Peripheral T cell lymphoma with a regulatory T cell phenotype: a Mexican case not associated with HTLV-1 virus infection

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Abstract Peripheral T cell lymphomas are aggressive neoplasms with an overall bad prognosis. As occurred with B cell lymphomas, some T cell lymphomas have been correlated with a normal T cell counterpart. According to the actual WHO classification of tumors of hematopoietic and lymphoid tissues, the only T cell lymphoma characterized by a T_{reg} phenotype is adult T cell leukemia/lymphoma (ATCLL), an entity defined by its etiologic association with HTLV-1 infection. We present a case of peripheral T cell lymphoma with a T_{reg} phenotype not associated with HTLV-1 infection. We describe its pathological and clinical characteristics and discuss the presence of a T_{reg} phenotype in T cell lymphomas.

Keywords T cell lymphoma · T_{reg} · FOXP3

Introduction

Peripheral T cell lymphomas (PTCL) are aggressive neoplasms characterized by an overall poor prognosis.

Regulatory T cells (T_{regs}) are a subpopulation of T helper lymphocytes specialized in suppressing inflammatory responses. They suppress proliferation and activation of other T cells, maintaining the balance between immunity and tolerance. Their presence as part of the inflammatory reaction to some neoplastic disorders has been associated with a weaker cytotoxic immunologic response to tumors but also, for some entities, with a better prognosis [1–3]. T_{regs} are characterized by the expression of the forkhead transcription factor family

member: FOXP3; they also express surface cell markers like CD4 and CD25, all easily detected by immunohistochemical methods [3].

As occurred with B cell lymphomas, efforts have been made to correlate PTCLs with a normal T cell counterpart. For example, anaplastic large cell lymphoma (ALCL), enteropathy-associated T cell lymphoma (EATL), and subcutaneous panniculitis-like T cell lymphoma are thought to derive from an effector/memory $CD8^+$ T cell, mycosis fungoides from effector $CD4^+$ T cells, and angioimmunoblastic lymphoma (AIL) from follicular helper (T_{FH}) T cells [4]. Exemptions are not rare and phenotypic plasticity is a well-recognized problem when trying to classify T cell lymphomas.

As a group, PTCL not otherwise specified (NOS) remain poorly understood. While early studies failed to classify PTCL NOS according to a CD8/cytotoxic or a CD4/helper immunophenotype, a gene expression profiling (GEP) study published in 2007 by Piccaluga et al. found that overall, the PTCL-NOS gene expression pattern was more similar to activated CD4 T cells, with only a minority of cases resembling activated CD8 T cells. Interestingly, immunophenotypic analysis for CD4 and CD8 did not correlate with different GEP groups [5, 6].

According to the actual WHO classification of tumors of hematopoietic and lymphoid tissues, the only T cell lymphoma characterized by a T_{reg} phenotype is adult T cell leukemia/lymphoma (ATLL), an entity defined by its etiologic association with HTLV-1 infection; in spite of this some cutaneous T cell lymphomas (CTCL) and at least three cases of PTCL NOS with a T_{reg} phenotype have been reported (one from Germany and two from South America), these cases were not associated with HTLV-1 infection [7–16].

We report a case of PTCL NOS showing a bona fide T_{reg} phenotype, and review the pertinent literature.

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Clinical history

A 61-year-old woman presented with a 2-month history of intermittent abdominal pain and lower limb edema. Physical examination revealed a palpable abdominal mass. The CT-scan documented a circumferential wall thickening of the small-bowel that was 25-cm long affecting the proximal and middle jejunum. Multiple mesenteric, aortic, and retroperitoneal lymphadenopathies were also noted; hepatosplenomegaly was absent. No history of chronic diarrhea, malabsorption, weight loss, or fever was reported.

