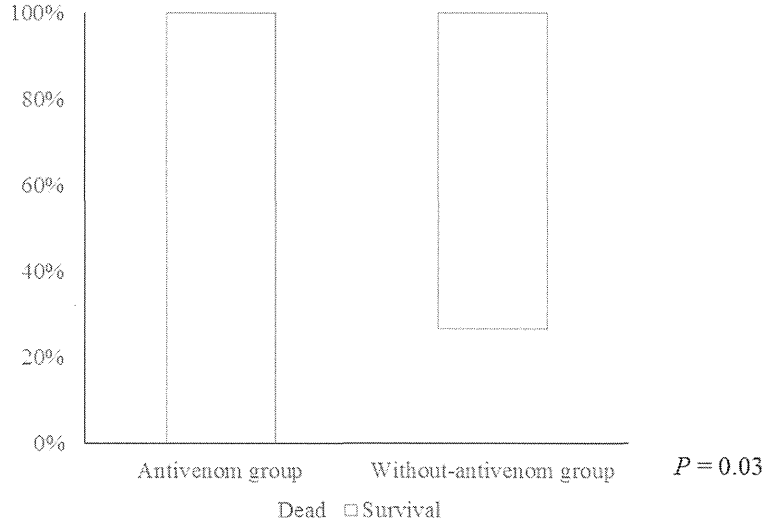

Figure 1 Comparison of hospital mortality between the antivenom and the without-antivenom groups. Hospital mortality in the antivenom group was significantly better than that in the without antivenom group (0% vs. 26.7%, $P = 0.03$).

	Renal failure requiring hemodialysis	No need for hemodialysis	Total
Antivenom group	1	18	19
Without-antivenom group	6	9	15
Total	7	27	34

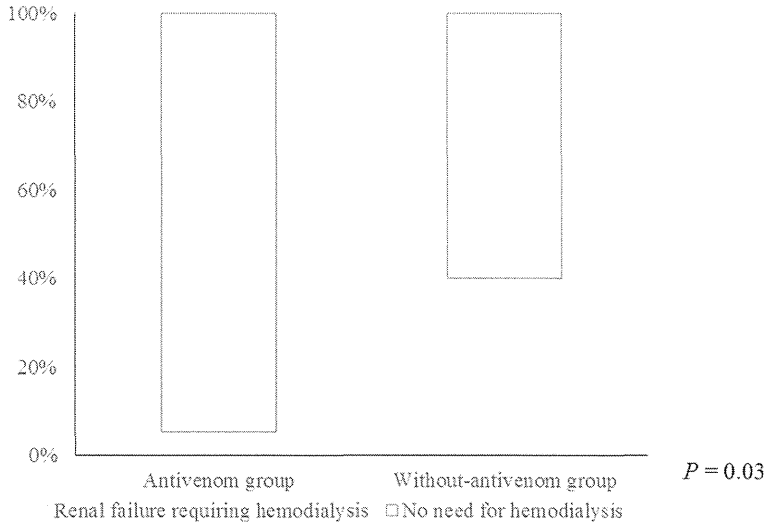

Figure 2 Comparison of the number of patients developing renal failure requiring hemodialysis between the antivenom and the without antivenom groups. The number of patients developing renal failure requiring hemodialysis was significantly lower in the antivenom group (5.3% vs. 40.0%, $P = 0.03$).

Gando et al. argued that the guiding principal in the treatment of DIC is the specific and vigorous treatment of the underlying disorder [6]. Considering our current understanding of the pathophysiology of *R. tigrinus* bites, it is obvious that managing DIC with heparin is contraindicated in the acute phase because patients develop bleeding manifestations [8]. On the other hand, antivenom represents a specific, definitive, and effective treatment in this phase. It appeared that administering *R. tigrinus* antivenom following bites can lead to complete clinical recovery without progression to MODS, even in the presence of severe DIC. Thus, antivenom effectively treats the acute symptoms and can prevent disease progression. If there is appropriate preparedness for anaphylaxis, antivenom should be used in patients with *R. tigrinus* bites.

A major adverse effect of antivenom is serum sickness disease, which usually occurred in 4–10 days after administration of antivenom [9]. Rashes, itching, joint pain, fever, lymphadenopathy, malaise, and renal failure are typical symptoms [9,10]. Because the number of patients developing renal failure requiring hemodialysis was significantly lower in the antivenom group, the close association between antivenom administration and renal failure was not considered. In the present study, although the numbers in the present survey are still too low to make any comprehensive assessment, the initial anaphylactic reaction rate was also lower than the 2.4%–9% rate observed with *G. blomhoffii* antivenom [11,12].

There are many limitations to the present study. Notably, the present study had a retrospective design and a relatively small sample size. Selection bias may also have been an issue because only cases reported to our center were used, and many cases may have remained undiagnosed or misdiagnosed because of the unfamiliar symptoms presented by this rare snakebite. Finally, because tissue plasminogen activator (t-PA) was not evaluated, the primary activation of fibrinogenolysis remains unclear. Furthermore, plasminogen activator inhibitor-1 (PAI-1), which induces the suppression of fibrinolysis, was not evaluated. Further study is required to clarify the pathophysiology of *R. tigrinus* bites.

Conclusions

In our small retrospective study, antivenom administration was likely to be effective in the management of *R. tigrinus* bites. Apparently, further research is required to confirm its efficacy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TH, AS, AY, YA, and YK collected the patient data. TH, MM, AG, HK, YK, JI, YA, KK, and MH treated patients. TH wrote the manuscript. MA, KS, and YK revised and edited the manuscript. All authors read and approved the final manuscript.

