CASE REPORT

Differential Diagnosis Between Venomous (*Bothrops jararaca*, Serpentes, Viperidae) and “Nonvenomous” (*Philodryas olfersii*, Serpentes, Dipsadidae) Snakebites: Is It Always Possible?

Carlos R. de Medeiros, MD, PhD^{1,2,3}; Marcelo R. Duarte, MSc⁴; Solange N. de Souza, BSN⁵

¹Laboratório de Ecologia e Evolução, Instituto Butantan, São Paulo, Brazil; ²Centro de Assistência Toxicológica, Instituto da Criança do Hospital das Clínicas da Faculdade de Medicina da USP, São Paulo, Brazil; ³Curso de Medicina, Centro Universitário São Camilo, São Paulo, Brazil; ⁴Laboratório de Coleções Zoológicas, Instituto Butantan, São Paulo, Brazil; ⁵Hospital Vital Brazil, Instituto Butantan, São Paulo, Brazil

Bites of “nonvenomous” snakes can sometimes be mistaken for the bites of venomous snakes. As an example of this confusion, this report describes confirmed bites by *Philodryas olfersii* and *Bothrops jararaca*. In the first case, a 55-y-old man with a history of controlled hypertension was bitten on his right forearm by *P. olfersii*. Physical examination revealed extensive edema, erythema, and widespread ecchymoses throughout his right upper limb. Laboratory tests indicated leukocytosis and high D-dimer levels, but normal coagulation, suggestive of a resolved recent coagulopathy. He received only supportive treatment. In the second case, a healthy 35-y-old man was bitten by *B. jararaca*. Although the anatomic region of the bite and the results of physical examination were similar to those in the first case, laboratory tests showed mild coagulopathy, leukocytosis, and high D-dimer levels. The patient was treated with antivenom. In both cases, the 20-min whole blood clotting test results were normal. Patients bitten by *P. olfersii* may present with local symptoms resembling *B. jararaca* envenomation. Without snake identification and the detection of venom-induced consumption coagulopathy, especially in places where the 20-min whole blood clotting test is the only clotting test available, it is almost impossible to establish an accurate and safe differential diagnosis. In this context, the best alternative is to take the risk of prescribing antivenom for a possible *P. olfersii* bite rather than failing to do so for a real *Bothrops* bite. Late treatment for *Bothrops* bite can result in severe complications and sequelae.

Keywords: non-front-fanged colubroids, nonvenomous snake, antivenom

Introduction

Non-front-fanged colubroid (NFFC) snakes comprise approximately two-thirds of the described species of advanced snakes.¹ However, the medical significance of the majority of the NFFC taxa is unknown,¹ and their bites can sometimes be mistaken for the bites of front-fanged venomous snakes.² Here we describe the cases of 2 confirmed bites, 1 by *Philodryas olfersii* (Lichtenstein, 1823) (Figure 1A), an NFFC snake, and the other by *Bothrops jararaca* (Wied, 1824) (Figure 2A), a pit viper, as examples of how this confusion can occur. Both patients

were admitted to the Hospital Vital Brazil (HVB), Instituto Butantan, São Paulo, Brazil, a hospital specializing in the care of patients involved in accidents caused by venomous animals. In both cases, the snakes were brought to the hospital by the patients and identified by technicians or researchers at the Laboratório de Coleções Zoológicas. The identifications were made from voucher specimens that were housed in the herpetologic collection of Alphonse Richard Hoge, Instituto Butantan, São Paulo, Brazil.

Details of Cases

CASE 1

A 55-y-old man with a history of controlled hypertension was bitten on the dorsal surface of the distal third of his right forearm while trying to capture an adult *P. olfersii*

Corresponding author: Carlos R. de Medeiros, MD, PhD, Rua Guilhermina, 313, Vila Romero, São Paulo, SP, Brazil; e-mail: carlos.medeiros@butantan.gov.br.

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Figure 1. (A) *Philodryas olfersii* (Lichtenstein, 1823), a nonfront-fanged colubroid snake; living specimen photographed in the municipality of Jundiá (23°11'11"S, 46°53'03"W), about 38 km from São Paulo. (B) *Philodryas olfersii* (Instituto Butantan, São Paulo, Brazil number 89209) was brought by the Case 1 patient. Adult female, total length 87.5 cm, mass 80 g, origin Cabreúva (23°18'27"S, 47°7'59"W), about 87 km from São Paulo. (Photos by Marcelo Ribeiro Duarte).