Complete blood count showed $4.6 \times 10^9/\text{L}$ leukocytes, with a normal differential hemoglobin of 8 g/dL, and a platelet count of $455 \times 10^9/\text{L}$. The liver enzymes were within normal limits, and the lactate dehydrogenase level was 130 IU/mL.

Biopsies from the intestinal lesion were reported as PTCL, NOS, with a T_{reg} phenotype. The bone marrow biopsy did not show infiltration. Her Ann Arbor Stage was III AE with a low-intermediate International Prognostic Index risk and a good performance status.

The patient was treated with standard doses of CHOEP and achieved a complete remission after six cycles. Twelve months later, she presented with fever, weight loss, and diaphoresis; a colonic recurrence was documented and treated by ICE (ifosfamide, carboplatin, and etoposide). The patient suffered from severe ifosfamide toxicity and nonconvulsive epilepsy that was aggravated by pneumonia. She died 21 months after the diagnosis.

Materials and methods

Routine hematoxylin and eosin (H&E) sections were prepared using standard techniques from formalin-fixed paraffin blocks. Immunohistochemical analyses included the following monoclonal antibodies: CD3, CD20, LMP-1 (BioSB) CD4, CD7, CD5, CD30, TIA 1 (Biocare), CD56 (Dako), CD8 (NeoMarkers), PD-1 (cell marque), CD25 (Novocastra), CD10, BCL-6, Granzyme B, and FOXP3 (Abcam).

In situ hybridization for EBV-encoded RNA (EBER) was performed on the biopsy. The EBER detection kit was purchased from Dako (Glostrup, Denmark). The detection process was conducted according to the manufacturer's instructions.

T cell clonality: DNA was extracted from formalin-fixed, paraffin-embedded tissue sections. This purified DNA was used to assay for clonal rearrangements of the T cell receptor (*TCR*) γ genes by polymerase chain reaction (PCR) using the method described by McCarthy et al. [17].

Molecular detection of HTLV-1: DNA was extracted from formalin-fixed, paraffin-embedded tissue sections. PCR was

performed using primers that detect the TAX and long terminal repeat (LTR) regions of HTLV-1 as follows:

HTLV-tax-F: 5'-GGATACCCAGTCTACGTGTTTG-3'
 HTLV-tax-R: 5'-CGGAACATTGGTGAGGAAGGC-3'
 HTLV-LTR-F: 5'-CCAGACTAAGGCTCTGACGTCTC-3'
 HTLV-LTR-R: 5'-CCTGAGCTCTAAACTTACCTAGACG-3'

Products were examined using polyacrylamide gel electrophoresis [18].

Results

The jejunal endoscopic biopsy revealed a monotonous lymphoma diffusely infiltrating and expanding the lamina propria (Fig. 1). The tumor cells were large- to medium-sized lymphocytes with round nuclei, fine chromatin, and 1–3 visible nucleoli. Mitotic activity was high. A moderate villous atrophy without ulceration was noted; interestingly, intraepithelial lymphocytes (IELs) were nearly absent and tumor-infiltrating lymphocytes were sparse. All biopsies lacked normal intestinal mucosa. The colonic recurrence showed the same cohesive morphology with few tumor-infiltrating lymphocytes.

Immunohistochemically, the tumor cells expressed T cell markers (CD3, CD5, and CD7) and a T_{reg} phenotype characterized by diffuse positivity for CD4, CD25, and FOXP3. A T_{FH} immunophenotype was explored using PD-1, BCL-6, and CD10; all three antibodies were negative. Cytotoxic markers (CD8, Granzyme B, and TIA-1) were negative within the tumor and positive in IELs. Tumor infiltrating lymphocytes included B and T mature lymphocytes. Tumor cells were also negative for CD20, CD56, CD30, LMP-1, and EBER in situ hybridization.

Analysis by PCR of paraffin-embedded tissue showed clonal rearrangements of the *TCR- γ* (data not shown). A PCR for HTLV-1 was performed using DNA extracted from negative and positive controls and the patient's biopsy. While a band at the correct position with both primer sets was found in the positive control, no amplification was found in the patient's specimen, indicating that this lymphoma is not associated with HTLV-1 infection (Fig. 2).

