Letter to the editor

Myelodysplastic syndrome accompanied by basophilia and eosinophilia with t(5;12)(q31;p13)

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The t(5;12)(q31-35;p12-13) translocation is rare among cytogenetically categorized myeloid diseases. Here we describe a case of MDS with basophilia followed by leukocytosis, basophilia and eosinophilia with t(5;12)(q31;p13).

A 44-year-old man was referred to Tsukuba University Hospital due to severe anemia and thrombocytopenia in August 2005. Peripheral blood showed hemoglobin 4.5 gm/dl with MCV 109 fl, platelets 73×10^9 l^{-1} and white blood cells 4.9×10^9 l^{-1} with 23% basophils, 3% eosinophils and 0% blasts. Bone marrow was slightly hypocellular marrow with trilineage dysplasia. Cytogenetic examination of the bone marrow cells revealed 46,XY. A diagnosis of MDS-RAEB2 was made according to the WHO classification. Two months later, his white blood cell (WBC) count gradually increased with emerging eosinophilia. Peripheral blood showed white blood cells 27.5×10^9 l^{-1} with 54% basophils, 29% eosinophils and 0% blasts. Bone marrow was hypercellular with relative increase of immature cells. Cytogenetic exmination of his bone marrow cells revealed 47,XY,t(5;12)(q31;p13), +8[5]/46,XY[15]. We tried short-term administration of Imatinib in our case but saw no response. We next started administration of hydroxyurea. The

WBC count temporarily increased to maximum of 87.3 × 10^9 l^{-1}, and then gradually decreased. Three months later, he received unrelated allogenic bone marrow transplantation following a myeloablative preparation regimen of cyclophosphamide (120mg/kg) and total body irradiation (12Gy) in March 2006. Currently, he is healthy with negative test for t(5;12)(q31;p13).

Recently, human long fatty acyl CoA synthetase gene, *ACS2*, on 5q31 was identified as a fusion partner of *ETV6* in acute myeloid leukemia (AML) and MDS cases with t(5;12)(q31;p13)[1]. We also performed RT-PCR for *ETV6-ACS2* from the bone marrow cells following the published method [1] and an amplified DNA fragment was detected (fig.1A). DNA sequencing of the DNA fragment revealed an out-frame fusion of exon 1 of *ETV6* gene to exon 1 of *ACS2* gene (fig.1B). Expressions of interleukin-3 (*IL-3*) or nterleukin-5 (*IL-5*) were detected in the bone marrow cells of our case while no expression was seen in controls (fig.1C,D), which may be related to the cause of eosinophilia or basophilia as previously suggested [2, 3].

We have summarized the published reports of hematological disorders accompanied by t(5;12)(q31;p12-13) (Table 1). A remarkable male preponderance (14/15) can be seen. Only two cases (case 8 and case 16) were

accompanied by basophilia (Table 1, [1, 4]). On the other hand, 15 of 18 cases (83%) were accompanied by eosinophilia (Table.1, [1-13]). *ETV6-ACS2* fusion gene was identified in seven cases. Eight cases seem to be classified as MDS / MPD by WHO criteria. These cases may be typified as a distinct subgroup of myeloid disorders. Another nonrandom translocation which involves the short arm of the chromosome 12 and the long arm of the chromosome 5 is the t(5;12)(q33;p13) [14]. The translocation juxtaposes the *ETV6* gene with the platelet-derived growth factor receptor β (*PDGFRβ*) gene. It is of clinical importance that imanitib mesylate is effective for patients with rearrangement of the *PDGFRβ* gene [15]. Our patient received a course of imatinib without response. It is important to determine the precise breakpoint or identify the fusion gene in hematological malignancy with t(5;12) to ensure an appropriate choice of therapy.

We experienced a rare case of MDS with t(5;12)(q31;p13) with basophilia and eosinophilia. Further studies are needed to understand the precise mechanism of disease by the translocation or the resultant fusion gene.

