INTRODUCTION

The key updates in the revised 2016 WHO criteria for the recategorization of acute myeloid leukemia (AML) are as follows [1-3].
1) Two new provisional entities, AML with BCR-ABL1 and AML with mutated RUNX1 were added to one of the AML subtypes with recurrent genetic abnormalities (abbreviated as RGA in the following text). 2) AML diagnosis with mutated CEBPA required biallelic mutations instead of a single mutation. 3) The diagnostic precedence of AML with myelodysplasia-related changes (abbreviated as MRC in the following text) over AML with NPM1 or biallelic CEBPA (CEBPA bi) mutations was clarified for patients showing myelodysplasia-associated cytogenetic abnormalities. 4)
del(9p) was removed from the definition of cytogenetic abnormality for MRC. 5) Erythroleukemia, defined as ≥50% bone marrow (BM) erythroid cells and ≥20% myeloblasts among non-erythroid cells, was removed from the AML category.

Since the publication of the revised 2016 WHO criteria, several studies have been undertaken on AML reclassification [4-9]. Half of these studies have investigated erythroleukemia or erythroid-dominant AML, the subtype that underwent critical changes in the revised criteria [4, 6, 7]. The remaining studies have focused on cases harboring a RUNX1 mutation [5] or cases with NPM1 and CEBPA mutations [8, 9]. Unfortunately, there are no real-world data on the systemic comparison of AML categorization based on the two classification systems with a large number of patients. From the viewpoint of hematopathologists, it is important to ensure the best course of treatment for patients with AML by providing the most up-to-date and refined diagnostic information to the treating physician. Considering this, in this study, we categorized AML cases based on the previous and revised WHO criteria and identified discrepant cases in a large patient cohort. We analyzed the frequency, categorization patterns, and features of discrepant cases and characterized the AML subtypes that have undergone major changes under the revised criteria.

**MATERIALS AND METHODS**

1. Patients

The BM archive of our laboratory was searched for newly diagnosed patients with AML from January 2009 to December 2018. We reviewed patient data including karyotype, presence of multilineage dysplasia (MLD), mutational status (NPM1 and CEBPA), as well as a prior history of myelodysplastic syndrome (MDS), myelodysplastic/myeloproliferative neoplasm (MDS/MPN), cytotoxic chemotherapy, or radiotherapy. MLD was defined when dysplasia was present in 50% or more cells in at least two hematopoietic cell lines [1]. Of the 1,195 consecutive patients with AML in our BM archive, 10 were excluded owing to an absence of cytogenetic data, and a total of 1,185 cases were analyzed in the present study. We divided the patients into the following seven categories based on the WHO criteria; RGA, MRC, therapy-related AML (abbreviated as TR in the following text), AML not otherwise specified (abbreviated as NOS in the following text), AML associated with Down syndrome (abbreviated as DS in the following text), AML with subcategory not determined (abbreviated as ND in the following text), and MDS. Patients with TR who had recurrent cytogenetic or genetic abnormalities remained in the TR subcategory [1]. We omitted the detailed characteristics of the patients for each category because we focused on their categorization based on the previous and revised WHO criteria and the recognition of re-categorized cases. This study was approved by the institutional review board of Asan Medical Center (2019-1274) and was performed in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

2. Mutational analyses and cytogenetics

FLT3-internal tandem duplication (ITD) was detected using PCR and fragment analysis as described previously [10]. Until December 2017, NPM1 and CEBPA mutations were detected using bidirectional Sanger sequencing as reported previously [11, 12]. Thereafter, mutations were primarily analyzed using a customized hybridization capture-based next-generation sequencing (NGS) platform that targeted 141 genes including FLT3, NPM1, CEBPA, and RUNX1 that are involved in the pathogenesis of hematologic malignancies. However, we continued to use FLT3-ITD fragment analysis to calculate the FLT3-ITD allelic ratio, which has a prognostic significance in AML with mutated NPM1 [13]. The subtype of AML with mutated RUNX1 was not considered in the present study because of inadequate data regarding RUNX1 mutation. As genetic profiling based on NGS data is beyond the scope of the present study, we omitted these details for the NGS assay. Recurrent fusion genes were detected using the HemaVision multiplex reverse-transcriptase (RT)-PCR kit (Bio-Rad Laboratories, Hercules, CA, USA). Cytogenetic analysis was performed using the conventional G-banding technique applied to unstimulated BM or blood samples. At least 20 metaphase cells were analyzed, if possible. Cytogenetic abnormalities were described following the procedures described by the 2016 International System for Human Cytogenomic Nomenclature [14].

3. Statistical analyses

Descriptive statistics including frequency and distribution were calculated. A Sankey diagram was drawn using R and an R package, ‘ggplot2,’ was used to visualize the pattern of recategorization. Overall survival (OS) was calculated from the date of diag-
nosis to the date of death (uncensored) or the last follow-up (censored). OS was compared using a log-rank test and plotted using Kaplan-Meier curves. Results with \( P \) values less than 0.05 were considered significant. The MedCalc program (version 19.0.3, MedCalc Software, Acacialaan, Belgium) was used to perform the statistical analyses.

