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Complex Genetic Evolution and Treatment Challenges in Myeloid Neoplasms: A Case of Persistent t(2;3)(p15~23;q26)/*MECOM* Rearrangement, *SF3B1* Mutation, and Transient *TNIP1::PDGFRB* Chimera

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Abstract. *Background/Aim: Myelodysplastic syndromes (MDSs) are clonal bone marrow disorders characterized by ineffective hematopoiesis. They are classified based on morphology and genetic alterations, with SF3B1 variants linked to favorable prognosis and MECOM rearrangements associated with poor outcomes. The combined effects of these alterations remain unclear. We report an MDS patient carrying both SF3B1 and MECOM alterations who developed transient eosinophilia accompanied by a TNIP1::PDGFRB chimera in a subset of MECOM-affected cells. Case Report: A 73-year-old woman was diagnosed with myeloid neoplasia with excess blasts and multilineage dysplasia (MDS-EB1). Six months later, SF3B1 mutations were identified, leading to a diagnosis of MDS-SF3B1. Despite azacitidine treatment, her condition worsened, showing hypercellular bone marrow and eosinophilia. Genetic analysis revealed a t(2;3)(p15~23;q26)/MECOM rearrangement and TNIP1::PDGFRB chimera. Imatinib eradicated eosinophilia and reduced TNIP1::PDGFRB-positive cells, but the MECOM-clone persisted. Subsequent treatments, including hydroxyurea, mercaptopurine, and low-dose cytarabine, were ineffective. FLT3 mutations and high EVI1 transcript levels were later detected. The patient succumbed to progressive disease. Conclusion: This case highlights the complexity of MDS and the importance of genetic abnormalities in treatment planning. Persistent MECOM rearrangement and the TNIP1::PDGFRB chimera emphasize the need for further research into resistance mechanisms.*

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Myelodysplastic syndromes (MDSs) are clonal bone marrow disorders characterized by ineffective hematopoiesis which leads to cytopenias. This results in anemia, increased susceptibility to infections due to neutropenia, and bleeding due to thrombocytopenia. Diagnosing MDS can be challenging and requires a combination of clinical features, bone marrow and peripheral blood morphology, immunophenotyping, and genetic testing.

Current MDS classification schemes incorporate morphologic features such as myeloblasts in blood and/or bone marrow, degree of dysplasia, presence of ring sideroblasts, bone marrow fibrosis, and bone marrow cellularity. Additionally, three genetically defined entities are recognized: MDS with del(5q) as the sole cytogenetic abnormality, MDS with mutation in the splicing factor 3b subunit 1 (*SF3B1* on chromosome sub-band 2q33.1) gene (MDS-SF3B1), and MDS with mutation in the tumor protein p53 (*TP53* on chromosome sub-band 17p13.1) gene (1-5). MDS-SF3B1 is generally associated with a more favorable prognosis. However, the presence of additional genetic aberrations can influence the response to therapy, disease progression, and prognosis (1, 2). Common co-occurring genetic

aberrations in MDS-SF3B1 include mutations in the *TET2* (37%), *DNMT3A* (25%), *ASXL1* (15%), and *RUNX1* (9%) genes, as well as the del(5q) cytogenetic abnormality (7%) (1, 2).

The *MDS1* and *EVI1* complex (*MECOM*) locus at chromosome sub-band 3q26.2 encodes a zinc-finger transcription factor involved in hematopoiesis, apoptosis, development, and cell differentiation (6, 7). Cytogenetic aberrations affecting the *MECOM* locus are found in both MDS and acute myeloid leukemia (AML) and result in increased gene expression. Overexpression of *MECOM* is generally associated with poor clinical outcomes and resistance to therapy (6-8). Furthermore, the presence of additional genetic abnormalities may influence the prognosis (9).

Although both *SF3B1* and *MECOM* aberrations are involved in MDS and AML, they represent distinct genetic abnormalities with different impacts on disease progression and prognosis. The coexistence of these mutations is rare (9-12), and their combined impact on disease course and response to treatment is not well-documented, underscoring the need for further research in this area. However, an association between *SF3B1* mutations and *MECOM* rearrangements has been observed (9, 12). In myeloid neoplasms with *MECOM* rearrangements, 28% also carry *SF3B1* mutations (9, 12).

Here, we report a MDS-SF3F1 carrying a t(2;3)(p15~23; q26)/*MECOM* rearrangement and fusion of the TNFAIP3 interacting protein 1 (*TNIP1*) gene at 5q33.1 with the platelet-derived growth factor receptor beta (*PDGFRB*) gene at 5q33.2 (*TNIP1::PDGFRB)*.

