Evaluation of FoxP3 Expression in Peripheral T-Cell Lymphoma

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Abstract

Peripheral T-cell lymphomas (PTCLs) are biologically heterogeneous and have not been successfully correlated with specific T-cell subsets. We investigated PTCL, not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AILT), and anaplastic large cell lymphoma (ALCL) cases for FoxP3 expression to determine a potential derivation from regulatory T (T_{reg}) cells. One PTCL-NOS case strongly expressed FoxP3 in the neoplastic T cells and showed unusual histomorphologic features with a dense infiltration of the lymph node by immunoblastic T cells and almost no reactive background infiltrate. The patient died shortly after diagnosis, suggesting that biologic properties of T_{reg} cells may have contributed to the rapidly fatal clinical course. All remaining PTCL-NOS and AILT cases showed FoxP3 positivity only in the reactive infiltrate. Among ALCL cases, 4 of 6 ALK+ cases displayed weak and inhomogeneous FoxP3 expression in the tumor cells. FoxP3+ PTCL-NOS presumably derived from bona fide T_{reg} cells occurs but seems rare in the Western population.
has been described as an important transcription factor that is essential for the differentiation of T cells into regulatory CD4+/CD25+ T cells.\(^1\) Lack of functional FoxP3 leads to a human autoimmune syndrome called IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked).\(^18\) Besides natural T\(_{\text{reg}}\) cells that express FoxP3 constitutively, so-called adaptive/induced T\(_{\text{reg}}\) cells have been described that express FoxP3 only after induction.\(^6-8,10,15,17,19,20\) In solid tumors, the occurrence of T\(_{\text{reg}}\) cells among tumor-infiltrating lymphocytes has been proposed to facilitate invasive growth by suppression of the immune responses.\(^21,22\)

Given that FoxP3 is a crucial transcription factor that is specifically expressed in T\(_{\text{reg}}\) cells,\(^23-25\) we screened 83 peripheral T-cell lymphomas (PTCLs) for this marker to determine if T\(_{\text{reg}}\) cells may represent the normal counterpart of a subset of PTCL. We identified 1 PTCL, not otherwise specified (NOS) with strong and uniform FoxP3 expression, suggesting that it may be derived from natural T\(_{\text{reg}}\) cells. Furthermore, we demonstrated that FoxP3 is expressed in an inhomogeneous manner in ex vivo tissue of anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma (ALCL), pointing to an induced mode of FoxP3 expression as a consequence of ALK deregulation, in concert with recently published data of ALK+ ALCL cell lines expressing FoxP3.\(^26\)

### Materials and Methods

#### Immunohistochemical Analysis

We studied the expression of FoxP3 (rabbit polyclonal, dilution 1:50; Abcam, Cambridge, England) in lymph node specimens from 83 cases of PTCL by conventional immunohistochemical analysis. All cases had been diagnosed according to the WHO classification and were characterized by histochemical analysis. All cases had been diagnosed according to the WHO classification and were characterized by histochemical analysis.

Of the study cases, 67 were paraffin-embedded material comprising 23 PTCL-NOS (9 of these were formerly diagnosed as T-immunoblastic non-Hodgkin lymphoma according to the Kiel classification), 16 AILT, 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). Because PTCLs contain numerous reactive T cells, we studied 16 frozen tumor samples from additional patients using double stains. These included 7 cases of AILT and 9 cases of PTCL-NOS that have been reported previously.\(^27\)

The 20 ALCL cases were further characterized for expression of CD4 (1F6, dilution 1:5; Loxo, Dossenheim, Germany), CD8 (C8/144B, dilution 1:20; DakoCytomation, Hamburg, Germany), CD30 (dilution 1:10; DakoCytomation), CD25 (2A3, dilution 1:10; Becton Dickinson Immunocytometry Systems, San Jose, CA), CD45RO (ACT-1, dilution 1:500; DakoCytomation), FAS (B-10, dilution 1:250; Santa Cruz, Santa Cruz, CA), and CTLA-4 (BN13, dilution 1:200; BD Biosciences, San Diego, CA).

Immunohistochemical analysis was performed according to standard protocols. Following deparaffinization, tissue sections were heat-treated for 6 minutes at 121°C using target-retrieval solution, pH 6.1 (DakoCytomation) for the antibodies CD25, FAS, CTLA-4, and FoxP3. For ALK1, CD4, CD8, CD45RO, and CD30 staining, heat treatment in citrate buffer, pH 6.0, was applied.

