HTLV-1: A View from the Rheumatologist

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Introduction

There are four human T-cell lymphotropic viruses described (named HTLV-1 to HTLV-4), but only HTLV-1 and HTLV-2 are associated with infection in humans [1]. The human T-cell lymphotropic virus type 1 (HTLV-1) is part of the genus *Deltaretrovirus* of the subfamily *Orthoretrovirinae* of the family of retroviruses [2] and was the first human retrovirus discovered [3]. There are six known subtypes (A to G), with cosmopolitan subtype A being the most common in infections [4, 5]. The modes of transmission in order of effectiveness are the following: (1) transfusion of non-leukocyte depleted contaminated cellular blood products (up to 64%), (2) mother to child transmission (10–25% by breastfeeding, especially more than 6 months, and 3–5% with transplacental exposure), and (3) sexual intercourse (1% per year in serodiscordant couples, mainly from male to female) [4, 6–9]. The use of common needles and organ transplantation are also supposed to be mechanisms of transmission [10–13].

Epidemiology

There are approximately 10–20 million people infected worldwide [4, 14], and 90–95% of them remain as asymptomatic carriers [5]. There may be an underestimation of the global prevalence of HTLV-1 infection because serological screening is made basically in healthy blood donors and pregnant women [1, 5]. In children, the prevalence of the infection increases from 2 years of age getting stable during puberty [15], and in adults the prevalence increases with age being higher in females than males [7]. This is because of the known ways of transmission: prolonged breastfeeding and sexual intercourse (with higher transmission from males to females), respectively [7]. Interestingly, there is a geographic distribution with clusters of high prevalence, with a tendency of being in the same latitude, besides areas of medium or low prevalence. The most important highly endemic areas are some islands of southwest Japan such as Shikoku, Kyushu, and Okinawa with up to 37% of seroprevalence [5]. Some Caribbean islands and Sub-Saharan African countries such as Benin, Cameroon, and Guinea-Bissau show prevalence close to 5% [5, 16, 17]. In South America, there is some correlation in places with the same latitude and altitude (near the coasts), with a prevalence of 1–5% in countries such as Brazil, Perú, French Guyana, or Colombia, and less than 1% in Chile and Argentina [5, 18–20]. Other isolated highly endemic areas are the Mashad region in Iran, some aborigines in the north of Australia, first-nations in North America, and Romania in Europe [4, 7, 21]. Of note, molecular and genomic studies of the Cosmopolitan Subtype A, which is endemic in Japan, the Caribbean, South America, North and West Africa, and the Middle East, suggest dissemination from a common ancestor [4].

Spectrum of the Disease

As described above, about 90–95% of patients infected by HTLV-1 are asymptomatic carriers. Among those who will present a condition, the manifestations include the following: (1) adult T-cell leukemia/lymphoma (ATLL) in 2–6% [22], (2) HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in 2–3% [6, 7, 23], and (3) other inflammatory conditions such as arthritis, uveitis, Sjögren's syndrome, dermatitis, thyroiditis, bronchiolitis-alveolitis-pneumonitis, myositis, nephritis and hepatitis – cholangitis (without exact data of the prevalence or incidence of these manifestations) [5, 24–28]. Of interest, the superinfection of HTLV-1 virus with *Strongyloides stercoralis* (a gastrointestinal parasite) predisposes the appearance of ATTL in those patients [29].

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Virus Characteristics, Pathophysiology, and Mechanisms of Damage

HTLV-1 has two relevant proteins: Tax and HBZ. Tax (p 40) is an important protein in viral transcription that also has the particularity of modifying transduction pathways of the infected cell such as NF-kB, CREB, SRF, NFAT, and AP-1; this leads to the transactivation of genes that code for IL-2 receptor α chain (CD25), interferon-γ, and intercellular adhesion molecule 1 (ICAM1) [7, 30–36]. HBZ can act as a microRNA promoting the function of the transcription factor E2F1 and the proliferation of the infected cell; as a protein produces decreased expression of Tax [37, 38].

