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**Genetic changes in refractory relapsed acute myeloid leukemia with *NPM1* mutation: A case report**

Wang SL.Genetic changes in R/R AML

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**Abstract**

BACKGROUND

Acute myeloid leukemia is often associated with gene mutation or chromosome abnormality, which is an important factor affecting prognosis. The 5-year survival rate of patients with acute myeloid leukemia without hematopoietic stem cell transplantation is low. For patients who only received chemotherapy and whose first remission lasted > 5 years, there are few reports of gene spectrum changes between relapse and initial diagnosis.

CASE SUMMARY

We report a 41-year-old woman who presented to our hospital with complaints of dizziness, poor appetite and wasting. She was diagnosed with acute myelomonocytic leukemia (M4b) with *NPM1* mutation and only received chemotherapy. Her first remission lasted > 5 years. New genetic variants were detected upon relapse that may have been related to relapse and chemotherapy resistance.

CONCLUSION

Mutations in *WT1 (R394fs/A387fs)/PTPN11 T73I/ETV6 S350P* and *JAK2 W659R* may be related to relapse and chemotherapy resistance in acute myeloid leukemia.

**Key Words:** Acute myeloid leukemia; *NPM1* mutation; Genetic variants; *WT1*; Case report

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**Core Tip:** We report apatient with relapsed refractory acute myelomonocytic leukemia. Compared with the gene spectrum at initial diagnosis, new genetic variants were detected. We speculate that mutations in *WT1 (R394fs/A387fs)/PTPN11 T73I/ETV6 S350P* and *JAK2 W659R* may be related to relapse and chemotherapy resistance.

**INTRODUCTION**

Chemotherapy is the main treatment for acute myeloid leukemia (AML) patients who cannot undergo hematopoietic stem cell transplantation, but 5-year overall survival is < 40%[1,2]. It is known that some genetic variation or cytogenetic abnormalities are important factors affecting the prognosis of AML[3,4]. Here, we report a case of acute monocytic leukemia with normal karyotype and *NPM1* mutation. The patient had complete remission with chemotherapy but relapsed 5 years later. New genetic variants and chromosomal abnormalities were detected when she relapsed. We found new gene mutations that may be related to chemoresistance of AML.

**CASE PRESENTATION**

***Chief complaints***

A 41-year-old woman presented to our hospital in July 2016 to address a 2-mo history of dizziness, poor appetite and wasting.

***History of present illness***

At admission, the patient was actively suffering from dizziness, headache, poor appetite, gum pain and unintentional weight loss (approximately 10 kg in the 2 mo prior).

***History of past illness***

In 2011, the patient had undergone hysterectomy for cervical cancer. Since it was early-stage cancer, no chemotherapy or radiotherapy was performed after the operation.

***Personal and family history***

The patient’s personal and family histories were unremarkable.

***Physical examination***

The patient had moderate anemia and slightly swollen gums. There was no sternal tenderness or superficial lymphadenopathy. Her liver and spleen were not palpable under the ribs.

***Laboratory examinations***

On July 16, 2019, bone marrow showed that the proportion of naive monocytes was 53%, and the proportion of promyelocytes was 18% (Figure 1A). A routine blood test indicated a white blood cell count of 19.4 × 109/L (normal range: 4-10 × 109/L), hemoglobin level of 87 g/L (normal range: 110-150 g/L) and platelet count of 113 × 109/L (normal range: 100-300 × 109/L).

***Imaging examinations***

Imaging examination showed no obvious abnormality.

***Further diagnostic work-up***

Karyotype analysis showed 46, XX [14]. The following 11 common genes showed mutations: *NPM1* exon 12; *DNMT3A* exon 2 c.27C>T, p.P9P; *TET2* exon 3 c.652G>A, p.V218M, c.3117G>A, p.S1039S; *TET2* exon 9 c.4140T>C, p.H1380H; and *ASXL1* exon 12 c.3759T>C, p.S1253S (Table 1).

