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Toxicon 151 (2018) 79–83

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Case report

Severe haemolysis and spherocytosis in a dog envenomed by a red-bellied black snake (*Pseudechis porphyriacus*) and successful treatment with a bivalent whole equine IgG antivenom and blood transfusion

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ARTICLE INFO

Keywords:
Snake venom
Haemolysis
Snake antivenom
Snakebite
Red-bellied black snake
Pseudechis porphyriacus
Enzyme immunoassay
Dog
Veterinary

ABSTRACT

This case report describes a dog envenomed by a red-bellied black snake (RBBS; *Pseudechis porphriacus*) that experienced severe and life-threatening haemolysis. The dog presented with hypersalivation, facial swelling, mildly prolonged activated clotting time and the absence of neurological deficits. Envenomation was confirmed by positive identification of the snake and retrospective measurement of RBBS specific venom antigen (24 ng/mL) in serum. The dog was initially hospitalised, treated with intravenous fluids and one vial of tiger-brown snake antivenom which is recommended for RBBS envenomation in Australia. However, after 3.5 d the dog's PCV had declined to 15% and the dog was dull and tachycardic. A second vial of tiger-brown antivenom followed by a packed red blood cell transfusion was administered. A rapid clinical improvement within 12 h was observed. No free RBBS venom was detected in serum at any time point after the first vial of antivenom. Longitudinal haematology and biochemical profiling was performed to 62 d post-envenomation and revealed a gradual recovery in the haematocrit to normal reference range. Spherocyte numbers on blood smear were highest at 5 d post-envenomation and gradually declined to undetectable after 62 d. This case highlights the potential for unpredictable, severe and life-threatening anaemia resulting from RBBS envenomation in dogs.

1. Introduction

The Australian red-bellied black snake (RBBS; *Pseudechis porphyriacus)*, is a frequent cause of snakebite in dogs within the geographical regions of Australia where the snake is found (Heller et al., 2007; Padula et al., 2016). The clinical envenomation syndrome observed in dogs typically manifests as varying degrees of myopathy, haemolysis, pigmenturia and local tissue swelling (Padula et al., 2016). Occasional canine cases may develop rapid and potentially fatal neurotoxicity requiring mechanical ventilation to support respiration (Padula and Leister, 2017b). However, in many cases RBBS envenomation is mild and responds well to antivenom therapy and simple veterinary supportive care (Gordon, 1958; Padula and Winkel, 2016). Notwithstanding this, some canine RBBS snakebite patients develop severe anaemia from haemolysis necessitating blood transfusion, leading to prolonged recovery times and ultimately increased veterinary costs (Trigg and McAlees, 2015).

The venom of the RBBS contains, amongst many components, a 16.6 kD haemolytic and toxic phospholipase enzyme named pseudexin, which accounted for 25% of the dried venom mass (Vaughan et al., 1981). Relative to other venomous Australian elapids, RBBS venom has notably lower lethality in mice with a reported subcutaneous LD50 of 2.5 mg/kg (Broad et al., 1979). Pseudexin and whole RBBS venom have been reported to effect both direct and indirect haemolysis of mouse red blood cells *in vitro* (Vaughan et al., 1981). Comparative *in vitro* studies of the direct haemolytic effects of various snake venoms on human red blood cells found only minor activity of tiger snake (*Notechis scutatus*) and brown snake (*Pseudonaja textilis*) venoms in comparison to powerful effects of RBBS venom (Doery and Pearson, 1961). Marked haemolysis has been reported clinically following RBBS envenomation in dogs (Heller et al., 2006; Padula and Leister, 2017b; Padula and Winkel, 2016; Trigg and McAlees, 2015). The associated haemoglobinuria and myoglobinuria has potential to cause acute renal failure in the dog (Heller et al., 2006). In contrast, the problem of clinically severe haemolysis was not reported in a series of 81 human cases of RBBS snakebite (Churchman et al., 2010). This suggests that there are different

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https://doi.org/10.1016/j.toxicon.2018.07.005
Received 14 March 2018; Received in revised form 25 June 2018; Accepted 5 July 2018
Available online 06 July 2018
0041-0101/

physiological responses to RBBS venom between dogs and humans. In a brief report of 100 dogs treated for RBBS envenomation in the Sydney area, 30 had haemolysed serum, 64 had pigmenturia, and 10 dogs required blood transfusion (Goodman and Angles, 2012).

