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Snake bites by the jararacuçu (*Bothrops jararacussu*): clinicopathological studies of 29 proven cases in São Paulo State, Brazil

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Summary

The jararacuçu, one of the most dreaded snakes of Brazil, southern Bolivia, Paraguay and northeastern Argentina, is a heavily-built pit viper which may grow to a length of 2.2 m. Up to 1000 mg (dry weight) of highly-lethal venom may be milked from its venom glands on a single occasion. It has accounted for 0.8% to 10% of series of snake bites in São Paulo State, Brazil. We examined 29 cases of proven jararacuçu bites recruited over a 20-year period in two São Paulo hospitals. Severe signs of local and systemic envenoming, (local necrosis, shock, spontaneous systemic bleeding, renal failure) were seen only in patients bitten by snakes longer than 50 cm; bites by shorter specimens were more likely to cause incoagulable blood. Fourteen patients developed coagulopathy, six local necrosis (requiring amputation in one) and five local abscesses. Two became shocked and four developed renal failure. Three patients, aged 3, 11 and 65 years, died 18.75, 27.75 and 83 h after being bitten, with respiratory and circulatory failure despite large doses of specific antivenom and intensive-care-unit management. In two patients, autopsies revealed acute renal tubular necrosis, cerebral oedema, haemorrhagic rhabdomyolysis at the site of the bite and disseminated intravascular coagulation. In one survivor with chronic renal failure, renal biopsy showed bilateral cortical necrosis; the patient remains dependent on haemodialysis. Effects of polyspecific *Bothrops* antivenom were not impressive, and it has been suggested that anti-*Bothrops* and anti-*Crotalus* antivenoms should be given in combination.

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Introduction

Among the lance-headed pit vipers (genus *Bothrops*) of Latin America, *B. asper/xanthogrammus* and *B. atrox* are the longest but the jararacuçu (*B. jararacussu*) (Figure 1), also known as urutu dourado and surucucu tapete, is the most heavily built. The name jararacuçu comes from the Tupi word yararakusú, meaning a large jararaca (*B. jararaca*).[1] A jararacuçu 1.5m long may have a girth of 22 cm, and the maximum length may exceed 2.2 m. This species is found in tropical forests, swamps and river banks (Figure 2) of Brazil as far south as Rio Grande do Sul[2] on several islands (Ilha Comprida, Cananéia, I. de São Sabastião and I. do Cardoso), in southern Bolivia, Paraguay and northeastern Argentina (Figure 3).[3] The average venom yield is 247 (range 149–385) mg (dry weight) and, exceptionally, up to 1000 mg dry weight at one milking; its lethal potency is much higher than venoms of most other *Bothrops* species, approaching that of the neotropical rattlesnake (*Crotalus durissus terrificus*).[4–6] Fortunately, this species bites humans infrequently. Thus, in Brazil from 1902 to 1945, among 6601 cases of snake bites, 657 (9.95%) were attributed to *B jararacussu* with 11 deaths.[7] At the Hospital Vital Brazil (HVB), Instituto Butantan, in São Paulo during the 12 years 1954–1965, 14/1718 snake bite cases (0.82%) were caused by this species with one death[8] while among 730 cases collected in 7 years, 1.2% were caused by this species.[9] In Santa Catarina, 7/29 *Bothrops* identified as responsible for bites during an 18-month period were *B. jararacussu*.[10] In this report, we review 29 cases of proven *B. jararacussu* bites treated over a period of 20 years in São Paulo, Brazil.