**FINAL DIAGNOSIS**

Acute myelomonocytic leukemia (M4b) with *NPM1* mutation.

**TREATMENT**

On July 19, 2016, the “idarubicin - cytarabine (IA)” regimen was administered, consisting of idarubicin at 10 mg for days 1-3 plus cytarabine at 0.1 g q12h on days 1-7. On August 3, 2016, bone examination showed complete remission (Figure 1B). On August 25, 2016, the IA regimen was given again. On September 18, 2016, the patient was treated with lumbar puncture and intrathecal injection of cytarabine plus dexamethasone. No abnormality was found in the cerebrospinal fluid examination. However, the patient refused hematopoietic stem cell transplantation for economic reasons. We chose high-dose cytarabine (3.0 g q12h on days 1, 3 and 5 q4w) as consolidation therapy, and four cycles of cytarabine were given starting on September 28, 2016. The minimal residual leukemia cell count was 5.23 × 10-2 after consolidation treatment. Due to minimal residual leukemia, two courses of the “MA” regimen (mitoxantrone 10 mg days 1-3 + cytarabine 75 mg q12h days 1-7 q12w) and the “DA” regimen (daunorubicin 40 mg days 1-3 + cytarabine 75 mg q12h days 1-7 q12w) were given, starting on September 8, 2017. After the last chemotherapy treatment, bone marrow examination showed complete remission (Figure 1C). Routine blood tests were conducted every 3-6 mo.

In August 2021, the patient was re-hospitalized in our department due to recurrent leukemia (Figure 1D). The karyotype analysis of bone marrow cells showed: 46, X, t (X; 3) (p11.2; P13) [6]/46, XX [14]. Molecular pathological gene mutation reports showed mutations of the following genes: *NPM1* exon 11 NM\_002520:c.863\_864insCCAG (p.W288fs); *TET2* exon 3NM\_001127208: c.1588C>T(p.Q530\*); *WT1* exon 7 NM\_024426:c.1180\_1186delins8 (p.R394fs), NM\_024426:c.1157dupC (p.A387fs); *PTPN11* exon 3 NM\_002834:c.218C>T (p.T73I); *ETV6* exon 6 NM\_001987:c.1048T>C (p.S350P); and *JAK2* exon 15 NM\_004972:c.1975T>C (p.W659R)(Table 2)*.*

IA chemotherapy was given on September 27, 2021. On November 1, 2021, we observed 8% naive cells in the peripheral blood. A regimen of azacytidine at 100 mg on days 1-7 and venetoclax at 400 mg on days 1-28 was given on November 5, 2021. The minimal residual leukemia cell count was 5.9 × 10-3 after the first cycle of treatment and 8.6 × 10-3 after four cycles of treatment (Figure 1E). After seven cycles of treatment, naive cells reappeared in the peripheral blood.

**OUTCOME AND FOLLOW-UP**

The patient was subsequently treated with the “HA” regimen (cytarabine 0.15 g q12h days 1-7 + homoharringtonine 3.5 mg days 1-7) and the “CV” regimen (cytarabine 15 mg q12h days 1-10 + venetoclax 400 mg days 1-28) on June 10, 2022. Unfortunately, remission was not achieved (Figure 1F). At the last follow-up, the patient had pancytopenia, and the proportion of naive cells was 70%. Blood transfusion was administered.

**DISCUSSION**

AML is a highly heterogeneous hematological tumor, often accompanied by gene mutations and chromosomal abnormalities. According to the European LeukemiaNet, AML can be divided into low, medium and high risk[5,6]. It is known that AML with normal karyotype and *NPM1* mutation without *FLT3-ITD* mutation has a better prognosis, but our patient also had mutations in *DNMT3A*, *TET2* and *ASXL1*. According to the European LeukemiaNet risk classification (2017), this patient was classified as high risk due to the *ASXL1* mutation.

