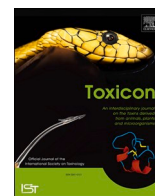




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Brown spider (*Loxosceles* sp.) bite and COVID-19: A case report

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ABSTRACT

We present the case of a 32-year-old male patient hospitalized during the COVID-19 pandemic because of a Brown spider bite on his lower lip. The Brown spider accident occurred in southern Brazil; at hospital admission, the patient presented on his lip: edema, pustules, necrotic regions, and ulcerations. The patient complained of lower back pain, fever and dyspnea. Laboratory tests showed monocytosis, leukocytosis, neutrophilia, increased D-dimer levels, C-reactive protein, glutamate-pyruvate transaminase, delta bilirubin, creatine phosphokinase, procalcitonin, and fibrinogen. The patient was hospitalized and a multi-professional team carried out the treatment. The medical team diagnosed loxoscelism with moderate changes. The dentist treated the oral cavity. The patient began to develop nausea, vomiting, and desaturation episodes during hospitalization. A computed tomography of the chest was performed, which showed signs of viral infection. The RT-PCR test for COVID-19 was positive. The systemic conditions worsened (renal dysfunction, systemic inflammatory response, pulmonary complications). This condition may have resulted from the association of the two diseases (loxoscelism and COVID-19), leading to the patient's death. This case illustrates the difficulties and risks in treating patients with venomous animal accidents during the pandemic, and the importance of a multi-professional team in treating such cases.

1. Introduction

The Brown spider is part of the arachnid genus *Loxosceles*. Accidents caused by these spiders cause loxoscelism, a condition characterized by cutaneous injuries with dermonecrotic lesions and, in more severe cases, by visceral or systemic changes, including intravascular hemolysis with hemolytic anemia, thrombocytopenia and acute renal failure (Chaves-Moreira et al., 2019; da Silva et al., 2004; Isbister and Fan, 2011). Accidents involving these spiders have been described worldwide; however, they are most common in South America, where, in countries such as Brazil, Argentina and Peru, they are considered a public health problem. Accidents caused by Brown spider bite (in South America the species *Loxosceles intermedia*, *L. laeta* and *L. gaucho* predominate) correspond to the most severe form of bites by spiders in Brazil (Campesi et al., 2014; Chippaux, 2015). The southern states of Brazil (Paraná and Santa Catarina) are the regions with the highest number of accidents caused by Brown spiders (da Silva et al., 2004; Lopes et al., 2020; Marques-da-Silva and Fischer, 2005). In 2020, the capital of the state of Paraná had the lowest number of accidents associated with Brown

spiders in the last 28 years (472 cases) (SSC/PR/Brazil, Secretaria de Saúde de Curitiba, Paraná, Brazil, 2021). It is believed that these data are related to the COVID-19 pandemic because people have been much more at home during this period and have exercised increased care regarding cleaning (the main form of prevention). However, in Brazil, in the last ten years, approximately 80,000 accidents involving species of these spiders were described (SINAN, Sistema de Informação e Agravos de Notificação, 2019).

The diagnosis of a Brown spider bite, when there is no capture of a spider involved, is based on the signs and symptoms presented by the victim, their clinical history, anamnesis, and the endemic presence of spiders in the patient's region. There is no laboratory test available for the diagnosis of Brown spider bite (da Silva et al., 2004; Isbister and Fan, 2011; Lopes et al., 2020). The venom of *Loxosceles* spiders is enriched in toxins containing molecular masses between 3 and 45 kDa. Of these toxins, the family of phospholipases D, also called dermonecrotic toxins, are the most studied and characterized from the molecular, functional and pathological points of view (Gremski et al., 2014, 2020). Phospholipases D from *Loxosceles* spider venom are toxins that stimulate an

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uncontrolled inflammatory response (the hallmark of envenomation). This is responsible for dermonecrosis, in addition to being involved in intravascular hemolysis and kidney disorders, which have been described in injured patients (da Silva et al., 2021; Gremski et al., 2014; Polli et al., 2021).

