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Acute myeloid leukemia with a novel *AKAP9::PDGFRA* fusion transformed from essential thrombocythemia: A case report and mini review

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ABSTRACT

Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy associated with various combinations of gene mutations, epigenetic abnormalities, and chromosome rearrangement-related gene fusions. Despite the significant degree of heterogeneity in its pathogenesis, many gene fusions and point mutations are recurrent in AML and have been employed in risk stratification over the last several decades. Gene fusions have long been recognized for understanding tumorigenesis and their proven roles in clinical diagnosis and targeted therapies. Advances in DNA sequencing technologies and computational biology have contributed significantly to the detection of known fusion genes as well as for the discovery of novel ones. Several recurring gene fusions in AML have been linked to prognosis, treatment response, and disease progression. In this report, we present a case with a long history of essential thrombocythemia and hallmark *CALR* mutation transforming to AML characterized by a previously unreported *AKAP9::PDGFRA* fusion gene. We propose mechanisms by which this fusion may contribute to the pathogenesis of AML and its potential as a molecular target for tyrosine kinase inhibitors.

1. Introduction

AML is the most common type of acute leukemia in adults and accounts for the most deaths annually from leukemia. Approximately 50% of patients with AML die from their disease [1], indicating an urgent need for novel treatment options for this disease.

AML results from oncogenic transformation and blocked differentiation of cells in the myeloid lineage. These undifferentiated cells proliferate in the bone marrow (BM), peripheral blood (PB), and other tissues, and blasts accumulating in the BM are responsible for the clinical manifestation of the disease [2]. At the molecular level, AML is a heterogeneous hematological malignancy characterized by a broad spectrum of genomic changes involved in the impaired regulation of hematopoietic stem cell differentiation and self-renewal processes [1]. The genomic alterations include gene mutations, epigenetic changes, and chromosome rearrangement-related gene fusions [1-3]. Many of these gene fusions and point mutations are recurrent and have been employed in risk stratification over the last three decades [2]. The existence of certain balanced reciprocal chromosomal rearrangements such as t(15;17), t(8;21), and inv(16)/t(16;16), or a complex karyotype (with $\geq$3 chromosome alterations) reflects genetic alterations that are known to be pathogenic in AML [2,4]. In addition to chromosomal rearrangements, several recurring somatically acquired mutations have also been identified in AML patients. These somatic mutations can be grouped into early acquired mutations, such as those affecting the DNA methyltransferase 3A gene (*DNMT3A*) and late acquired mutations such as those involving the FMS-like tyrosine kinase 3 (*FLT3*) and nucleophosmin 1 (*NPM1*) genes [5]. Mutations of other genes, such as *JAK2* and *CALR*, are considered driver events in myeloproliferative neoplasms (MPN), which include diseases such as polycythemia vera essential thrombocythemia (ET) [6]. The application of various technologies such as karyotyping, chromosomal microarray analysis (CMA), and next-generation sequencing (NGS) has revealed novel genomic changes, establishing diagnostic algorithms, classification, and risk stratification systems, and detection of minimal residual disease [2].

Fusion genes are well recognized for their role in tumorigenesis and

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their proven efficacy in clinical diagnosis and targeted therapy. Advances in sequencing technologies and computational biology have contributed significantly to the identification of fusion genes and the discovery of novel fusions, and the specificity of fusion genes to distinct neoplastic tissues has provided significant clinical benefit [7]. The WHO now designates groups of AML patients based on defining genetic abnormalities that include the following fusions such as *RUNX1::RUNX1T1, CBFB::MYH11, PML::RARA*, among others [6]. Multiple other recurrent fusion genes that have also been identified in AML patients, many of which have been associated with prognosis and response to therapy [3,7-19]. Here, we present a case with a long history of essential thrombocythemia (ET) with a *CALR* mutation, which transformed to AML characterized by a novel *AKAP9::PDGFRA* fusion gene.

