Research Article

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Co-infection By Leptospirosis and Covid 19: The Role of the Cytokine Storm

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ABSTRACT

Leptospirosis is a bacterial infection caused by the spirochete leptospira interrogans, which is considered a zoonotic disease transmitted by exposure to or direct contact with contaminated soil, water, or urine of animals. The clinical manifestations vary from asymptomatic patients to critical processes with multiple organ failure and risk of mortality. On the other hand, SARS-CoV-2 infection is caused by a new RNA virus transmitted mainly through respiratory droplets that, like leptospirosis, presents manifestations that vary from mild to severe. These two infections, despite their differences in terms of ethology, share a similar pathophysiology in which there is excessive activation of the immune system mediated by cytokines, which through the recruitment of cells, infiltrate organic tissues causing loss of function, acute respiratory distress syndrome and renal failure among others, for this reason, it is important to mention that when evidencing confection by these pathologies the patient's prognosis becomes unfavourable. From this document we seek to review the pathophysiological and immunological mechanisms involved in the response to both infections in order to clarify the inflammatory mediators involved in the so-called "cytokine storm".

KEYWORDS: Leptospirosis; COVID 19; clothing; cytokine storm; SARS-CoV-2

ABBREVATIONS: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TMPRSS2: through trans membrane protease serine 2; TLRs: Toll-like receptors; PAMPs: Pathogen-associated molecular patterns; AP-1: activator protein 1; TNF: tumour necrosis factors; TGF-β: transforming growth factor-β; STAT1: signal transducer and activator. of transcription 1; NSP1: non-structural protein 1

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INTRODUCTION

At the end of 2019 in Wuhan, China, the appearance of a new disease was reported for the first time, which was later called "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2); [1]. The ethology was identified as the presence of an RNA virus belonging to the enveloped single-stranded Coronavirus family, with a diameter of between 60 nm and 140 nm, with peaks of 9 to 12 nm that give it the appearance of a "solar corona" (Figure 1). And that it is composed of 30 to 32 kilogausses, being the largest of all RNA viruses [2,3]. This virus has the bat as a natural reservoir; however, through genetic recombination it can adapt to new hosts, infecting humans through intermediate hosts [4].

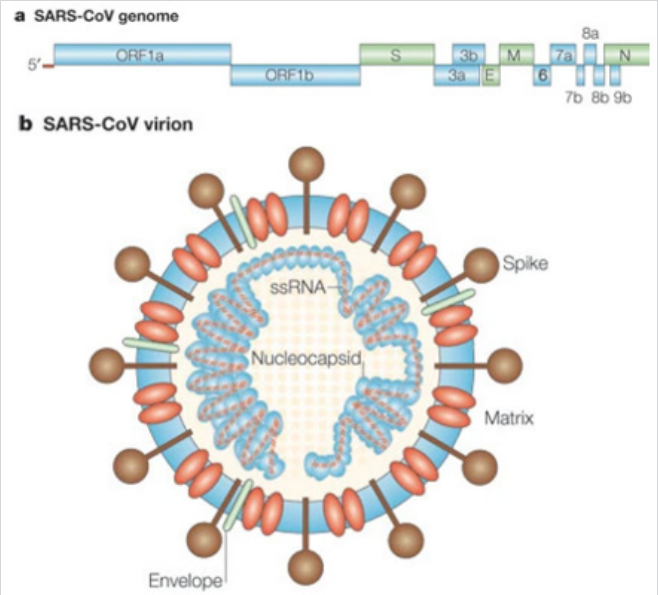

Figure 1: Structure and genome of Sars Cov 2.

After virus inoculation, it binds to receptors on the host cell and through endocytosis or membrane fusion and enters the host cell via the S protein on the viral surface, which binds to the converting enzyme receptor. of angiotensin 2 (ACE-2), which is expressed mainly in lung epithelium, alveolar macrophages and endothelial cells, once bound to it the protein undergoes photolytic cleavage through trans membrane protease serine 2 (TMPRSS2) for fusion of the virus. After membrane fusion, the virus content is released inside the cells of the alveolar epithelium, inside which the viral RNA replicates to synthesize viral proteins [5,6]; (Figure 2).

