

# A unique rearrangement of *PDGFRα* and *ETV6* in a patient with acute myeloid leukemia with myelodysplasia-related changes progressed from chronic myelomonocytic leukemia

Prasad Koduru<sup>1\*</sup>, Naga Guruju<sup>1,2</sup>, Prapti Patel<sup>3</sup>, Jiadi Wen<sup>1</sup>, Kathleen Wilson<sup>1</sup> and Sara Monaghan<sup>1</sup>

\*Correspondence: [Prasad.Koduru@UTsouthwestern.edu](mailto:Prasad.Koduru@UTsouthwestern.edu)



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<sup>1</sup>Department of Pathology, UT Southwestern Medical Center, Dallas, TX 75390, USA.

<sup>2</sup>Integrated Genetics (Labcorp), 2000 Vivigen Way, Santa Fe, NM. 87505, USA.

<sup>3</sup>Department of Medicine, Division of Hematology and Oncology, UT Southwestern Medical Center, Dallas, TX 75390, USA.

## Abstract

Platelet derived growth factor receptor alpha (*PDGFRα*) undergoes different types of rearrangements creating fusion genes in myeloid neoplasms. Cryptic deletion at 4q12 creating *FIP1L1/PDGFRα* fusion is the most frequent and is associated with hypereosinophilia. The other infrequent but recurrent abnormality involving *PDGFRα* seen in myeloid neoplasms is a t(4;12)(q12;p13), which creates a fusion gene with *ETV6* and activates *ETV6* via the tyrosine kinase domain of the *PDGFRα*. We characterized a new t(4;12;6) translocation which developed during transformation to acute myeloid leukemia (AML) in a patient with chronic myelomonocytic leukemia (CMML). Standard G-band karyotype analysis and fluorescence in-situ hybridization study (FISH) analysis with a tricolor 4q12 probe and *ETV6* was performed on the bone marrow (BM) involved by AML. The karyotype showed a t(4;12;6)(q12;p13;p21.3). FISH showed fusion between *PDGFRα* and *ETV6*. Patient did not respond to treatment with imatinib or to standard induction chemotherapy for AML, and expired 11 months from diagnosis. This is the first report of a variant t(4;12;6) and *ETV6/PDGFRα* fusion that developed during transition from CMML to AML and did not respond to imatinib.

**Keywords:** CMML, transformed AML, *ETV6/PDGFRα* fusion

## Introduction

Morphological and cytogenetic features categorize myeloid neoplasms into myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), myeloproliferative neoplasms (MPN) and AML [1]. Specific genetic abnormalities are identified in some subtypes of these diseases. These abnormalities frequently target transcriptional factors involved in controlling cell proliferation and differentiation and are associated with different clinical outcomes. Balanced chromosome rearrangements that lead to gene fusions are frequent in AML. In contrast, gain and/or loss of chromosomes or chromosome segments are frequent in MDS, and in MDS/MPN. CMML is a myeloid neoplasm with features characteristic of both a MDS and MPN [2]. Persistent peripheral blood (PB) monocytosis and less than 20% blasts are major features of CMML. Clonal cytogenetic abnormalities have been reported in about 30% of these patients; these include trisomy 8, and monosomy 7 or del(7q), but none are specific to CMML [3-6]. About 15-20% of these patients progress to AML, and the transformation is ac-

companied by increasing complexity of genetic abnormalities.

An interstitial cryptic deletion within chromosome band 4q12 is a recurrent abnormality in chronic myeloid neoplasms with hypereosinophilia. This deletion fuses 5'-*FIP1L1* with the 3'-*PDGFRα* and leads to constitutive activation of *PDGFRα*. This abnormality is also rarely seen in AML or precursor T-lymphoblastic lymphoma [7]. Patients with *FIP1L1/PDGFRα* fusion respond well to treatment with imatinib [8-11]. Other infrequent rearrangements of 4q12 are translocations with several other regions in the genome, and each of these affect the negative regulatory domain of *PDGFRα*. These patients usually respond to treatment with imatinib.

*ETV6*, located at 12p13 belongs to *ets* family of transcription factors [12], and codes for ubiquitously expressed nuclear protein that plays an important role in hematopoiesis in BM [13]. Rearrangement of *ETV6* with *PDGFRα* (at 4q12) has been reported in AML, but more frequently involves other translocation partners that leads to fusion genes with tyrosine kinases or transcription factors [14-16]. Other molecular alterations

of leukemogenic nature in *ETV6* include deletion leading to haploinsufficiency and heterozygous mutations that result in loss of tumor suppressor activity [17-19]. Here we report the clinical, pathologic, and cytogenetic features of a patient with AML with myelodysplasia-related changes that had a t(4;12;6) (q12;p13;p21) and had developed as a transformation from CMML.