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LETTER TO THE EDITOR Open Access

Rhabdophis tigrinus is not a pit viper but its bites result in venom-induced consumptive coagulopathy similar to many viper bites

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Abstract

As a response to the recent article by Hifumi et al. published in the *Journal of Intensive Care*, the present correspondence clarifies the family-level taxonomy of the yamakagashi (*Rhabdophis tigrinus*). Further, the relevance of the term 'venom-induced consumptive coagulopathy,' instead of disseminated intravascular coagulation, in describing the procoagulant coagulopathy of *R. tigrinus* is highlighted.

Keywords: Viperidae, Colubridae, Natricinae, *Rhabdophis*, Coagulopathy

Correspondence

Anjana Silva

Dear Editor,

I read with interest, the research article titled 'Clinical characteristics of yamakagashi (*Rhabdophis tigrinus*) bites: a national survey in Japan, 2000–2013' by Hifumi et al. [1] published recently in the *Journal of Intensive Care*. Under-reporting of snakebites has been a challenge in confronting the global burden of snakebite. Therefore, studies such as Hifumi et al. are with high value for the field of clinical toxinology as the authors have comprehensively described nine cases of *R. tigrinus* bites by providing clues for the pathophysiology of envenoming.

One major issue in the clinical reporting of snakebites is lack of emphasis on the taxonomic identity of the offending snakes, often leading to confusions [2]. Since the clinical reporting of snakebites is primarily done by the clinicians, this could be expected. In Hifumi et al. [1], *R. tigrinus* has been erroneously mentioned as a pit viper species (family: Viperidae, subfamily: Crotalinae). *R. tigrinus* has long been placed within the family Colubridae, under the subfamily Natricinae and genus *Rhabdophis* [3,4], and therefore is not a pit viper but is a colubrid. Although some authors have suggested treating natricines as a separate family called Natricidae [5], recent molecular work confirmed the placement of natricines within the Colubridae as a subfamily [6]. All vipers (family: Viperidae) are venomous and possess front fangs. Pit vipers are an evolutionarily distinct group within the family Viperidae. As opposed to viperids, most of the snakes of the largest snake family Colubridae are non-venomous and do not possess true venom glands or venom delivery systems. Few mildly venomous snake groups within this family, such as the genus *Rhabdophis*, possess rear fangs as well as Duvernoy's glands which produce venom-like secretions and associated low-pressure venom delivery systems [7].

The pro-coagulant nature of *R. tigrinus* venom is primarily due to its prothrombin activating effects and weak thrombin-like effects. This leads to hypofibrinogenemia resulting hemorrhage in envenomed patients [1,8]. However, Hifumi et al. [1] described the above pathological process as the disseminated intravascular coagulation (DIC) with fibrinolytic phenotype. Interestingly, this pathological process has been described with the term 'venom-induced consumptive coagulopathy' (VICC) seen in many viperid snake groups (including many pit vipers) and Australian elapids. Although VICC is similar to DIC in many ways, VICC differs from the former by not usually

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resulting in end-organ effects, rapid onset and resolution, and the difference in the mechanism of initiation [9]. Hence, I suggest that the term VICC [9] is more suitable than DIC used by the authors to describe the coagulopathy due to *R. tigrinus* bites.

Response

Toru Hifumi, Atsushi Sakai, Akihiko Yamamoto, Masahiro Murakawa, Manabu Ato, Keigo Shibayama, Akihiko Ginnaga, Hiroshi Kato, Yuichi Koido, Junichi Inoue, Yuko Abe, Kenya Kawakita, Masanobu Hagiike, Yasuhiro Kuroda

Dear Editor,

We thank Dr. Silva for his comments on our article.

We completely agree that *Rhabdophis tigrinus* is a rear-fanged venomous snake present in paddy fields [10] and that its venom shows strong plasma coagulant activity, with prothrombin activating effects and weak thrombin-like effects that result in hemorrhagic symptoms [8]. Because *R. tigrinus* has no grooved fangs, envenomation does not occur in most bites; therefore, *R. tigrinus* has long been considered nonvenomous [10,11].

However, we totally disagree with his suggestion that 'venom-induced consumptive coagulopathy' (VICC) is a more suitable term than 'disseminated intravascular coagulation' (DIC) with a fibrinolytic phenotype used to describe coagulopathy due to *R. tigrinus* bites.

First, we would like to provide the details of coagulation markers of case 5 in our previous studies [1,11]. A healthy 40-year-old man was admitted with severe coagulopathy that developed after *R. tigrinus* bites. On admission, he demonstrated significantly elevated levels of thrombin-antithrombin III complex (TAT, 60 ng/mL; normal range, <3–4 ng/mL), plasmin-alpha 2-plasmin inhibitor complex (PIC, 22.3 μg/mL; normal range, <0.8 μg/mL), and fibrinogen degradation products (FDPs, 592 μg/mL). He subsequently developed severe hypofibrinogenemia (50 mg/dL). Antivenom was administered 28 h after being bitten; after 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 TAT, PIC, and FDP levels normalized. He was discharged on day 6 of admission. These coagulation markers fulfilled the diagnostic criteria for DIC with a fibrinolytic phenotype [12].

