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Human T-lymphotropic virus type 1 and novel coronavirus disease 2019; More complex than just a simple coinfection

Samaneh Sajjadi [a], Sepideh Hejazi [b,*], Sahar Ravanshad [a], Reza Jafarzadeh Esfehani [c,d]

[a] Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Science, Mashhad, Iran
[b] Lung Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Blood Borne Infections Research Center, Academic Center for Education, Culture and Research (ACECR)-Khorasan Razavi, Mashhad, Iran
[d] Stem Cells and Regenerative Medicine Department, Academic Center for Education, Culture, and Research (ACECR)-Khorasan Razavi, Mashhad, Iran

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ABSTRACT

The recent coronavirus disease 2019 (COVID-19) significantly affected many people worldwide, especially those with underlying diseases. While some people with underlying illnesses, including cardiovascular diseases, are more vulnerable to develop severe COVID-19, other populations, including people who have autoimmune diseases, may develop severe diseases similar to the general population. The severity and outcome of COVID-19 are reviewed in individuals with underlying viral diseases, including acquired immune deficiency syndrome and hepatitis, however, some infectious diseases, including human T-lymphotropic virus type 1 (HTLV-1) diseases, is under-reported in the literature. HTLV-1 is a sexually transmitted disease that is endemic in some parts of the world. Infected patients may develop clinical symptoms of HTLV-1 associated myelopathy / tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia (ATL) or may remain asymptomatic during their life. To the best of our knowledge, no clinical studies evaluate the severity and outcomes of SARS-CoV-2 infection in HTLV-1 infected patients. We aimed to review the pathogenesis of both of these viral infections and discuss their similarities in provoking immune responses. Although HTLV-1 infected patients may have had variable degrees of inflammation and immune system dysregulation, the available data is limited to conclude that HTLV-1 infected patients may be more vulnerable to developing severe COVID-19 in contrast to the general population.

1. Introduction

In the last months of 2019, a novel contagious respiratory infection was reported from Wuhan city in China and named coronavirus disease 2019 (COVID-19). During the first months of 2020, the world health organization declared a global pandemic as the SARS-CoV-2 infection spread rapidly worldwide and infected many individuals. Primary reports declared the infection fatality rate of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to be 0.68%, with considerable variation across different regions of the world (Meyerowitz-Katz and Merone, 2020). The disease had different manifestations in every individual, varying from mild respiratory symptoms to severe respiratory distress requiring mechanical ventilation (Goshayeshi et al., 2021). The disease is usually manifested by early manifestations including fever and new-onset cough, while other respiratory tract symptoms develop gradually (Grant et al., 2020; Mair et al., 2021). The disease may manifest by gastrointestinal symptoms in some patients, and neurologic disorders have been reported in the literature (Goshayeshi et al., 2021; Nasserie et al., 2021; Cha et al., 2020). The infected patients develop a variable degree of abnormal laboratory markers, including increased C reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, and decreased albumin, eosinophils, and lymphopenia (Zhang et al., 2020; Saeedian et al., 2021).

Moreover, various immunologic abnormalities, including increased secretion of inflammatory cytokines, may occur in different stages of the disease. Increased inflammation and the cytokine storm resulting in end-organ damage are considered the leading underlying cause of death in COVID-19 patients. However, the disease does not have the same clinical

Abbreviations: COVID-19, coronavirus disease 2019; HTLV-1, human T-lymphotropic virus type 1; ATL, adult T cell leukemia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HBV, Hepatitis B virus; HCV, Hepatitis C virus; CMV, cytomegalovirus; HAM/TSP, HTLV-1 associated myelopathy – tropical spastic paralysis; HBZ, HTLV-1 bZIP factor; INFs, Interferons; ACE2, Angiotensin-converting enzyme 2; Th, T helper; Treg, regulatory T cell; CTLs, cytotoxic T lymphocytes.

* Corresponding author at: Department of Internal Medicine, Ghaem Hospital, Ahmad-Abad Street, Mashhad, Iran.
E-mail address: Hejazis@mums.ac.ir (S. Hejazi).

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manifestations and outcomes in every individual (Jafarzadeh-Esfehani et al., 2020). Similar to many other infectious diseases, it has been demonstrated that specific populations may be more susceptible to become infected and develop severe diseases. Early studies reported that underlying diseases including diabetes, hypertension, cardiovascular diseases, chronic kidney, liver, and pulmonary diseases are related to disease severity and mortality among hospitalized patients (Shams et al., 2021; Baradaran et al., 2020).