The haematological effects of RBBS venom in dogs were first studied experimentally over 100 years ago by the direct injection venom (Martin, 1893). Martin found that 0.2 mg/kg of RBBS venom injected intravenously into dogs was fatal. Subsequent death-as-endpoint studies in laboratory animals were conducted in the 1920s by Charles Kellaway. Kellaway injected RBBS venom subcutaneously into monkeys, rats, mice, rabbits, cats, guinea pigs and horses and described the ensuing clinical signs and outcomes (Kellaway, 1930). Studies of this type would be very difficult to obtain animal ethics approval in the current era and are not likely to be repeated. Consequently, detailed case reports must now be utilised to expand clinical knowledge of the RBBS envenomation syndrome and document treatment responses in dogs.

The following case report is the first case to report serum venom and antivenom concentrations in a dog with severe haematological complications requiring blood transfusion following a confirmed RBBS envenomation.

2. Case report

A 10.9 kg, four-year-old desexed male Cavoodle dog first presented to his primary care veterinarian because of excessive salivation and a large swelling on the left side of the lip. The dog was suspected to have an insect hypersensitivity reaction and was treated by injection with subcutaneous dexamethasone (0.2 mg/kg; Dexapent, Ilium, Australia), chlorpheniramine maleate (0.5 mg/kg; Niramine, Jurox, Australia) and amoxycillin-clavulanic acid (10 mg/kg; Noroclav, Norbrook, Australia) and discharged home. Immediately upon returning home the owners found a deceased RBBS with evidence of multiple bite wounds in the backyard where the dog was housed. The dog was presented to the Animal Emergency Service approximately 1 h and 40 minutes following the initial clinical signs noted by the owners.

On presentation the dog's mentation was dull but no obvious neurological deficits were noted on initial examination. An 8 cm × 5 cm soft subcutaneous swelling was noted on the left commissure of the lip and severe hypersalivation. The dead snake was also presented for examination and positively identified using scale counting (Cogger, 1978) as a RBBS by the consulting veterinarian.

A cephalic intravenous catheter was placed, and a blood sample collected for baseline packed cell volume (PCV), total protein (TP), blood gas analysis, activated clotting time (ACT) and a serum sample frozen within one hour of collection for subsequent RBBS venom ELISA.

The initial blood results revealed mild haemoconcentration, grossly haemolysed serum and mild hyperglycaemia. The initial ACT was prolonged at 200 s in black top tube (reference range 90–120 s), and a repeated ACT at 4 h post-antivenom remained mildly prolonged at 101 s in grey top tube (60–90 s).

Snake envenomation was suspected based on the history, clinical signs and positive identification of RBBS. RBBS venom antigen was subsequently confirmed by ELISA (24 ng/mL) in frozen serum sample collected immediately on presentation (Fig. 1). The dog was hospitalised and one vial of bivalent tiger-brown snake antivenom was administered intravenously over 10 min. No adverse reactions were noted on administration of the antivenom. Repeat blood sample 4.5 h following administration of antivenom showed no further RBBS venom in serum. The patient was commenced on isotonic crystalloid intravenous fluids (Compound sodium lactate; Baxter, Australia) at a rate of 6 mL/kg/h and maropitant (Cerenia, Zoetis, Australia) 1 mg/kg by subcutaneous injection was administered due to continued hypersalivation. During the first 12 h of hospitalisation methadone (Methone, Troy, Australia) was administered every 4 h at a dose 0.2 mg/kg intravenously; thereafter pain relief was then continued with methadone 0.3 mg/kg by subcutaneous injection every 6 h and tramadol 2 mg/kg

