



Case Reports of Adult T-Cell Leukemia/Lymphoma in Italy: Is it as Rare as we Think?

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Abstract

In this work we report two cases of Adult T-cell Leukemia/Lymphoma (ATLL), diagnosed through a span of a year in our Center of Hematology and Bone marrow Transplantation Unit in Piacenza (Italy). Human T- Lymphotropic Virus type 1 (HTLV-1) related disorders are extremely rare, even more in Western countries, thus they might be challenging to recognize. According to the increasing phenomena of migrations and the presence of multi-ethnic societies, we believe that such cases might rise in the near future. We describe here two paradigmatic case-reports of aggressive ATLL (Table 1), focusing on common clinical features, clue-laboratory tests and diagnostic tools.

Case Series

Case 1

M.P.M., a 51 year-old man from Gambia, lived in Piacenza since 2016 as a refugee. During medical visits planned for migrants he was discovered to be affected by previous pulmonary tuberculosis, Chronic Obstructive Pulmonary Disease (COPD) and emphysematous bullae with severe restrictive lung failure. On September 2019 he presented to emergency room for abdominal pain, weight loss and appearance of large inguinal lymph nodes. Laboratory tests showed leukocytosis with lymphomonocytosis, increased LDH and severe hypercalcemia (Table 1). Peripheral blood smear evidenced large immature lymphoid cells resembling "flower cells" and flow-cytometry analysis showed 44% of clonal T-lymphocytes. CT-scan detected bulky abdominal nodes (maximum 8.5 cm) and splenomegaly and confirmed bilateral inguinal lymph nodes. Surgical biopsy of an inguinal lymph node showed big large lymphocytes, centroblastic-like, CD3, CD43, CD2, CD4 positive, more than 50% CD30 positive, CD7, CD5, CD8, CD56, CD57, B-granzyme, CD10, BCL-6, ALK, CD79a, CD20, CD23, MUM-1 negative; ki67 index was 75%. Bone marrow biopsy was positive for

Table 1: Clinical presentation clue-laboratory tests, imaging and diagnostic tools of two patients affected by acute ATLL.

	Pt #1	Pt #2
B-symptoms	Yes	Yes
WBC (/mm ³)	10550	4730
Hb (g/dl)	14.8	11.9
PLT (/mm ³)	174000	258000
LDH (U/L)	703	438
Calcium total/ionized (mg/dl)	12.7/6.88	17.01/8.7
Uric acid (mg/dl)	9.6	14.8
Creatinine (mg/dl)	1.16	2.48
CT-scan	Abdominal nodes, spleen	Cervical, mediastinal, axillar, abdominal nodes, spleen, bone
PET	ND	Lymphnodes and bone
Lymphnode biopsy	CD2, CD3, CD4, CD43, CD30 (more than 50%) pos; CD7, CD8 neg; ki67 75% (inguinal)	CD2, CD3, CD4, CD5 (partially), CD25, CD99, bcl2, MUM1, MYC (almost 60%) pos; CD7, CD8, CD30 neg; ki67 90% (submandibular)
Bone marrow biopsy	T-cell infiltrate (20%-25%)	T-cell infiltrate (10%)
HTLV-1 antibodies	190	98
HTLV-1 RT-PCR on PB and tissue	pos	pos

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infiltration by T cells. These data were suggestive for Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL NOS). Once confirmed the diagnosis of T-cell lymphoma, specific therapy for hypercalcemia as per local protocol and chemotherapy with CHOP scheme (cyclophosphamide, adriamycin, vincristine, methylprednisolone) was started. While infectious screening for HBV, HCV, HIV, EBV, CMV and toxoplasma was negative, the HTLV-1 virus serology on plasma and RT-PCR on tissue specimens and peripheral blood turned out to be positive: This prompted us to the diagnosis of HTLV-1 associated Adult T-Cell Leukemia/Lymphoma (ATLL). As soon as the HTLV-1 tests were available, we reviewed the clinical case with the infectious disease specialist and the patient underwent an antiviral therapy with zidovudine and Interferon-alpha (AZT/IFN- α), associated to chemotherapy with vincristine, Prednisone, Etoposide and Cyclophosphamide (OPEC) for 6 courses. Given the diagnosis of ATLL, leukemic subtype, we chose a mild chemotherapy regimen in association with AZT/IFN- α because our patient was not eligible to hematopoietic stem cell transplantation due to comorbidities and poor performance status.

