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Case report

Fatal stroke after *Bothrops* snakebite in the Amazonas state, Brazil: A case report

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ABSTRACT

Bothrops atrox is the snake responsible for the majority of snakebites in the Brazilian Amazon. Patients generally evolve to local manifestations such as edema, pain and ecchymoses. Systemic effects of *B. atrox* venom are usually restricted to blood incoagulability and spontaneous bleeding. However, in a few cases, bleeding in the central nervous system may occur, which can lead to sequels and deaths. Here, we report a case of a 59 year-old woman who presented edema, pain and ecchymoses on the right foot, headache, nausea, diarrhea, hypertension and blood incoagulability after the bite by *Bothrops* snake in the Brazilian Amazon. This case evolved with stroke resulting in death despite the antivenom and conservative therapy employed. In addition, we were able to identify the presence of venom in the patient's brain tissue after death. Direct action of toxins present in the snake's venom in the induction of systemic hemorrhage allied to blood incoagulability and hypertension presented by the patient could be involved in the mechanism of stroke in this case.

1. Introduction

Bothrops envenoming usually result in local clinical features (i.e. edema, pain and ecchymoses) as well as systemics effects (i.e. coagulation disorders and systemic spontaneous bleeding) (Ribeiro et al., 1998; Ribeiro and Jorge, 1990), in consequence mainly of the action of metalloproteinases, phospholipases A_2 and serine proteinases (Calvete et al., 2011; Sousa et al., 2013). These accidents may evolve with complications such as necrosis, secondary bacterial infection, compartment syndrome and acute renal failure (Ribeiro and Jorge, 1990), being the main causes of death renal and respiratory failure, shock, sepsis and rarely hemorrhage in the central nervous system (Ribeiro et al., 1998). In a study on the prevalence of cerebrovascular complications in *Bothrops* envenoming, it was found that 2.6% of the victims developed a cerebrovascular event, of which about 60% died and 40% remained with sequelae (Mosquera et al., 2003). Here, we describe a case of fatal stroke after *Bothrops* snakebite in the Brazilian Amazon.

2. Case report

A 59 year-old woman was bitten in the fifth right toe by a snake inside her house in the rural area of Manaus, Amazonas State, in Brazil. One hour and a half after the bite she was admitted at the reference hospital with intense local pain, swelling and ecchymosis on the right foot, and severe headache, nausea and episodes of diarrhea. No systemic bleeding was observed. Patient identified the snake as "*surucucurana*", a local name for *B. atrox*, but did not bring it with her to the Health Facility. She denied previous diabetes and

Abbreviations: IV, Intravenous; SVMPs, Snake Venom Metalloproteinases; SVSPs, Snake Venom Serine proteinases; PLA_2, Phospholipases A_2.

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hypertension. On admission blood pressure was 200/110 mmHg and respiratory frequency was 18 bpm. Her blood was incoagulable and coagulogram was altered (Table 1). No other clinical manifestations were observed.

Pre-medication was given (IV hydrocortizone 500 mg, IV promethazine 50 mg, IV dexchlorpheniramine and IV ranitidine 50 mg). Symptomatic medication for pain was also administered (IV dipirona 1 g). After premedication, the patient experienced episodes of vomiting and was administered IV metoclopramide 10 mg. Subsequently, she received sublingual captopril 50 mg. She received 80 mL de *Bothrops* antivenom after 2 h and a half from the bite. However, approximately 1 h after administration of antivenom, the patient experienced sweating, cold and clammy skin, tachycardia, sialorrhea, aphasia and decreased level of consciousness, not responding to verbal stimuli, but to painful stimuli. Blood pressure was 190/130 mmHg. The patient received IV furosemide 80 mg, IV omeprazole 40 mg and venous hydration. Administration of antivenom was discontinued. She was transferred comatose to the intensive care unit with 5 point on the Glasgow Coma Scale, isocorics pupils with photoreaction and required mechanical ventilation. Blood pressure was 230/130 mmHg. The patient received IV hydralazine 20 mg, IV midazolam 50 mg, IV fentanyl 2 mg and IV omeprazole 40 mg. Sedation was interrupted, being administered IV mannitol 20 g and IV hydantal 250 mg.

On the second day after the bite, the patient remained comatose and on mechanical ventilation, evolving with mydriatic pupils without photoreaction, with 3 point on the Glasgow Coma Scale, hemodynamically unstable, hypothermia, bradycardia and anuria. She received IV hydantal 250 mg and IV omeprazole 40 mg. On the third day after the bite, the patient showed no clinical improvement, showing hypothermia, bradycardia and hypotension. On this day, the patient had a cardiorespiratory arrest and died. The patient evolved without local complications, such as necrosis and secondary bacterial infection. Laboratory tests during hospitalization are shown in Table 1. Computed tomography was requested during the hospitalization period, but was not performed.

