

Diseases caused by human T-lymphotropic virus type 1 (HTLV-1)

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ABSTRACT

INTRODUCTION: Human T-lymphotropic virus type 1 (HTLV-1) belongs to the Retroviridae family (genus *Deltaretrovirus*) and is directly involved in carcinogenesis. The HTLV-1 genome is represented by plus-strand RNA, which is transcribed into proviral DNA and then integrated into the genome of the host cell. After integration, HTLV-1 is present in the cells in the form of a provirus. As in the case of the human immunodeficiency virus, the main targets of HTLV-1 are CD4⁺ T lymphocytes. The virus is transmitted sexually, through blood transfusion, and breastfeeding by biological fluids – sperm, blood, and breast milk. The epidemiology of HTLV-1 remains a mystery: clusters of high endemicity are often located near areas where the virus is virtually absent.

AIM: To analyze and discuss the clinical picture, diagnostics, and treatment of diseases caused by HTLV-1.

METHODS: A literature search was conducted in the databases PubMed, eLIBRARY.ru, and cyberleninka.ru using the keywords: “HTLV-1” + “diseases”, “HTLV-1” + “diagnosis”, “HTLV-1” + “epidemiology”, “HTLV-1” + “treatment”, “HTLV-1” + “Russia” in English and Russian languages. The primary search was conducted for papers published in 2020–2024.

RESULTS: HTLV-1 infection is associated with diseases such as T-cell leukemia/lymphoma and myelopathy/tropical spastic paraparesis. HTLV-1 infection causes pathologies in most organs of the human body. Because diseases associated with HTLV-1 are most often asymptomatic, etiological diagnoses are performed at the stage of pathological development or when screening donor blood for pathogens.

CONCLUSION: In this review, we analyzed and discussed the clinical manifestations and course of diseases caused by HTLV-1, their diagnosis, and treatment. The lack of reliable population-based studies on the prevalence of this virus is alarming. In fact, HTLV-1 is diagnosed only in blood donors and pregnant women. Currently, this virus is considered endemic to several territories (Africa, Australia, the Middle East, Japan, etc.) and some indigenous peoples. However, we consider it important to draw the attention of both epidemiologists and clinicians to HTLV-1, given the unprecedented migration flows and international connections in the modern world.

Keywords: human T-lymphotropic virus type 1, diseases, clinic, diagnostics, treatment

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Citation: Radygina LV, Mochalova LV. Diseases caused by human T-lymphotropic virus type 1 (HTLV-1). MIR J 2024; 11(1), 57-69. <https://doi.org/10.18527/2024115769>.

Received: February 6, 2024

Accepted: March 25, 2024

Published: June 5, 2024

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Funding: No additional financial support was received for this work.

Conflict of interests: The authors declare no conflicts of interest.

INTRODUCTION

At least 20 million people are infected with human T-lymphotropic virus type 1 (HTLV-1) worldwide [1]. HTLV-1 is endemic to the islands of Melanesia and southwestern Japan, countries of South America, the Caribbean, Central Africa, and the Middle East, including some areas of Iran [2]. As tourism and economic and political ties with African and Middle Eastern countries expand, this infection become relevant in other regions, including the Russian Federation.

This virus is transmitted through the body fluids of infected individuals. Cases of viral transmission through breast milk, blood, and semen have been described [3].

A study by Takao et al. in 2023 [4] showed that even healthcare professionals in the HTLV-1 endemic Japan have poor knowledge of diseases associated with this virus.

Most HTLV-1-infected individuals are asymptomatic carriers. In 2–5% of infected people, diseases such as adult T-cell leukemia/lymphoma (ATLL), HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), cardiovascular diseases, and uveitis develop 30–50 years after the viral infection [2].

