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CASE REPORT

A Case of Acute Myeloid Leukemia with Myelodysplasia-Related Changes, *SET-NUP214* Fusion, and Complex Karyotype

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SUMMARY

Background: **The *SET-NUP214* fusion formed by cryptic t(9;9)(q34;q34) or del(9)(q34.11q34.13) is a rare gene rearrangement. This rearrangement has been reported mostly in T-cell acute lymphoblastic leukemia, but only rarely in acute myeloid leukemia (AML). The acute leukemia cases with the *SET-NUP214* fusion gene show typical immunophenotype, karyotype, and poor treatment response. However, the cytogenetic or genetic changes in AML with *SET-NUP214* fusion are not well understood.**
Methods: **The diagnosis was made based on a combination of the morphology, immunophenotyping, multiplex reverse transcriptase-polymerase chain reaction, FISH, karyotype, Sanger sequencing, next-generation sequencing, and microarray analysis.**
Results: **The author reports a rare case of AML with myelodysplasia-related changes, *SET-NUP214* fusion gene, and complex karyotype that was resistant to induction chemotherapy, making diagnosis and treatment difficult.**
Conclusions: **Further studies, including cytogenetic and molecular analyses, are needed to determine the pathophysiology and clinical significance for this rare gene rearrangement.**
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KEYWORDS

acute myeloid leukemia with myelodysplasia-related changes, *SET-NUP214* fusion, complex karyotype

CASE PRESENTATION

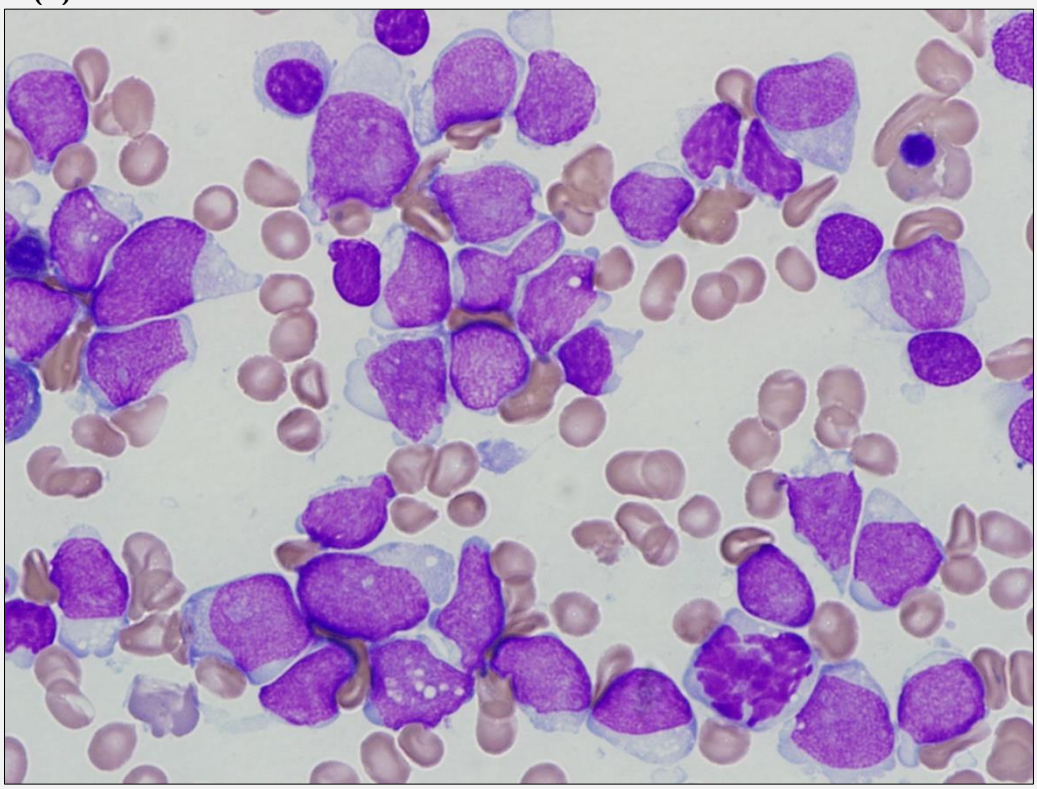
A 16-year-old man with dyspnea, general weakness, and fever was referred to the emergency department. The laboratory results showed a leukocyte count of 2.57 x 10^9/L, hemoglobin of 54 g/L, and platelet count of 143 x 10^9/L. Peripheral blood smears showed 52% blasts. Bone marrow (BM) aspirate smear showed 76.8% blasts with medium size, round or slightly indented nuclei, one or two nucleoli, and agranular cytoplasm (Figure 1A). BM biopsy also showed hypercellular marrow with blasts. The blasts were positive for CD13, CD33, CD117, CD34, HLA-DR, and CD7 in immunophenotyping analysis. However, these cells did not express cytoplasmic myeloperoxidase (cMPO), cCD3, CD5, CD10, CD19, CD20, CD22, cCD22, or cCD79a,

Table 1. Clinical and genetic characteristics of AML with *SET-NUP214* fusion gene from the literature.