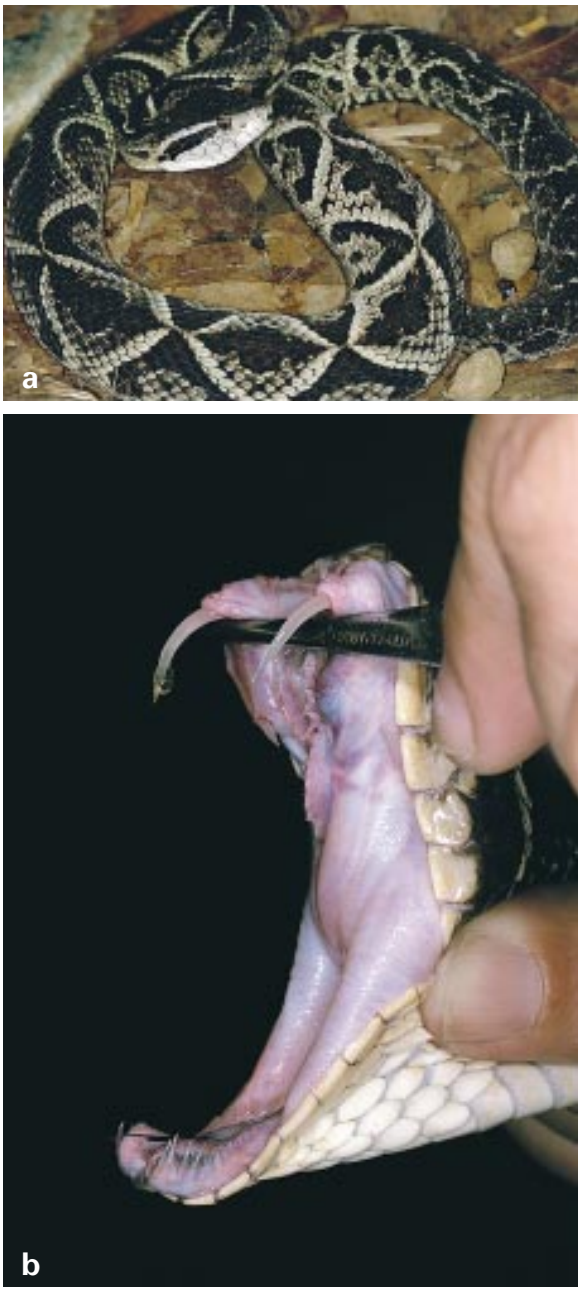

Figure 1. a Jararacuçu (*Bothrops jararacussu*). Living specimen more than 1 m long from São Paulo State, Brazil. **b** Showing long fangs.

Methods

An analysis was made of case-records of patients admitted to the HVB during the period 1975–1991 in which the snake responsible for the bite was identified as *B. jararacussu* by the Herpetology Laboratory, Instituto Butantan.

From 1991–5, a prospective study was carried out of patients severely envenomed by snakes in the São Paulo area. During this period three out of seven patients with proven bites by *B. jararacussu* were transferred from HVB, to the Hospital Universitário, University of São Paulo (HU) for investigation and intensive care.

Details of history, physical examination and labor-

Figure 2. Biotope of *Bothrops jararacussu* in the rain forest at Iguazú National Park, northeastern Argentina.

Figure 3. Above, distribution of *Bothrops jararacussu*; below, location of the 29 cases of bites in São Paulo State. Eight bites occurred at Juquitiba

atory investigations were recorded on standard proformas.

Immunodiagnosis

In one patient (Patient 3) the diagnosis was confirmed by detection of *B. jararacussu* venom by enzyme immunoassay. Each well of a 96-well microtitre plate (Polysorp, Nunc Ltd) was coated with 100 µl of 20 µg/ml $F(ab')_2$ purified from commercial horse polyspecific Bothrops antivenom (Instituto Butantan) using a protein G column on a FPLC system. The wells were washed as described by Theakston *et al.*[11] Wells were then blocked for 2 h at 37°C with 200 µl PBS containing 1% gelatine (PBSG) and rewashed. Patients' sera (100 µl) diluted 1:10 in PBSG (gelatine 0.5%) plus 10% normal human serum (NHS) were added to each well in duplicate. A standard curve for concentrations of *B. jararacussu* venom of 3000–1 ng/ml was also prepared using PBSG plus 10% NHS. The plate was then incubated for 2 h at 37°C, and subsequently rewashed. PBSG (100 µl) containing 5 µg/ml rabbit anti-*B. jararacussu* IgG purified by protein A chromatography was added to each well, and the plates were incubated for a further 2 h at 37°C. The plate was then rewashed and 100 µl goat anti-rabbit IgG peroxidase conjugate (Sigma, Cat. no A-6154) was added at a final dilution of 1:4000 in PBSG plus 0.05% Tween 20 for 1 h at 37°C. The colour was developed using 700 µg/ml OPD dissolved in citrate buffer, pH 5.0 plus 30% H_2O_2 (v/v). The reaction was stopped after 20 min

substrate incubation by adding 50 µl of 30% H_2SO_4 to each well. The optical density was recorded using a through-the-plate ELISA (Titertek, Multiskan, Eflab) reader at 492 nm absorbance. The concentration of *B. jararacussu* venom in the patient's samples was determined by reference to the standard curve.

Results

Records of 29 cases of proven bites by *B. jararacussu* were available for analysis; 22 were part of the retrospective series (1975–1991), seven were studied prospectively (1991–1995). Diagnosis was based on identification of the dead snake in 28 cases. The jararacuçus ranged in length from 27 to 159 cm.

Three people were bitten while handling the snakes at the Instituto Butantan. Patients were referred from the following municipal areas of São Paulo State: Juquitiba (8 patients), Tapíraí (3), Ubatuba (2), Bertioga (1), Cachoeira Paulista (1), Caraguatatuba (1), Miracatu (1), Pedro de Toledo (1), Juquiá (2), São Paulo (3), Santos (1), Piedade (1), Pindamonhangaba (1), Itaquaquecetuba (1), Iporanga (1), Embu Guaçu (1), Pinheiro (1) (Figure 2). Most bites occurred between 6 am and 6 pm (Table 1). The patients ranged in age from 3 to 61 (median 27.0) years.

The foot or ankle was bitten in 41.4% of patients. About one third reached hospital within 3 h of the bite, but about one quarter took more than 12 h (Table 2). Clinical features of the patients are shown in Table 3. Of the 14 showing evidence of coagulopathy, all had whole blood clotting times >20 min, six were bleeding from the site of the bite, but only two showed spontaneous systemic bleeding (haematemesis, haematuria, haemoptysis and bleeding from gingival sulci). Only one of the 29 patients with proven bites by *B. jararacussu* showed no signs of envenoming. One other patient, a woman, received a spray of venom in her eye when a jararacuçu struck against the mesh of its cage at Instituto Butantan. She developed conjunctivitis, a subconjunctival haemorrhage and corneal erosion, from which she made a complete recovery.

