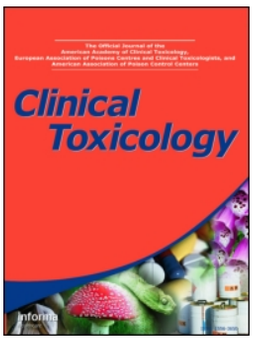

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SHORT COMMUNICATION

Acute kidney injury induced by thrombotic microangiopathy in two cases of *Bothrops* envenomation

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ABSTRACT

Context: *Bothrops* snakes are the most frequent agents of snakebites in South and Central America. Acute kidney injury (AKI) is one of its complications and has multifactorial origin. Thrombotic microangiopathy (TMA)-induced AKI in snakebites is uncommon and is not described in *Bothrops* envenomation.

Case details: We report two cases of patients bitten by young *Bothrops jararaca* who developed AKI induced by TMA. Both patients evolved with mild envenomation and received the specific antivenom within 4 h after the snakebite. None of them had hypotension or shock, bleeding or secondary infection. Patient 1 (P1) was diabetic and using oral hypoglycemic drugs, and patient 2 (P2) was hypertensive without regular use of medication. On admission, both patients had levels of fibrinogen lower than 35 mg/dL, D-dimer higher than 10,000 ng/mL. They evolved with AKI, thrombocytopenia, normal coagulation assays, anemia, lactate dehydrogenase (LDH) elevation, low haptoglobin levels, negative direct antiglobulin test, and presence of schizocytes in peripheral blood. Only P1 required renal replacement therapy, and plasmapheresis was not required. Both patients were discharged and did not require outpatient dialysis, and subsequently had normal creatinine levels.

Discussion: TMA may occur in *Bothrops jararaca* envenomation, even in mild cases that received early specific antivenom.

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Acute kidney injury; *Bothrops*; snakebite; thrombotic microangiopathy

Introduction

Bothrops snakes (lance-headed vipers) are the commonest causative agent of human snakebites in South and Central America. *Bothrops* envenomation can manifest local inflammatory signs and hemostatic disorders. Metalloproteinases and phospholipases A_2 are responsible for the inflammatory reaction. Hemorrhagic metalloproteinases cause hemorrhage, by damaging the structure of capillary vessels. Procoagulant metalloproteinases (prothrombin activators and factor X activators) and serine proteinases ("thrombin-like enzymes") induce the formation of microclots, with the consequent consumption of clotting factors, especially fibrinogen [1].

Acute kidney injury (AKI) is one of the systemic complications in patients bitten by *Bothrops* snakes, and it is reported in 1.4–38.5% of cases of *Bothrops* envenomation in South America. The pathophysiology of AKI in *Bothrops* envenomation involves several factors, such as the release of inflammatory mediators, hemodynamic changes, disseminated intravascular coagulation, intravascular hemolysis, and a possible direct action of venom toxins in the kidneys [2]. AKI associated with thrombotic microangiopathy (TMA) is uncommon and is described after snakebites by *Pseudonaja sp.*, *Daboia russelii* (Russell's viper), *Hypnale* sp, *Cerastes sp*, *Oxyuranus scutellatus, Pseudechis* sp, *Notechis scutatus* [3], but there are no reports for *Bothrops* envenomation. Herein we report two confirmed human case of *B. jararaca* envenomation with anemia, thrombocytopenia and AKI consistent with TMA diagnosis.

Case details

Case 1

A 71 year-old woman with non-insulin-dependent diabetes mellitus was bitten by a young *B. jararaca* snake on the right hand. On admission at the hospital, she had blood pressure (BP): 171/92 mmHg; heart rate (HR): 62 bpm; axillar temperature (axT°): 35 °C; oxygen saturation (SO_2): 95%; glucose test strip: 142 mg/dL, and mild edema and ecchymosis on palmar region. Antivenom was administered 4 h after the bite [four vials of *Bothrops* antivenom (BAV)]. The BAV is a polyvalent equine antivenom [$F(ab')_2$] against *Bothrops* species, manufactured by Instituto Butantan, São Paulo, Brazil.