2. Case report

The patient, an elderly female with a 10-year history of elevated platelet count, underwent a BM biopsy when her platelet count steadily increased in the absence of symptoms. The biopsy revealed findings consistent with ET, with normal cytogenetics and without mutation of *JAK2. CALR* mutation testing and NGS were not performed at that time. Approximately 2 ½ years later, a second BM biopsy was performed when the patient began having worsening symptoms, including increasing leukocytosis and profound thrombocytopenia in the setting of anemia.. The biopsy revealed a hypercellular marrow with 5-9% blasts, while still retaining a normal karyotype but showing a pathogenic exon 9 mutation in the *CALR* gene, p.L367fs*46; c.1099_1150del at 11% allele frequency (Table 1). She was started on 5-azacitidine; however, five months later, a BM biopsy was notable for 37% blasts positive for CD33, CD34, CD117, and HLA-DR, consistent with a diagnosis of AML, and the karyotype at that time showed a novel translocation, t(4;7)(q12;q21.2), in 17 of 20 metaphase spreads examined. She was referred to our center for urgent management and was started on induction chemotherapy with CPX-351 (cytarabine and daunorubicin). A day-14 marrow showed response to therapy, with a hypercellular marrow (80%) that displayed panmyelosis (trilineage hyperplasia), granulocytic hyperplasia, and megakaryocytic atypia without an increase in blasts, consistent with residual/persistent myeloid disease. The fact that the marrow was hypercellular after CPX-351 treatment may indicate that the chemotherapy redirected the affected clone back into a chronic MPN state. A PB specimen revealed normocytic normochromatic anemia, leukocytosis, and thrombocytosis. Chromosome microarray analysis (CMA) and NGS of DNA from a BM sample revealed no detectable genomic imbalances, the *CALR* deletion at 3.2% allele frequency, and no other pathogenic variants (Table 1). No cancer-associated fusion transcript was detected by targeted RNA NGS of the BM, although expression levels from the t(4;7) in the blast subpopulation may have been lower than the limit of detection.

The patient attained a complete remission based on International Working Group criteria. She was offered an allogenic stem cell transplant, but she refused and elected consolidative management with further CPX-351. Eight months later, the patient developed a relapse of her AML. Flow cytometry of PB demonstrated a left-shifted maturation pattern with 5% CD34/CD117-positive myeloblasts. Furthermore, the myeloid population displayed signs of dysgranulopoiesis, including reduced side scatter, indicative of hypogranulation, and aberrant CD56 coexpression in a myelomonocytic subpopulation. Karyotypic analysis detected the same reciprocal translocation, t(4;7)(q12;q21.2), identified earlier in all 15 metaphases examined (Fig. 1A). CMA was abnormal with copy neutral loss of heterozygosity (cnLOH) of 21q11.1qter and loss of a small segment in band 2p13.1 in virtually 100% of the DNA from a PB sample (Fig. 1B). Blood RNA NGS analysis detected *AKAP9::PDGFRA* fusion transcripts (Fig. 2) consistent with the translocation. Additional mutations detected at AML relapse are presented in the lower portion of Table 1; these included a *RUNX1* p.Arg162Lys mutation that was homozygous due to cnLOH of 21q, which encompasses the *RUNX1* locus at 21q22.12. Heterozygous pathogenic mutations included *WT1* p.Arg462Leu, *DNMT3A* p.Arg882His, and *MYC* p.Thr73Ala. The patient's condition deteriorated, with symptoms including acute dyspnea with increased night sweats. At this time, she was again offered salvage treatment but declined, and she was started on supportive measures, dying shortly thereafter. A signed consent form was obtained from the patient at the time of registration, which would allow the patient's data to be presented as a case report.

Table 1
Summary of the features of the DNA variant detected at various times during the patient's disease course.

