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Case Report

# Chronic myelomonocytic leukemia with *ETV6-ABL1* rearrangement and *SMC1A* mutation

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ABSTRACT

Chronic myelomonocytic leukemia (CMML) is a rare malignant neoplasm of the blood-forming cells in bone marrow characterized by persistent monocytosis. Although most patients with CMML show clonal genetic aberrations, there is no known cytogenetic or molecular genetic finding that is specific to CMML. We report a patient who had a clinical and morphological presentation consistent with CMML. The genetic work-up showed an *ETV6-ABL1* fusion consequent to a 9;12 translocation, and a missense mutation in *SMC1A* (c.1757G>A, p.Arg586Gln). The *SMC1A* mutations are recurrent, albeit rare, in myeloid malignancies, without an established clinical significance in CMML. *ETV6-ABL1* fusion is a rare but recurrent genetic aberration found in various hematologic malignancies involving both the lymphoid and myeloid lineage, but to the best of our knowledge, CMML is an exceptionally rare presentation of *ETV6-ABL1* rearranged neoplasm. *ETV6-ABL1* fusion is often formed through complex rearrangements, and usually cryptic by routine G-banded chromosome analysis. The diseases associated with this rearrangement generally have an aggressive course, hence detecting or excluding this rearrangement during diagnostic work-up is critical for treatment planning.



## Introduction

Chronic myelomonocytic leukemia (CMML) is a rare malignant disorder of the blood-forming cells in bone marrow. The main characteristic of CMML is persistent monocytosis, but the disease shows features of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasm (MPN) [1]. Most patients with CMML show clonal genetic aberrations, however, there is no known cytogenetic or molecular genetic finding that is specific to CMML.

*ETV6-ABL1* fusion is a rare but recurrent genetic aberration found in various hematologic malignancies involving both the lymphoid and myeloid lineage [2–7]. The clinical presentation of the neoplasms with *ETV6-ABL1* fusion resembles *BCR-ABL1*-positive neoplasms. It has been reported in a variety of hematological disorders including acute lymphocytic leukemia (ALL), acute myeloblastic leukemia (AML), atypical chronic myeloid leukemia (aCML), and other myeloproliferative neoplasms [8,9]. The prognosis is generally unfavorable with conventional treatment protocols. Less than 40 patients have been reported since the first description of this fusion by Papadopoulos and colleagues in 1995 [10]. However, the frequency of *ETV6-ABL1* rearrangement in hematologic neoplasms is likely underestimated, as the fusion gene is usually derived from complex, often cryptic, chromosomal rearrangements [11,12].

Mutations in cohesion complex genes have been reported in various myeloid neoplasms, however, the prognostic significance of the cohesion complex mutations has not been elucidated [13–15]. The cohesin complex is a heterotetramer of SMC1A, SMC3, RAD21, and STAG1/STAG2 proteins. Cohesin complex mutations typically coexist with other genetic aberrations, and they mostly are observed in subclones but rarely in founding clones [14]. Among the genes encoding cohesion complex proteins, mutations in *STAG2, RAD21* and *SMC3* have been reported in 2–6% of patients with myeloid neoplasms, and mutations in *SMC1A* and *STAG1* have been reported <1% [15].

We report a patient who had an *ETV6-ABL1* fusion due to a 9;12 translocation and a pathogenic *SMC1A* variant. The clinical presentation and morphological assessment of the bone marrow indicates

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a diagnosis of CMML, which to the best of our knowledge, is a rare presentation of both an *ETV6-ABL1* rearranged and a *SMC1A* mutated hematological neoplasm.

## Materials and methods

### *Clinical presentation*

A 55-year-old male presented to the emergency department with complaints of progressive fatigue and weakness. In the 2 months preceding his admission to the emergency department he had suffered cold and flu-like symptoms, sore throat, intermittent abdominal pain radiating towards his back, decreased appetite, increased thirst, occasional sweating, and blurry vision. Physical examination in the emergency department was notable for enlarged lymph nodes and an abdominal mass. CT scan of the abdomen and pelvis showed marked splenomegaly (21.4 cm) with possible infarcts and extensive lymphadenopathy. CBC data revealed a marked leukocytosis ($95.9 \times 10\text{^}3/\mu L$) including neutrophilia, monocytosis, eosinophilia and 15% blasts suspicious for an advanced myeloid neoplasm. The patient was admitted for further evaluation.