The laboratory tests on admission are presented on Table 1. After 24 h of BAV therapy the fibrinogen level was 153 mg/dL, international normalized ratio (INR) was 1.1, activated partial thromboplastin time ratio (APTTr) was 0.87, and creatinine was 2.84 mg/dL. The patient evolved with no signs of bleeding or hypotension. However, she developed anuria, and was submitted to renal replacement therapy (RRT) on second day post-bite. On the other hand, thrombocytopenia,

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Table 1. Laboratorial data of patients 1 and 2, bitten by *Bothrops jararaca* snakes, on admission at hospital.

	Patient 1	Patient 2	Normal range
Hemoglobin	15.7	12.8	13–16 g/dL
Hematocrit	46	38.5	37–49 %
White blood cells	9,250	13,340	4,500–13,500/μL
Platelets	94	159	150–400x10^3/μL
C reactive protein	<5	<5	<5 mg/L
International normalized ratio	1.44	Unclottable	–
Activated partial thromboplastin time ratio	1.28	Unclottable	–
Fibrinogen	<35	<35	200–400 mg/dL
D-dimer	>10,000	>10,000	<500 ng/mL
Urea	41	81	10–50 mg/dL
Creatinine	0.78	1.49	0.7–1.2 mg/dL
Sodium	142	143	135–145 mEq/L
Potassium	4.7	5.2	3.5–5.0 mEq/L
Creatine kinase	261	NA	38–174 U/L
Lactate dehydrogenase	237	501	100–190 U/L
Total bilirubin	0.59	0.79	≤1.0 mg/dL
Indirect bilirubin	0.47	0.56	≤0.7 mg/dL
Alanine aminotransferase	19	33	10–49 U/L
Aspartate aminotransferase	21	16	<34 U/L
Glucose	167	105	≤99 mg/dL

NA: not available.

anemia, and increased LDH were observed (Figure 1). The nadir of thrombocytopenia occurred on day 6 post-bite (Figure 1), concomitant with the detection of schizocytes in the blood film. The direct antiglobulin test (DAT) was negative, and the haptoglobin level was decreased [12 mg/dL (NFR: 30-200)] on day 6 post-bite. Thrombocytopenia reverted spontaneously after day 7 (Figure 1) and renal function recovery occurred 8 weeks after snakebite, requiring RRT in the first 4 weeks. Plasmapheresis was not performed.

Case 2

A 70-year-old woman, with a medical history of hypertension, was bitten by a *B. jararaca* snake (Figure 2(a)) in her hand. Soon after the snakebite, she manifested edema, pain and ecchymosis in hypothenar region. After 4 h of the snakebite, on admission at the hospital, she was hypertensive (BP 190/110 mmHg), HR: 129 b.p.m., axT°: 36.2 °C, SO_2: 98%, and with mild edema and ecchymosis at the site of the bite (Figure 2(b)), and no systemic bleeding. Four vials of BAV were prescribed. Laboratory tests on admission are presented on Table 1. The fibrinogen level was 44 mg/dL and 189 mg/dL at 6 h and 30 h after antivenom administration, respectively. Six hours after antivenom therapy the INR and APTTr were 1.4 and 1.1, respectively, and creatinine was 2.8 mg/dL. On the following days, increased LDH level, thrombocytopenia, and anemia were noticed (Figure 1), and the highest creatinine level was seen on second day post-bite (5.15 mg/dL). On day 3 after the bite, schizocytes were detected (Figure 2(c)) in the blood film, the haptoglobin level was <10 mg/dL and DAT was negative. The ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity level measured on second day after bite was normal (776 ng/mL; NR: 666 ± 135 ng/mL), as well as the complement C3 (113.7 mg/dL; NR: 90–180 mg/dL) and C4 levels (28.4 mg/dL; NR: 10–40 mg/dL). Platelet count and creatinine level improved spontaneously and neither RRT nor plasmapheresis was performed. Four weeks after the bite the creatinine level was normal.

