

Human T lymphotropic virus related adult T-cell leukemia / lymphoma – presentation, prognosis and treatment. Case report

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ABSTRACT

We present the case of a patient diagnosed in SUUIB Hematology with adult T-cell leukemia- lymphoma. The particularities of this case are the delay in diagnosis, the apparent onset of disease with severe eye and skin determination in the leukemic phase, and the particular lung involvement in the final stage of the disease.

Keywords: ATLL, HTLV1

Patient B.R., a 49 year old woman, contacted the Hematology Department of Bucharest University Emergency Hospital in November 2007 for investigation of a lymphocytosis. When the patient presented herself, there were no subjective complaints, no peripheral adenopathy, no organomegaly, mild leukocytosis with absolute lymphocytosis (Hb 13.3 g/dl, WBC 19.2 X 10⁹/L, S 35%, Lymph 47%, Mo18%, Plt 228 X 10⁹/L), kidney samples, LDH and serum calcium within normal limits. The immunophenotype of the peripheral blood revealed atypical T lymphocytes CD4+ CD3- CD8-. The patient attended no further check-ups until March 2011, by which time she had lost about 5 kilograms in one month and had extensive maculopapular, intense itching skin lesions and conjunctival hyperemia. Ophthalmic and dermatological controls recommended antihistamine treatment, but following treatment the lesions spread.

Physical examination revealed conjunctival hyperemia, maculopapular and nodular lesions in the upper and lower limbs, bilateral axillary lymphadenopathies, with sizes reaching up to 2 cm, hepatomegaly (palpable about 2 cm below the costal line) and splenomegaly (with lower pole palpable 2 cm below costal line). Laboratory investigation revealed leukocytosis (31 X 10⁹/L) with lymphocytosis (64%). Peripheral blood smears indicated polymorphic lymphocytes, some with vacuoles. Bone marrow aspiration showed 22% polymorphic lymphocytes, some large, with condensed chromatin, irregular nucleus, basophilic cytoplasm. The immunophenotypical examinations of the peripheral blood and bone marrow confirmed once more the mature phenotype of the helper T-cell CD3+ CD4+ CD8- CD7- CD5-/+ CD2+ TCR alpha/beta+ CD25+ (see Figure 2). Laboratory analyses showed normal serum calcium 10.32 mg/dl (N

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8.2 to 10.7 mg/dl), and a high LDH level that was 3 times than normal value, 555 U/L (N 120-190 U/L). The computer tomography shows adenopathies in the mediastinum, with diameters up to 9 mm, in the abdomen (celiacs 1.5 cm, interaortocav 1 cm, lateroaoortic 3/1.5 cm, mesenteric 1 cm, distal external iliac up to 3.3 cm on the left and 2.3/1.4 cm on the right), spleen 13.3 cm. The histopathological and immunohistochemical examinations of bone and skin biopsy confirmed lymphomatous determination in these regions. Bone marrow examination revealed interstitial and intertrabecular nodular lymphoid infiltrates, with medium cells, with irregular nuclei, representing 25% of cellularity, with preserved residual haematopoiesis, CD3+ and CD20- in tumour cells. Skin biopsy revealed in the superficial dermis, perivascular, areas of polymorphic lymphocytic infiltration, with small, medium and large cells; epidermotropism-rare tumour cells ascended in the epidermis or arranged in „single file” in the basal layer. Immunohistochemistry established the cutaneous involvement of non-Hodgkin T-cell lymphoma with expression of CD3+ CD4+ CD8+ CD25+ in frequent tumour cells. In front of an activated T lymphocyte phenotype, the next step was to investigate the serology for HTLV1. Infection with HTLV1 (Human T-cell leukemia virus type-1) was confirmed by Southern blot. Lymphocytosis over 4000/mm³ with atypical lymphocytes more than 5%, increased LDH more than twice the normal value, bone marrow and skin involvement established the diagnosis of adult T-cell leukemia/lymphoma HTLV1 + acute variant, evolved from the chronic variant, which patient

had presented 4 years ago (lymphocytosis with atypical lymphocytes more than 5%, LDH and serum calcium value within normal limits). Anti-retroviral therapy (ART) – Combivir- was initiated at Infectious Diseases Hospital. When the patient was readmitted to our Hematology Department, physical examination revealed expansion of the skin lesions (see Figures 4 and 5), of the peripheral adenopathy and hepatosplenomegaly. Blood count showed marked leukocytosis ($135,4 \times 10^9/L$) with lymphocytosis, with atypical lymphocytes – „flower cell” – 89% – small cells, with irregular nucleus, slightly incised, with slightly condensed chromatin, little slightly basophilic cytoplasm, with vacuoles (see Figure 1).