### Clinical history

The patient, a 70 year old male, initially presented with progressive weakness and chest pain. The complete blood count (CBC) revealed a white blood cell count (WBC) of  $100.0 \times 10^9/L$ . The BM was hypercellular with a granulocytic predominance, 5-10% blasts and a normal karyotype. Tests for *JAK2 V617F* and *BCR/ABL1* were negative and a diagnosis of CMML was rendered. Treatment included high dose hydroxyurea and allopurinol, which resulted in an adequate reduction of the WBC. Treatment was changed to azacytidine, but the patient was admitted with chest pain after six cycles of therapy (i.e., 8 months after initial diagnosis).

Upon readmission the CBC revealed WBC of  $223.9 \times 10^9/L$ , hemoglobin 7.7g/dL, and platelets  $27 \times 10^9/L$ . The PB film revealed many circulating blasts and immunophenotyping by flow cytometry was consistent with AML. He was treated with aggressive hydration, allopurinol, hydroxyurea, and red cell and platelet transfusions. Concurrent computerized tomography (CT) of the abdomen and pelvis also detected enlarged retroperitoneal lymph nodes, a large abdominal mass, and bone metastases. A CT guided biopsy of the abdominal mass revealed low-grade follicular lymphoma. The BM evaluation confirmed the AML and also disclosed a low level of involvement by follicular lymphoma. Cytogenetic analysis of the BM specimen showed an abnormal karyotype. FISH for t(8;21) (*RUNX1/RUNX1T1*) and inv(16) (*CBFB*) were normal, whereas a 4q12 probe detected a rearrangement in *PDGFR $\alpha$* . He was then given hydroxyurea, methylprednisolone and allopurinol. The patient was referred to our hospital for treatment with imatinib (600mg/day) for AML and high dose methylprednisolone (1g/day x 3 days) and rituximab (375 mg/m<sup>2</sup>) for the follicular lymphoma. After 7 days of imatinib, PB blast counts continued to increase. Therefore, therapy was changed to induction chemotherapy with cytarabine (100mg/m<sup>2</sup>/day x 5 days) and idarubicin (13mg/m<sup>2</sup>/day x 2 days). CT imaging showed a decrease in the bulky abdominal adenopathy and splenomegaly. However, a day 15 BM evaluation showed persistent AML. Due to persistent leukemia and poor performance status the patient opted for palliative care and expired 11 months from the initial diagnosis of CMML.

### Materials and methods

#### Morphology and flow cytometry

Slides of PB films and BM aspirate smears (Wright-Giemsa stain) and BM (hematoxylin and eosin stain) were reviewed. Flow cytometry was performed at our hospital using a 4-color

FACSCalibur flow cytometry instrument with CELLQuest software (Becton Dickinson, San Jose, CA) and analyzed with Paint-A-Gate software (Becton Dickinson). BM processing and antibody staining were performed as previously described [20].

#### Chromosome analysis and FISH study

Whole BM was cultured for 24hrs in RPMI1640 supplemented with 10% fetal bovine serum, 1% L-glutamine and 1% Pen-strep. These short term cultures were harvested following standard protocols. Air-dried metaphase spreads were trypsin-G-banded and karyotypes were described following ISCN 2009. FISH probes used in this study were purchased from Abbott Molecular (Des Plaines, IL); these were used following the standard FISH protocol (co-denaturation of the probe and target at 74°C for 4min, hybridization over-night at 37°C, and washing at 72°C for 2min). Images were captured using the Applied Spectral Imaging (Carlsbad, CA) software.

#### Cytogenomic microarray analysis (CMA)

Cytogenomic microarray analysis was performed with DNA extracted from bone marrow using an Agilent CGH+SNP 180k microarray platform (Agilent GGXChip+SNP v1.0 4-plex CGH) according to the manufacturer's protocol (Agilent Technologies, Santa Clara, CA). Data interpretation was performed using Genoglyphix software (Perkin Elmer, Waltham, MA). This data were deposited into NCBI GEO data base with the accession number GSE80263.

