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CASE REPORT

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Severe COVID-19 in HIV/*Leishmania infantum* coinfected patient: a successfully managed case report

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Abstract

Background Coronavirus disease 2019 originated in China and swiftly spread worldwide, posing a significant threat to public health. Caused by SARS-CoV-2, it manifests as a flu-like illness that can escalate to Acute Respiratory Distress Syndrome, potentially resulting in fatalities. In countries where HIV/*Leishmania infantum* is endemic, the occurrence of concurrent SARS-CoV-2/HIV/*Leishmania infantum* infections is a reality, prompting inquiries into appropriate clinical management.

Case presentation We present the case of a 48-year-old woman who was hospitalized for 36 days across three different hospitals in the state of Pernambuco, Brazil. She was diagnosed with SARS-CoV-2/HIV/*L. infantum* coinfection. The patient exhibited severe COVID-19 symptoms, including fever, productive cough, and dyspnea. Throughout her hospitalization, she experienced oxygen saturation levels of ≤ 93%, along with fluctuations in blood pressure, respiratory rate, and heart rate. Her blood tests revealed lymphopenia, leukopenia, and neutropenia, while laboratory results indicated abnormal levels of d-dimer, AST, ALT, lactate dehydrogenase, ferritin, and C-reactive protein. A computed tomography scan revealed 75% involvement of the lung parenchyma with patchy ground-glass opacities.

Conclusion Against all odds, the patient was discharged. The leukopenia associated with HIV/*L. infantum* may have played a decisive role. Further studies are necessary to better understand diagnostic strategies and clinical management measures for HIV/*L. infantum* coinfected patients who are susceptible to SARS-CoV-2 infection.

Keywords SARS-CoV-2, HIV, Leishmaniasis, Coinfection, Case report

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Background

SARS-CoV-2 is the etiological agent of Coronavirus Disease 2019 (COVID-19), declared a pandemic on March 11, 2020 [1]. As of March 10th, 2023, more than 670 million cases and over 6 million deaths have been reported worldwide [2]. COVID-19 is characterized by immune dysregulation that can progress to a hyperinflammatory syndrome, leading to respiratory failure and multiple organ dysfunction. The incubation period ranges from 2 to 14 days, after which the patient may experience flu-like symptoms such as fever or chills, cough, fatigue, runny nose, sore throat, myalgia, and difficulty breathing, or they may be asymptomatic [3]. In the acute phase of the disease, the patient may develop respiratory failure requiring supplemental oxygen, a condition known as Acute Respiratory Distress Syndrome (ARDS) [4].

Regarding the hemogram, COVID-19 patients may exhibit leukopenia, characterized by direct infection of lymphocytes and subsequent functional immunosuppression, or leukocytosis, which is associated with a worse prognosis [5]. On the other hand, cases of neutropenia may also be observed, potentially contributing to a better outcome [6]. Laboratory data may reveal abnormal values of certain markers such as C-reactive protein (CRP), d-dimer, ferritin, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), which can serve as predictors of severe prognosis [7–10].

In HIV patients or those with visceral leishmaniasis (VL), the hemogram often indicates leukopenia, accompanied by lymphopenia and neutropenia, as a result of immunosuppression caused by the direct infection of both the virus and the parasite [11, 12]. Certain laboratory biomarkers may also be altered due to a high viral load, such as CRP and d-dimer, respectively [13, 14]. Additionally, ferritin and LDH levels are associated with disease progression in HIV and VL patients [15, 16]. Changes in AST and ALT levels are common in VL patients due to the tropism of *L. infantum* for liver cells. [17].

It is worth noting that *L. infantum* is one of the opportunistic agents of Acquired Immunodeficiency Syndrome (AIDS), and the coinfection of HIV/*L. infantum* represents a global public health concern. Patients with this coinfection have an elevated risk of parasite relapse, as well as an increased likelihood of mortality [18].

Given the widespread transmission of COVID-19, the potential for multiple SARS-CoV-2/HIV/*L. infantum* infections becomes a reality, particularly in regions where *L. infantum* is endemic. Moreover, there is a lack of published data regarding the impact of SARS-CoV-2 infection on HIV/*L. infantum* coinfected patients, including clinical, immunological, and laboratory aspects [19]. Therefore, this case report serves to underscore a multiple SARS-CoV-2/HIV/*L. infantum* coinfection and its associated clinical, immunological, and laboratory characteristics.

