

Clinical profile of human T-lymphotropic virus type I: a forgotten infection in pediatrics

Juliana Mejía-Mertel^{1,*}, Nicolás Gómez-Banoy², Juan Pablo Rojas-Hernández^{3,4}, Eduardo Gotuzzo-Herencia⁵

Summary

The Human T-lymphotropic virus type 1 (HTLV-1), a retrovirus with oncogenic properties, affects around ten to twenty million people worldwide. The most common disorders associated with HTLV-1 infection are T-cell leukemia/lymphoma (ALT) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Studies have reported other clinical manifestations in HTLV-1 seropositive patients, including inflammatory disorders, co-infections with opportunistic agents, and pulmonary diseases.

Objective: Here, we aim to describe a cohort of juvenile patients with confirmed HTLV-1 infection that showed clinical manifestations other than neurological symptoms.

Methodology and patients: Retrospective analysis of clinical data describing background and clinical findings of 12 juvenile patients with confirmed HTLV-1 infection, attended during January 2018 to February 2020 in a pediatric referral hospital in Cali, Colombia.

Results: 11 out of 12 patients were from Colombia's Pacific coast, 10 suffered from significant nutritional deficiencies. Six exhibited dermatological findings, 3 compatible with infective dermatitis. None of the cases exhibited clinical or laboratory findings suggesting ALT or HAM/TPS. Eight patients had structural lung disease assessed by chest Computed Tomography (CT) scans; 4 of them tested positive for galactomannan antigen in bronchoalveolar fluid suggesting pulmonary aspergillosis, and 2 others exhibited a positive PCR testing for tuberculosis. Three patients were diagnosed with autoimmune disorders; 1 patient with Crohn's Diseases, 1 case of autoimmune thrombocytopenic purpura, and a patient with Vogt-Koyanagi-Harada syndrome (non-granulomatous uveitis).

Conclusions: There is a broad range of clinical manifestations in pediatric HTLV-1 patients, and the clinician should consider structural pulmonary disease, opportunistic co-infections and autoimmune disorders in the diagnostic algorithm.

Key words: Human T-lymphotropic virus 1, retroviridae, child, HTLV-1 Infections.

Perfil clínico del virus linfotrópico humano tipo I: una infección olvidada en pediatría.

Resumen

El Virus Linfotrópico de células T humanas tipo 1 (HTLV-1), retrovirus con propiedades oncogénicas, afecta alrededor de 10-20 millones de personas mundialmente. Las manifestaciones más comúnmente asociadas a HTLV-1 incluyen leucemia/linfoma de células T (ALT) y mielopatía asociada a HTLV-1/ paraparesia espástica tropical (HAM/TSP). Estudios han reportado otras manifestaciones clínicas en pacientes positivos para HTLV-1, incluyendo enfermedades inflamatorias, coinfecciones con gérmenes oportunistas y enfermedad pulmonar. El **objetivo** es describir clínicamente una cohorte de pacientes pediátricos con infección por HTLV-1 confirmada que presentan manifestaciones clínicas diferentes a síntomas neurológicos. **Metodología y pacientes:** Análisis retrospectivo de historia clínica describiendo procedencia y hallazgos clínicos en 12 pacientes con infección por HTLV-1 confirmada, atendidos durante el periodo de Enero de 2018 a Febrero de 2020 en un hospital pediátrico de referencia en Cali, Colombia. **Resultados:** Once de 12 pacientes procedían de la costa Pacífica Colombiana, 10 con deficiencias nutricionales significativas. Seis mostraron compromiso dermatológico, 3 compatibles con dermatitis infectiva. Ningún paciente presentó hallazgos clínicos o paraclínicos sugestivos de ALT o HAM/TPS. Ocho pacientes presentaron enfermedad pulmonar estructural evidenciada por TAC de tórax; 4 de ellos con antígeno galactomanan positivo en lavado broncoalveolar, sugiriendo aspergilosis pulmonar, y otros 2 resultaron con PCR positiva para tuberculosis. Tres pacientes presentaron enfermedades autoinmunes concomitantes: uno con Enfermedad de Crohn, uno con Púrpura Trombocitopénica Autoinmune, y un paciente con Síndrome de Vogt-Koyanagi-Harada. **Conclusiones:** Existe un amplio rango de manifestaciones clínicas en pacientes pediátricos con HTLV-1, considerando enfermedad pulmonar estructural, coinfecciones oportunistas y enfermedades autoinmunes dentro del algoritmo diagnóstico.

