An Overview of Human T-Lymphotropic Virus Type 1 Lung Injury

Ápio Ricardo Nazareth Dias1,2, Luiz Fábio Magno Falcão1,3† and Juarez Antônio Simões Quaresma1,2*†

1 Health and Biologic Center, State University of Pará, Belém, Brazil, 2 Tropical Medicine Centre, Federal University of Pará, Belém, Brazil, 3 University of São Paulo, São Paulo, Brazil

Previous studies have demonstrated the development of pulmonary impairment in individuals infected with human T-lymphotropic virus type 1 (HTLV-1). Complications, such as alveolitis and bronchiectasis, were found in individuals who developed tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP-HAM) due to chronic inflammation. These patients exhibited increased levels of lymphocytes (CD4+ and CD25+), cytokines (IL-2, IL-12, and IFN-γ), inflammatory chemokines (MIP-1α and IP-10), and cell adhesion molecules (ICAM-1) in the bronchoalveolar lavage fluid, with the result of chronic inflammation and lung injury. The main lesions observed at Chest high-resolution computed tomography were centrilobular nodules, parenchymal bands, lung cysts, bronchiectasis, ground-glass opacity, mosaic attenuation, and pleural thickening. It can lead to progressive changes in pulmonary function with the development of restrictive and obstructive diseases. Recent studies suggest a causal relationship between HTLV-1 and pulmonary diseases, with intensification of lesions and progressive decrease in pulmonary function. This summary updates a previous publication and addresses the general lack of knowledge regarding the relationship between TSP-HAM and pulmonary disease, providing direction for future work and the management of these individuals.

Keywords: HTLV-1, HAM/TSP, chest CT, pulmonary disease, pulmonary function

INTRODUCTION

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus with an incidence of approximately 20 million worldwide, with a higher prevalence in Africa, Japan, and America (1). In Latin America, Brazil has a high prevalence, mainly in the states of Maranhão, Bahia and Pará (2, 3). The virus is the etiological agent of tropical spastic paraparesis/HTLV-1-associated myelopathy (TSP-HAM) and adult T-cell lymphoma (ATL) (4).

There is a relationship between HTLV-1 and pulmonary diseases in individuals with TSP/HAM, these individuals exhibit pulmonary diseases with characteristics of lymphocytic inflammatory infiltrates (5–8). Individuals with ATL develop pneumopathies caused by opportunistic infections due to ATL cell proliferation, which leads to a low expression of naive T cells, increased expression of FoxP3+ and interleukin-10 (IL-10), and an increased number of Treg cells (CD4+ and CD25+), which suggests the development of immunodeficiency (9). Furthermore, HTLV-1 carriers, because
of a mild immunodeficiency characterized by a low expression of IL-1b and IL-17 interleukins (10) have a higher risk of infection with Mycobacterium tuberculosis (11, 12), high mortality rates, and an increased likelihood of hospitalization for pulmonary tuberculosis (13) (Figure 1).

TSP-HAM individuals have a major risk to development of lung injuries, being the major radiological findings bronchiectasis, centrilobular nodules, and ground-glass opacities (14–16); lesions are attributable to chronic inflammation resulting from the effects of the virus in situ (17–20). Lung inflammation may be the causal agent of lung volume obstruction, flow limitation, and the development of restrictive and obstructive lung diseases in TSP-HAM patients (17, 19, 21).

Recent publications, including a systematic review and a cohort study developed by our research group, have suggested a causal relationship between HTLV-1 infection, the development of lung injury (20, 22), and the evolution of lung disease in HTLV-1 infected individuals (23). This scientific literature review aims to update our previous publication (19) with these recent findings on HTLV-1 pulmonary disease and the existing lack of knowledge regarding the effects of this infection on the respiratory system.

PATHOPHYSIOLOGY OF TSP-HAM RELATED PULMONARY DISEASE

Immune Response

The chronic pulmonary inflammation in TSP-HAM individuals can be caused by an exacerbated immune response. The elevation of T lymphocytes in the bronchoalveolar lavage fluid (BALF) of HTLV-1 individuals pulmonary involvement is characterized by a cytokine storm, with high expression of soluble IL-2 receptors (IL-2R), as well as, interleukins (IL-2, IL-12), and interferon (IFN-γ) (8, 24, 25).

