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Human T-cell lymphotropic virus type 1 (HTLV-1) was the first retrovirus identified in human beings. The prevalence of infection is estimated to be 5-10 million people. The great majority of infected individuals are lifelong asymptomatic carriers. However, 5% of infected patients may develop different clinical manifestation such
as adult T cell leukemia (ATL) and a chronic inflammatory central nervous system (CNS) disease called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [1]. The development of HTLV-1-associated diseases seems to be regulated by different factors, including viral, host and environmental determinants [2]. Several studies regarding viral genome fail to determine a specific genotype exclusively associated with HAM/TSP or ATL [3]. Although some reports correlate specific viral point mutations with an increased virus replication [4]. Nowadays, the best predictor of HAM/TSP is the proviral load (PVL). Patients with HAM/TSP presents high PVL when compared to asymptomatic individuals [5,8]. However, some infected patients who present high PVL never develop the disease. This suggests that other factors contribute to disease progression [9]. Among then, the host immune response seems to play a crucial role in clinical manifestation. In fact, a strong immune response is seen in HAM/TSP patients [2]. In our recent report “Temporal lesions and widespread involvement of white matter associated with multi-organ inflammatory disease in human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)”, [9] we investigated an unusual presentation of HTLV-1 infection, characterized by a case of HAM/TSP with multi-organ inflammatory disease and encephalic involvement. The pro-inflammatory response appears to be crucial in the pathogenesis of HAM/TSP in both classic presentation of the disease, as also in atypical cases [2,9,11].

The increased proliferation or migration of HTLV-1 infected and/or HTLV-1 specific cells to CNS seems to be related with neuropathogenesis. The proviral load in cerebrospinal fluid (CSF) is higher than PVL in peripheral blood mononuclear cells (PBMCs) [5,9,12,13]. Furthermore, the aggravation of neurological symptoms coincides frequently with an increase in HTLV-1 PVL in both PBMC and in CSF [14]. The increased viral infection of host cells may be associated with a poor immunological control and may cause a persistent inflammation of CNS contributing to neuropathogenesis.

Host genetic characteristics, such as human leukocyte antigen (HLA) genotype, are associated to the PVL. In this context, individuals with HLA-A*02 or HLA-Cw*08 presents an effective cytotoxic T lymphocyte (CTL) response against HTLV-1 and in consequence can control the proviral load. On the other hand, HLA-B*5401 and HLA-DRB1*0101 are linked to HAM/TSP [15,16].

Another issue that is related with an increased PVL is the proviral integration site in host genome. In HAM/TSP patients, the provirus is predominantly integrated into transcriptionally active units which predisposes to a high proviral load and consequently to disease progression [17].

The humoral immune response seems to play a secondary role in HTLV-1 control. The proviral load was directly proportional to anti-HTLV-1 antibodies in CSF [5]. However, in a study developed by our group, there was an inverse correlation between the PVL in CSF and intrathecal synthesis of antibodies anti-HTLV-1 in HAM/TSP patients. Thus, these antibodies produced in CNS may play a protective role [13].

The interaction among all these factors leads to a high, moderate or low proviral load. If there is an increased viral replication, and consequently a vast antigen expression in infected individual, a strong stimulation of the immune system, with the presence of inflammation and autoimmune reaction is observed, which lead to disease progression.

Three mechanisms have been proposed to explain immunopathogenesis of HAM/TSP:

1) “Cytotoxic model”: Glial cells get infected by HTLV-1 and are lysed mainly by cytotoxic T lymphocytes (CTL) which causes neurological damage;

2) “Bystander model”: Damage related to the production of myelinotoxic cytokines, such as TNF-α, interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon-γ (IFN-γ) by HTLV-1 activated T CD4+, T CD8+ and microglia.

3) Autoimmune response due to chronic peripheral activation, leading to an impairment of the immunological tolerance to myelin antigens. In this case, humoral immunity to HTLV-1 proteins (mostly Tax protein) cross react against neuronal antigens (such as neuron-specific ribonucleoprotein- hnRNP) [11,18,19].

The inflammatory response is well characterized in CNS. In fact, HAM/TSP individuals, presents moderate lymphocytic pleocytosis, raised protein content in CSF, as well as intrathecal synthesis of total (oligoclonal IgG bands) and specific antibodies, [2,5,9,11,12,14,20] and an increase in the concentration of pro-inflammatory markers, such as neopterin, TNF-α, IL-6 and IFN-γ in CSF [2,5].

There is also a marked lymphocytes infiltrates (largely CD8+) in affected individuals. In classical cases of HAM/TSP, the initial lesion in CNS (up to 3 years after the disease onset) is characterized by inflammation. The leptomeninge, perivascular and parenchyma are densely infiltrated by CD4+ and CD8+ T lymphocytes, as by B-cells and foamy macrophages. During disease progression, there is a reduction in the number of inflammatory cells and an evolution to white matter degeneration. Therefore, the patient presents a mild to severe spinal cord atrophy (mainly at lower thoracic level) with thickening of leptomeninges [3].

In uncommon situations of HTLV-1 multi-organ involvement, the provirus was detected in different compartments associated with an intense inflammatory
response characterized by CD4+ e CD8+ T cells tissue infiltration in several organs [9,10,21]. Moreover, the temporal lesions and the widespread involvement of white matter recently observed in the studied patient are uncommon and highlights the possibility of extra spinal cord impairment. For hypothesis, it could be associated with an intense and diffuse inflammatory reaction.

In conclusion, HAM/TSP is an infectious and inflammatory disease with consequently demyelination. Some atypical cases present as multi-organ inflammation triggered by HTLV-1 infection and an immune system imbalance.

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Conflict of interest

The authors declare that they have no conflicting interests.

References