Palabras clave: Virus linfotrópico humano de células T tipo 1, retrovirus, niños, infecciones por HTLV-1.

1 Department of Pediatrics, Libre University sectional Cali, Valle del Cauca, Colombia.

2 Weill Center for Metabolic Health and Division of Cardiology, Department of Medicine, Weill Cornell Medicine, New York, NY, USA.

3 Department of Pediatrics, Division of Infectious Diseases, Club Noel Children's Clinic Foundation, Cali, Valle del Cauca, Colombia.

4 Department of Epidemiology, Libre University sectional Cali, Cali, Valle del Cauca, Colombia.

5 Department of Internal Medicine, Division of Tropical and Infectious Diseases, Peruana Cayetano Heredia university, Lima, Perú.

* Autor para correspondencia.

Correo electrónico: drecalde5552@cue.edu.co

Universidad Libre Sede Valle del Lili Cra. 109 #No. 22 -00. Tel (2) 5240007

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Introduction

Human T-lymphotropic virus type 1 (HTLV-1) is member of the *Retroviridae* family and it is classified as an oncovirus¹. It was isolated in 1980 making it the first human retrovirus to be identified². HTLV-1 infection has been mainly studied in the adult population as the causative agent of T-cell leukemia/lymphoma (ALT)^{3,4} and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)⁵. The prevalence of HTLV-1 infection varies broadly depending on the demographic region, affecting predominately intertropical regions in Africa, Japan, Melanesia, Australia, and South America (Chile, Perú, Brazil, Ecuador and Colombia)⁶⁻⁸. The Pacific coast of South America is known to have the highest prevalence of HTLV-1 infection, as described in demographic distribution studies in Perú⁹ and Colombia¹⁰, and it further affects afro-descendant and indigenous communities^{11,12}. It is estimated that 10 to 20 million people worldwide are infected^{5,6}, although the majority remain asymptomatic. Similar to other retroviruses, screening for the infection can be done with enzyme immunoassay or by a particle agglutination test. Confirmation tests include indirect immunofluorescence assays and Western Blot¹³. The modes of transmission for HTLV-1 include mother-to-child transmission, primarily through prolonged breast-feeding; sexual transmission; and transmission with contaminated blood products, which underlines the importance to test blood products for this particular virus^{14,15}.

Traditionally, HTLV-1 infection has been associated with low morbidity, since only 5% of HTLV-1 infected individuals develop ALT or HAM/TSP⁵. However, studies have shown that HTLV-1 seropositive individuals may present with a broad range of clinical manifestations, including inflammatory syndromes (uveitis, thyroiditis, and alveolitis), neurological symptoms not explained by myelopathy (polyneuropathy, myositis, dysautonomia), and opportunistic co-infections (strongyloidiasis, tuberculosis, and aspergillosis)⁷. Some studies have even shown that HTLV-1 infection may be associated with clinical depression and nutritional deficiencies^{16,17}. However, the vast majority of patients that are HTLV-1 positive remain asymptomatic, and the precise mechanisms underlying the development of symptoms in a subgroup of patients remain to be determined¹⁴.

