Therapeutics, Pharmacology and Clinical Toxicology
Vol XIV, Number 2, June 2010
Pages 152-154

CASE REPORT

THE ROLE OF HTLV IN ONCOGENESIS (CASE PRESENTATION)

Victoria Bîrluțiu[1], Cristina Rezi[2]

[1.] *Associate Professor, Infectious Diseases Clinic Sibiu*
[2.] *Resident physician, County Clinical Hospital Sibiu*

Abstract. Adult's T cell leukemia/lymphoma is an endemic pathology in South-Eastern Asia, Japan and the Caribbean area, generated by the infection with Human T Leukemia Virus 1 (HTLV-1). We present the case of a 62-year old patient, diagnosed with T cell leukemia, with positive anti HTLV-1 antibodies and comorbidities with unfavorable evolution. Although the evolution of HTLV-1 infection is generally considered as being slow, posing a moderate risk, our patient's evolution was rapidly progressive in the absence of antiviral therapy, with acute hepatic failure possibly secondary to an association of chronic C hepatitis.
Keywords: HTLV-1, leukemia, lymphoma, hepatitis C

Introduction

Human T-cell lymphotropic viruses types 1 and 2 (HTLV-1 and 2) are viruses with transmission similar to that of HIV infection (sexual transmission, exposure to contaminated blood, intravenous drug use, breastfeeding from seropositive mother), frequently present concomitantly (coinfections), serotype 1 being more frequent in the Southern Hemisphere, while HTLV-2 is more frequent in the Northern Hemisphere.

The HTLV-1 infection is endemic in the South of Japan, the Caribbean, South America, Africa, the HIV/HTLV-2 coinfections having been identified predominantly in Europe and the US [1]. Despite a prevalence of 10-20 million HTLV infections, a small number of persons are symptomatic.

Another similarity between HIV and HTLV-1 is the affinity towards the CD4+ T cells, while HTLV-2 acts on the CD8+ cells, even manifesting a protective role for the progression of HIV infection.

Although included in the retroviridae family, as is HIV, they present significant differences: they stimulate lymphocyte proliferation, they do no present cytopathic effects or clonal replication, as compared to the immunologic drop, the cytopathic activity and the active replication which are characteristic for HIV.

HTLV-1 is associated with adult T cell leukemia (as identified in 1979) and with progressive neurologic affliction, HAM/TSP (HTLV-1-associated myelopathy/tropical spastic paraparesis), uveitis, chronic infectious dermatitis.

HTLV-2 is suspected to possibly be involved in HAM/TSP, an increase in the susceptibility to bacterial infections.

HTLV-3 and HTLV-4 have been recently identified; their role in human pathology being currently under evaluation [2, 3].

HTLV-1 is included in the Deltaretrovirus genum, it has a diameter of 100 nm, proteolipid envelope and icosaedric capsid distribution; is possesses one-strand positive-sense RNA and 3 important structural enzymes: integrase, protease and reverse-transcriptase. It is found intracellular after attachment to the GLUT-1 receptor (Glucose transporter 1); under the action of viral RNA reverse-transcriptase it is transformed into one-strand DNA, it is inserted in the host-cell DNA as

Victoria Bîrluțiu
Șos. Alba Iulia, Nr. 79, Bl. 23, Ap. 8
Loc. Sibiu, Jud. Sibiu, cod 550052
email: victoriabirlutiu@yahoo.com

provirus, under the action of the integrase. HTLV replication is minimal, with initial nondetectable viremia, the cell affliction being due to cell-cell contact, and later on being dependant on cellular mitosis. The consequence of this type of multiplication is its good genomic stability, compared to that of HIV, which is exposed to an extreme genomic variation, due to a rapid replication rate [4].

The organism's response to the presence of HTLV is generated through cell mediation, through CD8+ class I lymphocytes, with a lytic aggressive activity in the CNS in cases of HAM/TSP, thus accentuating the myelopathy.