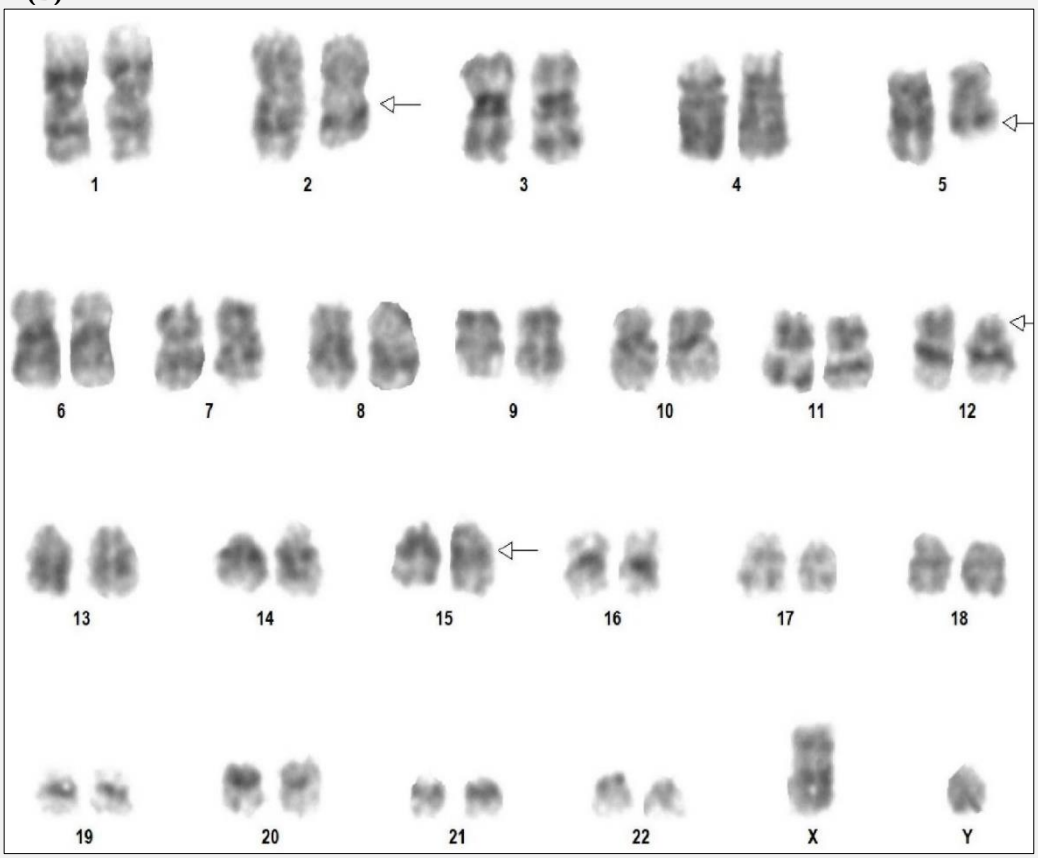
No. case	Year	Gender/ age	Diagnosis	Immunophenotype (positive results)	BCR-ABL1 FISH	Karyotype	SET-NUP214 fusion transcript	Array CGH/ microarray	Follow-up	Reference
1	2007	M/35 y	AML-M4	MPO,CD13,CD33, CD11b,CD15,CD34	del(9)(q34)/ABL1	46,XY	5' SET exon7-NUP214 exon18 3'	del(9) (q34.11q34.13)	Allogenic PBSCT	Rosati et al. [4]
2	2019	M/46 y	AML-M1	MPO,CD33,CD7, CD71,CD34,	del(9)(q34)/ABL1	59-90,XXXY, -1, -2, -5, -7, -7, -10, -13, -13, -16, -17, -18, -21 [cp23]	5' SET exon8-NUP214 exon18 3'	NT	Allogenic PBSCT	Jeong et al. [6]
3	2022	M/16 y	AML-M0 (FAB)/ AML-MRC (WHO)	CD13,CD33, CD117,CD7,CD38, HLA-DR,CD34	del(9)(q34)/ABL1	46,XY,add(2) (q21),del(5) (q22q35),del (12)(p11.2p13), der(15)ins (15;?) (q15;?)[14]/46, XY[6]	5' SET exon8-NUP214 exon18 3'	del(9) (q34.11q34.13)	CR	Present case