Materials and Methods

Ethics statement. The study was approved by the Regional Ethics Committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge, http://helseforskning.etikkom.no; 2010/1389/REK sør-øst A). All patient information has been de-identified.

G-banding and karyotyping. Bone marrow cells were cytogenetically investigated using standard methods (13). Chromosomal preparations were G-banded using Leishman's stain (MERCK KGAA, Darmstadt, Germany) and karyotyped according to the 2020 Guidelines of the International System for Human Cytogenomic Nomenclature (14).

Fluorescence in situ hybridization (FISH) analyses. FISH analyses were performed using the *EVI1* (*MECOM*) break-apart and *PDGFRB* break-apart probes, both purchased from Oxford Gene Technology (OGT, Begbroke, Oxfordshire, UK). According to the manufacturer, the *EVI1* (*MECOM*) break-apart probe consists of three components: a 158 kb red-labeled (R) probe located telomeric to the *MECOM* gene; a 181 kb green-labeled (G) probe that includes the centromeric region of the *MECOM* gene; and a 563 kb blue-labeled (B) probe covering a region centromeric to the *MECOM* gene. In normal cells, two co-localized red/green/blue (R/G/B) signals are expected. The *PDGFRB* break-apart probe consists of a 107 kb red-labeled (R) probe positioned centromeric to the *PDGFRB* gene and a 154 kb green-labeled (G) probe located telomeric to the *PDGFRB* gene. In normal cells, two red/green (R/G) fusion signals are expected. FISH analyses were performed following the manufacturer's protocol, with fluorescent signals captured and analyzed using the CytoVision system (Leica Biosystems, Newcastle upon Tyne, UK).

Array comparative genomic hybridization (aCGH) analysis. aCGH was performed using the CytoSure array products (OGT) following the company's protocols. Annotations are based on human genome build 19.

RNA sequencing, reverse transcription polymerase chain reaction (RT-PCR) and Sanger sequencing analyses. Total RNA was extracted and sent to the Genomics Core Facility, Norwegian Radium Hospital, Oslo University Hospital for RNA sequencing. The software FusionCatcher was used to find fusion transcripts (15). The presence of fusion transcripts was confirmed by reverse transcription (RT) polymerase chain reaction (PCR) and Sanger sequencing. In brief, 1 μg of total RNA was reverse-transcribed and cDNA, corresponding to 20 ng total RNA, was used as a template in subsequent PCR amplification using the primers TNIP1-Ex13F1 (5'-GGG CCC TCC TAA GGA AAC AG-3') and PDGFRB-Ex12R1 (5'-TAC TCA TGG CCG TCA GAG CTC-3'). The PCR products were subsequently sequenced with the primers M13F-TNIP1-Ex13F2in (5'-TGTAAAACGACGGCCAGT GGA AAC AGG AGC TGG TCA CG-3') and M13R-PDGFRB-Ex12R2in (5'-CAGGAAACAGCTATGACC GGC CGT CAG AGC TCA CAG AC-3') using the BigDye Direct Cycle Sequencing Kit (Thermo Fisher Scientific, Waltham, MA, USA). Sequencing was performed using an Applied Biosystems SeqStudio Genetic Analyzer system (Thermo Fisher Scientific). The sequences obtained by Sanger sequencing were compared with the National Center for Biotechnology Information (NCBI) reference sequences using the Basic Local Alignment Search Tool (BLAST) (16). The reference sequences were NM_006058.5 for TNFAIP3 interacting protein 1 (*TNIP1*), transcript variant 5 and NM_002609.4 for platelet derived growth factor receptor beta (*PDGFRB*), transcript variant 1. The BLAST-like alignment tool (BLAT) and the human genome browser at UCSC were also used to map the sequences obtained by Sanger sequencing, on the Human GRCh37/hg19 assembly (17, 18).

Results

Case report. Table I presents the MDS-disease progression, the genetic data, and the treatment details of the patient. A 73-year-old female was referred for evaluation due to pancytopenia. Her medical history included a cervical conization for carcinoma *in situ* (CIN3) at the age of 48 and the excision of a nodular basal cell carcinoma at the age of 72. In October 2016, she was diagnosed with myeloid neoplasia with excess blasts (5-10% $CD34^+$ cells in the bone marrow biopsy) and multilineage dysplasia (MDS-EB1). The karyotype was 46,XX (see below).