Biological samples showed hypercalcemia of 12.1 mg/dl, an LDH about 3.5 times what is normal (658 U/L). Due to the aggressive evolution of the condition, we decided to initiate VCAP-AMP-VECP protocol, with antiretroviral therapy. The patient received five cycles of chemotherapy. The evolution was slowly favourable, with blurring and disappearance of the skin lesions and of the conjunctival hyperemia, decrease of the spleen size, disappearance of the peripheral adenopathies, gradual decline in the number of leukocytes and transient disappearance of the atypical lymphocytes in peripheral blood, normalization of serum calcium and LDH value. Due to increased infectious risk the treatment was combined with prophylactic antibioticotherapy: trimethoprim sulfamethoxazole, acyclovir and flucovim. Because the chemotherapy were followed by severe aplasia, especially persistent leucothrombocytopenia, even under treatment

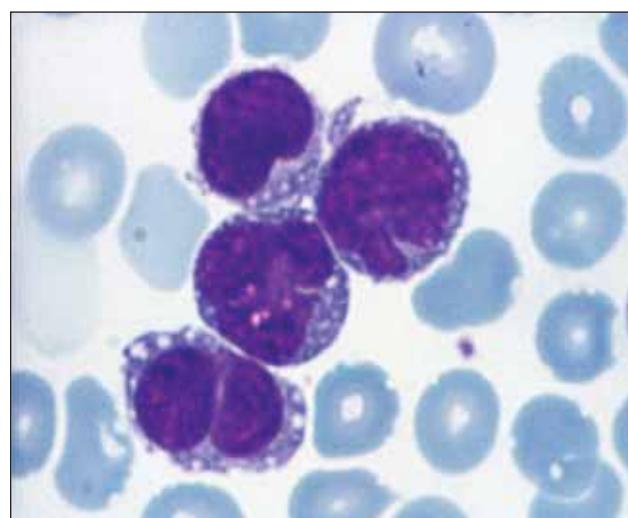
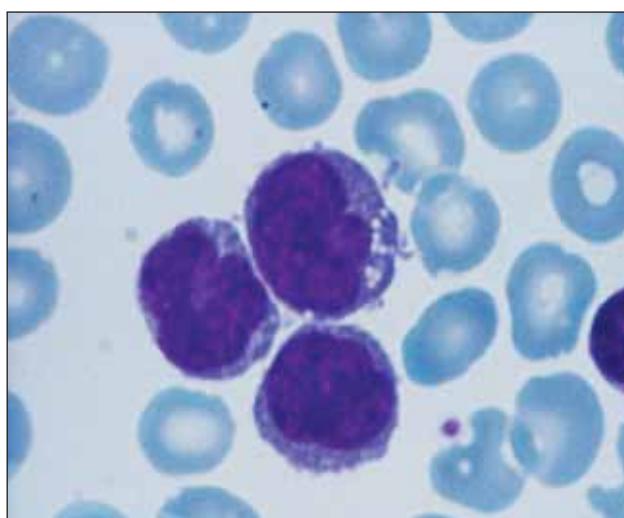


FIGURE 1. Optical microscopy of peripheral blood in ATLL patients – „flower cell” – small cells, with irregular nucleus, slightly incised, with slightly condensed chromatin, little slightly basophilic cytoplasm, with vacuoles