CD4+ T lymphocytes (CD4+ TLs) have a pivotal role in HTLV-1 infection and can change their behavior leading to activation, cell proliferation, and cytokine synthesis in response to viral proteins [39]. CD4+ TLs infected with HTLV-1 produce the C-C motif chemokine 22 (CCL22) which can attract other CD4+ TLs that express CCL22 receptor (CCR4+) in their surface, making CD4+ CCR4+ TLs the main infected cells [40, 41]. Indeed, the above mechanism has emerged as an interesting therapeutic target [42]. HTLV-1 promotes a TH1 phenotype response, with increased levels of IL-2, IL-6, Interferon gamma (IFN-γ), and TNF alpha especially in the spinal fluid and blood of patients with HAM/TSP [43, 44]. The Tax protein has been shown to affect the above-described transcription factors and cellular cascades such as Rho-GTPases and the JAK/STAT pathway [28, 31, 38].

The regulatory T lymphocytes (Tregs) are CD4+ T lymphocytes that express the forkhead box protein P3 (FOXP3) transcription factor and have the peculiarity of inhibiting the activation of other lymphocytes [45]. Alterations in the expression of FOXP3 have been linked to the presence of inflammatory diseases [46]. In HAM/TSP and ATTL, it has been observed that HTLV-1 increases the expression of FOXP3 by means of Tax, causing a diminished antiviral response because of lower activity of the CD8+ cytotoxic T lymphocytes (CD8+ CTL) [47]. On the other hand, the underexpression of FOXP3 could lead to a more inflammatory CD4+ T lymphocyte phenotype [7, 41].

CD8+ CTL can recognize Tax protein as the main antigen of HTLV-1 and suppress viral activity [48], but an excess in their activity has been also linked to inflammatory damage in the host [49]. Data from Japan suggest that certain HLA I alleles could confer to CTLs a different quality in their response: *HLA-A∗02* or *HLA-Cw∗08* can act as protective decreasing proviral load and the risk of HAM/TSP in infected patients, while *HLA-B∗54* could stimulate an inefficient phenotype to CTLs, making them proclive to inflammatory damage in the host and increasing the risk of HAM/TSP [49–51].

Data about the mechanism of inflammation and damage in HTLV-1 infection come mainly from HAM/TSP studies. The "innocent bystander" is the most accepted hypothesis [52, 53]: CTLs are the main responsible for the tissue damage in the presence of HTLV-1-infected CD4+ TLs, with an important role of IFN-γ and in a lesser extent, TNF alpha and IL-6 [6, 7, 54, 55].

HAM/TSP

Risk Factors and Neuropathology

The risk factors for the development of HAM/TSP are listed in Table 16.1, being proviral load the strongest predictor [50, 56–58]. In neuropathology, there are mononuclear infiltrates in the central nervous system (CNS) predominantly in the upper thoracic spinal cord and around the blood vessels [59, 60]. CNS develops a loss of spinal cord volume at months or years from the beginning of the disease [61].

Clinical Course

The clinical picture corresponds to a chronic or subacute history of weakness and stiffness of lower extremities, with frequent falls and problems with climbing stairs or rising from a chair [6, 7]. Often, there is neuropathic lumbar pain which can radiate down to one or both legs, lower limbs paresthesia, sphincter disorders such as constipation or urinary incontinence/retention, and erectile dysfunction in males [7, 69, 70]. The physical examination shows spastic gait and bilateral lower limb hypertonia, hyperreflexia (clonus of one or both ankles can be present), and extensor plantar reflex; sensory signs are unusually seen [71, 72]. Data from a study of 123 patients from the Caribbean isle of Martinique showed

Table 16.1 Principal risk factors for development of HAM/TSP

Proviral load	More than 1% of DNA copies per 100 peripheral blood mononuclear cells (PBMCs) [57, 58]
Patient genetics	HLA class I genotype *HLA-DRB1∗0101* [62] *HLA-B∗07* [63] *HLA-B∗54* [56] Single Nucleotide Polymorphisms (SNPs) *IL-6* – 634C [50, 51] *TNF* – 963A [63]
Demographics	Female gender [6, 64] ≥50 years old [6, 65]
Route of transmission	Blood transfusion [66] Solid organ or bone marrow transplantation [67, 68]

that from the onset, the median time to use a walking aid was 6 years and the median time to use a wheelchair was 21 years. Patients more than 50 years old at onset and a high HTLV-1 viral load were predictors of rapid evolution to the use of the aids named above [73].

