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CASE REPORT

Human T-lymphotropic virus type 2 subtype b in a patient with chronic neurological disorder

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Introduction

Human T-cell lymphotropic virus is a retrovirus described worldwide. There are four HTLV types: HTLV-1 to 4. Only HTLV-1 and 2 are linked to human disease. The majority of infected individuals remain asymptomatic. However, it is estimated that 5 % of HTLV-1-infected patients present a clinical neurological disorder called HTLV-1-associated myelopathy (HAM/TSP) (Osame 1990). The diagnosis of HAM/TSP is made according to WHO criteria. The presence of specific antibodies in both blood and CSF, associated with slowly progressive spastic paraparesis, characterizes HAM/TSP (Osame 1990; Puccioni-Sohler et al. 2001). HTLV-1 infection has also been related with others neurologic manifestations, such as sensory neuropathy, cognitive deficit, myositis, erectile dysfunctions, and isolated bladder dysfunction. These rare clinical presentations may be associated with HAM/TSP (Biswas et al. 2009). HTLV-2 is endemic among Amerindians and has been reported at a high prevalence in intravenous drug abusers in the USA, Europe, and Asia (Araujo and Hall 2004; Morimoto et al. 2007). The presence of disease in HTLV-2 infection is rare. Previous studies reported an association between HTLV-2 infection and the development of a clinical manifestation similar to HAM/TSP as well as sensory neuropathy (Harrington et al. 1993; Jacobson et al. 1993; Lehky et al. 1996; Araujo and Hall 2004; Biswas et al. 2009). Four genetic HTLV-2 subtypes (a, b, c, and d) have been described. All documented cases of HTLV-2 and neurological disturbances are associated with HTLV-2a (Harrington et al. 1993; Jacobson et al. 1993; Lehky et al. 1996; Araujo and Hall 2004). The present study reports the first case of HAM/TSP-like illness caused by HTLV-2b, in a patient from Brazil. This patient was also co-infected with hepatitis C virus (HCV).

Case report

A 53-year-old white man from Rio de Janeiro, Brazil, reported a 5-year history of lower limb weakness and urinary incontinence. He had history of treatment for chronic HCV infection and intravenous drug use. Neurological examination revealed spastic paraparesis, hyperreflexia of the lower limbs, and bilateral Babinski sign. Routine blood tests, folic acid, vitamin B12, rheumatoid factor, antinuclear factor (ANF), LE cells, Waaler Rose, and thyroid hormones (TSH, T3, and T4) concentration were normal, but for reactive serology for HCV. Serologic test for syphilis (VDRL) was negative. The presence of HTLV-1/2 antibody in serum was evaluated by ELISA (Diasorin, UK). HTLV-2 infection was confirmed by discriminatory Western blot (GD21,p29, p36, and Rgp46-II). The *tax* gene was recovered by PCR and sequenced to confirm HTLV type. The predict amino acid

