

Implications of human T-lymphotropic virus in pregnancy: A case report and a review of the diagnostic criteria and management proposal

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Abstract. Human T-lymphotropic virus (HTLV) is considered to be the most highly oncogenic existing virus, being the cause of several fatal diseases such as adult T cell leukemia-lymphoma (ATL) and HTLV-I-associated myelopathy (HAM). The main transmission methods are unprotected sexual intercourse, vertical transmission and breastfeeding and direct exposure to infected blood or tissue. The identification of infected mothers prior to delivery is a highly important step in preventing mother to child transmission. Universal antenatal screening for HTLV is not recommended in Romania, although there are sufficient data demonstrating the risk of vertical transmission. We present the case of an HTLV-1-infected pregnant woman, with an aim to highlight: i) points of strategy for the management of HTLV during pregnancy; ii) the particularities of the course of pregnancy; and iii) the aspects that show the importance of knowing the status regarding the HTLV infection antepartum. The case was particular due to the ascendant proviral load during the pregnancy period, which led to the initiation of antiretroviral therapy and the particular pregnancy outcome with preterm rupture of membranes and fetal growth restriction. According to current recommendations,

pregnant women infected with HTLV-1 should be advised to refrain from donating blood, body organs, or other tissues. There is no evidence of the number of individuals infected with this virus in Romania at present, and the diagnosis can only occur by chance. A specific treatment or immunization for HTLV infection does not currently exist, thus preventive methods are the only tool to reduce the prevalence and mortality of this infection.

Introduction

Human T-lymphotropic virus (HTLV) is considered to be the most oncogenic virus existing, due to its association with several fatal diseases, such as adult T cell leukemia-lymphoma (ATL) and HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). It is the first retrovirus discovered (1). The pathologies associated with HTLV-1 infection are characterized by a high morbidity and a median 8 month survival rate. The two diseases ATL and HAM present separately and are linked to the method of transmission: Respectively ATL with breastfeeding and HAM with blood transfusion, overlapping cases being extremely rare (2).

In contrast to human immunodeficiency virus (HIV) infection, the HTLV viremia is of extremely low level; the infection occurs through the transmission of infected lymphocytes and no cell free viral particles (3). HTLV-1 manifests a CD4 T cell tropism, and after infecting the cell, the RNA genome suffers reverse transcription, resulting in a DNA sequence, which induces cellular transformation by viral gene products, interacting with host proteins and altering their function (4). Regarding the pathogenesis, HTLV type 1 is similar in multiples ways with HIV-1, but the differences are also notable. First, the replication rate is much lower in the HTLV-1 infection, having a high fidelity replication, which results in high genetic stability with reduced chance of immune escape. Secondly, the T cells infected with HTLV-1 suffer mainly transformation and proliferation, but not death (5).

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HTLV-1 affects about 5-10 million individuals worldwide, with a prevalence that grows directly proportional with age and preponderantly affects women. The main transmission methods are unprotected sexual intercourse, vertical transmission mainly through breastfeeding, although transplacental transmission can also occur, as well as direct exposure to infected blood or tissue. The risk of developing ATL following infection with HTLV-I is estimated to be 2 to 5%, usually after several decades (6). The clinical features of ATL include generalized lymphadenopathy, hepatosplenomegaly, immunosuppression, hypercalcemia, lytic bone and skin lesions; patients with ATL are also at risk for HTLV-I-associated myelopathy (2,7,8). HAM/TSP is characterized by an insidious onset of progressive weakness and spasticity of one or both legs, hyperreflexia, ankle clonus, extensor plantar responses, detrusor instability and back pain (9).

The presence of HTLV-1 antigen in breastmilk has been previously demonstrated (7). Breastfeeding in such cases is associated with a high infection risk, respectively a 4-fold increased risk compared to bottle-fed infants. Once infected, 10% of the cases will progress to one of the diseases mentioned above. Taking into account that treatment for these cases remains limited, prevention becomes essential.

The identification of infected mothers prior to delivery is a highly important step in preventing mother-to-child transmission. The diagnosis of HTLV infection relies on anti-HTLV antibody detection by enzyme linked immunoassay (ELISA) or chemiluminescent microparticle immunoassay (CMIA), requiring further confirmation by western blot analysis and detection of HTLV DNA by polymerase chain reaction (PCR) (10-12).