A selective T-cells infiltration occurs in the lungs, with an accumulation of HTLV-1-specific CD8+ T cells in BALF, and the occurrence of specific immune responses in lung tissues (7, 26). The high-expression of lymphocytes, and its interaction with cytokines (IL-2, IL-12 and IFN-γ) and chemokines (MIP-1α and IP-10) leads to chronic pulmonary inflammation and lung injury (25, 27). It is known that HTLV-1 infection induces an abnormal frequency and phenotype of FoxP3+CD4+T cells (28). The higher expression of Foxp3 mRNA in the BALF of patients with HTLV-1-related lung diseases suggests the involvement of regulatory T cells in the pathogenesis of lung injuries (8).

Chronic Inflammation

TSP-HAM individuals exhibit alveolitis, a high proviral load (29), and increased levels of cytokines and inflammatory chemokines in the BALF in comparison to asymptomatic carriers (8, 25, 27, 30). The lymphocytosis in the lungs results in a higher expression of proinflammatory cytokines (31–33).

Lymphocytosis and the presence of HTLV-1 provirus in the BALF (7), elevated levels of macrophage inflammatory protein (MIP-1α), interferon g-induced protein kDa (IP-10), and chemokines are linked with the activation and recruitment of inflammatory cells (30, 34). The pulmonary epithelium expresses intercellular adhesion molecule-1 (ICAM-1), a chemokine that facilitates the adhesion of neutrophils to cells of the respiratory epithelium (30, 34) and induces lung tissue injury and chronic inflammation in situ (16) (Figure 2).
Lung Injury
The development of lung injuries, mainly bronchiectasis and centrilobular nodules are related to alveolitis and bronchiolitis (27, 35). These lung injuries cause scarring in the lung tissue and fibrosis, which can induce traction bronchiectasis in a cycle of chronic lung injury (17). TSP-HAM individuals have a bronchiectasis relative risk of 8.4 (95% CI 2.7-26.1, p = 0.0002) in comparison to asymptomatic carriers and other HTLV-1 related diseases (16). Other imaging findings reinforce the existence of a causal relationship between pulmonary diseases and HTLV-1; the centrilobular nodules indicate peripheral bronchiolitis and alveolitis at sites of injury, probably due to lymphocytosis (7). Ground-glass opacity is characteristic of pneumonia and has a higher prevalence among patients with HTLV-1 than in the general population (15).

CT FINDINGS
Chest high-resolution computed tomography is the gold standard method to observe lung injuries. Previous studies have shown that the characteristic lesions observed in HTLV-1 infected individuals are bronchiectasis (8, 16, 17, 24, 25, 27), bronchiectasis is characterized by bronchial dilatation (36). Other lung injuries, such as centrilobular nodules, ground-glass opacity, pleural thickening, and parenchymal bands, were also found (14, 15, 17, 36) (Figure 2).

The studies about HTLV-1 related lung diseases shows that these abnormal CT findings are more common in TSP-HAM individuals than asymptomatic carriers (16, 17, 23), their higher frequency of lung injury can be explained by their major in situ inflammatory processes (8, 17, 24, 25, 27) and is associated with high HTLV-1 proviral load (37, 38). These individuals also exhibit three or more lesions types, and a combination between bronchiectasis and other lesions in HRCT, such as pleural thickening, parenchymal bands, interlobular septum thickening, centrilobular nodules, and parenchymal bands (17). A follow-up study shows the intensification of these lesions, and an increase in the frequency of four types: ground-glass opacity, bronchiectasis, centrilobular nodules, and pleural thickening between TSP-HAM individuals previous evaluated (23).

PULMONARY FUNCTION
Individuals with TSP-HAM can develop changes in pulmonary function, due to pulmonary inflammation and lung lesions, which may progress to obstructive or restrictive lung disease (17, 21). An analysis of pulmonary function in these individuals showed a reduction in vital capacity (VC) and forced expiratory volume in one second (FEV1), these alterations are related to restrictive lung disease, and airway obstruction, respectively (17).

Other findings were a reduction in peak expiratory flow, which is very sensitive in most diseases that affect the lungs, alteration in the 50% Forced expiration flow (FEF50%), common alteration in the early stages of obstructive lung disease, and reduction in 25-75% Final Expiratory Flow (FEF 25-75), that is linked to histological changes in the peripheral airways and obstruction (17, 21, 23).

