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LETTER TO THE EDITOR

Acute myeloid leukemia with a cryptic *NUP98/PRRX2* rearrangement developing after low-dose methotrexate therapy for rheumatoid arthritis

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Dear Editor,

NUP98 is known to be fused to at least 31 different partner genes in both de novo and therapy-related leukemia [1]. Chromosomal translocations juxtaposing the class II homeobox gene *PRRX2* with *NUP98* loci have been reported in therapy-related acute myeloid leukemia (AML), but their clinical significance is unclear [2, 3]. Here, we report a case of AML harboring a cryptic *NUP98/PRRX2* translocation following low-dose methotrexate (MTX) therapy for rheumatoid arthritis.

A 72-year-old Japanese woman presented with anemia, thrombocytopenia, elevated WBC counts, and the appearance of blasts in the peripheral blood. The patient had been diagnosed with rheumatoid arthritis and was subsequently treated with low-dose MTX. The duration of the MTX therapy was 221 months and the accumulated dose was approximately 5000 mg. Bone marrow examination disclosed 55.6% blasts, most of which were positive for myeloperoxidase and specific esterase; the immunophenotype was $CD13^+$, $CD33^+$, MPO^+, and partially positive for CD4, CD16, CD34, CD64, and HLA-DR. Bilineage dysplastic changes (dysgranulopoiesis and dyserythropoiesis) were observed in the bone marrow specimens. Based on these findings, acute myeloid leukemia with myelodysplasia-related changes was diagnosed. The patient showed *FLT3-ITD*, *RUNX1*, and *WT1* mutations (Table 1). A *FLT3* internal tandem duplication mutation was detected by PCR. Although both G-banding and multicolor fluorescence in situ hybridization (FISH) analyses of the bone marrow cells showed a normal karyotype, a *NUP98* disruption was detected in 95.1% of the cells by break-apart FISH analysis (Fig. 1a–c). FISH analysis using the *NUP98* break-apart probes, the subtelomere probes of chromosome 9, and the centromere probes of chromosome 9 and 11 revealed a hidden reciprocal translocation involving 9q and 11p15 (*NUP98*) (Fig. 1d, e). Reverse transcription-PCR and subsequent sequencing analyses allowed for detection of the *NUP98/PRRX2* fusion transcript with the same breakpoint as the previously reported case (Fig. 1f, g) [2]. Although the patient achieved hematological remission following standard induction and consolidation chemotherapy, her AML relapsed 2 months later. At the time of submission of this report, the patient was alive and receiving gilteritinib following anthracycline chemotherapy.

NUP98/PRRX2-positive hematological malignancies are rare and there have been only two other reported cases (Table 1). Both patients developed therapy-related AML after chemotherapy with topoisomerase II inhibitors or alkylating agents against antecedent malignancies. Our patient had no history of malignancy and chemotherapy. There have been some reports of AML development in rheumatoid arthritis patients treated with MTX, although it remains unclear whether low-dose MTX therapy may serve a role in pathogenesis of AML [4, 5]. In the present case, long-term MTX therapy for rheumatoid arthritis could be causally associated with the development of AML. *NUP98* fusions have been reported to be associated

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Table 1 Summary of published cases of *NUP98/PRRX2*-related neoplasm

Case number	Age/sex	ATCD	Treatment	Diagnosis	Karyotype	FISH (*PRRX2*)	RT-PCR	Molecular mutation	Clinical course
1	65/F	DLBCL	TOPOII, ALK	Therapy-related AML	46,XX,der(9)(q34),der(11)(p15)[8]/46,XX[15]	NA	*NUP98* exon 11-*PRRX2* exon 2	NA	NA
2	45/M	PV	ALK	Therapy-related AML	47,XY,der(5)t(5;11)(q35;q13),add(11)(p15),+mar1[5]/48,idem,+mar2[10]	Positive	NA	NA	NA
3	72/F	RA	Low-dose MTX	AML-MRC	46,XX[20]	NA	*NUP98* exon 11-*PRRX2* exon 2	*FLT3-ITD* (AR:0.8), *RUNX1*_S141L, *WT1*_S364fs	Complete response after intensive chemotherapy but relapse within 2 months