(female, total length 87.5 cm, mass 80 g) (Figure 1B). The snake was in the backyard of his house, located in a rural area in the municipality of Cabreúva (23°18'27"S, 47°7'59"W), about 87 km from the city of São Paulo. Upon arrival at the HVB, 10 h post-bite, the following data were recorded: blood pressure 155/87 mm Hg, heart rate 111 beats·min⁻¹, axillary temperature 35.8°C, and oxygen saturation 95% on room air. The patient reported pain extending from the bite site to the underarm. Physical examination revealed the presence of semicircular bite marks and severe edema, erythema, and widespread ecchymoses throughout his right upper limb (Figure 3A–C). He denied having used a tourniquet.

Laboratory test results on admission are presented in Table 1. The fibrinogen level, prothrombin time, international normalized ratio (INR), activated partial thromboplastin time, 20-min whole blood clotting test (WBCT20), and platelet count were all within the normal ranges. However, leukocytosis and increased levels of urea, creatinine, D-dimer, and C-reactive protein (CRP) were observed. All of the initial test results normalized spontaneously by the second day of hospitalization, except for the D-dimer level, which continued to increase, and a subsequent increase in the creatinine kinase level. The patient was discharged after treatment with anti-inflammatory

drugs and corticosteroids. Within 2 d, he no longer had any pain, and swelling showed significant improvement. He recovered completely after 3 wk.

CASE 2

A healthy 35-y-old man presented with a bite on the dorsal surface of the distal third of his right forearm from an adult *B. jararaca* (female, total length 92.6 cm with mutilated tail, mass 254 g) (Figure 2B) sustained while working in his vegetable garden. His home was located in a rural area in the municipality of Itapeverica da Serra (23°43'03"S, 46°50'58"W), about 30 km from the city of São Paulo. Two hours after the snakebite, he was admitted to the HVB with blood pressure 149/76 mm Hg, heart rate 63 beats·min⁻¹, axillary temperature 36.2°C, and oxygen saturation 98% on room air. He reported pain and swelling, which quickly progressed from the bite site toward his hand and elbow. On physical examination, he displayed excoriations at the bite site and extensive edema, erythema, and sparse ecchymosis throughout his right upper limb (Figure 3D–F). Laboratory tests on admission (Table 1) showed leukocytosis, coagulopathy with fibrinogen consumption, and thrombocytopenia, despite the normal WBCT20.

Figure 2. (A) *Bothrops jararaca* (Wied, 1824), a pit viper; living specimen photographed in the municipality of Cotia (23°00'25"S, 47°08'04"W), about 38 km from São Paulo. (B) *Bothrops jararaca* (Instituto Butantan, São Paulo, Brazil number 91432) brought by the Case 2 patient. Adult female, total length 92.6 cm (mutilated tail), mass 254 g, origin Itapeverica da Serra (23°43'03"S, 46°50'58"W), about 30 km from São Paulo. (Photos by Marcelo Ribeiro Duarte).

Figure 3. (A, B) Patient bitten by *Philodryas olfersii* on the dorsal surface of the distal third of his right forearm. Physical examination revealed severe edema, erythema, and widespread ecchymoses throughout his right upper limb. (C) Bite site detail showing semicircular bite marks. (D, E) Patient bitten by *Bothrops jararaca* on the dorsal surface of the distal third of his right forearm. Physical examination revealed severe edema, erythema, and widespread ecchymoses throughout his right upper limb. (F) Bite site detail showing excoriations caused by snake's dentition. (Photos by Carlos Roberto de Medeiros).

Eight vials of anti-*Bothrops* antivenom (BAV) were diluted and administered intravenously. BAV is a polyvalent antivenom containing equine-derived antibody fragments [(F(ab')₂] against the venom of 5 *Bothrops* species (*B. jararaca*, *B. neuwiedi*, *B. alternatus*, *B. moojeni*, and *B. jararacussu*), manufactured by Instituto Butantan, São Paulo, Brazil. According to the manufacturer, 1 mL neutralizes the lethality of 5 mg standard *B. jararaca* venom. The patient's INR and fibrinogen values reached normal limits 19 h after antivenom administration. On Day 2 after the bite, the patient was afebrile, with erythema and increased temperature at the bite site and elevated CRP. He was treated with chloramphenicol owing to a secondary

infection at the bite site. No microbial culture was performed. He was discharged after 4 d with a normal thrombocyte count, but with edema that persisted for approximately 2 wk.