Disease status	Gene	Protein change	cDNA change	Allele frequency	Reference transcript	Clinical interpretation[4]
ET (initial)		none detected				
ET (progressed)	*CALR*[1]	p.Leu367fs*46	c.1099_1150del		ENST00000316448	Tier 2
AML in remission[2]	*CALR*	p.Leu367fs*46	c.1099_1150del	3.2%	ENST00000316448	Tier 2
	FANCA	p.Ala118Val	c.353C>T	47.8%	ENST00000389301	VUS
	DDR2	p.Ile98Met	c.1464A>G	48.1%	ENST00000367921	VUS
	CD79A	p.Ala156Val	c.467C>T	45.3%	ENSP00000221972	VUS
AML in relapse	*FANCA*	p.Ala118Val	c.353C>T	52.2%	ENST00000389301	VUS
	DDR2	p.Ile98Met	c.1464A>G	49.5%	ENST00000367921	VUS
	CD79A	p.Ala156Val	c.467C>T	46.3%	ENSP00000221972	VUS
	RUNX1[3]	p.Arg162Lys	c.485G>A	96.4%	ENST00000300305	Tier 1
	WT1[3]	p.Arg462Leu	c.1385G>T	42.9%	ENST00000332351	Tier 1
	DNMT3A[3]	p.Arg882His	c.2645G>A	45.9%	ENST00000321117	Tier 2
	MYC[3]	p.Thr73Ala	c.217A>G	46.7%	ENST00000377970	Tier 2
	FLT4	splice acceptor	c.2021-2A>C	13.9%	ENST00000393347	VUS
	FLT3	p.Leu939_Thr940 insArgThrLeu	c.2817_2818ins	46.7%	ENST00000241453	VUS
	EZH2	p.Asp293Gly	c.878A>G	48.8%	ENST00000320356	VUS
	IKZF1	p.Tyr503Asp	c.1507T>G	49.7%	ENST00000331340	VUS

[1] The *CALR* deletion of 52 nucleotides was identified by single gene PCR and Sanger sequencing when the patient was tested for her ET at a primary care facility. Subsequent sequencing, when the patient had developed AML, was performed at tertiary care centers that performed NGS using targeted cancer gene panels.

[2] Twenty-six additional DNA variants present in both remission and relapse states are synonymous codons, general population SNPs, or classified in ClinVar as Benign or Likely Benign.

[3] The *RUNX1, WT1*, and *DNMT3A* mutations have clinical relevance in AML, and the *MYC* mutation has been seen in lymphomas, https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=175621694.

[4] VUS: variant of uncertain significance. Tier definitions: Li, M. M. et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A Joint Consensus Recommendation of the Association For Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J. Mol. Diagn. 19, 4–23 (2017).

