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Brain, liver and kidney lesions associated with *Loxosceles intermedia* envenomation in guinea pigs

Lesões encefálicas, hepáticas e renais associadas ao envenenamento por *Loxosceles intermedia* em cobaias

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Abstract: The venom of *Loxosceles* spiders is characterized by a complex protein composition, which underlies the clinical condition known as loxoscelism. This syndrome is characterized mainly by gravitational spreading dermonecrotic lesions, but also, in rare cases, it can involve severe systemic complications, such as renal failure and hematological disorders. Although the pathophysiological mechanism of cutaneous loxoscelism is widely investigated, the neurological manifestations associated with the venom are rare and poorly researched. The present study aimed to investigate the histopathological alterations in guinea pigs' (*Cavia porcellus*) liver, kidney, and central nervous system (CNS) inoculated with *Loxosceles intermedia* venom. Sixteen guinea pigs were challenged with venom doses ranging from 11.627 to 350 µg/animal intradermally in the intrascapular region, while two additional animals were used as controls, receiving only 0.9 % saline solution in the same application region. Microscopic evaluation of hepatic and renal tissues demonstrated hepatic necrosis and acute renal tubular necrosis, respectively. In the CNS, lesions compatible with lymphoplasmacytic and histiocytic encephalitis, moderate focal gliosis, and neutrophilic margination in certain regions of the brain were identified. These neurological findings in guinea pigs exposed to *L. intermedia* venom are unprecedented, providing new evidence of CNS susceptibility to *Loxosceles* venom.

Keywords: brown spider; loxoscelic venom; central nervous system; encephalitis; loxoscelism.

Resumo: O veneno das aranhas do gênero *Loxosceles* caracteriza-se por uma composição proteica complexa, a qual está na base da condição clínica conhecida como loxoscelismo. Essa síndrome é caracterizada principalmente por lesões dermonecróticas de disseminação gravitacional, mas também, em casos raros, pode envolver complicações sistêmicas graves, como insuficiência renal e distúrbios hematológicos. Embora o mecanismo fisiopatológico do loxoscelismo cutâneo seja amplamente investigado, as manifestações neurológicas associadas ao veneno são raras e pouco pesquisadas. O presente estudo teve como objetivo investigar as alterações histopatológicas no fígado, rim e sistema nervoso central (SNC) de cobaias (*Cavia porcellus*) inoculadas com veneno de *Loxosceles intermedia*. Dezesseis cobaias foram desafiadas com doses de veneno variando de 11,627 a 350 µg/animal por via intradérmica na região intraescapular, enquanto dois animais adicionais foram usados como controle, recebendo apenas solução salina a 0,9 % na mesma região de aplicação. A avaliação microscópica dos tecidos hepático e renal

demonstrou necrose hepática e necrose tubular renal aguda, respectivamente. No SNC, foram identificadas lesões compatíveis com encefalite linfoplasmocítica e histiocítica, gliose focal moderada e marginação neutrofílica em certas regiões do cérebro. Esses achados neurológicos, em cobaias expostas ao veneno de L. *intermedia* são inéditos, fornecendo novas evidências da suscetibilidade do SNC ao veneno de *Loxosceles*.

Palavras-chave: aranha-marrom; veneno loxoscélico; sistema nervoso central; encefalite; loxoscelismo.

1. Introduction

Spiders of the genus *Loxosceles* have a worldwide distribution, especially in South America, with approximately 170 species described [1]. Among these species, *L. intermedia* has been identified as the main responsible for accidents in Brazil, with the number of reported cases in the country having risen exponentially in recent years, becoming a public health concern [2,3]. They are capable of injecting only a few microliters of venom, which consists of a complex molecular composition of proteins [4]. Three families of toxins are described in the composition of loxoscelic venom: (i) phospholipases D (PLD); (ii) metalloproteinases, characterized as astacins; and (iii) knottins. Other less expressed toxin families are present and include serine proteases and serine protease inhibitors, hyaluronidases, allergen factors, and a histamine-releasing factor [5].