However, the characteristics and clinical outcomes of coinfection of SARS-CoV-2 with other infectious viruses are not widely studied. It has been demonstrated that coinfection with SARS-CoV-2 and respiratory infections, including Influenza A and *Chlamydia pneumoniae,* is commonly detected, and viral coinfection is associated with higher mortality than bacterial coinfection COVID-19 outbreak (Alosaimi et al., 2021). A recent systematic review and meta-analysis on the epidemiology of SARS-CoV-2 and Human Immunodeficiency Virus (HIV) demonstrated that HIV-infected patients are at higher risk of SARS-CoV-2 infection and mortality from COVID-19 (Ssentongo et al., 2021). Similarly, the adverse effect of SARS-CoV-2 infection in patients with previously diagnosed viral diseases, including hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV), has been previously discussed in the literature (Aghbash et al., 2021). However, the effect of prior infection with human T-lymphotropic virus type 1 (HTLV-1) is not addressed in the literature. Therefore, in the present review, we discussed the underlying immunological similarities of SARS-CoV-2 and HTLV-1 infection to evaluate the impact of coinfection with SARS-CoV-2 infection in HTLV-1 disease.

1.1. HTLV-1 infection and its impact on human health

HTLV-1 is a sexually transmitted disease introduced in 1980 and has been recently considered a health topic by the World health organization (WHO) (Poiesz et al., 1980). The widespread of this viral infection and its considerable mortality and morbidity in some countries raised medical scientists' awareness worldwide (Einsiedel et al., 2016; Gruber, 2018). There is no specific treatment available for the disease, and prevention from the transmission has been suggested as an effective strategy in managing the disease and reducing the mortality rate (Marino-Merlo et al., 2020). Although HTLV-1 is the most common oncogenic virus, the carriers are usually unaware of the disease and transmit the infection (Gessain and Cassar, 2015). Regarding the considerable number of asymptomatic carriers, determining the true prevalence of the disease is not possible, and it has been estimated that approximately 20 million people are carrying the virus worldwide (Gessain and Cassar, 2015). The prevalence of the disease has been reported to be higher in specific regions, including Japan and the African continent, and it has been estimated that only 5% of the infected people may become symptomatic and develop the disease during their lifetime (Gessain and Cassar, 2015). HTLV-1 associated myelopathy – tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia (ATL) are the most common diseases associated with HTLV-1 (Oliveira et al., 2018; Barros et al., 2013). The main target of the virus is the immune cells, and impaired immune function is responsible for the development of both ATL and HAM/TSP (Oliveira et al., 2018). While the infected patients are considered to have different severity of immune system dysregulation, prevention of infection with other viral or bacterial infections is strongly recommended (Gessain and Cassar, 2012).

1.2. Pathogenesis of HTLV-1

Cellular immunity is the main target of HTLV-1. The suppressor T cells, including T-Helper lymphocyte type 2 (Th2) and regulatory T lymphocyte (Treg) in healthy individuals, are the main reservoirs of the virus. HTLV-1 patients face reduced level of IgE, IL-4 and IL-5 and, therefore, are more vulnerable to developing mite and helminth infections (Guerreiro et al., 2005). Individuals infected or carrying HTLV-1 develop different severity of immunodeficiency. While it has been demonstrated that HTLV-1 carriers have subclinical disease courses, patients with ATL develop more severe immunodeficiency phenotypes and are more vulnerable to different infections. Impaired production of T lymphocytes and adaptive immunity is the major underlying cause of abnormal immune phenotype in HTLV-1 patients (Miyazato and Matsuoka, 2014). The immunologic abnormalities in HTLV-1 patients can be summarized in three ways, mainly depending on the HTLV-1 bZIP factor (*HBZ*) and *Tax*. *Tax* and *HBZ* are the primary HTLV-1 genes crucial for viral transcription and T cell proliferation (Yasunaga, 2020). Regardless of viral transcription, *Tax* is a trans activator of oncogenic pathways, and *HBZ* can change the immunophenotype of infected immune cells, enhancing their proliferation (Yasunaga, 2020). During the infection, *HBZ* induces unstable overexpression of *FOXP3*, leading to an inflammatory phenotype by producing inflammatory mediators, including INF-y. Moreover, *HBZ* impairs cellular immunity by inhibiting the production of Th1 cytokines. *Tax* induces expression of C-C Motif Chemokine Ligand 22 (*CCL22*) attracting non-infected Treg suppressing the immune response for clearing the infection (Miyazato and Matsuoka, 2014). Therefore, the infected patients develop a dysregulated immune system alongside increased inflammation.