In the 7 AILT and 9 PTCL-NOS cases with available frozen material, we studied the expression of FoxP3 (goat polyclonal, dilution 1:200; Abcam), CD4 (MT310, dilution 1:10; DakoCytomation), CD25 (ACT-1, dilution 1:2,000; DakoCytomation), CD45RO (UCHL1 FITC, dilution 1:10; Dianova, Hamburg, Germany), and FAS and CTLA-4 by fluorescence double stainings with the respective TCR \(\beta\) antibody (Beckman Coulter, Marseille, France) recognizing the TCR \(\beta\) segment that is rearranged and expressed by the neoplastic cells as previously shown.\(^28\) Fluorescence images were evaluated by using confocal laser scanning microscopy (Leica TCS2, Leica, Bensheim, Germany).

#### Statistical Analysis

We compared FoxP3 expression between ALK+ and ALK− ALCL cases by using the \(\chi^2\) test. A \(P\) value less than .05 was considered statistically significant. Cluster analysis was performed to compare CD4, CD25, CD45RO, FAS, CTLA-4, and FoxP3 expression among ALCL cases.

#### Polymerase Chain Reaction for HTLV-1 Detection

The FoxP3+ PTCL-NOS was studied for a potential association with a human T-cell lymphotropic virus (HTLV)-1 infection by a polymerase chain reaction (PCR) that detects the presence of proviral HTLV-1 DNA in the tumor. Primary and nested primers were used according to Costa et al.\(^29\) For this part of the study, 500 ng of DNA template, in a final volume of 25 µL, was amplified in a reaction mixture containing a final concentration of 0.2 µmol/L primer, 0.25 mmol/L deoxynucleoside triphosphates (Fermentas, St Leon-Rot, Germany), and 1 × Taq polymerase buffer with 2 mmol/L of magnesium chloride and 0.65 U of Taq polymerase (Taq DNA polymerase, recombinant, Invitrogen, Karlsruhe, Germany). PCRs were run for 35 cycles in a thermocycler (Masterecycler gradient, Eppendorf, Wesseling-Berzdorf, Germany). After a 5-minute denaturation at 94°C, each cycle consisted of 30 seconds at 94°C, 30 seconds at an annealing temperature of 60°C, and 1 minute 30 seconds at 72°C followed by a final extension step of 7 minutes at 72°C. PCR products of the expected size were separated on an EtBr-stained agarose gel and purified (JETSORB gel extraction kit, Genomed, Loehne, Germany). Aliquots of 7 µL were used for sequencing analysis with 1 µmol/L of the

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respective primer and 2 µL of BigDye Terminator v3.1 Cycle Sequencing Reaction Mix (Applied Biosystems, Foster City, CA) in a final volume of 10 µL. Samples were analyzed in a 3130xl Genetic Analyzer (Applied Biosystems).

Ethics Approval

Ethics approval for the entire study was obtained from the ethics committee, Medical Faculty, University of Würzburg, Würzburg, Germany. In general, the procedures followed the Helsinki Declaration of 1975. Informed patient consent was not required by the ethics committee because diagnostic specimens can be used for research purposes after anonymization.

Results

AILT and Other Subtypes of PTCL

Among the 83 PTCL cases studied, the neoplastic T cells in all 23 AILT cases were completely FoxP3−. FoxP3 positivity could only be detected in a few cells of the reactive infiltrate (data not shown). Likewise, the neoplastic cells of the 8 cases belonging to other T-cell lymphoma subtypes (cutaneous, intestinal, and hepatosplenic T-cell lymphoma and T/NK-cell lymphoma, nasal type) were also completely negative for FoxP3 expression.

PTCL, Not Otherwise Specified

Among 14 PTCL-NOS cases primarily studied, only 1 case strongly and uniformly expressed FoxP3. All remaining 13 cases were negative. The results of the single stains in paraffin-embedded tissue were in agreement with those obtained in frozen specimens from 9 patients by fluorescence double staining and, thus, confirmed the presence of only a few FoxP3+ reactive T cells, whereas the neoplastic clone was FoxP3−.

Because the only case that showed strong FoxP3 expression in the neoplastic cells corresponded to the immunoblastic variant of PTCL-NOS (according to the Kiel classification), we studied 9 additional PTCL-NOS cases showing immunoblastic morphologic features. However, in all of these cases, the neoplastic cells were also negative for FoxP3.

