First case report of a NUP98-PMX1 rearrangement in de novo acute myeloid leukemia and literature review

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Abstract

Background: The nucleoporin 98 (NUP98)-paired related homeobox 1 (PMX1) fusion gene, which results from t(1;11) (q23;p15), is rare in patients with acute myeloid leukemia (AML). Currently, only two cases of chronic myeloid leukemia in the accelerated phase or blast crisis and three cases of therapy-related AML have been reported. Here, we first report a patient with de novo AML carrying the NUP98-PMX1 fusion gene.

Case presentation: A 49-year-old man diagnosed with AML presented the karyotype 46,XY,t(1;11)(q23;p15)[20] in bone marrow (BM) cells. Fluorescence in situ hybridization analysis using dual-color break-apart probes showed the typical signal pattern. Reverse transcription-polymerase chain reaction (RT-PCR) analysis suggested the presence of the NUP98-PMX1 fusion transcript. The patient received idarubicin and cytarabine as induction chemotherapy. After 3 weeks, the BM aspirate showed complete remission, and the RT-PCR result for the NUP98-PMX1 fusion gene was negative. Subsequently, the patient received three cycles of high-dose Ara-c as consolidation chemotherapy, after which he underwent partially matched (human leukocyte antigen–DP locus mismatch) unrelated allogeneic hematopoietic stem cell transplantation (HSCT). The follow-up period ended on September 30, 2020 (6 months after HSCT), and the patient exhibited no recurrence or transplantation-related complications.

Conclusion: This is the first report of a patient with de novo AML carrying the NUP98-PMX1 fusion gene. The reported case may contribute to a more comprehensive profile of the NUP98-PMX1 rearrangement, but mechanistic studies are warranted to fully understand the role of this fusion gene in leukemia pathogenesis.

Keywords: De novo, Acute myeloid leukemia, Case report, NUP98-PMX1

Background

The nucleoporin 98 (NUP98) gene encodes a 98 kDa protein and is located on chromosome 11p15. NUP98 is part of the nuclear pore complex and regulates the transport of proteins between the cytoplasm and nucleus. Structurally, the N-terminus of NUP98 contains numerous phenylalanine-glycine (FG) and glycine-leucine-phenylalanine-glycine (GLFG) repeats. The first and third functional domains consist of FG and GLFG repeats, respectively. The second domain contains the Gle2-binding sequence, which is the binding site of the RNA export factor RAE1, and the fourth domain is the RNA-binding site [1–3]. Translocations involving the NUP98 gene are rare but play important roles in the initiation and development of hematopoietic malignancies. To date, the NUP98 gene has been implicated in hematopoietic development and found to fuse with more than 30 partner genes and contribute to the onset of leukemia.
These partner genes can be separated into two categories, namely homeobox (HOX) and non-homeobox (non-HOX) genes. HOX genes represent a class of transcription factors that share a conserved DNA-binding motif called homeodomain (HD) and include seven clustered “class I” HOX genes (HOXA9, HOXA11, HOXA13, HOXC11, HOXC13, HOXD11, and HOXD13) and five non-clustered “class II” HOX genes (HHEX, Gsx2, Prrx1, Prrx2, and Pou1f1). Non-HOX genes share a coiled-coil domain and include multiple genes (DDX10, TOP1, and NSD1).

The rearrangement of t(1;11)(q23;p15) involving NUP98 and the class II HOX gene paired related homeobox 1 (PMX1) has been rarely reported thus far. To date, only five cases of NUP98-PMX1 fusion have been reported, involving chronic myeloid leukemia in the accelerated phase, blast crisis, or therapy-related acute myeloid leukemia (AML) (Table 1) [5–8]; no case of de novo AML carrying the NUP98-PMX1 fusion gene has been reported. Furthermore, there is insufficient information regarding the clinical features, appropriate treatment, and outcomes of patients with the NUP98-PMX1 fusion gene.

This is the first report of de novo AML in a patient carrying the NUP98-PMX1 fusion gene. For a comprehensive understanding of this specific translocation, we have further reviewed the relevant literature.