Discussion

We describe two cases of AKI induced by TMA in *B. jararaca* envenomation. TMA are due to inherited or acquired disorders characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ injury [4]. In both cases reported herein, we observed thrombocytopenia and MAHA, characterized by negative direct COOMB, presence of schizocytes in blood smears, decreased haptoglobin levels, and increased LDH levels, and normal blood coagulation tests. *Bothrops* venom thereby may be an additional trigger of TMA.

Endothelial cell injury/dysfunction has been reported as the key promotor for TMA pathogenesis, leading to exposure of thrombogenic components to coagulation proteins and platelets. Under the presence of uncontrolled inflammation and/or of genetic and acquired abnormalities of complement or hemostasis mediators, the endothelium becomes a target, resulting in vascular damage as observed in TMA [5]. Experimentally, TMA has been reported in Wistar rats injected *B jararaca* venom, characterized by the development of anemia, hypofibrinogenemia, thrombocytopenia and the presence of schizocytes in blood circulation. The occurrence of TMA was dependent on coagulation activation and intravascular thrombin generation, once TMA was abrogated by pre-treatment of animals with warfarin, an inhibitor of synthesis of vitamin K-dependent coagulation factors, showing that it was a consequence of disseminated intravascular coagulation [6]. Hemorrhagic metalloproteinases such as *jararhagin*, isolated from *B. jararaca* venom, may induce a systemic proinflammatory condition by releasing interleukin (IL)-1β, IL-6 and tumor necrosis factor-α release by cells [7], and activating and up-regulating gene expression of inflammatory mediators such as E-selectin, VCAM-1, IL-8 and matrix metalloproteinase (MMP)-10 [8]. Furthermore, *Bothrops* venom activates the complement system [9]. Thus, this intricate concert of toxins dysregulating homeostasis during snake envenomation may evoke a condition of systemic inflammatory response, leading to endothelial damage.