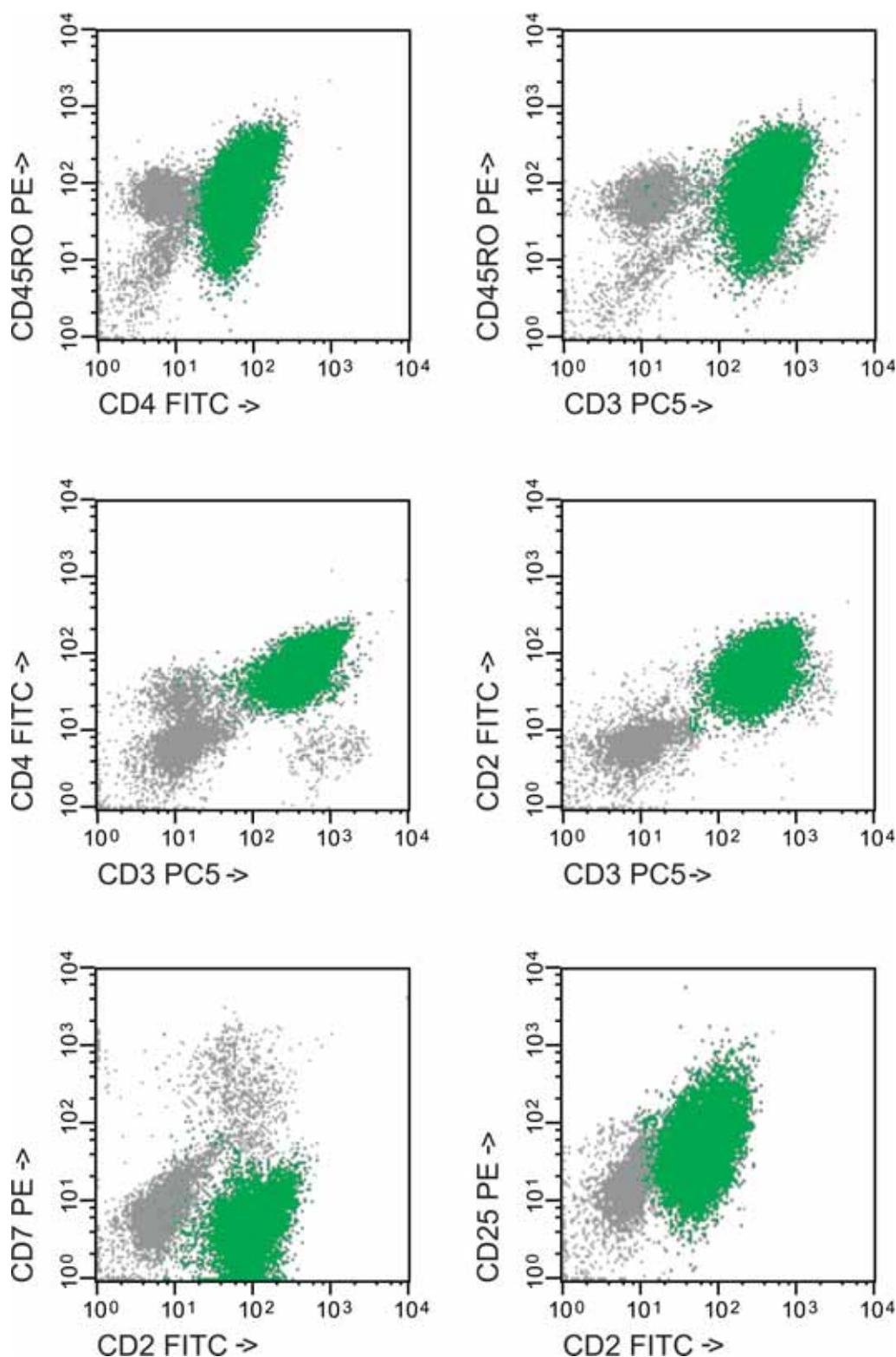


FIGURE 2. Dot-plot histograms represents immunophenotypical analysis of the peripheral blood and bone marrow confirmed once more the mature phenotype of the helper T-cell CD3+ CD4+ CD8- CD7- CD5-/+ CD2+ TCR alpha/beta + CD25 +.

with granulocyte growth factors and substitution treatment, with the improvement of disease status (after 5 complete cycles), we choose to continue treatment with interferon + ART.

The patient remained balanced until October 2011, when skin lesions reappeared and atypical lymphocytes recurred in peripheral blood. Her general condition deteriorated gradually, so



FIGURE 3



FIGURE 4

FIGURES 3 and 4. Photos showing maculopapular and nodular lesions on the skin in patient with ATLL

that in January 2012, she was admitted to our hospital with marked weight loss, about 8 kilograms in one month, irritating cough, dyspnoea. Laboratory values were normal for haematological parameters, serum calcium within normal limits, but LDH value increased approximately 5 times normal (1151 U/l, N 81-234 U/l). Due to bacteriological examination (cytology and cultures of sputum, bronchoalvelolar lavage, blood cultures), reevaluation of infectious diseases excluded infection with BK and other germs, and under treatment with broad-spectrum antibiotics pulmonary lesions progressed. The chest radiography revealed disseminated micronodular opacities in both lung fields, some with central necrosis. Computed tomographic scan confirmed the lung injury and raised suspicion of pleural, pericardial infiltration and infiltration of the great omentum, and reveals axillary, mediastinal and abdominal lymph nodes, with diameter up to 1 cm (see Figure 5).