**Case presentation**

On August 12, 2019, a 49-year-old man who presented with fever was referred to the Changhai Hospital (Shanghai, China). The peripheral blood counts of this patient were as follows: white blood cells, $34 \times 10^9/L$ (with 26% blasts); hemoglobin, 74 g/L; and platelets, $92 \times 10^9/L$. The bone marrow (BM) aspirate showed that 22.5% of blast cells were positive for peroxidase staining. Immunophenotypic analysis using multiparameter flow cytometry revealed that the blast cells were myeloperoxidase+, cluster of differentiation (CD)13+, CD33+, CD123+, CD34+, CD117+, CD38+, CD11c+, CD64+, CD14+, CD11b+, human leukocyte antigen (HLA)–antigen D related−, cytoplasmic CD79a+, CD7−, cCD3−, CD19−, CD4−, CD10−, CD15−, CD56−, CD2−, and CD16−. The antibodies against CD7, CD19, CD13, CD10, CD14, CD15, CD123, CD38, and CD13 were purchased from BD Biosciences (San Jose, CA, USA), and other antibodies were purchased from Beckman Coulter (Brea, CA, USA). A total of 1 mL freshly isolated whole BM aspirate was collected, of which 400 µL was stained with monoclonal antibodies for 15 min at room temperature. Following red blood cell lysis, BM cells were washed, collected, and analyzed following the manufacturer’s instructions using a FACS Aria II instrument (BD Biosciences).

The karyotype of the patient was 46,XY,t(1;11) (q23:p15) [20] (Fig. 1). Fluorescence in situ hybridization (FISH) analysis using dual-color break-apart probes was performed with Isis Software (MetaSystems, Germany). Hybridized chromosome slides were analysed using an epifluorescence microscope Axio imager A2 (Carl Zeiss, Germany). The result showed the typical split signal pattern as split 3′-end (green) and 5′-end (red) probe signals along with a single normal unsplit red-green signal pair (yellow). This indicated that NUP98 was disrupted as a result of translocation (Fig. 2). Then we performed

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### Table 1 Summary of six cases of leukemia with NUP98-PMX1 rearrangement

| Case no | Year | Sex | Age (years) | Primary diagnosis | Current diagnosis | Karyotype | Treatment | Outcome | References |
|---------|------|-----|-------------|-------------------|-------------------|-----------|-----------|---------|------------|
| 1       | 1999 | M   | 55          | NHL stage III, gastric cancer | t-AML | 46,XYt(1;11) (q23;p15) | Topo II inhibitor, MACOP-B | Dead | [5] |
| 2       | 2007 | M   | 74          | Liposarcoma | t-MDS/t-AML | 46,XYt(1;11) (q23;p15) (17)/46,XY[t3] | Doxorubicin, ifosfamide, radiation | Dead | [6] |
| 3       | 2004 | M   | 42          | CML-AP | CML-AP | 46,XYt(1;11) (q21;p15),t(9;22) (q34;q11)[30] | Hydrea, Myleran | Dead | [7] |
| 4       | 2004 | F   | 44          | Breast carcinoma | t-AML | 46,XXt(1;11) (q25;p15) (17)/46,XX[t3] | Adriamycin, Cytoxan, S-FU, BMT | Dead | [7] |
| 5       | 2006 | M   | 51          | CML-CP | AML (CML BP) | 46,XYt(1;11) (q23;p15),t(9;22) (q34;q11) | Hydrea, arabinosylcytosine, aclacinomycin, daunorubicin | – | [8] |
| 6       | 2020 | M   | 49          | De novo AML | De novo AML | 46,XYt(1;11) (q23;p15)[20] | Idarubicin, cytarabine, BMT | Alive | Current report |