These toxins have significant medical relevance due to the clinical syndrome observed in their victims, called loxoscelism [5]. The most prevalent manifestation of this clinical condition is cutaneous involvement, primarily characterized by the development of a dermonecrotic lesion with gravitational spreading [6]. Systemic manifestations, although less common, are severe, usually culminating in renal failure and hematological disorders, which can lead to death [7]. Records of neurological disorders caused by loxoscelic venom are very rare. To date, there are only two clinical reports of the occurrence of neuropathies associated with *Loxosceles* in humans, involving ischemic lesions in the globus pallidus and optic neuropathy [8,9].

However, information on the effects of the venom on the central nervous system (CNS) is scarce. In this context, the objective of this study was to report the pathological microscopic changes in guinea pigs experimentally exposed to the loxoscelic venom, with emphasis on the CNS, liver, and kidneys.

2. Material and methods

This study was approved by the Ethics Committee for the Use of Animals (CEUA) of the Universidade Federal de Minas Gerais (UFMG) (CEUA protocol No. 131/2020). A total of 16 adult male guinea pigs (*Cavia porcellus*) with an average body weight of 600 g were used in this study. The animals were kept in a vivarium at the UFMG, in individual metal cages (42 x 38 x 55 cm), in a constant light/dark cycle of 12 hours, with controlled temperature (23±2ºC). The animals received water, commercial feed, and hay ad libitum.

A pool of *L. intermedia* venom from the Venom Bank of the Laboratory of Immunology and Biochemistry at the UFMG was used. The total protein concentration of the venom sample was determined using the Lowry method. For this purpose, a standard curve was prepared, from which an average calibration factor was obtained to calculate the protein concentration of the venom, which revealed a protein concentration of 3.5 µg/µL. Several doses of *L. intermedia* venom were applied to guinea pigs to evaluate its systemic effect, based on the LD 50 of mice (which corresponds to 350 µg) and the protein concentration that could be injected by an adult specimen of the *L. intermedia* spider.

Sixteen guinea pigs received *L. intermedia* venom (doses ranging from 11.6 to 350.0 µg/animal) intradermally using a sterile disposable insulin syringe in the interscapular region, which was previously trichotomized (Table 1). To standardize the volume applied, 0.9 % saline solution was added to a final volume of 25 µL. These doses were selected based on two criteria: (i) the estimated amount of venom injected by adult spiders (20–200 µg of protein/bite, corresponding to a few microliters of venom), for the lower, regular, and higher doses [10]; (ii) and the reported LD_{50} values in mice (0.45 mg/kg, s.c.), for the higher doses [5]. Two animals were used as controls and received 25 µL of 0.9 % under the same conditions. All animals were clinically evaluated during the experiment.

Table 1. Experimental distribution of the doses of *L. intermedia* venom used in guinea pigs.

Groups/Doses	N
Control	2
High doses	
350 µg/animal	1
210 µg/animal	1
140 µg/animal	1
76.755 µg/animal	1
47.985 µg/animal	1
29.995 µg/animal	1
Moderate doses	
28.477 µg/animal	1
24.762 µg/animal	1
21.533 µg/animal	1
18.725 µg/animal	1
Low doses	
17.795 µg/animal	1
15.475 µg/animal	1
14.068 µg/animal	1
12.789 µg/animal	1
11.627 µg/animal	1

The experimental period lasted 72 hours, after which all surviving animals were euthanized using isoflurane in accordance with all applicable laws, regulations and according to the recommendations of CEUA/UFMG. Necropsy was performed immediately after euthanasia or following spontaneous death within the 72-hour experimental period, and tissues were collected for histopathological analysis. Samples of liver, kidneys, and brain were collected from representative regions without stereotaxic coordinates to provide a general histopathological assessment. The tissue sections were fixed in 10 % buffered formalin, embedded in paraffin, sectioned in a microtome (4 µm thickness), and stained with hematoxylin and eosin (HE) for examination under a light optical microscope.

3. Results and discussion

Control animals, which received 0.9 % sodium chloride solution, did not present any type of local or systemic alteration. All animals challenged with loxoscelic venom, regardless of the dose, presented pruritus at the site of application, minutes after the injection. Although guinea pigs and rats are used as a model of systemic loxoscelism because they present a discreet local manifestation, four animals that received the lowest doses (11.6 µg/animal and 18.7 µg/animal) presented erythema, hemorrhagic halo, and formation of eschar at the site of venom application, similar to clinical reports of milder cases [11]. However, six animals that received higher doses at various concentrations (21.5 µg/animal and 76.8 µg/animal), in addition to urticarial reactions, became prostrate, dehydrated, and died 24 hours later.