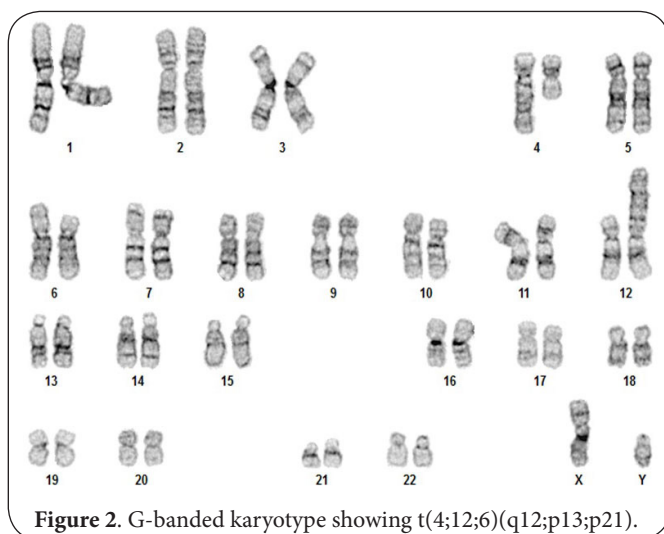
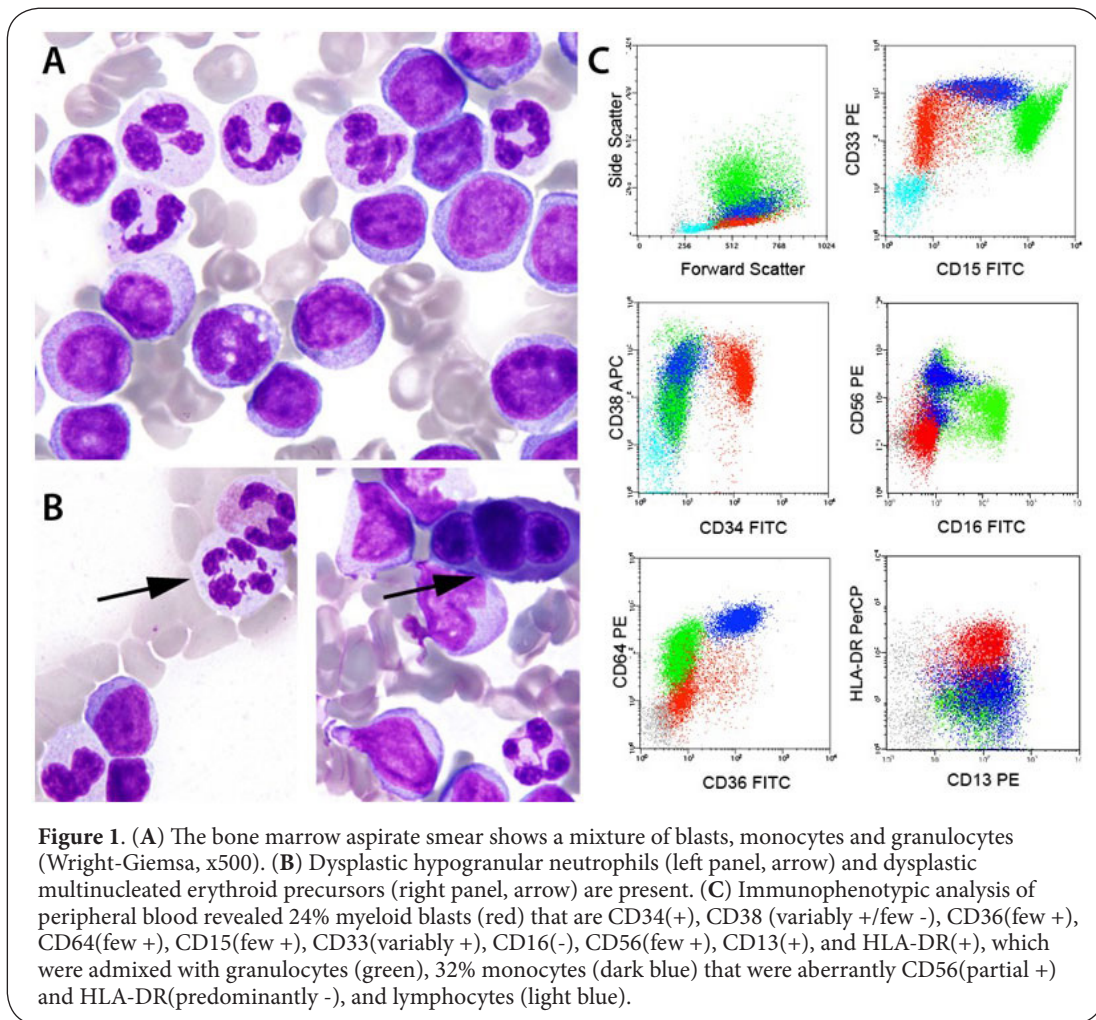
### Results

#### Morphology and flow cytometry

The BM aspirate smears at the time of the diagnosis of AML revealed 50% myeloid blasts, an increased proportion of monocytes and maturing granulocytes, dysgranulopoiesis and dyserythropoiesis (Figures 1A and 1B). The BM biopsy was >90% cellular and also showed a focal paratrabeular infiltrate of small B-cells, which accounted <5% of the cellularity. Flow cytometry on the PB identified 24% myeloid blasts and 32% monocytes with aberrant CD56 expression (Figure 1C) and 1.1% kappa monotypic B-lymphoid cells (not shown). The leukemia was classified as "AML with myelodysplasia-related changes [21]." A bone marrow evaluation 14 days after induction chemotherapy was 90% cellular with persistent AML (i.e., 47% myeloblasts).