Abbreviations: FISH - fluorescence in situ hybridization, CGH - comparative genetic hybridization, M - male, AML-M1 - acute myeloid leukemia with maturation, AML-M4 - acute myelomonocytic leukemia, del - deletion, NT - not tested, PBSCT - peripheral blood stem cell transplantation, CR - complete remission, FAB - French-American-British.

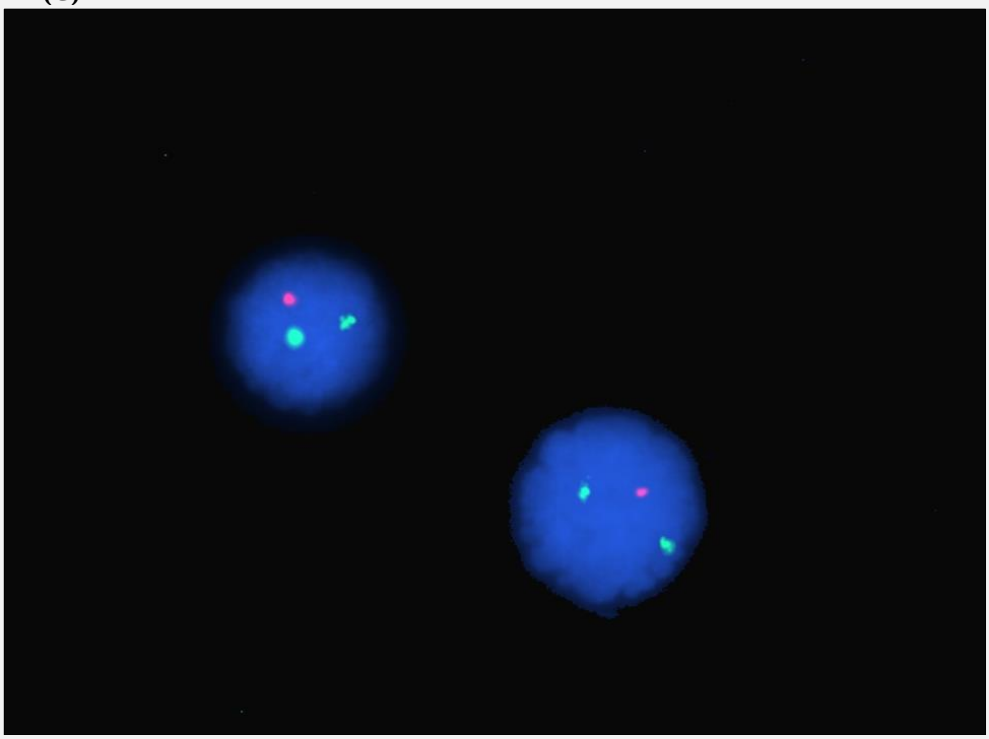
(A)



(B)



(C)



(D)