In March 2017, six months later, she experienced progressive bone marrow failure. Following a new diagnostic work-up, the diagnosis was revised to MDS-SF3B1 upon the detection of mutations [c.1998G>C p.(Lys666Asn) VAF 48.7% and c.2359dupA p.(Ile787Asnfs*21) VAF 8.5%] (1). In June

2017, the number of myeloblasts was increased (10% $CD34^+$ cells). By September 2017, eleven months after her initial diagnosis, $CD34^+$ cells accounted for 15-20% of the bone marrow cells, and treatment with azacitidine was initiated.

In April 2019, nineteen months thereafter, she experienced progressive bone marrow failure and prominent blood eosinophilia despite ongoing treatment with azacitidine. A trephine biopsy revealed hypercellular bone marrow (95% cellularity) with a low number of myeloblasts ($CD34^+$ cells 1%) and massive eosinophilia (65-70% of the cellularity). The karyotype was 46,XX,t(2;3)(p15~23;q26)[10], and molecular genetics showed high levels of *PDGFRB*-transcripts. Imatinib was prescribed.

In June 2019, three months later, AML was diagnosed alongside a myeloid sarcoma involving the colon sigmoideum. Myeloblasts constituted 40% of the bone marrow cellularity and displayed the following immunophenotype: $CD34^+CD13^+CD14^-CD15^{(+)}CD16^-CD33^+CD36^-CD64^-CD117^+cyMPO^-$. Eosinophilia was no longer present. Both *FLT3-TID* (10%) and *FLT3-TKD* (5%) mutations were detected along with high levels of *EVI1* transcripts. Hydroxyurea and mercaptopurine were added to imatinib for two months, which was followed by one cycle of low dose cytarabine with no effect. The patient succumbed to progressive disease in September 2019.

Cytogenetic examinations of bone marrow cells at diagnosis initially revealed a normal karyotype 46,XX[20]. However, cytogenetic analyses conducted in April 2019 and June 2019 identified an abnormal karyotype 46,XX,t(2;3)(p15~23;q26)[10] (Table I, Figure 1A). These findings prompted us to re-examine the metaphase spreads obtained at diagnosis. The re-examination confirmed the presence of the t(2;3)(p15~23;q26) in the primary diagnostic sample (Table I).

FISH analysis was also performed on re-examination of the sample obtained at diagnosis. The *EVI1* (*MECOM*) break-apart probe detected a rearrangement of the *MECOM* locus in 68% of the examined interphase nuclei (Table I). No rearrangement of the *PDGFRB* locus were detected using the *PDGFRB* break-apart probe.

In the sample obtained in April 2019, FISH analysis of metaphases using the *EVI1* (*MECOM*) break-apart probe showed a red/green signal on the normal chromosome 3, a green signal on the der(3)t(2;3)(p15~23;q26), and a red signal at the distal part of the short arm of the der(2)t(2;3)(p15~23;q26) (the blue signal of the probe was not shown) (Figure 1B). FISH analysis using the *PDGFRB* break-apart probe revealed a red/green signal on one chromosome 5 and a red signal on the other chromosome 5, indicating a deletion that included the part of the chromosome 5, where the distal part (green signal) of the probe hybridized (Figure 1C).

The simultaneous use of both the *EVI1* (*MECOM*) and *PDGFRB* break-apart probes on interphase nuclei revealed that in 6 nuclei, there was no rearrangement of either *MECOM* or *PDGFRB*, 42 nuclei exhibited split of the *MECOM* probe (indicating a rearrangement of *MECOM*), and 52 nuclei showed rearrangements of both *MECOM* and *PDGFRB* loci. This suggests that the *PDGFRB* rearrangement occurred in a subset of cells already carrying the *MECOM* aberration (Figure 1D and E).

In the sample obtained in June 2019, *MECOM* rearrangement was detected in 88% (177 out of 202) of the examined interphase nuclei. Rearrangement of the *PDGFRB* locus was detected in only 6% (12 out of 215) of examined interphase nuclei (Table I).

aCGH on sample obtained in April 2019 revealed an approximately 890 Kbp submicroscopic deletion (Figure 2A). It started within the *PDGFRB* gene (sequence of the deleted probe: AAG AAA GGT GAA TAA ATG AAG CAC ACT CAT ACA GGT GCA TGT ATG CAT AAG GAC GGG CAG) and extended to approximately 5 Kbp proximal to the *TNIP1* gene at 5q33.1 (sequence of the deleted probe: TTA AGC CTA GAT TTC ACA GAG TCA ATC ATA ATC TTG TGC CAG TCC CTT AAG AGT ATA CAG) (Figure 2B). This result was consistent with the FISH data obtained using the *PDGFRB* break-apart probe (Figure 1C).

