ORIGINAL ARTICLE

Isochromosome 11q is Associated with Unique Characteristics and Poor Prognosis in Patients with Acute Myeloid Leukemia

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SUMMARY

Background: Isochromosome 11q in patients with acute myeloid leukemia is rarely reported, and little is known about its main features.

Methods: The presence of isochromosome 11q was identified in four patients (three adults and one child) from screening 441 patients with an acute myeloid leukemia diagnosis between 2009 and 2018 by using R-banding and fluorescence in situ hybridization.

Results: The child, patient 1 with unreported isochromosome (partial 11q isochromosome), accompanied with t(1;11) translocation, initially achieved remission after receiving chemotherapy. However, 4 months later this patient experienced a relapse. While multiple treatments were tried, it had no effect and the patient survived for 16 months. The remaining patients with isochromosome 11q exhibited numerical/structural chromosomal abnormalities involving myelodysplastic syndrome-related chromosomes 5, 7, 8, and 20. In patients 2 and 3, we found a derivative chromosome 21. Patient 3 was newly diagnosed with acute myeloid leukemia and was treated with many chemotherapy protocols, unfortunately with no effect. The patient then received traditional Chinese medicine and survived for 10 months, although she still has not achieved complete remission. Patients 2 and 4 received chemotherapy but experienced rapid disease progression and died within 2 months.

Conclusions: In summary, patients with isochromosome 11q/partial 11q isochromosome have a poorer prognosis, especially for isochromosome 11q. Furthermore, these chromosome aberrations may be risk factors for the presence of isochromosome 11q or myelodysplastic syndrome-related genes, both of them may be associated with a failure to respond to treatment and poor outcomes. Hence, these discoveries may lay a foundation to study mechanisms and explore treatments.

KEY WORDS

Isochromosome 11q, acute myeloid leukemia, fluorescence in situ hybridization

INTRODUCTION

Patients with acute myeloid leukemia have multiple chromosomal abnormalities that generally involve chromosome 11, particularly the 11q23 region [1-3]. The proto-oncogene MLL, which is located at 11q23, encodes a DNA-binding protein that methylates histone H3 lysine 4 and positively regulates the expression of many genes, including multiple Hox genes [4]. Hence, MLL aberrations are often associated with poor prognosis. Patients with acute myeloid leukemia rarely carry the isochromosome 11q [1,5,6]. The relatively few cases that have been reported to date are often accompanied by structural and/or numerical abnormalities, such as those involving chromosomes 5, 7, 8, and 17 [7]. These patients appear to be refractory to chemotherapy regimens. However, little is known about the mechanisms involved in this resistance to treatment [1,6,8,9].

To better characterize this isochromosome, we analyzed four patients with isochromosome 11q/partial 11q isochromosome and present a detailed picture of their clinical and laboratory features as assessed by morphology, immunology, cytogenetic, and molecular biology, as well as the treatment they received. In addition, we used 21 commercially available probes to perform interphase and metaphase chromosomes by fluorescence in situ hybridization in all four patients. Fluorescence in situ hybridization can help identify the mechanisms involved in forming such karyotypes and provide information on the prognostic impact of gene alterations and chromosomal abnormalities.

MATERIALS AND METHODS

Case selection

The patients were admitted to hospital and bone marrow specimens were collected at the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University from June 2009 to June 2018. We examined 441 patients diagnosed with acute myeloid leukemia (according to French-American-British criteria), and only four cases had 11q abnormalities (4/441). We reviewed the patients’ electronic records, including performance status, treatment regimen, response to induction therapy, and survival. The ethics committee of the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University approved the data collection and sample analysis. All patients provided written informed consent (including parents for patients under 18 years of age), in accordance with the Declaration of Helsinki.