When a venomous animal affects the regions of the oral cavity and annexed structures, dental surgeons should be present in multi-professional teams to assist in the diagnosis and treatment of changes in site of the bite because the treatment of alterations in the mouth is the specialty of dental surgeons (Dare et al., 2012; de Souza et al., 2017; Lopes et al., 2020). In the case of a Brown spider bite involving the oral cavity, local treatment by a dentist is intended to reduce local inflammation, promote analgesia, prevent local and systemic infections, and maintain skin integrity (Chaves-Moreira et al., 2019; da Silva et al., 2004; Isbister and Fan, 2011).

Regarding the COVID-19 pandemic, patients who have had an accident with spiders could have had their symptoms confused with COVID-19 because both diseases can manifest symptoms like fever, weakness, headache, nausea, vomiting diarrhea. This can raise doubts regarding the diagnosis of loxoscelism in the period when cases of COVID-19 are prevalent (Futrell, 1992; Malaque et al., 2011; Wang et al., 2020). In addition, because of the COVID-19 pandemic, patients with accidents involving venomous animals were at risk of not having access to a hospital bed due to overcrowding, or they were exposed to COVID-19 on admission to hospitals due to the high risk of contamination with the SARS-CoV-2 virus in the hospital setting (Boccia et al., 2020). Furthermore, in this period of pandemic, Brazil had 200,000 new cases of COVID-19 daily, Brazilian hospitals were often overcrowded, and health professionals were overloaded, making it difficult to treat patients (Gormeli Kurt and Gunes, 2020; Ritchie et al., 2020; Zeiser et al., 2022). These factors may well have complicated the diagnosis and treatment of patients who suffered spider bites during the COVID-19 pandemic.

We report the case of a patient who had a Brown spider bite on his

lower lip during the COVID-19 pandemic. He required hospitalization for the treatment of local and systemic manifestations, and during hospitalization he acquired COVID-19, which aggravated his health condition. It is interesting to note that both these pathological conditions exacerbate the inflammatory response, and therefore professionals involved in the treatment of both conditions need to be aware of complications that can result from uncontrolled inflammatory response activated by a viral cycle, and by the phospholipases D toxins present in Brown spider venom. This case report was prepared following the CARE Guidelines (Riley et al., 2017).

2. Case description

We describe a clinical case that occurred in December 2020 in the city of Ponta Grossa (Paraná, Brazil; Latitude: 25.0945, Longitude: 50.1633; 25° 5' 40" South, 50° 9' 48" West). A 32-year-old man, living in a rural area, was sleeping at night and felt an itching and burning sensation in his lower lip; he hit his face, and when he woke up he noticed that he had just killed a Brown spider that had been on his lip (Fig. 1A). Due to an increase in volume and pain in the region, which rose over a few days, he sought medical assistance at a University Hospital five days after the accident. He kept the dead Brown spider in a pot and brought it with him to hospital. Clinically, the patient presented swelling on his lips and complaints of pain in the region of the bite. The patient also complained of lower back pain, fever and dyspnea; he presented with oxygen saturation of 90–91%. He reported no comorbidities or ongoing use of medication.

The patient had significant lip edema, extending from the chin to the right cervical zone-II. The lips presented drainage of serous liquid, with pustules on the upper lip, focal hemorrhagic lesions, and areas of pallor; the necrotic areas were more evident on the lower right lip. Mouth opening was limited, and lip sealing was not possible. The patient presented multiple ulcerations on the jugal and labial mucosa in the intraoral cavity, which were more exacerbated on the right side, and