HTLV-1 is endemic in southwestern Japan, the Caribbean, Central and South America, intertropical Africa and the Middle East; due to high prevalence of infection, a national HTLV-1 screening program for pregnant women was started in 2011 in Japan. Despite the aforementioned information, universal antenatal screening for HTLV is not recommended in Romania, although there are sufficient data demonstrating mother-to-child transmission. The main reasons why this screening program has not been implemented in other countries include the difficulty in diagnostic testing, and the prevalence and impact on the health system, which is not valid reasoning (13,14).

In the present report, we present the case of a HTLV-1-infected pregnant woman, with an aim to highlight: i) points of strategy for the management of HTLV during pregnancy; ii) the particularities of the course of pregnancy; and iii) the aspects that show the importance of knowing the status regarding the HTLV infection antepartum.

Case report

A 34-year-old woman presented to the obstetrics service for specialized control in the context of a positive pregnancy test. The patient's personal medical history included HTLV-1 infection, diagnosed 4 years prior, randomly, after blood donation. From the gynecologic anamnesis, we noted an abortion on request, with no post-procedural complications and a modified cytology result, namely ASC-US. At this point, the obstetrical clinical evaluation was normal, with normal sonographic aspect

of an early pregnancy. The patient was counseled regarding the risks associated with the HTLV infection in pregnancy and directed to the infectious disease specialist for consultation and specific recommendations. As for the cytology result, an HPV test was recommended. The pregnancy course was uneventful, except for the result of the HPV16 test, which was positive according to the protocol. A colposcopy exam was performed with no lesions found and no treatment was instituted at that time. According to the infectious disease specialist advice, the patient was carefully monitored biologically and virologically. At the beginning of the third trimester, maternal serum HTLV antibodies were significantly increased, from 220 copies HTLV-1/10⁶ peripheral blood mononuclear cells (PBMCs) to 1194 copies HTLV-1/10⁶ PBMCs.

Regarding the fact that there is a strong correlation between the HTLV-1 proviral load and the clinical status and manifestation of carriers, the decision by mutual agreement, through interdisciplinary consultation, was to institute combined antiviral treatment lamivudine and zidovudine (300+600 mg). Multivitamin supplementation was maintained for the entire pregnancy duration. Subsequently, the viral load decreased, being 872 copies HTLV-1/10⁶ PBMCs close to the time of birth. At 37 weeks of gestation, preterm premature rupture of membranes occurred and a male fetus of 2,440 grams, with an APGAR score at 1 min of 9 was delivered by Cesarean section. Interestingly, the pathological examination of the placenta did not reveal any suggestive changes in chronic villi inflammation or any suggestive cellular changes for a viral infection. The newborn had an excellent adaptation and a smooth neonatal period. The neonate and the mother were discharged 3 days postpartum. The mother received ablactation treatment (cabergoline), as the obstetrician and neonatologist decided feeding with age-adapted formula. The first neonatal test, at 2 weeks of birth, showed the presence of HTLV 1+2 antibodies most likely of maternal origin, having a value of 130 copies HTLV-1/10⁶ PBMCs. Other abnormalities on general blood tests were not registered. The particularity of this case consists in the increased proviral load during the pregnancy period, which led to the initiation of antiretroviral therapy and the particular pregnancy outcome with preterm rupture of membranes and fetal growth restriction.

Discussion

A biomarker to identify those infected patients susceptible to develop HTLV-1-related pathology has not been described, to date. However, it is speculated that viral load would have a significant influence in this direction. In the context of pregnancy associated with a degree of immunomodulation, an increase in viral load is likely. Various risk factors for HTLV-1 infection have been reported in pregnant women or in women of reproductive age which include: increasing age, young age at first sexual intercourse, history of abortion and history of transfusion, history of sexually transmitted infections, multiparity, low income, low educational level, high number of sexual partners, and relatives with history of leukaemia/lymphoma. Considering that the HTLV-I carrier mothers generally detected belong to a low socio-economic class, it should be interesting to study the role of malnutrition in susceptibility to infection, take into account the magnitude of hypovitaminosis

and the impact of it on immunological system, especially in low income class and endemic areas (15-19). Anyway, we did not find any risk factor in our case, the age of the mother being under 40, and healthy supplemented nutrition proving ineffective in prevention of viral load increase.