During hospitalization he needed high flow oxygen therapy for type-1 respiratory failure due to *Stenotrophomonas maltophilia* infection superimposed to his anamnestic lung disease. He achieved only a partial and transitory response and he died on February 2020 for progressive disease and infectious complications, which are very common in this subset of patients due to the underlying immunodeficiency.

Case 2

M.L. a 25 year-old Ghanaian girl came to Italy when she was a child together with her family and lived with her partner, an Italian guy. On September 2020 she noticed hard swelling on her neck, axillary and inguin. Moreover, she experienced night sweats, weight loss, and fever up to 40°C, asthenia and nausea. Thus, she decided to go to Emergency Room: Laboratory investigations detected acute renal failure (creatinine 2.95 mg/dl), severe hypercalcemia (calcium 17.5 mg/dl), increased LDH, beta-2 microglobulin and uric acid (Table 1). Further examinations by CT-scan and CT/PET evidenced an 18-FDG avid disease in both sides of diaphragm, spleen and bone marrow, with multiple osteolytic areas. Trucut biopsy of submandibular lymph node evidenced large lymphocytes CD3, CD2, CD5 (partially), CD4, CD25, BCL-2, MUM1, CD99 positive; almost 60% cells were MYC positive; CD7, CD8, CD56, CD57, B-granzyme, TdT, CD20, CD79a, CD10, BCL- 6, cyclin-D1, CD23, CD21, CD30, CD1a and CD34 markers tested negative; Ki67 proliferation index was 90%. Considering the geographical provenience and the high-burden disease, we initially hypothesized a Burkitt Lymphoma, but the immunohistochemical analysis was negative for a B-cell pattern and the EBER-1 test was negative for EBV; on the other hand, serology and molecular analysis were both positive for HTLV-1, consistent with the diagnosis of acute Adult T-Cell Leukemia/Lymphoma (ATLL). Firstly, we aimed to correct the severe hypercalcemia by volume expansion with crystalloids infusion, corticosteroids iv, zoledronic acid iv and loop diuretics. Moreover, therapy with rasburicase and allopurinol lowered hyperuricemia. Debulking with iv steroids and prophylaxis against opportunistic infections with acyclovir, cotrimoxazole and fluconazole lead to an improvement of her general conditions. She then preferred to move to another Hospital, nearer to her home, to start an intensive chemotherapy program and eventually allogeneic stem cell transplantation. In the meantime, we advised her partner to be tested for HTLV-1.

Discussion

The prevalence of HTLV-1 infection varies worldwide, with clusters in Japan, the sub-Saharan Africa, South America, Caribbean islands and foci in Middle East and Melanesia [1]. The latest notable study conducted in 2012 from Institute Pasteur de Paris, estimates 5 to 10 millions of infected individuals over a population of approximately 1.5 billion worldwide, and derived from available epidemiological data. Thus, the real prevalence is not known and tends to be underestimated [2]. Sporadic cases of HTLV-1 infection are seen in Europe, mostly France and United Kingdom, according to data resulting from pregnant women and blood-donor registries and population studies. The risk of spreading of HTLV-1 infection in Spain has also been reported and clusters are described in Romania [3,4]. Since two decades, Italy has been one of the first reception points for migrants from the Mediterranean Sea, yet it seems to be one of the European countries with the lowest prevalence of HTLV-1. It was unexpected for us to see two patients affected by ATLL in a span of a year in a small town as Piacenza, thus we believe that studies about the real impact of this phenomenon in non-endemic areas are needed [5,6].