Morphologic and flow cytometric immunophenotyping

Peripheral blood smears and bone marrow aspirate smears were reviewed for all cases. The bone marrow cells were stored in methanol-acetic acid fixative at -20°C until examination. Blast percentage, bone marrow cellularity, and morphology were assessed. Laboratory data were collected, including white blood cell count, hemoglobin level, and platelet count. Cell surface antigens were detected by flow cytometry (BD, FACSCantoTM-II, American), and further analyzed using extended panels designed to characterize acute myeloid leukemia, in accordance with methods described previously [10-12].

Conventional karyotyping

Bone marrow cells were cultivated for 24 - 48 hours without mitogen stimulation, after which they were incubated with 200 ng/mL colchicine (Sigma, Germany) for 1 hour. Next, the bone marrow cells were resuspended in 0.075 M KCl at 37°C for 30 minutes, followed by three washes with Carnoy’s fixative (25% acetic acid in methanol). At least 20 cells in metaphase, as identified by R-banding and Giemsa stain, were examined, and ISCN nomenclature (2009) was used to describe the chromosomal abnormalities.

Fluorescence in situ hybridization

We used 21 commercially available probes to perform interphase and metaphase chromosomes by fluorescence in situ hybridization for all four patients. The details of the 21 probes are listed in the supplementary Table S1. The bone marrow cells were harvested, incubated in 0.075 M KCl, fixed in a 3:1 methanol:glacial acetic acid at 4°C, and dropped onto microscope slides. The slides were aged in 2 x SSC at 37°C for 20 minutes, immediately hydrated in a -20°C precooled ethanol series (70, 90, and 100% ethanol for 2 minutes each) at room temperature, and air-dried. The probe was denatured in a water bath at 78°C for 7 minutes. The slides were hybridized in a humidified chamber overnight at 41°C, then rinsed with 0.1 x SSC at 46°C for 10 minutes, immediately hydrated in a -20°C precooled ethanol series (70, 90, and 100% ethanol) at room temperature, and air-dried. Finally, the slides were stained with 10 μL DAPI-antifade solution and mounted with coverslips. Images were captured using a Nikon 80-A1 fluorescent microscope and analyzed with the image analysis software A1. The chromosomes in 200 interphase cell nuclei were analyzed using probes in accordance with the manufacturers’ recommended protocols.

RESULTS

Patients’ clinical and laboratory findings

Between 2009 and 2018, a total of 441 patients were diagnosed with acute myeloid leukemia in our hospital, but only four patients (one female and three male) were...
Table 1. Clinical, morphological and immunophenotypic data on patients with i(11q)/partial i(11q).

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (Y)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>WBC (x 10^9/L)</th>
<th>Hb (g/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Juvenile cells ratio</th>
<th>Percent blasts</th>
<th>Immuno-phenotype</th>
<th>Treatment</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>1/M</td>
<td>AML</td>
<td>23.4</td>
<td>123</td>
<td>194</td>
<td>0.18</td>
<td>55.5</td>
<td>CD7(+), CD14(+), CD15(+), CD33(+), MPO(+)</td>
<td>DA, IA, VP16+HD-Ara-c</td>
<td>/</td>
</tr>
<tr>
<td>1</td>
<td>b</td>
<td>2/M</td>
<td>AML</td>
<td>5.8</td>
<td>145</td>
<td>107</td>
<td>N</td>
<td>25</td>
<td>CD15(+), CD33(+), MPO(+)</td>
<td>VP16+HD-Ara-c, DA</td>
<td>D/16</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>77/M</td>
<td>AML-M4b</td>
<td>56.6</td>
<td>41</td>
<td>36</td>
<td>0.85</td>
<td>56.8</td>
<td>CD13(+), CD33(+), CD34(+), HLADR(+)</td>
<td>CAG</td>
<td>D/2</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>65/F</td>
<td>AML-M5</td>
<td>2.17</td>
<td>66</td>
<td>29</td>
<td>0.1</td>
<td>38</td>
<td>CD34(+), CD117(+), MPO(+), HLADR(+)</td>
<td>Decitabine+ Mitoxantrone, Chinese medicine</td>
<td>A/10</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>69/M</td>
<td>AML-M5a</td>
<td>35</td>
<td>80</td>
<td>84</td>
<td>N</td>
<td>81</td>
<td>CD13(+), CD15(+), CD33(+), CD34(+)</td>
<td>Ara-c</td>
<td>D/1</td>
</tr>
</tbody>
</table>

Note: * - At first diagnosis of disease, b - At the first relapse.