The 17 patients bitten by snakes longer than 50 cm are compared with the 12 bitten by snakes shorter than 50 cm long in Table 3. Severe signs of local and systemic envenoming, such as necrosis, shock, spontaneous systemic bleeding and renal failure, were seen only in those bitten by larger snakes, but bites by the smaller specimens were more likely to cause incoagulable blood (7/12, 58%).

Three of the 29 patients died (10.3%); of these

Table 1 Time of day when 26 bites by *Bothrops jararacussu* occurred*

Time of day	No. of cases	%
0600–1200	10	38
1200–1800	12	46
1800–2400	2	8
2400–0600	2	8
Total	26	100

*Three cases of bites to snake handlers have been excluded.

Table 2 Interval between time of 29 bites by *Bothrops jararacussu* and admission to hospital in São Paulo

Time (h)	No. of cases	%
0–1	3*	10.5
1–3	6	21
3–6	9	31
6–12	1	3
12–24	3	10
>24	4	14
Unknown	3	10.5
Total	29	100

*Bites inflicted on snake handlers at Instituto Butantan.

Table 3 Clinical features of 29 patients with proven bites by *Bothrops jararacussu* (1975–1995)

Snake length...	<50 cm long	>50 cm long	Total
n	12	17	29
Male patients	5	14	19
Female patients	7	3	10
Site of bite			
Foot/ankle	7	5	12
Leg/thigh	2	7	9
Hand/arm	2	5	7
Unrecorded	1	0	1
Clinical features			
No symptoms/signs	0	1	1
Pain	11	17	28
Swelling	11	16	27
Bruising	7	11	18
Blistering	1	6	7
Necrosis	0	6	6
Abscess	0	5	5
Amputation	0	1	1
Shock	0	2	2
Spontaneous systemic bleeding	0	2	2
Renal failure	0	4	4
Blood coagulation			
Normal	4	9	13
Incoagulable	7 (58%)	7 (41%)	14
Unrecorded	1	1	2
Deaths (case fatality)	0	3 (18%)	3 (10%)

two were children (aged 3 and 11) and one was a 65-year-old man. All three had been bitten by large *B. jararacussu*. Further details of these patients are given below.

Illustrative case reports

Patient 1

A 3-year-old girl was bitten three times on the front of the left thigh near the groin while playing in front of her house in a rural suburb of Miracatu, São Paulo State at 17:20 on 12.1.91. The snake responsible was a *B. jararacussu* 1.59 m long (Figure 4). At a hospital in nearby Juquitiba, she was given four ampoules of a polyvalent *Bothrops/Crotalus* antivenom and was taken to HVB at 20:10. She had been vomiting and was found to be shocked, with a tachycardia of 160/min, and had not passed urine since the bite. There was bleeding from the bite wound and local ecchymoses. She was transferred immediately to HU. On admission at 20:30, she was comatose, pale, peripherally cyanosed and hypothermic, with a weak pulse, very poor peripheral circulation and irregular gasping respiration. There was rapid deterioration with bradycardia, apnoea and finally circulatory failure, but she was resuscitated with external cardiac massage and positive-pressure ventilation. On 13.1.91, a further 15 ampoules of Instituto Butantan polyvalent *Bothrops* antivenom was administered by slow intravenous infusion. She was then transferred to the intensive care unit. Two hours later her condition again deteriorated. She was shocked and deeply comatose with absent light reflexes and dilating pupils. At the site of the bite on the left thigh were three puncture marks approximately 5 cm apart (Figure 5). The whole limb was swollen and ecchymotic with swelling of the adjacent area of her trunk. There was evidence of hypovolaemic shock and disseminated intravascular coagulation. Ten ampoules of *Crotalus*

Figure 4. Female *Bothrops jararacussu* 1.59 m long, which bit Patient 1 at Miracatu, near Juquitiba, Sao Paulo State.

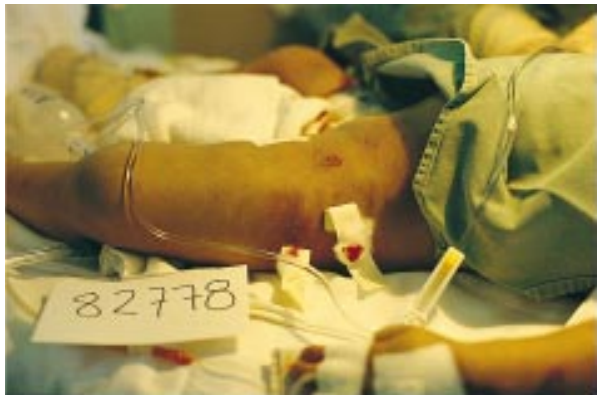

Figure 5. Patient 1, 6 h after being bitten on the left thigh. Two of the three widely spaced fang puncture marks are visible; there is extensive swelling and bruising of the thigh.

antivenom were given, because some authorities believe that this antivenom is more effective in *B. jararacussu* envenoming than *Bothrops* polyspecific antivenom. Volume expanders, blood transfusion, vasoactive drugs and ventilatory support were also provided. Initial laboratory results showed severe metabolic acidosis (pH 6.65, pO_2 76 mmHg, pCO_2 30.6 mmHg, bicarbonate 3.5 mmol/l), hyponatraemia (Na^+ 132 mmol/l), hyperkalaemia (K^+ 5.8 mmol/l), creatinine 1.3 mg/dl and elevated creatine kinase levels (1578 IU/l). There was anaemia (Hb 6.7 g/dl, haematocrit 22%), leucocytosis of 52×10^9/l with band forms and marked eosinophilia (metamyelocytes 1%, band forms 29%, segmented forms 5%, eosinophils 24%, lymphocytes 40%, monocytes 1%), thrombocytopenia (89×10^9/l), prolongation of prothrombin and partial thromboplastin times to >2 min, and hypofibrinogenaemia (0.4 g/l).