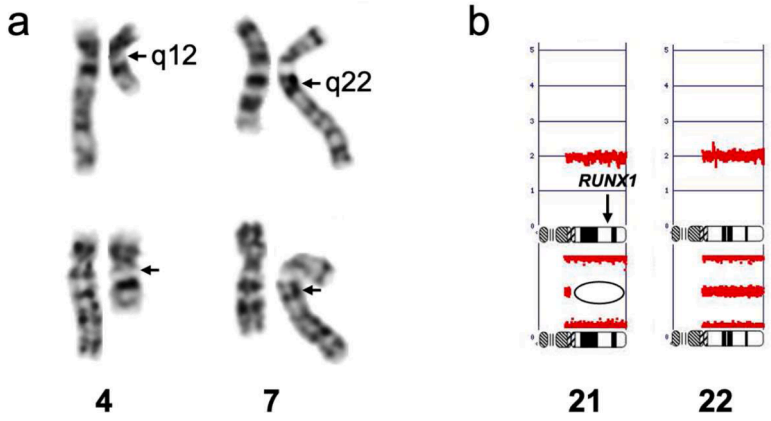

Fig. 1. Karyotypic and chromosome microarray analysis (CMA) findings at the time when the patient's AML was in relapse. **a)** Partial karyotypes of two metaphases from a leukemic peripheral blood sample, each showing a reciprocal translocation between the long arms of chromosomes 4 and 7, t(4;7)(q12;q21.2). The sample was harvested directly and after 24 hours, and all 15 metaphases available showed the t(4;7). Arrows indicate breakpoints in the rearranged chromosomes. Note that the same translocation was seen at the time of diagnosis of AML. **b)** DNA copy number and allele profiles of chromosomes 21 and 22 (normal reference chromosome) exhibiting normal copy number of chromosome 21 but allelic loss (open oval symbol) of entire long arm of 21 (21q) due to copy neutral loss of heterozygosity (cnLOH) in ~100% of DNA. For both chromosomes, the y axis depicts DNA copy number (*Upper*) and allele peaks (*Lower*). Allele peak panels normally show three distinct "bands," as for entire chromosome 22 and for the short arm of 21 (21p), representing all homozygous (*Top* and *Bottom* bands) and heterozygous (*Middle* band) allele calls. In this case, there is cnLOH for nearly all of 21q, including the locus where the leukemia-related gene *RUNX1* is located at 21q22.12.

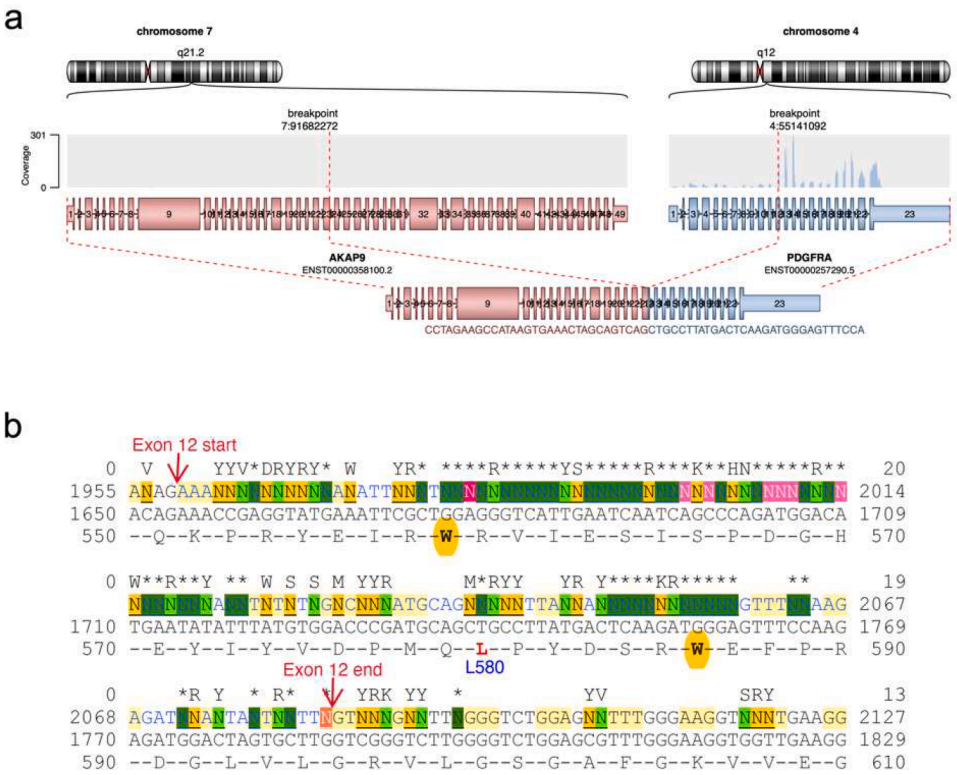

Fig. 2. Depiction of the *AKAP9::PDGFRA* fusion gene seen at the time when the patien had AML. **a)** Schematic indicates the translocation fusion breakpoints in chromosome bands 4q12 and 7q21.2, with precise nucleotide locations of each chromosomal breakpoint shown. The fusion occurred between *AKAP9* exon 23 (encoding amino acid Q1867) and *PDGFRA* exon 12 (encoding amino acid L580), causing an in-frame chimeric fusion gene. **b)** Nucleotide map of *PDGFRA* exon 12 (arrows indicating start and end sequences) and encoded amino acids. Amino acid L580 resides between the two tryptophans (W559 and W586) in the JM domain of PDGFRA.