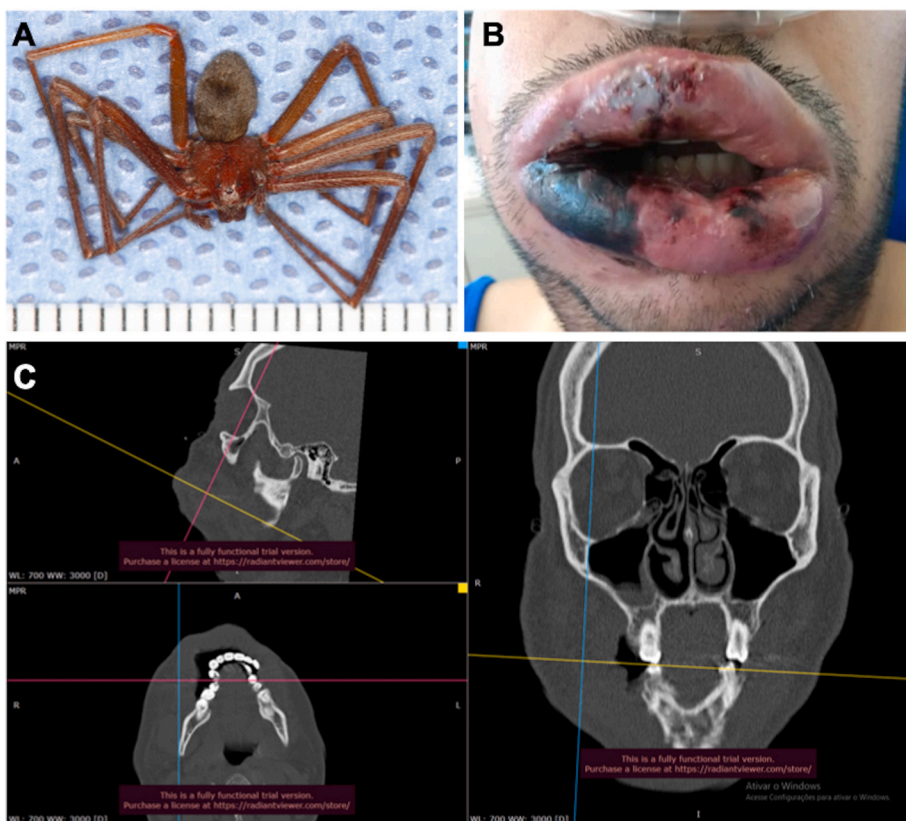


Fig. 1. (A). Brown spider (*Loxosceles* sp.) captured by patient. Characteristic violin-shaped darkened area on the cephalothorax. (B). Multiple ulcerations on the jugal and labial mucosa in the intraoral cavity are more exacerbated on the right side and associated with necrotic areas. (C). Computed tomography of the face and neck showed an inflammatory lesion in the subcutaneous tissue of the labial region, notably on the right, without significant purulent collections. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

were associated with necrotic areas (Fig. 1B). According to the Brazilian Ministry of Health, clinical signs of burning pain, focal hemorrhagic lesions mixed with pale areas of ischemia (marble plaque) and necrosis, which the patient presented, can point to the diagnosis of an accident with *Loxosceles* due to the highly characteristic clinical presentation of the lesion (Brazilian Ministry of Health, 2001). Besides that, blood analysis on the first day of hospitalization showed red blood cells and platelets in normal parameters. However, the patient had altered white blood cells presenting lymphopenia, monocytosis, leukocytosis and neutrophilia (Fig. 3). A coagulogram test showed a slightly increased international normalized ratio (INR) of 1.18 (reference range 0.9–1.1). There were also increases in the following parameters: D-dimer, C-reactive protein, glutamate-pyruvate transaminase, delta bilirubin, creatine phosphokinase, procalcitonin and fibrinogen (Fig. 3 and Table 1). Urinalysis was also altered, with proteinuria and hematuria (Table 1). This incident occurred during the COVID-19 pandemic and the patient tested negative for COVID-19 (RT-PCR test) before hospitalization.

The differential diagnosis was performed with necrotic cutaneous-mucosal lesions, vascular insufficiency, drug reactions, burns, traumatic lesions, and multiple resistant *Staphylococcus aureus* infection. All of the latter were ruled out due to the clinical characteristic of the lesion, the medical history, the location of the accident (rural area in the south of Brazil), and the systemic changes that presented, which all confirmed a *Loxosceles* spider accident (Brazilian Ministry of Health, 2001).