#### Cytogenetics and FISH

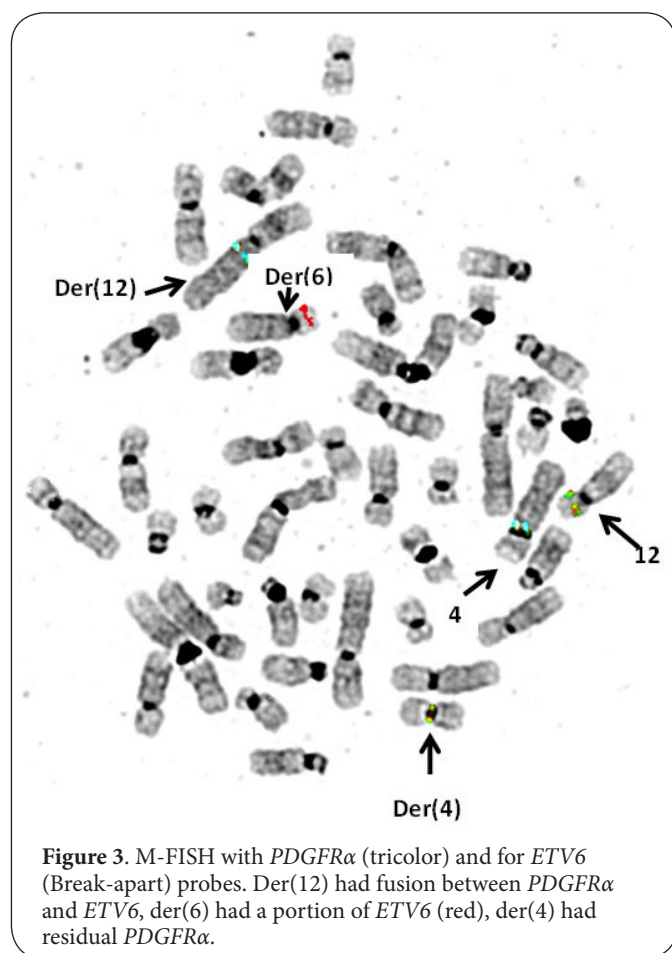
A total of 20 metaphases were evaluated from the over-night cultured cells of the BM specimen obtained at 8 months after initial diagnosis; an abnormal karyotype: 46,XY,t(4;12;6) (q12;p13;p21) was found in 17 metaphases (Figure 2). FISH analysis was performed with D5S721, D5S23/*EGR1*, D7Z1/D7S522, D8Z2/D20S108, *RUNX1/RUNX1T1*, *PML/RARA*, *CBFB*, *FIP1L1/PDGFR $\alpha$*  (tri-color 4q12 probe), and *MLL* probes. *FIP1L1/PDGFR $\alpha$*  probe showed clonal separation of *PDGFR $\alpha$*  from *FIP1L1* in 78% of cells and the D8Z2 probe detected three copies in 2.5% of cells (above our cut-off limit for normal pattern); the



latter finding suggests the presence of a minor clone with trisomy 8 which is under the limit of detection by standard cancer cytogenetic analysis of 20 metaphases. All other probes

showed normal signal pattern. Since the karyotype showed a t(4;12;6) we performed FISH with *ETV6* break-apart probe on G-banded metaphases. This showed that *ETV6* was rearranged and 5'-region translocated to 6p21. Double hybridization with 4q12 probe and *ETV6* break-apart probe showed a fusion signal between *PDGFRα* and *ETV6* at 12p13 (**Figure 3**). A BM specimen 14 days after induction chemotherapy had the above abnormal karyotype in 18 of the 20 metaphases evaluated.

CMA analysis of DNA extracted from the diagnostic bone marrow specimen identified four regions of copy neutral absence of heterozygosity (AOH) with the following karyotype: arr[hg19] 6p25.2p24.3(2,518,736-10,211,449) x2 hmz, 6p23p22.1(14,337,193-27,405,743) x2 hmz, 10q22.3q23.1(78,337,899-85,795,678) x2 hmz, 16p13.3(115,072-5,794,233) x2 hmz. No significant copy number gain or loss was identified, indicating no loss or gain at the sites of the chromosomal breakpoints identified by the conventional cytogenetic analysis. All four of the regions of AOH were copy neutral. Two were present on the short arm of chromosome 6 (chr6:2518736-10211449 and chr6:14337193-27405743), one on the long arm of chromosome 10 (chr10: 78337899-



85795678) and one on the short arm of chromosome 16 (chr16: 115072-5794233).