3. Discussion

The deletion in exon 9 of *CALR* (c.1099_1150del, p.Leu367fsTer46) initially observed when the patient had ET overlaps the DNA nucleotide regions reported by others in patients with myeloproliferative neoplasms, including myelofibrosis and ET. Klampfl et al. [20] and Nangalia et al. [21] identified a somatic 52-bp deletion in exon 9 of the *CALR* gene (c.1092_1143del) that results in the same frameshift and premature termination (L367fsTer46) as in our case. In one of these studies, 36 types of somatic insertions or deletions in *CALR* exon 9 were identified, each of which caused a frameshift to the same alternative reading frame and generated a novel C-terminal peptide in the mutant calreticulin protein encoded by *CALR* [20]. Additionally, overexpression of the most common deletion mutant resulted in cytokine-independent growth *in*

vitro due to activation of STAT5.

AML is a heterogeneous hematological malignancy with a poor prognosis [1]. Despite advances in research into the pathophysiology and treatment of AML, there are still challenges in its management. Although a large proportion of patients reach the first stage of remission after induction chemotherapy, many cases relapse within a year, and re-induction chemotherapy becomes unsuccessful [22]. The precise mechanisms of AML relapse and treatment failure are not yet fully understood. Therefore, investigating the pathological and genetic mechanisms underlying AML and its resistance to therapy is important for the development of more effective therapeutic targets for AML. Unlike the *CALR* mutation connected with ET, which showed decreased allele frequency during AML remission and was absent at relapse, we posit that the somatic *AKAP9::PDGFRA* gene fusion is a critical oncogenic driver associated with the development of AML in our patient.

Likewise, pathogenic mutations of other genes (*RUNX, DNMT3A*, and *WT1*) observed when our patient developed AML, have also been implicated in leukemogenesis. The *RUNX1* mutation, RUNX1 p.Arg162Lys, was homozygous due to cnLOH of 21q (Fig. 1B). *RUNX1* acts as a tumor suppressor in myeloid cells, and p.Arg162Lys is an inactivating mutation. AML with mutant *RUNX1* was added as a provisional category of AML with recurrent genetic abnormalities in the 2016 WHO classification of myeloid neoplasms and acute leukemia [4]. However, *RUNX1* mutations in AML overlap with such a broad range of defining molecular features that in 2022, the WHO concluded that it lacked enough specificity to define a standalone AML type [6]. *RUNX1* is also a frequent site of gene rearrangements involving multiple gene partners, including *RUNX1::RUNX1T1*, which arises from an (8;21)(q22;q22) translocation. WT1 p.Arg462Leu is predicted to inactivate the tumor suppressor function of the *WT1* gene. *WT1* mutations have been reported in 5-10% of AML patients, with most mutations resulting in protein truncations. DNMT3A p.Arg882His inactivates the DNA methylation activity that provides epigenetic inhibition of early oncogenic gene expression. *DNMT3A* mutations have been reported in 15-20% of AML cases, and they have been found in hematopoietic stem cells of AML patients.

