Case Report

Coexistence of T-Large Granular Lymphocyte Leukemia and Peripheral T Cell Lymphoma-NOS with Indolent Behavior

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Abstract. T-cell lymphomas and leukemias are highly heterogeneous groups of rare disorders. We report a case of a 68-year-old man patient who developed two different T-cell neoplasms (Large Granular Lymphocyte Leukemia [LGLL] in 2018 and Peripheral T-cell non-Hodgkin lymphoma not otherwise specified [PTCL-NOS] in 2019) with a previous diagnosis of B-cell marginal zone lymphoma in 2010, treated with two lines of chemo-immunotherapy. The coexistence of these different T-cell neoplasms is rarely reported in the literature. Moreover, it is usually described as an LGLL transformation into PTCL-NOS; differently from these examples, herein, the simultaneous conditions appear to be driven by different T-cell clones. Furthermore, the PTCL-NOS had quite unusual behavior, with good disease control without intensive treatment. Because of these features, it could belong to a subgroup of indolent PTCL-NOS, not yet described in the WHO classification of T-cell neoplasms, which could benefit from less aggressive treatment.

Keywords: PTCL-NOS, LGLL, Aggressive T-cell lymphomas, Indolent T-cell lymphomas.

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Introduction. Mature T lymphoproliferative disorders are a spectrum of clinically and biologically heterogeneous diseases. Pathogenesis is not fully understood, although immune imbalance, intracellular signaling alterations, microenvironment, and inflammatory stimuli seem to play a fundamental role. Primary diagnostic sites can be solid tissues, lymph nodes, or peripheral blood (PB).¹,²

Large Granular Lymphocyte Leukemia (LGLL) is a rare lymphoproliferative disorder usually diagnosed from PB, which can arise from both T Cytotoxic Lymphocyte and NK cells. The first finding is usually the identification of an increased number of circulating Large Granular Lymphocytes (LGLs) that should be in number > 2 x 10⁹/L (normal value: < 0.3 x 10⁹/L), even if several LGLL cases could present with an inferior lymphocyte count; in this instance, the demonstration of clonality is mandatory for diagnosis.³,⁴

In particular, T-LGLL sustained by the proliferation of CD3⁺ T-LGLLs is the most frequent variant of the disease.⁵ Diagnosis requires the demonstration of clonal lymphocytosis of LGLs (provided by T-cell receptor [TCR] gene rearrangement analysis).⁵

A peculiar feature of the disease is the association with autoimmune disorders and secondary neoplasms. Isolated neutropenia (absolute neutrophil count [ANC] <1.50 x 10⁹/L) is the most common clinical condition, although low hemoglobin (Hb) and platelets (Plts) levels...
Peripheral T-cell non-Hodgkin lymphoma not otherwise specified (PTCL-NOS) is a broad category of heterogeneous T cell diseases that cannot be further classified into any of the existing entities defined by the World Health Organization classification (WHO). The diagnosis of PTCL-NOS is based on typical histopathological features, an aberrant T-cell immunophenotype, and a clonal TCR gene rearrangement. Although a PTCL-NOS specific prognostic score has been proposed, the International Prognostic Index (IPI) is still the recommended scoring system to assess the prognosis in patients affected by this condition.

Nowadays, anthracycline-based regimens represent the standard first-line treatment: the prognosis is generally poor, with a 5-year overall survival (OS) of 20-30%, even if some authors suggest the existence of an indolent PTCL variant with a good prognosis and possibility of spontaneous regression.

The case we report describes the story of a patient with a previously diagnosed (and treated) marginal zone B-cell lymphoma (MZL), who is currently affected by concomitant T-LGLL and PTCL-NOS with indolent behaviour.