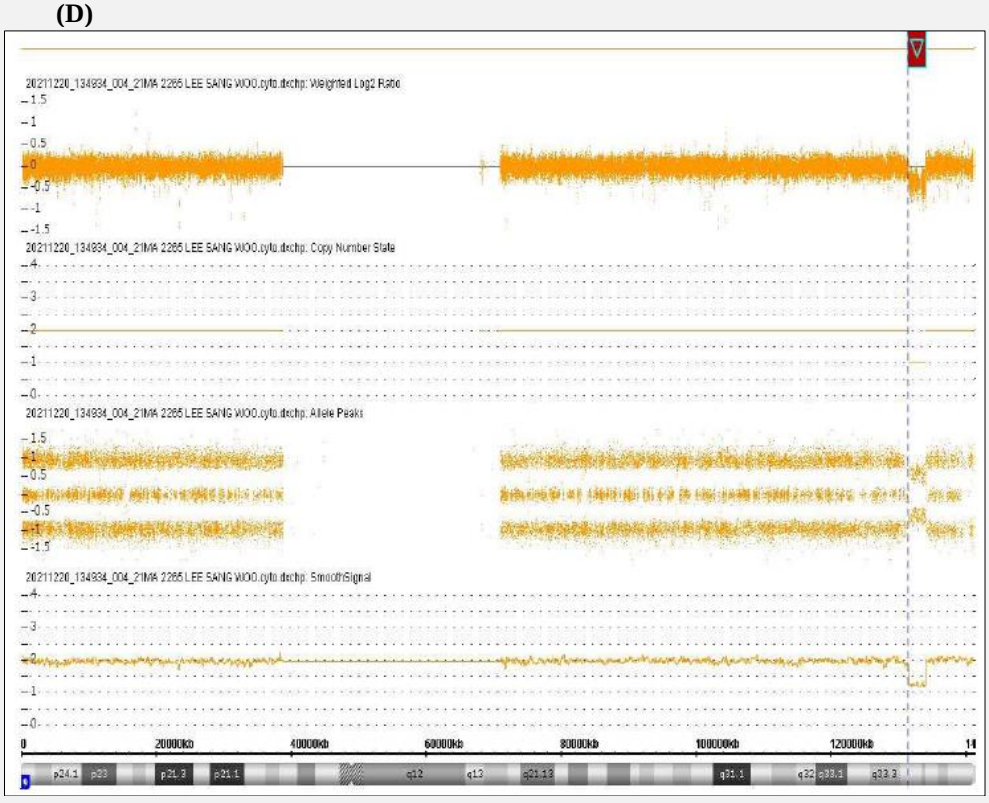


Figure 1. Morphologic, cytogenetic, and molecular findings.

(A) Bone marrow aspirate smear showing blasts (Wright stain, x 1,000). (B) Karyotype demonstrating 46,XY,add(2)(q21),del(5)(q22q35),del(12)(p11.2p13),der(15)ins(15;?)(q15;?)[14]/46,XY [6]. (C) FISH using a *BCR/ABL1* probe revealed one red (*ABL1*) and two green (*BCR*) signals, indicating 9q34 deletion. (D) Microarray analysis showing a 2.6 Mb deletion from 9q34.11 to 9q34.13.

suggesting AML-M0 according to the French-American-British (FAB) classification. Multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) with HemaVision (DNA Diagnostic A/S, Risskov, Denmark) revealed a 381 base pair *SET-NUP214* fusion transcript. The karyotype was 46,XY,add(2)(q21),del(5)(q22q35), del(12)(p11.2p13),der(15)ins(15;?)(q15;?)[14]/46,XY [6], indicating AML with myelodysplasia-related changes (AML-MRC) (Figure 1B). The molecular tests, such as *NPM1*, *CEBPA*, *FLT3-ITD*/*TKD*, and *Kit* mutations, conducted by Sanger sequencing were negative. Next-generation sequencing (NGS) using Oncomine Myeloid Research Assay (Thermo Fisher Scientific Inc, Frederick, MD, USA) revealed no genetic abnormalities. Since *SET-NUP214* rearrangement can occur in either del(9)(q34.11q34.13) or t(9;9)(q34;q34)[5], further studies were performed to differentiate them. Because *ABL1* (9q34.12) is located between *SET* (9q34.11) and *NUP214* (9q34.13), FISH with a *BCR*/*ABL1* probe showed *ABL1* loss in 90.9% (370/407) (Figure 1C). Microarray analysis confirmed that the *SET-NUP214* fusion was generated by del(9)(q34.11 q34.13) (Figure 1D), showing a 2.6 Mb deletion from 9q34.11 to 9q 34.13 with additional copy number variations: a 605 kb deletion at 2q37, a 7.9 Mb deletion from 2q37.1 to 2q 37.3, a 24.6 Mb duplication from 4p16.3 to 4p15.2, a 79.8 Mb deletion from 5q21.1 to 5q35.3, an 11.8 Mb deletion from 12p13.2 to 12p12.1, a 4.3 Mb deletion from 15q15.1 to 15q15.3, a 3.7 Mb deletion from 15q 22.2 to 15q22.31 and a 4.6 Mb deletion from 15q24.1 to 15q25.1.