NHL, non-Hodgkin lymphoma; CML, chronic myelogenous leukemia; AP, accelerated phase; CP, chronic phase; AML, acute myeloid leukemia; t-AML, treatment-related acute myeloid leukemia; MDS, myelodysplastic syndrome; BP, blast phase; MACOP-B, methotrexate with doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; S-FU, 5-fluorouracil; BMT, bone marrow transplant.
reverse transcription-polymerase chain reaction (RT-PCR) analysis of the BM cells. The sequences of primers were referred to the previously reported of Nakamura et al. [5]. RNA was extracted from the BM cells with the Trizol reagent (15596026, Thermo Fisher Scientific, Inc., Waltham, MA, USA). PCR was performed on the Agilent SureCycler 8800 (Agilent Technology Inc., Santa Clara, CA, USA) according to the manufacturer's instructions. Sequence analysis of this product confirmed the NUP98-PMX1 fusion transcript (Fig. 3). The sequence datasets are available in the Additional file 1. Next-generation sequencing analysis revealed FMS-like tyrosine kinase-3 (FLT3)-internal tandem duplication (ITD) and neuroblastoma RAS (NRAS) mutations. The sequence datasets are available in the Additional file 2. Therefore, the patient was diagnosed with de novo AML with the NUP98-PMX1 fusion gene.

The patient received idarubicin and cytarabine (idarubicin, 8 mg/m²/day on days 1–3; cytarabine, 100 mg/m²/day on days 1–7) as induction chemotherapy. After 3 weeks, the BM aspirate showed complete remission. The second RT-PCR result for the NUP98-PMX1 fusion gene was negative, and the second mutation analysis showed that FLT3-ITD and NRAS mutations were cleared. Subsequently, the patient received three cycles of high-dose Ara-c (3 g/m² q12 h on days 1–3) as consolidation chemotherapy. During chemotherapy, BM aspiration was performed before each consolidation therapy, and the NUP98-PMX1 fusion gene was invariably negative. Then, the patient underwent a partially matched (HLA-DP locus mismatch) unrelated allogeneic hematopoietic stem cell transplantation (HSCT) along with myeloablative conditioning with busulfan (3.2 mg/kg/day on days –8 to –6), cyclophosphamide (1.8 g/m²/day on days –5 to –4), and anti-thymoglobulin (8 mg/kg dose divided over 3 days). The patient had received mononuclear and CD34+ cells (6.5 × 10⁸/kg and 2.5 × 10⁸/kg, respectively). The prophylaxis regimen for acute graft versus host disease consisted of cyclosporine A, mycophenolate mofetil,
and short-term methotrexate. Engraftment was confirmed on day 14 after HSCT by the peripheral absolute neutrophil count of more than $0.5 \times 10^9/L$ for 3 consecutive days and platelet count of more than $20 \times 10^9/L$ for 7 consecutive days. The follow-up period ended on September 30, 2020 (6 months after HSCT), and the patient exhibited no recurrence or transplantation-related complications. The study was conducted according to the guidelines of the Declaration of Helsinki, and the patient provided an informed consent.

**Discussion and conclusion**

*NUP98* gene fusions interfere with the expression of downstream transcription genes and participate in cell proliferation, differentiation, and nucleocytoplasmic exports, thereby promoting myeloid leukemogenesis. Moreover, *NUP98* gene fusions co-occur with a set of additional mutations, including *FLT3*-ITD and other events contributing to increased cell proliferation [9–14]. Although translocations with *NUP98* involvement are rare, they are recurrent in different types of leukemia. Generally, the frequency of *NUP98* gene fusion has been reported to be less than 5% in adult AML [13, 15, 16]. The presence of *NUP98* gene fusions defines a high-risk leukemia subset and has been shown to result in remarkably high induction failure and poor survival [9, 10, 13–21]. Notably, patients with AML harboring *NUP98* gene fusions with concomitant *FLT3*-ITD have a worse prognosis than those without genetic aberrations, and the poor outcomes are determined by the interaction between *NUP98* gene fusions and *FLT3*-ITD [10, 12, 22]. Thanasopoulou et al. [23] found that co-expression of *FLT3*-ITD increased cell proliferation and maintained self-renewal ability in a *NUP98* gene fusion-positive mouse model.