Oncological diseases

ATLL is an aggressive disease caused by dysfunction of CD4⁺ T lymphocytes [5]. CD4⁺ T cells play a central role in the adaptive immunity of the host. HTLV-1 infection leads to impairment of T cells function and differentiation, resulting in their immune evasion. Immune imbalance in ATLL is aggravated by the accumulation of genetic and epigenetic changes in the key genes associated with host immunity [6]. Angiogenesis, which is the formation of new blood vessels, plays a crucial role in carcinogenesis. Even asymptomatic HTLV-1 carriers show increased expression of genes associated with angiogenesis [7]. Inflammatory cytokines and chemokines, including soluble tumor necrosis factor receptor 2 (sTNFR2), which is used as a biomarker of ATLL, are involved in the pathogenesis of ATLL in addition to angiogenesis [8].

To date, no measures have been developed to prevent ATLL. The results of treatment for ATLL in general leave much to be desired: overall survival is 8–55 months [1].

HTLV-1 can cause several other types of cancer. The most common are cervical cancer in women and non-Hodgkin lymphoma (ATLL-non-Hodgkin) in men. The 5-year survival rate of HTLV-1 carriers with non-ATLL neoplasms is 26–47% in women and 22–34% in men [9].

Cardiovascular diseases

Cardiac involvement in patients with HTLV-1 infection is mainly observed in cases of aggressive ATLL. Isolated damage to the heart valve is extremely rare: only three histologically proven cases have been described in patients with ATLL. Differential diagnostics of isolated heart valve lesions associated with ATLL and progressive heart failure is necessary [10].

HTLV-1 is an independent factor in the development of atherosclerosis [11]. Asymptomatic HTLV-1 infection is associated with hypertension, possibly through endothelial activation [12].

Respiratory diseases

Lung damage associated with HTLV-1 infection involves the interstitium, airways, and alveoli. Different clinical presentations, such as interstitial pneumonia, bronchiolitis, or alveolitis, develop depending on the affected lung structures [13].

Bronchioloalveolar disease associated with HTLV-1 infection typically has a chronic, progressive form. Diffuse panbronchiolitis or bronchiectasis is usually revealed in patients using computed tomography (CT), while interstitial pneumonia is sometimes detected. High levels of polyclonal CD4⁺ and CD25⁺ lymphocytes were observed in the bronchoalveolar fluid of the patients, reflecting the infiltration of HTLV-1-infected T cells in the lungs. No HTLV-1-specific antiviral drugs are available to date; therefore, current treatment regimens include corticosteroids, macrolide antibiotics, and pirfenidone [14]. A correlation was found between high HTLV-1 viral load and lung damage with the development of bronchiectasis, as well as higher mortality in this cohort than in the general population [15].

The complications reported in HAM/TSP cases include alveolitis and bronchiectasis. In addition to increased levels of CD4⁺ and CD25⁺ lymphocytes, high concentrations of cytokines (IL2, IL12 and IFN γ), inflammatory chemokines (macrophage inflammatory protein, MIP1 α ; CXCR3-binding chemokine, IP10/CXC10), and cell adhesion molecules (intercellular adhesion molecule 1, ICAM1), which are prognostic markers of chronic inflammation and lung damage, were detected in the bronchoalveolar lavage of these patients [16].

Problems arise in the differential diagnosis of bronchioloalveolar disease associated with HTLV-1 infection and fibrotic chronic hypersensitivity pneumonitis. In this case the results of chest CT scan, lung biopsy, and detection of antibodies for HTLV-1 in bronchoalveolar lavage are critical [17].

Gastrointestinal diseases

The clinical course of ATLL is highly heterogeneous and affects many organs, including the gastrointestinal tract [18]. Gastric, small intestinal and colonic lesions have been reported in patients with ATLL [19]. In the initial stage, ATLL can manifest as isolated acute hepatitis [20].