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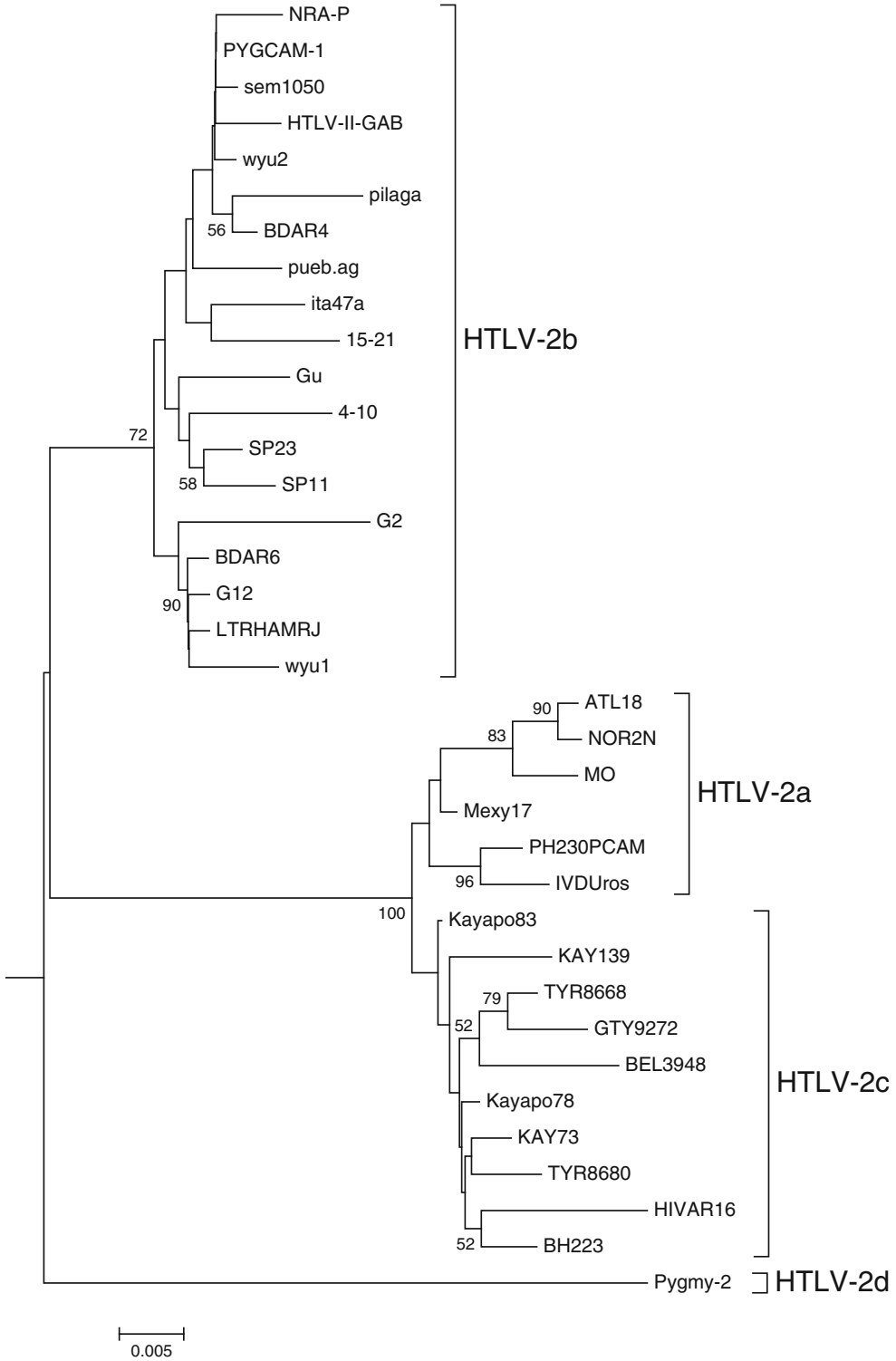

Fig. 1 Genetic Analysis of 653-bp LTR sequence from infected subject (LTRHAMRJ) and HTLV-2 reference sequences. The neighbor-joining tree was inferred under a Tamura-3 parameter evolutionary model and gamma-distribution. Bootstrap values using 1,000 replicates. The accession numbers of GenBank sequences are NRA (L20734); PYGCAM-1 (Z46888); Sem 1050 (U10263); ATL 18 (U10252); Ita47a (U10254); NORN2N (U10258); PUEB.AG (U10261); WYU1 (U12792); Wyu2 (U12794); 4–10 (U73016); 15–21 (U73017); SP23 (AY442386); Sp11 (AY442374);G2 (AF074965); G12 (L11456); Kayapo83 (AF139390); HTLV-II-GAB (Y13051); MO (M10060); Mexy17 (L42510); PH230PCAM (Z46838); IVDUros (AF054272); TYR8668 (AF306729); GTY9272 (AF306727); BEL3948 (AF306724); Kayapo78 (AF139388); Kay73 (L42509); TYR8680 (AF306730); HIVAR16 (JN222964); BH223 (AY509600); Kay139 (L42508); Pilaga (AF054271); BDAR4 (JN222945); BDAR6 (JN222947); Pygmy-2 (Y14365); GU (X89270)

sequence revealed that the provirus presented an extended Tax, characteristic of HTLV-2b. LTR sequence was obtained and the phylogenetic analysis confirmed the HTLV-2 subtype b (Fig. 1). The *tax* and LTR sequences accession numbers in GenBank are KJ826466 and KJ826465, respectively. HTLV-2 relative quantification was evaluated using real-time PCR targeting the *tax* gene. The proviral load was 39 times higher in the present patient sample when compared with other HTLV-2 symptomatic patient (Silva et al. 2002) (2–[delta][delta]Ct=5,27).