Gene fusions are estimated to be responsible for 20% of cancer morbidity worldwide [23]. Growing evidence has revealed many important oncogenic implications of fusion genes, ranging from mechanisms of fusion formation to pathological outcomes, against which targeted therapies have shown sometimes remarkable clinical efficacy [7]. Fusion genes are primarily created as the consequence of structural chromosomal rearrangements, mainly via translocations and inversions. These types of events are well known to play crucial roles in the early steps of tumorigenesis [7,23], and therefore gene fusions have been shown to be associated with many hematological and solid cancers [24, 25]. AML is one of the malignancies best studied by NGS, showing a highly heterogeneous genomic landscape [12]. The 5th edition of the WHO Classification of Hematolymphoid Tumors now designates groups of AML/acute promyelocytic leukemia (APL) patients based on defining genetic abnormalities that include the following fusions: APL with *PML::RARA* and AML with one of the following: *RUNX1::RUNX1T1; CBFB::MYH11; DEK::NUP214; RBM15::MRTFA*; and *BCR::ABL1* [6]. Other genes involved in a variable fusions include *KMT2A; MECOM*; and *NUP98*. The driving roles of fusion genes during tumorigenesis have been recognized for several decades, with efficacies demonstrated in clinical diagnosis and targeted therapy [7]. The association between *NUP98* fusions with various *HOX* genes and AML has been described in several studies [3,8-10]. Cases of AML with the *BCR::ABL1*/t(9;22)(q34;q11), which we recognize from chronic myeloid leukemia and acute lymphoblastic leukemia, have also been reported in AML [11].

The *AKAP::PDGFRA* fusion we detected in an AML patient has not been reported previously. A-kinase anchor proteins (AKAPs) are a diverse group of constitutively expressed proteins that bind the protein kinase A (PKA) regulatory subunit and restrict the holoenzyme to particular loci within cells [22]. The AKAP9 protein, also known as Yotiao, is encoded by the *AKAP9* gene located at chromosome band 7q21.2. AKAP9 has been linked with the development, metastasis, and/or prognosis of many human cancers, including AML [22] as well as neoplasms of the colon [26], bladder [27], breast [28], thyroid [29], mouth [30], lung [31], prostate [32], and skin [33] The molecular mechanism(s) by which *AKAP9* contributes to the development of most of these tumors is not well understood. In patients affected by radiation-related thyroid papillary carcinomas, a paracentric inversion of the long arm of chromosome 7 results in an in-frame fusion of the *AKAP9* N-terminus (exons 1-8) with the C-terminal catalytic domain of the serine-threonine kinase gene, *BRAF* [34]. The resulting AKAP9::BRAF fusion protein exhibits constitutive kinase activity, which results in aberrant, proliferative signaling. Moreover, the AKAP9::BRAF fusion protein was found to transmit mitogenic signals to the MAPK pathway and to transform NIH3T3 cells. *AKAP9-BRAF* gene fusions have also been reported in sclerosing malignant melanomas [35].

Similarly, the in-frame *AKAP9::PDGFRA* fusion gene is predicted to result in constitutive PDGFRA type III receptor tyrosine kinase activity. Interestingly, Baxter et al. [36] reported a rare variant translocation, t(4;22)(q12;q11), in two patients with a chronic myeloid leukemia-like myeloproliferative disease. An unusual in-frame *BCR::PDGFRA* fusion was identified in both patients, with breakpoints occurring at two different *BCR* introns joined to *PDGFRA* exon 12, the same exon affected in our case. The FIP1L1::PDGFRA fusion tyrosine kinase causes chronic eosinophilic leukemia. Notably, while FIP1L1 was found to be dispensable for PDGFRA activation, disruption of the auto-inhibitory juxtamembrane (JM) domain, encoded by exon 12 of the *PDGFRA* gene, is required for constitutive kinase activation and leukemic transforming potential of *FIP1L1::PDGFRA* [37]. Importantly, this kinase activity and transforming potential is dependent on disruption occurring between the two tryptophans in the JM domain. In our case, breakpoints in *AKAP9* exon 23 (Q1867) and *PDGFRA* exon 12 (L580) result in an in-frame chimeric fusion gene. Amino acid L580 resides between the two tryptophans (W559 and W586) in the JM domain of PDGFRA, and the fusion at L580 would be expected to disrupt the auto-inhibitory JM while leaving the kinase domain intact (Fig. 2**a,b**). Thus, we hypothesize that the resulting AKAP9::PDGFRA fusion protein would have constitutive kinase activity, with the ability to transmit mitogenic signals through signaling pathways, such as the AKT pathway, to promote oncogenic transformation, cell proliferation, and cell survival.