Case presentation

A 48-year-old female patient, born in the state of Pernambuco, Brazil, was admitted to the ward at Agamenon Magalhães Hospital (AMH), Department of Health, in the state of Pernambuco on July 1st. She presented with fever and weight loss over the past four months, along with a productive cough. In the five days leading up to admission, she experienced respiratory distress, dysuria, and tachycardia. Due to worsening respiratory symptoms, a real-time RT-PCR test (BIOMOL OneStep kit) for SARS-CoV-2 was conducted on July 3rd, which returned positive results. Treatment with ceftriaxone (1 g/day) and azithromycin (500 mg/day) was initiated. At AMH, the patient was hospitalized for four days (from July 1st to July 5th) and maintained an average oxygen saturation of 97%. Laboratory findings revealed leukopenia of 3,670 cells/mm3, lymphopenia of 771 cells/mm3, and a peak circulating C-reactive protein (CRP) level of 7.7 mg/dL (Table 1).

After confirming the diagnosis of COVID-19, the patient was transferred on July 5th to the designated COVID-19 referral hospital, Alfa Hospital (AH), also located in Recife, the capital of the state of Pernambuco. Upon admission, a new real-time RT-PCR test (CDC Protocol – respiratory virus- CDC/Atlanta/EUA) for SARS-CoV-2 was conducted, yielding a positive result. Additionally, three tuberculosis smear microscopies were performed, all yielding negative results.

She was initiated on ceftriaxone (1 g every 24 h), azithromycin (500 mg every 24 h), and sulfamethoxazole + trimethoprim (800 mg + 160 mg every 24 h). Additionally, she received enoxaparin (40 mg every 24 h), paracetamol (750 mg every 8 h), and ondansetron (2 mg/mL every 8 h). On July 15th, the patient's clinical condition improved, with the absence of dyspnea and cough. In terms of clinical outcomes, her body temperature averaged 36 °C, blood pressure ranged from 110/60 mmHg to 130/80 mmHg, respiratory rate varied from 13 to 20 breaths per minute, heart rate ranged from 85 beats per minute to 120 beats per minute, and oxygen saturation ranged between 96 and 98%. Laboratory results indicated peak d-dimer values of 2,470 ng/mL; lactate dehydrogenase (LDH) of 470 U/L, and CRP of 48.8 mg/dL (Table 1).

For further investigation of previous episodes of fever and weight loss, the patient was transferred to the ward at the Clinical Hospital (CH), Federal University of Pernambuco, Recife, on July 15th, with a regular general condition, conscious, oriented, and afebrile. As

Table 1 Hemogram data, laboratory findings, and clinical condition during three hospital admissions

	AMH	AH	CH
Hemogram			
Leukocytes (cells/mm^3)	3,670	2,700	1,040–3,360
Neutrophils (cells/mm^3)	N/A[a]	N/A	200–1,965
Neutrophils (%)	70	43.2–48.7	22.1–78
Lymphocytes (cells/mm^3)	771	N/A	200–1,000
Lymphocytes (%)	21	42.9	10–58.2
Platelets (cells/mm^3)	128,000	174,000–214,000	128,000–189,000
Laboratory findings			
Prothrombin time (sec.)	N/A	N/A	12.5–13.4
D-dimer (ng/mL)	N/A	2,470	540
INR	N/A	N/A	0.94–1.02
AST (U/L)	18	35	18.8–325.8
ALT (U/L)	14	35	36.1–365.4
Total bilirubins (mg/dL)	N/A	N/A	0.3–0.6
Direct bilirubin (mg/dL)	N/A	N/A	0.1–0.4
Creatinine (mg/dL)	N/A	N/A	0.7–1.3
Lactic dehydrogenase (U/L)	N/A	470	438.8
Ferritin (ng/mL)	N/A	N/A	465
C-reactive protein (mg/dL)	7.7	21.8–48.8	0.3–6
Urea (mg/dL)	19	18	8.4–29.7
Clinical condition during hospitalization			
Temperature (°C)	N/A	35.9	36–39.2
Blood pressure (mmHg)	N/A	110/60–130/80	100/60–190/80
Respiratory frequency (mpm)	N/A	13–20	18–24
Heart frequency (bpm)	N/A	85–120	72–110
Saturation (%)	97.1	96–98	92–99

[a] Not Applicable – indicates missing data

prophylactic medication, sulfamethoxazole + trimethoprim (400/80 mg every 24 h) was prescribed, in addition to enoxaparin (40 mg every 24 h). Investigation for visceral leishmaniasis was initiated by means of abdominal ultrasonography on July 21st, which showed no alterations in the liver or spleen. On the following day, a conventional PCR test (GoTaq® Green Master Mix—LITSR/L5.8S) for the detection of *L. infantum* DNA was performed, yielding a positive result. Thus, treatment with amphotericin B (4 mg/kg/day) was initiated. On the same day, real-time PCR was conducted for HIV investigation, and the result was positive, with a viral load of 440,089 copies/mL, CD4 count equal to 71 cells/mm3, and CD8 count at 803 cells/mm3.