Second, Dr. Silva cited a research conducted by Isbister who suggested that a snakebite does not cause DIC but instead causes coagulopathy and thrombotic microangiopathy in snake envenoming; this was reportedly because VICC was not characterized by important features of DIC, such as evidence of systemic microthrombi and end-organ failure [9].

A similar discussion has been made in the context of trauma, which also induces DIC with a fibrinolytic phenotype in the acute phase. Rizoli et al. conducted a prospective study and concluded that within 24 h of trauma, most severely injured patients have DIC scores 'suggestive of' or of 'overt DIC' in the International Society on Thrombosis and Haemostasis (ISTH) score but have no anatomopathologic evidence of DIC. Considering that pathologic findings are the gold standard for diagnosis, then, DIC is exceptionally uncommon, and the ISTH score should not be used for trauma [13].

Asakura described important principals that enhanced fibrinolytic-type DIC (DIC with a fibrinolytic phenotype) is associated with marked activation of fibrinolysis corresponding to activation of coagulation. Fibrinolysis is strongly activated, hemostatic plugs (thrombi due to hemostasis) are more easily dissolved, and bleeding symptoms tend to be severe. However, organ dysfunction seldom occurs [12].

Therefore, it is obvious that we cannot find evidence of systemic microthrombi and that patients do not develop organ dysfunction in the phase of DIC with a fibrinolytic phenotype.

Third, the previous literature was limited by the sample size (nine cases) [1]; therefore, we are now preparing the next manuscript. We further analyzed 25 cases from the previous study [1]. Over the 43-year study period (1970–2013), 34 patients were identified, and the number of patients developing renal failure who required hemodialysis was significantly lower in the antivenom group than in the without-antivenom group (5.3% vs 40.0%, $P = 0.03$). We assume that DIC with fibrinolysis phenotype does not persist throughout hospitalization and may be limited to the acute phase of injury for *R. tigrinus* bites. Renal failure requiring hemodialysis developed at a later phase of injury in 40% of patients not receiving antivenom. Examination of renal pathology revealed that glomerular fibrin thrombi and tubular necrosis were responsible for renal failure associated with *R. tigrinus* bites [14]. Indeed, Gando et al. reported that 24–48 h after severe traumatic injury, DIC with a fibrinolytic phenotype developed into that with a thrombotic phenotype, therefore resulting in fatal multiple organ dysfunction syndromes [15,16].

In conclusion, we continue to assert that *R. tigrinus* bites induced DIC with a fibrinolytic phenotype.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AnS wrote the correspondence. TH, AtS, AY, YA, and YK collected the patient data. TH, MM, MA, KS, AG, HK, YuK, JI, YA, KK, and MH treated the patients. TH wrote the manuscript. AY, AtS, and YaK revised and edited the manuscript. All authors read and approved the final manuscript.

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RESEARCH Open Access

Clinical characteristics of redback spider bites

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Abstract

Background: Redback spiders (*Latrodectus hasselti*) (RBSs) are venomous spiders that have recently spread to Asia from Australia. Since the first case report in 1997 (Osaka), RBS bites have been a clinical and administrative issue in Japan; however, the clinical characteristics and effective treatment of RBS bites, particularly outside Australia remains unclear. This study aimed to elucidate the clinical characteristics of RBS bites and to clarify the effectiveness of the administration of antivenom for treatment.

Methods: We performed a retrospective questionnaire survey from January 2009 to December 2013 to determine the following: patient characteristics, effect of antivenom treatment, and outcomes. To clarify the characteristics of patients who develop systemic symptoms, we compared patients with localized symptoms and those with systemic symptoms. We also examined the efficacy and adverse effects in cases administered antivenom.

Results: Over the 5-year study period, 28 patients were identified from 10 hospitals. Of these, 39.3% were male and the median age was 32 years. Bites most commonly occurred on the hand, followed by the forearm. Over 80% of patients developed local pain and erythema, and 35.7% (10 patients) developed systemic symptoms. Baseline characteristics, vital signs, laboratory data, treatment-related factors, and outcome were not significantly different between the localized and systemic symptoms groups. Six patients with systemic symptoms received antivenom, of whom four experienced symptom relief following antivenom administration. Premedication with an antihistamine or epinephrine to prevent the adverse effects of antivenom was administered in four patients, which resulted in no anaphylaxis. One out of two patients who did not receive premedication developed a mild allergic reaction after antivenom administration that subsided without treatment.

Conclusions: Approximately one third of cases developed systemic symptoms, and antivenom was administered effectively and safely in severe cases. Further research is required to identify clinically applicable indications for antivenom use.

Keywords: Redback spider, Antivenom, Systemic symptom

Background

Redback spiders (*Latrodectus hasselti*) (RBSs) are venomous spiders that produce the neurotoxin (alpha-latrotoxin) [1]. The adult female is characterized by a spherical black body with a prominent red stripe on the upper side of the abdomen (Figure 1a). Females have a body length of approximately 10 mm, and the male measures only 3–4 mm [2]. Although widely distributed in Australia, it has recently spread to Southeast and West Asia [3-5].

Symptoms of RBS bites are usually mild and localized, such as local pain and erythema. However, fatal cases had been reported before the development of antivenom (Figure 1b), which is manufactured by the immunization of horses [6,7]. Since the first case reported in Osaka in 1997, RBS bites have been a clinical and administrative issue in Japan [8,9]. Despite this, the clinical characteristics and optimal treatment of RBS bites, particularly outside Australia remain unknown.