Laboratory samples recorded hypoproteinæmia, hypoalbuminaemia, normal serum calcium value, a rapid increase in the number of lymphocytes, of LDH value, which remained nonresponsive to treatment (chemotherapy, interferon, ARV). Patient's general condition dete-

riorated rapidly, with widespread skin lesions, recurrence of conjunctival hyperemia and of a corneal ulceration, worsening dyspnea, appearance of polyserositis, and evolution towards death.

ADULTS T-CELL LEUKEMIA/LYMPHOMA

Adult T-cell leukemia/lymphoma is a neoplastic mature activated CD 4+ CD25+ T-cell lymphocytes associated infection with human lymphotropic virus (HTLV1), the first retrovirus described, which belongs to the Retroviridae family. Genetic information contained in the viral RNA is reverse transcribed with an RNA dependent polymerase in a DNA, which is then incorporated into the host genome. Viral genome is transmitted from one cell to another through the formation of „viral synapse” (1). Infection influences T-cell gene expression, leading to their increased proliferation. The disease occurs in endemic areas of infection with HTLV1: Japan, Caribbean, West Africa, the Middle East, Brazil. Recently Romania and Iran were introduced as endemic areas (2,3). Infection is acquired mostly in childhood. HTLV1 transmission is through breastfeeding (risk of transmission is approxi-

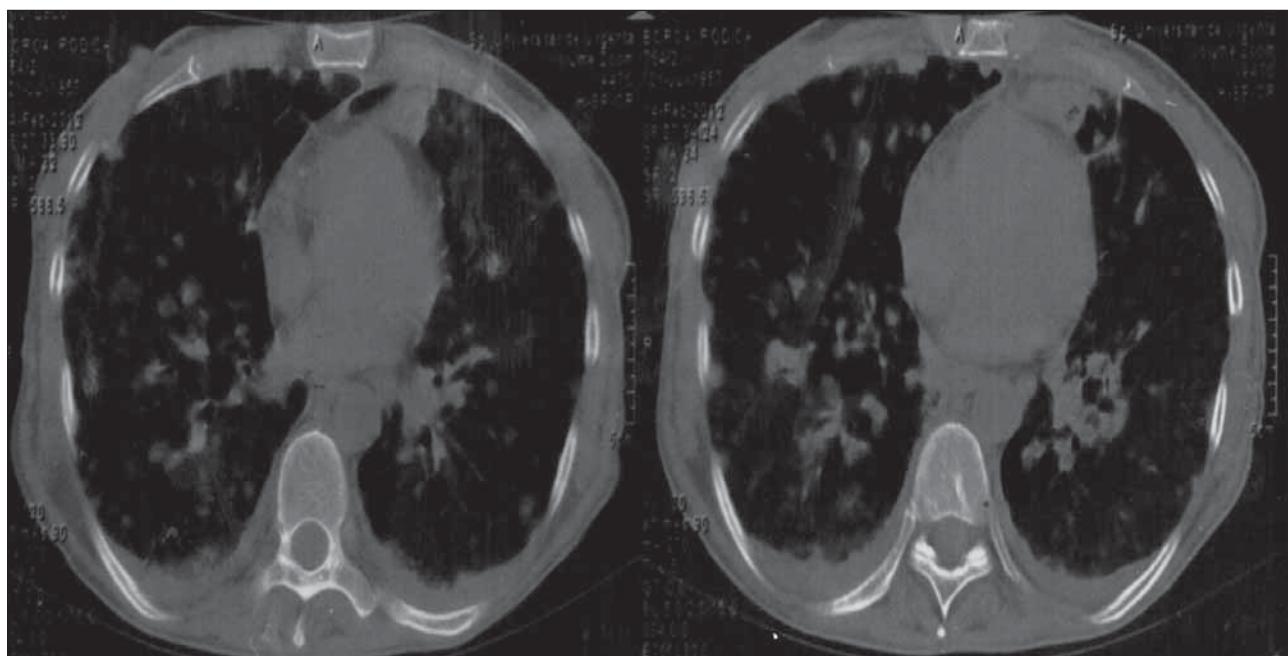


FIGURE 5. Computed tomographic scan: disseminated micronodular opacities in both lung fields, some with central necrosis.

mately 20% and correlate with duration of breastfeeding, viral load, the quantity of maternal antibodies (4-6), sexual contact (increased risk for prolonged exposure and proviral load) (7) or contact with blood from an infected person or infected blood products (risk of seroconversion is 40-60% and is increased in immunocompromised recipients) (8). It occurs only in adults, and the age at diagnosis is between 20 and 80 years (an average of 58 years), more frequently in men (1.5:1), and only at 2.5% of HTLV1 carriers (9,23).