Adult's T cell leukemia/lymphoma is endemic in South-Eastern Asia, Japan and the Caribbean region, being caused by the HTLV-1 infection. Patients frequently present adenopathies, hepatosplenomegaly, lytic bone lesions, and leukemic hematological pattern. Meanwhile, cutaneous lesions develop: erythema, papules and nodules. The cells can be either small or large, with hyperlobed nuclei, flower or clover-shaped. The evolution over time is slow, presenting a moderate risk.

The transformation ability is attributed to the Tax protein which acts as a viral LTR transcriptional activator which recruits other transcriptional coactivators, interacts with a variety of cellular proteins, influences the cytokine production, the nucleocytoplasmic transport, the replication of chromosomal DNA, mitosis, proliferation, viral replication and apoptosis.

Case presentation

We present the case of a 62-year old male patient, from the urban area, which presented to the Clinic of Infectious Diseases Sibiu for fever, dysphagia, chewing difficulties, asthenia, inappetency, weight loss, recent generalized cutaneous papulo-nodular pruriginous lesions.

The patient's personal history revealed TB pericarditis, coronary artery bypass which had required numerous blood transfusions, high blood pressure, mixed chronic hepatitis (hepatitis C virus and toxic-carential hepatitis).

The **clinical objective examination** revealed: mediocre-altered clinical state, without scleral-tegumentary jaundice, without apparent adenopathy, physiologic breath sounds, normal pulmonary percussion, without additional murmurs, rhythmical, strong cardiac sounds, HR=80/min, BP=120/70 mmHg, IInd degree rigid hepatosplenomegaly, ulceronecrotic lesions of the oral cavity.

Due to the fact that the patient presented biologic parameters suggestive for leukocytosis (56700 leukocytes/mm^3), with 85% lymphocytosis, we requested a hematologic consult, which resulted in suspicion of T-cell lymphoproliferative syndrome. The patient was transferred to the Fundeni Clinical Institute for immunophenotyping, and the diagnosis of adult T-cell leukemia/lymphoma was established, with positive anti HTLV-1 antibodies. The patient's clinical state altered abruptly, the patient developing intense jaundice (with total bilirubin levels of 31mg/dl, direct bilirubin levels of 30mg/dl), with moderate hepatocytolysis syndrome, significant leukocytosis 126900/mm^3, thrombocytopenia, coagulation issues both on the intrinsic and on the extrinsic pathway, comatose state.

The patient was started on dexamethasone 40mg/day, Ursofalk 4 tablets/day, Phenobarbital, Vincristine 1 mg (low doses of chemotherapics because of the hepatic failure). The patient was discharged at the family's request with worsened clinical state, in hepatic coma, with fetor hepaticus, cutaneous-mucous hemoragipar syndrome (purpura, epistaxis), oliguria, hyperchrome urines, upper limb edema, significantly regressed cutaneous nodular lesions, with admittance of the patient to the Hematology Ward, Sibiu.

Paraclinical investigations revealed the following: L **78300**-48500-35300-43100-42500/mm^3, Hb 12.7-10.5-9.6-11.3-10.5g/dl, Ht 36.7-30.5-28.7-30.7-29.6%, Thb **24000**-38000-115000-62000-100000/mm^3, reticulocytes 9.2%, fibrinogen 225mg/dl, negative fibrin monomers, PT 23.9 -19-18-17.9 sec (TQ 34-45-49-48%), APTT 32-33.5-29.5-28.5 sec, R 1.10-1.15-1.02-0.98, IgG 1372mg/dl, IgA 331mg/dl, IgM 168mg/dl, glycemia 123mg/dl, urea 94-152-**198** mg/dl, creatinine 1.18-**1.95** mg/dl, uric acid 3.7 mg/dl, Ca 5-4.6 mEq/l, FAS 64-79-80u/l, TGP 79-75u/l, TGO 129-116u/l, GGT 140-110-90u/l, cholinesterase **3572** u/l, BT **58**-57.6-40mg/dl, BD **32.37**-33.26-31.03mg/dl, ELFO: PT 5.5-5.9g/dl, A 56.9%, α1 3.6%, α2 6.7%, β1 7.9%, β2 5%, γ 19.9%, A/G 1.32, positive Adler reaction, negative hemocultures.