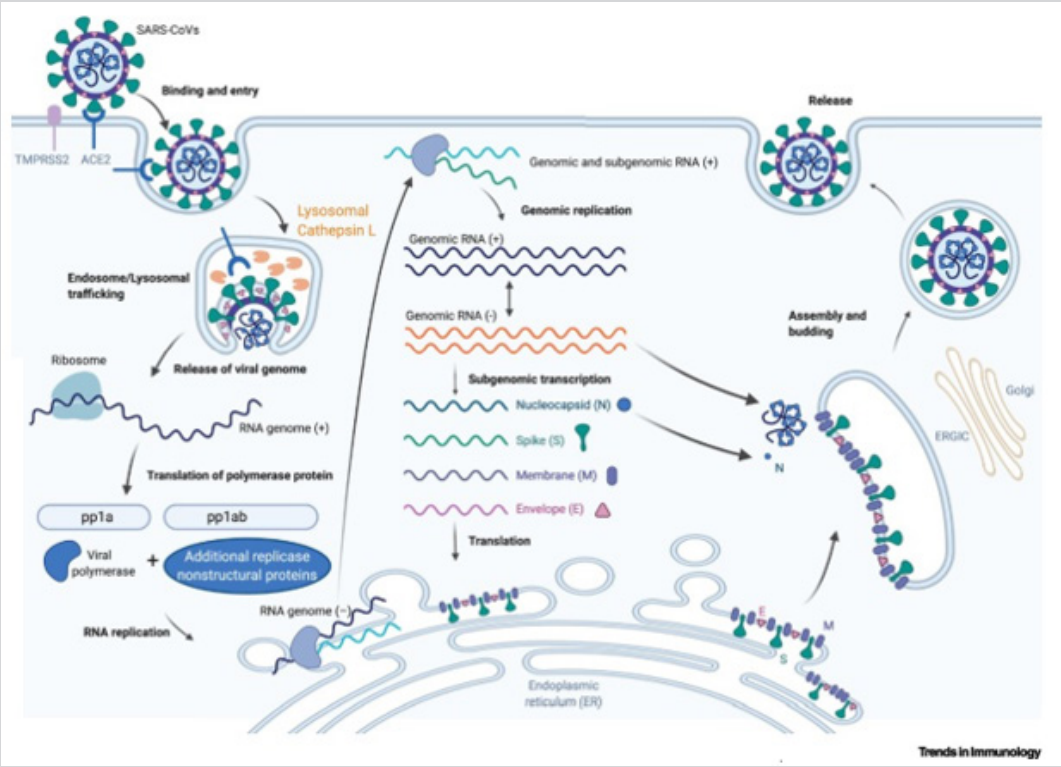

Figure 2: SARS-CoV-2 infection mechanism.

After entering the incubation phase (2 to 14 days) (asymptomatic), the virus infects the nasopharynx and upper respiratory tract with spread to other cells dependent on the interaction between cells with the immune system through cytokine signaling. Detecting abnormal RNA through pattern recognition receptors (PRRs) activates defense factors such as interferon regulatory factor (IRF) and nuclear factor kB (NF-kB) resulting in the induction of type I interferon and III (IFN) and the transcription of primary antiviral defense proteins in addition to the expression of proinflammatory cytokines and chemokines that facilitate the recruitment of immune system cells such as IL-6, tumor necrosis factor (TNF), CCL chemokine ligand (CCL), among others [7-9].

System releases C3a anaphylatoxins. And C5a simultaneously in the endothelium, thus generating the recruitment and amplification of inflammation [10,11].

Due to the particular characteristics of SARS-Cov-2, this immune response that would normally eliminate other viruses is altered and could instead play an important role in the course of the disease towards the most serious and even fatal forms of infection. The same 9 [11,12]; [Figure 3]. Due to the abnormal immune response in the presence of the SARS-Cov-2 virus, it is possible to find other infections concomitant to it, which due to their similar symptoms can be overlooked, a situation that has been previously described in Leptospirosis infection.