Severe cases of cutaneous loxoscelism, with local edema, vasospasm, ischemia, and eschars have been described in rabbits6. Although rabbits have a different local response to loxoscelic venom in contrast to guinea pigs, this comparison emphasizes the variability of local tissue responses across species. Surprisingly, in four animals that received the highest doses (between 105.0 and 350.0 µg/animal), the local effects were milder, with discreet edema and without the formation of a hemorrhagic halo. However, these animals became prostrate, presented pasty feces, and died 30 hours later. Possibly, in dermonecrotic wounds, the toxins of the venom could remain in the site longer, unlike smaller lesions that favor greater absorption and distribution of the venom throughout the organism [12].

Another complementary hypothesis is that higher doses of venom also imply higher amounts of proteases and hyaluronidases, which rapidly permeabilize tissues and facilitate the systemic dispersion of other toxins, such as PLDs. These mechanisms could explain the attenuated local effects despite the higher doses. All animals from the lower concentration (11.627 to 18.725 µg/animal) died from euthanasia, 72h after the inoculation. Mortality occurred at about 24 h in animals administered with 21.533–47.985 µg/animal, whereas those given higher concentrations (76.775–350 µg/animal) died later, around 30 h after inoculation (Figure 1).

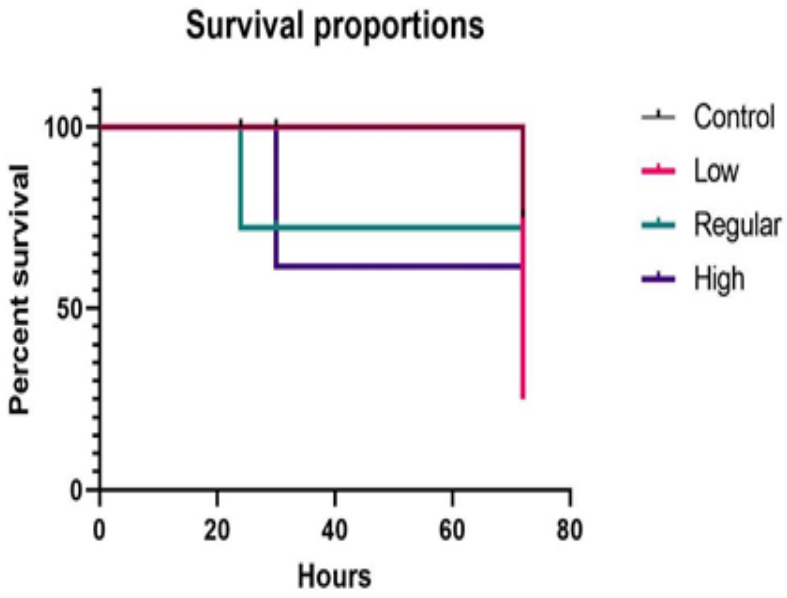

Figure 1. Survival proportions of guinea pigs after *L. intermedia* venom inoculation at low, regular, and high doses.

Although considered rare, there are reports of kidney and liver histopathological alterations in victims of *Loxosceles* spider bites [7,13]. In this study, there was moderate multifocal liver degeneration (Figure 2a), which was the most common change in animals that received doses ranging from 18.8 µg/animal and 210.0 µg/animal. Severe liver coagulation necrosis (multifocal to coalescent) (Figure 2b) was observed in animals that received doses between 12.8 µg/animal and 105.0 µg/animal, and a dose of 24.7 µg/animal was associated with severe diffuse hepatic congestion (Figure 2c). Ten animals inoculated with *L. intermedia* venom (doses between 17.8 µg/animal and 350.0 µg/animal) presented acute tubular necrosis characterized by vacuolar degeneration of the proximal and distal tubules (Figure 2d). Six animals (doses ranging from 21.5 µg/animal to 350.0 µg/animal) showed dilation of the proximal and distal convoluted tubules due to deposition of hyaline material suggestive of protein accumulation (Figure 2e). Two animals (12.8 µg/animal and 47.9 µg/animal) also showed accumulation of proteinaceous material in the tubular lumen, but without evidence of tubular degeneration (Figure 2f). Similar lesions were seen in the kidneys of mice 24 h after injections of various doses of *L. intermedia* venom, including acute tubular necrosis and deposition of hyaline material within the proximal and distal tubules, dilation of the proximal convoluted tubules, and renal hemorrhage [7,14].

