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Additional Genomic Aberrations Identified by Single Nucleotide Polymorphism Array-Based Karyotyping in an Acute Myeloid Leukemia Case with Isolated del(20q) Abnormality

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Prognosis is known to be better in cases with isolated chromosomal abnormalities than in those with complex karyotypes. Accordingly, del(20q) as an isolated abnormality must be distinguished from cases in which it is associated with other chromosomal rearrangements for a better stratification of prognosis. We report a case of an isolated del(20q) abnormality with additional genomic aberrations identified using whole-genome single nucleotide polymorphism array (SNP-A)-based karyotyping. A 39-yr-old man was diagnosed with AML without maturation. Metaphase cytogenetic analysis (MC) revealed del(20)(q11.2) as the isolated abnormality in 100% of metaphase cells analyzed, and FISH analysis using D20S108 confirmed the 20q deletion in 99% of interphase cells. Using FISH, other rearrangements such as BCR/ABL1, RUNX1/RUNX1T1, PML/RARA, CBFB/MYH11, and MLL were found to be negative. SNP-A identified an additional copy neutral loss of heterozygosity (CN-LOH) in the 11q13.1-q25 region. Furthermore, SNP-A allowed for a more precise definition of the breakpoints of the 20q deletion (20q11.22-q13.31). Unexpectedly, the terminal regions showed gain on chromosome 20q. The patient did not achieve complete remission; 8 months later, he died from complications of leukemic cell infiltrations into the central nervous system. This study suggests that a presumably isolated chromosomal abnormality by MC may have additional genomic aberrations, including CN-LOH, which could be associated with a poor prognosis. SNP-A-based karyotyping may be helpful for distinguishing true isolated cases from cases in combination with additional genomic aberrations not detected by MC.

Key Words: Deletion, Chromosome 20, Isolated, AML, Cytogenetics, Single nucleotide polymorphism, Array

INTRODUCTION

Deletion of the long arm of chromosome 20q [del(20q)] is one of the common recurring chromosomal abnormalities associated with myeloid malignancies [1]. When del(20q) is present as an isolated abnormality, it is associated with a good prognosis for MDS as defined by the International Prognostic Scoring System (IPSS) [2]. However, the prognosis of MDS is less favorable with a high rate of transformation to acute leukemia when del(20q) is part of a complex karyotype. Accordingly, del(20q) as an isolated abnormality must be distinguished from cases of other chromosomal rearrangements for better stratification of prognosis. For de novo AML, isolated del(20q) is known to be associated with poor response to treatment and reduced survival [1, 3].

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Recently, single nucleotide polymorphism array (SNP-A)-
based karyotyping has been applied as a high-resolution whole-
genome scanning tool. A major advantage of SNP-A over meta-
phase cytogenetic analysis (MC) is its ability to detect hidden
chromosomal defects, including submicroscopic (cryptic) aber-
rations or copy neutral loss of heterozygosity (CN-LOH). SNP-A
can be used to identify CN-LOH through simultaneous mea-
surement of DNA copy number and information of genotype
calls. CN-LOH cannot be recognized by conventional MC, FISH,
or array comparative genomic hybridization (array CGH) be-
cause it shows long stretches of homozygosity without a concur-
rent change in the gene copy number [4]. Regions of CN-LOH
may contain pathologically relevant genes harboring deleterious
homozygous mutations that may impact clinical outcomes [4,
5]. For example, CN-LOH of 9p is associated with JAK2 homo-
yzgous mutations [4, 5].

Here, we report a case of an isolated del(20q) abnormality
identified using MC, but with the additional genomic aberrations
identified using SNP-A-based karyotyping.

**CASE REPORT**

A 39-yr-old man presented with fever for a month (February
2007). Initial laboratory evaluation showed a white blood cell
(WBC) count of 61×10⁹/L with 96% blasts, a hemoglobin count
of 91 g/L, and a platelet count of 47×10⁹/L. Bone marrow (BM)
analysis revealed that 96% of nucleated cells were replaced by
myeloblasts of variable sizes and some azurophilic granules.
Cytochemical analysis showed that the myeloblasts were posi-
tive for Sudan black B (SBB) but negative for myeloperoxidase
(MPO), naphthol AS-D chloroacetate esterase (SE), and α-
naphthyl butyrate esterase (NSE) stains. Flow cytometric immu-
nophenotyping of BM revealed that leukemic cells were positive
for CD13, CD33, CD56, and HLA-DR and negative for CD34,
CD14, CD19, and CD3. The diagnosis of AML without matura-
tion was made on the basis of WHO classifications of tumors of
hematopoietic and lymphoid tissue 2008 [2].

Conventional cytogenetic analysis using BM aspirates revealed
20 metaphases with 46,XY,del(20)(q11.2) (Fig. 1). FISH analysis
with D20S108 (Abbott Molecular/Vysis, Des Plaines, IL, USA)
probe confirmed a 20q12 deletion in 99% of interphase cells; nuc
ish(D20S108 ×1) [198/200]. Using FISH, other rearrange-
ments such as BCR/ABL1, RUNX1/RUNX1T1, PML/RARA,
CBFB/MYH11, and MLL were found to be negative (data not
shown).