Case Report. The story of our patient begins in 2010 when, at the age of 60, he was referred to the hematology clinic because of cervical lymphadenopathy, detection of mild anemia (Hb: 11.2 g/dL), and relative lymphocytosis (ANC: 2.87 x 10^9/L, Ly: 3.71 x 10^9/L) in routine complete blood count (CBC). Screening for hepatitis viruses, HIV, EBV, CMV, Treponema Pallidum, Toxoplasma Gondii, autoimmunity screening, and inflammatory markers were all negative. The immunophenotypic profile of PB lymphocytes identified clonal B cell population. A whole-body computed tomography (CT) scan revealed several lymphadenopathies (cervical, abdominal, pelvic localization); a subsequent morphological and immunohistochemical study of bone marrow (BM) showed medullary involvement by MZL. Considering the advanced stage (Ann Arbor stage IV), the patient was started on R-CHOP immuno-chemotherapy (Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Vincristine, Prednisone), achieving complete remission of the disease.

In April 2018, due to progressive neutropenia (ANC: 0.73 x 10^9/L) and CT dokumented recurrence of lymphadenopathies (mediastinal and deep abdominal), he was reassessed with viral and autoimmunity screening, then BM biopsy, that concluded for disease relapse. As a result, second-line chemotherapy was started, according to R-Bendamustine (Rituximab, Bendamustine) regimen. The patient completed only four cycles since may be found. Treatment is based on immunosuppressive agents.

Peripheral T-LGLL and PTCL-NOS with indolent B-cell lymphoma (MZL), who is currently affected by may be found. Treatment is based on immunosuppressive agents.

In September 2018, our patient was hospitalized because of febrile neutropenia: at the admission, CBC showed Hb: 12.9 g/dL, Plts: 82 x 10^9/L, ANC: 0.56 x 10^9/L, Ly: 0.4, with LDH: 185 U/L. On suspicion of lymphoma recurrence, the patient was reassessed by BM aspiration and biopsy, PB immunophenotypic, and morphological examination. In addition, folates and cobalamin levels, serologic and molecular essay for B and C hepatitis, Epstein Barr virus, Parvovirus, Cytomegalovirus, and HIV were investigated: all these tests were negative. A small interstitial T cell infiltration (3%) was observed at BM biopsy, and immunophenotypic analysis of marrow aspirate (lymphocyte gate) highlighted a 10% of clonal cytotoxic T lymphocytes (CD3+, CD57+, CD8+, CD2+, CD5+). Cytomegalovirus, and HIV were investigated: all these tests were negative. A small interstitial T cell infiltration (3%) was observed at BM biopsy, and immunophenotypic analysis of marrow aspirate (lymphocyte gate) highlighted a 10% of clonal cytotoxic T lymphocytes (CD3+, CD57+, CD8+, CD2+, CD5+). Morphological examination of PB smear revealed numerous LGLs (Figure 1): the immunophenotypic profile of PB lymphocytes was equal to that found in the BM aspirate (14% of total lymphocytes). Febrile neutropenia resolved after two weeks of large spectrum antibiotic therapy.

Hemolytic anemia (HA) occurred with Hb: 9.1 g/dL, reduced haptoglobin (28 mg/dL), raised reticulocyte count (119 x 10^9/L; normal range: 30-110 x 10^9/L); direct and indirect Coombs test were positive, total bilirubin and lactate dehydrogenase (LDH) levels resulted within normal ranges. HA was managed with corticosteroid therapy (Prednisone 1 mg/Kg for three weeks, then tapered to progressive reduction, so suspension). A subsequent whole body re-evaluation CT scan documented a new complete remission of the disease.

In October 2019, because of severe neutropenia, thrombocytopenia, mild anemia (Hb: 11 g/dL, Plts: 86.000 x 10^9/L, ANC: 0.49 x 10^9/L; Ly: 0.4 x 10^9/L), itching, and LDH: 185 U/L, he was hospitalized and treated with prophylactic antibiotic therapy and G-CSF support. Furthermore, he was reassessed by viral and autoimmunity tests, CT scan, PB lymphocytes immunophenotypic profile, BM aspiration, and BM biopsy. The whole-body CT scan highlighted multiple lymphadenopathies (cervical, mediastinal, deep abdominal, and pelvic; Ø max 27 mm in the deep abdomen). Peripheral blood T cells immunophenotype
Figure 1. Large granular lymphocytes detected on peripheral blood smear. The cells have large clear cytoplasm with azurophilic granulations of various sizes and an eccentric and irregularly shaped nucleus.