Regarding the recent COVID-19 outbreak, the coinfection of viral diseases, including HTLV-1 with the SARS-CoV-2 infection, has been neglected in the literature (Araujo and Martin, 2020). While the coinfection of SARS-CoV-2 with other infectious diseases has been estimated to occur in half of the deaths from COVID-19 and people living with HTLV-1 (PLHTLV-1) are at increased risk of mortality from viral coinfection, it has been hypothesized that HTLV-1 carriers and those who develop HAM/TSP or ATL would be at increased risk of developing lethal COVID-19 (Lai et al., 2020; Journo and Martin, 2021). Up to now, the SARS-CoV-2 infection in HTLV-1 infected patients is not studied; however, both diseases share somehow similar immunologic properties, and interpretation of their mutual effect could be interpreted based on their pathogenesis.

1.3. SARS-CoV-2 and HTLV-1 effect on immune system dysregulation

Interferons: The SARS-CoV-2 invades the human body by replicating in the upper respiratory tract, and an appropriate host response reduces the chance of the development of COVID-19. Even though a healthy and intact lung epithelium acts as a barrier for various viral and bacterial infections, the production of antiviral interferons (INFs) is among the early responses of the innate immune system (Cheemarla et al., 2021). The role of IFN-γ as an initiator of the immune response during early invasion is essential for the development of COVID-19. IFN-γ secreted from Th1 cells, fight against the virus, and signal other immune cells to the respiratory tissue (Heuberger et al., 2021). Moreover, the mucosal membrane increases the expression of Angiotensin-converting enzyme 2 (ACE2) receptors in response to the increased level of IFN-γ and further facilitates the entry of more viruses into the epithelial tissue (Heuberger et al., 2021). An increase in ACE2 receptor expression as a receptor for SARS-CoV-2 increases the chance of becoming more severely infected (Pinto et al., 2020). However, the expression of ACE2 receptor in HTLV-1 patients has not been studied, and further experimental studies are warranted in this population. It has been demonstrated that some viral pathogens, including the SRAS-CoV-2, delay the INF response in the respiratory mucosa as late secretion response after the establishment of the virus is much less effective in preventing disease development (Cheemarla et al., 2021). Therefore, we may conclude that SARS-CoV-2 driven inflammation could be a double-edged sword in developing COVID-19 (Heuberger et al., 2021). The more active and robust the immune response, the more replication and virus release (Heuberger et al., 2021). Therefore, specific clinical conditions linked to overproduction of IFN-γ, including the advanced age and chronic inflammatory states, may suffer from more severe forms of COVID-19 (Heuberger et al., 2021).

Although T lymphocytes are the main target of HTLV-1, other immune cells, including neutrophils, may become infected by the virus (Guerreiro et al., 2005). Spontaneous neutrophil activation is a marker of immune perturbation in HTLV-1 patients, and it has been demonstrated that these patients have increased levels of IFN-γ and activated neutrophils in contrast to the healthy population (Guerreiro et al., 2005). Guerreiro et al. reported that the increased neutrophil activation is mainly due to an increased level of IFN-γ or directly because of the HTLV-1 rather than the number of neutrophils (Guerreiro et al., 2005). The *Tax* gene trans-activates other genes leading to proliferation and activation of T cell lymphocytes (Guerreiro et al., 2005). The spontaneous activation increases IFN-γ production (Guerreiro et al., 2005). Clinical studies demonstrated similar findings indicating that INF-y is higher in HAM/TSP and asymptomatic carriers than in healthy individuals (Bidkhori et al., 2020). Moreover, it has been reported that HTLV-1 patients have an increased CD25+ CD45Ro+ and immune cells producing INF-y compared to healthy subjects (Coutinho et al., 2014). Asymptomatic carriers have more efficient cytotoxic T lymphocytes immune response than those developing clinical symptoms (Rajaei et al., 2019). These findings are similar to COVID-19 patients with different severity, indicating that patients with severe disease have increased levels of IFN-γ (Kwon et al., 2020). Therefore, preexisting increased level of IFN-γ in HTLV-1 patients may interfere with the development of infection during the early stages of the disease, depending on the severity of the underlying infection.