For the SNP-A, DNA was extracted from BM (QIAGEN DNA
purification kit; Qiagen, Hilden, Germany) according to the
manufacturer’s instructions. SNP-A was performed using a
Genome-wide Human SNP 6.0 Array (Affymetrix, Santa Clara,
CA, USA) and analyzed using Genotyping Console Version 4.0
software (hg18) (Affymetrix). In order to detect the somatic ori-
gin copy number alterations distinguished from constitutional
delete CNVs, the lesions identi-
ified using SNP-A were compared with the database of genomic
variants (http://projects.tcag.ca/variation/). When regions of copy
number changes were located within those of CNVs, we did not
consider them as the somatic changes and excluded them from
the final results. To detect somatic CN-LOH, we excluded homo-
yzgous stretches of DNA regions less than 25 Mbp in the inter-
stitial chromosomal regions, except those encompassing telo-
eric regions of the chromosome, according to an algorithm
adopted in a previously published study [4]. The SNP-A identi-

ified CN-LOH of 11q13.1-q25, not detected by MC (Fig. 2); arr
11q13.1q25 (65,966,684-134,375,799) ×2 hzm. Furthermore,
SNP-A allowed for a more precise definition of the breakpoints
of the 20q deletion (20q11.22-q13.31); arr 20q11.22q13.31 (32,
253,686-55,192,062) ×1 (Fig. 2). Unexpectedly, the terminal re-
regions showed a gain on chromosome 20q; arr 20q13.31q13.33
(55,192,062-59,271,669) ×3 (Fig. 2).

The patient received 2 cycles of standard induction chem-
otherapy (daunorubicin 60 mg/m²×3 days and Ara-C 200 mg/m²×7
days), but he did not achieve complete remission. Four
months after the initial diagnosis (June 2007), he presented with
paralysis in both legs. Cerebrospinal fluid analysis revealed 100%
of leukemic cells with a WBC count of 0.38×10⁹/L and RBC
count of 0.01×10⁹/L, indicating central nervous system (CNS)
involvement in the leukemia. He received intrathecal chemo-
therapy with cytarabine (15 mg/m²). One month later (July 2007), BM biopsy showed hypercellular marrow with abnormal localization of immature precursors (ALIP), and MC revealed 100% of metaphase cells with del(20)(q11.2). Three months later (October 2007), he died due to invasive pulmonary aspergillosis and neurologic complications induced by leukemic cell infiltrations of the CNS (Table 1).

**DISCUSSION**

In the present study, we described a case of isolated del(20q) abnormality with additional 11q CN-LOH identified using SNP-A-based karyotyping. Our patient was found to have CNS involvement in the leukemia and was unable to achieve remission. During the follow-up, no additional abnormalities or clonal evolutions were detected by MC. This result suggests that identifying additional CN-LOH using SNP-A may be associated with a poor prognosis.

An isolated del(20q) is generally associated with a better prognosis in MDS, whereas AML patients have a significantly shorter overall survival [1-3]. Cases that have del(20q) with one or more additional chromosomal abnormalities predict a poor prognosis [3]. Therefore, we hypothesized that AML patients with isolated del(20q) may have, in fact, additional chromosomal abnormalities not identified by MC. One study also showed that additional CN-LOH or copy number changes could be identified by SNP-A analysis in patients with del(20q) as the isolated abnormality by MC [6].

As for the prognostic impact of 11q CN-LOH, one study showed that the 11q CN-LOH region was present only in a few fractions of the cells in the MDS phase; however, in the late relapse AML sample, the 11q CN-LOH region was present in more than 90% of leukemic cells. This finding suggests that clones with 11q CN-LOH may have conferred a selective growth advan-

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**Table 1.** Laboratory findings of the patient with del(20q) at diagnosis and during follow-up

| Date     | Bone marrow morphology | Cytogenetics | FISH (20q deletion) | SNP-A                        |
|----------|------------------------|--------------|---------------------|------------------------------|
| Feb. 2007| AML without maturation | 46,XY,del(20)| 99%*                | Loss, 20q11.22-q13.31 (23 Mb); Gain, 20q13.31-q13.33 (4 Mb); CN-LOH, 11q13.1-q25 (68 Mb) |
| Mar. 2007| Normocellular          | 46,XY,del(20)| 40%                 | NT                           |
| Apr. 2007| Hypocellular           | 46,XY [9]    | 9%                  | NT                           |
| May 2007 | Hypocellular           | 46,XY [3]    | 27%                 | NT                           |
| Jul. 2007| Hypercellular          | 46,XY,del(20)| 58%                 | NT                           |

*FISH using BCR/ABL1, AML1/ETO, PML/RARA, CBFB/MYH11, MLL probe; no rearrangement.
Abbreviations: SNP-A, single nucleotide polymorphism array; CN-LOH, copy neutral loss of heterozygosity; ALIP, abnormal localization of immature precursors; NT, not tested.
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Additional aberrations in an AML case with isolated del(20q) was located between bands 20q11.22 and 20q13.31 (23 Mbp), and the distal region was duplicated (20q13.31-q13.33, 4 Mbp). For the commonly deleted region (CDR) of chromosome 20q, a study using SNP-A defined 2 CDRs [6]; CDR1 was located between bands 20q11.23 and 20q12 and CDR2 was within bands 20q13.12. The deleted regions in our case encompassed these 2 CDRs. Similarly to our case, another study demonstrated that the 20q deletion showed an interstitial pattern according to SNP-A in most cases [6]. The rarity of true monosomy 20 suggests that retained or duplicated genes on chromosome 20 are essential for the survival of mutant clones [6]. Taken together, these findings indicate that tumor suppressor genes are located in the deletion region and oncogenes, in the duplicated region of chromosome 20.

In summary, we report a case of an isolated del(20q) abnormality with additional genomic aberrations identified using SNP-A-based karyotyping. This study suggests that a presumably isolated chromosomal abnormality according to MC may have additional genomic aberrations, including CN-LOH. SNP-A-based karyotyping may be helpful for identifying true isolated cases from cases in combination with additional genomic aberrations not detected by MC. Further study is needed to determine whether additional aberrations identified by SNP-A have a negative effect on prognosis in larger cohorts of AML patients.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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