Laboratory Studies

The presence of positive HTLV-1 antibodies from an enzyme-linked immunoassay (ELISA) requires confirmation by western blot or detection of viral nucleic acid [6, 7]. A lumbar puncture analysis can show a normal or nearly normal protein concentration and mononuclear count in cerebrospinal fluid (CSF); also, there could be a higher HTLV-1 viral load in CSF lymphocytes than peripheral blood mononuclear cells (PBMCs) [74]. On plasma, a profile of elevated concentrations of β2 microglobulin and calgranulin B and low apolipoprotein A2 levels can differentiate HAM/TSP of asymptomatic carriers [75]. On brain MRI, there can be asymmetrical periventricular and/or subcortical white matter lesions which look different from alterations seen in multiple sclerosis; as mentioned above, compromise of the spinal cord is cervical and thoracic areas with atrophy in chronic stages [76, 77]. The presence of T2 hyperintensity in the spinal cord on MRI study suggests a rapidly progressive clinical course [78].

Diagnosis of HAM/TSP

A progressive spastic paraparesis with impaired gait (with or without sensory or sphincter abnormalities), the presence of HTLV-1 in serum or CSF and the exclusion of other conditions that can resemble HAM/TSP are necessary for a *definite* diagnosis. If in the previous clinical picture is observed isolated lower limb spasticity/hyperreflexia or isolated Babinky sign (with or without sensory or sphincter abnormalities) instead of the progressive spastic paraparesis, the diagnosis is *probable*. When any clinical feature described above is present and HTLV-1 is positive in serum or CSF but other conditions that can mimic HAM/TSP have not been ruled out, the diagnosis is *possible* [79].

Treatment of HAM/TSP

The use of baclofen and botulinum toxin injections for spasticity [80, 81]; gabapentin, pregabalin, or tricyclic antidepressants for neuropathic pain [82]; physical therapy for motor disturbances; and specific treatment of sphincter disorders are examples of the symptomatic approach for management of HAM/TSP [83].

Regarding drugs trying to modify the natural history of the disease, studies have been focused on diminishing the HTLV-1 proviral load or to modify the immune response of the host. Corticosteroids (CS) are often used in recently onset (≥3 years) or progressive HAM/TSP, especially in the beginning of the disease. Results are seen on motor disability but data about other issues such as sphincter disorders or neuropathic pain is scanty [6, 7, 84, 85]. Oral CS have been useful in some observational studies [84, 86]. A prospective observational Brazilian study of 39 patients that received methylprednisolone 1 g/day bolus for 3 days every 3–4 months (also physical therapy and antispastic drugs in some of them) showed a 24.5% improvement from baseline in the Incapacity Status Scale after 2.2 years mean follow-up. This benefit showed to be significant until the third set of infusion [85]. A randomized, double-blind, placebo-controlled study of six months combination therapy between zidovudine and lamivudine in 16 patients, showed no significant changes in pain, bladder function, disability score, gait, proviral load or markers of T-cell activation or proliferation between the two arms at 48 weeks of follow-up [87]. Interferon alpha (IFN-α) was probed in a randomized, double-blind, multicenter, multidose trial of 48 patients. In a total follow-up of 8 weeks, 3.0 MU of IFN-α for 4 weeks was significantly better than 0.3 MU (but not than 1.0 MU) for improvement of motor dysfunction, urinary disturbances, and changes of neurologic signs without a difference in symptomatic side effects [88]. In a recent uncontrolled, phase 1–2a study of Mogamulizumab (an anti CCR4 monoclonal antibody), 21 patients received different doses of the drug with promising results in the decrease of proviral load, CSF inflammatory markers, spasticity, and motor disability [42]. Other therapies such as methotrexate, azathioprine, cyclosporine A, IFN-β, pentoxifylline, danazol, valproic acid, IL-2 receptor antagonist, and plasmapheresis have been tried in open trials and case series with disparate results [7, 84, 89–93].

Consequences of HAM/TSP

Overall, a patient with HAM/TSP lives 15 years less than the general population. The motor disturbances make necessary the use of a walking aid in the first decade since the onset of disease and the use of a wheelchair at 21 years of evolution on average [73]. The most affected areas of functionality in HAM/TSP patients, using the Functional Independence Measure (FIM) score, are the locomotion (walking and stairs) and bladder management items [94]. The bladder issues make the patients prone to urinary infections, urinary obstruction, social discomfort, sleep and mood disturbances and low quality of life [6, 7, 95–97]. Chronic lumbar and lower limb pain is also a concern, with a prevalence of 90% in HAM/TSP patients [98].