Compared to the adult population, studies focused on pediatric/juvenile HTLV-1 infection and its clinical manifestations are scarce. Most reports describe the development of neurological symptoms directly associated with HAM/TSP in children¹⁸⁻²⁰. Another common finding is infective dermatitis, which serves as a marker for the development of neurological manifestations in the pediatric population⁵. Pulmonary symptoms and radiological findings associated with HTLV-1 infection have been reported in adult cohorts, mainly parenchymal abnormalities, including thickening of bronchovascular bundles, ground-glass opacity and bronchiectasis²¹⁻²³. However, these pulmonary findings have not been extensively studied in the pediatric population. Here, we aim to clinically describe

a cohort of juvenile patients with confirmed HTLV-1 infection and no neurologic symptoms, that presented with a high rate of pulmonary disease and opportunistic co-infections. It is important for clinicians to consider the wide variety of clinical manifestations in pediatric HTLV-1 seropositive patients and their potential pulmonary compromise.

Methods

Patients and diagnosis

A descriptive, retrospective cohort study was conducted in our referral pediatric hospital in Cali, Colombia. It included all pediatric patients (1 to 18 years of age) diagnosed with HTLV-1 infection, between January 2017 to February 2020.

Clinical suspicion of HTLV-1 infection was raised based on a high-risk demographic background (African-Colombian and indigenous patients), along with clinical manifestations suggesting immunocompromise, nutritional deficiencies, inflammatory disorders or chronic pulmonary diseases. Screening for HTLV infection was performed with ELISA serological testing and later confirmed with a Western Blot exam.

Data and analysis

The patients demographic and clinical data were collected from medical records and institutional databases between January 2017 to February 2020.

Patient Evaluation

The clinical history and laboratory tests from patients with confirmed HTLV-1 infection by Western Blot were examined. Age of diagnosis and region of origin was assessed. Nutritional status was determined according to the Centers for Disease Control and Prevention (CDC) classification²⁴. All patients had a complete blood count, peripheral blood smear and clinical assessment of lymph nodes to screen for ALT. The clinical history, including anamnesis and physical exam, were reviewed to assess potential neurological manifestations compatible with HAM/TSP. Associated diseases and potential opportunistic infections were also studied. Three consecutive stool tests were performed to rule out *Strongyloides* coinfection. An HIV ELISA test was performed to test coinfection with this virus. Patients presenting with respiratory symptoms and/or sepsis were initially studied with a conventional chest radiography and/or chest computed tomography scan. If parenchymal damage was observed in imaging studies, a fibrobronchoscopy with bronchoalveolar lavage was performed. Several studies were carried out in the bronchoalveolar fluid, including a galactomannan test, tuberculosis PCR, film array, bacterial and fungal cultures. Those presenting with manifestations of inflammatory diseases were assessed according to their clinical findings. Inflammatory Bowel Disease (IBD) was confirmed with colonoscopy and intestinal biopsy. The diagnosis of autoimmune thrombocytopenic purpura with persistent thrombocytopenia rulling out malignancy by flow cytometry. The diagnosis of Vogt-Koyanagi-Harada syndrome was made by a retinologist after ocular angioresonance evaluation.

Ethics statement

This study and the review of medical records were submitted to and approved by the medical ethics committee of the Club Noel Children's Hospital Foundation on the date February 20th 2020.

Results

Demographic and Clinical Features

Twelve patients with confirmed HTLV-1 infection were included in this study, seven males and five females (Table 1). Eleven patients were originally from and resided in the central and southern regions of the Colombian Pacific coast. Ten patients had underweight per BMI calculation according to the CDC index.

Importantly, none of the patients showed clinical or laboratory signs of ALT. Moreover, none of the individuals presented with neurological symptoms and their physical exam did not exhibit abnormalities suggestive of HAM/TSP. Regarding dermatological symptoms, six out of the twelve patients presented findings (four with infective dermatitis and two with scabies).