PDGFRA rearrangements are associated with various unusual adult myeloid neoplasms such as chronic eosinophilic leukemia, hypereosinophilic syndrome, chronic myelomonocytic leukemia, systemic mastocytosis with chronic eosinophilic leukemia, as well as AML with eosinophilia [14,38-40]. *FIP1L1* is the most common partner gene in *PDGFRA* fusions [16], but other partners including *BCR, KIF5B, CDK5RAP2, STRN*, and *ETV6* have been reported in chronic eosinophilic leukemia [38,39]. The *FIP1L1::PDGFRA* fusion leads to overactivation of PDGFRA, a type III receptor tyrosine kinase. The *FIP1L1::PDGFRA* fusion has been proposed as a surrogate marker for the diagnosis of chronic eosinophilic leukemia, hypereosinophilic syndrome, and systemic mastocytosis, making the tyrosine kinase inhibitor imatinib a treatment alternative [38,39]. *FIP1L1::PDGFRA* fusion is also associated with eosinophilia-associated AML patients [13-15]. Shah et al. reported a patient in whom *FIP1L1::PDGFRA* was discovered during evolution from chronic myelomonocytic leukemia to AML that was resistant to conventional therapy; however, imatinib treatment resulted in a durable complete remission [40]. In another unusual case, an AML patient in relapse was found to have both *DEK::NUP214* and *FIP1L1::PDGFRA* fusions without marked eosinophilia in the PB or BM [15]. At no time during her disease course did the patient reported here have eosinophilia.

The efficacy of imatinib has been demonstrated in *FIP1L1::PDGFRA*-positive hematologic malignancies, even if they present with an aggressive clinical phenotype [13]. Li et al. detected *PDGFRA::ETV6* fusions in 7 of 15 AML cases with t(4;12)(q11;p13), and all had a poor

clinical outcome despite various conventional therapies, leading the investigators to conclude that there may be a role for tyrosine kinase inhibitor therapy in such cases [16]. Germane to this, the identification of the *PML::RARA* fusion in APL led to the discovery of an effective tretinoin-based molecular therapy [17,18]. The RUNX1::ETO chimeric protein has been associated with a subtype of AML with prolonged median survival [19]. Therefore, the identification of well-known fusion genes for diagnostic purposes and the continued discovery of new fusions are important, as our knowledge and understanding of these alterations can facilitate decisions about appropriate targeted therapies for individual patients [7,24]. In the case of the AKAP::PDGFRA chimeric protein, future studies are needed to determine if this is a recurrent change in AML and if its predicted constitutive tyrosine kinase activity can be targeted by a tyrosine kinase inhibitor.

4. Conclusion

The molecular and prognostic heterogeneity of AML requires additional biomarkers and potential targets for personalized therapies. The novel AKAP9::PDGFRA fusion product reported here has not been previously associated with AML. Hence, future investigations of it as a molecular target for tyrosine kinase inhibition in selected patients with AML may contribute to their disease management.

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CRediT authorship contribution statement

Yavuz Sahin: Writing – review & editing, Writing – original draft, Validation. **Jianming Pei:** Visualization, Formal analysis, Data curation. **Don A. Baldwin:** Methodology. **Nashwa Mansoor:** Data curation. **Lori Koslosky:** Methodology, Data curation. **Peter Abdelmessieh:** Writing – review & editing. **Y. Lynn Wang:** Writing – review & editing. **Reza Nejati:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Joseph. R. Testa:** Writing – review & editing, Writing – original draft, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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