Infective Dermatitis Associated with HTLV-1 (IDH)

The first description of IDH was made in Jamaica in 1966, but then it was also reported in other prevalent areas of HTLV-1 infection such as other Caribbean isles, Japan and Brazil [99–102]. The onset of IDH occurs in childhood with an average age of 2 years and a tendency to improve into adulthood; a third of the cases can initiate at the first year of life [102, 103]. Also, there is a slight predominance in females (60%) [6]. Some risk factors associated with IDH are the presence of HLA class II haplotype DRB1∗DQB1∗ (1101-0301) and an elevated proviral load [104, 105]. The presence of IDH in childhood has been linked to later development of ATTL or HAM/TSP [26, 106, 107]. A Brazilian study showed that 44% of 74 patients with ATTL had dermatitis suggestive of IDH during childhood [108] and another study in the same country demonstrated 30% of the occurrence of HAM/TSP in 20 patients with a history of IDH [107].

In skin biopsies of patients with IDH, there is an important proliferation of CD4+ and CD8+ lymphocytes with an elevated CD4+/CD8+ ratio; also infiltration of non-activated CD8+ CTLs is another finding [26, 101, 109]. There are large quantities of IFN-γ produced by CD57+ cells in dermis and epidermis of patients with IDH [110]. *Staphylococcus aureus* and/or β-*hemolytic Streptococcus* superinfection is common in IDH and the stimulation of T cells due to antigens of these bacteria could offer a larger amount of cells for HTLV-1 replication [6, 26]. The histopathology shows chronic dermatitis that can mimic mycosis fungoides [111]. A mild to moderate epidermal and dermal lymphocytic infiltrate suggest an active immune response to HTLV-1 [111].

The clinical features of IDH consist of a severe exudative dermatitis with scaling or crusting of the scalp, forehead, eyelids, paranasal area, neck, retroauricular areas, external ear, axillae, or groin. Other common findings are a chronic watery nasal discharge, crusts in the anterior nares, blepharoconjunctivitis, lymphadenopathy and a generalized papular rash [26, 100]. As mentioned above superinfection with gram-positive cocci is habitual.

There are three major important items that must be present for the diagnosis of IDH: dermatitis of ≥2 sites, chronic watery rhinorrhea, and HTLV-1 seropositivity. Besides the aforementioned, early childhood onset and/or the good response of dermatitis with the use of antibiotics with a quick recurrence upon withdrawal are needed to meet the diagnostic criteria for IDH [100].

The treatment of IDH is based on long term use of antibiotic therapy, with a tendency to relapse at withdrawal. Continuous prophylactic therapy could be used. Also, the use of topical antibiotics or emollients can be useful. For pruritus, topical CS or antihistamines are indicated [26, 102].

Uveitis Associated with HTLV-1 (UAH) and Other Ocular Manifestations

The first report of uveitis associated with HTLV-1 (UAH) was made in Japan in 1989 [112]. UAH has been associated with the presence of HAM/TSP and autoimmune hyperthyroidism; interestingly HTLV-1 carriers under treatment for autoimmune hyperthyroidism may be prone to the development of UAH [113]. CD4+ TLs infected by HTLV-1 virus get into the aqueous humor with a higher proviral load than PBMC's; the mechanisms that explain how these infected lymphocytes get into this immune-privileged zone are not elucidated. These cells produce large amounts of IL-2, IL-6, IFN-γ, and TNF alpha as well as other cytokines that provoke intraocular inflammation [114, 115].

UAH is more common in females than males in a 3.5:1 ratio, especially women under 50 years old and is unilateral in 60%. The most important symptoms are "foggy" vision, ocular floaters, blurring of vision, ocular hyperemia, ocular pain, and photophobia. The most common type of presentation is panuveitis (49.6%) with moderate to severe vitreous opacities and mild anterior uveitis and retinal vasculitis, followed by intermediate uveitis (28.9%) [114]. The treatment of UAH consists of the use of topical/systemic CS and mydriatics. Relapsing is common [116]. The most important consequences are cataract and glaucoma [114].

Keratoconjunctivitis sicca and interstitial keratopathy have been related to patients with HAM/TSP. The latter manifestation was associated in a third of cases with uveitis and without response to local CS therapy [116].