The differential diagnosis included T/NK T cell lymphoma, a common entity in Central/South America, characterized by frequent extranodal presentation, yet negativity for CD56, cytotoxic markers, and EBER in situ hybridization, excluded it.

Moderate villous atrophy and large cell morphology seen in the jejunal biopsy could suggest a diagnosis of EATL; neither type I nor type II variants are characterized by a CD4 immunophenotype, the first being generally CD4-, CD8-, CD30⁺ and the second CD4-, CD8⁺, CD56⁺; both types usually

Fig. 1 Jejunal biopsy. **a** Diffuse lymphomatous infiltration (H&E, $\times 100$). **b** Detail of the monotonous large cells with fine chromatin and visible nucleoli; tumor infiltrating lymphocytes are rare (H&E, $\times 400$). CD3, CD4, FOXP3, and CD25 (IHC, $\times 200$)

express cytotoxic granule associated proteins like TIA1 and Granzyme B, which were negative in our case. While IELs in type I EATL may have an aberrant CD4⁻, CD8⁻, CD56⁻ immunophenotype, type II EATL IELs have a characteristic CD4⁻, CD8⁺, CD56⁺ immunophenotype; IELs in our case had a normal CD4⁻, CD8⁺, CD56⁻ immunophenotype. Moreover,

the lack of chronic diarrhea or malabsorption history discouraged this diagnosis. Negativity for CD30 excluded ALCL. [7, 19].

Recently, cases of primary small intestinal CD4⁺ T cell lymphomas with an indolent behavior have been described; all reported cases, originally diagnosed as refractory celiac disease, presented with diarrhea and weight loss, which was absent in our case. These cases were composed of small- to medium-sized lymphocytes with a low proliferative index, infiltrating the lamina propria, which is concordant with an indolent behavior; moreover, all cases were negative for T_{reg} markers (CD25 Foxp3) and featured CD4⁺ IELs [20, 21]. Morphologic, immunophenotypic, and clinical differences excluded this diagnosis.

Fig. 2 Molecular analysis for HTLV-1

Discussion

We describe a case of PTCL NOS with a full T_{reg} phenotype that histologically resembles other three cases previously reported (from Peru and Germany) (Table 1). Morphologically, all cases share a monotonous neoplastic infiltrate constituted by cohesive large size, “immunoblastic-like” cells, with prominent nucleoli and

Table 1 Clinicopathologic features of PTCL NOS with a T_{reg} phenotype reported in the literature

Case	A	Symptoms	Region involved	DHL IU/mL	B2M	Stage	Tx	Evolution	Morphology/IHC
Bonzheim et al. [15]	59	Asymptomatic	Cervical, mediastinal, axillary, intra-abdominal, retroperitoneal, and inguinal lymph nodes	Elevated		IV	CHOEP	Died 1 month after diagnosis due to repeated infections during neutropenia after chemotherapy.	Variably medium-sized or large atypical T cells with convoluted nuclei and mostly prominent nucleoli. With a diffuse cohesive pattern. Few tumor-infiltrating reactive T or B cells. FOXP3+, CD4+, CD25-
Beltran BE et al. [16]	48	Epistaxis, nasal congestion, no B symptoms or lymphadenopathy	Extranodal: cavum	214	NL	I AE	CHOP + RT	Recurred 2 years later (tonsil, cervical lymph nodes and duodenal mass) treated with ICE and GDP. Died 46 months after diagnosis.	Large, pleomorphic cells with clear cytoplasm, vesicular nuclei and distinct nucleoli
Beltran BE et al. [16]	65	Weight loss without fever or night sweats	Cervical and inguinal lymphadenopathies	NL	3	III B	CHOP	Recurred 7 months later, (cervical and axillary adenopathies) treated with ICE. Died 36 months after diagnosis.	Numerous mitosis CD3+, CD25+, FOXP3+, CD4- Large cells with abundant clear cytoplasm. Numerous mitosis CD3+, CD4+, CD25+, FoxP3+
Present case	61	Abdominal and lumbar pain, no B symptoms	Jejunal mass, retroperitoneal and periaortic lymphadenopathies	130		III AE	CHOEP	Recurred 1 year later (colon), treated with ICE. Died 21 months after diagnosis.	Cohesive monomorphic large cells with fine chromatin and 1–3 visible nucleoli CD3+, CD4+, CD25+, FoxP3+