The patient's past medical history was unremarkable. The family history was inconspicuous for a neoplastic disorder. Personal history included history of smoking (1 pack per day) and occupational exposure to gases from organic matter produced in a steel factory.

The physical examination showed lymphadenopathies involving the anterior/posterior cervical chains, left supraclavicular area, and left axilla. Abdominal exam showed an enlarged spleen which extended down to just above the pelvic bone, almost to the midline of the abdomen.

The EKG and chest X-ray were normal. The echocardiogram showed evidence of a left ventricular apical mass, which had characteristics of a tumor given vascularity and MRI characteristics, and was suspicious for sarcoma, specifically angiosarcoma. There was no evidence of tissue invasion. In addition, there was a low-attenuation area within the left ventricle, suggestive of a thrombus.

CBC data at presentation were notable for marked leukocytosis (WBC $95.9 \times 10\text{^}3/\mu L$), normochromic normocytic anemia (RBC $2.38 \times 10\text{^}6/\mu L$, HGB 7.8 g/dL, HCT 23.3%, MCV 97.9 fL, MCH 32.8 pg, MCHC 33.5 g/dL, RDW 17.6%), and thrombocytopenia (PLT $68 \times 10\text{^}3/\mu L$). The leukocytosis included prominent neutrophilia with a broad left shift (promyelocyte 1%, myelocyte 16%, metamyelocyte 10%, band 15%, segmented neutrophil 15%), eosinophilia (7%), monocytosis (20.1%), and increased blasts and promonocytes (11%).

The patient was admitted and started on hydroxyurea. The day of the bone marrow biopsy he had received 2 doses of hydroxyurea. At that time the bone marrow was markedly hypercellular (nearly 100%) with monocytosis (33%) with increased blasts/promonocytes (blast equivalents) (11%), eosinophilia (12%), mild dysgranulopoiesis and dysmegakaryopoiesis and mild reticulin fibrosis (MF-1), morphology consistent with an advanced myeloid neoplasm with monocytosis (Fig. 1A–C).

Flow cytometry demonstrated a relative monocytosis (40% of the leukocytes) with a spectrum of maturation. The monocytes expressed CD4, CD11b, partial CD13, CD14 partial, CD33, CD38, HLA-Dr partial, and dim aberrant CD56 (16%). The monocytes included a subset (14% of the monocytes; 5.4% of the leukocytes) with immature immunophenotype (lack of CD14) compatible with promonocytes and monoblasts (Fig. 1D). In addition, a separate population of cells (0.01% of the leukocytes, 24 events) with an aberrant precursor B-cell immunophenotype (bright CD10, CD19, dim CD22, CD34, dim CD38, dim CD45, and moderate CD58) was identified. The significance of this finding is considered uncertain. Myeloid blasts were not increased.

### *Methods*

Chromosome analysis was performed on metaphase preparations from bone marrow using standard procedures. The International System for Human Cytogenetic Nomenclature (ISCN 2016) [16] was used for the karyotypic description.

FISH studies using FIP1L1/CHIC2/PDGFRA, PDFRB, D8Z2/FGFR1, CBFB, ASS1/ABL1/ BCR probe sets (Abbott Laboratories, Abbott Park, IL) and ETV6 break-apart probe (MetaSystems Group, Inc., Newton, MA) were performed on interphase nuclei, and on metaphases with the ASS1/ABL1/ BCR and ETV6 probes. Two hundred interphase cells were scored for each probe combination.

Genomic SNP microarray analysis (GMA) was performed using the CytoScan HD platform (Thermo Fisher Scientific, Waltham, MA) on DNA extracted from bone marrow, and data analysis was performed with Chromosome Analysis Suite (ChAS) v.3.1 software (Thermo Fisher Scientific). Genomic linear positions were reported per NCBI build 37 (hg19).