In terms of HTLV-1- associated diseases and opportunistic infections, none of the patients had a positive HIV ELISA test, and stool tests were all negative for *Strongiloides*. Most patients (eight) presented with respiratory symptoms such as coughing with sputum, dyspnea and respiratory distress. Ini-

tially, chest X-rays were performed, showing signs of chronic pulmonary disease such as bronchiectasis, pneumatocele, reticulonodular opacities. Posteriorly, chest CT scans were performed to further characterize these lesions, showing chronic inflammation, bronchiectasis, and subpleural bullae as the major findings (Figure 1). Given the degree of pulmonary compromise, additional testing was carried out to rule out potential pulmonary co-infections. Four out of eight patients with structural lung disease and respiratory symptoms had positive galactomannan test in (cut off > 0.5) suggesting pulmonary aspergillosis; interestingly, none of them had a positive serologic test to diagnose systemic aspergillosis. Additionally, two patients exhibited positive gene PCR testing for *Mycobacterium tuberculosis* in bronchoalveolar fluid. All fungal cultures were negative. One of the patients died from pulmonary sepsis.

Regarding other clinical manifestations and inflammatory diseases, one patient presented with weight loss, bloody stools, intermittent diarrhea and fever, ruling out an infectious etiology by repeated stool examination and stool culture. A colonoscopy and intestinal biopsy finally revealed histologic findings compatible with IBD, specifically Crohn's disease.

Other patient presented with acute fever and general symptoms that progressed to acute visual loss with a neurological clinical exam revealing II and III cranial nerves compromised.

Table 1. Clinical characteristics of HTLV1 patients in present study

Case	Age at diagnosis	Genre	Place of origin	Underweight (BMI)	Presenting symptoms	Lung damage	Pulmonary Coinfection	Autoimmunity	Dermatologic findings	Neurologic findings
1	14 years old	Male	Buenaventura, Valle de Cauca	Yes 14kg/m ²	Recurrent respiratory symptoms, failure to thrive	Yes	Pulmonary aspergillosis	No	No	No
2	8 years old	Female	Mosquera, Nariño	Yes, 11kg/m ²	8 months of respiratory symptoms, weight loss	Yes	Pulmonary aspergillosis	No	No	No
3	10 years old	Female	Buenaventura, Valle del Cauca	Yes 12.9kg/m ²	1 month of respiratory symptoms, weight loss	Yes	Pulmonary tuberculosis	No	Infective dermatitis	No
4	8 years old	Male	Buenaventura, Valle del Cauca	Yes 12.4kg/m ²	Recurrent respiratory symptoms, failure to thrive	Yes	Pulmonary tuberculosis	No	No	No
5	16 years old	Male	Timbiquí, Cauca	Yes 14.2kg/m ²	Respiratory symptoms, weight loss	Yes	None	No	Infective dermatitis	No
6	6 years old	Female	Buenaventura, Valle del Cauca	Yes 13.2kg/m ²	1 year respiratory symptoms and skin lesions	No	Bacterial pneumonia	No	Infective dermatitis	No
7	6 years old	Male	Tumaco, Nariño	Yes 13.4kg/m ²	Bloody stools since 1 year of age, failure to thrive	Yes	None	Crohn's Disease	Scabies	No
8	7 years old	Female	Buenaventura, Valle del Cauca	Yes 14kg/m ²	3 years of respiratory symptoms	Yes	Pulmonary aspergillosis	No	Infective dermatitis	No
9	16 years old	Male	Buenaventura, Valle del Cauca	No 26kg/m ²	12 years of respiratory symptoms	Yes	Pulmonary aspergillosis	No	No	No
10	1 years old	Male	Medio San Juan, Chocó	Yes (W/H: -2 SD)	Thrombocytopenia and failure to thrive	No	N/A	No	Scabies	No
11	12 years old	Female	Cali, Valle del Cauca	No 23.4kg/m ²	Headache and acute loss of vision	No	N/A	Vogt Koyanagi Hadara Syndrome	No	No
12	1 years old	Male	Buenaventura, Valle del Cauca	Yes (W/H: -3 SD)	3 days of respiratory symptoms	No	N/A	No	No	No