At the beginning of hospitalization, the patient was treated by the medical team with dexamethasone; enoxaparin; peripherally acting analgesic and centrally acting analgesics; and the antibiotics clindamycin and ceftriaxone with azithromycin. Computed tomography of the face and neck showed an inflammatory lesion in the subcutaneous tissue of the labial region, notably on the right, without significant purulent collections, which did not indicate the need for surgery. There were also prominent cervical reactive lymph nodes in the upper right region (Fig. 1C). The medical team then decided on conservative treatment, with follow-up regarding necrosis, and debridement after the area of wound necrosis was demarcated with a reduced risk of spreading the effect of the venom. After stabilizing the clinical situation, the patient was referred to a plastic surgeon. On the sixth day of hospitalization, the patient presented multiple resistant *Staphylococcus aureus* in a sputum collection. The medical team changed the antibiotics that were being used to just vancomycin and clindamycin. For the first 15 days of hospitalization, the patient presented with mild dyspnea and remained on oxygen support with a nasal catheter at low flow (1–2 L).

On the 15th day of hospitalization, the patient's laboratory tests showed signs of systemic loxoscelism, such as increased C-reactive protein showing an intense inflammatory process, increased urea and creatinine levels showing renal alteration, changes in coagulogram, and anemia (Fig. 3). Because of the renal alteration, vancomycin was suspended on the 26th day of hospitalization (Brazilian Ministry of Health, 2001; Gremski et al., 2020; Sinha Ray et al., 2016). The hospital dentistry team had been monitoring the patient daily from the beginning of hospitalization to provide care regarding the oral cavity. The dentistry team carried out infection control of the oral cavity, helped the patient to perform oral hygiene with 0.12% chlorhexidine, applied collagenase

to necrotic portions and sunflower oil to ulcerated parts, and debrided necrotic tissue that became loose (20 days after the accident, when the area of necrosis had already been demarcated) (Fig. 2A). On the 25th day of hospitalization, the labial condition showed clinical improvement, with a reduction in edema, and remission of the necrotic and ulcerated portions. The patient was able to perform oral opening and no longer presented painful symptoms. The healing process occurred on the lip, with significant loss of tissue on the right portion of the lower lip (Fig. 2B).

During hospitalization, the patient presented persistent acute renal injury associated with the systemic use of vancomycin or Brown spider venom intoxication (Gremski et al., 2014, 2020; Sinha Ray et al., 2016), so the use of vancomycin was suspended on the 26th day of hospitalization. The patient subsequently started having nausea, vomiting, and loss of appetite, which did not improve with medication. On the 28th day of hospitalization, the patient had an episode of subtle oxygen desaturation (65–75%), tachypnea, and required 6 L of oxygen in a mask (SARS-CoV-2 RT-PCR: positive). The patient was immediately referred to the COVID intensive care unit (COVID-ICU) of the hospital. A computed tomography of the chest showed the typical signs of COVID-19 viral pneumonia, with “crazy paving” patterns presenting consolidations surrounded by ground-glass opacities. According to the Hospital Pandemic Influenza Preparedness Committee, lung involvement was more than 75%. After a day in the COVID-ICU, it was soon necessary to perform orotracheal intubation due to intense tachypnea, and respiratory distress associated with desaturation. Blood tests on the first day of COVID-ICU showed normocytic and normochromic anemia, lymphocytopenia, and neutrophilia in the hemogram (Fig. 3). In addition, the patient presented a significant increase in urea and creatinine, D-dimer, and C-reactive protein (Fig. 3).

On the 37th day of hospitalization, the patient showed improvement in the mouth changes treated by the dental surgeon, with remission of the necrotic and ulcerated parts. The healing process resulted in lip asymmetry with scar tissue formation, and plastic surgical reconstruction was recommended after hospital discharge (Fig. 2C). During the patient's stay in the COVID-ICU, the dental team continued monitoring him to assess possible oral changes associated with COVID-19, and to assist the oral hygiene care team to prevent infections such as ventilator-associated pneumonia. Over the time that he spent in the COVID-ICU, the patient began to present a worsening systemic condition, with acute renal failure; sepsis in the lung, soft tissue and bloodstream by multiple resistant *Staphylococcus aureus*; ventilator-associated pneumonia by positive Burkholderia in orotracheal aspirates; and respiratory distress.