Massively parallel sequencing analysis was performed on genomic DNA, which was fragmented to approximately 300 bp on a Covaris LE220 instrument (Covaris, Inc., Woburn, MA) and ligated to xGen Dual Index adapters (Integrated DNA Technologies, Inc. (IDT), Coralville, IA) using the Kapa Hyper Prep Kit (Roche, Indianapolis, IN). Fragments corresponding to approximately 700 genes previously found mutated in cancers were captured with a custom pool of xGen Lockdown probes and the xGen Hybridization and Wash Kit (IDT). The final library was sequenced on a HighSeq4000 instrument using a $2 \times 150$ paired end sequencing kit (Illumina, Inc., San Diego, CA). Data was analyzed with a custom pipeline utilizing BWA-MEM for sequence alignment and multiple variant callers were used to identify a variety of variant types with high sensitivity: Lofreq for single nucleotide variations (SNVs), Scalpel for indels 2–60 bp, and Manta for indels $>50$ bp and Pindel for FLT3-ITDs. Analysis was limited to genes known to be associated with myeloid neoplasms (the list of genes analyzed can be found at http://ltd.aruplab.com/Tests/Pub/2011117).

Clinically significant variants were selected through our standard operating procedures. First, variants with an allele frequency less than 0.1%, and those with a population frequency greater than 3% (per 1000 Genomes [17] or the Genome Aggregation Database (gnomAD) [18] were removed. Then, reportable variants were subjected to a rigorous curation process, including review of prior myeloid malignancy cases at ARUP, the Catalogue of Somatic Mutations in Cancer (COSMIC) [19], Human Gene Mutation Database (HGMD) [20], and the medical literature.

## Results

Chromosome analysis performed on bone marrow showed added material of unknown origin in the long arm of chromosome 9 (Fig. 2A) in 20 cells analyzed and the karyotype was reported as 46,XY,add(9)(q34)[20]. Interphase FISH analysis with ASS1/ABL1/ BCR tri-color dual fusion probe set (Abbott Laboratories, Abbott Park, IL) showed an additional ABL1 signal, concerning for an *ABL1* rearrangement with a partner other than *BCR* (ISCN: nuc ish(ASS1 $\times$ 1,ABL1 $\times$ 3,BCRx2)[188/200]). In order to better characterize this abnormality, sequential metaphase FISH analysis was performed with the same probe set. This analysis showed two red/aqua signals on the normal and derivative chromosome 9, and an extra ABL1 signal (red) localized to the short arm of chromosome 12, suggestive of an *ETV6-ABL1* rearrangement (Fig. 2B).

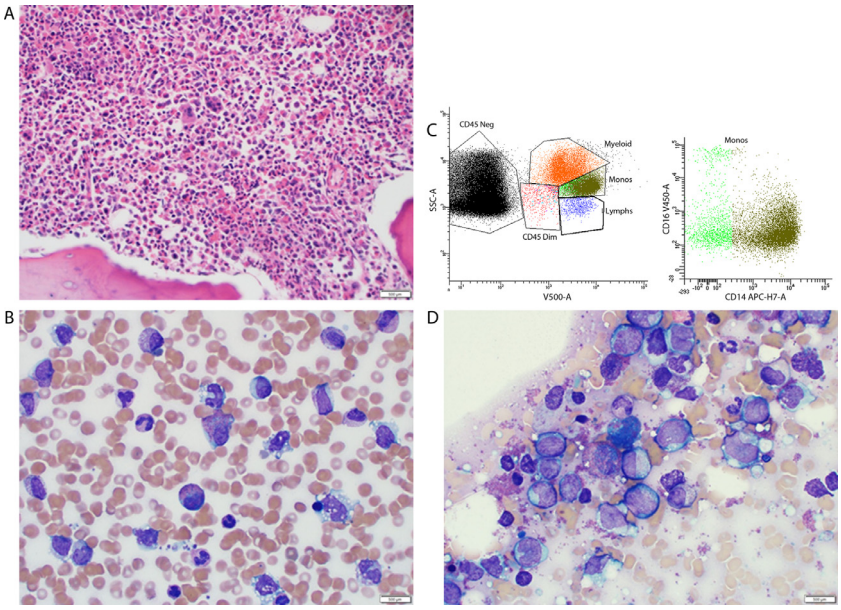


**Fig. 1. (A)** Peripheral blood smear (500X). Leukocytosis including neutrophilia with broad left shift, monocytosis, eosinophilia, and increased blasts/promonocytes. The eosinophils have a spectrum of maturation with mild atypia (hypogranulation, Harlequin cells). **(B)** CD45/side scatter images demonstrate a monocytosis (40% of the leukocytes). A subset of the monocytes (14%) lack expression of CD14, compatible with promonocytes and monoblasts. **(C)** Bone marrow touch imprint (500X). Monocytosis with increased blasts/promonocytes (11%), mild dysgranulopoiesis, and eosinophilia. **(D)** Bone marrow core biopsy (200X). Markedly hypercellular bone marrow with relative myeloid hyperplasia, eosinophilia, dysmegakaryopoiesis, and mild reticulin fibrosis (MF-1 on reticulin stain, not shown).