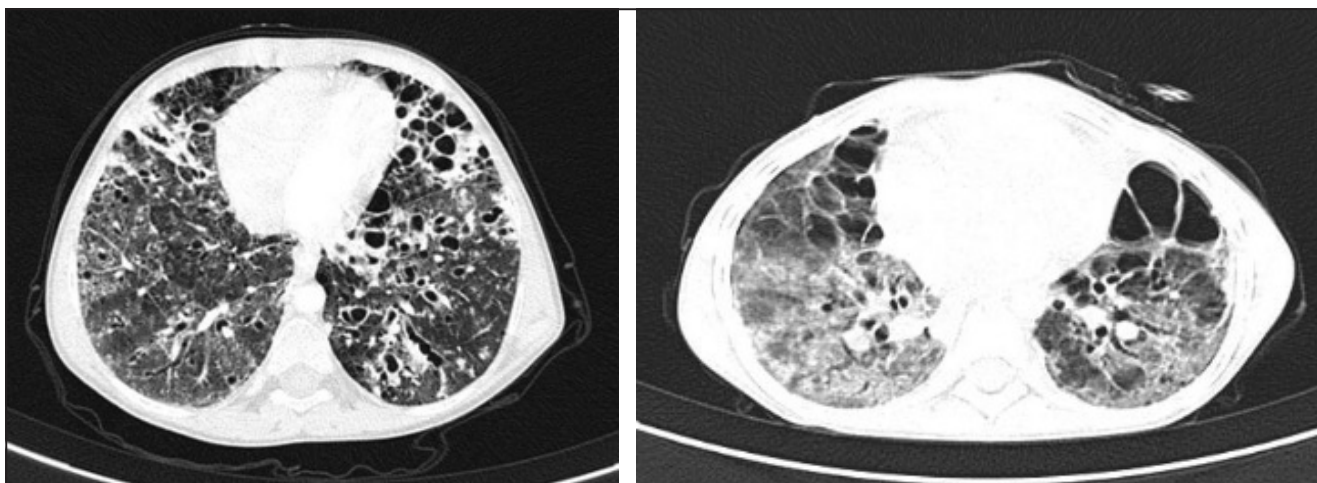


Figure 1. Chest CT scan with chronic pulmonary damage of a patients coinfectd with aspergillosis.

Image A. Radiological findings described as ground-glass opacity diffusely distributed in both lungs with multiple bronchiectasis involving predominantly lung bases. Cystic images diffusely distributed in both lungs, some subpleural and other centrilobular.

Image B. Radiological findings described as ground-glass opacity diffusely distributed in both lungs, septal enlargement, cystic bronchiectasias predominantly in the upper lobe, subpleural bullae mainly in the apex.

Infectious causes were ruled out by CSF culture and meningeal PCR (film array), then, assessed with ocular angiogram with a later evaluation by a retinology specialist concluding severe non granulomatous bilateral panuveitis, optic nerve edema, multifocal retinal detachment.

Finally, another patient presented with a history of long-lasting hospitalization in the pediatric intensive care unit due to extreme thrombocytopenia without adequate response to corticosteroids, also ruling out other autoimmune diseases, malignancy and other causes of acquired immunodeficiency.

Discussion

In the present study, we describe the clinical presentation and diagnostic testing of twelve pediatric patients with confirmed infection by HTLV-1. Our main observation was that none of the patients exhibited signs, symptoms or laboratory findings suggesting ALT or HAM/TSP, the two main entities associated with HTLV-1 infection, but rather presented with respiratory symptoms and were found to have an important degree of structural pulmonary disease. Similar to previous reports in the literature, infective dermatitis was a frequent finding in these pediatric patients²⁵. Another important observation was that most individuals in this cohort presented with nutritional deficiencies and underweight, which could be directly associated to chronic HTLV-1 infection or a risk factor for it. It is important to note the origin of these patients and the difficult socioeconomical conditions in the Colombian pacific coast as a bias. For most patients the clinical suspicion for HTLV-1 infection was only raised after a torpid clinical course and recurrent visits to the emergency department in other institutions.