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Figure captions

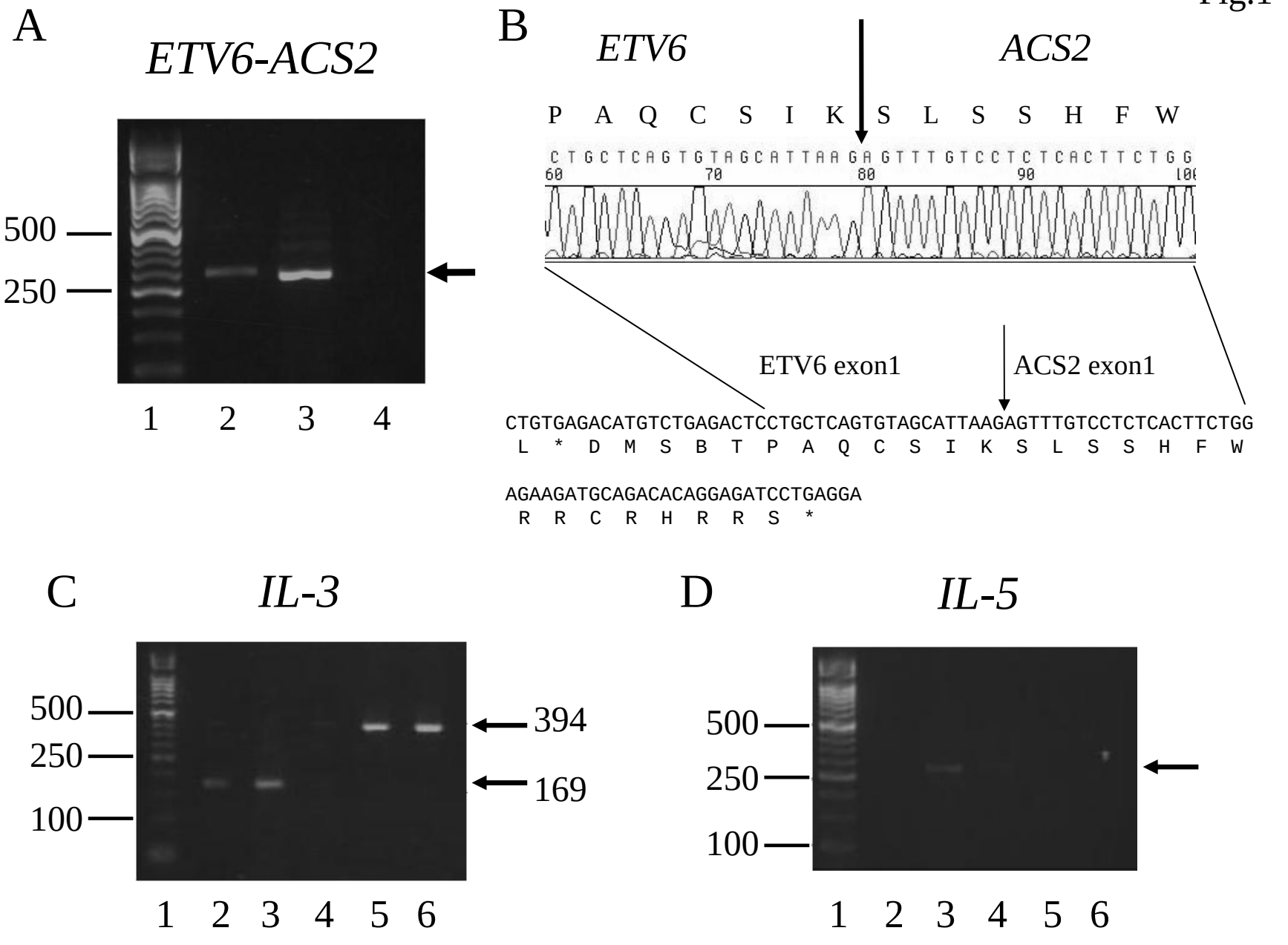
Fig. 1. (A) RT-PCR amplification of *ETV6-ACS2* fusion. Lane 1: 50bp ladder marker; lane 2: bone marrow at initial presentation in August 2005; lane 3: bone marrow with basophilia and eosinophilia in December 2005; lane 4: bone marrow after alloBMT in April 2006. (B) DNA sequencing of the RT-PCR product revealed a fusion between *ETV6* exon 1 and *ACS2* exon 1. Arrows indicate the breakpoint. Lower line represents putative coding region of *ETV6-ACS2* fusion[1]. (C,D) RT-PCR of *IL-3* (C) and *IL-5* (D) genes. Lane 1: 50bp ladder marker; lane 2: bone marrow at initial presentation in August 2005; lane 3: bone marrow with basophilia and eosinophilia in December 2005; lane 4: bone marrow after alloBMT in April 2006; lane 5 and 6: bone marrow from lymphoma patients without involvement. Transcription of *IL-3* was detected as a 169 bp fragment. The 394 bp fragment is due to an amplification of contaminated genomic DNA[2].