Autopsy showed subarachnoid and intraparenchymal hemorrhage, as shown in Figs. 1 and 2, respectively, and determined intracranial hypertension as cause of death. No other alteration was described in the necroscopic examination. Venom detection in brain tissue was performed by immunohistochemistry (Supplementary material) and is shown in Fig. 3. The venom was immunolocalized in some areas of the patient's brain. The positive region is represented by the brown spots indicated with the arrows (Fig. 3E and F) appearing only in the group where an antibody produced against the *B. atrox* venom was used. The groups which were treated only with the blocking solution (Fig. 3A and B) or normal serum rabbit IgG (Fig. 3C and D) not show brown spots. The tissue from patient's heart not was positive for venom (data not show).

Table 1
Laboratory tests during hospitalization.

	D1	D2	D3
Erythrocyte/μL	3.65×10^6	2.58×10^6	3.01×10^6
Hemoglobin g/dL	11.1	7.8	8.9
Hematocrit %	31.7	22.9	26.4
Leukocytes/μL	8800	2700	900
Neutrophils %	89	67.7	59
Lymphocytes %	4	23.2	40
Platelets/μL	242,000	148,000	143,000
Prothrombin activity (%)	27	85.5	61.9
INR	2.59	1.10	1.36
Glycemia mg/dL	241	195	196
Creatinine mg/dL	–	–	2.2
Urea mg/dL	–	41	46
Calcium mg/dL	–	8.5	10.4
Na^+ mEq/L	–	157	157
K^+ mEq/L	–	1.8	2
Cl^- mEq/L	–	125	125

References ranges: erythrocyte (4.7–6.1 × 10^6/μL); hemoglobin (13–16 g/dL); hematocrit (40–52%); leukocytes (4000–10,800/μL); neutrophil (42.1–5.2%); lymphocytes (25–40%) platelets (130,000–400,000/μL); prothrombin activity (100%); INR (1); glycemia (70–110 mg/dL); creatinine (0.7–1.5 mg/dL); urea (15–40 mg/dL); calcium (8.5–10.1 mg/dL); Na^+ (136–145 mEq/L); K^+ (3.5–5.1 mEq/L); Cl^- (98–107 mEq/L). D1: in the first day after snakebite; D2 and D3: 2 and 3 days after snakebite.

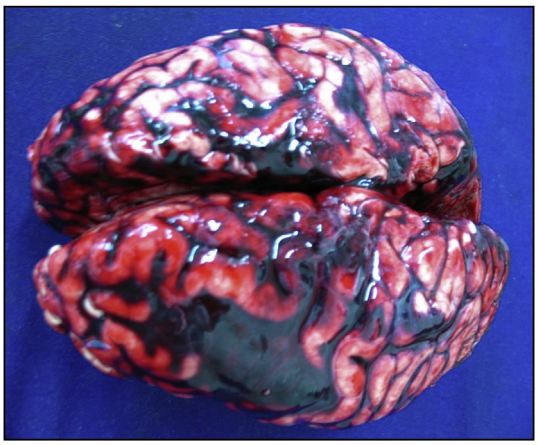

Fig. 1. Subarachnoid hemorrhage after fatal snakebite by *Bothrops atrox*.

3. Discussion

We describe the occurrence of stroke after snakebite in the Brazilian Amazon, an uncommon finding, which resulted in death. This snakebite was diagnosed and treated as an accident with snake in the genus *Bothrops*. Despite the patient not coming along with the dead snake to the Health Facility, she identified the snake as "*surucucurana*", a popular name attributed to *B. atrox*, which is considered the main cause of snakebite in the Amazon (Cardoso et al., 2009). Accidents caused by *B. atrox* have more local clinical features such as blisters, necrosis and abscesses and systemic effects mostly related to blood coagulation disorders and spontaneous bleeding (Pardal et al., 2004). In Brazil, the specific treatment of *Bothrops* snakebites is the administration of the *Bothrops*, *Bothrops-Lachesis* or *Bothrops-Crotalus* antivenoms. *Bothrops* antivenom has been efficient in neutralizing the coagulant and hemorrhagic activities of *B. atrox* venom in pre-clinical assessments and clinical trials (Pardal et al., 2004; Sousa et al., 2013). In this present case, *Bothrops* antivenom was administered in time < 6 hours after the bite and the coagulability was restored after 24 hours of the administration of antivenom.

Signs of neurological damage after snakebite are most often related to the activities toxins present in the venoms, due to the anticoagulant/procoagulant activities and/or neurotoxicity of its components (Del Brutto and Del Brutto, 2012). Death cases caused by cerebral hemorrhage in patients bitten by viper snakes have been described (Pinho and Burdmann, 2001; Mosquera et al., 2003; Kitchens and Eskin, 2008; Kouyoumdjian et al., 1991). Autopsy of this patient showed subarachnoid and intraparenchymal hemorrhage. In a study with patients who presented stroke following *Bothrops* spp. snakebite, seven patients presented intracranial bleeding and hemorrhages were located in the subcortical white matter of the cerebral hemispheres, in the cerebellum and in the subarachnoid space (Mosquera et al., 2003). Patients bitten by viper