Using the FusionCatcher software with the fastq files from the RNA sequencing data, a *TNIP1::PDGFRB* chimeric transcript was found: AGG AAA CAG GAG CTG GTC ACG CAG AAT GAG TTG CTG AAA CAG CAG::AAG CCA CGT TAC GAG ATC CGA TGG AAG GTG ATT GAG TCT GTG AGC. In the *TNIP1::PDGFRB* chimeric transcript exon 13 of *TNIP1* (accession number NM_006058.5) fused in-frame with exon 12 of *PDGFRB* (accession number NM_002609.4). The existence of the *TNIP1::PDGFRB* chimeric transcript was also confirmed with RT-PCR together with Sanger sequencing (Figure 2C). The resulting 1013 amino acid-residues protein is predicted to be a chimeric TNIP1::PDGFRB protein tyrosine kinase which contains the amino acids residues 1-465 of the TNIP1 protein (NCBI Reference Sequence: NP_006049.3) and the amino acids residues 559-1106 of PDFGRB protein (NP_002600.1) (Figure 2D and E).

Discussion

This work investigated the progression of a myeloid neoplasm, aiming to provide a genetic explanation for its development. The medical history of the patient included cervical conization for carcinoma *in situ* and excision of a nodular basal cell carcinoma. Given this history, the myeloid neoplasm was considered a primary malignancy.

At the genetic level, a t(2;3)(p15~23;q26) chromosome translocation was found in the bone marrow cells of the patient, resulting in *MECOM* rearrangement. The t(2;3)(p15~23;q26) translocation is a recurrent genetic abnormality observed in myeloid malignancies (19-21). The breakpoint on the p arm of chromosome 2 is variable, while the breakpoint on chromosome

Table I. *Timeline of disease progression alongside the results of genetic investigations and treatment.*

Date	Diagnosis	Genetic investigations	Treatment
October 2016	MDS-EB1: Multilineage dysplasia and 5-10% CD34+ cells (as observed in the trephine biopsy)	Initial G-banding examination revealed a normal karyotype, 46,XX[20], but this was due to poor chromosome quality Retrospective G-banding examination detected an abnormal karyotype, 46,XX,t(2;3)(p15~23;q26) Retrospective FISH investigations detected rearrangement of *MECOM*	
March 2017	Revised to MDS-SF3B1	*SF3B1* mutations [c1998G>C p.(Lys666Asn) VAF 48,7% and c2359dupA p.(Ile787Asnfs*21) VAF 8,5%]	
June 2017	10% $CD34^+$ cells bone marrow cells (as determined by flow cytometry)	Not done	
September 2017	15-20% $CD34^+$ bone marrow cells (as observed in the trephine biopsy) Treatment with azacitidine was initiated	Not done	Treatment with imatinib was initiated in May 2019
April 2019	Hypercellular bone marrow (95%) with a low number of myeloblasts (1% $CD34^+$ cells) and massive eosinophilia (65-70% of cellularity)	High levels of *PDGFRB*-transcripts were detected G-banding examination detected an abnormal karyotype, 46,XX,t(2;3)(p15~23;q26)[10] FISH investigations detected rearrangement of *MECOM* and deletion of the distal part of *PDGFRB* in a subset of the cells carrying the *MECOM* aberration aCGH detected an 886 Kbp deletion: arr[hg19] 5q32q33.1(149,508,484-150,394,977)x1 RNA sequencing identified the *TNIP1::PDGFRB* chimeric transcript Sanger sequencing verified the *TNIP1::PDGFRB* chimeric transcript	
June 2019	AML with 30-40% $CD34^+$ bone marrow cells, along with a myeloid sarcoma involving sigmoid colon Eosinophilia was no longer present.	FLT3-TID (10%) and FLT3-TKD (5%) mutations were detected High levels of *EVI1* transcripts were observed G-banding examination revealed an abnormal karyotype, 46,XX,t(2;3)(p15~23;q26)[10] FISH investigation identified rearrangement of *MECOM* in 88% and deletion of the distal part of *PDGFRB* in 6% of the interphase nuclei	Treatment with hydroxyurea and mercapto-purine in combination with imatinib was started. This regimen was later substituted with low-dose cytarabine for one cycle starting in August.
September 2019	Succumbed from progressive disease	Not done	

MDS-EB: Myelodysplastic syndrome with excess blasts; AML: acute myeloid leukemia; FISH: fluorescence in situ hybridization; aCGH: array comparative genomic hybridization; ITD: internal tandem duplication; TKD: tyrosine kinase domain.