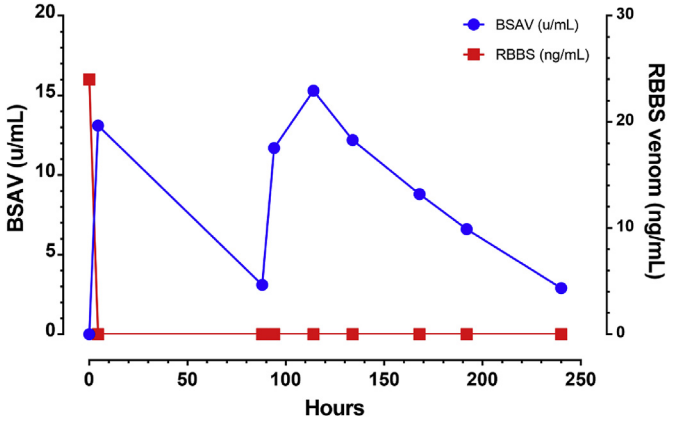

Fig. 1. Serum RBBS venom antigen and brown snake antivenom (BSAV) concentration by hours post-admission measured retrospectively using ELISA.

orally every 6–8 h as required. Amoxycillin-clavulanic acid (Amoxyclav, Apex Laboratories, Australia) 12.5 mg/kg previously commenced by the referring veterinarian due to swelling at the suspected bite site was continued orally every 12 h.

Serial blood samples were taken during the period of hospitalisation to monitor PCV (Fig. 2) and blood gas analysis (data not shown). Severe anaemia with a PCV of 15%, dull mentation and tachycardia (140 bpm) developed 84 h post-treatment. Blood samples were collected for Direct Antiglobulin test (DAT) prior to further treatment which subsequently returned a positive result. At this time point an additional vial of tiger-brown bivalent antivenom was administered intravenously over 30 min. Preparation was made for a blood transfusion. The dog was blood typed as DEA1.1 negative and a packed red blood cell (pRBC) transfusion of 156 mL of DEA1.1 negative blood was then administered over 3 h and dexamethasone (0.5 mg/kg; Dexapent, Troy, Australia) administered by intravenous injection. Fluid therapy was changed to intravenous isotonic crystalloid (Plasma-Lyte 148, Baxter, Australia) and rate reduced to 3 mL/kg/h. PCV improved to 22% by 1 h following the completion of the pRBC transfusion. Amoxycillin-clavulanic acid and tramadol were both discontinued and a 25 μg fentanyl patch (Durogesic, Janssen-Cilag, Australia) was applied for analgesia of the myositis. The dog's serum CK reached a peak of 15,608 at 3 d post-admission. At 5.5 d post-admission the dog was discharged home from hospital with PCV of 27%.

Subsequent blood samples were collected for monitoring of complete blood count, biochemistry, and blood smear analysis at 5 d, 16 d, 23 d, 41 d, 51 d and 62 d post-admission. (Tables 1 and 2 & Fig. 3). Haematocrit had normalised at 16 d and increased to a maximum of

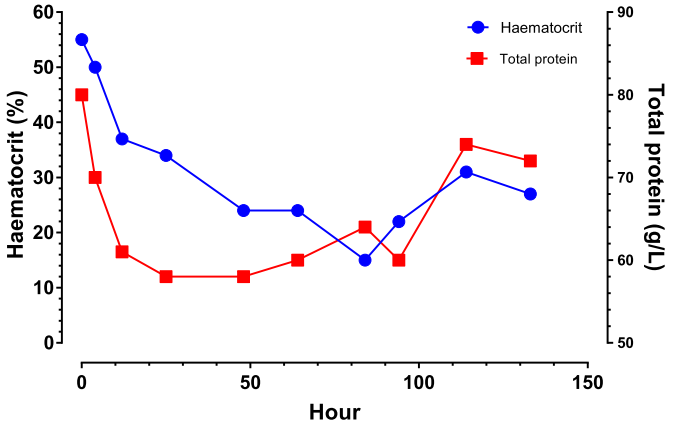

Fig. 2. PCV and total serum protein concentrations during the hospitalisation period.

Table 1
Clinical haematology results by time post-admission.