**RESULTS**

1. Frequency of categorization in patients with AML

Based on the 2008 WHO criteria, the number of patients in each category was as follows: RGA 551 (46.5%), MRC 327 (27.6%), NOS 211 (17.8%), TR 47 (4.0%), DS 4 (0.3%), and ND 45 (3.8%). Based on the revised criteria, the number of patients in each category was as follows: RGA 542 (45.7%), MRC 286 (24.1%), NOS 237 (20.0%), TR 46 (3.9%), DS 4 (0.3%), MDS 25 (2.1%), and ND 45 (3.8%). The ND category was obtained using the incomplete mutation (\( NPM1 \) and/or \( CEBPA \)) data. Application of the revised criteria redistributed a subset of each category into another category. Overall, this redistribution resulted in a slight increase in the NOS category and a slight decrease in the RGA and MRC categories under the revised criteria. Generation of the MDS category represented a relocation of erythroleukemia cases with blasts < 20% of the total marrow cells (Fig. 1). The overall concordance rate of categorization between the two criteria was 93.4% (1107/1185) and 78 discrepant cases (6.6%) were identified.

**Fig. 1.** Comparison of categorization based on the previous and revised WHO criteria. Categories based on the previous 2008 WHO criteria are shown on the left, and categories based on the revised 2016 WHO criteria are shown on the right. The gradient colors represent the diagnostic categories and the widths of the bands are proportional to the counts of cases in each category based on the previous and revised criteria. Abbreviations: RGA, AML with recurrent genetic abnormalities; MRC, AML with myelodysplasia-related changes; NOS, AML not otherwise specified; TR, therapy-related AML; ND, AML with subcategory not determined; DS, AML associated with Down syndrome.
2. Features and categorization patterns of discrepant cases

Table 1 summarizes the recategorization patterns of discrepant cases and their details. Among the discrepancies, RGA to NOS was the most common recategorization and included cases with a single mutation of CEBPA. The recategorization of MRC to MDS was the second most common and encompassed cases of erythroleukemia. The MRC to RGA was the third most common recategorization and included AML with mutated NPM1, AML with mutated CEBPA, and AML with BCR-ABL1, respectively. Miscellaneous recategorizations were MRC to NOS, MRC to ND, NOS to MDS, TR to MDS, and ND to RGA.

3. Characterization of specific subtypes

We further analyzed the categorization patterns in patients with specific subtypes that underwent critical changes in the revised 2016 criteria. Patients with NPM1 mutation revealed 145 (91.2%) agreements and 14 (8.8%) discrep-

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Table 1. Summary of discrepant cases between the previous and revised WHO criteria and the basis for recategorization

| 2008 WHO | Revised 2016 WHO | Rationale for recategorization |
|----------|------------------|------------------------------|
| RGA (N=31) | NOS (N=28) | CEBPA mutation and mutated NPM1 |
| MDS (N=3) | Erythroleukemia and mutated NPM1 |
| MRC (N=41) | MDS (N=20) | Mutated NPM1 (N=11)/CEBPA (N=4)/BCR-ABL1 (N=3) |
| RGA (N=18) | NOS (N=2) | del(9q) and CEBPA |
| ND (N=1) | del(9q) and CEBPA |
| NOS (N=4) | RGA (N=3) | BCR-ABL1 |
| MDS (N=1) | Erythroleukemia |
| TR (N=1) | MDS (N=1) | Erythroleukemia |
| ND (N=1) | RGA (N=1) | BCR-ABL1 |

Abbreviations: RGA, AML with recurrent genetic abnormalities; MRC, AML with myelodysplasia-related changes; TR, therapy-related AML; NOS, AML not otherwise specified; ND, AML with subcategory not determined; NA, not available.
ancies. The majority (85.5%) of cases were categorized as RGA. A subset of patients (N=16, 10.1%) was categorized as MRC using the previous criteria and was split into MRC (N=5, 3.1%) and RGA (N=11, 6.9%) using the revised criteria. Another subset of patients was subjected to TR categorization (N=4, 2.5%) and RGA to MDS recategorization (N=3, 1.9%), which included erythroleukaemia with mutated NPM1 (Table 1, Fig. 2A). Patients with CEBPA<sup></sup>b mutation (N=51, 4.3% of all patients) revealed 47 (92.2%) agreements and 4 (7.8%) discrepancies. Similar to patients with NPM1 mutation, the majority (84.3%) of cases were categorized as RGA. A subset of patients (N=8, 15.7%) was categorized as MRC using the previous criteria and was split into MRC (N=4, 7.8%) and RGA (N=4, 7.8%) using the revised criteria (Table 1, Fig. 2B). In total, 15 cases with NPM1 or CEBPA<sup></sup>b mutations were identified within the MRC to RGA recategorization. Among these, 11 cases with mutated NPM1 were previously categorized as MRC owing to a prior history of MDS or MDS/MPN (N=6), MLD (N=4), and del(9q) (N=1). The remaining four cases with CEBPA<sup></sup>b mutation were previously categorized as MRC owing to the presence of del(9q) in all cases (Table 2). Patients with a prior history of MDS or MDS/MPN showed shorter OS compared to those with MLD or del(9q) (P=0.026; Fig. 3).