Table 1 Cases of myeloproliferative disorders with t(5;12)(q31;p12-13) Table 1 Cases of myeloproliferative disorders with t(5;12)(q31;p12-13)

No.	Diagnosis	Age/Sex	WBC (x109/L)	Eo(%)	Ba(%)	Hb (g/dL)	Platelet (x109/L)	Karyotype	Detection of ETV6-ACS2	Therapy	Follow-up (mons)	Status	Ref.
1	aCML	49/M	NG	increase	NG	NG	NG	46,XY,t(5;12)(q31;p13)	RT-PCR	NG	NG	NG	[2]
2	aCML	34/M	NG	increase	NG	NG	NG	46,XY,t(5;12)(q31;p12-p13)	ND	NG	14+	alive	[6]
3	aCML	53/M	49.0	0	0.88	5.6mM	52	47,XY,t(5;12)(q31;p12),+10	ND	polychemo-therapy	9	dead of sepsis	[7]
4	aCML	40/M	46.9	12	1.2	6.8mM	52	46,XY,t(5;12)(q31;p12)	ND	allo-SCT	14	dead	[7]
5	HES (aCML?)	43M	26.5	18	NG	NG	NG	46,XY,t(5;12)(q31;p12)	ND	HU,VCR,allo-SCT	48	dead of fungal infection	[8]
6	aCML/CMMoL	16/M	46.4	6	3	12.0	213	46,XY,t(5;12)(q31;p12)	ND	IFN,HU	NG	NG	[9]
7	CMMoL	41/M	32.4	11	2.6	15.2	202	46,XY,t(5;12)(q31;p12)	ND	HU	31+	alive	[10]
8	MDS	68/F	8.8	3	69	8.4	37.5	46,XX,t(5;12)(q31;p13)	RT-PCR	AraC	NG	dead of sepsis	[1]
9	MDS	27/M	41.1	42	NG	NG	NG	46,XY,t(5;12)(q31;p13)	RT-PCR	NG	1	dead of sepsis	[1]
10	MDS	8/F	33.7	6.2	1.0	12.9	322	46,XX,t(5;12)(q31;p12-p13)	ND	HU	84+	alive	[3]
11	MDS	7M	NG	increase	NG	NG	NG	46,XY,t(5;12)(q31;p13), -8,+12	ND	HU,IFN	48+	alive	[11]
12	EoL	59/M	136.0	94	1.3	12.5	116	46,XY,t(5;12)(q31;p12)	ND	HU,BU	3	dead of brain stroke	[5]
13	AML	53/M	59.5	69	3	NG	59.5	46,XY,t(5;12)(q31;p13)	RT-PCR	polychemo-therapy	9	dead of eos. infiltration	[1]
14	MPD→EoL	59/M	20.9	10	3	4.2	40	46,XY,t(5;12)(q31;p12), t(19;21)(p13;q22)	ND	BU,6TG	3	dead	[12]
15	AML-relapse	30/M	41.1	42	2.4	13.4	370	46,XY,t(5;12)(q31;p12)	ND	NG	1	dead of sepsis	[13]
16	PV	29/M	11.2	16	NG	21.0	522	46,XY,t(5;12)(q23-31;p13)	FISH	HU	42+	alive	[4]
			9.6	15	15	16.5	484						
17	PV/AML	31/F	18.2	NG	NG	13.0	278	46,XX,t(5;12)(q23-31;p13)	FISH	HU, purinethol, AraC	11	dead of hemorrhage	[4]
18	MDS	44/M	22.7	39	42	5.5	85	47,XY,t(5;12)(q31;p13),+8	RT-PCR	HU,AraC,STI571, alloSCT	8+	alive	Present case

Abbreviations: Eo,eosinophils; Baso,basophils; Mono,monocytes: NG,not given; aCML,atypical chronic myeloid leukemia; MDS, myelodysplastic syndrome; AML, acute leukemia; EoL, Eosinophilic leukemia; alloSCT, allogenic stem cell transplantation; IFN, interferon; HU, hydroxyurea; BU, busulfan; VCR, vincristine; ND, no determination

Fig.1


A
ETV6-ACS2
500
250
1 2 3 4
B
ETV6
ACS2
P A Q C S I K S L S S H F W
C T G C T C A G T G T A G C A T T A A G A G T T T G T C C T C T C A C T T C T G G
60 70 80 90
ETV6 exon1
ACS2 exon1
CTGTGAGACATGTCTGAGACTCCTGCTCAGTGTAGCATTAAGAGTTTGTCCTCTCACTTCTGG
L * D M S B T P A Q C S I K S L S S H F W
AGAAGATGCAGACACAGGAGATCCTGAGGA
R R C R H R R S *
C
IL-3
500
250
100
394
169
1 2 3 4 5 6
D
IL-5
500
250
100
1 2 3 4 5 6