The four regions of AOH in this patient encompassed over 400 genes, including 242 OMIM genes. Evaluation of gene function for each of these genes was conducted using GeneCards encyclopedia ([www.genecards.org](http://www.genecards.org)), and annotated by the area of interest utilizing UCSC, Ensemble, Uniprot, MGI mutation, GO/KEGG pathway, OMIM diseases, and MalaCards diseases [22]. This evaluation indicated that 6 genes, *E2F3*, *GMNN*, *CHTF18*, *TELO2*, *CCNF* and *PKMYT1* have a cell cycle function; 7 genes, *TXNDC5*, *SOX4*, *PRL*, *AXIN1*, *ZNF598*, *NRG3* and *DNAJA3* have a function related to apoptosis; 8 genes, *DEK*, *ID4*, *TRIM38*, *ZMIZ1*, *IL32*, *CREBBP*, *GLIS2* and *PGP* have been reported to be related to established leukemic entities; and 8 genes, *PKMYT1*, *IL32*, *RIPK1*, *PRPF4B*, *NRG3*, *MLST8*, *PGP* and *PDPK1* have been linked to tyrosine kinase signaling pathways. The identification of these regions of AOH and their associated gene content point to the fact that homozygous aberrations in these genes may play a critical pathogenetic role in this neoplasm. Of particular interest are those genes related to tyrosine kinase signaling pathways and the fact that this particular neoplasm is known to involve constitutive activation of the tyrosine kinase domain *PDGFRα* of by the

fusion partner. The identification of additional genes associated with tyrosine kinase signaling may ultimately provide insight into potential targeted treatment strategies.

### Literature data for *ETV6/PDGFRα* fusion

A search of Mittelman's database [23] and PubMed had identified 37 cases of leukemia with a t(4;12) or its variant (one case) (Table 1). Among these 28 patients had AML, three had ALL, 2 had RAEB, and one each had natural killer cell leukemia, polycythemia vera, chronic eosinophilic leukemia, and an undifferentiated leukemia. There were 22 males and 12 females (M/F ratio 2), and gender not reported for three cases. Median age at diagnosis was 54 years (range 3 to 82). Cytogenetically the karyotype was pseudo-diploid with the karyotype t(4;12) in 19 patients; in the remaining 18 patients the karyotype had at least one additional abnormality. All patients had combination chemotherapy (regimen varied) at diagnosis. Survival data were reported for 21 patients; 10 patients deceased (7 males, 3 females) at a median survival of 5.5 months (range <1 to 96 months); one of these was treated with imatinib after identifying *ETV6/PDGFRα* fusion, but had no response [24]. Eleven patients (7 males, 4 females) were alive at a median follow up of 19 months (range 3 to 93 months); one of these was treated with imatinib after identifying *ETV6/PDGFRα* fusion [25]. Four other patients were alive after bone marrow transplantation (BMT). Among 25 adult patients with AML, survival data were available for 16 patients; eight were alive at a median follow up of 19 months, and eight deceased (median survival 4 months); two other patients are alive after BMT. Among the eight alive six (85.7%) had pseudo-diploid karyotype and two had additional abnormalities; among the eight deceased five (62.5%) had pseudo-diploid karyotype and three had additional abnormalities; however this difference is not significant (p=0.57).

### Discussion

This is the first case of AML with a three way translocation, t(4;12;6) that created a fusion gene between *PDGFRα* and *ETV6*. The patient did not respond to treatment with imatinib or induction chemotherapy. Receptor tyrosine kinases *PDGFRα*, *PDGFRβ* and *FGFR1* have been deregulated by the formation of fusion genes, and these are implicated in the pathogenesis of myeloid and lymphoid neoplasms with clonal eosinophilia. Genetic alteration affecting *PDGFRα* most commonly presents as MPN, but also has been rarely reported in AML, and in precursor T-lymphoblastic leukemia with clonal eosinophilia. In myeloid and lymphoid neoplasms with eosinophilia one of the typical cytogenetic alterations is cryptic deletion at 4q12; this fuses *FIP1L1* with *PDGFRα* [8,26]. Other rare cytogenetic abnormalities involving *PDGFRα* reported in hematolymphoid neoplasms include t(4;22)(q12;q11), ins(9;4)(q33;q12q25), t(2;4)(p24;q12) and t(4;12)(q12;p13) [27-30]. These patients respond well to treatment with imatinib [8,31,32]. Furthermore, a few longitudinal studies have shown a close association with the