Table 2. Karyotype.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) 46, XY, t(1;11)(q12;q23)[6]/47, XY, +21, idem[4]/49-50, XY, +6, +16, +16, idem[CP6]/46, XY, N[1]^a</td>
</tr>
<tr>
<td></td>
<td>2) 50, XY, t(1;11)(q12;q23), +6, +6, +16, +16 [10]/46, XY, N[1]^b</td>
</tr>
<tr>
<td>2</td>
<td>48, XY, del(5)(q33), +del(8)(p12), i(11q), +14, der(21) [8]/49, XY, del(5)(q33), +del(8)(p12), i(11q), +14, +18, der(21)[9]/52-54, XY, del(5)(q33), +del(8)(p12), i(11q), +14, +17, +18, +18, der(21)[CP5]</td>
</tr>
<tr>
<td>3</td>
<td>46, XX, +8,i(11q), -17, del(21)(q21)[8]/46, XX, del(2)(q24), +8, i(11q), -17, del(21)(q21)[2]</td>
</tr>
<tr>
<td>4</td>
<td>43-45, XY, -5, +der(12), -17, -19, -20[CP10]</td>
</tr>
</tbody>
</table>

Note: * - At first diagnosis of disease, b - At the first relapse.

Isocromosome 11q in Acute Myeloid Leukemia

enrolled in our study (4/441). The patients’ baseline demographic information and other features are summarized in Table 1. The patient ages ranged from 1 to 77 years old, with a median age of 53 years. Three (75%)
Figure 1. BM morphologic features. All patients exhibit dysplasia and cytoplasmic granules.

A-1 (patient 1): Large blasts and prominent cytoplasmic granules.
A-2 (patient 1) at relapse: Large blasts, small cytoplasmic vacuoles. The cytoplasm is filled with prominent granules, much more so than at the first visit.
B (patient 2): Large blasts, juvenile cells with double nuclei (arrow), and prominent cytoplasmic granules.
C (patient 4): Large blasts with double nuclei (arrow).

were adults and one (25%) was a child (18 months old). Physical examination of the child (patient 1) at first diagnosis revealed hepatosplenomegaly (the liver extended 2 cm below the costal margins). In addition, several palpable submaxillary lymph nodes were found in patient 2, some of which were as large as 15 x 10 mm.

Morphologic and immunophenotypic findings
The median percentage of bone marrow blasts was 57.8% (range: 38% - 81%) (Table 1). Bone marrow aspirates showed active proliferation of leukemic cells, and all of the patients exhibited dysplastic cells c large blasts that contained prominent granules and cytoplasmic vacuoles (Figure 1A-1, B, and C). In patient 1, there was a sharp increase in the number of visible granules at relapse (Figure 1A-2). To discriminate between acute myeloid leukemia and acute promyelocytic leukemia, peroxidase staining was performed for patient 1. The peroxidase staining results were strongly positive at first diagnosis but only weakly positive in blast cells at relapse; however, the number of granules increased sharply at relapse. The other three patients exhibited negative/weakly positive peroxidase staining. Auer rods were visible in patient 3 (Figure S1). The three adult patients expressed typical myeloid-associated markers and early antigens such as CD34. Only the child (patient 1) had myeloid lineage antigen expression, accompanying CD7 and no CD34 expression.