Cellular immunity: It has been demonstrated that symptomatic and severe COVID-19 patients have increased viral load, neutralizing antibodies and CD4 and CD8 responses. On the other hand, asymptomatic patients tend to have higher level of CD3 cells, CD19 B lymphocytes, colonal expansion of CD4 T lymphocyte populations, and natural killer cells (Boyton and Altmann, 2021). T cell lymphocytes of patients with asymptomatic infection produce a lower level of TNF, IFN-γ, and IL-6 than patients with symptomatic COVID-19 (Boyton and Altmann, 2021). Therefore, even the asymptomatic patients have increased CD4 T lymphocytes, producing various pro-inflammatory cytokines. Regardless of the severity of the COVID-19, every affected patient face an imbalance in immune cell counts and functions. The imbalance between T helper (Th17) and Treg has been considered the underlying mechanism of many autoimmune diseases. Moreover, it has been demonstrated that viral replication is directly associated with the pro-inflammatory response of Th17 (Tarokhian et al., 2018; Lee, 2018). Among severe COVID-19 patients, an imbalance of TH17/Treg cells results in an exaggerated immune response (Wu and Yang, 2020). During COVID-19, shifting from CD4+ T-cell balance from Treg cells to Th17 cells induces pro-inflammatory cytokine response and increased inflammation (Wu and Yang, 2020). During severe COVID-19 infection, the number of activated and effector T cells increases resulting in exhaustion and depletion of senescent T cells (Fenoglio et al., 2021). Fenoglio et al. demonstrated that both CD4+ and CD8+ lymphocytes express PD-1 associated with the exhaustive phenotype (Fenoglio et al., 2021). However, they also reporteded that despite expressing PD-1, these cells also produce considerable inflammatory mediators, including IFN-γ (Fenoglio et al., 2021). Moreover, the number of senescent T lymphocytes producing inflammatory cytokines, including IL-6, increases even during mild COVID-19 (Fenoglio et al., 2021). Also, increased IL-6 levels have been reported in viral infections, including HCV and CMV infections similar to the SARS-CoV-2 infection (Aghbash et al., 2021). On the other hand, in some viral diseases including HBV infection, a decrease in CD4+ and CD8+ T cells results in abnormal cytokine production, including IL-2 and TNF-a, resulting in decreased antiviral responses during SARS-CoV-2 infection (Aghbash et al., 2021). While CD8+ T cells require IL-2 for expansion, individuals who lose early production of IL-2 from CD4+ T cells fail to control viral replication (Brooks et al., 2005). During HTLV-1 infection, preexisting increased production of IL-2 and TNF-a may alter SARS-CoV-2 replication.

However, in some viral infections, including HTLV-1, the role of Th17 in the development of infection depends mainly on the stage of the viral disease and host immune system (Tarokhian et al., 2018). During viral infections, depletion of these cells from peripheral blood resulted in control of the infection. However, there are conflicting reports regarding the role of Th17 in HTLV-1 infection. In HAM/TSP patients, there is a reduced number of Th17 cells and decreased number of CD4+ T-cell (CD39+ CD25+) with immunosuppressive (Leal et al., 2013). The latter increases CD4+ T-cell secreting IL-2, TNF-α, and INF- γ during viral infection (Leal et al., 2013).

On the other hand, Th1 cells and Th1/Treg are increased in HAM patients compared to HTLV-1 asymptomatic carriers indicating a more pro-inflammatory response in HAM patients (Goon et al., 2002). Among the HTLV-1 infected patients, activation of Th1 response is a double edge sword. Based on many unknown and known factors includign viral load, the increased Th1 response may produce a robust antiviral cytotoxic T cell response and control of viral infection, and on the other hand, the increased pro-inflammatory mediators may damage uninfected cells (Glowacka et al., 2013). Although there is no evidence regarding the effect of SARS-CoV-2 infection in HTLV-1 infected patients, it may be hypothesized that the SARS-CoV-2 infection has different effects in patients with different severity of HTLV-1 disease. While patients with severe COVID-19 show an increased population of Th17 cells and decreased Treg cells, it is unclear whether HTLV-1 infected patients with decreased Th17 and increased CD4+ T-cell (CD39+ CD25+) develop severe disease. In the same vein, late seroconversion is common among HTLV infected patients that highlights the need for using molecular techniques alongside of other diagnostic tests. It's not clear either SARS-CoV-2 infection before or after the seroconversion has the same effect as delayed seroconversion and ineffective cellular immunity promote clonal proliferation of HTLV-1 transformed cells (Kalfaoglu et al., 2021).

Moreover, severe COVID-19 patients have impaired *FOXP3* expression and hyper activated T cells (Satou et al., 2012). Among patients with defective *FOXP3* expression, the negative feedback of IL-2 response cannot be regulated, and immune system activation occurs (Satou et al., 2012). It has been reported that *FOXP3* express in 80% of ATL patients, and defective expression of *FOXP3* is also seen in HTLV-1 patients (Miyazato and Matsuoka, 2014). Also, HTLV-1 induces expression of *FOXP3* in T cells of HAM/HSP patients and HTLV-1 carriers (Miyazato and Matsuoka, 2014). Although some HTLV-1 infected patients may have increased CD4+ FOXP3+ cells, some of these cells with different expression levels of *CD45RA* are non-suppressive and induce inflammatory phenotype (Toulza et al., 2008). It has been demonstrated that HTLV-1 patients had an increased level of *Foxp3* in CD4+ cells, and only a tiny proportion of these cells express the Tax protein (Tendler et al., 1991). Moreover, there is a negative correlation between the lysis of infected CD4+ by CD8+ cells and the amount of CD4+/FoxP3+/Tax- cells (Tendler et al., 1991). The FoxP3+ cells can suppress the cytotoxic T lymphocytes (CTLs) (Tendler et al., 1991).