A age, NL normal, B2M β 2microglobulin, Tx treatment, IHC immunohistochemistry, IU international units, DHL lactic dehydrogenase, CHOP cyclophosphamide/doxorubicin/vincristine/prednisone, CHOEP, ICE ifosfamide/carboplatin/etoposide, RT radiotherapy, GDP gemcitabine/dexamethasone/cisplatin

fine chromatin. Characteristically, the reactive infiltrate was scant.

Several studies have associated ATLL to a T_{reg} phenotype, postulating T_{regs} as the normal counterpart for this lymphoma [7, 22–26]. Recently, some groups have challenged this point of view, considering that HTLV-1 can induce via its Tax protein both an increased circulating nontumoral T_{reg} population and an increased FOXP3 expression in infected cells [27]. Another study found that only 36 % (60 of 169) of ATLL cases from Japan showed FOXP3 expression in lymphoma cells [28], supporting the idea that the T_{reg} phenotype could be induced rather than being present from the beginning [27].

Our case lacked most of the clinical manifestations expected for the chronic, smoldering, acute, or lymphomatous forms of ATLL. Lymphocytosis with peripheral blood circulating cells, cutaneous lesions, bone lesions, hypercalcemia, hepatosplenomegaly, and bone marrow infiltration were all absent [7].

The prevalence of HTLV-1 infection in the general Mexican population has not yet been defined. In America, it is known that Brazil, Colombia, Peru, and the Caribbean are endemic areas (2–10 % of their healthy adult population is infected). The virus has also been reported in Ecuador, Paraguay, Chile, and Argentina [29]. The largest survey done in Mexican population analyzed 1,078 serum samples of different risk groups, from 6 Mexican states. Of these, only 12 were positive by agglutination test and none was positive by Western blot analysis; other studies have confirmed this low prevalence in the north of the country [30, 31]. All these factors and a negative PCR test for HTLV-1 infection discouraged a diagnosis of ATLL.

Bonzheim et al. analyzed 83 PTCL: 32 PTCL NOS, 23 AIL, 20 ALCL (14 ALK– and 6 ALK+), and 8 other types of T cell lymphoma (2 cutaneous, 4 intestinal, 1 hepatosplenic, and 1 T/NK-cell lymphoma, nasal type), and found only 1 case with diffuse FOXP3 immunohistochemical positivity. Histologically, their case was also characterized by a diffuse growth pattern of medium and large atypical T cells with prominent nucleoli, being originally diagnosed, according to the Kiel classification, as the immunoblastic variant of PTCL-NOS. As in our case, this case showed a scant reactive inflammatory background, which the authors remarked as unusual among PTCL, evoking a possible inhibitory role derived from a retained T_{reg} cell function of the neoplastic cells.

Immunohistochemically, their case was diffusely positive for FOXP3 and CD4 while negative for CD25. As in the present case, HTLV-1 proviral DNA was not amplifiable by PCR. The patient died during the chemotherapy-induced neutropenic phase due to repeated infections 1 month after the diagnosis. The authors speculated that T_{reg} function might have significantly suppressed antitumor immunity, which contributed to progression. They concluded that this rare phenotype could represent an adverse risk factor in PTCL-NOS [15].