Cytogenetics
The four patients with isochromosome 11q/partial 11q isochromosome, also had other numerical/structural chromosomal abnormalities at the time of diagnosis and relapse (Table 2). The karyotypes exhibited high hypodiploidy (42 - 45 chromosomes) and/or low hyperdiploidy (47 - 50 chromosomes). The patients’ cells contained 43 - 50 chromosomes. Patient 1 exhibited t(1;11) (q12;q23) translocation with 3’ to the partial MLL gene region amplification (including telomere 11q) at diagnosis and relapse (Figure 2A, B, and E). The remaining three adult patients exhibited the isochromosome 11q (3/4) (Figure 3A, 4A, 5A). Patient 2 had a complex karyotype, with chromosome abnormalities including del (5)(q33), del(8)(p12), trisomy 14, and trisomy 8 (Figure 4B).
3A). Patient 3 exhibited del(21)(q21), del(2)(q24), +8, and -17 (Figure 4A, B). Patient 4 exhibited loss of chromosomes 5, 17, 19, and 20, as well as der(7) (Figure 5A).

In summary, 2 of 4 patients with the isochromosome 11q also had chromosome 5 abnormalities, including del(5) and loss of chromosome 5. Patient 2 and patient 3 had trisomy 8. Patient 4 had lost chromosome 20 (1/4). Chromosome 21 abnormalities were observed in 2 patients (2/4), including del(21) and der(21) (q21).

**Inter-phase and metaphase chromosomes by fluorescence in situ hybridization analysis**

Metaphase fluorescence in situ hybridization using MLL (KMT2A) probes revealed two non-overlapping fusion signals located on the long and short arm of chromosome 11, indicating the presence of the isochromosome 11q (Figure 3B, 4C, 5D). To further confirm the presence of isochromosome 11q, we used telomere probes for 11q. *IGH/CCND1* (located at 14q32/11q13) and *ATM* (located at 11q22.3), and found that isochromosome 11q was present in the three adult patients (Figure 3D, 3F, 5C, 5E). Fluorescence in situ hybridization analysis detected MLL rearrangement and amplification in patient 1 at diagnosis and relapse (Figure 2B). However, when probed for *IGH/CCND1* and *ATM*, this patient exhibited the normal signals of two green and two red signals (2G2O), indicating that there was no amplification on 11q.

**Figure. 2. Karyotype and fluorescence in situ hybridization (FISH) analysis (patient 1).**

A: karyotype (R-banding) at relapse: 50, XY, t(1;11)(q12;q23), +6, +16, +16. 1q- (red arrow), 11q+ (blue arrow), +6 x 2 (green arrow). B: FISH analysis with GLP MLL probe (located at 11q23). The picture shows one yellow, five red, and one green signals (1F5O1G). 1F was located on a native chromosome 11, and 1G was located on 11q+ (green arrow). 1O was located on 1q12, and the remaining 4O were located on idic(11q) (red arrow). The green signals indicate chromosome 12p. C: FISH with the telomeric probe Vysis 11q at diagnosis. The signals were located on 11q and 1q12. D: FISH with the telomeric probe Vysis 11q at relapse, showing six signals on idic(11q) (red arrow). In addition, MLL was amplified in the subtelomeric region of chromosome 11. E: FISH with the GLP GLP GLP IGH/CCND1 probe (located at 14q32/11q13) showing two green and two red signals (2G2O), indicating that there was no amplification on 11q.
Figure 3. Karyotype and fluorescence in situ hybridization (FISH) analysis (patient 2). A: Karyotype (R-banding): 48, XY, del(5q)(q33), +del(8)(p12), i(11q), +14, der(21), del(5q)(q33)(dar arrow), der(8)(p12) (red arrow), i(11q) (blue arrow), +14 (green arrow), der(21) (pink arrow). B: FISH analysis with GLP MLL probe (located at 11q23). In metaphase, there was one yellow signal on a native chromosome 11, and the remaining four yellow signals (red arrow) were located on i(11q) x 2. C: FISH analysis with the GLP IGH/CCND1 dual color probe (located at 14q32/11q13). There were three red and three green signals (3O3G). The 3G signal was on chromosome 14 x 3 (green arrow), 2O was on an i(11q) (red arrow), and 1O was on a native chromosome11, indicating that patient 2 had an extra chromosome 14 and an i(11q). D: FISH analysis with the GLP ATM probe (located at 11q22.3). Four red signals (red arrow) were observed on two chromosomes, implying that two i(11q) chromosomes were present. E: FISH analysis with the GLP RUNX1-RUNX1T1 dual color fusion probe (located at 21q22/8q22). In metaphase, three RUNX1T1 signals (red arrow) were observed on chromosomes 8 x 3, and one RUNX1 signal (green arrow) each was observed on a chromosome 21 and a derivative chromosome 21. F: FISH with the telomeric probe Vysis 11q (spectrum red). In metaphase, there were three red signals (red arrow) on two chromosomes, which were confirmed as i(11q) and a chromosome 11.