Although *NUP98* has a series of functionally diverse partner genes, the most observed *NUP98* fusion partners belong to the *HOX* gene family. The *NUP98-HOXA9* gene, resulting from t(7;11)(p15;p15), is the most common fusion gene. Patients with AML harboring the *NUP98-HOXA9* rearrangement were found to have poorer overall survival (OS) and relapse-free survival (RFS) than those not harboring this rearrangement, even when patients with low-risk karyotypes were excluded (median OS: 13.5 months vs. 20 months, $P=0.045$; median RFS: 6 months vs. 12 months, $P=0.003$) [13, 16].

*PMX1* is a member of the class II *HOX* gene family located at 1q23. The function of *PMX1* in the hematopoietic system and leukemogenesis remains unknown. Moreover, the formation of the *NUP98-PMX1* fusion gene caused by t(1;11)(q23;p15) is rarely reported, and its clinical features and outcomes remain to be clarified. To date, only five cases with *NUP98-PMX1* have been reported (Table 1). *NUP98-PMX1* juxtaposition was confirmed in this patient using RT-PCR and FISH. As shown in Table 1, five of the six patients (including the patient described here) were male. The median age of patients at diagnosis was 50 years (range 42–74 years). Thus, it seems the t(1;11)(q23;p15) occurs at a higher frequency in older male patients, though more cases are needed to solidify this relationship.

The mechanisms of the *NUP98-PMX1* fusion protein underlying leukemogenesis remain unclear. Studies have reported that *NUP98-PMX1* but not *PMX1* has the ability to impair differentiation and promote proliferation of hematopoietic progenitor cells in vitro [24]. Mice transplanted with *NUP98-PMX1*-transduced BM cells has a potent effect on induction of myeloproliferative disease [24, 25]. Moreover, the fusion protein might act as an oncogenic transcription factor. It has been shown that the in-frame fusion of PMX1 HD and the N-terminal GLFG repeat of NUP98 results in strong transcriptional activation and PMX1 HD upregulation [5]. Constitutive expression and alteration of the transcriptional activity of PMX1 HD may substantially contribute to myeloid leukemogenesis. This evidence further supports the involvement of *NUP98-PMX1* in the occurrence and development of myeloid leukemia.
Since *NUP98* gene fusions are now recognized as markers of a high-risk leukemia subset, current treatment paradigms often utilize chemotherapy followed by HSCT during the first complete molecular remission. Our patient with *NUP98-PMX1* and concomitant *FLT3-ITD* achieved molecular remission after induction chemotherapy. Subsequently, he underwent HSCT and was disease-free at the time of the last visit. However, the excellent prognosis of our patient may be due to the relatively short follow-up period.

Since reports of patients carrying the *NUP98-PMX1* fusion gene are limited, it is difficult to deduce any conclusions involving the prognostic significance of this gene. This is the first report of a patient with de novo AML carrying the *NUP98-PMX1* fusion gene, which may contribute to a more comprehensive profile of this genetic rearrangement. In the future, mechanistic studies are needed to investigate the role of the *NUP98-PMX1* fusion gene in leukemia pathogenesis.

### Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-021-00979-y.

#### Additional file 1

Nucleotide sequences of *NUP98-PMX1* fusions by Sanger sequencing.

#### Additional file 2

The patient’s genome sequencing datasets.

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### Authors’ contributions

WF, AH and YL collected, verified and interpreted patient information, WF and AH drafted the manuscript, HC, GT and JW performed karyogram and gene detection, and analyzed the data. YL, LG, JW, JY and XN diagnosed and treated the patient. LG and JY reviewed and revised the manuscript. XN designed the research, interpreted the data, and critically reviewed and revised the manuscript. All authors read and approved the final manuscript. The authors thank Editage (www.editage.cn) for English language editing.

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### Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files. The details of the variant analysed during the current study are available in the SRA database, under the accession number PRJNA728242.

### Declarations

#### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Changhui Hospital and was conducted in accordance with the guidelines of the Declaration of Helsinki.

#### Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

#### Competing interests

The authors declare that they have no competing interests.

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