Over the next few hours her Glasgow Coma Score declined to 3, and her pupils dilated. Swelling and bruising of the left thigh increased. Shock, coma, anaemia, respiratory failure and metabolic acidosis proved refractory to treatment, blood urea and creatinine rose, and she developed bradycardia unresponsive to drugs and died 18.75 h after the bite (at 12:00 on 13.1.91).

On autopsy, at the site of the bite there was extensive rhabdomyolysis with haemorrhagic foci but no inflammatory infiltration of leucocytes (Figure 6). There was haemorrhage and necrosis in the subcutaneous tissues (Figure 7). There was cerebral oedema. The pituitary appeared normal. The lungs were haemorrhagic with an inflammatory infiltration of neutrophils in septa and alveoli; there was oedema and deposition of intra-alveolar fibrin.

Hepatic sinusoids and portal tracts were infiltrated with polymorphonuclear cells, mainly eosinophils (Figure 8). There was fatty necrosis of the pancreas with haemorrhage of the parenchymal cells. The

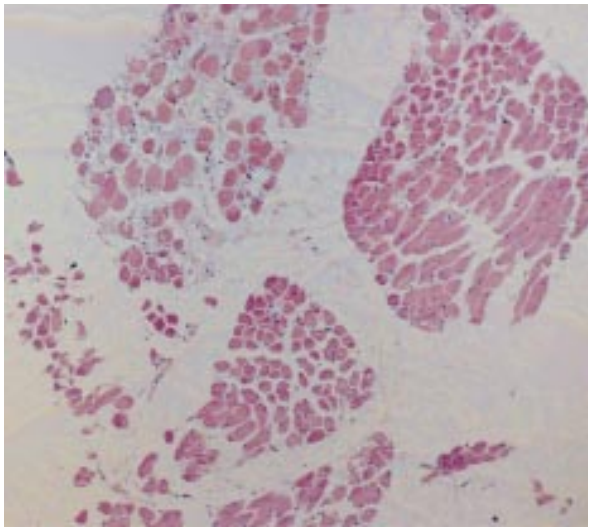

Figure 6. Patient 1. Rhabdomyolysis without inflammatory infiltrate near the site of the bite.

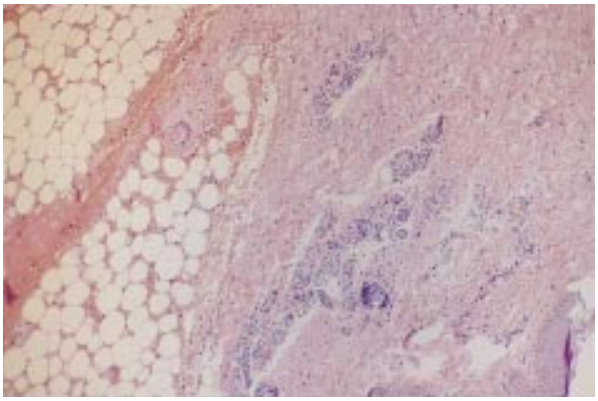

Figure 7. Patient 1. Haemorrhage and necrosis in the dermis and haemorrhage in subcutaneous fat near the site of the bite.

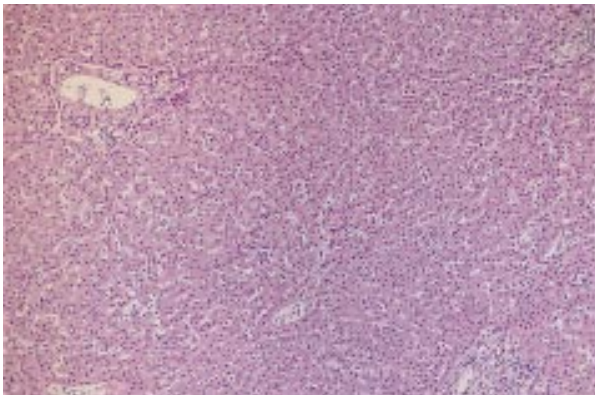

Figure 8. Patient 1. Polymorphonuclear cell infiltrate of hepatic sinusoids.

kidneys showed acute tubular necrosis with deposition of brown granulomatous pigment and crystals, in the distal tubules. Lymphoid tissue showed a marked accumulation of eosinophils. The adrenal glands appeared normal. The predominance of eosinophils in the infiltrates suggested the possibility of an anaphylactoid reaction to the large volumes of antivenom she had received, but there had been no clinical features of such a reaction.

Patient 2

A 35-year-old farm labourer was struck twice on the right forearm by a *B. jararacussu* 1.1 m long in Juquitiba, São Paulo State at 05:00 on 12/12/93. He was admitted to HVB 9 h later. Painful swelling had spread from the bite site to the right shoulder and anterior chest wall. He had a persistent tachycardia (96–122 beats/min), tachypnoea (25–32 breaths/min), low-grade fever and normal blood pressure, but had passed no urine since the bite. He was given eight vials of Instituto Butantan specific antibothropic serum intravenously. Four more vials of the same antivenom were given later because of the prolonged prothrombin time. On the next day he was still oliguric (100 ml/12 h) and the urine was dark. He was then transferred to the ICU of HU.