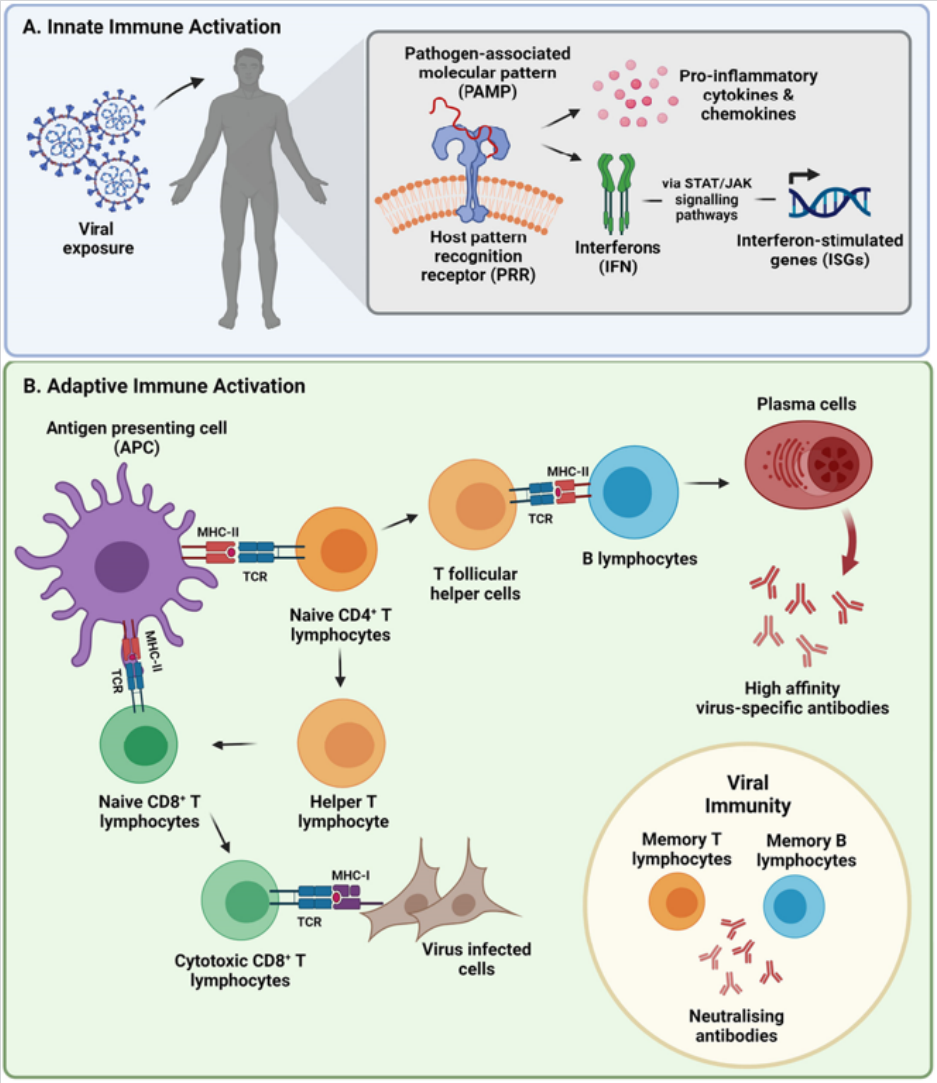

Figure 3: Activation of the immune system in SARS-CoV-2 infection.

Leptospirosis is a zoonotic disease, caused by a bacterium called Leptospira interregna that infects approximately 1 million people a year [13], with the possibility of generating clinical manifestations that vary from mild and even asymptomatic conditions to severe and potentially fatal clinical conditions such as Weil's Syndrome [14,15]. It is transmitted through exposure to or direct contact with soil, water, or urine from animals contaminated with the bacteria. The portal of entry is cuts, abrasions on the skin or oral or genital conjunctivas mucosa [16,17]. After its entry into the mucosa, through proteolysis enzymes, the bacterium is allowed to spread via the haematogenous route, remaining in the bloodstream during the leptospiremia phase [18]. Pathogen infection activates the innate immune system to trigger the inflammatory response via pathogen-associated molecular patterns (PAMPs) recognized by PRRs such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NOD-NLR). These bindings trigger a signalling cascade mediated by NF-kB and activator protein 1 (AP-1), promoting the expression of cytokines, prostaglandins and nitric oxide which in turn increase vascular permeability to allow entry of the immune system [13,19]. The cytokines involved in the attraction of the immune system are mainly IL-1β, IL-6, IL-12, interferon's (IFN) and tumour necrosis factors (TNF).

