

Novel GMPS::ARHGEF26-AS1 Fusion Gene in Ph+ Acute Myelocytic Leukemia with Additional Chromosome Abnormalities

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Philadelphia chromosome-positive acute myeloid leukemia (Ph+ AML) is a rare condition, and its additional genetic abnormalities remain largely unclear.^{1,2} Here, we describe a case of Ph+ AML with extra chromosomal changes. Using RNA sequencing, we identified a novel fusion gene, GMPS::ARHGEF26-AS1. Both genes involved are related to GMP biological functions.

A 53-year-old woman presented with gum swelling and pain, which slightly improved after taking oral cefixime. Her complete blood count showed a white blood cell count of $53.84 \times 10^9/L$, hemoglobin at 79 g/L, and a platelet count of $79 \times 10^9/L$. Bone marrow aspiration revealed that myeloblasts made up 75.5% of the cells, while promyelocytes accounted for 15.5% (Figure 1a). Bone marrow biopsy demonstrated markedly hypercellular marrow (around 90% cellularity) with diffuse proliferation of abnormal cells comprising about 90% of nucleated cells. These abnormal cells were small to medium in size, with moderate cytoplasm and oval to irregular nuclei containing finely dispersed chromatin. Special stains showed negative Prussian blue staining (indicating no iron deposition), MF-1 grade reticulin fibrosis (World Health Organization Classification), and Masson's trichrome staining indicating grade 0 collagen fibrosis. Flow cytometry revealed that about 95.46% of nucleated cells were abnormal, strongly expressing CD34; expressing CD117, CD13, CD33, CD123, and HLA-DR; partially expressing CD56; weakly expressing CD38 and CD9; and showing no expression of CD7, CD15, CD64, CD11b, CD22, CD5, CD2, CD20, CD19, CD10, CD4, CD14, CD36, intracellular MPO, TDT, cytoplasmic CD79a, cytoplasmic CD3, or surface CD3. The immunophenotype was most compatible with AML-M1/M5, with a strong preference for M5. Karyotype analysis showed 45, XX, der(3), der(5) t(3; 5)(q26; q11), -7, t(9; 22)(q34; q11.2) [20] (Figure 1b). Molecular testing detected the BCR::ABL1

(p190) fusion gene by PCR. Targeted next-generation sequencing with a 56-gene panel (Supplementary Table 1) identified an SF3B1 gene mutation (c.2098A > G, VAF 50.9%). The diagnosis was Ph+ AML. Induction chemotherapy with the IA regimen (idarubicin 10 mg day 1, 20 mg days 2-3; cytarabine 200 mg days 1-7) was given along with dasatinib. Four weeks later, bone marrow aspiration showed hypocellular marrow with 25.5% of myeloblasts and 10% promonocytes, indicating non-remission. She then underwent re-induction with the HEA regimen (homoharringtonine 4 mg days 1-7, etoposide 0.1 days 1-5, cytarabine 200 mg days 1-7). Sadly, she died of cardiac arrest shortly after entering myelosuppression.

Total RNA was isolated from the bone marrow mononuclear cells collected during the initial diagnostic evaluation. Transcriptome sequencing was then conducted. Using the STAR-fusion software, we identified a novel GMPS::ARHGEF26-AS1 fusion gene (Figures 1c-e), along with the BCR::ABL1 fusion and an additional novel ABL1::MIF fusion. These findings were further confirmed using a second software tool, SOAPfuse (see Supplementary Figures 1-5).

The human *guanosine monophosphate synthase* (GMPS) gene is located at chromosome 3q25.31 and belongs to the glutamine aminotransferase family. In the de novo synthesis of GMP, GMPS catalyzes the final step, which involves aminating xanthosine 5' monophosphate to GMP. GMP is then further phosphorylated to produce guanosine triphosphate (GTP). GTP plays a role in various essential biochemical processes. It serves as a primer for DNA replication, supplies guanine nucleotides for RNA transcription, and functions as an energy source in the tricarboxylic acid cycle. GMPS is also known to perform other non-catalytic roles.³



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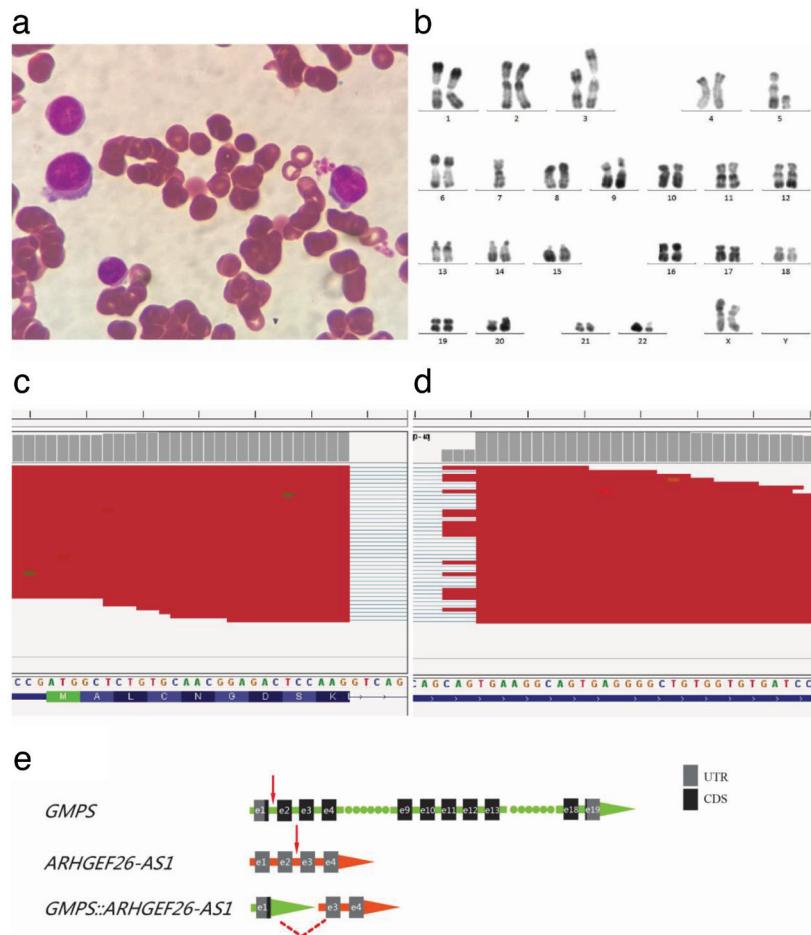