As time passed in the COVID-ICU, the patient's systemic condition continued to be severe. On day 53, hematological tests showed worsening kidney conditions, with increased urea and creatinine even after three dialysis attempts in the previous days. C-reactive protein levels also remained high, indicating a severe infection. Ventilatory parameters were at maximum level, with 100% inspired oxygen fraction (IOF2). The patient continued to show a drop in saturation, and hemodynamic instability, requiring a progressive increase in a double-dose vasoactive drug. At 53 days of hospitalization the patient presented with cardio-respiratory arrest, and despite rescue measures performed by hospital staff, he did not respond to rescue efforts and died.

3. Discussion

In this report, we present the case of a patient who suffered a bite from a Brown spider and who, during the treatment phase, was infected with the SARS-CoV-2. Accidents caused by spider bites are a public health problem in several regions, such as the Americas, Africa, Southern Europe, and China, due to the high number of occurrences and their severity, which can be fatal (Camplesi et al., 2014; Chippaux, 2015; da Silva et al., 2004; Lopes et al., 2020).

Spiders of the genus *Loxosceles* are widely distributed around the

Table 1
Laboratory tests at the beginning of hospitalization.

Parameter	Results	Reference range
Urine protein (proteinuria) (g/24h)	0.39	Less than 0.15
Red blood cells in urine (hematuria) (cells/mL)	8000	Until 5000
Hyaline casts (casts/mL)	750	Absent
Glutamate-pyruvate transaminase (units/L)	25	<50
Delta bilirubin (mg/dL)	0.56	0.00 to 0.20
Creatine phosphokinase (units/L)	281	38 to 174
Procalcitonin (ng/mL)	3660	<2
Fibrinogen (mg/dL)	1080	200 to 400



Fig. 2. (A). Fifteen days of hospitalization. Infection control of the oral cavity was performed, helping the patient to perform oral hygiene with 0.12% chlorhexidine, applying collagenase to necrotic portions and sunflower oil to ulcerated parts, and debriding the necrotic tissue that became loose. (B). On the 25th day of hospitalization, the labial condition showed clinical improvement, with a reduction in edema, and remission of the necrotic and ulcerated portions. The healing process on the lip occurred, with significant loss of tissue from the right part of the lower lip. (C). On the 37th day of hospitalization, the lip alteration improved the clinical condition, with remission of necrotic and ulcerated parts, resulting in lip asymmetry with scar tissue formation.

globe, with the highest occurrences in temperate and tropical regions (da Silva et al., 2004; Lopes et al., 2020). In Brazil, spider bites consisted of 21% of attacks and 6% of deaths by terrestrial venomous animals, with variation dependent on the region and state (Chippaux, 2015). The species responsible for the bite was not identified in 32% of these envenomations. *Loxosceles intermedia* were involved in 67% of cases in which the species was recognized (Marques-da-Silva and Fischer, 2005). The south and southeast parts of Brazil are most affected by accidents (in Paraná the incidence of envenomation per 100,000 population was 87.95) (Chippaux, 2015; da Silva et al., 2004; Marques-da-Silva and Fischer, 2005). Our clinical case refers to a Brown spider (*Loxosceles* sp.) bite that occurred in the southern region of Brazil.

There are no specific tests to diagnose loxoscelism; however, signs and symptoms can be used to indicate whether there has been a spider bite (Gremski et al., 2020; Isbister and Fan, 2011). Symptoms such as myalgias, indisposition, fever, chills, nausea, vomiting, and skin alterations are associated with loxoscelism (Jerusalem and Salavert Lleti, 2018; Lopes et al., 2020). This diagnosis should be considered in endemic areas in relation to patients with such manifestations (da Silva et al., 2004; Lopes et al., 2020). In the reported case, the patient presented skin alterations with necrotic and ulcerated portions, which is common in cases of loxoscelism, and occurs due to the indirect action of phospholipase D and other venomous components. The latter activate the release of pro-inflammatory cytokines, causing inflammation and cell death. In addition, the patient presented with lower back pain, fever and dyspnea, as well as hematological alterations such as leukocytosis, neutrophilia, and hyperbilirubinemia (Jerusalem and Salavert Lleti, 2018; Lopes et al., 2020). He also developed increased urea and creatinine levels, and thrombocytopenia throughout the period of hospitalization, all of which are compatible with the clinical appearance of patients affected by Brown spider bites (Chaves-Moreira et al., 2019; Lopes et al., 2020).