HTLV1 can induce a number of neoplastic diseases with leukemic expression (as smouldering, chronic, acute type), nodal involvement (Hodgkin-like type, pleomorphic small cell type, pleomorphic medium and large cell type, anaplastic large cell type), skin involvement (erythema, papule, nodule), liver involvement (sinus or portal infiltration) or bone marrow involvement (infiltration with or without fibrosis). Reactive diseases associated with HTLV1 infection have also been described, some confirmed (HTLV1 associated myelopathy, HTLV1 associated uveitis, HTLV1 associated lymphadenitis), and others unconfirmed (HTLV1 associated bronchopneumopathy, HTLV1 associated atropathy, HTLV1 associated nephropathy) (9).

Depending on the clinical characteristics and prognosis, four clinical forms of ATL have been described in Shimoyama Classification: acute, lymphomatous, chronic and smouldering (10).

The **smouldering form** is characterized by normal numbers of lymphocytes, at least 5% atypical T-cells in peripheral blood, absence of hypercalcemia, LDH value up to a level 1.5 times normal, the absence of adenopathies, the absence of hepatosplenic, gastrointestinal, bone and CNS involvement, and the absence of ascites and pleural effusion. Skin and lung damage may be present. If the number of atypical lymphocytes in peripheral blood is less than 5%, at least one cutaneous or pulmonary impairment must be histologically proven.

The **chronic form** is characterized by an absolute lymphocytosis ($4 \times 10^9/1$ or more), and atypical T lymphocytes more than 5%, LDH value not exceeding twice the upper limit of normal, the absence of hypercalcemia or CNS, bone, gastrointestinal involvement. Ascites and pleural effusion are also absent. Adenopathy, hepatosplenic cutaneous or pulmonary involvement may be present. The Japan Clinical Oncology Group (JCOG) described three risk factors (blood urea nitrogen, serum albumin, and the serum LDH value) which defined two subgroups for chronic form: favourable and unfavourable, with implications for prognosis and treatment decision. Increased blood urea nitrogen level above the normal upper limit, serum albumin level below the normal lower limit, and LDH above the upper limit of normal was defined as unfavourable chronic ATL, whose prognosis is as poor as for other aggressive ATLs (11-13).

The lymphomatous form is described by lymphocytosis and atypical T-cells less than 1%, and nodal or extranodal involvement has been histologically proven.

The acute form (leukemia) involves large numbers of leukocytes and more than 5% atypical lymphocytes, eosinophilia, cutaneous involvement, generalized adenopathy, hepatosplenomegaly, hypercalcemia with or without lytic lesions, increased serum LDH level (over 2 times normal). Most patients have T lymphocyte immunosuppression related damage, causing frequent opportunistic infections such as *Pneumocystis carinii*, *Strongiloides*. Progression from a smouldering or chronic form to an acute form is slow and occurs in 25% of cases.

Morphologically, a neoplastic cell is typically medium-large size, sometimes with pronounced nuclear polymorphism, with coarse chromatin, with distinct nucleoli; blastic looking cells with dispersed chromatin are present in varying numbers; the cell appearance (young or mature) does not correlate with clinical outcome, except for chronic and smouldering forms, in which lymphocytes are morphologically similar to normal lymphocytes. The characteristic aspect is described as a „flower cell“ – with intense cytoplasmic basophilia.

The specific immunophenotype is of a mature helper T lymphocyte: CD2+ CD3+ CD5+, CD7-frequently, CD4+ D8- in most cases. There are expressed markers of activation cell (CD25+ highly expressed in most cases). The converted large cells can be CD30+, but are always negative for ALK (anaplastic lymphoma kinase) and cytotoxic molecules. There are expressed frequently CCR4 and FOXP3- which are characteristic for regulatory T-cells (9,14).