In addition to these infectious conditions, the presence of cytomegalovirus (CMV) was also investigated through real-Time PCR (iCycler iQ) on July 24th, which yielded a positive result with 2,540 copies/mL detected. The patient presented pruritic burning ulcerated lesions in the vulva and gluteal regions with clinical features suggestive of herpes, and consequently, treatment with acyclovir (400 mg every 8 h) was initiated, leading to improvement in the clinical condition.

The patient remained in the ward for 22 days (from July 15th to August 7th) and exhibited the following clinical outcomes: body temperature ranging from 36 to 39.2 °C, blood pressure fluctuating between 100/60 and 190/80 mmHg, respiratory rate varying from 18 to 24 breaths per minute, heart rate ranging from 72 to 110 beats per minute, and oxygen saturation fluctuating between 92 and 99%. During this period, sputum bronchoscopy was performed to investigate other potential causative agents of pulmonary disease, such as *Pneumocystis jirovecii*, *Mycobacterium tuberculosis*, and CMV; however, the results were negative. A chest CT scan revealed ground-glass opacities affecting approximately 75% of the lung parenchyma.

Regarding the hemogram, notable presence of leukopenia was observed, with levels ranging from 1,040 to 3,360 cells/mm3. Moderate to severe neutropenia was also noted, with values ranging from 200 to 1,965.6 cells/mm3 (22.1%-78%). Lymphopenia ranged from 200 to 1,000 cells/mm3 (20%-58.2%). Laboratory findings indicated CRP values of 6 mg/dL, d-dimer of 540 ng/mL, ferritin of 465 ng/mL, LDH of 438.8 U/L, aspartate aminotransferase (AST) levels exceeding 51 U/L, and alanine aminotransferase (ALT) levels exceeding 63 U/L (Table 1).

The patient was discharged on August 7th due to clinical and laboratory improvement. Treatment for leishmaniasis was administered with amphotericin B 50 mg (4 mg/kg/day) from July 29th to August 6th. Additionally, she commenced ART treatment on August 6th, consisting of dolutegravir 50 mg/day, tenofovir 300 mg/day, and lamivudine 300 mg/day. A timeline depicting the clinical and laboratory evolution, as well as the treatments administered, is summarized in Fig. 1.

Discussion and conclusion

A severe COVID-19 patient with HIV/*L. infantum* coinfection, admitted to three different hospitals and discharged after 36 days of hospitalization, was reported. Leukopenia, lymphopenia, and neutropenia, along with other abnormal laboratory findings, were observed during the three hospitalizations.

According to Qu et al. [20], leukopenia and lymphopenia are common in patients with COVID-19, possibly due to leukocyte infection by SARS-CoV-2. In severe

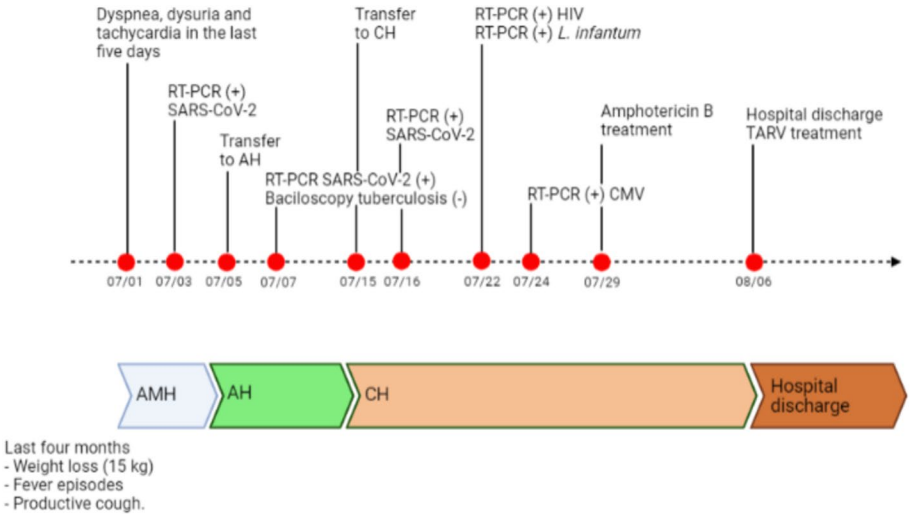

Fig. 1 Main clinical evolution, laboratory findings and treatments during the patient's hospitalization

COVID-19 cases, leukopenia and lymphopenia may be observed in over 70% of patients compared to controls [21]. The neutropenia observed here may be an important factor associated with HIV and CMV infections, as these viruses can damage bone marrow progenitors and lead to autoimmune depletion [22].