After the bite of a Brown spider, a set of clinical manifestations called loxoscelism may include not only local complications but also systemic changes, such as intravascular hemolysis, hemolytic anemia thrombocytopenia, and renal failure; these cases are rarer but are more severe, and can lead to death (Gremski et al., 2014, 2020; Lajoie et al., 2013). This case was cutaneous loxoscelism with mild systemic symptoms. The symptoms were mild because they included changes such as thrombocytopenia, thrombocytopenia, uremia, lymphocytopenia, leukocytopenia, neutrophilia, and increased level of C-reactive protein. However, the systemic alterations were more evident after the patient acquired COVID-19. The laboratory results indicated that loxoscelism caused systemic changes in the patient such as high levels of inflammation and renal alteration. Therefore, what caused the patient's death was the unfortunate coincidence of acquiring COVID-19 while being treated in hospital for the spider bite. This condition caused COVID-19 to

aggravate the effects of loxoscelism, and the lung changes caused by the COVID-19 virus made treatment difficult. In 2020, COVID-19 led to the death of just over 230,000 Brazilians, which corroborates the fact that being hospitalized during this period brought the risk of acquiring COVID-19 due to the high rate of patients hospitalized with the disease. Furthermore, when patients with some type of systemic changes acquired COVID-19 they were in a risk group for death from the illness (Izcovich et al., 2020; Ritchie et al., 2020).

Phospholipase-D members family is the venom proteins of Brown spiders, which are the most studied, and biochemically and functionally characterized, and has as substrates cell membrane phospholipids such as sphingomyelin and lysophosphatidylcholine. When the latter are cleaved, they generate known bioactive metabolites, such as ceramide-1-phosphate and lysophosphatidic acid, or cyclic lipids by transphosphatidylolation (Chaim et al., 2011; Lajoie et al., 2013). In turn, these metabolites are believed to be associated with modulating inflammatory processes by stimulating the production of cytokines and chemokines by various cell types, including endothelial and fibroblast cells (Rivera et al., 2015). Endothelial fibroblast cells produce vasoactive substances, such as IL-1, IL-6, tumor necrosis factor-alpha, and acute phase C-reactive protein. Thus, the endothelium is directly associated with an exacerbated inflammatory response in patients affected by Brown spider bite (Chaim et al., 2011; Gremski et al., 2014, 2020; Lajoie et al., 2013). SARS-CoV-2 generates a so-called "storm of cytokines", a term used to refer to the uncontrolled immune response to the virus, which causes severe alterations to patients, potentially leading to death (Vaninov, 2020). The fact that the referred patient had an association of diseases (loxoscelism plus COVID-19), both of which result in alterations that can lead to an exacerbated inflammatory response associated with systemic alterations, explains the rapid evolution of the patient's illness, which led to his death.

The presence of the dental surgeon in the multidisciplinary team was essential in the context of this case. The dental surgeon was a specialist in the treatment of oral changes, and was the professional who performed the care regarding the local treatment of the Brown spider bite, in addition to acting in the ICU environment to help control secondary infections associated with the oral cavity (Hocková et al., 2021; Silva et al., 2014). Thus, this case report also validates the role of the dental surgeon in a hospital environment working within multidisciplinary teams, since treatment of the oral cavity made by that professional can provide improvements in quality of life and the general health condition of hospitalized patients.