Other inflammatory mediators: The abnormal level of other inflammatory mediators has been addressed in the literature, and there are some similarities between HTLV-1 and SARS-CoV-2 infections. For example, HAM/TSP and HTLV-1 carriers have increased levels of INF-y and TNF, similar to those with severe COVID-19 infection (Kwon et al., 2020; Gomes et al., 2021). It has been demonstrated that IL-7 is increased in HAM/TSP patients compared to the healthy population (Monneret et al., 2020). However, severe COVID-19 infected patients are reported to have decreased IL-7, and IL-7 has been considered a possible therapeutic option for severe patients (Hasan et al., 2021; Chen et al., 2021). It has been demonstrated that COVID-19 severity is positively correlated with IL-18 (Bidkhori et al., 2020). Among HLTV-1 infected patients, the increased viral load has been positively correlated with IL-18 levels (Tjan et al., 2021). Similar to patients with severe COVID-19, carriers and HAM/TSP patients have decreased levels of IL-12 compared to healthy subjects (Yang et al., 2021). It has been hypothesized that an increased level of IL-12 during the early phase of

COVID-19 is responsible for the prevention of virus separation. Therefore, the reduced IL-12 during the early phase of the coinfection with SARS-CoV-2 may result in faster disease development (Cojocaru et al., 2010).

1.4. SARS-CoV-2 infection in specific populations

Severe COVID-19 infection is associated with impaired Th1 response and lower Th1/T follicular helper cells (TFH), indicating a redirection from CD4+ differentiation to TFH. In the same vein, Th17- and Th2-oriented TFH cells suggest developing an inflammatory/autoimmune disease that cannot control the infection. Therefore, many researchers consider COVID-19 an autoimmune disorder with inflammatory properties. It has been reported that more than one-fourth of patients with an autoimmune disorder tend to develop other autoimmune diseases (Akiyama et al., 2021). In the same way, a recent systematic review and *meta*-analysis demonstrated that COVID-19 disease is more common among individuals with an autoimmune disease in contrast to the general population, and there was a relationship between using corticosteroids and the development of COVID-19 (Quaresma et al., 2015). However, the risk of developing severe disease or mortality from COVID-19 was not more significant among those with autoimmune diseases than the general population or people with other diseases (Quaresma et al., 2015). Considering HTLV-1 infection as a disease modulating immune function, HAM/TSP patients are more likely to develop autoimmune diseases, including lupus erythematosus and rheumatoid arthritis (Marcus et al., 2021).

On the other hand, HTLV-1 infected patients may be also be considered to have an immunodeficient disease. While most of the underlying immunopathology of HTLV-1 disease is mainly because of T lymphocyte dysfunction, a recent report suggested that patients with immunodeficiency syndromes are not at significantly increased risk of developing COVID-19 or increased mortality (Babaha and Rezaei, 2020; Delavari et al., 2021). However, the immunodeficiency during HTLV-1 infection seems different from those reported in previous studies, as cellular immunity is the main target of the HTLV-1 rather than humoral immunity Araya et al., 2011. While effective cellular immunity and T cell activation are mandatory for control of the SARS-CoV-2 infection, HTLV-1 infected patients with dysregulated T cell function and increased IFN associated cytokines could be at increased risk of developing more severe COVID-19.

2. Conclusion

Our current knowledge about the outcomes of COVID-19 in HTLV-1 infected patients is scarce and needs further research. Based on the available evidence, the effect of SARS-CoV-2 infection on patients in different stages of the HTLV-1 infection, including asymptomatic patients, carriers, or patients with HAM/TSP or ATL, cannot be interpreted. Although the SARS-CoV-2 and HTLV-1 infections do not have similar pathogenesis, the abnormal cellular immunity in HTLV-1 patients highlights disease prevention strategies for these patients as a high-risk group during the COVID-19 outbreak. While patients infected with HTLV-1 have a variable degree of immune dysregulation, future studies should evaluate the effect of SARS-CoV-2 on HTLV-1 carriers, patients with HAM/TSP, or ATL separately.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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