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CORRESPONDENCE

Progression of adult T-cell leukemia/lymphoma from smoldering to acute type due to branched subclonal evolution

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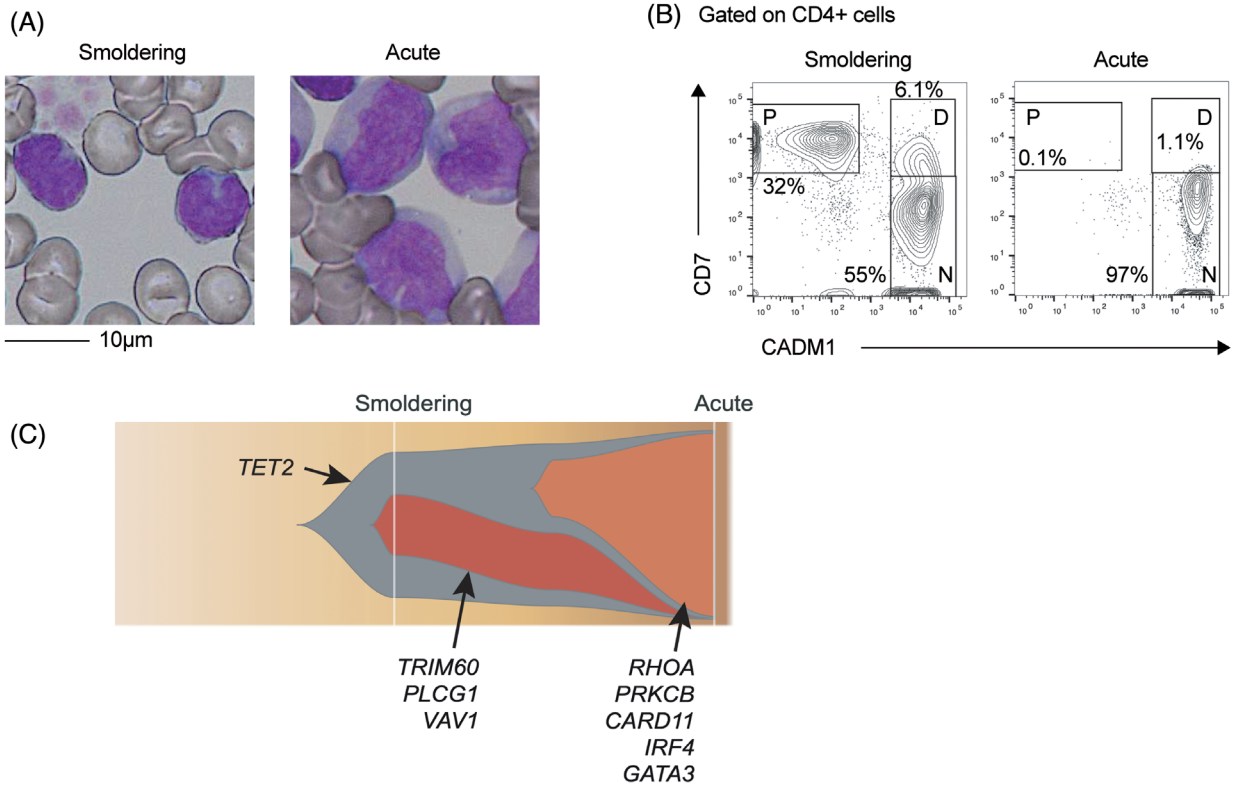
KEYWORDS
ATL, clonal evolution, HTLV-I, T-Cell lymphoma

Adult T-cell leukemia/lymphoma (ATL) is a disease with a poor prognosis that occurs in patients with HTLV-1 infection and is classified according to the Shimoyama classification into smoldering, chronic, lymphoma, and acute types [1]. The disease may transform from the smoldering type, which simply requires careful monitoring, to the acute type, which requires immediate treatment [2, 3]. The pathological mechanisms of acute transformation of ATL have not been sufficiently elucidated, except in some limited cases in which the acquisition of novel mutations to the dominant clones conferred survival fitness in the acute phase [3–5]. This type of clonal change is referred to as linear evolution, and accumulated genetic and/or epigenetic alterations are assumed to contribute to the stepwise progression of the disease. Here, we present the case of a middle-aged patient with ATL that had transformed from smoldering to acute type, with branched evolution of subclones, in the space of approximately one year.

The case is a 40-year-old man whose mother had developed ATL; and had been tested for HTLV-1 antibodies, which revealed infection with HTLV-1. At this point, the patient had 15% abnormal lymphocytes in peripheral blood and was diagnosed with smoldering ATL. The targeted sequencing of CD4+ CADM1+ cells in this phase revealed a *TET2*-mutated clone, with subclones with additional mutations in *TRIM60*, *PLCG1*, and *VAV1* (Figure 1C,D). The patient was followed up regularly for blood testing; after 14 months, headache, facial paralysis, and disturbed consciousness were observed. A detailed examination revealed that the patient had developed acute type ATL with central nervous system involvement. At that time, both the cytoplasm and nuclei of the ATL cells were larger compared with those seen when the patient had smoldering-type ATL and almost all CD4+ cells in the peripheral blood were CD7- CADM1+ (Figure 1A,B). The cells from this fraction were subjected to next-generation sequencing analysis.