situ hybridization. In metaphase, this patient exhibited a derivative chromosome 21 (Figure 3E). MYC amplification was found in patient 3. Patient 3 had a mark chromosome combined with chromosome 8 and partial chromosome 21 in metaphase (Figure 4D and 4E), but the inter-phase fluorescence in situ hybridization signals were normal. For patient 4, probing for D7S522/CSP7 (located at 7q31/7p11-q11) showed that 7q was still present but indicated centromere loss, and the other copy of chromosome 7 was normal, showing one green and one red signal (Figure 5B). The CSF1R/D5S23 DS721 probe exhibited one green and one red signal, confirming deletion of chromosome 5 (Figure 5F). Furthermore, probing for GLP P53/1q21 showed that the gene encoding TP53 was deleted in patients 3 and 4. The other inter-phase and metaphase chromosomes by fluorescence in situ hybridization results from all four patients are listed in Table S2.
Figure 4. Karyotype and fluorescence in situ hybridization (FISH) analysis (patient 3).

A: Karyotype (R-banding): 46, XX, del(2)(q24), -17, del(21)(q21). B: FISH with the telomeric probe Vysis 8q showing three signals on chromosomes 8 x 3. C: FISH analysis with the GLP MLL probe (located at 11q23). D: FISH analysis with the GLP 13/21 dual color probe (located at 13q14/21q22). In metaphase, there were two green signals on native chromosome 13 and two red signals on native chromosome 21. E: FISH analysis with the GLP TEL/RUNX1 dual color probe (located at 12p13/21q22) showing two red signals (TEL: red arrow) on 12p x 2. One green signal was located on a chromosome 21, and the other on derivative chromosome 21. Two native chromosomes 13 had two green signals (green arrow).

Follow-up and outcomes

Treatment response and outcome data are shown in Table 1. At the last follow-up, only one patient was alive, whereas the other three patients had died of organ failure and lung infection (Figure 6). The median overall survival was 6 months (range 1 - 16 months). All patients enrolled in our study were treated with chemotherapy at our hospital. The child (patient 1) initially responded to treatment with DA, IA, and VP16, combined with HD-Ara-c, and achieved complete remission. Unfortunately, the patient relapsed after 4 months, exhibiting active bone marrow cell proliferation and blast cell levels of up to 25%. The child stopped responding well to DA and VP16+HD-Ara-c and died of infection 2 months later. During this period, RUNX1-RUNXIT1, PML/RARA, PLZF/RARAa, and NPM/RARAa were not detected. Patients 2 and 4 received Ara-c and CAG, respectively, but did not survive as long as patient 1. Only one female patient (patient 3) was newly diagnosed. She was treated with Decitabine with Mitoxantrone, but no effect. After leaving the hospital, the patient received traditional Chinese medicine for 9 months and regularly visited the hospital, but still has not achieved remission.
Figure 5. Karyotype and fluorescence in situ hybridization (FISH) analysis (case 4).