	Time post-admission/Result							Reference Range
	2 d	5 d	16 d	23 d	41 d	51 d	65 d	
Hb, g/L	**90**	**98**	129	143	154	165	176	115–180
Red Cell Count								
RCC x10^{12}/L	**3.6**	**4.0**	5.2	5.8	6.3	6.7	7.1	5.0–8.0
HCT, L/L	**0.29**	**0.33**	0.42	0.50	**0.56**	0.52	0.55	0.37–0.55
MCV, fL	**80**	**83**	**81**	**86**	**89**	**77**	**77**	63–74
MCH, pg	25	25	25	25	25	25	25	20–25
MCHC, g/L	314	**297**	311	**289**	**277**	319	322	310–360
NRBC,/100 WBC	0	0	**3**	0	0	0	0	
Reticulocytes, %	1.0	**3.0**	**3.4**	1.7	1.0	1.2	ND	< 2.1
Platelets, x10^9/L	201	clumped	294	clumped	clumped	203	clumped	200–900
White Cell Count								
WBC x10^9/L	**20.6**	**37.7**	13.6	13.6	9.5	8.7	9.2	6–14
Neutrophil x10^9/L	**18.5**	**34.7**	8.7	9.0	4.5	4.5	5.6	4.1–9.4
Band Neutrophil x10^9/L	0.21	**3.39**	0	0	0	0	0	
Lymphocytes x10^9/L	1.4	0.8	1.8	2.3	2.1	2.1	2.0	0.9–3.6
Monocytes x10^9/L	0.6	2.3	0.4	0.4	**0.1**	0.5	0.5	0.2–1.0
Eosinophil x10^9/L	0	0	**2.72**	**1.90**	**2.85**	**1.57**	1.10	0.1–1.2
Basophil x10^9/L	0	0	0	0	0	0	0	< 0.11
Red Cell Morphology								
Spherocytes	+ +	+ + +	+ +	+ +	+	+		
Spherocytes/HPF	80–100	100–120	50–60	30–40	2–3	0–1	0	
Anisocytosis	+	+ +	+	+				
Polychromasia		+	+					

+ mild, + + moderate, + + + marked/severe.
ND = not done.
Values in bold are outside normal reference range.

Table 2
Serum biochemistry by time post-admission.

	Time post-admission/Result							Reference Range
	3.5 d	4 d	5 d	23 d	41 d	51 d	65 d	
CK, U/L	**15,608**	**10,774**	**5596**	214	290	278	226	0–400
Bilirubin, umol/L	ND	ND	7	< 2	< 2	< 2	< 2	0–10
AST, U/L	ND	ND	**117**	50	52	37	41	1–80
ALT, U/L	ND	ND	**120**	66	49	33	30	0–80
GGT, U/L	ND	ND	< 5	5	< 5	5	**16**	0–5
ALP, U/L	ND	ND	112	56	47	40	33	1–120
TP, g/L	ND	ND	66	65	64	64	69	55–78
Albumin, g/L	ND	ND	33	36	35	**37**	**38**	22–36
Globulin, g/L	ND	ND	33	29	29	27	31	25–40
Urea, mmol/L	8.2	ND	**9.3**	6.9	4.6	6.3	5.2	2.5–9
Creatinine, umol/L	55	ND	55	70	104	85	82	40–140
Glucose, mmol/L	ND	ND	ND	4.1	ND	4.4	ND	3.5–6.7
Haemolysis[a]	ND	ND	**3+**	**1+**	**3+**	**1+**	Nil	

ND = not done.
Values in bold are outside normal reference range.
[a] Serum Haemolysis Index: 1 + Mild; 2 + Moderate; 3 + Marked.

56% at 41 d. Spherocytes were appreciated on blood film analysis (Fig. 5) with the maximum estimated count occurring at 5 d post-admission, which gradually reduced to undetectable at 62 d post-admission. The patient showed no evidence of further haematological or clinical abnormalities at 62 d.