Mechanistic studies suggest HTLV-1 associated inflammatory disease may be due to a genetically determined inefficient T-cell response to the infection^{21,26}. Recently, pulmonary complications associated to HTLV-1 infection, such as alveolitis and

bronchiectasis, were reported in an Australian indigenous community and a Japanese adult cohort^{21,23}. However, to the best of our knowledge, there are no published reports of HTLV-1 associated lung disease in children. We found eight out of twelve HTLV-1 seropositive patients presented with respiratory symptoms and had a clear evidence of structural pulmonary lesions in their chest CT scans, consisting of interstitial damage, bronchiectasis and subpleural bullae. Further research and reports are warranted in the pediatric population to alert clinicians of pulmonary complications in these patients. Also, future studies should focus on establishing risk factors that could predispose to lung lesions in the context of pediatric HTLV-1 infection.

The few reports that have studied the association between HTLV-1 and tuberculosis have been carried out in countries where both infections are endemic. A study in Brazil found that in adult population there is a threefold risk of acquiring pulmonary tuberculosis when there is an underlying HTLV-1 infection²⁷. Consistently, we found that two out of eight patients in our cohort had pulmonary tuberculosis and important pulmonary compromise. Both HTLV-1 and tuberculosis are neglected diseases associated to social vulnerability, however, the mechanism driving the increased susceptibility of developing tuberculosis in the HTLV-1 infected patient is still unknown. The other opportunistic-like agent we found in the bronchoalveolar fluid of our patients was *Aspergillus spp.* To the best of our knowledge, there are currently no reports of pulmonary aspergillosis in pediatric patients with HTLV-1 infection. Pulmonary aspergillosis can definitely accentuate the pulmonary inflammation and scarring, worsening the child's prognosis. We suggest that these two opportunistic infections (tuberculosis and aspergillosis) should be considered when evaluating pulmonary symptoms in a HTLV-1 seropositive pediatric patient, since they are both susceptible to treatment. An association between HTLV-1 and Strongyloidiasis and/or HIV has been widely described²⁸; however, we did not find co-infection with these agents in our study.

Finally, HTLV-1 has been associated to the development of autoimmune diseases in adults, including Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjögren's Syndrome, uveitis, and thyroiditis⁷. The biological mechanism behind this correlation is still being studied; current reports suggest a loss of tolerance to self-antigens and cell function modification mediated by the HTLV-1 infection²⁹. Interestingly, we found three patients expressing different types of autoimmune disease, one presented with Crohn's Diseases, another with autoimmune thrombocytopenic purpura, and the other was diagnosed with Vogt-Koyanagi-Harada syndrome (granulomatous uveitis).

In conclusion, most of the published literature regarding HTLV-1 focuses on the adult population, and the studies carried out in the pediatric population mostly concentrate on neurological or dermatological manifestations of this infection. It is important for the clinician to keep an open mind and consider alternative manifestations of HTLV-1 infection, including pulmonary disease, opportunistic co-infections, and inflammatory disorders. Furthermore, HTLV-1 infection has not been yet included in the list of neglected diseases, and we believe this should be addressed in order to improve detection and treatment. An early diagnosis can lead to better care and quality of life for pediatric patients. It is also crucial to diagnose this disease in childhood and potentially identify the mode of transmission, which is in many cases mother-to-child. This could lead to better control of this neglected infection that affects predominantly vulnerable population in low-income countries.

Ethical disclosures

Protection of human and animal subjects. No experiments were performed in animal nor humans.

Confidentiality of data. Patient's data were anonymized

Competing interests. None declared.

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Ethical approval. This research was approved by the Ethics Committee of the University.

Conflict of interest. The authors have no conflicts of interest to declare.

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