Arthritis Associated with HTLV-1

The first reports that linked an inflammatory arthropathy with HTLV-1 virus came from ATTL and HAM/TSP patients [117, 118]. Arthritis associated with HTLV-1 is a chronic inflammatory arthropathy which is indistinguishable from Rheumatoid arthritis (RA) [119]. The most common joints affected are from hands and knees, and rheumatoid factor or antinuclear antibodies can be positive [120]. Interestingly, a Japanese study made in Nagasaki with 113 female patients diagnosed as RA found that in 13.2% (95% CI 5.1–21.2) of those patients, the disease was attributable to HTLV-1 infection, without clinical or laboratory differences between HTLV-I–infected and HTLV-I–uninfected RA patients [121]. Another prospective study from the United States showed an elevated incidence of arthritis in blood donors infected with HTLV-1 or HTLV-2 [122].

The clues that associate the presence of arthritis in HTLV-1 infected patients are the following: (1) Atypical lymphocytes (as ATTL like cells) have been observed in synovial fluid and synoviocytes of HTLV-1 infected patients

[123, 124]. (2) HTLV-1 proviral DNA has been found in the DNA of synovial fluid cells and synovial tissue cells [123]. (3) The presence of Tax mRNA and protein in synovial stromal cells [125]. (4) HTLV-1 has tropism for synovial cells *in vitro* [126]. (5) Higher proviral load in blood and synovium have been observed in patients who develop arthropathy versus asymptomatic patients, but similar to HAM/TSP patients. A possible mechanism of development of the arthritis is that T lymphocytes get into synovial space in response to HTLV-1, which is synovial cell tropic [6, 127].

There is no consensus in the treatment of arthritis associated with HTLV-1, with CS commonly used [6]. Also, anti-TNF agents seem to be less effective in HTLV-1 positive patients with RA [128]. More studies are needed to evaluate the use of DMARDS or biological therapy.

Sjögren's Syndrome Associated with HTLV-1 (SSAH)

A study made in Nagasaki, Japan, showed that 13% of 36 patients with primary Sjögren's syndrome (SS) were positive for HTLV-1. No difference was seen in xerostomia, xerophthalmia, enlargement of parotid glands, photosensitivity or Raynaud's phenomenon between patients with SS with or without antibodies to HTLV-1; but extra-glandular manifestations such as uveitis, myopathy, or recurrent fever were more frequent in the group of HTLV-1 positive patients [129]. Another report from Nagasaki found that in 135 patients with primary SS and 97 patients with secondary SS, 25% and 29.2% of them had anti-HTLV-1 antibodies, respectively. Also, there were no differences in the presence of Antinuclear (ANA), anti-Ro or anti-La antibodies between SS patients with or without seropositive for HTLV-1 [130]. Also, another Japanese study demonstrated that salivary IgA antibodies to HTLV-1 were common among seropositive patients with Sjögren's syndrome compared to patients with HAM/TSP or asymptomatic carriers [131]. There is no specific management for SSAH.

Inflammatory Myopathy Associated with HTLV-1 (IMAH)

The presence of HTLV-1 has been linked to polydermatomyositis (PM) [132, 133], inclusion body myositis (IBM) [134, 135], and dermatomyositis (DM) to a lesser degree [136]. Some studies have shown an increased seroprevalence of HTLV-1 in PM and IBM patients compared to controls [132, 134]. HTLV-1 has demonstrated to be myotoxic *in vitro* [137] and CD4+ TLs infected by HTLV-1 virus infiltrate the muscle tissue with no evidence myocyte infection [138]; CD8+ CTLs directed to Tax protein have been found in muscles of patients positive for HTLV-1 [133, 139] and anti-Tax cytotoxic T cells are chronically recruited within inflamed tissues of patients with IMAH [139]. A Jamaican retrospective study of 38 patients with polymyositis, of whom 24 were seropositive for HTLV-1, showed that the latter had a longer time between the onset of symptoms and diagnosis, more frequent admissions to hospital and lesser chest pain, dyspnea or joint swelling than the seronegative. No difference was seen for ANA, creatine kinase, or anti-Jo-1 antibodies [132]. IMAH can be resistant to CS or other immunosuppressants [6].