3. Methods

The dog was hospitalised in the Pet Intensive Care Unit, Brisbane, Australia. RBBS venom antigen concentration were measured by a RBBS specific sandwich ELISA as described previously (Padula and Winkel, 2016). The RBBS sandwich ELISA is highly specific for

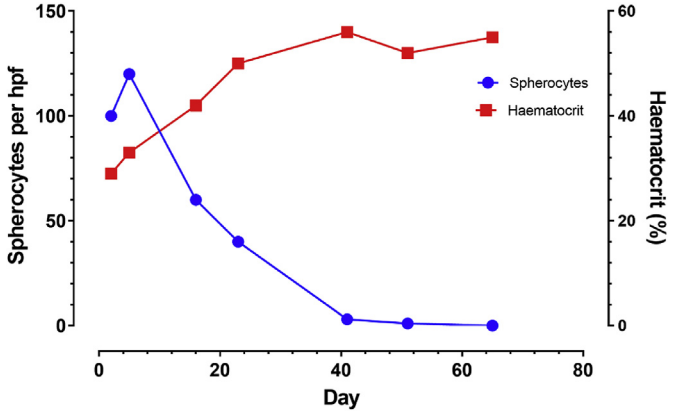

Fig. 3. Haematocrit and number of spherocytes per high powered field (x1000) presented by days post-admission.

detection of RBBS venom with limited cross reactivity (< 10%) with tiger snake (*Notechis scutatus*) and (< 1%) brown snake (*Pseudonaja textilis*) venoms (Fig. 4). Measurement of serum antivenom concentration was performed using an indirect ELISA with whole brown snake venom (*Pseudonaja textilis*) as the coating antigen. The experimental antivenom was a whole equine IgG caprylic acid fractionated bivalent tiger and brown snake antivenom as previously described (Padula and Leister, 2017a). The antivenom was formulated to contain a minimum of 4000 units of antivenom activity for tiger and 4000 units for brown snake. One unit of antivenom is defined as the amount of antivenom sufficient to neutralise the lethal effects of 0.01 mg of venom in mice challenged with five lethal doses of venom. PCV was measured during hospitalisation by centrifugation and manual measurement in micro-haematocrit tube. An external diagnostic laboratory (QML Pathology, Brisbane, Australia) was used to obtain haematology and biochemistry profiles. Blood smear reviews and semi-quantitative analyses were performed by a single pathologist.