In fact, the three modes of HTLV-1 transmission are mother to child, sexual transmission, and transmission with contaminated blood products [7]. While in underdeveloped countries the transmission during delivery is common, in Western countries people of Caucasian background may have acquired HTLV-1 through sexual contacts with a partner originating from an HTLV-1 endemic area. That's the reason why we advised the partner of patient #2 to undergo a HTLV-1 test, in order to establish appropriate methods to prevent its subtle spreading. Indeed, given the long latency of the provirus integrated in CD4+ cells, most people are asymptomatic carriers until one of the T-cell infected clones undergo monoclonal expansion and lead to malignant transformation [8]. It is estimated that approximately 2% to 4% of people infected with HTLV-1 will develop the ATLL [7].

Four clinical subtypes of ATLL are recognized: Indolent (chronic and smouldering) and aggressive (acute and lymphoma) ones. Abnormal lymphocyte in peripheral blood smear more than 1%, either with or without lymphocytosis, defines the acute form versus the lymphoma type. Common clinical features to suspect this rare subtype of aggressive leukemia/lymphoma are wide spread lymph node involvement, hypercalcemia, increased LDH and uric acid. Clonal T-cells express CD2, CD3, CD5 antigens, but usually lack CD7; CD25 antigen is generally strongly expressed. Most cases are CD4 positive and CD8 negative. The large transformed cells may be positive for CD30, but are negative for ALK. The hypothesized cells of origin are the CD4+, CD25+, FOXP3+ Treg cells, which would be consistent with the disease's characteristic association with immunodeficiency [9]. Taking into account the geographical provenience of the patients, it should be considered the differential diagnosis with Burkitt Lymphoma (BL), an aggressive B-cell lymphoma, c-myc rearranged and EBV-positive in its endemic variant [10,11]. HTLV-1 serology is essential and mandatory for diagnosis, and molecular testing by RT-PCR in both tissue and peripheral blood are recommended, especially if immunohistochemical pattern is not completely clarifying between ATL and PTCL [12].

Moving to the therapeutic algorithm, the eligibility to transplantation drives the initial choice. For patient #1 we chose a less intensive chemotherapy approach, due to his underlying lung disease and poor performance status. A retrospective small study

demonstrated the non inferiority of OPEC/MPEC (vincristine or methotrexate, prednisone, etoposide, cyclophosphamide) to VCAP-AMP-VECP regimen (VCAP, vincristine, cyclophosphamide, doxorubicin, and AMP, prednisone; doxorubicin, ranimustine, and prednisolone; and VECP, vindesine, etoposide, carboplatin, and prednisolone) in elderly patients and/or not suitable for HSCT (hematopoietic stem cell transplantation) [13,14]. Moreover, AZT/IFN was added as maintenance therapy because patients with the acute subtype tend to respond better to antiretroviral therapy. The reverse transcriptase zidovudine 500 mg/die to 1000 mg/die in association with interferon- α 3 MU three times a week may exert either an antiviral or a cytotoxic effect. Schedules could be modified due to tolerability and side effects [15]. Finally, target therapy with Brentuximab Vedotin has been recently approved in combination with CHP (cyclophosphamide, doxorubicine, and prednisone) as first line treatment in CD30+ PTCL, according to the encouraging results of the ECHELON-2 study [16]. The study cohort included very few cases of ATL (7 out of 452 patients affected by PTCL), thus the use of Brentuximab Vedotin needs to be further explored in this setting of patients. Nevertheless, we believe that it could represent a promising salvage therapy in relapsed and refractory diseases, as was the case of our patient #1 [17].

In conclusion, HTLV-1 infection is increasing worldwide, even in non-endemic areas, due to migrations and “melting pot” societies. Strategies to prevent its transmission are urgent as well as the suspicion of HTLV related acute lymphoma/leukemia, especially in cases of aggressive and widespread lymph node disease, hypercalcemia and kidney-function alteration. Serology and molecular tests for HTLV-1 detection are essential for prompt diagnosis in order to choose the best therapeutic approach for this rare and challenging disease.

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