Subsequent microarray analysis did not show any copy number changes involving the *ABL1* or *ETV6* loci, ruling out the possibility of a complex rearrangement such as nontandem duplication of *ABL1* followed by an insertion. Furthermore, sequential metaphase FISH analysis with the ETV6 break-apart probe confirmed rearrangement of these loci (Fig. 2C). Thus, the karyotype could be updated to t(9;12)(q34;p13) based on the FISH and microarray results.

Additional FISH analysis showed no evidence for rearrangements involving 4q12 (FIP1L1/CHIC2/PDGFRA), 5q33.1 (PDFRB), 8p12 (FGFR1) or 16q22 (CBFB). A small subset of cells also showed evidence for 4 copies of the *FGFR1* locus at 8p12, accompanied by 4 copies of the D8Z2 probe at the centromere of chromosome 8, in 31/200 (15.5%) cells, indicating tetrasomy 8. This finding could not be confirmed by chromosome analysis, however the genomic microarray analysis showed evidence of tetrasomy 8 as well as trisomies of chromosome 6 and chromosome 11 in approximately 5% of the specimen. The clinical significance of this low percentage clone remains uncertain.

To rule out possible driver mutations associated with myeloid neoplasms, a massively parallel sequencing based myeloid panel was performed, and a rare *SMC1A* variant (NM_006306.3: c.1757G>A, p.Arg586Gln) was detected at an allele frequency of 42% with a coverage of about 750 (Fig. 2D).

In the context of the chromosome analysis and molecular genetic results, which excluded recurrent genetic abnormalities associated with myeloid neoplasms with eosinophilia, the bone marrow findings were classified as chronic myelomonocytic leukemia, type 2 (CMML-2), proliferative type under 2016 WHO Classification [21].

The induction therapy was initiated with Dacogen+LD-AraC (Dacogen 20 mg/m$^2$ Days 1–5 and CI Ara-C 100 mg/m$^2$ Days 6–10), with a plan to perform haploidentical PB-SCT was planned and treatment was initiated with Fludarabine (30 mg/m$^2$ IV x5 day D-6 through Day −2), Cyclophosphamide (14.5 mg/kg IV x2 days Day −6 and Day −5), and TBI (400cGy Day −1). GVHD prophylaxis was with post-transplant Cyclophosphamide at 50 mg/kg on Day +3 and Day +4, Cyclosporine and mycophenolate mofetil.

Chromosome analysis 3 months after the SCT, showed donor cells in the 20 cells analyzed, and STR analysis showed 98% donor cells. Twenty-four months after the initial diagnosis the patient is in remission.

## Discussion

The *ETV6-ABL1* rearrangement is a rare but recurrent genetic aberration found in a variety of hematological neoplasms [22]. However, this rearrangement may have been underreported. Previous reports have demonstrated that the *ETV6-ABL1* gene fusion is often the result of complex chromosome rearrangements, involving additional chromosomes other than 9 and 12 [23]. When only chromosomes 9 and 12 are involved the *ETV6-ABL1* fusion gene has been shown to reside at either 9q34 or 12p13 [11]. Furthermore, due to the genes being in an opposite transcriptional orientation relative to the centromere on their native chromosomes, at least three breakage and rejoining events are required to form an in-frame fusion transcript (*ABL1* 3′ to *ETV6*) [24]. Hence, the diagnosis is often incidental due to the complex, and often cryptic, nature of the rearrangements that can create the fusion.

The pathogenetic mechanism leading to the neoplastic transformation is not clearly understood. The *ETV6* gene located at 12p13.1 is a member of the E26 transformation-specific (ETS) family of transcription factors and plays a crucial role in embryonic development and hematopoietic regulation [25]. Fusions involving *ETV6* with a wide variety of genes in various hematological malignancies have been described [25]. The *ETV6-ABL1* fusion protein has a structure similar to *BCR-ABL1*, and the fusion results in constitutive activation of the tyrosine kinase domains [26,27]. Both fusion proteins initiate similar downstream events, and have analogous effects on cellular proliferation, cell survival, and transforming capacity [28,29].