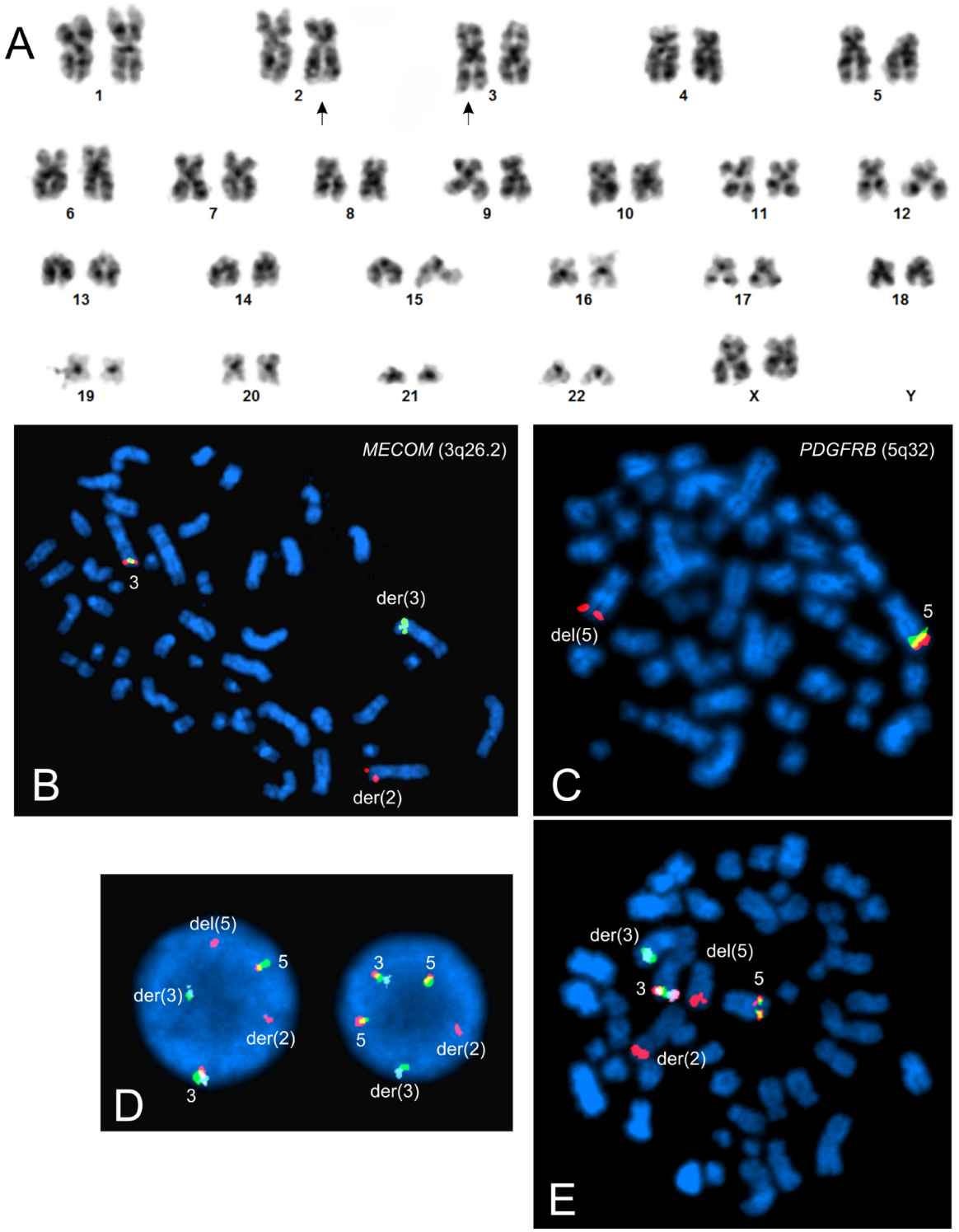

Figure 1. *G-banding and fluorescence in situ hybridization (FISH) analyses of bone marrow cells from April 2019, when bone marrow failure and eosinophilia were detected. (A) Karyogram showing a neoplastic clone with 46,XX,t(2;3)(p15~23;q26); arrows highlight the abnormal chromosomes. (B) FISH with the MECOM probe shows the distal red part hybridizing to der(2)t(2;3), and the green part to der(3)t(2;3), with co-hybridization on the q arm of the normal chromosome 3. (C) FISH with the PDGFRB probe reveals that both red and green parts co-hybridize to one chromosome 5, while only the red signal hybridizes to the other chromosome 5, indicating a deletion [del(5)]. (D) Interphase nuclei show co-hybridization of MECOM and PDGFRB probes, with one nucleus showing rearrangements in both loci and another showing only MECOM rearrangement. (E) FISH of the metaphase spread confirms MECOM rearrangement and PDGFRB co-hybridization to the normal chromosome 5 and del(5).*