Therefore, this study aimed to elucidate the clinical characteristics of RBS bites and the factors associated with developing systemic symptoms. We also aimed to

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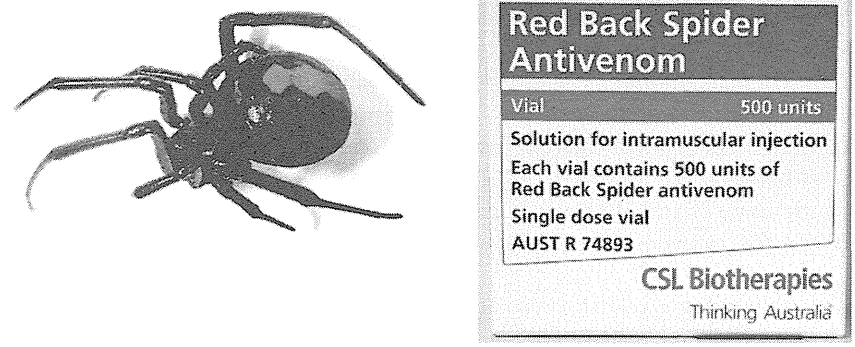

Figure 1 Redback spider and an example of the antivenom. (a) The left image shows a female Redback spider. **(b)** The right image depicts an example of the antivenom used for Redback spider bites.

clarify the effectiveness of the administration of antivenom for treatment.

Methods

This is a retrospective observational study. The institutional review board of the Kagawa university hospital approved this cross-sectional, survey-based study (Heisei 26-029).

Patients and setting

We prepared a questionnaire to examine the clinical characteristics of RBS bites in Japan. The questionnaires consisted of initial screening survey (phase I survey) and survey for clinical data (phase II survey). The initial screening questionnaire (phase I survey) was sent to 470 sentinel medical institutions originally used for the national surveillance for infections of antimicrobial resistant bacteria and severe influenza to cover major hospitals in all areas of Japan, such as University Hospitals, National Hospitals, and Red Cross Hospitals. The questionnaire was about the absence or presence of patients with RBS bites and was sent in January 2014 and collected by March 2014. Completed questionnaires were received from 297 (63.2%) sentinel medical institutions, with four hospitals that responded to having treated patients with RBS bites.

The questionnaire for obtaining clinical data (phase II survey) was sent to those four hospitals that responded to having treated patients with RBS bites in the phase I survey. We also sent the questionnaire (phase II survey) to seven other hospitals that possessed antivenom against RBS in May 2014. The surveillance period of the questionnaire spanned 5 years, i.e., from January 2009 to December 2013.

Data collection

The following parameters were recorded: age, gender, date of injury, bite location, clinical symptoms (local pain, erythema, edema, sweating, headache, nausea, abdominal numbness, systemic pain, and others), vital signs (systolic blood pressure and body temperature), laboratory data (white blood cell and platelet counts, creatinine kinase, and aspartate aminotransferase), treatment-related factors (analgesics and antivenom), effectiveness and adverse effects of antivenom, and outcomes (days in hospital, days in intensive care unit (ICU), and in-hospital mortality).

Diagnosis of RBS bites and definition of systemic symptoms

No definite diagnostic criteria exist. Diagnosis of RBS bites was based on either the patient's history or the positive identification of RBS presented by the patient. Systemic effects were considered to include sweating, headache, nausea, abdominal numbness, systemic pain, fever, hypertension, parasthesia, fasciculations, and cardiac effects [10]. In the current study, patients with systemic symptoms were defined as those who developed at least the abovementioned one symptom.

Treatment of RBS bites

The definitive treatment for RBS envenomation in Australia is the use of a specific RBS antivenom produced by Commonwealth Serum Laboratories (CSL) [11]. Because RBS antivenom has not been approved by the Ministry of Health, Labour and Welfare in Japan, clinicians

have to privately purchase and import it from CSL. In Australia, the indications for RBS antivenom are patients with signs of systemic envenomation, those with pain not controlled with simple analgesia, or for those who require repeated doses of opiates [12]. In the current survey, the decision to administer antivenom was made by individual doctors and was not based on any protocol.

Primary data analysis

Patient characteristics, treatment-related factors, and outcomes were compared between the localized and the systemic symptoms groups using Mann-Whitney *U* test and the Fisher's exact test for categorical variables, as appropriate.

Two-tailed *P*-values of ≤0.05 were considered statistically significant. Statistical analysis was performed using JMP version 11 (SAS, Cary, NC, USA).

Results

Demographic data and clinical characteristics of all study patients

Over the 5-year study period, 28 patients were identified from 10 hospitals. The areas where RBS bites were reported were limited to three prefectures: Osaka, Nara, and Fukuoka (Figure 2). The patient characteristics are summarized in Table 1; 39.3% were male and the median age was 32 years. The most common sites for bites were the hand (42.9%) and the forearm (17.9%). Over 80% of patients developed local pain and erythema, and systemic symptoms occurred in 10 patients (35.7%). Antivenom was administered to six patients, four (14.3%) were admitted to hospital, and one required care at ICU. All patients recovered without lasting adverse effects.

Comparison between the localized and systemic symptoms groups

We compared the clinical characteristics between the localized and systemic symptoms groups to clarify the characteristics of patients that develop systemic symptoms; our results are summarized in Table 2. There were no significant differences between the two groups in terms of baseline characteristics, vital signs, laboratory data, treatment-related factors, and outcomes.