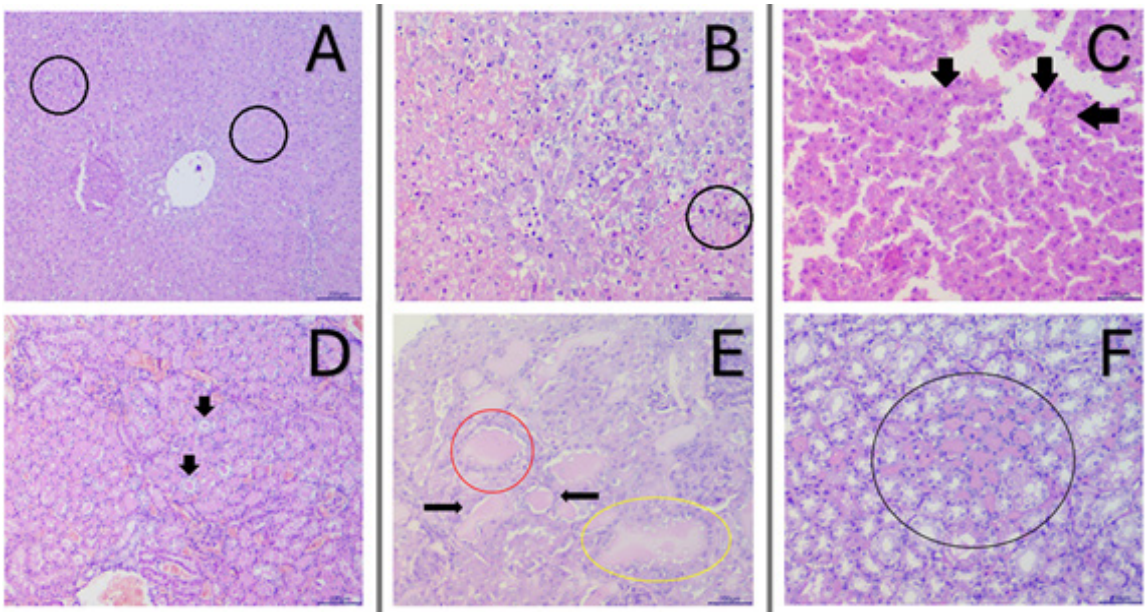

Figure 2. Liver and kidney of guinea pigs inoculated with of *L. intermedia* venom. (A) Multifocal Hepatic Degeneration (circled in black). Magnification 100×. (B) Severe liver coagulation necrosis. Magnification 200x. (C) Severe diffuse hepatic congestion. Magnification 400x. (D) Degeneration of proximal and distal tubules with formation of hyaline casts (black arrows). Magnification 100x. (E) Marked diffuse degeneration and dilatation of the urinary space with hyaline casts (blue arrows). Amorphous eosinophilic material in Bowman's capsule and renal tubules, with tubular dilatation and vacuolization (outlined in red and black). Magnification 200x. (F)Multifocal moderate dilatation of distal and proximal tubules due to accumulation of amorphous eosinophilic material (suggestive of protein), outlined in red. Magnification 200x.

In the present investigation, histopathological evaluation of the CNS was performed in all animals inoculated with *L. intermedia* venom. However, microscopic alterations were observed in two animals that received doses of 14.1 µg/animal and 21.5 µg/animal of *L. intermedia* venom, which developed multifocal lymphoplasmacytic and histiocytic encephalitis (Figure 3a), and moderate focal gliosis in the animal that was inoculated with 21.5 µg/animal (Figure 3b). In addition, there was mild intravascular neutrophilic margination in animals inoculated with 29.9 µg/animal and 47.9 µg/animal (Figure 3c). This is the first time that such lesions have been described in animals with systemic loxoscelism.

