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Does the leishmaniasis protects against SARS-CoV-2

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ABSTRACT
The relationship between leishmaniasis and COVID-19 remains uncertain, with no evidence suggesting that leishmaniasis provides protection against COVID-19. Leishmaniasis, transmitted by sandflies, and COVID-19, caused by the SARS-CoV-2 virus, are unrelated diseases with distinct transmission modes. It is essential to rely on established preventive measures for COVID-19, such as vaccination and hygiene practices, as leishmaniasis requires separate medical attention. Some studies suggest that visceral Leishmania-COVID-19 co-infection may reactivate asymptomatic leishmaniasis. Severe COVID-19 cases may exacerbate parasitic multiplication and organ involvement. The immunological response to visceral leishmaniasis may increase susceptibility to subsequent SARS-CoV-2 infection, emphasizing the importance of an effective immune response. Cutaneous leishmaniasis may confer cross-protection against COVID-19, particularly in tropical regions. IFN-γ plays a critical role in parasite control and antiviral defense, highlighting its importance in both diseases. Further research is needed to understand the mechanisms underlying the interaction between SARS-CoV-2 and leishmaniasis.

KEY WORDS:
Lieshmaniasis,SARS,COV-2.

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INTRODUCTION

The COVID-19 pandemic, caused by the innovative severe acute respiratory syndrome coronavirus (SARS-CoV-2), has exposed individuals and nations globally, impacting various facets of life including social, economic, political, and healthcare systems. (1) Moreover, COVID-19 infections have disrupted neglected tropical diseases (NTDs) control efforts, notably affecting the management of leishmaniasis, encompassing both visceral and cutaneous forms, thus challenging resource allocation and medication accessibility. The flagellate protozoan Leishmania (L.) donavani is responsible for visceral leishmaniasis (VL) in Iraq. (2) This parasite undergoes an indirect life cycle, utilizing female flies of the genus Lut zomyia as vectors, with humans serving as intermediate hosts. Transmission occurs through sand fly bites, blood transfusions, transplacental routes, and exceptionally, organ transplantation. (3).

In this region, the disease is widespread, affecting 13 countries. In 2019, the Middle East reported 96% of the cases, with Venezuela, Paraguay, Argentina and Colombia, (4) following suit. Subclinical forms of visceral leishmaniasis (VL) are common among individuals infected with L. (L.) donovani, showing no apparent signs or symptoms. However, approximately 25% of those infected may experience fever, pancytopenia, dry cough, diarrhea, hepatosplenomegaly, and weight loss. (5) These symptoms can lead to hemorrhages and secondary bacterial infections, posing significant risks, especially for immunosuppressed patients. (6).

Visceral leishmaniasis tends to manifest opportunistically in immunosuppressed patients, particularly those undergoing treatment with immunosuppressive drugs like TNF-α antagonists and corticosteroids.(7,8) These medications hamper the production of cytokines by TH1 lymphocytes, which are crucial for combating L. (L.) donovani infection.(9) In regions where VL is endemic, immunosuppressed individuals face an elevated risk of mortality if coinfected with COVID 19 , leading to exacerbation of their clinical condition.(10) In such cases, immune system depression hampers the inflammatory response, resulting in inadequate stimulation of IFN-γ production in reaction to viral infection. (11) .Visceral leishmaniasis, caused by the protozoan L. donovani, exhibits symptoms such as fever, malaise, and arthralgia, which can sometimes overlap with those of COVID-19, making it challenging to distinguish between the two conditions (12).

It is crucial to promptly diagnose visceral leishmaniasis (VL) in immunosuppressed individuals and inhabitants of endemic regions to prevent fatal outcomes. As per Galvão-Castro et al. (13), there is a polyclonal activation of B cells in Visceral Leishmaniasis (VL), this can result in clinical presentation resemble autoimmune disorders. (14) In this particular case, the patient was immunosuppressed due to treatment with medications for rheumatoid arthritis and later pemphigus vulgaris, indicating a heightened risk for developing autoimmune disorders a condition referred to as autoimmune diathesis, necessitating the administration of elevated doses of immunosuppressive medications. (15) . Autoimmune diseases have a complex etiology, influenced by various factors including genetics, immunology, hormones, and the environment. (16).

In the case of the patient with rheumatoid arthritis predisposed to autoimmune conditions, these factors likely played a significant role in the development of pemphigus vulgaris. Another patient, residing in an endemic region and possibly infected with leishmania infantum chagasi through a sand fly bite, may have triggered pemphigus vulgaris activation. Chiossi and Roselino's research supports these findings. (17).

Flores et al. (18) and Qian et al. (19) demonstrated that immunogenic proteins found in sand fly saliva, such as Maxadilan and LJM11, are associated with the present of autoantibodies targeting transmembrane glycoproteins known as desmoglein 1 (Dsg1). This immune response contributes to the onset of the disease. The severity of the condition is evident through severe hepatic impairment and thrombocytopenia, leading to hemorrhage and subsequent hospitalization. The use of elevated corticosteroids doses to manage the disease has led to immunosuppression, exacerbating the severity of visceral leishmaniasis (VL) as outlined in previous research (21).