Details of cases who received antivenom

The details of six patients who received antivenom are summarized in Table 3. Antivenom administration relieved symptoms in four patients who developed systemic symptoms. Premedication with an antihistamine or epinephrine to prevent the adverse effects of antivenom was administered in four patients, which resulted in no anaphylaxis. One out of two patients who did not receive premedication developed a mild allergic reaction after antivenom administration that subsided without treatment.

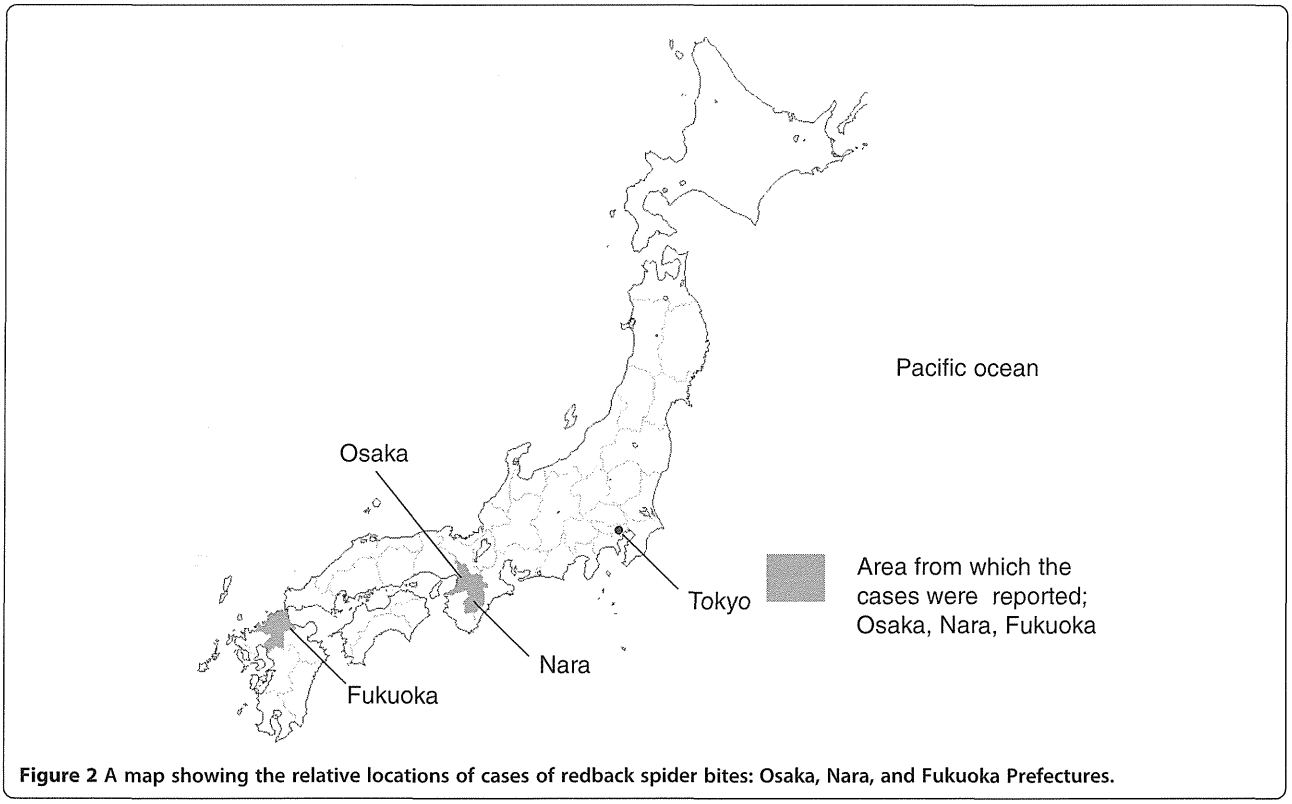

Figure 2 A map showing the relative locations of cases of redback spider bites: Osaka, Nara, and Fukuoka Prefectures.

Table 1 Population characteristics (*n* = 28)

Characteristics	Values
Age (years)	32 (15.5–56.5)
>65 years	4 (14.3%)
<15 years	6 (21.4%)
Gender, male, n (%)	11 (39.3)
Bite site	
Hand	12 (42.9)
Forearm	5 (17.9)
Clinical symptoms	
Local	
Local pain, *n* (%)	25 (89.2)
Edema, *n* (%)	13 (46.4)
Erythema, *n* (%)	24 (85.7)
Systemic symptoms	10 (35.7)
Sweating, *n* (%)	2 (7.1)
Headache, *n* (%)	2 (7.1)
Nausea, *n* (%)	4 (14.8)
Numbness on the abdomen, *n* (%)	2 (7.1)
Systemic pain, *n* (%)	2 (7.1)
Others (high grade fever at 39°C light headedness), *n* (%)	2 (7.1)
Vital signs on admission	
SBP (mmHg)	132 (123–150)
BT (°C)	36.8 (36.4–37.1)
Laboratory data	
WBC (/mm^3)	9,000 (6,597–9,600)
Platelet count (×10^4/mm^3)	23.6 (17.8–28.9)
CK (IU/L)	156 (73–170)
AST (IU/L)	33 (22–52)
Treatment	
Antivenom, *n* (%)	6 (21.4)
Analgesics, *n* (%)	8 (28.6)
Outcome	
Hospital admission, *n* (%)	4 (14.3)
ICU admission, *n* (%)	1 (3.6)
Mortality, n (%)	0 (0)

Data are presented as median (interquartile range, IQR) for continuous variables and *n* (percentage) for categorical variables.
SBP systolic blood pressure; *BT* body temperature; *WBC* white blood cell; *CK* creatine kinase; *AST* aspartate aminotransferase.