In the context of HIV/*L. infantum* coinfection, lymphopenia is common due to the tropism of HIV for TCD4 lymphocytes and the replication of *L. infantum* in TCD4 and TCD8 lymphocytes, which can lead to severe immunosuppression [11, 23, 24]. Leukopenia and neutropenia may also be observed due to the presence of these two pathogens together. It is important to highlight that the primary immunological mechanisms governing the clinical evolution of patients co-infected with *Leishmania infantum*, HIV, and other infections remain unclear. The literature suggests that patients co-infected with *Leishmania infantum* and HIV have a worse prognosis compared to those infected only with *Leishmania infantum*, primarily due to pronounced pro-inflammatory responses from the reticuloendothelial system. This also may explain the pulmonary clinical manifestations observed in the patient in this study.

HIV can impair macrophage phagocytosis, thereby promoting the intracellular replication of *Leishmania*. Furthermore, HIV can induce macrophages to produce E2 prostaglandin, cyclooxygenase 2, and TGF-β, which in turn stimulate *Leishmania* replication within these cells.

Another mechanism involves the expression of lipophosphoglycan (LPG) on the surface of *Leishmania*, which may trigger the expression of LTR proteins from the HIV proviral DNA in T cells via the NF-κB pathway. Additionally, it is noteworthy that TNF-α, induced by *Leishmania* infection, may enhance HIV replication (Casado et al., 2015 [25]; Guedes et al., 2018 [26]; Okwor & Uzonna, 2013 [27]).

In the present case, SARS-CoV-2 infection occurred following immunosuppression caused by HIV/*L. infantum*. The literature suggests that HIV-immunosuppressed patients with COVID-19 are more prone to developing a severe clinical course, as SARS-CoV-2 can propagate more readily within the body in the absence of a rapid adaptive immune response for viral clearance [24]. Moreover, HIV-immunosuppressed patients can potentially act as sources for heightened viral loads and the emergence of variants [24]. HIV-positive individuals also have a high hospitalization rate due to their increased vulnerability to opportunistic infections and other complications [24].

Laboratory findings may play an important role in the complex interaction between SARS-CoV-2, HIV, and *L. infantum*. In this case, levels of CRP, d-dimer, ferritin, LDH, AST, and ALT were altered. During COVID-19, CRP levels may reflect the extent of lung damage and disease severity [7]. CRP functions as a complement to the innate and adaptive immune systems, and its expression is induced in response to factors secreted by macrophages, particularly IL-1, IL-6, and TNF [28–30]. In this case, the patient exhibited a peak CRP level of 48.8 mg/dL and 75% involvement of lung parenchyma. Furthermore, it is noteworthy that the highest CRP value in our case was observed on the ninth day of the disease, which corresponds to the stage of disease progression, typically occurring between 4 to 12 days, and can be classified as a severe predictor [30]. Elevated CRP levels can also be observed in patients with visceral leishmaniasis (VL), as it serves as a marker of

inflammatory reactions and cytokine activation [31]. In HIV-positive patients, CRP levels are elevated only during ART use or non-intercurrent infections [14].

D-dimer is another important serum marker of note in the present context. It results from the degradation of fibrin, an important protein for clot formation. Elevated circulating levels of d-dimer are associated with alterations in the coagulation process and the possibility of thrombosis formation [32]. In this case, d-dimer values reached 2,470 ng/mL, suggesting abnormalities in the coagulation process. Up to a nine-fold elevation in d-dimer levels, along with the presence of lymphopenia, has been associated with COVID-19 mortality in moderately and critically ill patients hospitalized in Wuhan, China [33]. Additionally, the cut-off value for predicting mortality during hospitalization was determined to be 2000 ng/mL [33]. D-dimer levels also increase in visceral leishmaniasis and are associated with the activation of intravascular coagulation, particularly in its severe form [34]. In HIV patients, elevated levels of d-dimer result from high levels of circulating viral RNA and the absence of antiretroviral treatment (ART), as well as high levels of CRP and IL-6. Particularly in women, high rates of d-dimer at an early age may also be related to HIV opportunistic diseases [13]. In this case, high levels of d-dimer may be related to circulating HIV RNA, as well as concomitant infections such as SARS-CoV-2 and *L. infantum*, and elevated CRP values.