The DAT (Coomb's test) was performed by an external laboratory

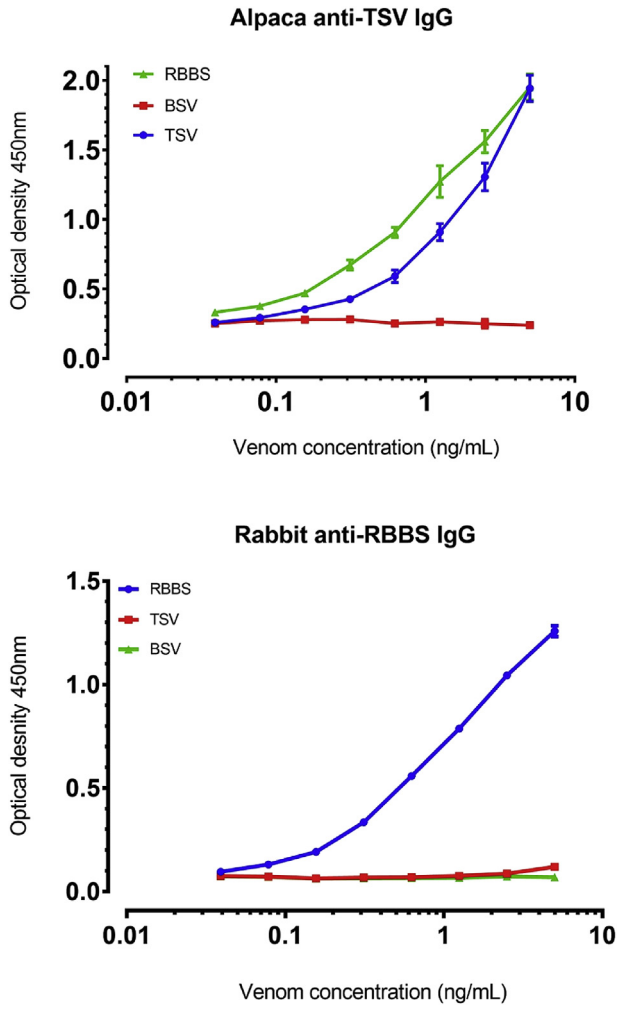

Fig. 4. Cross reactivity of red bellied black snake venom (RBBS; *Pseudechis porphyriacus*), tiger snake (TSV; *Notechis scutatus*) and brown snake (BSV; *Pseudonaja textilis*) in the venom antigen sandwich ELISA using: (a) alpaca anti-TSV (IgG); and (b) rabbit anti-RBBS (IgG) as the capture antibody. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

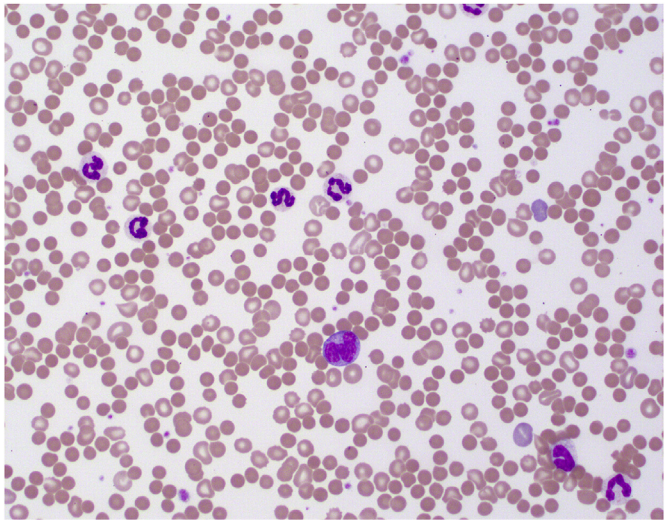

Fig. 5. Wrights stained peripheral blood smear from RBBS envenomed dog at 5 d post-envenomation showing RBC anisocytosis and marked spherocytosis (x500 magnification).

(QML Pathology, Brisbane, Australia) using a commercial canine anti-globulin reagent (ImmunoO™, MP Biomedicals, USA). The anti-globulin reagent used was polyvalent and the manufacturer stated it was prepared by hyperimmunisation of rabbits against canine IgM, IgG and C3 proteins.

4. Discussion

This case demonstrates the potential for unpredictable, severe and life threatening haemolytic effects following RBBS envenomation in the dog. The dog described here presented shortly after envenomation and was promptly treated with antivenom. However, 3.5 d after admission the dog developed a severe anaemia with sufficient transfusion triggers (tachycardia, dull mentation) to warrant a blood transfusion. It is possible that without administration of pRBC at this time the haematocrit would have continued to drop which may have been fatal. At the time of severe anaemia there was no RBBS venom detected in serum, although antivenom was present in adequate concentrations to neutralise any immediate lethal effects. This may indicate that no further antivenom was required at this time – however the patient showed a very rapid clinical improvement in gross haemolysis of the serum within hours of further antivenom administration and transfusion. The rapid clinical improvement may have been coincidental or may indicate technical issues with attempting to measure free venom in the presence of high concentrations of antivenom (O'Leary and Isbister, 2014).

The positive DAT result obtained 3.5 d after envenomation is puzzling, however we do not necessarily interpret this as supporting a diagnosis of immune mediated haemolytic anaemia (IMHA). IMHA is the result of anti-RBC antibody and complement proteins binding to the surface of RBC resulting in lysis, distortion of RBC membranes and microscopic morphological abnormalities. The very short amount of time between envenomation and the DAT positive result would be too brief to get any significant anti-RBC antibody formed which typically takes at least 7–10 d discounting IMHA as a cause. The clinical signs and prompt recovery without immunosuppression were also not consistent with canine IMHA. We speculate that the positive DAT result may be an agglutination artefact due to high levels of equine antivenom present in the dogs serum at that time. Macroscopic RBC agglutination was described when human, rabbit and mouse RBC preparations were mixed with various equine derived antivenom products (León et al., 2007). The presence of anti-human erythrocyte antibodies was also visualised by direct immunofluorescence microscopy in polyvalent antivenom (León et al., 2007). It is not known if the antivenom used in this dog bound directly to RBC causing agglutination in the Coomb's test. Further experimental studies would be required to investigate the presence of anti-dog erythrocyte antibodies in equine derived plasma (and antivenom) and the potential effect of this on DAT results. False positive results to acetylcholine receptor antibody were documented in two human patients undergoing treatment and diagnosis for flaccid paralysis of undetermined cause; the result was attributed to treatment with equine polyvalent antivenom and circulating equine immunoglobulin (Sundar et al., 2017).