The most common morphological feature associated with *ETV6-ABL1* rearrangement is eosinophilia (Table 1). In most of the reported cases, eosinophilia was either present at diagnosis, or developed shortly after [30]. Monocytosis has not been previously associated with this fusion product (Table 1). However, *ETV6* rearrange-

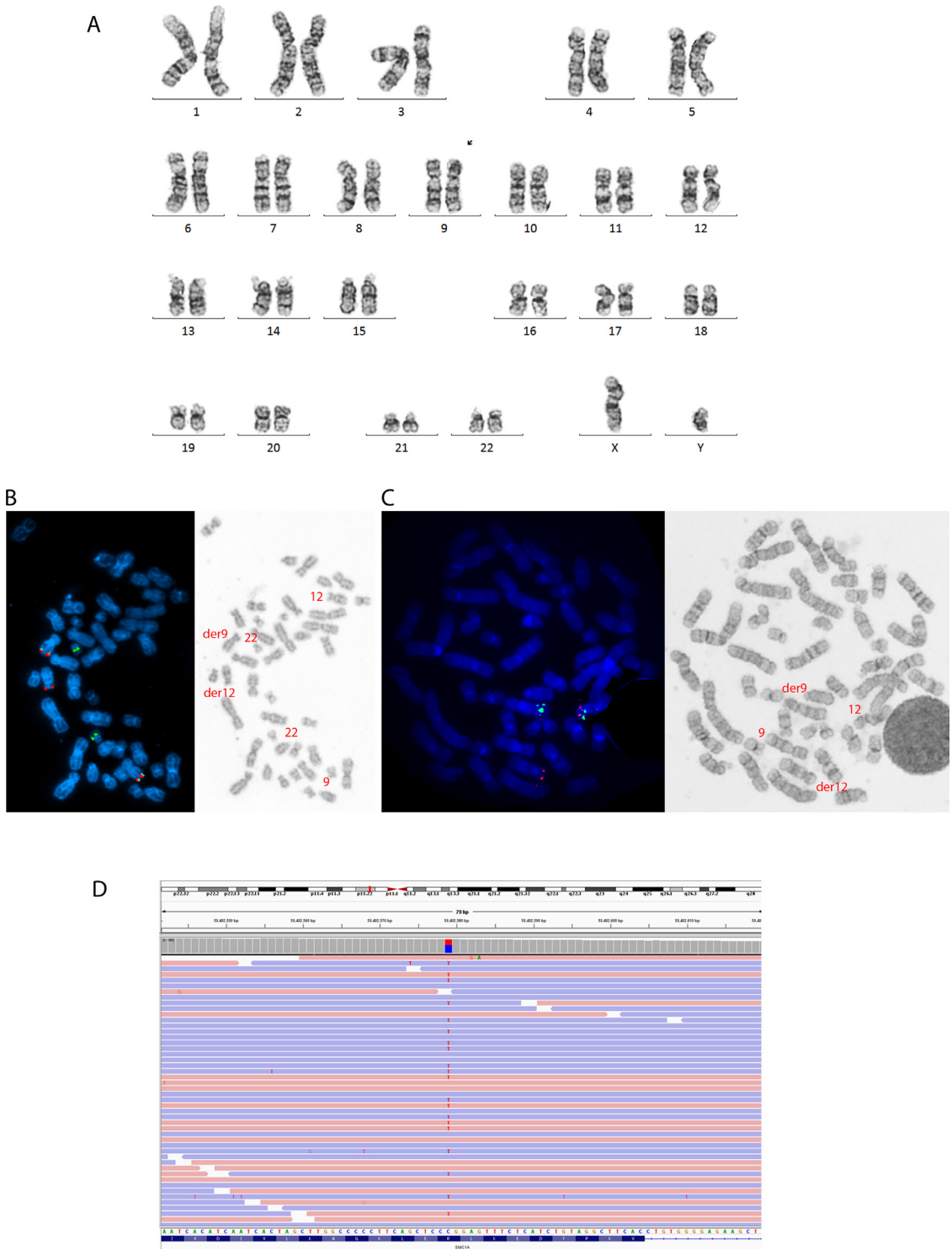


**Fig. 2.** **(A)** Karyotype showing a male chromosome complement with added material on the long arm of chromosome 9, designated as 46,XY,add(9)(q34). Both chromosome 12 homologues appear normal at this resolution. **(B)** Sequential metaphase FISH analysis performed with the ASS1/ABL1/BCR probe set showing the ABL1 signal (red) on the short arm of chromosome 12, designated as ish der(12)t(9;12)(q34.1;p13)(ABL1+). **(C)** Sequential metaphase FISH analysis performed with the ETV6 break-apart probe showing the 3′ETV6 signal (red) on the short arm of chromosome 12, and the 5′ETV6 signal on the long arm of chromosome 9, further supporting ETV6-ABL1 rearrangement (ish t(9;12)(q34.1;p13)(5′ETV6+;5′ETV6-). **(D)** Massively Parallel Sequencing showing a missense variant (C to T) in *SMC1A*. The pink and blue bars show positive (5′ to 3′) strand and the negative (reverse-complement) strand reads, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 1**
Summary of clinical and cytogenetic findings in patients with myeloid neoplasms who have been shown to have *ETV6-ABL1* fusion. Reported karyotypes show the heterogeneity and cryptic nature of this rearrangement. Eosinophilia is a common finding, however monocytosis has not been reported before.

| Patient | Age | Sex | Diagnosis | Eosinophilia | Monocytosis | Karyotype | BMT | Follow-up | Reference |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 55 | M | CMML-2 | Y | Y | 46,XY,add(9)(q34) | Y | remission (>12 m) | Current patient |