The cerebrospinal fluid (CSF) was collected by lumbar puncture. Total and specific cellular count, glucose, and total protein were normal. Bacterial, fungal, and mycobacterial cultures of CSF were negative as also the immunological test for syphilis. The presence of HTLV-1/2 antibodies in CSF was detected by ELISA. Blood-cerebrospinal barrier dysfunction was not observed. There was no intrathecal synthesis of total IgG (by IgG Index).

Magnetic resonance of brain and dorsal spine, electroneuromyography, and somatosensory evoked potentials were also normal.

The study was approved by the ethics committees of the HUGG/UNIRIO and HUCFF/UFRJ. The patient signed the consent inform.

Discussion

This study unequivocally showed the presence of HTLV-2b infection in a case of chronic spastic paraparesis, clinically indistinguishable from HAM/TSP. This is the first description of HAM/TSP-like illness caused by this HTLV-2 subtype that had not been identified before in Rio de Janeiro/Brazil.

Jacobson et al. (1993) reported the first case of HTLV-2 infection associated with neurological disorder (Jacobson et al. 1993). However, even with some countries presenting high prevalence of infections due to this HTLV type, there are only a few reports concerning neurological manifestations in HTLV-2 infection (Jacobson et al. 1993; Lehky et al. 1996; Araujo and Hall 2004).

HTLV co-infections are not rare particularly in some risk groups (Araujo and Hall 2004). In our report, the patient presented HCV chronic infection. HCV can result in some extrahepatic manifestation (EHM) such as neuropathy, whose immunopathological mechanisms are related to symptomatic disease. In our study, neuropathy was excluded by normal electroneuromyography. Furthermore, he did not present any evidence of an autoimmune disorder.

The patient presented normal CSF, but for the presence of HTLV-1/2 antibodies. This finding has also been observed in the majority of HTLV-2-infected individuals with neurological alterations. Increased protein concentration and intrathecal synthesis of antibodies are rarely reported (Lehky et al. 1996; Araujo and Hall 2004) was not observed.

It is well established that the proviral load influences the disease progression in HTLV-1-infected individuals (Murphy et al. 2004; Silva et al. 2007; Melamed et al. 2013; Rosadas et al. 2013). In this context, Murphy et al. (2004) showed that the proviral load is higher in HTLV-1 than in HTLV-2-infected individuals. This could explain why disease progression is most commonly associated with HTLV-1 infection (Murphy et al. 2004). HTLV-1 and HTLV-2 present different forms of regulatory Tax protein that seems to be related with the viral pathogenesis. Higuchi and Fujii (2009) described that HTLV-1 and HTLV-2-infected T-cells grow equivalently in environments with high concentration of T-cell growth-promoting cytokines (such as interleukin-2). However, under conditions of low levels of these cytokines, as is observed in vivo, HTLV-1-infected cells can grow more efficiently than HTLV-2-infected T-cells. This difference may be linked with the diversity of Tax protein in these viral types. This would result in an increased expansion of HTLV-1-infected T-cell and a high proviral load (Higuchi and Fujii 2009).

Regarding the HTLV-2 subtypes, to date, only HTLV-2a has been associated with neurological disorders. Murphy et al. (2004) demonstrated that HTLV-2a-infected individuals presented a high proviral load when compared to those with HTLV-2b. This could lead to more severe infection caused by HTLV-2a, which may determine its association with disease. Interestingly, it was previously reported that HCV-infected patients show higher levels of circulating cytokines, such as interleukin-2, than non-infected individuals (Sofian et al. 2012). By hypothesis, the HCV co-infection could be contributing to the proliferation of HTLV-2b-infected T-cells in the reported case. Lehky et al. (1996) observed that three of four patients with neurological disorder associated with HTLV-2a were co-infected with HCV.

In fact, the proviral load of the studied patient was higher than other HTLV-2a symptomatic patient that was previously described (Silva et al. 2002).

These findings confirm that HTLV-2b may be related to neurological disorders and serve as an alert to the possible role of HCV co-infection in the neuropathogenesis of HTLV-2 infection.

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Conflict of interests The authors declare that they have no conflict of interest.

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