Discussion

In the current survey, all 28 cases recovered well. Six cases received antivenom, of which four had symptomatic relief with no serious adverse effects. One out of two patients who did not receive premedication developed a mild allergic reaction after antivenom administration that subsided without treatment. Notably, 36% of patients developed systemic symptoms. No significant factors associated with systemic symptoms were identified.

In Australia, antivenom is recommended for patients with signs of systemic envenomation. Indeed, those with severe or systemic symptoms and patients at greater risk, such as children, pregnant women, and the elderly, are more likely to receive antivenom [12,13]. Conversely, no indication has been provided for antivenom use in clinical practice in Japan. Five out of six cases in the current survey (four cases with systemic symptoms and one pediatric case) received antivenom based on the indications used in Australia. Although four cases out of ten that developed systemic symptoms recovered with RBS antivenom, the remaining cases with systemic symptoms recovered without antivenom. We identified no cases among pregnant women. Given these facts, further research is required to identify the appropriate clinical indications for antivenom use in Japan.

Alpha-latrotoxin causes synaptic vesicle exocytosis from the presynaptic terminal, via a calcium-dependent mechanism, leading to the release of catecholamines and acetylcholine [14]. Therefore, although the primary impact of the envenomation can be mild, it is assumed that these substances, together with hypertension induced by persistent pain, worsen the condition among both elderly patients with comorbidities and pregnant women. In such populations, antivenom administration may be considered.

RBS antivenom is manufactured by the immunization of horses. Therefore, there is a risk of adverse events such as anaphylaxis and serum sickness disease [15,16]. In studies in Australia, allergic reactions to the antivenom have been rare (<2%) [7]. However, Mamushi antivenom, which is also manufactured by the immunization of horses, causes a 2.4%–9% rate of anaphylactic reactions in Japan [17,18]. In the present study, none of the four cases that received antivenom with premedication against anaphylaxis had an adverse reaction. However, one case that did not receive premedication developed a mild allergic reaction. Therefore, premedication with an antihistamine and/or epinephrine should be used when the perceived benefit is greater than the risk of adverse effects.

The serious concern with the current treatment of RBS bites is that RBS antivenom is not approved by the Ministry of Health, Labour and Welfare. Therefore, clinicians are required to privately import it from Australia. Moreover, in 2013, all imports from Australia were suspended due to the low production of RBS antivenom by CSL. In 2013, the Ministry of Health, Labour and Welfare of Japan launched a research group to evaluate the safety and efficacy of antivenom and to organize and maintain information on RBS bites [19]. In the group, domestic

Table 2 Comparison between the groups with local and systemic symptoms

	Limited to local (*n* = 18)	Systemic (*n* = 10)	*P* value
Age (years)	30.5 (10.8–52.3)	32.5 (18.5–59.8)	0.49
>65, *n* (%)	3 (16.7)	1 (10)	1.00
<15, *n* (%)	5 (27.8)	1 (10)	0.37
Gender, male, *n* (%)	6 (33.3)	5 (50)	0.44
Bite site			0.12
Hand	11 (61.1)	1 (10)	
Forearm	2 (11.1)	3 (30)	
Other/unknown	5 (27.8)	6 (60)	
Vital signs on admission			
SBP (mmHg)	135 (111–156)	130 (125–136)	0.67
BT (°C)	36.9 (36.4–37.1)	36.7 (36.5–36.8)	0.59
Laboratory data			
WBC (/mm^3)	7,697 (5,398–9,550)	9,000 (7,350–9,750)	0.46
Platelet count (×10^4/mm^3)	23.3 (17.8–30.4)	23.6 (18.0–28.9)	0.88
CK (IU/L)	123 (65–169)	159 (85–190)	0.62
AST (IU/L)	35 (23–51)	28 (22–61)	0.77
Treatment			
Antivenom, *n* (%)	2 (11.1)	4 (40)	0.15
Analgesics, *n* (%)	5 (27.8)	3 (30)	1.00
Outcome			
Hospital admission, *n* (%)	1 (5.6)	3 (30)	0.12
ICU admission, *n* (%)	0 (0)	1 (10)	0.36

Data are presented as median (interquartile range, IQR) for continuous variables and *n* (percentage) for categorical variables.
SBP systolic blood pressure; *BT* body temperature; *WBC* white blood cell; *CK* creatine kinase; *AST* aspartate aminotransferase.

production of RBC antivenom was carefully discussed, and this production started since April 2014.

There are many limitations to this study. A major limitation is that it had a retrospective design and a relatively small sample size. Selection bias may also have occurred because not all cases were collected. We conducted the current survey with 470 sentinel medical institutions originally used for the national surveillance for infections of antimicrobial resistant bacteria and severe influenza with response rate of 63.2%. Many cases may have remained undiagnosed or misdiagnosed because of the unfamiliar symptoms presented by RBS bites. Given the number of patients included, multivariate analysis (logistic regression model) could not performed to identify the factors associated with developing systemic symptoms.

Conclusions

Approximately one third of cases developed systemic symptoms and antivenom was administered effectively and safely in severe cases. Further research is required to identify clinically applicable indications for antivenom use.