Discussion

Snakebite victims often bring snakes to the hospital or take pictures of the snake. When this occurs, provided that correct identification by an experienced professional takes place, a differential diagnosis is facilitated. Otherwise, because local clinical presentations may be

Table 1. Laboratory test results of patients bitten by *Philodryas olfersii* (Case 1) and *Bothrops jararaca* (Case 2)

Test	Case 1			Case 2				Reference range
	Philodryas olfersii bite			Bothops jararaca bite				
	Admission	First day	Second day	Admission	First day	Second day	Fourth day	
Hemoglobin (mg·dL ⁻¹)	16.6	14.1	13.5	15.6	14.8	13.6	13.4	13.5–17.5
Leukocyte (·μL ⁻¹)	17,450	13,100	11,290	18,690	13,230	11,200	6000	4500–11,000
Platelets (·μL ⁻¹)	238,000	204,000	206,000	15,000	72,000	83,000	207,000	150,000–400,000
Sodium (mEq·L ⁻¹)	-	140	141	142	142	140	–	136–145
Potassium (mEq·L ⁻¹)	-	4.6	3.7	3.2	4.3	4.7	–	3.5–4.5
Creatinine (mg·dL ⁻¹)	1.37	1.11	1.02	0.95	0.92	0.92	–	0.70–1.20
Urea (mg·dL ⁻¹)	65	52	43	25	20	19	–	17–49
AST (U·L ⁻¹)	21	–	22	22	–	26	37	≤40
ALT (U·L ⁻¹)	39	–	33	24	–	21	45	≤41
LDH (IU·L ⁻¹)	–	166	216	199	146	284	154	≤250
Creatinine kinase (IU·L ⁻¹)	149	–	213	145	132	245	120	≤190
C reactive protein (mg·dL ⁻¹)	1.4	1.4	0.5	<0.5	2.1	5.0	4.9	<0.5
Fibrinogen (mg·dL ⁻¹)	278	284	253	103	255	413	–	238–498
D-dimer (mg·L ⁻¹)	1.943	2.683	2.740	7.530	–	1.975	–	<0.500
PT (s)	13.4	–	12.5	17.2	15.7	14.8	–	11.5–14.5
aPTT (s)	25.7	–	25.2	30.8	29.5	29.3	–	25.4–36.9
INR	1.00	–	1.00	1.32	1.18	1.10	–	0.80–1.20
WBCT20 (s)	Coagulable	–	–	Coagulable	Coagulable	–	–	Coagulable

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; WBCT20, 20-minute whole blood clotting test.

similar, a differential diagnosis between venomous and “nonvenomous” snakebites can be difficult.²

Figure 3 shows that in both cases, the patients were bitten in the same anatomic region and had edema throughout the upper limb, associated with erythema and widespread ecchymoses. These symptoms are common in bites from *Bothrops* spp^{3,4} and have been frequently reported in bites from *P. olfersii*.^{5–7} In Case 1, the bite marks were semicircular and suggestive of a “nonvenomous” snakebite (Figure 3C). In Case 2, the patient displayed excoriations at the bite site rather than the classic 2 perforations of a bite from a pit viper (Figure 3F). Although some authors have considered examination of the bite marks useful in the differential diagnosis between venomous and “nonvenomous” snakebites, its isolated use

cannot be considered reliable owing to its low specificity.⁸ In a recent study, semicircular bite marks were observed in less than a quarter of 141 cases of bites by *P. olfersii*.⁵

Regarding the laboratory tests, in Case 1, the patient did not present with venom-induced consumption coagulopathy (VICC), only leukocytosis and high CRP and D-dimer levels, without consumption of fibrinogen and platelets or changes in prothrombin time, INR, or activated partial thromboplastin time. In the following days, D-dimer levels continued to increase (Table 1), accompanied only by a small increase in creatinine kinase, with no other changes suggestive of VICC. It is possible that these laboratory findings may have been due to extensive local inflammation. It has been shown that the principal effects of *P. olfersii* venom in mice are local

edema, inflammatory cell infiltration, and myonecrosis, probably mediated by metalloproteinases, serine proteinases, cysteine-rich secretory proteins, and other components present in *P. olfersii* venom.⁹ The patient was also seen only 10 h after the bite, which does not allow us to rule out the possibility of transient coagulopathy. However, no clinically documented or confirmed coagulopathy from envenomation by *P. olfersii* has been reported in the literature,⁵ and the continuous elevation of the D-dimer levels without fibrinogen or platelet consumption observed in subsequent days does not support this hypothesis. Nevertheless, further studies are needed to clarify this issue. However, the patient also showed acute kidney injury, which resolved after hydration. Because there was no substantial increase in lactate dehydrogenase and thrombocytopenia, it is unlikely to have been due to microangiopathic hemolytic anemia previously described in envenomation by other snakes.¹⁰ The drop in hematocrit may have been attributed to hemodilution caused by hydration and, at least in part, to extensive ecchymosis.