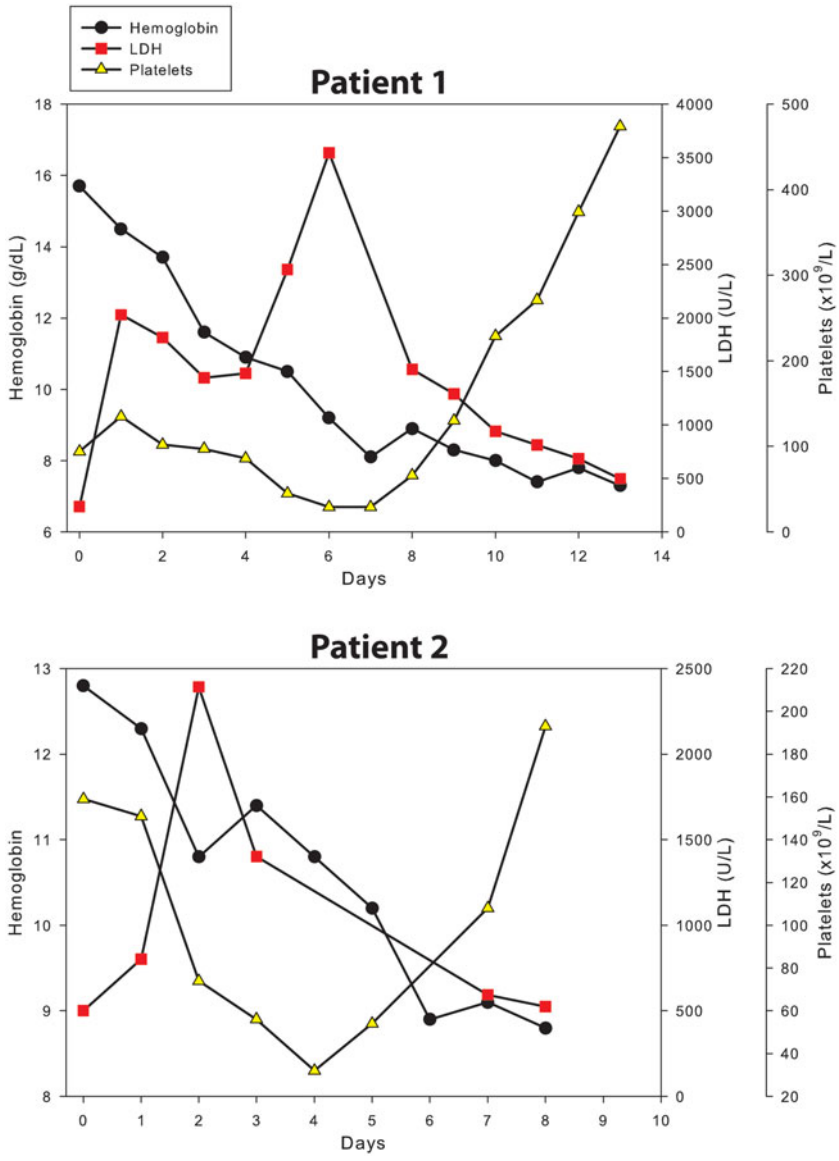

Figure 1. Time-course of platelet count, and levels of hemoglobin and LDH from patients 1 and 2 bitten by *B. jararaca*.

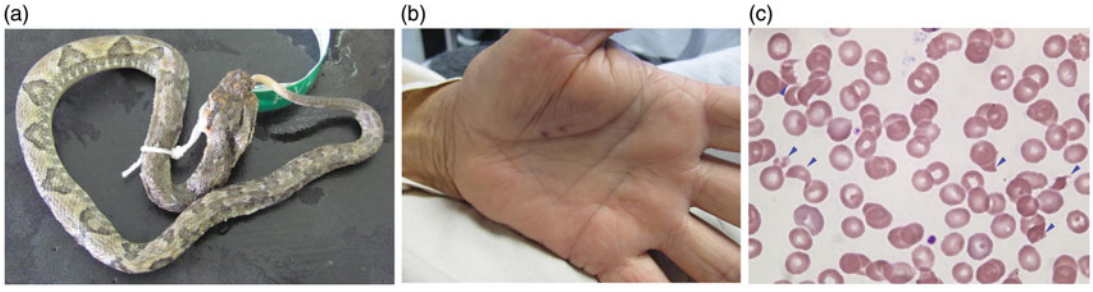

Figure 2. Images from patient 2: (a) the causative agent of the bite (female *B. jararaca*; total length 30.1 cm), (b) the site of the snakebite, and (c) the fragmented red blood cells (blue arrows) in the blood smear.

Both patients had normal renal function before *Bothrops* envenomation and there were no signs of hemodynamic instability, hemorrhagic events, infection or other factors that could cause AKI. Renal biopsy was not performed due to the presence of severe thrombocytopenia and the diagnosis of AKI induced by TMA was made by the presence of MAHA, thrombocytopenia and renal involvement. Both patients recovered renal function, with estimated glomerular filtration rate >60 mL/min/1.73m^2.

In addition to the early antivenom administration, therapeutic plasma exchange (TPE) is reported in the management of snakebite-induced TMA [10,11]. Li et al. [12]

suggested that the routine use of TPE has not significantly improved outcomes in TMA patients without severe ADAMTS13 deficiency. In both cases TPE was not performed and, as described in the literature, renal and hematological dysfunction recovered [3].

AKI induced by TMA may occur in mild cases of *B. jararaca* envenomation, even in those patients that received early specific antivenom. These cases may have a favorable outcome without TPE.

Ethical approval

The study was approved by Ethical Committee from Emilio Ribas Institute of Infectious Diseases (Protocol no. 72813317.0.1001.0061).

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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