According to the WHO classification, the patient was finally diagnosed with AML-MRC with *SET-NUP214* fusion. The patient was given induction chemotherapy with cytosine arabinoside and daunorubicin, but he only recovered slowly and had a persistent fever. Follow-up BM aspirate smear a month later showed 55.2% blasts, and karyotype showed persistent abnormal findings: 46, XY,add(2)(q21),del(5)(q22q35),del(12)(p11.2p13), der(15)ins(15;?)(q15;?),inc[1]/46,XY [1]. An additional NGS for ALL panel was performed to rule out other possibilities and an *FBXW7* mutation was detected. For refractory AML, a new chemotherapy regimen containing decitabine and venetoclax was tried. A month later, a BM aspirate smear showed complete hematologic (1.5% blasts) and cytogenetic remissions (normal karyotype).

DISCUSSION

The *SET-NUP214* fusion gene formed by cryptic t(9;9)(q34;q34) or del(9)(q34.11q34.13) is a rare genetic event in hematologic malignancies [1]. This rearrangement has mostly been reported in T-cell acute lymphoblastic leukemia (T-ALL), but rarely in B-cell ALL, acute undifferentiated leukemia (AUL), or acute myeloid leukemia (AML) [1,2]. According to conventional cytogenetic analysis, most cases with *SET-NUP214* fusion genes have normal karyotypes [2]. The present study reports a rare case of AML with myelodysplasia-related changes (MRC), *SET-NUP214* fusion gene, and complex karyotype. To the best of our knowledge, this is the first case of AML-MRC with *SET-NUP214* fusion gene.

The *SET-NUP214* fusion gene was first reported in an AUL patient as a reciprocal translocation t(9;9)(q34; q34) in 1992 [3], and it was followed in 2007 by an AML with normal karyotype and a cryptic 9q34 deletion [4]. To date, 45 cases of acute leukemia carrying *SET-NUP214*, including the present case, have been reported [1,5-7]. T-ALL was diagnosed in the majority of these patients (39/45, 86.7%), with an incidence of 3.0% - 10.3% [1]. Others accounted for < 15%, including AML (3/45, 6.7%), AUL (2/45, 4.4%), and B-ALL (1/45, 2.2%). Table 1 shows the clinical and genetic characteristics of two previous [4,6] and present cases of AML with *SET-NUP214* fusion genes.

The prominent and typical immunophenotype of blasts carrying *SET-NUP214* fusion gene was immaturity, including expressions of CD34 and CD7 [1]. In addition, myeloid markers such as CD13 and CD33 have been frequently reported in T-ALL with *SET-NUP214*. These findings suggest that leukemic transformation may have occurred at the early stages of cell differentiation [1]. The present case also showed a similar immunophenotype, making it difficult to differentiate from AUL or T-ALL.

According to Lee et al., recent cases of *SET-NUP214* rearrangements in Korea may be due to the active use of multiplex RT-PCR in new patients with acute leukemia [8]. They proposed cryptic gene rearrangements such as the *SET-NUP214* fusion gene require molecular diagnostic methods such as HemaVision. The *SET-NUP214* rearrangements have been reported to be mostly caused by del(9)(q34.11q34.13), but they can also be caused by t(9;9)(q34;q34) [1,2,5]. FISH with the *BCR-ABL1* probe would be helpful and array comparative genetic hybridization or microarray analysis would be required to confirm.

Sanger sequencing and NGS revealed no AML related genetic abnormalities in this case. These findings were similar to the previous AML case, which showed wild-type *FLT3* and *NPM1* [4]. On the other hand, *NOTCH1*, *PHF6*, or *HOXA* gene mutations were frequently found in T-ALL with *SET-NUP214* fusion gene [1]. The NGS for ALL panel did not detect *NOTCH1* or *PHF6*, which were on target gene list, but it detected an *FBXW7* mutation.

Previous studies have found that patients carrying the *SET-NUP214* fusion gene have a poor treatment response or a high rate of resistance to induction chemotherapy [1,9]. As a result of the *SET-NUP214* fusion gene and complex karyotype with myelodysplastic syndrome-related cytogenetic abnormalities, it was predicted that the treatment response would be poor. Following the failure of induction chemotherapy, the clinician requested that the laboratory results and diagnosis were

reviewed. Chemotherapy was changed for refractory AML, and complete remission was finally achieved. In conclusion, the author reports a rare case of AML-MRC with *SET-NUP214* fusion gene and complex karyotype, having difficulties in the diagnostic and treatment process due to its rarity and singularity. Further studies, including active cytogenetic and molecular analyses, are needed to determine the pathophysiology, laboratory characteristics, clinical significance, and treatment strategy for this rare gene rearrangement.

Declaration of Interest:
Author has no potential conflicts of interest to declare.

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