Finally, a reduction in maximum voluntary ventilation (MVV) was observed (17, 21, 23). Changes in MVV may be present both in diseases that affect the lungs and in adverse conditions that alter the mobility of the rib cage (39). HTLV-1 individuals tend to have decreased lung values and this may be
related to the development of motor changes related to myelopathy associated with TSP-HAM (17).

The downward trend in VC, FVC, and FEV1, with the maintenance of a normal ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) values, may indicate the development of restrictive lung disease; however, this restriction must be confirmed by measuring lung values and documenting total lung capacity below normal limits (40). The MVV measure is related to the level of physical activity in daily life and is applied to individuals with chronic obstructive pulmonary disease (41). Abnormal CT findings, with airway and lung scarring lesions observed in HTLV-1 individuals, associated with the low mobility that affects patients with TSP-HAM may play a key role in pulmonary function changes (17).

A follow-up study showed a decrease in lung function related to lung injuries observed by chest CT; the patient group with lung injury showed a tendency of decline in VC, FVC, FEV1, FEF25–75%, and MVV values (23). As shown in previous studies, lung injury and altered lung function are more common in TSP-HAM individuals (17, 21), with a major degree of lung involvement among those who developed TSP-HAM. It is possible that bronchiectasis and pleural thickening play key roles in the development of obstructive and restrictive lung disease, respectively (17).

**FUTURE DIRECTIONS**

The studies with Chest CT imaging shows that lung lesions are more common in TSP-HAM patients than asymptomatic individuals, suggesting that lesions at the pulmonary level follow the systemic inflammatory process. HTLV-1 infection is a systemic inflammatory disease characterized by chronic evolution. Observational studies conducted on these individuals do not allow for the determination of the pathophysiological mechanisms and their links to specific clinical presentations of patients infected with HTLV-1.

The development of lung lesions in HTLV-1 infected individuals has been described in several studies, but some points, such as the actual mechanism of action of the virus in the pulmonary system, the role of epigenetic factors and inflammatory imbalance in lung injury, and the death rate among those infected, remain unclear. These studies have a limited scope and describe only isolated clinical cases. They do not answer the question about the evolution and physiopathology of HTLV-1-related pulmonary disease.

There are a few prospective studies, such as follow-up and case-control studies, but they suggest a progressive characteristic of HTLV-1 pulmonary disease, and more studies are necessary to better understand the mechanisms of pulmonary involvement. Screening of these patients is very important to show the evolution of chronic inflammation at the pulmonary level, parenchymal lesions, and the development of new lung lesions in individuals with TSP-HAM. Periodic pulmonary evaluation is needed to improve the clinical management of these individuals. This review intends to update a review previously published by our research group, contributing to providing directions for future investigations.

**AUTHOR CONTRIBUTIONS**

AD, LF, and JQ contributed to conception and design of the study. AD, and LF wrote the sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

**ACKNOWLEDGMENTS**

The authors would like to thank the support of the “Programa de Apoio a Publicação Qualificada”.
Overview of HTLV-1 Lung Injury

12. Grassi MFR, dos Santos NP, Lirio M, Kritski AL, Almeida MCC, Santana LP, et al. Tuberculosis Incidence in a Cohort of Individuals Infected With Human T-Lymphotropic Virus Type 1 (HTLV-1) in Salvador, Brazil. BMC Infect Dis (2016) 16:491. doi: 10.1186/s12879-016-1428-z.

13. Bastos ML, Santos SB, Souza A, Finkmoe A, Bispo O, Barreto T, et al. Influence of HTLV-1 on the Clinical, Microbiological and Immunological Presentation of Tuberculosis. BMC Infect Dis (2012) 12:199. doi: 10.1186/1471-2334-12-199.

14. Okada F, Ando Y, Yoshitake S, Yotsumoto S, Matsumoto S, Wakasaka M, et al. Pulmonary CT Findings in 320 Carriers of Human T-Lymphotropic Virus Type 1. Radiology (2006) 240:559–64. doi: 10.1148/radiol.2402050886.

15. Yamashiro T, Kamiya H, Miyara T, Gibo S, Ogawa K, Akamine T, et al. CT Scans of the Chest in Carriers of Human T-Cell Lymphotropic Virus Type 1: Presence of Interstitial Pneumonia. Academ Radiol (2012) 19:952–7. doi: 10.1016/j.acra.2012.03.020.