Case 1: Gervais et al. [2]; Case 2: Romana et al. [3]; Case 3: this study

ATCD, antecedent; *DLBCL*, diffuse large B cell lyphoma; *PV*, polycythemia vera; *RA*, rheumatoid arthritis; *TOPOII*, topoisomerase II inhibitor; *ALK*, alkylating agent; *MTX*, methotrexate; *AML-MRC*, acute myeloid leukemia with myelodysplasia-related changes; *NA*, not available; *AR*, allelic ratio

with an unfavorable clinical outcome [1, 6, 7]. However, some *NUP98* chromosomal rearrangements are not detected in the karyotype due to subtelomeric localization of the breakpoints [6, 8, 9]. The present study shows that the *NUP98* and *PRRX2* translocation may also result from a cryptic chromosomal rearrangement and should be considered even in AML cases with an apparently normal karyotype. Although more cases are needed, adverse clinical

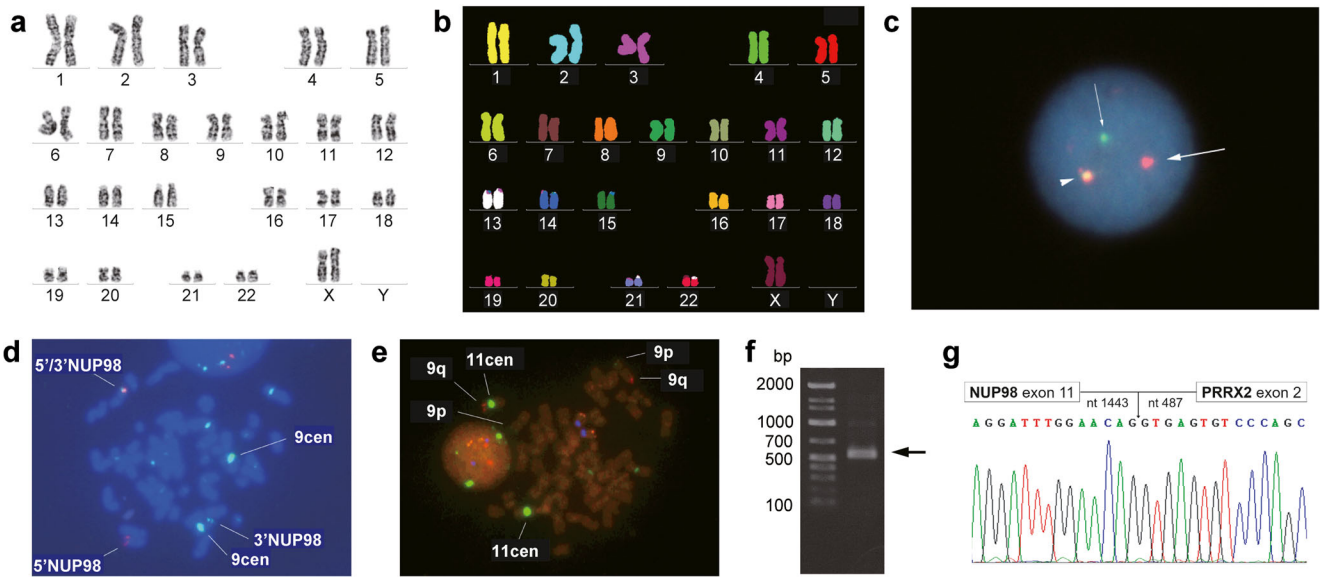

Fig. 1 Identification of *NUP98/PRRX2* fusion transcripts. **a**, **b** G-banding (**a**) and multicolor FISH (**b**) analyses of the bone marrow cells showed a normal 46, XX karyotype. **c** *NUP98* break-apart FISH analysis showed split red (*NUP98* 5′ region) and green (*NUP98* 3′ region) signals in 95.1% of the bone marrow cells. **d** FISH analysis using the *NUP98* break-apart probes and the centromere probe of chromosome 9 (green) revealed split a *NUP98* 3′ region (green) signal on 9q. **e** FISH analysis using the subtelomere probes of chromosome 9 and the centromere probe of chromosome 11 (green) revealed 9q probe (red) signal on 11p. **f** 542-bp *NUP98/PRRX2* fusion transcript product (arrow) was obtained at the expected size from the bone marrow sample by reverse transcription-PCR analysis using *NUP98* sense and *PRRX2* antisense primers. **g** Sequencing analysis confirmed that the band was an in-frame fusion between exon 11 of *NUP98* (including up to nt 1443 of GenBank Accession NM_016320) and exon 2 of *PRRX2* (beginning at nt 487 of GenBank Accession NM_016307).

outcome in this patient might indicate a potentially poor prognostic role of *NUP98/PRRX2* in AML.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient included in the study.

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