FIG. 1. Cytomorphology, cytogenetics, and molecular biological characteristics of the present case. (a) Bone marrow smear ($1000\times$, Wright staining). Blasts account for 91% of observed cells. These cells exhibit larger cell bodies with predominantly round nuclei and cytoplasm. The chromatin appears finely dispersed, while some nucleoli are prominently large and distinct. Cytoplasmic volume ranges from scant to minimal, with occasional variably sized granules present. Notably, the coarse granules are mostly spherical, occasionally showing fusion resembling atypical Auer rods. (b) G-banded karyotyping. The result is: 45, XX, der(3), der(5) t(3; 5)(q26; q11), -7, t(9; 22)(q34; q11.2). (c) and (d) are junction-reads of GMPS::ARHGEF26-AS1 fusion detected by STAR-Fusion software. IGV (Integrative Genomics Viewer) screenshots are exhibited. The sequence of GMPS moiety is in (c) and ARHGEF26-AS1 in (d), respectively. (e) Schematic of the GMPS::ARHGEF26-AS1 fusion. The exon 1 of GMPS(NM_003875.3) fuses with the exon 2 of ARHGEF26-AS1(NR_037901.1). Red arrows indicate breakpoint sites. The green dotted lines represent that the display of partial sequences is omitted.

UTR, untranslated region; CDS, coding sequence.

The role of *GMPS* in leukemia has not been well explored. Pegram et al.⁴ reported the first leukemia-related fusion gene involving *GMPS*, namely *MLL*::*GMPS*. The patient described was a boy with a history of neuroblastoma who developed therapy-related AML (FAB M4 subtype) at the age of 13 after undergoing multiple rounds of chemotherapy and radiotherapy. The study identified two distinct fusion patterns for *MLL*::*GMPS*: exon 7 or exon 8 of *MLL* fused with *GMPS* at position 150 of the full-length 2212-bp cDNA (accession: NM_003875). Additionally, experimental results showed that *GMPS* mRNA and protein levels were significantly higher in leukemia cell lines (such as HL60 and U937) and transformed lymphoblastoid cells compared to non-transformed quiescent cells.⁵

The *ARHGEF26-AS1* (*ARHGEF26* antisense RNA 1) gene is located on chromosome 3q25.2. *ARHGEF26-AS1* functions as an antisense RNA of *ARHGEF26*. The *ARHGEF26* gene is a member of the Rho guanine nucleotide exchange factor (Rho) family, and its role is to regulate the activity of Rho GTPases. When bound to GDP, Rho GTPase remains inactive. *ARHGEF26* facilitates the release of GDP from Rho GTPase and promotes GTP binding, thereby activating the Rho GTPase. *ARHGEF26* is involved in modulating cell membrane deformation and other regulatory functions.⁶

Current studies on *ARHGEF26-AS1* in cancer mainly focuses on solid tumors. This lncRNA has been shown to be an independent predictor of overall survival in patients with colorectal cancer and

has demonstrated significant correlations with clinical prognosis in intrahepatic cholangiocarcinoma and colorectal cancer.^{7,8} Furthermore, a prognostic model proposed by Maimaiti et al.,⁹ which included *ARHGEF26-AS1* along with eight other autophagy-related lncRNAs, indicated promise for improving the diagnosis and treatment of low-grade glioma.

This is the first report describing the *GMPS:ARHGEF26-AS1* fusion gene. Notably, both partner genes are related to GTP-related biological functions. As a result, this fusion could disrupt key survival pathways in cells and may contribute to treatment resistance. In addition, the *GMPS:ARHGEF26-AS1* fusion preserves only the first exon of *GMPS* and incorporates the *ARHGEF26-AS1* antisense RNA, suggesting its likely role as a non-coding RNA. In recent years, the role of non-coding genes in forming fusion genes has drawn increasing attention, and this fusion represents a new example. Informed consent was obtained from the patient.¹⁰

Informed Consent: Informed consent was obtained from the patient.

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Supplementary: <https://www.balkanmedicaljournal.org/img/files/balkan-2025.2025-4-64-supplementary.pdf>

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