4. Conclusion

Based on the outcome of this clinical case, it is possible to conclude that treating patients affected by systemic alterations caused by Brown

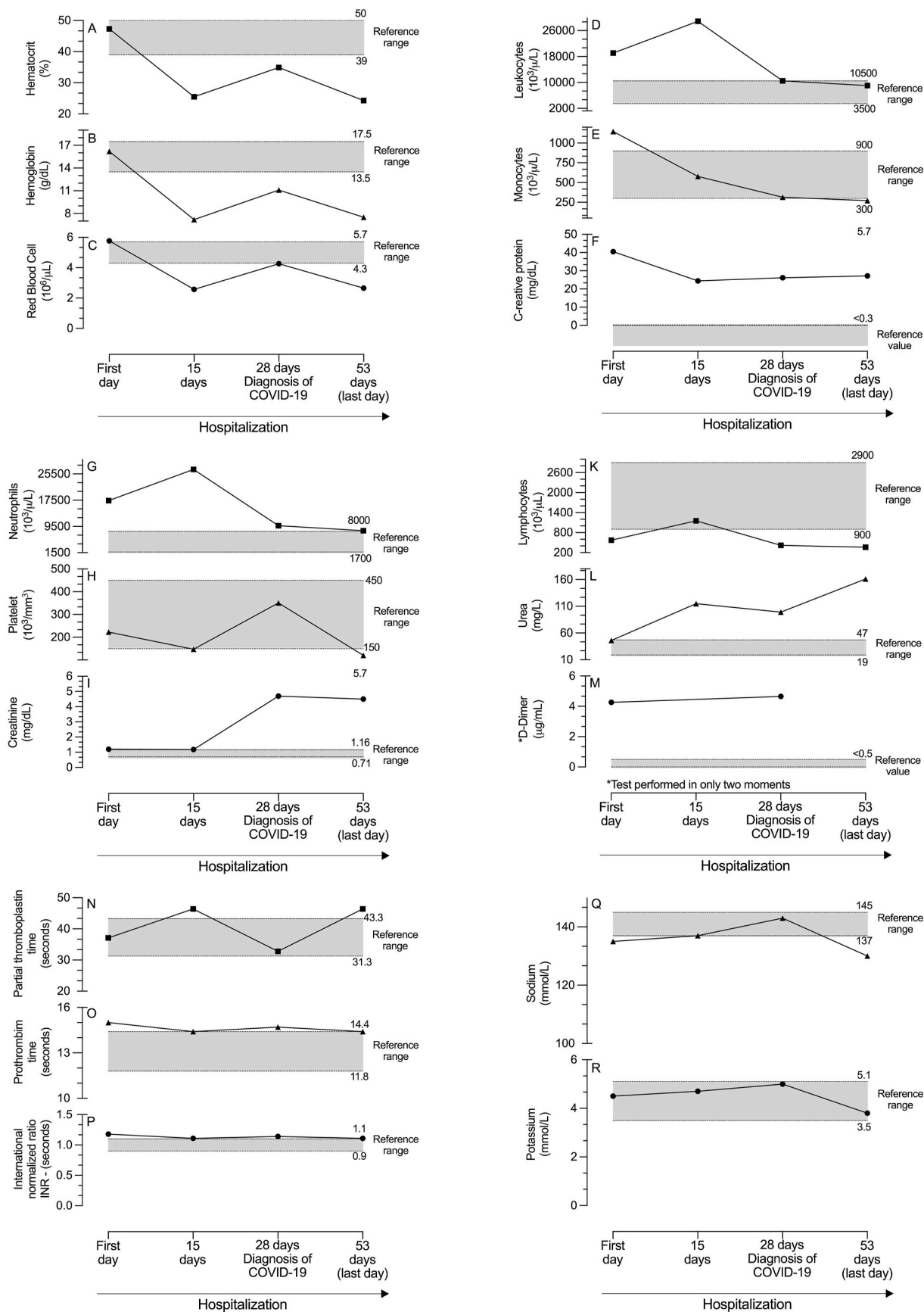


Fig. 3. Results of laboratory tests performed during the hospitalization period (the shaded area represents the reference value).

spider venom associated with COVID-19 needs special attention from a multi-professional team because when these diseases occur in tandem it can lead to a rapid evolution, possibly leading to death.

Credit author statement

Marceli Dias Ferreira: concept/design; data collection; data analysis/interpretation; drafting the article. Silvio Sanches Veiga: concept/design; critical revision of the article; approval of the article. Fábio André dos Santos: concept/design; critical revision of the article; approval of the article.

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Ethical statement

No ethical statement was required for this article; the patient gave his written permission to use his data.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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