Skin diseases

HTLV-1 is associated with non-tumor skin diseases [21]. Infectious dermatitis associated with HTLV-1 (IDH), a chronic recurrent infected eczema, has been observed in children [22]. Souza et al. [23] reported erythematous-squamous, exudative, and crusty lesions of the scalp, retroauricular areas, neck, axillae, groin, paranasal and perioral skin, ears, chest, abdomen, and other areas of the body in juvenile IDH, as well as the formation of crusts in the nostrils. The morphology of the lesions and areas affected by IDH in adults and adolescents were similar, with the exception of ankles and inframammary folds affection that was found only in the adult form of the disease. HAM/TSP was diagnosed by the same authors in six adult patients with IDH. Rosa et al. [22] described the progression of IDH in three young patients with ATLL. An infiltrative papular and nodular skin lesions, especially on the forehead, as well as on the lower and upper extremities, and skin rashes on the trunk consisting of non-pruritic erythematous reticulate macules and papules have been described in patients with ATLL, that were initially diagnosed with viral exanthema or drug rash [24]. Acute onset, the absence of previous skin lesions, histomorphological features of dermal and peripheral blood lymphocytes, as well as the patient's geographic location, give hints for the possible diagnosis of ATLL [25].

Fifty percent of adult patients with ATLL exhibit skin involvement. Sawada et al. [26] examined the relationship between skin rash type and survival time in 119 patients with ATLL. For patients with macular rashes, the median survival time was 188.4 months. The median survival times (in months) for patients with other types of skin lesions were as follows: plaque – 114.9, multipapular – 17.3, nodular tumor – 17.3, erythrodermic – 3.0. Thus, erythrodermic type lesions corresponded to the most unfavorable outcome of the disease (with several months survival rate), while spots and plaques corresponded to high survival rates (ten years or more).

Atypical skin lesions delay the diagnosis of ATLL and negatively affect patient survival rates [27]. Screening for HTLV-1 is recommended for patients with infectious

dermatitis, persistent hyperreflexia, gait disturbances, and for those arriving from endemic areas [28].

Lymphadenopathy

A dermatopathic reaction is a histopathological change in the lymph nodes that usually occurs in patients with inflammatory pruritic skin lesions. Occasionally, the same symptoms are observed in T cell skin lymphomas. Lymph node lesions, including reactive and neoplastic changes, have been reported in HTLV-1 carriers [29].

Chen et al. [30] described two cases of ATLL in adults: the main clinical sign of the disease was massive cervical or mediastinal lymph nodes. It is important to consider this ATLL phenotype in patients arriving from endemic areas, especially if they have hypercalcemia and bone involvement.

Diseases of the musculoskeletal system

A high prevalence of HTLV-1 infection has been observed in patients with rheumatic diseases. Sjögren's syndrome and rheumatoid arthritis (RA) are more common in patients with HAM/TSP than in the general population [31]. HTLV-1 infection may influence the clinical course of rheumatic diseases [32]. In HTLV-1-positive RA patients, symptoms of the underlying disease may progress [33].

Arthritis associated with HTLV-1 infection is relatively common [34]. This arthropathy is clinically characterized by symmetrical polyarthralgia. Enthesophytes in the absence of osteophytes as well as narrowing of the joint space, are revealed by X-ray [35].

Development of tenosynovitis caused by ATLL is rare. Hashimoto et al. [34] described a clinical case of bilateral wrist tenosynovitis and acute ATLL in a 60-year-old woman with RA.

Involvement of skeletal muscles in the pathological process of ATLL is also rare. Gorelik et al. [36] described four such cases, including a rare form of ATLL manifested by an intramuscular calf mass in a 58-year-old man.

Sjögren's syndrome

Sjögren's syndrome is an autoimmune disease that affects the exocrine glands, especially the salivary and lacrimal glands, and leads to a decrease in fluid production in the body [37]. Viruses are a possible cause of this disease. It has been shown that HTLV-1 is involved in the pathogenesis of Sjögren's syndrome [38]. HTLV-1 leads to the destruction of salivary glands, thereby causing dry mouth syndrome [37]. The involvement of HTLV-1 in the development of Sjögren's syndrome has been demonstrated in epidemiological studies [39].

Endocrinological diseases

A high prevalence of hypo- and hyperthyroidism was reported in patients with HTLV-1 infection [40]. HTLV-1 infection was described in thyroiditis [41]. A high HTLV-1 viral load correlates with the incidence of diabetes [42].

Diseases of the genitourinary system

An increased risk of genitourinary tract infections was found in men with a high HTLV-1 viral load [43]. In addition, these patients have a high probability of chronic kidney disease development [42].