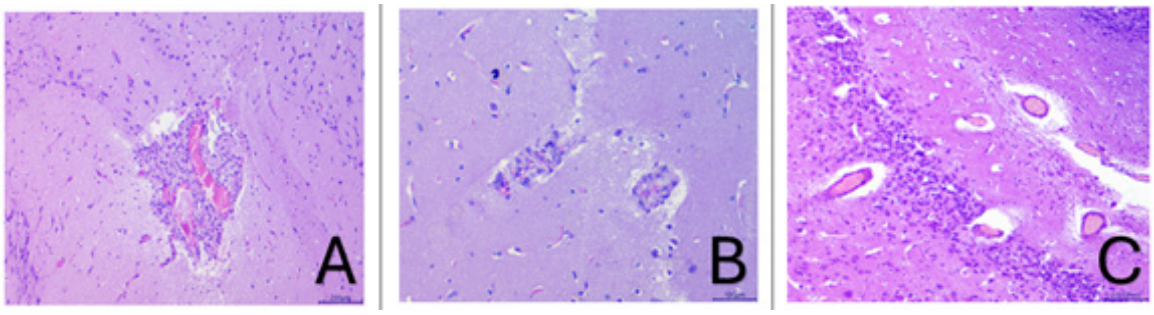

Figure 3. Brain of guinea pigs inoculated with 14.1 µg/animal (A), 21.5 µg/animal (B), and 47.9 µg/animal (C) of *L. intermedia* venom. (A) Cerebral Cortex: mild focal lymphoplasmacytic and histiocytic encephalitis (arrow). 100x magnification. (B) Cerebral Cortex: moderate multifocal lymphoplasmacytic and histiocytic encephalitis (arrow) with moderate multifocal gliosis. 200x magnification. (C) Cerebral Cortex: mild intravascular neutrophilic margination (arrow). 100 x magnification.

The pathophysiological mechanism of cutaneous loxoscelism is well understood, and many studies attribute the cutaneous lesions at the bite site to the action of PLDs, which trigger a dysregulated and exacerbated inflammatory response that causes significant tissue damage [15]. On the other hand, the mechanism of systemic loxoscelism appears to be more complex, as it can affect several tissues, organs, and cells, such as the liver and kidneys [16]. Mechanisms like those involved in the occurrence of cutaneous lesions may possibly be related to the development of the histopathological lesions observed in the cerebral cortex of guinea pigs in this experiment, since the occurrence of intravascular neutrophilic margination was a prominent alteration observed in one of the animals treated with *L. intermedia* venom.

Previous evidence demonstrates that PLDs play a fundamental role in this symptomatology through their ability to cleave phospholipids in various cell types. This toxin, both in its native and recombinant forms, is capable, on its own, of virtually reproducing all the clinical symptoms of loxoscelism [16]. Nevertheless, *Loxosceles* venom is highly complex in its composition, and there is evidence indicating that other toxins may also contribute to systemic effects [5,16]. For instance, metalloproteases and hyaluronidases may facilitate the spread of the venom to adjacent tissues and possibly to the systemic circulation, thereby granting access to more distant tissues [5]. In this experiment, early death was observed in animals inoculated with higher doses of *L. intermedia* venom, without the development of cutaneous alterations at the inoculation site, a finding not seen at the other doses. From this, it can be inferred that despite the higher concentration of PLDs, larger doses of venom also imply higher concentrations of proteases and hyaluronidases, which may facilitate broader toxin dispersion within the organism, attenuating local effects but enabling wider systemic dissemination of the venom, thereby increasing the severity of the condition observed in these animals before the full local effects could be exerted. These findings suggest a role for these toxic components in the possible development of more severe systemic manifestations, as observed in the animals that died prematurely.

Although considered rare, there are compelling reports of hepatic and renal disorders in victims of brown spider envenomation, which may lead to severe conditions. For instance, Córdova et al. reported the case of a 31-year-old woman who developed jaundice and decreased urine output 48 hours after a *Loxosceles* bite and, despite established treatments, had an unfavorable outcome, with severe multisystem involvement (hepatic, renal, and coagulation disorders), requiring intensive care support including hemodialysis and hemoadsorption [17]. Under experimental conditions, rats exposed to crude venom or to a recombinant PLD from *L. intermedia* showed impaired liver function [13]. The

alterations observed included hepatocyte degeneration (with swelling and apoptosis), inflammatory cell infiltration in the portal region, and signs of steatosis after 12 hours of exposure [13]. Within the first six hours following exposure to crude venom, marked elevations in serum markers of liver injury were also detected. In contrast, animals that received only purified PLD exhibited milder manifestations [13]. In the histopathological analyses of the animals assessed in this study, similar alterations were also identified, such as hepatocyte degeneration. However, interspecies differences were observed, consistent with the variations commonly reported in the response to loxoscelic envenomation across different organisms. Moreover, discrepancies among the experimental findings between animals further support the involvement of other toxins in systemic loxoscelism, in addition to PLDs.