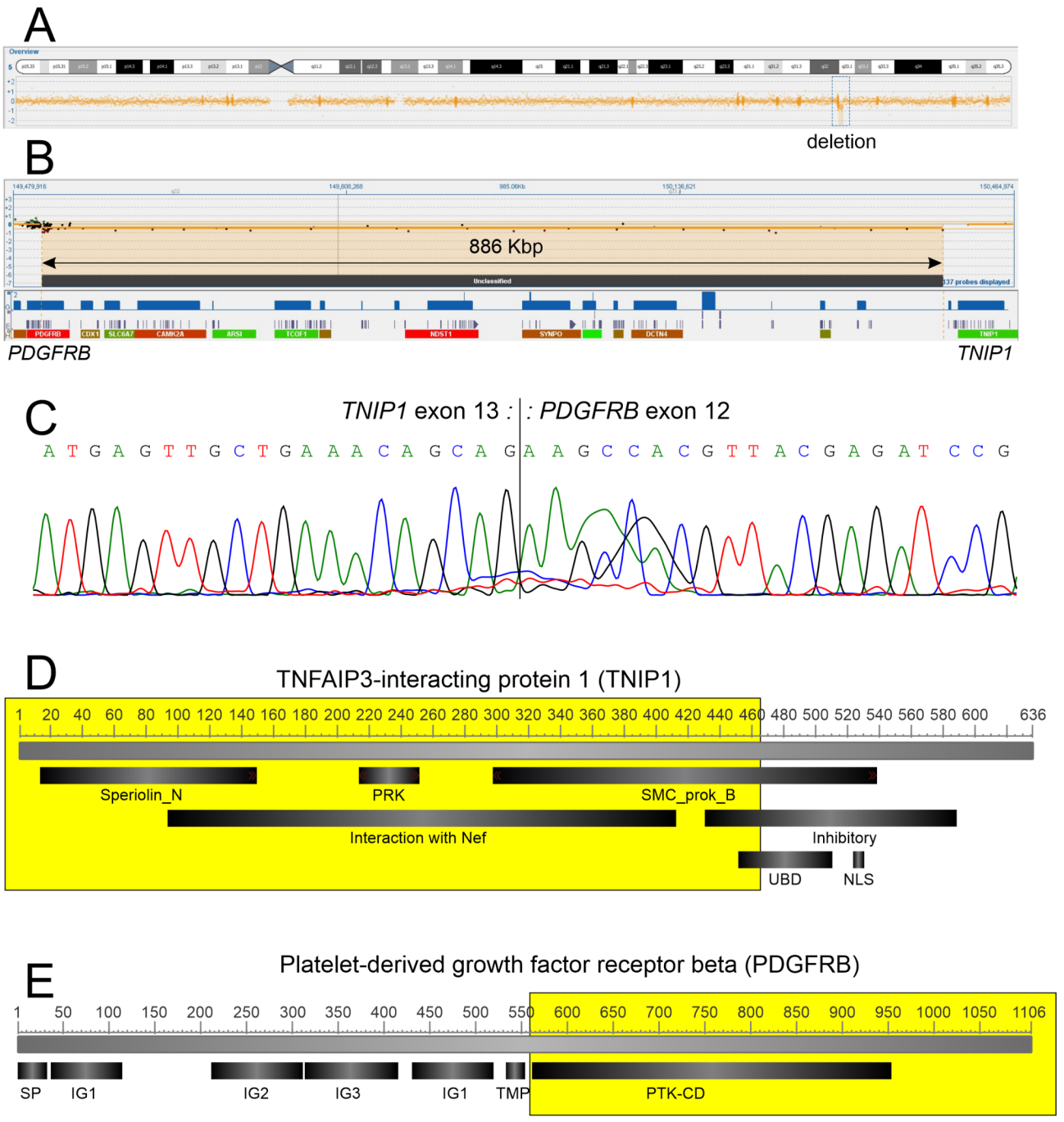

Figure 2. *The deletion in the q arm of chromosome 5 and the TNIP1::PDGFRB chimera. (A) Array comparative genomic hybridization (aCGH) showing the deletion in the q arm of chromosome 5. (B) The 886 Kbp deletion starts within the PDGFRB gene and extends to approximately 5 Kbp proximal to the TNIP1 gene at 5q33.1. (C) Partial sequence chromatogram showing the junction position in the TNIP1::PDGFRB cDNA amplified fragment. The exon numbers are based on the sequences with accession numbers NM_006058.5 for TNIP1 and NM_002609.4 for PDGFRB. (D) Diagram showing the TNIP1 protein with the following regions: Speriolin_N, rod shape-determining protein MreC (PRK), chromosome segregation protein SMC, common bacterial type (SMC_prok_B), interaction with Nef protein, region required for inhibitory activity of TNF-induced NF-kappa-B activation (inhibitory), ubiquitin-binding domain (UBD), and nuclear localization signal (NR). (E) Diagram showing the PDGFRB protein with the following regions. Signal peptide (SP), immunoglobulin domain (IG1), immunoglobulin (Ig)-like domain of platelet-derived growth factor (PDGF) receptors, alpha and beta (IG2), fourth immunoglobulin (Ig)-like domain of platelet-derived growth factor receptor (PDGFR) (IG3), transmembrane domain (TMP), catalytic domain of the protein tyrosine Kinase, platelet derived growth factor receptor beta (PTK-CD). The parts of the TNIP1 and PDGFRB proteins in yellow compose the chimeric TNIP1::PDGFRB protein.*

Table II. *Hematological neoplasm reported to carry TNIP1::PDGFRB chimera.*

Hematological neoplasm	Sex/ Age in years	Additional genetic aberrations	TNIP1 junction (NM_006058.5)	PDGFRB junction (NM_002609.4)	Reference
Ph-like ALL	M/Child	Not available	Exon 14	Exon 11	Roberts *et al*., 2014 (27)
CEL/MPN	M/70	*ATM, DNMT3A, TET2, RUNX1*	Exon 17	Exon 11	Ross *et al*., 2016 (28)
MPN	M/40	Not available	Exon 17	Exon 11	Maccaferri *et al*., 2017 (29)
Ph-like ALL	Not available	Not available	NA	NA	Reshmi *et al*., 2017 (30)
M/LN-Eo	F/0.5	Not available	Exon 11	Exon 13	Berking *et al*., 2023 (31)
MDS/MPN-Eo	F/65	*NRAS*	NA	NA	Saft *et al*., 2023 (32)