Tachycardia, tachypnoea, low-grade fever and a normal blood pressure were observed, and he was anuric and drowsy. There was massive swelling of the whole of the bitten arm and adjacent areas of the neck and hemithorax. Acute renal failure required prompt peritoneal dialysis (Table 4).

Because of persistent fever, the right arm was surgically explored. A subcutaneous abscess was drained and *Acinetobacter calcoaceticus* and *Enterobacter cloacae* were isolated. An open kidney biopsy was performed on the 30th day of hospital admission because of persistent renal failure. The histological appearances were of diffuse cortical and medullary necrosis (Figure 9) but a thin layer of viable cortex was discernible near the capsule. There was focal, global proliferative glomerulonephritis. A few glomeruli appeared viable (Figure 10). Acute

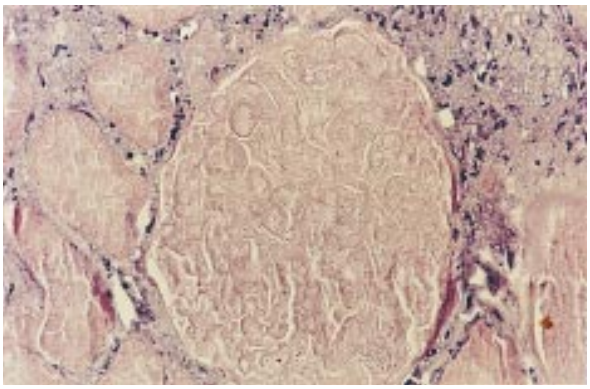

Figure 9. Patient 2. Renal biopsy. Renal cortical necrosis. The section shows an acellular glomerulus and necrotic tubular epithelial cells. Some nuclear debris remains in the interstitium.

Table 4 Laboratory findings (Patient 2)

Date...	13/12	14/12	15/12	16/12	18/12	25/12	3/1	13/1	3/2
Na^+ mEq/l	132	139	132	147	138	141	134	137	137
K^+ mEq/l	7.2	6.6	7.2	5.3	3.3	3.8	4.1	5.4	3.8
Urea nitrogen mg/dl	58	129	151	136	136	88	105	65	
Creatinine mg/dl	6.8	5.4	6.8	7.6	9.3	10.8	12.5	14	7.6
Creatine kinase U/l	7315	3500	7315	5340	631				
Lactate dehydrogenase U/l	4420		4420		2215				
Prothrombin time (s)	15.3	14.7 (70%)	15.3 (74%)	15 (88%)			15.1 (61%)	11.2 (100%)	
Platelets $\times 10^9$/l	59	57	59	36	68		255	248	
Haemoglobin g/dl	8.7	9.7	8.7	7.0	6.0	8.3		9.2	
Leucocyte $\times 10^9$/l	2800	9100	2800	3100	7800	7800			
Fibrinogen g/l	2.53								
FDP* µg/ml	128								
Bothrops venom antigen concentration ng/ml	62								

*Fibrin(ogen) degradation productions

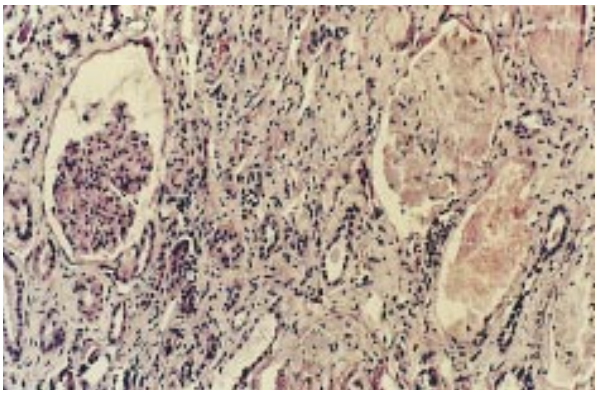

Figure 10. Patient 2. Renal biopsy. Necrotic glomerulus on the left with viable glomerulus and tubules on the right.

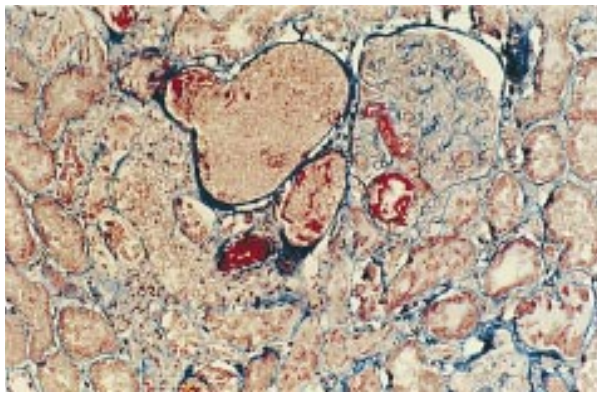

Figure 11. Patient 2. Renal biopsy (Masson's stain). In the glomerulus on the right, a capillary appears to be occluded with red-staining proteinaceous material, also seen in the wall of arterioles. This is probably fibrin, and the appearances suggest disseminated intravascular coagulation.

tubular necrosis was associated with tubular dilatation with desquamation of necrotic cells and cellular debris into the lumen. The viable tubules showed atrophy in some areas. Interstitial oedema was associated with a scanty infiltrate of lymphocytes, plasma cells and monocytes. Fibrin was detected in the walls of arterioles and there were fibrin thrombi in some glomerular capillaries (Figure 11).