One of the main manifestations of HTLV-1-associated HAM/TSP is urinary dysfunction [44]. Thus, urinary dysfunction was observed in 92% of the patients with HAM/TSP and progressed during the 6-year follow-up period. Voiding dysfunction is more pronounced in patients with an impaired gait [45]. Bladder dysfunction has been reported even in patients who do not meet the diagnostic criteria for HAM/TSP [46]. Urinary tract catheterization and administration of mirabegron effectively relieved voiding dysfunction symptoms [45].

Ophthalmic diseases

A close connection between HTLV-1 infection and uveitis was identified through clinical and laboratory studies in the 1980–1990s. Since then, ocular pathologies associated with HTLV-1 infection have been reported continuously. Generally, these pathologies include diseases such as keratoconjunctivitis sicca, interstitial keratitis, optic neuritis, and ophthalmological manifestations associated with ATLL in adults. Intraocular leukemic cell infiltration of the retina in ATLL patients was also described [47, 48].

Sexual transmission of HTLV-1 is considered a cause of uveitis with severe ocular inflammation [49]. The most common clinical presentation of uveitis in HTLV-1 is an intermediate form with varying degrees of vitreous opacities. It can occur in one or both eyes, and its onset can be acute or subacute [50]. Bilateral intermediate uveitis accompanied by symptoms, such as sight impairment and floating opacity, was most often detected in patients infected with HTLV-1. Unilateral anterior uveitis, in combination with blurred and painful eyes, is more common in the uninfected group [51]. HTLV-1-associated intermediate uveitis predominantly occurs in the second half of a patient's life and develops into a chronic form with a favorable prognosis [52]. Systemic complications in patients with HTLV-1-associated uveitis include Graves' disease and HAM/TSP [50]. Approximately 30% of the patients with

HTLV-1-associated uveitis develop secondary glaucoma [53].

Neurological diseases

HAM/TSP is neuroinflammation caused by the proliferation of T cells infected with HTLV-1 [54]. The increased incidence of ATLL in patients with HAM/TSP may be due to the emergence of HTLV-1-infected cells that are more prone to leukemogenesis. This is one of the reasons for the increased risk of ATLL development in patients with HAM/TSP [55].

One of the manifestations of HTLV-1 infection is pain syndrome, and its severe forms are typical of patients with mild symptoms and HAM/TSP. In the first case, HTLV-1-infected patients usually complained of frequent diffuse pain, mainly in the head and neck area, as well as in the lower extremities. These painful attacks are accompanied by enhanced levels of tumor necrosis factor (TNF α) and IFN γ [56]. HAM/TSP is a rare inflammatory disease that causes progressive neurological disorders such as spastic paraparesis, neurogenic bladder, and sensory impairment of the lower extremities [57]. Almost all patients with HAM/TSP experience erectile dysfunction [58]. Typically, HAM/TSP is slowly progressive; however, its symptoms can range from limited motor impairment after decades (very slow progression) to complete loss of motor function within a few years of disease onset (rapid progression) [59].

Immunomodulators, including corticosteroids, are typically used to slow disease progression. The prognosis and assessment of treatment effectiveness are difficult due to the slowly progressive nature of the disease; therefore, biomarkers are recommended for the clinical evaluation of HAM/TSP [57].

Potential biomarkers of functional prognosis and treatment response of HAM/TSP may include the chemokine CXCL10 and neopterin in the cerebrospinal fluid [57]. CXCL10 and neopterin levels in the serum and cerebrospinal fluid are prognostic markers of inflammation and are also used to monitor and treat HAM. In addition, indicators of neurodegeneration such as neurofilament light chains in the cerebrospinal fluid and blood can also be used to predict HAM [60].

Elevated levels of chitotriosidase-1 (CHIT1) in the cerebrospinal fluid correlate with the rapid progression of HAM/TSP [59]. Therefore, CHIT1 has been proposed as a biomarker for poor disease prognosis in patients with HAM/TSP.