MDS	M/35	*ASXL1* NP_056153.2:p.Gly649* *ETV6* NP_001978.1:p.Arg430Ile t(5;19)(q33; p13.2)	Exon 11	Exon 12	Qu *et al*., 2023 (33)
MDS	F/73	t(2;3)(p15~23;q26)/ *MECOM* rearrangement *SF3B1* NP_036565.2:p.Lys666Asn NP_036565.2:p.Ile787Asnfs*21	Exon 13	Exon 12	Andersen *et al*., 2024 (Present case)

Ph-like ALL: Philadelphia chromosome-like acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; CEL: chronic eosinophilic leukemia; M/LN: myeloid/lymphoid neoplasm; Eo: eosinophilia; M: male; F: female; NA: not available.

3 consistently occurs within the *MECOM* locus (19-21). This translocation is part of the non-classic 3q26.2/MECOM rearrangements, leading to the upregulation of *EVI1* and is associated with a poor prognosis (8).

In a series of eleven myeloid neoplasms carrying the t(2;3)(p15~23;q26) translocation, four cases (36%) also had mutations in the *SF3B1* gene (9). Generally, *SF3B1* mutations are strongly associated with *MECOM* rearrangements in AML (10, 12). In the present patient, *SF3B1* mutations were detected alongside the t(2;3)(p15~23;q26)/*MECOM* rearrangement.

Subsequently, treatment with the hypomethylating agent azacitidine may have triggered the eosinophilic phase, caused the 890 Kbp submicroscopic deletion on the q arm of chromosome 5, led to the formation of *TNIP1::PDGFRB* chimera, and resulted in high levels of *PDGFRB* transcripts, although the exact mechanism remains unclear. Negative effects of azacitidine treatment have been reported in elder patients. For instance, in a 70-year-old man with MDS, a novel chromosomal aberration was detected following azacitidine therapy (22). The initial karyotype was 47,XY,+8[2]/46,XY[28], but after treatment, a new clone emerged, resulting in the karyotype: 47,XY,+8[1]/46,XY,del(13)(q12q14)[7]/46,XY[12] (22). Additionally, a 76-year-old man with MDS developed eosinophilic pneumonia after beginning azacitidine therapy (23). In two men with CMML, aged 80 and 76, treatment with azacytidine led to disease progression with an increase in leukocyte count (24, 25). Furthermore, clonal selection in t-MDS and AML have been reported under azacitidine treatment, and in some patients was correlated with disease progression or relapse (26).