He was treated with oxacillin and cefoxitin, blood transfusion, intravenous fluids and diuretics. Chronic peritoneal dialysis was complicated by pseudomonal peritonitis. He survives on a chronic haemodialysis regimen.

Patient 3

A 65-year-old builder resident in Itaquaquecetuba, was bitten on the left calf by a large jararacuçu at 09:00 on 16.9.94. He had been bitten on two previous occasions by snakes and treated at HVB. He was an alcoholic with a history of chronic bronchitis. Since no antivenom was available at the local hospital, he was given corticosteroid and intravenous fluid and transferred to HVB. On admission at 16:45 on the same day, the diagnosis was confirmed by detecting 396 ng/ml *B. jararacussu* venom in the serum. The level had fallen to 144 ng/ml at 6 h and to zero 12 and 24 h later. A tight tourniquet had been applied proximal to the bite for about 30 min. There had been mild localized bleeding from the fang punctures, and progressive swelling and pain.

The patient was conscious, orientated, haemodynamically stable and afebrile. He complained of

pain in the left leg. Two bleeding fang punctures were seen on the left calf surrounded by a ring of bruising. Marked tender swelling extended up to the knee and there was painful left inguinal lymphadenopathy. Haematomas were forming at the site of venepunctures, but there was no bleeding elsewhere. His blood was incoagulable. Between 17:10 and 17:45, four ampoules of anti-*Bothrops* antivenom was given with no reaction. During the next 24 h the local signs increased, but the clotting time returned to normal. Despite rehydration he produced only 230 ml of dark urine over the next 24 h.

On the third day after the bite there was a spike of fever (38°C), tachycardia, hypotension and oliguria (urine output on the third day was 280 ml/24 h). He was given intravenous saline and dopamine, without clinical improvement and then transferred to HU for surgical treatment to the bitten limb. At this stage he was conscious, and breathing at a normal frequency but with prolonged expiration and diffuse added sounds. Blood pressure was 110/60 mmHg, pulse 94 per minute regular, temperature was 38°C, and there was swelling of the left lower limb. He was admitted for assessment of surgical debridement and drainage of an abscess on the left leg and fasciotomy. A Penrose drain was left in the wound.

He became agitated, tachycardic and sweaty. The blood pressure was 90/60 mmHg, pulse 100 per minute and there were persistent added chest sounds. He was treated with oxacillin, cefoxitin, extracellular fluid volume expansion with 2000 ml of saline and diazepam. Several hours after admission a metabolic acidosis was confirmed (arterial pH 7.2, bicarbonate 18.5 mEq/l). He had severe hypotension, blood pressure 80/40 mmHg, pulse 116 per minute, central venous pressure $+12$ cmH_2O and suffered two episodes of watery diarrhoea. His level of consciousness declined. The blood glucose fell to 50 mg/dl but treatment with an intravenous infusion of hypertonic glucose resulted in no clinical improvement. The ECG showed sinus tachycardia without evidence of myocardial ischaemia. He was transferred to the intensive care unit and mechanically ventilated because of his neurological deterioration, attributable to hypoxaemia and metabolic acidosis.

There was massive oedema of the left lower limb with leakage of large amounts of foul smelling sero/sanguinous/purulent material, bullae and signs of tissue necrosis demanding further surgical intervention. *Morganella morganii* was cultured from purulent blister fluid.

Despite infusions of dopamine and dobutamine (10 μg/kg/min) transfusion of packed cells and extracellular volume expansion with colloids and crystalloids, he remained hypotensive (blood pressure 80/40, 40/30 mmHg and finally undetectable) with tachycardia and acidosis. He was oliguric (310 ml in 24 h), urine specific gravity of 1020, fluid balance was $+1900$ ml in 24 h without considering the massive fluid extravasation into the left lower limb. He died 105 h after being bitten.

At autopsy, macroscopic appearances were unremarkable except for evidence of envenoming and surgical debridement in the left calf, some subarachnoid petechiae over the cerebral hemisphere and cerebral oedema. Microscopically, there was necrosis of muscle fibres and interstitial haemorrhage in the region of the wound and evidence of disseminated intravascular coagulation. There were fibrin thrombi in small sub-mucosal vessels of the intestine with ischaemic necrosis of the mucosa and in small cortical and meningeal vessels with local meningeal haemorrhage and cerebral oedema.

There were focal haemorrhages in the adrenal medulla, with depletion of the zona fasciculata, acute tubular necrosis and a fatty (alcoholic) liver with evidence of shock.