Histologically, the FoxP3+ tumor showed a diffuse growth pattern of variably medium-sized or large atypical T cells with convoluted nuclei and mostly prominent nucleoli. It is interesting that there was only a minor background infiltrate, which is rather unusual among PTCL cases. Immunohistochemically, the tumor cells expressed an αβ TCR (Vβ5.1) and CD4, CD45RO, FAS, and CTLA-4 and were negative for CD30 (data not shown). In contrast, CD25 was undetectable on the immunohistochemical level. There was no evidence of an HTLV-1 association because HTLV-1 proviral DNA was not amplifiable by PCR. In contrast, a lymph node from a patient with known HTLV-1 infection that was used as a positive control sample displayed HTLV-1–specific PCR products as confirmed by sequence analysis (data not shown).

The FoxP3+ tumor occurred in a 59-year-old man with pathologically enlarged cervical, mediastinal, axillary, intra-abdominal, retroperitoneal, and inguinal lymph nodes who was diagnosed with a T-immunoblastic non-Hodgkin lymphoma according to the Kiel classification at that time, which falls into the category of PTCL-NOS in the current classification.

!Image 1A. FoxP3+ peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (Giemsa, ×200).

!Image 1B. FoxP3+ PTCL-NOS (FoxP3/T-cell receptor Vβ fluorescence double staining [red, Vβ 5.1; blue, FoxP3; ×400]).
WHO classification. At diagnosis, the patient was in a good physical condition and had stage IV disease, no evidence of involvement of extranodal sites, and an elevated lactate dehydrogenase value. He received chemotherapy according to the CHOP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone) protocol. Five days later, his general condition deteriorated and, during the chemotherapy-induced neutropenia phase, he had repeated infections. One month after the initial diagnosis, the patient died.

**Anaplastic Large Cell Lymphoma**

We studied FoxP3 expression in 20 lymph node specimens from patients with ALCL, including ALK+ and ALK– tumors. We found expression of FoxP3 in 4 of 6 ALK+ ALCL and 1 of 14 ALK– ALCL cases. However, in contrast with the PTCL-NOS case described, FoxP3 expression was not strong and uniform, but rather relatively weak and variable among the tumor cells. On average, only 20% to 30% of the morphologically recognizable tumor cells were stained with FoxP3. The difference in FoxP3 expression between ALK1+ and ALK1– ALCL was statistically significant. In comparing the expression of other markers related to the T_reg cell phenotype, which were, except CD25, also expressed in the FoxP3+ PTCL-NOS case (CD4, CD25, CD45RO, FAS, and CTLA-4) we performed a cluster analysis of the immunohistochemical data obtained in the ALCL cases.

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| AILT, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; +, positive; –, negative; (+), weak positivity.

**Table 1**

**Fluorescence Double Staining of a Marker Panel in Combination With an Antibody Directed Against the Respective T-Cell Receptor Vβ Segment Rearranged and Expressed by the Neoplastic T Cells in 7 Cases of AILT and 9 Cases of PTCL-NOS**

**Image 21**

A. Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma (ALCL) (Giemsa, ×200). B. ALK+ ALCL (FoxP3 staining, ×200).
In contrast with the homogeneous staining pattern of FoxP3, FAS, and CTLA-4, a heterogeneous staining pattern was detected for CD4, CD25, and CD45RO among ALK+ and ALK– ALCL cases, indicating that ALCLs do not show the complete phenotype of T<sub>reg</sub> cells. Among the 11 CD4–ALCLs (Table 2), only 1 ALK+ ALCL (FoxP3–) expressed CD8 (data not shown).

**Discussion**

In this study, we tried to identify nodal PTCLs that may be derived from T<sub>reg</sub> cells. Surprisingly, we found only 1 FoxP3+ PTCL-NOS among 63 PTCL cases, excluding ALCL cases. To the best of our knowledge, T<sub>reg</sub> cell phenotypes have not been described in nodal PTCL in Western countries. We therefore conclude that the derivation of nodal PTCL from T<sub>reg</sub> cells occurs but is a rare event, at least within the white population.

It is tempting to speculate that some of the morphologic and clinical features of the case described herein may be explained by the retained regulatory function of the tumor cells. First, the tumor showed a growth pattern that is rare in PTCL-NOS because only a few tumor-infiltrating reactive T or B cells could be observed within the tumor cell infiltrate, and the growth pattern was almost cohesive. This paucity of reactive background cells may be caused by the immunosuppressive function of the tumor cells. Second, the regulatory T-cell function might have significantly suppressed antitumoral immunity, thereby contributing to the rapid progression of disease and poor clinical course of the patient. Although the majority of patients with PTCL-NOS have a poor clinical outcome, the rapid and fatal progression seen in the FoxP3+ case described herein differs from the typical clinical course of PTCL-NOS in general. Thus, FoxP3-expression and the associated regulatory phenotype might be an adverse biologic and clinical factor in rare PTCL cases that contributes to the aggressiveness of the tumor.