Likely, the immune response induced by visceral leishmaniasis heightened the patient's susceptibility to subsequent SARS-CoV-2 infection. (22, 23) . Research conducted by Viana et al. suggests that a TH1 response, characterized by the secretion of IFN-γ, TNF-α, and IL-10 by neutrophils, along with TNF-α production by monocytes, plays a crucial role in effectively managing parasitic activation. On the contrary, the lack of a cellular immune response plays a significant role in worsening leishmaniasis. This absence supports the activation of TH2 cells, consequently advancing the disease. (23) (23). As a result, the reduced inflammatory reaction resulted in lower IFN-γ production, which is

essential for an efficient antiviral response (24). This situation contributed to the emergence of a severe COVID-19 case and facilitated the proliferation and spread of the parasite, resulting in multi-organ involvement including the lymph nodes, spleen, bone marrow, and liver. The diagnosis of visceral leishmaniasis (VL) was confirmed through peripheral blood smear analysis combined with a blood cell count. This finding was unexpected, as peripheral blood typically exhibits low sensitivity for AVL diagnosis in immunocompetent patients due to low parasitemia levels (25).

Upon admission to the hospital, the patient presented with severe COVID-19 symptoms, characterized by elevated viral load detected through RT-PCR and pulmonary complications identified via CT scan. Miotti et al. (26) documented the initial case of co-infection involving Leishmania and SARS-CoV-2, resulting in a fatal outcome. Unfortunately, due to the brief hospitalization period and delayed diagnosis of visceral leishmaniasis (VL), treatment initiation was not feasible. Consequently, exacerbated manifestations stemming from both infections led to the patient's demise two days after hospital admission.

The immune response to Visceral leishmaniasis is marked by a CD4+ T cell reaction, leading to the secretion of elevated levels of IL-5 and IFN-γ, which have been linked to asymptomatic L. donovani infection.(27) Increased concentrations of IL-17 and IFN-γ have also been observed in individuals with asymptomatic L. donovani infection (28). Conversely, during the active phase of VL, heightened levels of TNF-α, IFN-γ, IL-6, and IL-10 in plasma have been detected (29). Nevertheless, elevated levels of IFN-γ have been linked to individuals who have been cured of VL or those with asymptomatic infection (30).

COVID-19 has been linked to Leishmania persistence; a phenomenon commonly observed in VL patients. Miotti et al. described two cases of Leishmania-COVID-19 co-infection , both in immunocompromised adult patients. (31) Exposure to leishmanial antigens impacts both innate and adaptive immune responses, as evidenced by the inability of peripheral blood mononuclear cells to generate IFN-γ (32). Up to 2022, three instances of Leishmania-COVID-19 co-infection have been recorded. Additionally, Antonis Pikoulas proposes that Leishmania-COVID-19 co-infection could potentially reactivate previously asymptomatic leishmaniasis (33). Cutaneous leishmaniasis (CL) represents the most prevalent form, with an estimated 600,000 to 1 million new cases annually, often resulting in lasting scars and significant psychosocial repercussions post-recovery (34).

Research conducted on individuals with scars from cutaneous leishmaniasis indicated a notable decrease in the occurrence of COVID-19 morbidity and mortality. (35,36). Significantly, decreased rates of COVID-19 incidence and case fatality have been noted in tropical and subtropical areas during the pandemic. This potential cross-protection, likely mediated by cutaneous leishmaniasis (CL), could elucidate the delayed onset of COVID-19 in endemic countries, presenting notable advantages to developing nations, particularly in the Mediterranean region (37).

The eradication of Leishmania multiplication involves cytotoxic CD8+ T cells, CD4+ helper T cells, and the secretion of IFN-γ. IFN-γ plays a pivotal role in initiating parasite control by stimulating infected macrophages to generate leishmanicidal molecules such as nitric oxide (NO), which can eliminate intracellular parasites (38). Additionally, IFN-γ serves as a critical cytokine for defending against viruses (39). However, prompt IFN responses are imperative for regulating SARS-CoV-2; failure results in viral replication within the lungs, circulation, and extensive tissue damage. Studies investigating SARS-CoV-2 infection have revealed elevated levels of IFN-γ-producing T cells across various patient demographics. (40)

An elevation in IFN-γ levels has been noted in children diagnosed with COVID-19, albeit not to the same extent as in adults, as indicated by several studies. This finding may help explain

why COVID-19 tends to be less severe in infected children. (41)(42)

Typical symptoms like fever, respiratory issues, fatigue, and sudden onset headaches overlap between malaria and COVID-19, which could result in misdiagnosis. Furthermore, crucial immune responses, such as interferons and neutralizing antibodies, may play a role in reducing COVID-19 prevalence in countries where leishmaniasis is common. (43) With SARS-CoV-2 spreading rapidly, it's crucial to comprehend its potential effects on protozoal infections. (43)

In endemic regions, numerous individuals might harbor simultaneous infections of SARS-CoV-2 alongside one or more neglected tropical disease (NTD) pathogens. Such concurrent infections could potentially modify susceptibility to and/or severity of COVID-19.

In summary, the connection between SARS-CoV-2 and leishmaniasis remains unclear and is believed to be linked to immunological factors. Further research is needed to elucidate the mechanisms by which SARS-CoV-2 may trigger visceral leishmaniasis reactivation and the protective mechanisms of cutaneous leishmaniasis against SARS-CoV-2(.50)

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