Another important marker is ferritin, a protein involved in iron homeostasis and serving as a serum marker of body iron stores [35]. Iron is considered toxic to cells due to its ability to induce reactive species, which can damage DNA and cellular proteins. Ferritin plays a crucial role in storing iron, thus preventing this damage. In our patient, ferritin levels were elevated, reaching 465 ng/mL. According to Abbaspour et al. [36], ferritin is a key protein in immune dysregulation, as its high serum levels result from pro-inflammatory processes and contribute to the formation of the cytokine storm. Elevated serum ferritin levels during admission and hospitalization of COVID-19 patients were associated with moderate and severe disease, respectively [37]. However, the study by Carubbi et al. [38] suggests an association only between elevated ferritin levels and severe lung involvement, highlighting the lack of difference in lung abnormalities found on CT scans between discharged patients and those who died. High serum ferritin levels are also evident in immunocompetent patients with visceral leishmaniasis (VL) and HIV patients, as the disease progresses and TCD4 lymphocyte count decreases [39, 40].

LDH is an enzyme found in tissues that can indicate levels of injury and is also important in infectious diseases. Elevated LDH levels were observed in the present study. High LDH levels are associated with tissue damage in various diseases, as well as in pulmonary disorders, which can lead to respiratory failure [41]. Consequently, LDH levels have also been linked to severity in COVID-19 patients [9, 42]. Additionally, LDH has demonstrated high sensitivity and specificity in predicting severity and mortality [39]. Furthermore, LDH levels may be altered in patients with visceral leishmaniasis (VL) and HIV [15, 16].

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), on the other hand, reflect liver function and are serum enzymes that may serve as predictors of COVID-19 severity. In the study by Tian and Yen [10], severe patients exhibited high levels of AST and ALT. This could indicate the degree of liver impairment due to SARS-CoV-2 infection in cholangiocytes, which have higher ACE2 expression [10]. Similarly, Wang et al. [43] demonstrated abnormalities in AST and ALT levels among severe COVID-19 patients. Importantly, *L. infantum* exhibits tropism for liver cells and, in conjunction with SARS-CoV-2 infection, can overwhelm the organ by inducing hyperinflammation [17]. In the present case, the elevated AST and ALT levels observed may result from coinfection by SARS-CoV-2 and *L. infantum* in the liver, but further studies are needed to evaluate these mechanisms.

Taken together, these laboratory findings provide important markers that may help predict the severity of COVID-19 in the context of coinfections. It is noteworthy that CRP, D-dimer, ferritin, LDH, AST, and ALT levels were elevated, indicating the possibility of disease exacerbation through various mechanisms. However, a severe outcome did not occur, which may be attributed to the interaction with HIV/*L. infantum* in the context of the cellular response, where each pathogen elicits a specific profile.

This is the first case report of a multiple infection involving SARS-CoV-2, HIV, and *L. infantum*. We believe that this work provides useful information for a better understanding of clinical outcomes, which may lead to improved diagnostic strategies and guide the implementation of management measures for HIV/*L. infantum* coinfected patients susceptible to SARS-CoV-2 infection, thereby contributing to a positive prognosis of the disease. The present case exhibits important features that could have led to a severe outcome of COVID-19, such as high levels of serum markers, lymphopenia, and a reticuloendothelial immune response. However, leukopenia was also evident, suggesting a possible relation with a severe outcome. The interaction between HIV and *L. infantum* may have played an important role here and deserves further investigation to elucidate the immunopathogenesis of this multiple infectious process.

Abbreviations

AMH Agamenon Magalhães Hospital
AH Alfa Hospital
CH Clinical Hospital

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Authors' contributions
P.C.S.F., V.Q.B and R.G.L.N. conceptualized and designed the study. P.C.S.F., P.A.F.N., L.P.C., W.L.B.J., D.L.G. and A.T.X. were involved in laboratory work. P.S. R.A. followed-up the patient. P.C.S.F., G.S.N.B., P.A.F.N., Z.M.M. and V.M.B.L carried out data collection, formal analysis and investigation. P.C.S.F. drafted the manuscript. G.S.N.B., P.S.R.A., V.Q.B. and R.G.L.N contributed with insertion/deletion of concepts, corrections and suggestions. V.Q.B. and R.G.L.N. obtained funding support. All authors read and approved the final version to be submitted.

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Availability of data and materials
Availability of data and materials The authors agree to make all data described in the manuscript freely available.

Declarations

Ethics approval and consent to participate
This study was carried out in accordance with the Declaration of Helsinki, and the protocol was submitted to the Human Research Ethics Committee (CEP) of the Center for Health Sciences at the Federal University of Pernambuco under protocol CAAE 33597220.5.0000.5208, and it was approved under protocol 4.227.624.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

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