Pulmonary Manifestations of HTLV-1 Infection (PMH)

Concerns about pulmonary manifestations of HTLV-1 infection began with cases of HAM/TSP patients that developed pulmonary lymphocytic inflammatory infiltrates [140, 141] and morphologic changes of the lungs in CT scan [142, 143]. A Japanese retrospective study found that 30.1% of 320 patients with HTLV-1 had pulmonary findings on CT scans. The abnormalities were consistent with centrilobular nodules (97%), thickening of bronchovascular bundles (56%), ground-glass opacity (52%), bronchiectasis (51%), interlobular septal thickening (29%), and consolidation (5%). Of them, 58 patients had a lung biopsy: a lymphocytic infiltration along respiratory bronchioles and bronchovascular bundles was the most prevalent finding [144]. The pulmonary manifestations of HTLV-1 infection are different between patients with ATTL and the presence of HAM/TSP or asymptomatic carriers (Table 16.2). Most patients with PMH are asymptomatic [6]. There is no specific treatment but unresponsiveness of long courses of CS has been described [142].

In patients with pulmonary disease and infection with HTLV-1, there are an increased number of T lymphocytes (CD4+ and CD 25+) in bronchoalveolar lavage fluid (BAFL) and a Th1 immune response with augmented production of IL-2R, IL-2, IL-12, and IFN-γ [146]. The degree of HTLV-1 proviral load in BALF is related to the number of lymphocytes in it [147]. In response to Tax protein, there are also elevated levels of MIP-1α and ICAM -1 which are implicated in activation and recruitment of inflammatory cells and high levels of IP-10, an important mediator in pulmonary fibrosis

Table 16.2 Pulmonary manifestations of HTLV-1 infection [145]

ATTL patients	Opportunistic infections: Pneumocystis, strongyloidiasis, tuberculosis Pulmonary leukemic infiltrates
HAM/TSP or asymptomatic patients	T lymphocytic alveolitis Interstitial pneumonia Bronchiolitis and diffuse panbronchiolitis Infections: Pulmonary cryptococcosis, tuberculosis, and community-acquired pneumonia

[148]. Also, a direct relationship exists between *Foxp3* and *HBZ* mRNA and the number of lymphocytes in BAFL of patients with lung manifestations in the context of HTLV-1 infection [146]. Interestingly, a higher number of CD8+ CTLs in BAFL than peripheral blood have been observed in patients infected with HTLV-1, a finding that could imply a selective infiltration in the lung in response to the virus [141, 149].

Some data suggest that proviral load and HTLV-1 serotype could impact in prognosis. A prospective cohort study of 840 indigenous Australian adults showed that a higher baseline HTVL-1c serotype proviral load (HTLV-1c pVL) in peripheral blood leukocytes was linked to higher mortality due to bronchiectasis-related events. HTLV-1c pVL was also associated with higher airway inflammation [150]. There is a frequent co-infection of HTLV-1 and tuberculosis (TB) with increased mortality, need for hospitalization, or probability of treatment for pulmonary TB [145, 151–153]. The higher susceptibility to TB could be explained due to lesser production of TNF alpha, while the severity of the pulmonary TB may be related to an exaggerated inflammatory response in the context of HTLV-1 infection [151].

Other Associations

The relationship between systemic lupus erythematosus (SLE) and HTLV-1 infection is controversial [154–156]. While there are some case reports that support the association [157–159], an Iranian cross-sectional case-control study of 1045 patients (130 SLE patients and 915 healthy controls) showed that HTLV-1 was not a predictor factor for SLE [154]. Another study suggests that SLE patients who are seropositive for HTLV-1 have an older age at onset of the disease, a higher lymphocyte count, and need for lower doses of CS for maintenance than seronegative patients [156]. There are four reported cases of mixed connective tissue disease in HTLV-1 carriers reported in the literature [160–163]. Tubulointerstitial nephritis (TIN) in Japanese HTLV-1 carriers have been associated with the presence of uveitis (TINU syndrome) in two patients and other patients with class I lupus nephritis [164, 165]. Some other cases of liver disease have been published (including autoimmune hepatitis and primary biliary cirrhosis) [6, 166]. Autoimmune thyroid diseases have been related to HTLV-1 [167, 168]; there are reports that link Hashimoto's disease with HAM/TSP and Basedow-Graves with uveitis [6, 169].

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