Although no immunosuppressive medications were administered to the dog following the second vial of antivenom, spherocyte numbers continued to decline and were no longer present at day 62, suggesting that no further formation of spherocytes occurred after the second vial of antivenom. This is contrary to what is expected with a patient with secondary IMHA, where spherocytes continue to form until immune suppression occurs and immune suppressive medications are required often for many months. This is supported by findings of a case series by (Ong et al., 2015) which presumed IMHA was secondary to elapid snake envenomation in dogs where one of the four dogs described did not receive immunosuppressive medication and had complete resolution of spherocytosis and microscopic agglutination 6 wk following initial diagnosis. This is suggestive that the spherocyte formation is primarily caused by the direct effects of the RBBS venom on RBC lipid

membranes, and not a secondary immune mediated process.

Tiger snake antivenom has for decades been the recommended antivenom treatment for RBBS envenomation in humans in Australia (Sutherland, 1976). It is a lower volume and lower cost product than the more specific Black Snake Antivenom (Seqirus, Parkville, Australia) which uses *Pseudechis australis* as the immunising venom. Administration of tiger snake antivenom may also reduce the frequency of acute and delayed adverse antivenom reactions. Interestingly tiger snake antivenom appears to have wide paraspecificity for neutralisation of many venomous south east Asian elapid snake species including *Naja* sp.(Minton, 1967), *Micrurus* sp. (Ramos et al., 2016), and many sea snakes (Baxter and Gallichio, 1976). Further supporting the use of tiger snake antivenom is the high degree of immunological cross reactivity previously demonstrated between notexin the principal neurotoxin and myotoxin from tiger snake venom, and pseudexin from RBBS venom (Middlebrook and Kaiser, 1989). Rabbit anti-sera to notexin bound equally strongly to purified pseudexin; reciprocally, antisera to purified pseudexin bound strongly to notexin. The cross reactivity between these venoms is utilised in a commercial Australian immunological snake venom detection kit (SVDK, Seqirus, Australia) that uses rabbit antibodies to *Pseudechis australis* to capture free venom to all black snake species (Cox et al., 1992). When RBBS venom was applied to the wells of the SVDK at 40 ng/mL this resulted in an optical density only 25% that of the homologous *P. australis* venom at the same concentration (Cox et al., 1992. Similarly, rabbit antibodies to tiger snake venom (*Notechis scutatus*) also captured RBBS venom but the optical density when both venoms were applied at 40 ng/mL was only 11% of the homologous venom type (Cox et al., 1992). Coagulants in RBBS venom have also been shown to be effectively neutralised by monovalent IgG to *Notechis scutatus* venom (Lane et al., 2011). Alpaca IgG specific for tiger snake venom was effective in binding to RBBS venom antigens (Fig. 4a). In contrast, rabbit IgG specific for RBBS venom appears to recognise only limited antigens in tiger snake venom (Fig. 4b). This may indicate that an antivenom made by production of antibodies against only RBBS venom may be ineffective in neutralising tiger snake venom although the converse situation appears effective.

In conclusion, this case highlights the potential for occasional and unpredictable severe life-threatening anaemia and its management following RBBS envenomation in the dog.

Acknowledgements

Thank you to Dr James Carmichael at the Albert Animal Hospital, Springwood. Sincere thanks to the owners of the dogs for their co-operation. Thank you to all staff at Animal Emergency Service, Veterinary Specialist Services and Pet ICU, Underwood, Qld for assistance during this study.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.toxicon.2018.07.005.

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