In addition to the above, the production of immunomodulatory cytokines such as IL-4, IL-10, IL-13 or transforming growth factor-β (TGF-β) has been described, which together counteract the massive response of proinflammatory cytokines in order to to prevent organic damage [20]. Despite this, Leptospira produces proteases such as thermolysin that affect the complement-mediated immune response. In the initial phase of infection, macrophages associated with cytokine activity phagocytise the bacterium, preventing the spread of the infection, while dendritic cells phagocytise the bacterium to play the role of antigen-presenting cells and stimulate the response through the major histocompatibility complex II (MHC-II), in addition dendritic cells express cytokines such as TNF-α, IL-12 and IL-10 [Figure 4]. It is at this point that an exaggerated immune response by the host can cause tissue damage and lead to severe disease [21,22].Stimulating factor and reactive oxygen species in joint action with chemokine such as CCL2, CCL-5, IFNγ-induced protein 10 (IP-10) and CCL3), contributed to its appearance, due to the activation of Th1 lymphocytes as well as Th2. In addition to this, it has been shown that SARS-CoV-2 inhibits the synthesis of type I and III IFN and through non-structural protein 1 (NSP1), accessory proteins ORF 6 and ORF3B induce a dysfunction of the signal transducer and activator. of transcription 1 (STAT1) that generate a decrease in the synthesis of interferon.

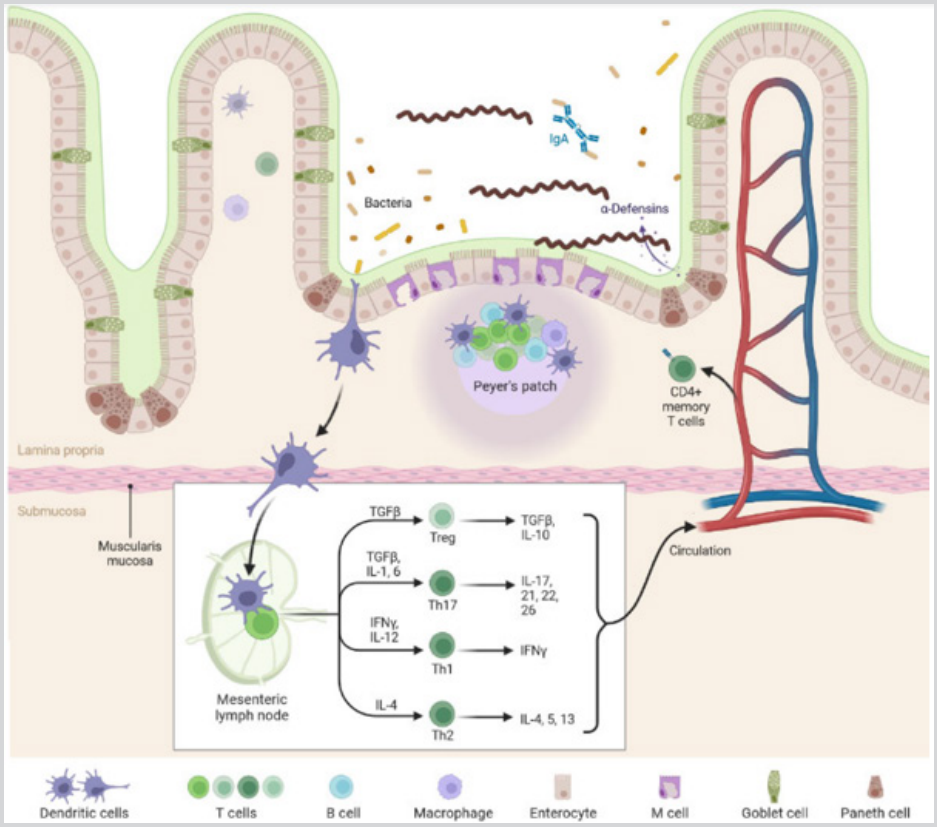

Figure 4: Immune response to leptospirosis infection.