Table 3 Cases administered with antivenom

Case	Age	Gender	Symptoms	Reason for administration	Premedication	Adverse effect	Clinical effect
1	6	M	Localized	N/A	Antihistamine	None	N/A
2	14	M	Systemic	Systemic symptoms (numbness on the abdomen)	Antihistamine	None	Pain relief
3	36	M	Systemic	Systemic symptoms (headache)	None	Flushing on the face	Pain relief
4	59	F	Systemic	Systemic symptoms (systemic pain, dizziness, nausea)	Epinephrine	None	Symptoms relief
5	68	F	Localized	Patient's wish	Antihistamine	None	N/A
6	87	F	Systemic	Systemic symptoms (severe systemic pain)	None	None	Pain relief

N/A not applicable.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
TH, SF, KS, MK, and YK collected the patient data. TH, MA, KS, AG, NK, HK, YK, JI, YA, KK, and MH participated in current research project. TH wrote the manuscript. TY, SA, AY, MA, and YK revised and edited the manuscript. All authors read and approved the final manuscript.

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JOURNAL OF INTENSIVE CARE

LETTER TO THE EDITOR Open Access

Update of antivenom supply for redback spider bites in Japan

Toru Hifumi[1*], Hisashi Taki[2], Akihiko Yamamoto[3], Manabu Ato[4], Yuichi Koido[5] and Yasuhiro Kuroda[1]

Abstract

In autumn 2014, with great effort by the Ministry of Health, Labour and Welfare, the research group will obtain several vials of redback spider (RBS) antivenom for emergency use. However, these small amounts of antivenom are insufficient to cover the demands from majority of hospitals in Japan. The research group carefully discussed the domestic RBS antivenom production by themselves for this emergency. We have now entered the second stage for large-scale antivenom production. Although the domestic production of RBS antivenom has started, great caution is required as we move forward with this plan.

Keywords: Redback spiders, Antivenom, Domestic production

Correspondence

Letter to the editor

We previously reported that symptoms of redback spider (RBS) bites are usually mild and localized, such as local pain and erythema [1]. However, fatal cases had been reported before the development of antivenom, which is manufactured by the immunization of horses [2,3].

RBSs were found in Metropolitan Tokyo on September 25, 2014, and they are rapidly becoming a nationwide problem in Japan [4]. The definitive treatment for RBS envenomation is to use the specific RBS antivenom produced by the Commonwealth Serum Laboratories (CSL) in Australia. However, a serious issue with the current practice is that RBS antivenom is used as an off-label drug in Japan and must be privately imported from Australia [1].

To compound this issue, RBS antivenom imports from CSL were suspended in autumn 2013. The Ministry of Health, Labour and Welfare (MHLW) launched a research group to evaluate the safety and efficacy of the antivenom and to organize and maintain information on RBS bites from April 2013 [1]. In autumn 2014, with great effort by MHLW, the research group will obtain several vials of antivenom for emergency use. However, these small amounts of antivenom are insufficient to cover the demands from majority of hospitals in Japan.

The research group carefully discussed the option for domestic RBS antivenom production by themselves for this emergency. The first stage started in April 2014. Over 5,000 RBSs were collected, and their venom was extracted by research group in the summer of 2014. We have now entered the second stage of development to evaluate the potency for large-scale antivenom production.

We foresee many difficulties in this process. First, because supplemental details of current RBS antivenom production were not obtained, we have had to refer to a method described over 60 years ago [5]. Second, not many horses were immunized due to the limited grant fund, raising the possibility that we will be unable to obtain enough antivenom, especially if the horses die. Third, because this is the first time we have attempted to produce RBS antivenom, unexpected problems may occur.

In conclusion, although the domestic production of RBS antivenom has started, great caution is required as we move forward with this plan.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TH, HT, AY, MA, YKoido, and YKuroda participated in the current research project. TH wrote the manuscript. HT, AY, MA, and YK revised and edited the manuscript. All authors read and approved the final manuscript.

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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

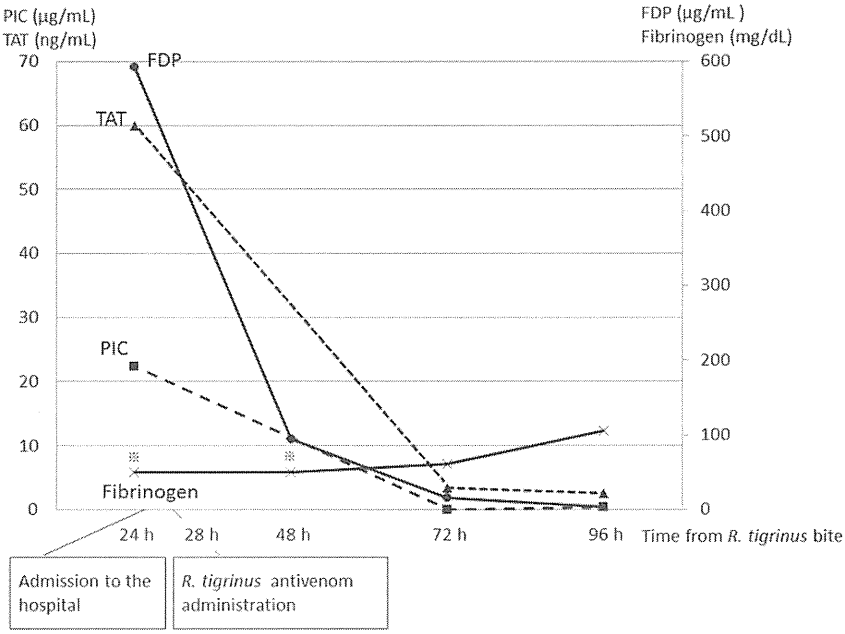

Fig. 1. Trends of coagulation markers in a 40-year-old man admitted with severe coagulopathy that developed after *Rhabdophis tigrinus* bites. Thrombin–antithrombin III complex (TAT), plasmin–alpha 2-plasmin inhibitor complex (PIC), and fibrinogen degradation product (FDP) levels were markedly elevated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