Neoplastic cells present monoclonal integration of HTLV19 in the genome of tumour cells (this is not found in healthy carriers). Almost all cases of ATLL have numerical or structural chromosomal abnormalities, but there is no one specific anomaly.

Survival varies from several weeks to more than one year for acute forms (median survival 6.2 months) and lymphomatous forms (median survival 10.2 months), while for chronic forms, evolution is longer (median survival 24.3 months), with the possibility to evolve to a more aggressive form. For the smouldering form, average survival could not be determined (15).

Death occurs after an opportunistic infection (*pneumocystis carinii*, herpes zoster, *Cryptococcus meningitis*), hypercalcemia.

Treatment for adult T-cell leukemia/lymphoma must be differentiated based on clinical form and prognostic factors.

The major prognostic factors are clinical factors (such as subclinical, age over 40 years, poor performance status, serum LDH level increased, more than three affected areas, hypercalcemia) and molecular factors (Ki 67 expression in ATL cells, suppressor p53 gene deletion or overexpression p15INK4B/p16INK4A and interferon Regulatory Factor 4).

Favourable chronic and smouldering forms are forms for which the prognosis is good. Currently there is a tendency to replace the „watch and wait“ option with treatment using Zidovudine +/- IFN, based on observations from a Japanese study, which suggests that survival at 5 years is higher in this situation (100% survival over 5 years versus 46% in use of other forms of treatment) (16).

Treatment for aggressive forms (acute form, lymphomatous and unfavourable chronic subtype) is different in Japan compared to other regions. Thus, in Japan LSG15 regime (VCAP-AMP-VECP) is considered the treatment of choice in aggressive forms, this protocol demonstrating superiority over CHOP-14, in a Phase III trial (JCOG9801). (17) Outside of Japan, Zidovudine (900 mg/day) + Interferon 5-6 MU^{m2}/day is preferred in acute form, while in the lymphomatous form chemotherapy remains the first-line indication (18,19).

For aggressive forms, if complete response is obtained, consolidation with allogeneic stem cells transplantation is indicated. These have the effect of graft against HTLV1 and graft against ATL. Utsunomiya *et al* reports disease free survival at 10 years for 4 patients out of 9 who also underwent allogeneic transplant (20). The indications, however, are limited by advanced age of patients and the high toxicity of the procedure. Reduced post-transplant survival was associated with being aged over 50 years, lack of complete response, male gender, use of cord stem cells (21).

To have a common language regarding the interpretation of results in clinical trials, response criteria (complete remission, partial response, very good partial response, no response) were formulated (22).

Normalization of blood counts and disappearance of all measurable lesions for at least one month was defined as **complete remission**. Identification in peripheral blood of less than 5% atypical lymphocytes is considered also as complete remission.

Very good partial response requires more than 5% of atypical lymphocytes in peripheral blood without any other measurable lesions.

Partial response is defined as more than a 50% decrease in the number of atypical lymphocytes and in the size of measurable lesions, for at least 30 days.

A decrease of less than 50% in the number of atypical lymphocytes or in the size of measurable lesions is considered **no response**. Any cases in which complete or partial response criteria do not last at least one month are also considered to be a lack of response.

Unsatisfactory responses to treatment means that studies for new therapeutic options are continuing. Agents such as arsenic trioxide, forodesine, bortezomib, lenalidomide, vorinostat pralatrexate are being tested in clinical trials.

Based on the characteristics of mature T-cell lymphocyte phenotype, studies exist relating to the effectiveness of some monoclonal antibodies in the treatment of adult T-cell leukemia/lymphoma. Daclizumab (anti-Tac antibody, anti IL2 receptor), denileukin diftitox (combined diphtheria toxin genetically IL2), siplizumab (anti-CD2 monoclonal antibody), alemtuzumab (anti-CD52 monoclonal antibody), KW 0761, CCR4 antibodies are being investigated in ongoing studies.

In the following, we will focus on several peculiarities of the presented case.

In November 2007, the patient contacted the Hematology Department of Emergency University Hospital Bucharest for investigation of a lymphocytosis, without subjective complaints. The immunophenotypical examinations of the peripheral blood performed at that moment identified a CD4+ T-cell phenotype: CD2+ CD5+ CD4+ CD7- CD3- TCR $\gamma\delta$, ratio H / S ~7/1. The diagnosis for that moment was of **positive for T-cell lymphoma CD4**, but it was not possible to complete the diagnosis, because the patient did not perform all recommended investigations until March 2011. This attitude is seen in most patients with the smouldering form of adult T-cell leukemia/lymphoma. Such patients are usually asymptomatic, and therefore the diagnosis is established by chance during routine checks. Most patients do not return for follow-up in the clinics where they were diagnosed. This is one of the reasons the prognosis is very difficult to estimate.