In patients with moderate-severe COVID 19, the cells show a higher expression of chemokine that promote the recruitment of macrophages, mast cells and T lymphocytes [23-27]. Because macrophages express the ACE-2 receptor, which is vital for virus fusion to the cell membrane, their recruitment to the site of infection can promote an increase in viral load and in turn increase the expression of inflammatory cytokines and chemokine. Which in the absence of regulatory cytokines cause damage to lung tissue [7]. Increased cytokines and chemokine excessively attract inflammatory cells resulting in their excessive infiltration into tissue causing lung injury due to induction of apoptosis in epithelial and endothelial cells, IFN-αβ and IFN-γ generate inflammatory cell infiltration through Fas and Fas ligand (FasL) or the TRAIL 5 receptor, which secondarily damages the epithelium and generates vascular leakage and oedema, with secondary hypoxia, being key in the syndrome of acute respiratory distress, as the main cause of death in patients infected by SARS-Cov-2 [1,8]. As evidenced by Mahmud [27] the down regulation of ACE2 induced by the SARS-CoV-2 virus suppresses the immunomodulatory effects making the cytokine-mediated response more prominent and, in addition, the inactivation of DABK induced by the SARS-CoV-2 virus. ACE2 altered by the virus generates a proinflammatory effect (ACE2/DABK/bradykinin B1) being a promoter of neutrophil recruitment and lung damage that precedes respiratory distress syndrome (Table 1). Which secondarily damage the epithelium and generate vascular leaks and oedema, with secondary hypoxia, being key in acute respiratory distress syndrome, as the main cause of death in patients infected by SARS-Cov-2 [29].

Regarding the similarities between the two pathologies, both leptospirosis and COVID 19 have similar incubation periods, both affect the respiratory system and respiratory distress syndrome is one of its main complications: regarding the symptoms, according to Gupta et al. [30] in patients with confection dyspnoea was the most significant symptom followed by acute kidney injury (AKI), bilirubinemia, leucocytosis and thrombocytopenia. In addition to this, in laboratory parameters there is a greater elevation of procalcitonin. According to Xavier et al. [23] both in the infection by COVID 19 and by leptospirosis, it was evidenced that the cytokine storm correlates with lung injury, multiple organ failure

and severe forms of the disease, a finding that agrees with what was evidenced by Ittyachen [26]. Since both infections cause an exaggerated immune response in the host, it was found that confection is associated with poor results compared to those with a single isolated infection [30], so it is vitally important, especially in tropical regions, to establish clinical suspicion. in the presence of symptoms such as fever, fatigue and pulmonary manifestations [15,24] and despite the fact that leptospirosis requires antibiotic management, in those patients with progression to acute respiratory distress syndrome, the association of steroids is important in order to modulate the exaggerated immune response and improve the prognosis of patients.

Table 1: Immunological alterations in the different presentations of the disease by COVID 19.

Immunological Event	Asymptomatic - Mild Symptoms	Severe Symptoms	Critics
Viral load	Moderate	Elevated	Very high
Alveolar macrophage	Moderate	Elevated	Very high
Macrophage M1	Moderate	Elevated	Very high
Macrophage M2	Moderate	Elevated	Very high
LI-6	Moderate	High	Very high
Neutrophils	Moderate	Elevated	Very high
Complement System	Moderate	Elevated	Very high
Natural Killer	Moderate	Low	Very low
MHCI - MHCII	Moderate	Altered	Very upset
T-Lymphocytes	Moderate	Low	Very low
The cells	Moderate	Altered / elevated	Altered / very high
Tc-Lymphocytes	Moderate	Low	Very low
B-Lymphocytes	Moderate	Elevated	Very high

CONCLUSION

Both COVID 19 infection and leptospirosis are entities that, despite their different ethology, share a similar pathophysiology that involves activation of the immune system mediated by cytokines, which in the most severe cases of both diseases is poorly regulated, generating a storm of cytokines that infiltrates the endothelium of the organs, generating dysfunction of the same, it is therefore that confections by both pathologies simultaneously has been associated with a poor progression of the same towards acute respiratory distress syndrome, this being one of the the main causes of mortality. From this, early identification of both pathologies is important, especially in tropical countries in order to establish early management and reduce the risk of complications.

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