Bothrops spp are the most common cause of human snakebites in South and Central America. *Bothrops* envenomation can manifest with local inflammatory signs and hemostatic disorders.^{3,4} Common signs and symptoms include pain, swelling, and bleeding, occurring within the first 6 h after envenomation.³ In Brazil, *Bothrops* envenomation severity is classified as mild, moderate, or severe and treated with 3 to 4, 6 to 8, or 12 vials of BAV, respectively. Mild cases are defined as the presence of mild local signs, such as edema. Moderate cases include regional edema, and severe cases include swelling around the full length of the affected limb, acute kidney injury, shock, and/or severe hemorrhage.³ These definitions do not take into account the presence or absence of coagulopathy.³ In Case 2, the patient was admitted 2 h after the bite, with extensive edema, erythema, and sparse ecchymosis throughout his right upper limb. In addition to leukocytosis and elevated D-dimer levels, he presented with active VICC as shown by the consumption of fibrinogen, as well as thrombocytopenia. WBCT20 coagulability was not sensitive enough to detect slight changes in coagulation.¹⁰ These are the classical alterations present in patients bitten by *Bothrops* spp in Latin America,^{3,4} which facilitated diagnosis in association with identification of the snake. VICC and thrombocytopenia regressed after the use of the antivenom (Table 1), and the secondary infection was effectively treated with antibiotics.

Differentiating between the 2 types of envenomation is extremely important because treatment involves the use of antivenom. Misuse of antivenom, despite identification of the snake, has been observed in cases of bites by *P. olfersii* reported in the literature.² Although *P. olfersii* venom exhibits immunologic cross-reactivities to polyvalent

BAV,¹¹ its use in the treatment of *P. olfersii* bites does not seem to be justified because no controlled clinical study has used the antivenom in the treatment of these patients. Thus, the problem is not restricted to the identification of snakes, but includes misinformation about the differences between the medical risks posed by front-fanged venomous snakes and NFFC snakes, thus contributing to the inappropriate treatment of these bites.^{2,5}

In many snakebite cases, the snake responsible remains unidentified, which frequently results in difficulties in deciding which antivenom to administer. However, the diagnosis of a venomous snakebite or determination of the snake possibly responsible for envenomation can be made using clinical criteria.¹² Clinical diagnosis depends on the recognition of envenomation symptoms observed in the patient. Localized symptoms of swelling, ecchymosis, blistering, and necrosis, or systemic symptoms such as hemorrhage, incoagulable blood, hypovolemic shock, neurotoxic signs, and rhabdomyolysis, may be observed depending on the genus of the envenoming snake (in Brazil the genera *Bothrops*, *Crotalus*, *Lachesis*, *Leptomicrurus*, or *Micrurus*).^{3,12} In Case 2, the presence of coagulopathy and the correct identification of the snake (*B. jararaca*) allowed for safe prescription of antivenom. However, because both factors are not always present, despite the presence of local symptoms, an alternative is the use of immunologic tests,¹² which are unfortunately not available in Brazil. Furthermore, in Case 2, the WBCT20 was not sensitive enough to detect mild VICC, which can be a problem in low-income settings where most snakebites occur and where bedside clotting tests, such as the WBCT20, play a major role in diagnosing coagulopathy.¹⁰ In Case 2, if we could not identify the snake and only used the WBCT20 for the diagnosis of VICC, it would have been dangerous to wait for the progression of symptoms or the diagnosis of coagulopathy; studies have shown that delayed treatment increases the risk of serious complications, such as necrosis and amputation.³

In the absence of snake identification, differentiating between bites by *P. olfersii* and *Bothrops* spp may be especially difficult in some regions of Brazil, where there are other crotaline species that, although relatively rare, can cause coagulopathy and local symptomology similar to envenomation from *Bothrops* spp, *Lachesis muta* (the only Bushmaster species in the Amazon rainforest and Atlantic Forest of Northeast and Southeast Brazil),¹³ and *Crotalus durissus ruruima* (present in the state of Roraima in Northern Brazil).¹⁴ Envenomation from other subspecies of Brazilian *Crotalus durissus* (species *cascavella*, *collilineatus*, *dryinas*, *marajoensis*, and *terrificus*) typically results in localized paresthesia at the bite site, with edema and erythema being rare or discrete,

confined to the bite site with ascending edema infrequently observed.¹⁴ Primary systemic symptoms after envenomation by these subspecies are neurotoxicity and myotoxicity (myasthenic facies, prostration, drowsiness, myalgia, hematuria, and kidney failure).¹⁴

Conclusion

Even if the health professional knows the difference in the medical risks posed by these 2 species, patients bitten by *P. olfersii* may present with local symptoms resembling mild-to-moderate *B. jararaca* envenomation. This situation can lead to a misdiagnosis in the absence of precise identification of the snake or sensitive tests to detect mild VCCI. The unavailability of immunologic tests worsens the situation. This combination of factors makes it almost impossible to establish a safe differential diagnosis of *Bothrops* spp envenomation and discard the need for antivenom. In this context, a reasonable alternative is to take the risk of prescribing antivenom for a possible *P. olfersii* bite, because failure to do so for a real *Bothrops* bite can result in severe complications and sequelae if treatment is delayed.

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