**Table 1. Clinical and cytogenetic features of patients with PDGFRA/ETV6 fusion.**

Age/Gender	Initial DX	Initial Tx	Later Dx	Karyotype	FISH	Tx	Survival (M)	Reference
77/F	AUL	NA	None	46,XX,t(4;12)(q12;p13)	ND	NA	NA	[60]
64/M	AML	FCR	AML	46,XY,t(4;12)(q12;p13), del(5)(q35)	ND	FCR, Imatinib/Gemtuzumab	No response	[24]
74/F	AML M1	NA	None	46,XX,del(10)(q11), t(4;12)(q13;p13)	ND	None	NA	[61]
33Y M	AML	Dauno+AraC	None	46,XY,t(4;12)(q11;p13)	ND	None	1M	[62]
29/M	RAEB	NA	None	46,XY,t(4;12)(q12;p13)	ND	None	LostF/U	[63]
76/F	NK-cell	Chemo	None	46,XX,t(4;12)(q12;p13)	ND	None	8+	[38]
70/M	AML M0	Chemo	None	46,XY,t(4;12)(q12;p13) 47,idem,+del(1)(p11p35)	ND	None	<1M	[38]
81/M	AML M0	Chemo	None	46,XY,t(4;12)(q12;p13)/ 46,idem,del(5)(q13q33)	ND	None	3+	[38]
54/M	AML M0	Chemo	None	46,XY,t(4;12)(q12;p13)	ND	BMT	50+	[38]
25/M	tAML	Chemo	None	46,XY,t(4;12)(q12;p13)	ND	None	12	[39]
51/M	MPD	Hydroxy carbomide	None	46,XY,t(4;12)(q2?3;p1?2)	ND	Imatinib	93+	[25]
42/F	AML-M2	NA	None	46,XX,t(4;12)(q12;p12-13)	ND	NA	13.3M	[64]
3/M	ALL-L1	NA	NA	47,XY,t(4;12)(q13;p12), del(1q),del(2q),der(3q) del(6)(q21q25),+mar	ND	NA	NA	[65]
4/M	ALL-L1	NA	NA	46,XY,t(4;12)(q13;p12), der(1)t(1;?)p36;?)	ND	NA	NA	[65]
70/F	t-AML	NA	None	46,XX,del(7)(q32q36)/47,idem,+2/ 47,idem, t(4;12)(q12;p13),+21	PDGFRα/ ETV6	NA	NA	[14]
41/M	AML M0	Chemo	None	46,XY,t(2;4;12)(p21;q12;p13)/+3 clones	+	None	3M	[41]
61/M	AML M2	Chemo	None	46,XY,t(4;12)(q11-12;p13)	ND	None	19+	[66]
43/M	AML M0	Chemo	None	46,XY,t(4;12)(q11-12;p13)	ND	None	31+	[66]
49/M	AML M2	Chemo	None	46,XY,t(4;12)(q11-12;p13)	ND	None	6+	[66]
57/M	AML-M5	Chemo	None	46,XY,t(4;12)(q12;p13)	PDGFRα/ ETV6	None	24+	[42]
NA	AML	NA	Relapse	46,XY,t(4;12)(q11;p13)	ND	None	NA	[67]
39/F	AML M1	HAM/HAM	None	45,XX,t(4;12)(q12;p13) dic(7;12)(q11;p13)	CHIC2/ ETV6	Chemo Aive	BMT	[68]
70/M	AML M0	Chemo	None	46,XY,t(4;12)(q13;p13)	ND	None	5M	[69]
18/F	AML M2	Chemo	NA	46,XX,t(4;12)(q12;p13)	ND	None	9+, BMT	[70]
67/M	MDS/RAEBt	Chemo	None	45,XY,-5,-7,+mar/42-43 idem,-11,-17,+der(?)hsr(11)(q23)/43,idem t(4;12)(q12;p13)	ND	None	6M	[71]
14/F	AML M2	Chemo	NA	46,XX,t(4;12)(q12;p13), i(17)(q10)	TEL+	NA	9+	[72]
47/F	PV	Busulfan	AML M4	46,XY,t(4;12)(q12;p13)	ND	Chemo	96M	[73]
47/M	AML M2		NA	46,XY,t(4;12)(q12;p13)	ETV6+	NA	NA	[45]
69 M	AML M0			46,XY,t(4;12)(q12;p13)/46, idem,-7,+11/46,idem, del(7)(q21)	ETV6+	NA	NA	[45]
59/M	AML M7	NA	NA	46,XY,t(4;12)(q12;p13)	NA	NA	2.5M	[74]
46/M	AML M4			46,XY,t(4;12)(q12;p13),-7,+6/46,XY,t(4;12),del(9q)	NA	NA	NA	[75]
11/F	ALL	ALL8	None	45,XX,t(4;12)(q13?;p12), der(7),der(21)	None	None	24+	[76]
Peds/F	AML M1	NA	NA	46,XX,-7,inv(3)(p25q21),del(6)q13q21),del(10)(q24), t(4;12)(q12;q13),+mar/47,XX,idem,+15	ND	NA	NA	[77]

Continuation of table 1.