In March 2011 the patient returned to Hematology Department with weight loss, conjunctival hyperemia, intensely itching maculopapular skin lesions, hepatosplenomegaly and

axillary lymph nodes up to 2 cm in diameter. The blood count revealed leukocytosis ($31,2 \times 10^9/L$) with 64% lymphocytosis. The immunophenotypical examinations of the peripheral blood revealed 85% atypical lymphocytes with T helper activated phenotype CD2+ TCR $\alpha\beta$ + CD4+ CD25+ CD45RO+. Biological: normal serum calcium, LDH 555U/l. HTLV1 infection was confirmed by Western blot. Skin and bone biopsies established lymphomatous involvement at this level based on histopathological and immunohistochemical examination. Lymphocytosis was over $4 \times 10^9/L$ with atypical lymphocytes more than 5%, LDH value increased more than twice normal, with bone marrow and skin involvement established the diagnosis of adult T-cell leukemia/lymphoma- acute form, evolved from the chronic form, which patient had presented 4 years ago (lymphocytosis with atypical lymphocytes more than 5%, while the LDH and serum calcium were within normal limits). The epidemiological investigation was unable to identify the source of infection for the patient. Viral screening performed for family members was negative.

Particular to the new presentation was an itching rash and conjunctival hyperemia, which were labelled as allergic and treated properly, which caused a delay in diagnosis of the progression disease of about two months (the patient was symptomatic from February 2011). Although there was no histological evidence, the lack of response to treatment recommended by the ophthalmologist, and the resolution of the conjunctival hyperemia through specific antiretroviral therapy and chemotherapy and its reappearance in the terminal stages of illness, raised the suspicion that conjunctival hyperemia was an HTLV1-associated ocular pathology.

The blood picture was completed quickly by the appearance of hypercalcemia, without accompanying lytic lesions being seen by radiological screening, while leukocytosis reached 150000/mmc values. This picture could have induced confusion with acute lymphoblastic leukemia in the absence of evidence of HTLV 1 infection and knowledge of patient history. Presence of more than 5% atypical lymphocytes in peripheral blood excluded the diagnosis of the lymphomatous form. Confirmation of infection with HTLV1 excluded the diagnosis of Sezary syndrome or other forms of cutaneous T-cell lymphoma. A treatment was introduced to rebalance the electrolyte, to correct hypercalcemia with hyperhydration, diuretics, corticosteroids, which gave a favourable evolution.

For the specific treatment of the disease, chemotherapy under the VCAP-AMP-VCAP protocol was chosen, together with antiretroviral therapy, because of the aggressiveness of the disease. Owing to the increased risk of infection, prophylactic antibioticotherapy consisting in trimethoprim sulfamethoxazole, acyclovir and flucovim was associated to the treatment. After performing five complete cycles, re-evaluation of the patient noted a partial response, with a 50% decrease in the number of atypical lymphocytes and measurable lesions, which were maintained for more than 30 days. Because the chemotherapy was followed by severe aplasia, especially persistent leucothrombocytopenia, even under treatment with granulocyte growth factors and substitution treatment, the treatment was reoriented towards interferon 9MU/day + Zidovudine 600 mg/day when the status of the disease improved (after 5 complete cycles).

Signs of progression of disease occurred in about 45 days after discontinuation of chemo-

therapy, initially with cutaneous involvement. Subsequently, the dominant signs were of a respiratory nature, in the form of dyspnoea and irritating cough. Radiography showed the dynamic progression of lung damage under broad-spectrum antibiotics. Given the transient improvement in pulmonary symptoms under antiretroviral and chemotherapy, and because no pathogens was identified in sputum and bronchoalveolar lavage, it was suspected that the pulmonary symptoms could be secondary either to lymphoid infiltrate or an HTLV1 associated bronchopneumopathy.

The option to enhance the response with allogenic stem cell transplant could not be followed due to the lack of a compatible related donor, and the absence of a complete response, suggesting a very low chance of survival. Both the progression from chronic to acute form and the overall survival of the patient matched the data cited in the specialist literature.

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