High levels of CXCR3-binding chemokines in the serum (CXCL9, CXCL10, and CXCL11) and increased levels of CCL2, CCL3, CCL4, CCL17, CXCL5, CXCL10, and CXCL11

in the cerebrospinal fluid (CSF) were detected in patients with HAM/TSP. In the typical and rapid progression of HAM/TSP, the CSF/serum ratio of CXCL10 levels is ≥ 1.0 , and there is also an elevated number of CXCR3⁺Tax⁺CD4⁺ T cells in the blood. The CSF/serum neopterin ratio can be used as a marker of HAM/TSP progression [61].

HAM biomarkers were described in detail by Saeidi et al. [62]. The authors examined the connection between XCL1 levels in the blood serum of patients with the development of multiple sclerosis and HAM, both of which are chronic inflammatory diseases of the central nervous system. It has been shown that increased expression of XCL1 promotes the migration of autoreactive T cells into the central nervous system and plays a crucial role in the development of inflammatory neurological diseases, including HAM and multiple sclerosis.

Expression of the tumor suppressor gene in human non-small-cell lung cancer (TSLC1) in CD4⁺ T cells may serve as a biomarker for HAM/TSP disease activity [63].

Low levels of IL9 were found in peripheral blood samples of patients with HAM/TSP. A correlation between the expression level of the IL9 gene (*IL9*) and the Babinski reflex was detected in the HAM/TSP group. It was also shown that Th9 cells prevent the progression of HAM/TSP and serve as protective factor [64].

Pentraxin-3 (PTX3) is an acute phase protein, whose plasma concentration increases during inflammation. Elevated PTX3 levels are associated with myelopathy caused by HTLV-1 infection. PTX3 can be considered as a potential diagnostic biomarker for HAM [65].

An increase in the number of T cells containing cell adhesion molecule 1 (CADM1), a marker of cells infected with HTLV-1, has been detected in 17% of patients with HAM/TSP [55].

A decrease in joint flexibility, assessed using a pendulum fleximeter, was observed in patients with TSP/HAM. In addition, a decrease in flexibility of the knee and ankle joints was observed in HTLV-1 infected patients without myelopathy, which can therefore be used as a prognostic marker for the development of myelopathy [66].

In addition to HAM/TSP, other neurological diseases associated with HTLV-1 have been reported. Tamaki et al. [67] described a case of HTLV-1-associated demyelinating neuropathy in a 78-year-old man. The disease manifested as limb paresthesia and sensory disturbances in the distal limbs with loss of deep tendon reflexes on the ATLL background. Corticosteroid therapy followed by intravenous immunoglobulin administration was effective and reduced symptoms.

Matsuura et al. [68] described a case of late-onset sporadic nemaline myopathy associated with HTLV-1

infection in a 70-year-old Japanese woman with gait disturbances, lumbar kyphosis, and respiratory dysfunction. Treatment with steroids led to an improvement in the patient's condition.

King-Robson et al. [69] described a case of encephalomyelitis combined with HTLV-1-associated myelopathy in a 53-year-old woman with symptoms of upper limb weakness, sensory loss, and cerebellar dysfunction. Corticosteroid therapy led to the patient's recovery.

Mizuma et al. [70] reported HTLV-1-associated encephalopathy and cerebellar lesions in an 87-year-old woman with progressive dysarthria and gait disturbance. Two courses of high-dose intravenous methylpredonine therapy reduced the cerebellar ataxia and edema.

Mental disorders

Cerebral changes occur in individuals with HTLV-1-associated myelopathy and appear to predominate in the subcortical regions [71].

Kalil et al. [72] found an association between HTLV-1 infection, neurocognitive impairment, and brain white matter lesions, the extent of which, as measured by magnetic resonance tomography, correlated with viral load. Based on these results, the authors suggested that HTLV-1-induced damage to the central nervous system is not limited to the spinal cord, but affects all parts of the nervous system.

HAM/TSP or asymptomatic HTLV-1 infection can lead to cognitive deficits. In this regard, it is important to assess cognitive functions and mental disorders in carriers of this virus [73].