(lymphocyte gate) confirmed an 11% of the original T-LGLL clone (CD3+, CD57+, CD8+, CD2+, CD5+, CD7-, CD56+, CD4-, CD30-). Surprisingly, BM biopsy showed a medullary infiltration by small T lymphocyte population different from that found in September 2018: CD45+ bright, CD3+ bright, CD2+ bright, CD4+ bright, CD27+, CD45RO+, TCR/αβ +, CD52+/-, CD8-, CD7-, CD30-, HLA-DR-, CD25-, CD56-. The diagnosis was: medullary infiltration (20%) by PTCL-NOS (Figure 2), IPI score 3 (intermediate-high risk).

Due to the patient's poor condition (ECOG grade 3), he was started on corticosteroid therapy (Prednisone 25 mg/die) as provisional bridge-therapy to evaluate the most appropriate approach to managing the dual condition.

Normalization of blood counts and improvement of itchy symptoms were achieved in a few weeks, and corticosteroid therapy was progressively tapered to 7.5 mg/die. The patient then refused to undergo a new intravenous chemotherapy regimen and continued to receive corticosteroids as palliative treatment. Corticosteroid therapy was definitively interrupted in May 2020 since bilateral aseptic osteonecrosis of the femoral head occurred. However, after surgical

Figure 2. Immunohistochemical staining for CD3 (picture A), CD8 (picture B), CD56 (picture C) and CD20 (picture D). Interstitial to diffuse pattern of growth (50-10%, mean value 20%) of T cell lymphocytes CD3 positive (picture A), CD8 negative (picture B), CD56 negative (picture C), CD20 negative (picture D). CD20 stain (negative, picture D) was useful to exclude an infiltrate of relapsed MZL, whereas CD8 and CD56 stains (both negative) confirmed the different T-cell infiltrate from that of LGLL diagnosis.
intervention for bilateral total hip arthroplasty, we decided to start therapy with antifolates drug (subcutaneous methotrexate – MTX - 10 mg/m²/week), with good control of symptoms and blood count until February 2021.

**Discussion and Conclusions.** Immune system impairment has been linked to lymphoproliferative disorders arising from B and less frequently by T cells.\(^1^1\) We described the case of a patient with immune system impairment (previous MZL treated with two lines of chemo-immunotherapy) who developed two T-cell neoplasms: firstly LGLL, then PTCL-NOS. The short time interval between MZL relapse and LGLL diagnosis could lead to hypothesize a reciprocal relationship. The correlation between these two conditions is described in the literature,\(^1^2\) and several hypotheses have been formulated. Goyal *et al.* and Viny *et al.*\(^1^2,^1^3\) agree on two main possible mechanisms: a common antigenic trigger or a humoral stimulus serving as a lymphocyte expansion supporter. However, B and T cell populations are unlikely to be clonally related.

On the other hand, the two T-cell lymphoproliferative disorders herein presented are only described in few reports,\(^1^4^-^1^6\) but authors always refer to a "transformation" of the previous T-LGLL into a T-cell lymphoma; furthermore, all these cases describe an aggressive behavior of the secondary lymphoma. The clinical behavior of our patient's PTCL NOS is quite unusual and could be framed as a particular subgroup in the subset of T-cell neoplasms, currently not described in WHO classification of T-cell neoplasms.\(^8^\) Our patient achieved a good control of disease, in line with the experiences of other authors, who reported stable disease or long-term survival even without intensive treatment.

Even if it seems difficult to distinguish indolent PTCL-NOS at diagnosis, Hayashi *et al.*\(^1^7\) described some characteristic features of these entities: regardless of nodal or extranodal involvement, lymphoid cells are typically small in size, with oval or slightly irregular nuclei and pale cytoplasm. Of note: all the described cases showed a Ki67 index <10%.\(^1^0,^1^7\)

Unfortunately, this marker was not investigated in our patient at the time of PTCL-NOS diagnosis and subsequently was not carried out due to insufficient material. Ki67 index seems to represent a reliable tool and, together with a precise morphological and genetic-molecular classification, could help define this entity better.

In this respect, it is essential to understand how to distinguish aggressive versus indolent PTCL-NOS to avoid overtreatment of these conditions and plan a proper follow-up.

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