Two similar cases from Peru were reported by Brady et al.; in both cases, the lymphoma was composed of large cohesive cells, with clear cytoplasm, vesicular nuclei, and visible nucleoli. The first case was positive for FOXP3+ and CD25+ but lacked CD4, while the second case showed the same full T_{reg} phenotype present in our case. These cases, as described in other T cell lymphomas, showed large Reed-Sternberg-like cells positive for EBER in situ hybridization; EBV activation being possibly induced by a T_{reg} -associated immunosuppression [16, 32, 33]. The present case lacked Reed-Sternberg-like cells, EBV infection, or other signs of immunosuppression.

These four cases of PTCL NOS with a T_{reg} phenotype showed variable clinical features; they all had different clinical stages, nodal and/or extranodal manifestations, and presented with or without B symptoms. The three cases from Central/South America showed a complete initial remission followed by variable progression-free survivals (7 months, 1 year, and 2 years); the three cases relapsed and patients died 36, 21, and 46 months after diagnosis, respectively. None of these cases reached a 5-year survival, known to be of 30 % in PTCL NOS, thereby suggesting a still worse prognosis for this phenotype [19].

A T_{reg} phenotype has also been claimed in some CTCL and ALCL. Berger et al. described in vitro transformation of CTCL cells to a T_{reg} phenotype after stimulation by immature dendritic cells charged with CTCL apoptotic debris [8]. A further study found increased levels of FoxP3 in peripheral blood mononuclear cells (PBMCs) of 3 of 12 HTLV-1 negative CTCL patients by quantitative real-time PCR [34]. Another study using the same technique analyzed 28 CTCL, 25 Sezary syndromes (SS), and 3 MF, and found 6 SS cases with extremely high expression levels for FoxP3 and CD25 [11]. A German study found FOXP3 expression in 4 of 5 MF with large cell transformation; these results are hampered by an exclusive cytoplasmic FOXP3 positivity seen in all figures [13].

Further studies using immunohistochemistry and FACS have showed that CTCL are generally negative for FOXP3 and that the proportion of T_{regs} in dermal infiltrates and peripheral blood varies among cases; Klemke et al. found significantly lower numbers of T_{regs} in biopsies and peripheral blood of patients with SS, carrying a worse prognosis than MF [35]. Gjerdrum et al. analyzed 86 patients with MF and CTCL unspecified and found that all cases were negative for FOXP3; nevertheless, they found that cases with increasing numbers of tumor infiltrating T_{regs} had a better prognosis [9].

A study from Denmark found FOXP3 immunohistochemical expression in 1 of 13 cutaneous ALCL (C-ALCL) analyzed; in this case, staining was intense, nuclear, and diffuse. They also found rare positive tumor cells in a case of lymphomatoid papulosis (LyP) and two other C-ALCL cases [12].

FOXP3 expression has been also reported in ALCL; Kasprzycka et al. demonstrated elevated expression in 4 of 4 ALK + ALCL cell lines by real-time quantitative PCR; they

also showed that lymphoid cells transfected with NPM/ALK acquired a T_{reg} cell phenotype [36]. Bonzheim et al. described FOXP3 positivity in 4 of 6 ALK + ALCL and in 1 of 14 ALK-ALCL. In these cases, only 20 to 30 % of tumor cells showed weak and variable immunohistochemical positivity for FOXP3, which was not followed by positivity for other T_{reg} markers. In view of these findings, the authors considered FoxP3 expression as aberrant instead of a part of a true T_{reg} phenotype [15].

We report a fourth case of PTCL NOS with a bona fide T_{reg} phenotype not associated with HTLV-1 infection. We agree with previous reports that the morphology and immunophenotype of this tumor could eventually place it as a separate entity. In view that three of these cases come from Central/South America, further studies are necessary to establish the real frequency of this phenotype in PTCL NOS from this population.

Conflict of interest The authors declare they have no conflict of interest.

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