Patient 4

An 11-year-old boy was bitten on the right leg by a large jararacuçu at his home in Cachoeira Paulista at 18:00 on 1.1.85. He was admitted to a hospital in Cruzeiro at which time his blood clotted in 4 min 7 s, the bleeding time was 1 min 38 s, haemoglobin 10 mg/dl, haematocrit 33%, white blood cell count 15.4×10^9/l (60% neutrophils), platelets 130×10^9/l. He was transferred to HVB where he was admitted at 17:30 on 3.1.85, 58 h after the bite. He was sleepy and pale, with tense swelling and ecchymoses of the entire bitten limb extending into the lumbar area and with swelling of the scrotum. Blisters were spreading from the site of the bite. He was vomiting blood, was oliguric and had a tachycardia of 124 beats per minute. He was treated with 8 vials of *Bothrops* antivenom (5 subcutaneously, 3 intravenously) with ampicillin, intravenous saline, furosamide, antihistamines (H_1 and H_2 antagonists) and analgesics. During the next 14.5 h he passed only 210 ml of urine and vomited repeatedly. The next day he was transferred to HU in poor condition; hypoactive, pale, icteric and clinically dehydrated with a blood pressure of 130/70 mmHg, pulse 140 beats per minute, respirations 36 per minute. The abdomen was tense and painful with reduced bowel sounds. Limb swelling was as before but there was a hyperaemic erythematous area in the mid-thigh region with more blisters containing bloodstained fluid. Limb pulses were normal. The blood clotted in 8 min, prothrombin time 13.5 s, APTT 45 s, thrombin time 15.3 s, fibrinogen 0.85 g/l, haemoglobin 7.5 mg/dl, haematocrit 26%, white blood count 4.6×10^9/l (neutrophils 62.5%), Na^+ 126 mmol/l, K^+ 7.6 mmol/l, creatinine 5.1 mg/dl,

urea 193 mg/dl, bilirubin 0.9 mg/dl (indirect), 1.4 (direct). *E. coli* was cultured from the blood. He was treated with fluids, analgesics, oxycycline and chloramphenicol and partial exchange transfusion. However, he developed progressive respiratory distress and cardiac failure, and died at 19:00 on 4.1.85, 83 h after the bite.

Discussion

The jararacuçu is feared more than any other *Bothrops* species in Brazil and adjacent countries. Partly it is the great size of this snake, with its relatively enormous triangular head, bulky body and striking markings; but the risk of death and severe sequelae is well known. In one notorious incident near Belo Horizonte, a large jararacuçu bit several members of a family and their dog in quick succession, killing three of them. In Brazil, there is a tendency for unusually large *Bothrops* snakes to be called 'jararacuçu' which may have invalidated some published accounts. For example, the first reported case of anterior pituitary insufficiency following snake bite, which occurred at Bento Gonçalves, Brazil, was attributed to 'urutu amarela'[12] (urutu amarelo = *B. jararacussu*) but this is more than 250 km southeast of the southernmost limit of this species' distribution at Tenente Portela, northern Rio Grande do Sul (Thales de Lema, personal communication).

This first report of a representative group of patients with proven bites by *B. jararacussu*, should, together with reliably attributed cases from the literature, allow an accurate description of the features of envenoming. Jararacuçu bites can be extremely painful;[13–16] all but one of our patients complained of local pain which was often severe. Local swelling, frequently involving the whole of the bitten limb and adjacent areas of the trunk, developed in all but two of our patients. One fang of a huge jararacuçu punctured a finger of the man who was milking it; within 12 h swelling had extended up to the shoulder.[13] A 29-year-old man bitten on the hand developed swelling of the arm and adjacent areas of trunk.[15] In Salvador, Bahia, Brazil, Teixeira treated three patients though to have been bitten by jararacuçus.[16] All developed swelling of the entire bitten limb. Extensive necrosis may develop. In our series, six of the 17 patients bitten by larger jararacuçus developed local blistering and necrosis, and in five there was abscess formation. A 42-year-old man bitten on the forearm by a 1.5m long jararacuçu developed frank necrosis within 24 h of the bite with abscess formation.[14] During the next month he developed ulceration from wrist to forearm with destruction of tendons, nerves and arteries. Twenty years after severe envenoming by a jararacuçu, a 48-year-old man developed a malignant tumour in a chronic ulcer at the site. This required mid-thigh amputation.[17] Advanced necrosis, said to have developed 'several days after the bite' is pictured by Rosenfeld (Case Number 2645, Figure 4, page 361).[8] All three of Teixeira's cases developed local blistering and necrosis.[16] Nausea and vomiting are early symptoms of systemic envenoming.[13,15,16] In several of our patients, shock and oliguria developed within hours of the bite.