Unavailability of purified HTLV-1 viral enzymes makes it difficult to create a specific treatment, thus, since HTLV-1 is very similar to HIV-1 regarding the mechanisms of reverse transcription, specific HIV antiviral treatment can be used in order to reduce the possibility of vertical transmission, but there have been only limited studies of specific antiretroviral therapy for HTLV-I infection (20-22). HTLV-1 differs by epidemiology and disease association from HTLV-2, thus these are two different retroviruses. After confirmation of infection, the patient, independently of her obstetrical status, should be counseled and should receive all the necessary information. First, the fact that HTLV-1 is not AIDS should be clarified (23). In addition, patients should be aware of the fact that HTLV-1 is a lifelong infection that can be transmitted through blood products, tissue, or breastfeeding. The preconception visit must include advice for protection, respectively using condoms at all times, except during the fertile period, and clear data concerning the risk of vertical transmission.

Another topic that has not been given enough attention in the literature is the possibility of stem cell storage at birth in HTLV-positive patients. In the process of umbilical cord storage, a sample of the mother's blood is collected and tested for HIV, hepatitis B and C and syphilis, but only in individual circumstances is the test for HTLV performed. The actual recommendation at recruitment for adult volunteer donor and maternal donor (cord blood donation) is of permanent exclusion for donors with HTLV-1 and -2, a fact justified by the high degree of immunosuppression of hematopoietic stem cell transplantation recipients and concomitant associated risk of infection. HTLV-1 has a predilection for CD⁺ T helper cells, thus the declared rate of transmission of 13-75% may be even greater in the case of hematopoietic stem cell product transplantation (24). In summary, pregnant women infected with HTLV-1 should be advised to refrain from donating blood, body organs, or other tissues. Regarding the pregnancy outcome of these cases, a high rate of premature ruptures of membranes (PROM) has been described among infected mothers, namely 25%; PROM also complicated our case. In addition, cases of HTLV infection have been associated with an increased risk of premature birth, but were not in turn associated with intrauterine growth restriction (25-32). Tohyama *et al* (33), described in 1992 a case of fetal hydrocephalus considered to represent a case of congenital HTLV-I infection; other reports analyzed the pathogenic role of inflammation on the development of fetal structural anomalies (34-36). Infection of the fetal part of the placenta constitutes another important evidence of the transplacental pattern of infection. One report concerning HTLV-I infection of the placenta, immunocytochemistry and PCR trophoblastic cells cultured from placentas of HTLV-I positive mothers, detected the virus in 22% of them; our case does not underline any particular aspect of the placenta, except the small volume of it (37,38).

The main complication remains mother-to-child breastfeeding, which ranges from 3.9 to 22%. An existing policy of universal HTLV-1/2 antenatal screening will reduce this rate

to 2.5% (39). Other possible causes of mother-to-child transmission include human leukocyte antigen system (HLA) type concordance between mother-and-child, high maternal viral load and concentration level of gp46 HTLV-1/2 antibodies; peripartum infection is possible as well (39). The real evidence of child infection can be detected after 12 months, when present maternal antibodies disappear.

Multiple cases of pregnancy associated with HTLV infection have been reported in the literature. Studies have been performed in areas where this infection is significantly present on a significant number of patients (19,28,30,40). Romania is the only country registered with a high prevalence of HTLV in Europe, being considered as having the same level of prevalence as South America (41). In this context, we consider that Romania imperiously needs to develop national strategies in order to prevent the spread of this viral infection and an infected population database to quantify the magnitude of epidemiologic parameters. Conversely, testing for HTLV is not included in the pregnancy monitoring protocol, thus the vertical transmission rate is not controlled. Our next step is to establish the Romanian prevalence of HTLV infection in pregnancy and the high-risk population group for carry and vertical transmission.

In conclusion, regarding all of the facts discussed above and using the case presented, we attempted to highlight the importance of including HTLV-1 and HTLV-2 testing in the pregnancy monitoring protocol. There is no evidence of the number of individuals infected with this virus in Romania at present, and the diagnosis can only occur by chance. A specific treatment or immunization for HTLV infection does not currently exist, thus preventive methods are the only tool to reduce the transmission. Specific information on prevention is lacking among the population and even among health providers, and thus they are not fully aware about the risks of this infection, especially in pregnancy associated with significant transmission.

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Availability of data and materials

Any additional information concerning the study can be requested from the corresponding author on reasonable request.

Authors' contributions

REB conceived the article after successful management of presented case. NT and ID performed the literature search and wrote the manuscript. CB and AN contributed to the

literature review. OM and TAG conducted the follow-up of the patient and contributed to the pathological examination of the placenta. REB, FF, CB and AN collected, assembled and interpreted the data, making the revision of the manuscript, critically for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Institutional Board of the 'Life Memorial Hospital' (Bucharest, Romania).

Patient consent for publication

The patient provided informed consent for publication of the case report.

Competing interests

The authors declare that they have no competing interests.

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