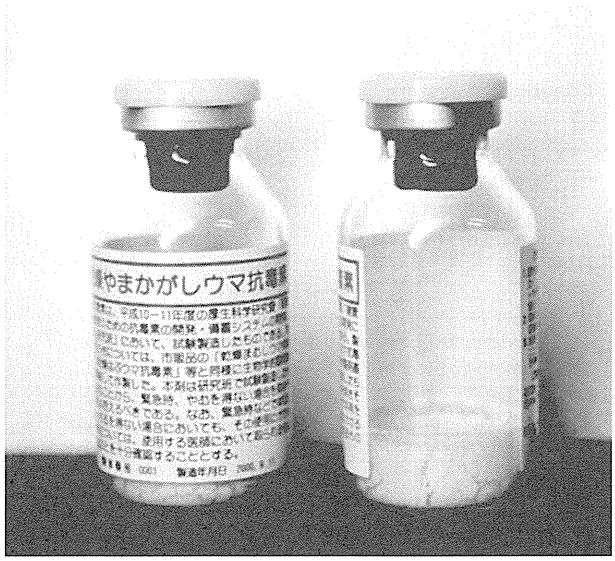

Fig. 2. Antivenom against yamakagashi (*Rhabdophis tigrinus*) was manufactured from hyperimmunized horses with support from Health Science Grants (1998–1999) by the Ministry of Health, Labour and Welfare, in 2000. It was freeze-dried to maintain its initial potency for longer periods.

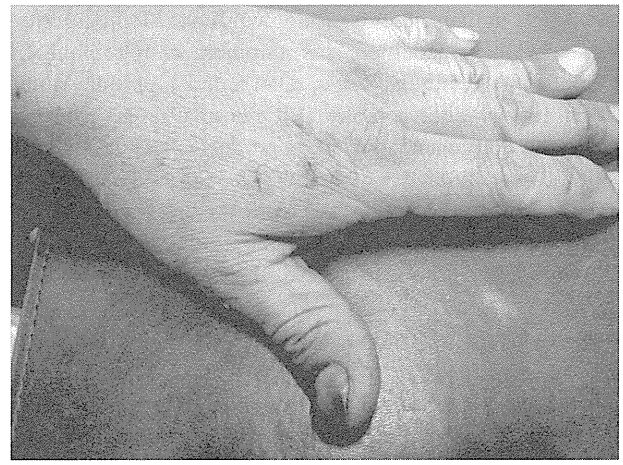

Fig. 3. Photograph of the patient's left hand on the third day of admission following *Rhabdophis tigrinus* bites, showing rhagades and scabs.

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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事　務　連　絡
平成２６年８月２８日

都道府県衛生主管部（局）　御中

厚生労働省健康局結核感染症課

セアカゴケグモ抗毒素について

日本国内におけるセアカゴケグモ対策につきましては、日頃から多大なる御尽力を賜り厚く御礼申し上げます。

さて、平成７年11月に大阪府において、オーストラリア原産のセアカゴケグモが発見されました。その後、セアカゴケグモは、日本各地に棲息地域を広げております。このような状況に鑑み、平成25年度からその咬傷の発生頻度や抗毒素治療に関する調査及び臨床研究を目的として、厚生労働科学研究費補助金研究事業（新型インフルエンザ等新興・再興感染症研究事業）「抗毒素の品質管理及び抗毒素を使用した治療法に関する研究」（研究代表者　一二三亨）を実施しております。

セアカゴケグモに咬まれると、咬まれた部位に軽い痛みを感じたり、熱感や掻痒感を伴う場合があることが報告されています。また、全身症状を呈する症例では、吐き気、腹痛、発熱、不眠症、めまい、頭痛、全身の発疹などが認められる場合があります。これまで、これらの症状の治療の一つとして、オーストラリアを拠点とするCSL社により製剤化されたセアカゴケグモ抗毒素（以下「抗毒素」という。）を医師が個人輸入し、セアカゴケグモに咬まれた者（以下「患者」という。）に投与する場合がありました。一方、現在、国内で保有されている抗毒素の有効期限は平成26年８月末までであり、また、オーストラリアから新たな抗毒素を輸入することも困難な状況となっております。

このような状況への対応として、本研究班では、抗毒素を用いた臨床研究を実施しており、有効期限が平成27年８月末までの抗毒素を保管しております。このため主治医が患者の症状を診察した結果、対症療法ではその症状の改善が見込めないと判断した場合、本研究班の研究代表者である一二三医師と主治医が相談した上で、一二三医師から患者に対して当該抗毒素を遠隔処方することができますので、必要に応じて、主治医から以下の連絡先まで御連絡ください。

抗毒素の投与に当たっては、臨床研究の一環として実施する必要があります