(D)

Chr	Gene	Amino acid change	Deleteriousness prediction				COSMIC v98 entry			VAF		
			SIFT	Polyphen2_HVAR	FATHMM	M-CAP	Hematology	Lymphoma	ATL	Smoldering, D	Smoldering, N	Acute
4	*TET2*	p.L1244fs	-	-	-	-	7	0	0	0.234	0.549	0.929
4	*TRIM60*	p.R324X	T	.	.	.	0	0	0	0.008	0.156	0.000
20	*PLCG1*	p.D1169G	D	D	T	0.096	2	2	2	0.005	0.093	0.000
19	*VAV1*	p.D840V	D	D	T	0.435	0	0	0	0.000	0.015	0.000
5	*SLIT3*	p.K134N	T	D	T	0.031	0	0	0	0.000	0.010	0.000
4	*TENM3*	p.A2471V	T	B	D	0.027	0	0	0	0.000	0.004	0.000
3	*TP63*	p.R618W	.	D	D	0.403	0	0	0	0.000	0.003	0.000
3	*RHOA*	p.K18N	D	D	D	0.216	1	1	0	0.000	0.000	0.484
16	*PRKCB*	p.D427N	D	D	T	0.125	96	96	91	0.000	0.000	0.453
7	*CARD11*	p.D401V	D	D	T	0.118	14	13	2	0.000	0.000	0.446
6	*IRF4*	p.L116P	T	D	D	0.453	0	0	0	0.000	0.000	0.340
10	*GATA3*	p.F234fs	-	-	-	-	2	0	0	0.000	0.000	0.068

SIFT_prediction: D: Deleterious; T: tolerated

Polyphen2_HVAR_prediction: D: Probably damaging , P: possibly damaging; B: benign

FATHMM_prediction:D: Deleterious; T: Tolerated

M-CAP: score>0.025: deleterious

FIGURE 1 Differences between smoldering- and acute-type adult T-cell leukemia/lymphoma (ATL) in this case. (A) Representative images of micrographs, (B) Representative plots of flow cytometry, (C) A fish plot, according to the variant allele frequency (VAF) of each mutation at each time point, (D) A summary of the information for each of the mutated genes.

Although the *TET2* mutation consistently constituted the major clone, increasing from 55% (smoldering-type phase) to 93% (acute type phase), by variant allele frequency, the subclones had been completely replaced (Figure 1C,D).

In this case, we demonstrated that the clinical progression of ATL from smoldering- to acute type was accompanied by a clonal change in tumor cells. *TRIM60*- and *PLCG1*-mutated subclones observed in the smoldering phase were expelled and completely substituted in the acute phase by a novel subclone with mutations in *RHOA*, *PRKCB*, *CARD11*, and *IRF4*, with a common parental clone with *TET2* mutation. We assumed that *RHOA* p. K18N was pathogenic, as this locus is next to the hotspot site (G17) and has been registered in the COSMIC

database. The newly detected subclone featured properties associated with poor prognosis. In mouse models, *CARD11* mutations are known to be involved in the oncogenicity of ATL [6], and cases of ATL with *IRF4* or *PRKCB* mutations are reported to have a significantly worse prognosis [7, 8]. Thus, this case directly illustrates that genetic mutations have various oncogenicities. The subclones with mutated *TRIM6 and PLCG1* have proliferative potential but are substituted by subclones with mutated *RHOA*, *PRKCB*, *CARD11*, *and IRF4*, which directly transform HTLV-1 infected cells into the aggressive phenotype. This branched evolution constitutes one of the mechanisms of disease progression and acute transformation. Our case illustrates that transformation mechanisms are diverse, with branched evolution being one of them. This diversity implies a limited role for initial genetic profiling in predicting long-term outcomes. We, therefore, recommend placing an emphasis on repeated genetic testing, especially in cases that experience disease progression, as potential therapeutic targets may change during this progression. This will take on greater importance in the era of more extensive molecular-targeted therapy. Further studies are warranted to reveal genetic mutations that confer aggressive properties to HTLV-1-infected cells.

AUTHOR CONTRIBUTIONS

K.J. treated the patient, interpreted the data, and wrote the paper. M.Y. performed the experiments and analyzed and interpreted the data. Y.S. and K.S. performed the experiments. M.M. and T.N.I. contributed the data of micrograph images. K.Y. and A.S. participated in the treatment of the patient. Y.N. and K.U. planned and guided the research, interpreted the data, and wrote the paper. All authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

Informed consent was obtained from the patient included in the study.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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