| 2 | 24 | F | CML | Y | N | 46,XX | N | remission (>7 m) | Kawamata et al., 2008 |
| 3 | 32 | M | CML | Y | N | 46,XY,t(12;14)(p12;q11-13) | Y | remission (>36 m) | Andreasson et al., 1997 |
| 4 | 59 | M | CML | Y | N | 46,XY,del(6)(p21),?t(9;12)(q34;p12) | N | ex | Van Limbergen et al., 2001 (patient 1) |
| 5 | 44 | F | CML | Y | N | 46,XX,t(9;12)(q34;p13) | N | na | Keung et al., 2002 |
| 6 | 72 | M | CML, B-LLT | na | na | 46,XY,t(12;17)(p11.2;p11.2) | N | na | Tirado et al. 2005 |
| 7 | 36 | M | CML, MBC | Y | N | 45,XY,−7,t(9;12)(q34;p13) | N | ex | Barbouti et al., 2003 |
| 8 | 46 | F | CML | Y | N | 46,XX,t(9;12)(q34;p13) | N | remission (>22 m) | Gancheva et al., 2013 |
| 9 | 65 | F | MPN | Y | N | 46,XX,t(5;9)(q13;q34) | N | ex | Meyer-Monard et al., 2005 |
| 10 | 61 | F | MPN | Y | N | 46,XX,ins(9;12)(q34;p13p13) | N | remission (>28 m) | Nand et al., 2009 |
| 11 | 73 | M | MDS→AML | Y | N | 46,XY,der(3)ins(3;12)(p25;p13p13) t(3;9)(p25;q34),t(5;18)(q13;p11.2), der(9)t(3;9),der(12)ins(3;12) (p25;p13p13)add(12)(p13) | N | na | Tirado et al. 2016 |
| 12 | 29 | M | AML-M2 | Y | N | 46,XY,t(8;12)(p21;p13) | Y | remission (>20 m) | La Starza et al., 2002 (patient 1) |
| 13 | 48 | M | AML-M1 | Y | N | 46,XY,t(9;12)(q34;p13) | N | ex | La Starza et al., 2002 (patient 2) |
| 14 | 38 | M | AML-M6/ CML, MBC | na | na | 49,XY,add(9)(q34),+11,+12,+19, der(22)t(1;22)(q21;q11) | N | ex | O'Brien et al., 2002 |

MBC: Myeloid Blast Crisis, B-LLT: B-lymphoblastic leukemia transformation, na: not available.

ments with other partner genes, such as *PDGFRB* at 5q32 [31] and *PER1* at 17p13.1 [32], are known to present with monocytosis. It is uncertain at this time, how the cellular microenvironment and other genetic factors interact to result in monocytosis. Reports of other patients with well-described morphological and clinical features, and additional studies are needed to further characterize this association.