A: Karyotype (R-banding): 43, XY, -5, der(7), i(11q), +der(12), -17, -19, -20, der(7) (red arrow), i(11q) (green arrow). 1G1O was located on one copy of chromosome 7. Only one red signal and no green signal were located on another copy, indicating deletion of the centromere (red arrow). C: FISH with the telomeric probe Vysis 11q showing three signals on an i(11q) and a chromosome 11. D: FISH analysis with the GLP MLL probe (located at 11q23). In metaphase, there was one yellow signal on chromosome 11, and the remaining two yellow signals (red arrow) were located on an i(11q). E: FISH analysis with the GLP IGH/CCND1 dual color probe (located at 14q32/11q13). There were three red and two green signals (3G2O). In metaphase, the three red signals were located on the same chromosomes, signifying an i(11q) (red arrow) and a native chromosome 11. F: FISH analysis with the GLP CSF1R/D5S721 dual color probe (located at 5q33/5p15). In interphase, only one green signal (green arrow) and one red signal (red arrow) (1G1O) were observed, indicating deletion of chromosome 5.

**DISCUSSION**

Isochromosome 11q is seldom seen in acute myeloid leukemia or in acute lymphoblastic leukemia [13]. In our study, patients with acute myeloid leukemia who had isochromosome 11q exhibited distinctive clinical and laboratory features. Abnormalities of chromosome 5, 7, and 20 that are related to myelodysplastic syndrome were recurrent in the four patients. To the best of our knowledge, one third of patients with myelodysplastic syndrome progress to acute myeloid leukemia [14]. Although myelodysplastic syndrome frequently represents an intermediate stage before transformation to more aggressive disease, it is still unknown how myelodysplastic syndrome progresses [15]. Next-generation sequencing has identified several recurrent genetic mutations that are associated with the dominant leukemic clone during progression from myelodysplastic syndrome to acute myeloid leukemia (e.g., FLT3 (13q12.2), NPM1 (5q35.1), RUNXI (21q22.12), and TP53 (17p13.1) [16]. According to literature, abnormalities of chromosomes 5q, 7, or 20 in the context of acute
myeloid leukemia are closely associated with myelodysplastic syndrome-related genes [17,18]. We therefore presume that the myelodysplastic syndrome-related genes are correlated with the short survival outcome in our study. Importantly, we wish to emphasize the two patients who exhibited derivative chromosome 21, del(21)(q21) and der(21). The derivative chromosome 21 is a recurrent event related to the poor prognosis of isochromosome 11q. According to the literature, karyotype aberrations usually involve the long arm of chromosome 11, particularly region 11q23, where the proto-oncogene MLL is located [1]. At the molecular level, MLL gene amplification in acute myeloid leukemia/myelodysplastic syndrome remains poorly characterized [19]. Therefore, the gene is an important prognostic factor. In agreement with the literature, 4 of 441 patients with acute myeloid leukemia who were screened for this study (0.9%) had isochromosome 1q/partial 11q isochromosome with poor prognosis and short survival, while among them, partial 11q had a longer survival time and were more sensitive to chemotherapy. The child (patient 1) in our study had t(1;11)(q12;q23) translocation accompanied by partial MLL amplification. In addition, metaphase fluorescence in situ hybridization showed that the segment of the MLL gene that is proximal to the telomere was amplified. Telomere amplification is a critical pathogenic factor in leukemia development [20].

Acute myeloid leukemia with MLL gene amplification is associated with a very complex karyotype and a high frequency of TP53 mutations. The TP53 gene plays important roles in maintaining genomic stability and integrity, and mutational inactivation of TP53 has been shown experimentally to result in gene amplification and aneuploidy [19]. Patients with acute myeloid leukemia and TP53 mutations tend to be older, and almost all have karyotypes that are associated with an unfavorable prognosis [21].

CONCLUSION

Isochromosome 11q creates genetic imbalance, which might initiate malignant transformation. Moreover, isochromosome 11q patients respond poorly to therapy, regardless of how intense it is. In addition, a new chromosome abnormality of partial 11q isochromosome was identified and had a longer survival time. Analyzing changes in myelodysplastic syndrome-related genes and chromosome 21 by metaphase fluorescence in situ hybridization may be a crucial characteristic of isochromosome 11q. Identifying isochromosome 11q is important for understanding cancer pathogenesis and can be useful for guiding the selection of individualized cancer therapy.

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Declarations of Interest:
The authors report no conflicts of interest regarding this work.

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