After induction of remission, bone marrow transplantation was the best treatment, but the patient refused the recommendation. She relapsed 5 years later, and the gene spectrum and chromosome examination were performed again. Compared with the gene spectrum at diagnosis, *WT1* (R394fs/A387fs), *PTPN11* T73I, *ETV6* S350P and *JAK2* W659Rmutations replaced the *ASXL1* and *DNMT3A* mutations. This is the first report of mutations in *WT1* (R394fs/A387fs), *PTPN11* T73I, *ETV6* S350P and *JAK2* W659R in a patient with relapsed refractory AML. Eisfeld *et al*[7] reported that the combination of *NPM1* and *WT1* mutations is an adverse prognostic combination. Krauth *et al*[8]confirmed that *WT1* mutations are independent adverse factors for event-free survival in AML patients.

*TET2* mutation is an early event in the stepwise progression from hematopoietic stem cells to myeloid malignancy, but there is still controversy over the prognostic impact of *TET2* mutation in AML. *TET2* mutation might be correlated with relapse of leukemia[9-11]. *JAK2* mutation has not been observed in the absence of *TET2* mutations[12]. *JAK2* V617F is the most common type of *JAK2* mutation but occurs rarely in ML[13]. Currently, there are no reports of the *JAK2* W659R mutation in AML. Alfayez *et al*[14]concluded that mutations in *PTPN11* had deleterious effects on survival. *ETV6* rearrangements often accompany other molecular mutations[15].

Routine chemotherapy was ineffective for this patient. However, azacytidine and venetoclax treatment achieved morphological remission and progression-free survival for 6 mo. We speculate that mutations in *WT1* (R394fs/A387fs), *PTPN11* T73I, *ETV6* S350P and *JAK2* W659R may be related to relapse and chemotherapy resistance.

**CONCLUSION**

We report a patient with relapsed refractory AML. Compared with the gene spectrum at diagnosis, new mutations were detected. We speculate that mutations in *WT1* (R394fs/A387fs), *PTPN11* T73I, *ETV6* S350P and *JAK2* W659R may be related to relapse and chemotherapy resistance. Larger studies are warranted to confirm this.

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**Footnotes**

**Informed consent statement:** Before treatment, patients and their families have signed informed consent for treatment.

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**Figure Legends**

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**Figure 1 Morphological observation of bone marrow cells (hematoxylin-eosin staining, magnification × 100).** A: Before chemotherapy; B: After induction therapy; C: After maintenance treatment; D: At first recurrence; E: After one cycle of venetoclax and azacytidine therapy; F: After one cycle of cytarabine, homoharringtonine and venetoclax therapy.

**Table 1 Gene testing before chemotherapy**

|  |  |
| --- | --- |
| **Gene** | **Variation content** |
| *NPM1* | Exon 12 |
| *ASXL1* | Exon 12 c.3759T>C; p.S1253S |
| *DNMT3A* | Exon 2 c.27C>T; p.P9P |
| *TET2* | Exon 9 c.4140T>C; p.H1380H |
| Exon 3 c.652G>A; p.V218M c.3117G>A; p.S1039S |
| *FLT3-ITD* | No gene mutation was detected |

**Table 2 Gene testing after the first recurrence**

|  |  |  |
| --- | --- | --- |
| **Gene** | **Variation content** | **Variation ratio** |
| *NPM1* | Exon 11 NM\_002520:c.863\_864insCCAG (p.W288fs) | 11.8% (1276X) |
| *TET2* | Exon 3 NM\_001127208:c.1588C>T (p.Q530\*) | 6.6% (2572X) |
| *PTPN11* | Exon 3 NM\_002834:c.218C>T (p.T73I) | 16.2% (2056X) |
| *ETV6* | Exon 6 NM\_001987:c.1048T>C (p.S350P) | 6.9% (1822X) |
| *JAK2* | Exon 15 NM\_004972:c.1975T>C (p.W659R) | 40.2% (1044X) |
| *WT1* | Exon 7 NM\_024426:c.1157dupC (p.A387fs) | 14.0% (1826X) |
| Exon 7 NM\_024426:c.1180\_1186delins8 p.R394fs) | 10.1% (1926X) |



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