SMC1A is one of the 4 subunits of the cohesin complex, others including SMC3, RAD21 and STAG2 [33,34]. The cohesin complex is a critical part of the cohesion of sister chromatids following DNA replication [34]. In addition, due to its interaction with BRCA1 and ATM, SMC1A is expected to have a role in DNA repair [34]. SMC1A/SMC3 are rod-shaped proteins that form heterodimers through interaction of a U-shaped hinge domain. The resulting heterodimer is a torus-shaped structure with conserved lysine and arginine residues at the interface. Neutralizing the torus positive charge does not significantly alter dimerization, rather it's been shown in *S. cerevisiae* to interfere with SMC3 acetylation, a step required during the S phase in DNA replication [34]. The p.Arg586Gln is predicted to be deleterious to protein structure and function per PolyPhen [35] and SIFT [36]. This amino acid is within the flexible hinge domain on the opposite side the dimerization interface [37]. However, how it may interfere with cohesion function is unknown. In addition to a role in DNA interaction, SMC1A plays a role in cell cycle regulation via interaction with and phosphorylation by ataxia-telangiectasia and RAD3-related (ATR). Interruption of the ATR/SMC1 axis has been proposed to lead to cell cycle checkpoint bypass in actively replicating cells and ultimately to neoplastic transformation, which may explain the role of *SMC1A* mutations in various neoplasms [14,38].

In addition to neoplastic disorders [13,15,39], mutations in *SMC1A* have been reported to cause Cornelia De Lange Syndrome (CdLS) [38] (OMIM 300590) and Wiedemann-Steiner Syndrome [40]. CdLS is characterized by dysmorphic features, intellectual disabilities, and growth delay [41]. Mutations in genes encoding SMC family proteins make-up a small portion of CdLS cases, while majority of mutations affect the *NIPBL* gene [41]. The lifespan has been reported to be slightly shorter, however predisposition to neoplastic disorders has not been reported to be part of the phenotypic spectrum [42]. The *SMC1A* mutation identified in this study also has been reported in a patient with CdLS [41], however, it was not reported if this patient had, or was at an increased risk of developing, a neoplasm. Due to the absence of clinical features suggestive of CdLS, as well as the allele frequency observed in this X-linked gene, this mutation is considered to have a somatic origin in our patient. However, this is unlikely a driver mutation in the neoplastic cells. The mutations reported in cohesion genes are typically mutually exclusive in myeloid malignancies [13,14]. Regardless, evidence continues to accumulate linking disruption of the cohesin complex or the cohesion pathway to many forms of cancer [43]. The clinical significance of these mutations have yet to be established. Cohesin mutations have been associated with poor overall survival in MDS patients, but do not correlate with overall survival, relapse-free survival, or complete remission rates in AML patients [14].

The diagnosis of CMML generally confers a poor prognosis and allogeneic stem cell transplantation is considered as the only curative option [2]. The *ETV6-ABL1* is also often associated with a poor outcome [44]. Since this fusion product is suggested to increase tyrosine kinase activity, similar to that of *BCR-ABL1* fusion, tyrosine kinase inhibitors (TKIs) have been considered in treatment [26,45]. In newly diagnosed CML, TKIs are the FDA approved first line of therapy where patients who respond have survival figures similar to that of the general population [46]. Transient clinical response to TKIs is reported in an acute leukemia patient with *ETV6-ABL1* fusion [8]. Similarly Barbouti and colleagues reported a patient with CML treated with TKIs showing initial response to treatment, however, at day 126 after starting imatinib mesylate relapsed into a second blast crisis and died shortly thereafter [47]. Therefore, an effective treatment strategy has yet to be developed.

In conclusion, we present a patient diagnosed with CMML, and extend the spectrum of hematological neoplasms associated with

*ETV6-ABL1* rearrangements to include monocytosis. Since this rearrangement can be cryptic, we recommend actively screening for *ETV6-ABL1* in diagnostic algorithms in the management of myeloproliferative neoplasms. Reports of additional patients with well-described clinical and morphological features, treatment choices and outcome data will allow for a better understanding of the pathogenesis and may result in developing targeted treatment strategies.

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## Conflict of interest

The authors declare no conflict of interest.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.07.004.

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