16. Honarbakhsh S, Taylor GP. High Prevalence of Bronchiectasis is Linked to HTLV 1-Associated Inflammatory Disease. BMC Infect Dis (2015) 15:1–7. doi: 10.1186/s12879-015-0002-0.

17. Falcão LFM, Falcão ASC, Sousa RCM, Vieira WB, Oliveira RTM, Normando VMF, et al. CT Chest and Pulmonary Functional Changes in Patients With HTLV Associated Myelopathy in the Eastern Brazilian Amazon. PloS One (2017) 12:e0186055. doi: 10.1371/journal.pone.0186055.

18. Einsiedel L, Pham H, Wilson K, Valley R, Turpin J, Bangham C, et al. Human T-Lymphotropic Virus Type 1c Subtype Provaliral Loads, Chronic Lung Disease and Survival in a Prospective Cohort of Indigenous Aus- tralians. PloS Neg Trop Dis (2018) 12:e0006281. doi: 10.1371/journal.pntd.0006281.

19. Dias ARN, Falcão LFM, Falcão ASC, Normando VMF, Quaresma JAS. Human T Lymphotropic Virus and Pulmonary Diseases. Front Microbiol (2018) 9:1879. doi: 10.3389/fmicb.2018.01879.

20. Normando VMF, Dias ARN, Silva ALSE, Pinto DS, Santos MCS, Rodrigues CL, et al. HTLV-I Induces Lesions in Pulmonary System: A Systematic Review. Life Sci (2020) 256:117797. doi: 10.1016/j.lfs.2019.117797.

21. Normando VMF, Falcão LFM, Vieira WB, Oliveira K, Santos M, Fazzii H, et al. Changes in Lung Function in Patients With Human T-Cell Lymphotropic Virus (HTLV) Associated Myelopathy Residents in the Eastern Brazilian Amazon. ERS J (2016) 48:PA4442. doi: 10.1183/13993003.cgress-2016.PA4442.

22. Einsiedel L, Chiong F, Jersmann H, Taylor GP. Human T-Cell Leukaemia Virus Type 1 Associated Pulmonary Disease: Clinical and Pathological Features of an Under-Recognised Complication of HTLV-1 Infection. Retrovirology (2021) 18:1. doi: 10.1186/s12977-020-00543-z.

23. Dias ARN, Vieira WB, Normando VMF, Franco KMVS, Falcão ASC, de Sousa RCM, et al. Computed Tomography With 6-Year Follow-Up Demonstrates the Evolution of HTLV-1 Related Lung Injuries: A Cohort Study. PloS One (2021) 16(12):e0261864. doi: 10.1371/journal.pone.0261864.

24. Sugimoto M, Nakashima H, Matsumoto M, Uyama E, Ando M, Araki S. Pulmonary Involvement in Patients With HTLV-1 Associated Myelopathy: Increased Soluble IL-2 Receptors in Bronchoalveolar Lavage Fluid. Am Rev Respir Dis (1989) 139:1239–35. doi: 10.1183/ajrccm.139.6.139.1239.

25. Yamazato Y, Miyazato A, Kawakami K, Yara S, Kaneshima H, Saito A. The Lungs of Human T-Lymphotropic Virus Type 1c Infection: A Cross-Sectional Survey in Remote Aboriginal Communities. Clin Infect Dis (2021) 73:e1498–506. doi: 10.1093/cid/ciaa1401.

26. Miller RK, Hankinson JATS, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of Spirometry. Eur Respir J (2005) 26:319–38. doi: 10.1183/09031936.05.0003405.

27. Haynes MJ. Basic Spirometry Testing and Interpretation for the Primary Care Provider. Can J Respir Ther (2018) 54:4. doi: 10.29390/cjrt-2018-017.

28. Pitta F, Takaki MY, Oliveira NH, Sant’anna TJP, Fontana AD, Kovelis D, et al. Relationship Between Pulmonary Function and Activity in Daily Life in Patients With COPD. Respir Med (2008) 102:2123–7. doi: 10.1016/j.rmed.2008.03.004.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher. Copyright © 2022 Dias, Falcão and Quaresma. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.