Regarding renal involvement, the alterations observed in guinea pigs in this experiment, such as tubular degeneration and dilation with accumulation of eosinophilic material, were quite similar to those reported in other species. Histopathological analyses of rat kidneys also revealed acute degenerative changes in tubular epithelial cells, accompanied by cellular debris within the tubular lumen and deposits of myoglobin and hemoglobin in the renal tissue [18]. In humans, renal biopsies likewise demonstrate acute tubular damage, with the presence of hyaline content suggestive of intratubular protein [19]. It is known that PLD directly affects the kidneys, causing nephrotoxicity through its ability to bind to renal cells [20]. Accordingly, acute renal failure has also been described as one of the main clinical manifestations associated with systemic loxoscelism and is considered the leading cause of mortality among affected patients [16].

The possible involvement of the CNS in systemic loxoscelism remains controversial, since *L. intermedia* venom has not been detected in the brain [21]. However, clinical cases of neurological impairment have been reported in humans, including a 63-year-old woman who developed bilateral asymmetric optic neuropathy following a *L. reclusa* bite, possibly related to inflammatory, vascular, or autoimmune mechanisms exacerbated by a previous meningioma [8]. Similarly, a 47-year-old man with severe systemic loxoscelism presented with ischemic brain injury attributed to PLD-induced microthrombosis associated with cytotoxic effects [9]. In a canine case of loxoscelism described by Vann *et al*. [22], necropsy findings showed a brain with signs of hemolysis and congestion, bloody fluid between the meninges, and focal areas of ischemic and hemorrhagic necrosis [22].

Experimentally, in mice with systemic loxoscelism induced by the inoculation of *L. reclusa* venom, susceptibility to the venom was observed, evidenced by increased activity of enzymes such as LDH-3, CK1, and CK2s [23]. Moreover, the association of these laboratory findings with clinical symptoms such as lethargy and postural changes made it possible to suggest the development of cerebrovascular shock in these animals [23]. Thus, it can be assumed that, although not fully elucidated, the mechanisms underlying the neurological alterations observed in guinea pigs in this experiment are likely indirect, since the venom is not capable of completely crossing the blood–brain barrier. These hypotheses are further supported by an experimental model in rats challenged with *L. apachea* venom at different concentrations (0.178 and 0.87 µg/g), in which the animals developed endothelial injury in the area postrema—a highly vascularized structure lacking a blood–brain barrier—and in the choroid plexus, which is directly involved in the blood–cerebrospinal fluid barrier. Therefore, the alterations reported in these regions were interpreted by the authors as incidental, resulting from the systemic distribution of the venom rather than from a specific tropism for the CNS [24].

4. Conclusion

In conclusion, the histopathological analysis revealed that *L. intermedia* venom can induce significant cerebral cortex alterations in guinea pigs, including lymphoplasmacytic and histiocytic encephalitis, mild intravascular neutrophilic margination, and moderate focal gliosis. These findings provide further evidence that the CNS is susceptible to the venom and can be indirectly affected in systemic loxoscelism, in agreement with scarce, but compelling clinical and experimental reports. Additionally, moderate hepatic degeneration and tubular necrosis were observed, reinforcing the notion that loxoscelic envenomation exerts a multisystemic impact.

Conflicts of interest statement

The authors declare no conflicts of interest.

Data availability statement

The full set of data supporting the results of this study was published in the article itself.

Author contributions

Conceptualization: C.D. Chávez-Olórtegui and M.M. Melo. Methodology: C.D. Chávez-Olórtegui and M.M. Melo. Investigation: P.B.U. Fernandes, M.D. Araújo, and A.P.B. França. Formal analysis: P.B.U. Fernandes, R.L. Santos, and A.F.M. Botelho. Data curation: P.B.U. Fernandes. Supervision: C.D. Chávez-Olórtegui and M.M. Melo. Writing – original draft: P.B.U. Fernandes and M.M. Melo. Writing – review & editing: P.B.U. Fernandes, R.L. Santos, A.F.M. Botelho, and M.M. Melo.

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