Leukocyte formula: N=0, S=40, E=0, B=0, L=54, M=6%, small group thrombocytes, polymorphic lymphocytes ranging from small lymphocytes to large ones, irregular flower-shaped nucleus, mature chromatin without nucleoli. Conclusion: aspect suggestive for adult T-cell leukemia/lymphoma.

The treatment included: parenteral hydration, vitamin therapy, hepatoprotectors, human

albumin, fresh frozen plasma, induced diuresis, antibiotherapy, corticotherapy (high doses), gastric protectors.

The evolution was slowly favorable at first, with clinical regression of the purpuric lesions, recovery from coma, with biologic increase in the number of thrombocytes to 100000/mm^3, decrease of leukocytes to 32000/mm^3. The patient eventually presented digestive hemorrhaging clinically evident through melena, with accentuation of the azoth retention syndrome, severe hypopotasemia, cardiac rhythm perturbation, dyspnea, polypnea, with severe metabolic acidosis (pH 7, HCO3 8mmol/l, oxygen saturation of 65). The patient entered a comatose state again and was discharged with worsened clinical state at the family's request.

Discussions

Although most cases of adult T-cell leukemia/lymphoma display a slow evolutive pattern, with moderate risk, the case that we have presented showed a rapidly unfavorable evolution in the absence of antiviral therapy, progression to acute hepatic failure and exitus, having a background of association with chronic viral hepatitis C. The aggressive outlines of leukemia induced by HTLV-1 require hematopoietic stem cells transplantation or combined chemotherapics, cyclophosphamide, hydroxydoxorubicin, vincristine and prednisolone at high doses, with favorable evolution in 66% of cases, out of which 25% with complete remission, the survival rate at 3 years being of 12.7% [5]. The use of other therapeutic regimens, such as VCAP (vincristine, cyclophosphamide, doxorubicin, prednisolone), AMP (doxorubicin, ranimustin, prednisolone), VECP (vindesine, etoposide, carboplatin, prednisolone) increase the rate of response to 72%, with 40% complete response. The use of bortezomid, proteasome inhibitor which blocks the degradation of kB inhibitors with anti-CD25 antibodies, inhibits the activation of NF-kB, strongly associated with oncogenesis. The use of zidovudine and alpha interferon confer a complete response in 58% of cases, and a partial response in 33% of cases. The antitumoral effect of the Tax-target vaccine is currently under evaluation.

It is also worth mentioning that a family investigation was performed, the patient's wife being detected positive for HTLV-1, and currently being asymptomatic.

References

1. Gifford R, Tristem M. The evolution, distribution and diversity of endogenous retroviruses. *Virus Genes* **26(3), 291–315 (2003)**

2. Retroviral Proteomics and Interactomes: Intricate Balances of Cell Survival and Viral Replication, Posted: 07/14/2008; *Expert Rev Proteomics*. **5(3):507-528(2008)** Expert Reviews Ltd.

3. Calattini S, Chevalier SA, Duprez R et al. Discovery of a new human T-cell lymphotropic virus (HTLV-3) in Central Africa. *Retrovirology* **2,30(2005)**.

4. Ruggiero E, Bona R, Muratori C, Federico M. Virological consequences of early events following cell-cell contact between human immunodeficiency virus type 1-infected and uninfected CD4+ cells. *J Virol*, **82:7773-7789(2008)**.

5. Yasunaga J, Matsuoka M. Human T-Cell Leukemia Virus Type 1 Induces Adult T-Cell Leukemia: From Clinical Aspects to Molecular Mechanisms, Posted: 05/14/2007; *Cancer Control.* **14(2):133-140 (2007)** H. Lee Moffitt Cancer Center and Research Institute, Inc.