Particularly, the strong FoxP3 expression in our case suggests that this tumor might have arisen from a natural T<sub>reg</sub> cell, even though the tumor cells were negative for CD25, which is a phenotype that has been described among T<sub>reg</sub> cells in humans and mice.6–13 A subgroup of CCR4+ PTCL-NOS was previously associated with T<sub>reg</sub> cells by a Japanese group because these tumor samples expressed FoxP3 at elevated levels as measured by quantitative real-time PCR. However, this study did not investigate whether FoxP3 was coexpressed in the tumor cells or derived from accompanying nonneoplastic T<sub>reg</sub> cells in the reactive infiltrate.30 Whereas a T<sub>reg</sub> cell phenotype has not been convincingly demonstrated in nodal PTCL, subsets of extranodal PTCL have been suggested to be derived from T<sub>reg</sub> cells. In 5 studies, cases of HTLV-1–associated adult T-cell leukemia/lymphoma (ATLL) have been shown to express FoxP3 and were, therefore, considered to be derived from T<sub>reg</sub> cells.31–35 It is interesting that these lymphomas are also characterized by a poor prognosis.1,36,37 Whereas purified tumor cells from peripheral blood mononuclear cells (PBMCs) or lymph nodes of patients with ATLL show in 50% to 100% of cases elevated FoxP3 expression by real-time PCR and immunohistochemical analysis, 1 study revealed widely varying results in Western blot analysis.33 In addition to ATLL, 1 of 3 cases of T-cell prolymphocytic

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+, positive; –, negative; (+), weak positivity.
leukemia showed evidence of FoxP3 expression in PBMCs studied by real-time PCR. Several studies suggest that FoxP3 expression may be induced in CD4+ T cells under certain circumstances. For example, Walsh et al demonstrated that FoxP3 expression and an associated regulatory phenotype correlated with retroviral HTLV-1 infection in cultured CD4+ T cells. Conversely, however, increased levels of FoxP3 were also found in PBMCs of 3 of 12 HTLV–cutaneous T-cell lymphomas by quantitative real-time PCR. This finding may be explained by the finding of Berger and colleagues, who were able to demonstrate that a regulatory T-cell phenotype can be induced in cutaneous T-cell lymphoma by cultivating purified PBMCs with dendritic cells loaded with apoptotic material. In our case, we demonstrated by PCR that the regulatory phenotype was not associated with an HTLV-1 infection.

In contrast with the aforementioned entities, the mode of FoxP3 induction in ALK+ ALCL seems to be different. Only a subset of tumor cells in ALK+ ALCL expressed FoxP3, and the level of expression varied among tumor cells, pointing to an intricate mechanism of FoxP3 regulation. Recent data suggest that FoxP3 may be up-regulated as a consequence of ALK deregulation in ALCL, as has been shown in ALK+ ALCL cell lines. In particular, Kasprzycka et al demonstrated elevated FoxP3 expression in 4 of 4 ALK+ ALCL cell lines as evidenced by real-time quantitative PCR, whereas by Western blot analysis, 1 of the cell lines showed strong and 3 showed weak FoxP3 expression. The same authors provided evidence that the regulatory T-cell phenotype was induced by ALK, as lymphoid cells transfected with NPM/ALK induced the Treg cell phenotype, and inhibition of NPM/ALK function in ALK+ cell lines suppressed the Treg cell phenotype. Furthermore, the authors identified STAT3, which is activated by NPM/ALK, as an effector of the Treg cell phenotype induction by activating IL-10, transforming growth factor β, and FoxP3 expression. In line with these results, we found significantly different FoxP3 expression between ALK+ and ALK– ALCLs. Only 1 of 14 ALK– ALCLs expressed FoxP3. Considering these findings together, the induced FoxP3 expression in ALK+ ALCLs seems to be an epiphenomenon following aberrant ALK overexpression without a real Treg cell derivation of the tumor cells. This conclusion may be additionally supported by our results that show a lack of other characteristics of Treg cells, as CD4, CD25, CD45RO, FAS, and, especially, CTLA-4 are not constantly coexpressed with FoxP3 (Table 2).

We describe a putatively natural Treg cell phenotype in a case of a nodal PTCL-NOS. Some of the morphologic and clinical peculiarities of this case may be explained by the retained Treg cell function in the neoplastic T-cell clone. Thus, although rare, a Treg cell phenotype may represent an adverse risk factor in PTCL-NOS.

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References