Age/ Gender	Initial DX	Initial Tx	Later Dx	Karyotype	FISH	Tx	Survival (M)	Reference
82/M	AML M1	NA	None	4,XY,t(4;12)(q11;p13)	None	None	NA	[37]
67/NA	AML-M0	NA	None	47,XY,t(4;12)(q12;p13),-21, +der(21)del(q?)x2	ND	NA	NA	[19]
64/NA	AML-M0	NA	None	46,XY,t(4;12)(q12;p13)	ND	NA	NA	[19]
66/F	tAML-M1	NA	NA	46,XX,t(4;12)(q12;p13)/ 46,idem,i(17)(q10)	ND	NA	16	[78]

development of clonal eosinophilia during the course of leukemia and response to treatment with imatinib. Zota et al., [33] reported a case of CMML in which a clone with *FIP1L1/PDGFRa* fusion transiently developed with concurrent PB and BM eosinophilia and regressed with imatinib treatment, whereas the initial CMML clone persisted and led to fatality. Shah et al., [34] reported the development of *FIP1L1/PDGFRa* fusion during transformation to AML associated with eosinophilia in a patient with an initial diagnosis of CMML that harbored trisomy 8. Similar fusion was reported in five patients with AML and eosinophilia; all these patients have responded positively to imatinib [7]. Sorour et al., [35] reported an AML patient with complex karyotype who responded to chemotherapy. However, the patient developed increasing eosinophilia; at this time BM was positive for *FIP1L1/PDGFRa* fusion. Patient responded well to imatinib, had allogenic BMT, relapsed with a D842V kinase resistant mutation in *FIP1L1/PDGFRa* domain and expired 15 months post BMT. *PDGFRa* abnormalities have not been reported in CMML without eosinophilia.

*ETV6* rearrangements in myeloid disorders are reported at a frequency of 0.5%; in AML it was detected at a frequency of 1.1%, but not in non-eosinophilic CMML [14]. Among the different translocation partners of 12p13, t(4;12)(q12;p13) is a recurring abnormality in adult AML with an incidence of 0.6% [36]. A review of the current literature identified 37 cases with a t(4;12) with a male to female ratio of 2:1. These tumors have common characteristics that include dysplasia of three hematopoietic lineages, pseudolymphoid morphology, absent or low myeloperoxidase activity, preservation of the platelet count, and megakaryocytes in BM [36]. Blast cells have been reported to be positive for CD7, CD13, CD33, CD34 and HLA-DR, suggesting that the leukemic cells have an immature myeloid stem cell origin [37].

Molecular structure of the cytogenetically identified t(4;12)(q11-12;p13) is heterogeneous. Cools et al., [38] reported four cases in which the t(4;12)(q12;p13) fused *BTL (CHIC2)* at 4q12 to *ETV6* at 12p13, resulting in the expression of a hybrid *BTL/ETV6* transcript. Cools et al., [39] reported another case of AML with a t(4;12) in which *GSH2*, an another gene telomeric to *CHIC2* at 4q12, fused with *ETV6*. Silva et al., [19] identified *ETV6* translocations not resulting in a fusion protein in two cases, but identified loss of *ETV6* by deletion, and heterozygous or

homozygous mutations in the *ETV6* gene in AML. Therefore they suggested that haplo-insufficiency of *ETV6* as a leukemogenic step in these leukemias. Yoshida et al., [40] reported an MPN with eosinophilia in which *ETV6* was fused with the C-terminus of *PDGFRa*.

Clonal genetic changes in *ETV6* have different clinical outcomes in leukemia. In pediatric ALL *ETV6* is fused with *RUNX1* in a cryptic t(12;21), and these patients have good prognosis; whereas *ETV6* rearrangements in AML are considered as having intermediate prognosis [14]. The survival data on AML patients with a t(4;12) also indicate inferior outcome with combination chemotherapy and a median survival of 4 months in about 55% of patients.

To the best of our knowledge, this is the first case of a three-way translocation t(4;12;6) involving *PDGFRa* and *ETV6* genes that developed during transformation from CMML to an AML without eosinophilia. Hamaguchi et al., [41] reported a three-way translocation, t(2;4;12)(p21;q12;p13) in a 41Y male with a diagnosis of AML-M0; but the involvement of *PDGFRa* was not determined and *ETV6* was not rearranged. The patient had no response to combination chemotherapy and expired 3 months from diagnosis. Al-Kali et al., [24] reported one case of AML with t(4;12) and did not responsive to imatinib treatment. Heaton et al. [42] reported *ETV6/PDGFRa* fusion by FISH in AML-M5 with karyotype t(4;12); complete remission was achieved with Idarubicin+Ara-c (3+7) regimen.