Treatment with imatinib, initiated in May 2019, led to disappearance of eosinophilia and a drastic reduction in the number of the cells carrying the *PDGFRB* aberrant FISH pattern, the *TNIP1::PDGFRB* chimera and high levels of *PDGFRB* transcripts. However, imatinib could not eradicate the clone carrying only the t(2;3)(p15~23;q26)/*MECOM* rearrangement. FISH analysis showed that this clone had increased to 88% of the bone marrow cells. Despite subsequent treatments, including a combination of hydroxyurea and mercaptopurine with imatinib, followed by one cycle of low-dose cytarabine, the clone did not respond. New secondary mutations, FLT3-TID (10%) and FLT3-TKD (5%), were detected in an already cellular background with high levels of EVI1 transcripts, and the patient ultimately succumbed to progressive disease.

The *TNIP1::PDGFRB* chimera is a rare recurrent fusion reported in only eight patients, including the present case (27-33) (Table II). To our knowledge, this is the first case where the *TNIP1::PDGFRB* chimera has been identified as a transient genetic event in MDS-SF3B1 following a *MECOM* rearrangement. The chimeric TNIP1::PDGFRB protein tyrosine kinase consists of 1013 amino acid residues, combining residues 1-465 from TNIP1 and 559-1106 from PDGFRB (Figure 2D and E), and possesses transforming properties (34-37). This chimera includes the Speriolin N-terminus, interaction with Nef, and rod shape-determining protein MreC regions from TNIP1 (NP_001239314.1), as well as the catalytic domain of the protein tyrosine kinase from PDGFRB

(NP_002600.1). It lacks the region of TNIP1 which is required for inhibitory activity of TNF-induced NF-kappa-B activation (38, 39) and the transmembrane region of PDGFRB, encoded by exon 11, which has been shown to be critical for the signaling and cell proliferation mediated by PDGFRB chimeras (40). Similarly to our patient, in two other patients carrying the *TNIP1::PDGFRB* chimera, the exon 11 of *PDGFRB* was also absent from the fusion transcript: *TNIP1* exon 11 fused to either exon 12 or exon 13 of *PDGFRB* (Table II) (31, 33). Additionally, in eosinophilia-associated neoplasms, *CDC88C::PDGFRB*, *DTD1::PDGFRB*, *GCC2-PDGFRB*, *MYO18A-PDGFRB*, and *PRKG2::PDGFRB* chimeric transcripts have been reported, in which exons 12 or 13 of the *PDGFRB* gene fused with partner genes. Despite the absence of exon 11 of *PDGFRB*, these chimeras possess oncogenic potential, are able to transform cells *in vitro*, and patients carrying those fusions respond to imatinib treatment (41-44).

The mechanism underlying the PDGFRB-mediated accumulation of eosinophils is not well understood. However, an *in vitro* study showed that the chimeric *ETV6::PDGFRB* gene stimulated the proliferation of human hematopoietic cells and induced eosinophil differentiation which required nuclear factor-κB (NF-κB) (45). A similar cellular behavior may be assumed for the *TNIP1::PDGFRB* chimera. Noteworthy is that NF-κB has been shown to regulate the promoter activity of *TNIP1* (46), which codes for an inhibitor of NF-κB activation (38, 39).

Conclusion

This case illustrates the complex genetic evolution of myeloid neoplasms, highlighting the challenges in treatment, particularly with azacitidine and imatinib. Persistent clones carrying the t(2;3)(p15~23;q26)/*MECOM* rearrangement led to disease progression and eventual patient demise. The emergence of the TNIP1::PDGFRB chimera underscores the need for further research to understand the mechanisms driving resistance and to develop more effective therapeutic strategies.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest.

Authors' Contributions

KA performed G-banding, karyotyping, fluorescence *in situ* hybridization, molecular genetic experiments, interpreted the data and draft the manuscript. GET made clinical evaluations, treated the patient, and draft the manuscript. MLH made clinical evaluations and provided clinical data. SS made the hematopathology evaluations. IP designed and supervised the research, interpreted the data and wrote the manuscript. All Authors read and approved of the final manuscript.

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