Coagulopathy was documented in 14 of our patients. It was more frequent in victims of smaller (58%) than larger snakes (41%), reflecting the higher content of procoagulant enzymes in the venom of younger animals.[18] This ontogenetic variation in venom composition has been described in other Bothrops species; *B. jararaca*,[19,20] *B. moojeni*[21] and *B. asper*.[22] Coagulopathy in *B. jararacussu* envenoming results from the procoagulant action of venom on fibrinogen and factor X.[23] *B. jararacussu* venom was less procoagulant than other *Bothrops* venoms.[19] However, venom from newborn *B. jararacussu* specimens possessed a potent procoagulant activity on factor II, X and fibrinogen.[18] Zaganelli *et al.* have isolated a serine protease from *B. jararacussu* venom that clots fibrinogen and has kallikrein-like activity.[24] A protein similar to thrombocytin[25] was found in *B. jararacussu* venom. It activated factor VIII, induced platelet aggregation and demonstrated mild thrombin-like activity.[26,27] Jararacin, a 73-amino-acid disintegrin isolated from *B. jararacussu* and *B. jararaca* venoms, inhibits *in vitro* aggregation of human platelets induced by ADP, collagen and thrombin, and binding of fibrinogen and von Willebrand factor (vWF) to the platelet membrane glycoprotein complex IIb/IIIa. Jararacin does not inhibit vWF binding to the platelet membrane glycoprotein complex Ib/IX induced by ristocetin or botrocetin.[28] Spontaneous systemic bleeding was observed in only two of our patients, less commonly than in those envenomed by other *Bothrops* species, where haematemesis,[16,17] haematuria,[13,16,17] epistaxis,[13] haemoptysis and melaena,[17] superfical capillary haemorrhages, widespread petechiae and even bleeding from the hair roots and nail borders[8] have been described. Intravascular thrombosis leading to pulmonary embolism and mesenteric thrombosis causing paralytic ileus have been reported.[17] *B. jararacussu* venom has greater myotoxic activity than other *Bothrops* venoms,[29] causing necrosis of striated muscle fibres[30] and release of creatine kinase into the circulation.[31] Two myotoxic proteins, bothropstoxins I and II, homologous to phospholipases A_2 but lacking enzymic activity, have been isolated from *B. jararacussu* venom.[32–34] Bothropstoxin II also has anticoagulant

activity.[33] Vidal and Stoppani isolated proteins with phospholipase activity.[35]

Several authors have observed that although local effects of *B. jararacussu* venom are similar to those of other *Bothrops* venoms, the systemic effects include neurotoxicity, blindness, blurred vision, difficulty in swallowing and paralysis, reminiscent of the action of *Crotalus* venoms.[36–39] Unspecified neurotoxic signs were also mentioned as features of envenoming by other authors.[16,40,41] However, some of these symptoms might be explained by cerebrovascular accidents, reported to be the cause of hemiplegia in two patients (Sesso J, Leo Wajchenberg B, de Ulhoa Cintra AB, unpublished abstract).

Hypotension and shock were prominent features of severe envenoming in this series (illustrative case reports 1–4 above) and in other published reports.[17] Hypovolaemia from extravasation into the massively-swollen, bitten limbs must have contributed and this was corrected by intravenous volume replacement. Jararacuçu venom, like the venom of *B. jararaca*, contains bradykinin potentiating peptides which inhibit angiotensin I conversion to angiotensin II.[42,43] Angiotensin II raises the blood pressure in several different ways; by vasoconstriction, increasing sympathetic tone and by stimulating aldosterone secretion.[44] Another possible mechanism of hypotension during the acute phase of envenoming by jararacuçu is haemorrhagic infarction of the anterior pituitary giving rise to ACTH deficiency. A true Addisonian crisis is unusual in pure ACTH deficiency, because some aldosterone secretion is maintained through the renin-angiotensin mechanism. However, this pathway may be blocked by the peptides mentioned above. This phenomenon has been described in patients envenomed by Russell's vipers in Burma and India,[45] and has been attributed to deposition of fibrin plugs in the small blood vessels of the pituitary resulting from venom procoagulants.[46] Chronic panhypopituitarism following a snake bite was first described in a 39-year-old man said to have been bitten by a jararacuçu 7 years previously in the region of Bento Gonçalves, Rio Grande do Sul, Brazil.[12] He had developed intense local itching, swelling and shivering immediately after the bite, followed by extension of swelling, bruising along the saphenous vein, haemoptysis and postural dizziness during the next 48 h. Later the swelling extended over his abdomen, and he developed a headache and became delirious. His first antivenom treatment was 5 days after the bite. He later developed symptoms of panhypopituitarism.[12]

Acute renal failure is a major life-threatening complication of envenoming by jararacuçu and other Bothrops species.[13,15,17,47] In our patients, acute tubular necrosis and bilateral renal cortical necrosis and diffuse glomerulonephritis with mesangial proliferation were confirmed histologically.[15,17,47] Renal cortical necrosis may be due to intravascular coagulation, direct toxic injury of renal vascular endothelium and/or vasospasm.[47] Thrombi in small arteries, arterioles and glomerular capillaries were found, suggesting that intravascular coagulation induced by *B. jararacussu* venom procoagulants caused ischaemia and renal cortical necrosis by vascular occlusion.

In the treatment of jararacuçu bites, *Bothrops* polyvalent antivenom, often used in large doses, has not proved very effective, despite the fact that all three manufacturers of antivenom in Brazil use *B. jararacussu* venom for raising their 'Antibotropico' and 'Antiophidico' polyvalent antivenoms.[48] Vital Brazil considered that *Crotalus* antivenom was more effective than *Bothrops* antivenom for treating patients envenomed by *B. jararacussu*.[13] More recently, Dias de Silva *et al.* found that *B. jararacussu* venom was less antigenic than other *Bothrops* venoms, and its lethal activity was inadequately neutralized by monospecific or polyspecific *Bothrops* antivenoms.[49] However, its procoagulant activity was neutralized by both *Bothrops* and *Crotalus* antivenoms.[50] Dos Santos *et al.* showed experimentally that the combination of antivenoms against *Crotalus* and *Bothrops* venoms was more efficient in the neutralization of lethal, myotoxic and procoagulant activities of *B. jararacussu* venom than *Bothrops* antivenom alone.[51]

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