



# Cytotoxic T-lymphocyte-associated antigen 4-positive aggressive adult T cell leukemia/lymphoma

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Dear Editor,

A 65-year-old Japanese man was admitted to our hospital with general fatigue. His laboratory tests revealed the following: white blood cell count,  $19.2 \times 10^9/L$ ; hemoglobin level, 114 g/L; platelet count,  $386 \times 10^9/L$ ; lactate dehydrogenase activity, 1125 U/L (normal, 124–222 U/L); soluble interleukin-2 receptor 170,000 U/mL (normal, 149–519 U/mL); and C-reactive protein level, 7.04 mg/dL. His serological study was positive for human T cell lymphotropic virus 1 (HTLV-1). Computed tomography scans showed multiple lymphadenopathy of the supraclavicular, axillary, mediastinal, paraaortic, and mesenteric regions. An axillary lymph node biopsy showed diffuse proliferation of atypical small to medium-sized lymphoid cells. (Fig. 1a). The lymphoid cells were positive for CD3, CD4, CD5, CD25, forkhead box P3 (FOXP3) (Fig. 1b), C-C chemokine receptor 4 (CCR4) (Fig. 1c), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (Fig. 1d), and negative for CD20. The tumor cells revealed monoclonally integrated HTLV-1 proviral DNA. These findings were consistent with a diagnosis of lymphomatous adult T cell leukemia/lymphoma (ATLL). Following treatment with CHOP therapy (a regimen of cyclophosphamide/doxorubicin/vincristine/prednisone), and LSG-15 [a regimen of VCAP (vincristine/cyclophosphamide/doxorubicin/prednisone)-AMP (doxorubicin/

ranimustine/prednisone)-VECP (vindesine/etoposide/carboplatin/prednisone)], his disease progressed, eventually infiltrating the central nervous system. The clinical course was also complicated by severe infections with methicillin-resistant coagulase negative *staphylococci* and methicillin-resistant *Staphylococcus epidermidis*. The patient died 8 months after diagnosis.

ATLL cells are believed to originate from regulatory T cells (Tregs), because ATLL cells possess the Treg phenotype, such as CD4 and CD25 [1], and usually express FOXP3, a master regulator of Tregs [2]. It has recently shown that FOXP3-positive cells are heterogeneous and do not always have a suppressive function, and that FOXP3-positive T cells can be dissected into three subpopulations: (1) effector Tregs (eTregs), which have a strong suppressive function; (2) naive Tregs, which have the potential to differentiate into eTregs upon antigenic stimulation; and (3) non-Tregs, which are a non-suppressive subpopulation [3, 4]. CCR4 is a seven-transmembrane Gprotein-coupled receptor that is selectively expressed by Th2 cells and Tregs. CCR4 induces homing of these leukocytes to sites of inflammation [5, 6]. CCR4 is highly expressed by eTregs and, to lesser extent, by non-Tregs [7]. The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a protein receptor specifically expressed by eTregs that is essential for their suppressive function [8].

The type of FOXP3-positive cells that serve as the point of origin for ATLL cells remains unclear. This is the first case report of nodal ATLL with an aggressive clinical course, in which almost all ATLL cells were immunostained positively for FOXP3, CCR4, and CTLA-4. This suggests that, in this case, the origins of the ATLL cells were eTreg cells. The aggressive clinical course, with opportunistic infections and resistance to a variety of chemotherapy agents, might be associated with the tumor cell origin: eTregs, weakening the patient's anti-tumor and anti-infection immune responses.

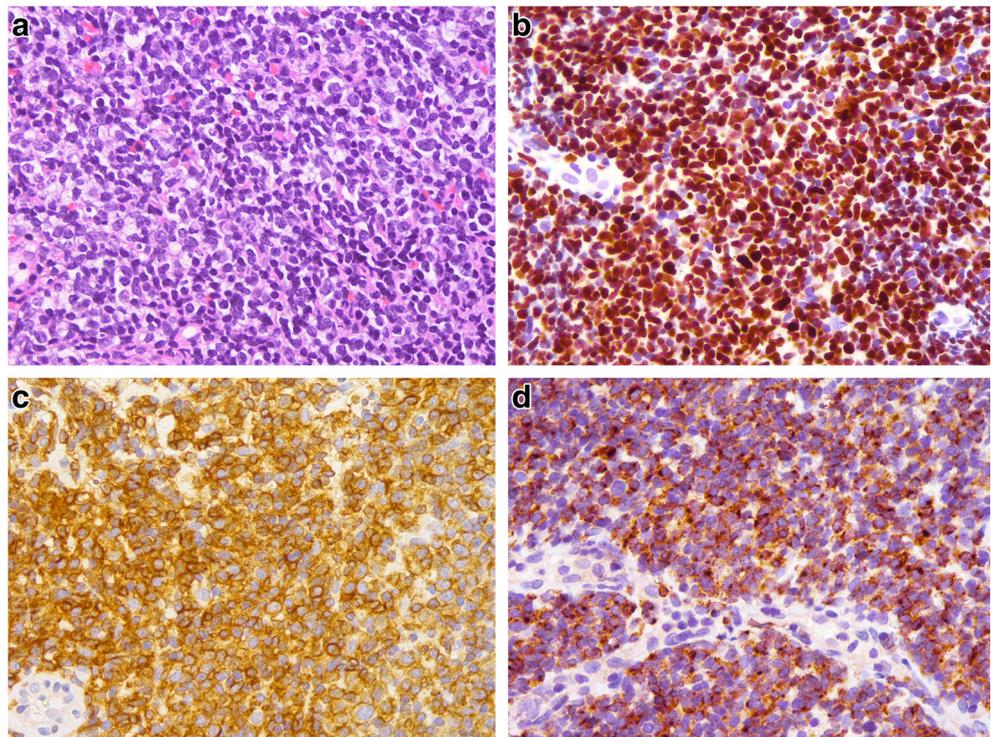
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**Fig. 1** Histological examination of lymph node biopsy specimen. **a** The tumor consisted of small to medium-sized lymphoid cells with slightly fine nuclear chromatin, (hematoxylin and eosin stain; objective magnification,  $\times 40$ ). **b** Almost all lymphoid cells were positive for FOXP3, (objective magnification,  $\times 40$ ). **c** Almost all lymphoid cells were positive for CCR4, (objective magnification,  $\times 40$ ). **d** Almost all lymphoid cells were positive for CTLA-4, (objective magnification,  $\times 40$ )



CTLA-4 expression in tumor cells could be a poor prognostic marker in patients with ATLL.

### Compliance with ethical standards

**Statement of informed consent** Informed consent was obtained from the patient.

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

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