The incidence of cognitive impairment was 16 times higher in the asymptomatic HTLV-1 group and 69 times higher in the HAM/TSP group than that in the uninfected population [74].

Recent publications have described the effect of HTLV-1, as well as human immunodeficiency virus, and hepatitis C virus on cognitive factors and neuropsychological profiles of their carriers. HTLV-1-positive patients had the lowest cognitive scores and the widest range of anxiety and depressive symptoms [75, 76]. Depression in patients with HAM/TSP negatively affects various areas of their daily life, including work performance [77].

CONCLUSION

The HTLV-1 virus, which was discovered over 40 years ago in 1980 [78], remains a major public health problem and poses a threat to human health. Unfortunately, to date, there are no etiologic drugs or vaccines against this virus;

therefore, prevention of diseases associated with HTLV-1 remains a relevant issue. Several preventive measures have been proposed including prenatal screening as well as blood and organ donor screening. However, the debate regarding the cost-effectiveness of these measures continues, fueled by the geographical heterogeneity of areas endemic for HTLV-1 infection [79, 80].

Studies on HTLV-1 in the Russian Federation are much less common than those on other tumor-associated viruses (human papillomavirus, hepatitis B and C viruses, human immunodeficiency virus, and herpesviruses) (see, for example, reviews [81, 82]). Apparently, this is because Russia is not an HTLV-endemic region. We found single publications related to the analysis of the prevalence of HTLV-1 in Russia in the databases. Thus, Morozov et al. [83] in 2005 identified sequences corresponding to exon 2 of HTLV-1 in the blood of 20 out of 50 patients with mycosis fungoides. All the patients lived in Moscow and the Moscow region. A few years later, Syrtsev et al. [84] discovered nucleotide sequences corresponding to the *tax* HTLV-1 gene (exon 2) and their transcripts in 21 out of 51 patients with mycosis fungoides. At the same time, they found specific antibodies to the Tax protein encoded by this gene, the main pathogenetic factor of viral carcinogenesis, in six out of 11 patients. HTLV-1 infection was detected among the Nivkhs, indigenous people from the Nogliksky District of Sakhalin Island (Far East, Russia) [85].

According to the Order of the Ministry of Health and Social Development No. 325 of July 25, 2003 “On the development of cell technologies in the Russian Federation”, all stem cell banks in Russian Federation should test the new cord/placental blood samples for antibodies to HTLV-1 and HTLV-2 upon their receipt (<https://normativ.kontur.ru/document?moduleId=1&documentId=59096>).

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According to the 2009 World Health Organization (WHO) recommendations [86], countries where HTLV is not endemic should consider screening for HTLV-1/2 infection before releasing blood and blood components for clinical use. Most screening and confirmatory tests are based on the detection of antibodies to HTLV-1. These include immunoblotting, radioimmunoprecipitation, and linear immunoassays (<https://www.who.int/news-room/fact-sheets/detail/human-t-lymphotropic-virus-type-1>).

Currently, there are no biological markers or clinical symptoms that can be used to predict the development or assess the risk of HTLV-1-associated diseases. HTLV-1 proviral load has been proposed as a possible indicator, but it is still unclear what level of proviral DNA (as a predictor) should be considered as a threshold, for example, when determining the risk of mother-to-child transmission of the virus. In collaboration with Member States and partners, WHO is developing guidance for HTLV-1 surveillance and prevention practices (<https://www.healthdirect.gov.au/htlv-1-infection>).

The development of an effective vaccine would limit or even prevent the transmission of HTLV-1. It will also lead to a reduction in the viral load in infected patients and, consequently, the likelihood of developing HTLV-1-associated diseases. Currently, several types of HTLV-1 vaccines are in development including vaccines that use peptide-proteins, that are encapsulated and contain an adjuvant; polyepitope; DNA, dendritic cells, or recombinant vaccinia virus, as well as other types. Most of these vaccines are at different stages of preclinical trials [79, 80].

The aim of this review on serious diseases associated with HTLV-1 infection is to attract the attention of researchers from various fields of fundamental and applied science to this retrovirus.

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