LETTERS TO THE EDITOR

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Clinical and Biological Characteristics of 14 NUP98-NSD1+ Adult Acute Myeloid Leukemia Patients

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To the Editor,

The 11p15 chromosome rearrangement could lead to the rearrangement of the nucleoporin 98 gene (NUP98), so as to form a new fusion gene [1]. The NUP98-NSD1 fusion gene occurs as a result of a cryptic t(5;11)(q35.2;p15.4) chromosomal translocation, in which the 12th exon of the N-terminal of the NUP98 gene is connected to the 6th exon of the C-terminal of the NSD1 gene, forming a chimeric protein [2]. The incidence of NUP98-NSD1 in pediatric acute myeloid leukemia (AML) is 3.8% [3]. Patients with NUP98-NSD1 usually occur in AML patients with a normal karyotype [4]. In pediatric and adult AML patients with normal chromosomal karyotypes, the positive rates are 16.1% and 2.3% [5]. Extensive researches on pediatric NUP98-NSD1+ AML patients are conducted, however, there are few studies on NUP98-NSD1+ adult AML patients.

A total of 507 adult patients with newly diagnosed AML were enrolled in department of hematology at the First Affiliated Hospital of Soochow University between January 2014 and March 2019 in this study. Chromosomal karyotype analysis was performed using bone marrow cell direct method and/or short-term culture method. Sequencing was performed using second-generation DNA sequencing technology [6]. Metric data with non-normal distribution was represented by M(Q1, Q3), and counting data was represented by cases.

Among the 507 patients, 14 cases (2.76%) were tested positive for NUP98-NSD1 gene, including 7 males and 7 females with a median age of 33.5 (18-51) years. The median white blood cell count was 43.8 (5.5-193.6) x 10^9/L, and the median bone marrow blast percentage was 72.05 (43-90.5)%. According to the FAB classification, patients were mostly distributed in M1 (4/14), M4 (3/14) and M5 (5/14). Half cases (7/14, 50%) were associated with a normal karyotype. Based on 2017 Europe Leukemia Net risk stratification, 4 patients were attributed to high risk, 5 medium risk, and 5 were included in low risk group. Among 14 patients, 4 patients (28.57%) were accompanied with FLT3-ITD mutation, 3 patients (21.43%) with biallelic mutation of CEBPA, and 2 patients (14.29%) were with KMT2C, WT1, and DNMT3A mutations, respectively.

All 14 patients received IA or DA+AAG regimens for induction chemotherapy, followed by conventional consolidation regimens of chemotherapy. One patient got no response (NR) to multiple...
courses of chemotherapy constantly, 2 patients gained partial response (PR), and 2 patients relapsed after remission. The results showed NUP98-NSD1+ adult AML was a very invasive disease with a poor prognosis. It was difficult to relieve through chemotherapy, and it prone to disease recurrence and progression. All 14 patients underwent hematopoietic stem cell transplantation subsequently, with 9 patients dying in 1-15 months after transplantation (4 dying from GVHD, 3 relapse, and 2 infection), and 5 patients surviving. The median overall survival (OS) was 14 months. Among the 4 FLT3-ITD+/NUP98-NSD1+ patients, 3 died (75% mortality) and 1 survived. Both DNMT3A+/NUP98-NSD1+ patients died (100% mortality).

Therefore, adult NUP98-NSD1+ AML patients usually have a younger onset age, and have higher tumor burdens. These people have poor prognosis, especially those with FLT3-ITD or DNMT3A mutations. Screening for NUP98-NSD1 gene should be routinely performed for initial diagnosis of AML patients to identify this high-risk anomaly early in order to evaluate prognosis.

<table>
<thead>
<tr>
<th>NO.</th>
<th>sex</th>
<th>age</th>
<th>WBC ($\times 10^9$/L)</th>
<th>BM Blasts (%)</th>
<th>FAB type</th>
<th>Karyotype</th>
<th>Mutations</th>
<th>Induction chemotherapy regimen</th>
<th>Chemotherapy effect</th>
<th>HSCT subtype</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>19</td>
<td>62.14</td>
<td>80.0</td>
<td>M5</td>
<td>+6</td>
<td>FLT3-ITD SETBP1</td>
<td>IA relapse</td>
<td>unrelated</td>
<td>death</td>
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<tr>
<td>2</td>
<td>M</td>
<td>18</td>
<td>159</td>
<td>48.0</td>
<td>M4</td>
<td>+8</td>
<td>C4F1R WT1 NOTCH1</td>
<td>IA PR</td>
<td>Haplo</td>
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<tr>
<td>3</td>
<td>F</td>
<td>50</td>
<td>11.9</td>
<td>67.5</td>
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<td>11p15 abnormal</td>
<td>FLT3-ITD NRAS RUNX1</td>
<td>DAC+AAG NR</td>
<td>sibling</td>
<td>death</td>
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<td>4</td>
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<td>39</td>
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<td>58.0</td>
<td>M2</td>
<td>Normal</td>
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<td>IA relapse</td>
<td>Haplo</td>
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<tr>
<td>5</td>
<td>F</td>
<td>37</td>
<td>9.0</td>
<td>43</td>
<td>M4</td>
<td>inv(16)</td>
<td>FLT3-TKD KIT</td>
<td>IA CR1</td>
<td>unrelated</td>
<td>survive</td>
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<tr>
<td>6</td>
<td>M</td>
<td>24</td>
<td>16.92</td>
<td>74.9</td>
<td>M1</td>
<td>complex</td>
<td>ETV1 KMT2C</td>
<td>IA CR1</td>
<td>Haplo</td>
<td>death</td>
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<td>7</td>
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<td>Haplo</td>
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<td>DNMT3A</td>
<td>IA PR</td>
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<td>death</td>
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<td>-</td>
<td>IA CR1</td>
<td>sibling</td>
<td>survive</td>
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<td>KRAS</td>
<td>IA CR1</td>
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<td>DNMT3A</td>
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<td>CR1</td>
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<tr>
<td>13</td>
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<td>123</td>
<td>M2</td>
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<td>biCEBPA CSF3R</td>
<td>IA</td>
<td>CR1</td>
<td>UCBT death</td>
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<tr>
<td>14</td>
<td>M</td>
<td>34</td>
<td>193.6</td>
<td>M1</td>
<td>Normal</td>
<td>NPM1</td>
<td>IA</td>
<td>CR1</td>
<td>sibling death</td>
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</tbody>
</table>

WBC: White blood cell; BM: Bone marrow; DAC: Decitabine; Haplo: Haplo stem cell transplantation; Sibling: Sibling stem cell transplantation; UCBT: umbilical cord blood transplantation.

**Keywords:** AML, adult, NUP98-NSD1, characteristics

**Ethics**
The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the First Affiliated Hospital of Soochow University (NO.nct03715621). Written informed consent was obtained from all patients and their families.

**Authorship Contributions**
Surgical and Medical Practices: Yan-jun Sun, Shen-qi Lu;
Concept and Design: Yan-jun Sun, Li-rong Li;
Data Collection or Processing: Wei Wang, Shen-qi Lu;
Analysis or Interpretation: Yan-jun Sun, Wei Wang, Shen-qi Lu, Li-rong Li;
Literature Search: Yan-jun Sun, Wei Wang;
Writing: Yan-jun Sun, Wei Wang, Shen-qi Lu, Li-rong Li.

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**Conflict of Interest**
No conflict of interest was declared by the authors.

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**References**