Survival of patients with *ETV6/PDGFRa* fusion appears to be different from *FIP1L1/PDGFRa* fusion in patients. This may have been due to different molecular structure of the fusion gene. In the *PDGFRa* the WW domain has inhibitory role [43], and its disruption by fusion with other genes is the key molecular mechanism of constitutive tyrosine kinase activity in these disorders [44]. In fact the WW domain was invariably disrupted in cases of MPN with eosinophilia and *FIP1L1/PDGFRa* fusion; these patients had constitutive tyrosine kinase activity and responded well to imatinib. An alternative mechanism of activation of tyrosine kinase activation of *PDGFRa* was detected in an AML patient with t(4;12) [25]. In this patient *ETV6* was fused to the N-terminus of *PDGFRa* and it had overridden the inhibitory effect of the intact WW domain in *PDGFRa*. In these instances kinase activity is obtained through oligomerization mediated by the fusion partner [25]. Molecular structure of

the fusion between in *PDGFRα* and *ETV6* was examined in a few cases of t(4;12). Curtis et al., [22] reported an MPN with eosinophilia and t(4;12) in which *ETV6* was translocated to the 5'-of an intact WW domain of *PDGFRα*; this patient responded to imatinib. Yoshida et al., [40] reported an another case in which *ETV6* fused to the C-terminus of *PDGFRα* and the patient did not respond to imatinib. Therefore, it is possible that in the current patient the WW domain in *PDGFRα* was intact and the fusion of DNA from chromosome 6p23 region may have been on the C-terminus of *PDGFRα*. This molecular configuration does not lead to increased tyrosine kinase activity in *PDGFRα*, and therefore the patient did not respond to imatinib. Thus molecular characterization of *PDGFRα* fusion genes is important in determining whether imatinib is a suitable agent in the management of these patients.

A t(6;12)(p21;p13) have been described in seven cases of different lymphoid malignancies [23,45-50]. Among these, *ETV6* rearrangement was confirmed by FISH in three [26,45,46], but the fusion partner was not identified. In a case of RAEB-1 with ins(6;12)(p22;p13) *ETV6* was fused with *KIAA0319* at 6p22 [51]. The *ETV6* probe used in this study was a break-apart probe; red signal covered the 5'-region whereas the green signal covered the genome beginning the 3'-end of the gene. FISH signal pattern on the abnormal metaphases showed a split in the red signal with a residual red signal on the der(12) and the split signal on the der(6p). Although the DNA at 6p21 that partnered in fusion with the 5'-region of *ETV6* was not identified, it is possible that the putative gene at 6p21 was deregulated. A number of genes have been mapped to the band 6p21; these genes include *FOXp4*, *TAF8*, and *CCND3*. Among these, constitutive activation of *CCND3* in different B-cell neoplasms has been well established [52,53]. In a case of chronic lymphocytic leukemia with t(6;12)(p21;p13) the *ETV6* gene was rearranged with a break in between exon 1 and exon 2, but the break at 6p21 was not molecularly defined [46]. In the current patient the three-way translocation may have led to three somatic oncogenic changes affecting *PDGFRα*, *ETV6* and possibly *CCND3*, or another gene at the breakpoint at 6p21.

Loss of genetic material acting as a leukemogenic event was excluded in this patient by CMA. No significant copy number loss or gain of chromosomal regions was identified. However, we observed four copy neutral regions of AOH with gene content. Copy neutral AOH may originate through segmental uniparental disomy which in turn leads to homozygosity for functionally relevant gene mutations in the tumor genome; this constitutes an important driving force in cancer [54]. Copy neutral AOH has been seen in about 20% AMLs [55-57] and these included 6p, 6q and on 16q [58,59]. Although additional specific genes critical to the tumorigenesis of this neoplasm have not been established, it is possible that homozygosity for one or more genes in these regions impacted the biological behavior of the leukemia cells.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

Authors' contributions	PK	NG	PP	JW	KW	SM
Research concept and design	✓	--	--	--	--	--
Collection and/or assembly of data	--	--	✓	✓	✓	✓
Data analysis and interpretation	--	✓	--	✓	✓	✓
Writing the article	✓	--	--	--	✓	✓
Critical revision of the article	✓	--	✓		✓	✓
Final approval of article	✓	✓	✓	✓	✓	✓
Statistical analysis	--	--	--	--	--	--

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