Patients harboring del(9q) (N=36, 3.0% of all patients) revealed 27 (75.0%) agreements and 9 (25.0%) discrepancies. In total, 22 patients (61.1%) were categorized as MRC using the previous criteria and were split into MRC (N=13, 36.1%), RGA (N=5, 13.9%), NOS (N=2, 5.6%), ND (N=1, 2.8%), and MDS (N=1, 2.8%) using the revised criteria. Among these, five cases in the MRC to RGA recategorization included those with CEBPA<sup></sup>b (N=4) or NPM1

Table 2. Characteristics and clinical outcomes of patients with mutated NPM1 or CEBPA<sup></sup>b included in the MRC to RGA recategorization

| Case No. | Sex/Age | FAB | Cytogenetic abnormality | FLT3-ITD (allelic ratio)/NPM1/CEBPA<sup></sup>b | Prior disease | MLD | FU time (m) | Clinical outcome |
|----------|---------|-----|-------------------------|----------------------------------|---------------|-----|-----------|-----------------|
| 1        | M/76    | M2  | 46, XY, del (9) [1]/46, XY [20] | -/+/-                           | -             | +   | 1.6       | Dead            |
| 2        | F/68    | M2  | 46, XX [20]               | +1.04/+/-                       | -             | +   | 6.3       | Dead            |
| 3        | F/44    | M1  | 46, XX [20]               | -/+/-                           | -             | +   | 43.9      | Dead            |
| 4        | M/71    | M2  | 46, XY [30]               | -/+/-                           | -             | +   | 3.3       | FU loss         |
| 5        | F/40    | M1  | 46, XX, del (9) [q21q34] [4]/46, XX [16] | +[NA]/+/-                       | -             | -   | 10.8      | FU loss         |
| 6        | M/45    | M2  | 46, XY [25]               | -/+/-                           | MDS           | +   | 6.8       | Dead            |
| 7        | F/75    | M2  | 47, XX, +8 [1]/46, XX [7] | +(1.31)/+/-                     | MDS           | -   | 3.0       | Dead            |
| 8        | M/49    | M1  | 46, XY [2]/46, XX [3]     | +(0.62)/+/-                     | MDS           | -   | 3.5       | Dead            |
| 9        | F/53    | M5  | 46, XX [20]               | -/+/-                           | CMML          | -   | 5.7       | Dead            |
| 10       | F/60    | M1  | 46, XX [30]               | -/+/-                           | MDS           | -   | 39.6      | Dead            |
| 11       | F/64    | M1  | 46, XY inv (9) [p12q13] c [20] | +(0.30)/+/-                     | MDS           | -   | 0.5       | FU loss         |
| 12       | M/56    | M1  | 46, XY, del (9) [p13] [6]/46, XY, del (9) [q21] [6]/46, XY [8] | -/+/-                         | -             | -   | 51.5      | Alive           |
| 13       | F/18    | M1  | 46, XX, del (9) [q13q32] [16]/46, XX [4] | +(0.03)/+/-                   | -             | -   | 50.4      | Alive           |
| 14       | M/39    | M1  | 45, X, -Y, del (9) [q22q34] [2]/46, XY [18] | -/+/-                         | -             | -   | 43.6      | Alive           |
| 15       | F/83    | M1  | 46, XX, del (9) [q13q22] [9]/46, XX, del (9) [q12] [2]/46, XX [9] | -/+/-                         | -             | -   | 30.6      | Alive           |

Abbreviations: CEBPA<sup></sup>b, biallelic CEBPA; MRC, AML with myelodysplasia-related changes; RGA, AML with recurrent genetic abnormalities; M, male; F, female; FAB, French-American-British classification; ITD, internal tandem duplication; NA, not available; CMML, chronic myelomonocytic leukaemia; MLD, multilineage dysplasia; FU, follow-up; m, month.

Fig. 3. Influence of MDS history on the outcomes of patients with AML harboring gene mutations identified in the MRC to RGA recategorization. Kaplan-Meier plots for overall survival according to the defining criteria for the MRC category using the 2008 WHO criteria, including multilineage dysplasia or del(9q) (N=9) and a prior history of MDS or MDS/MPN (N=6).

Abbreviations: MRC, AML with myelodysplasia-related changes; RGA, AML with recurrent genetic abnormalities; MDS/MPN, myelodysplastic/myeloproliferative neoplasm.
Table 3. Characteristics and clinical outcomes of cases of AML harboring *BCR-ABL1* according to the revised WHO criteria

| Case No. | Sex/Age | FAB | WBC (x10^9/L) | Hb (g/dL) | PLT (x10^9/L) | Cytogenetic abnormality | Isoform | FLT3-ITD/NPM1/CEBPA | FU time (m) | Clinical outcome |
|----------|---------|-----|---------------|-----------|--------------|------------------------|---------|----------------------|-------------|------------------|
| 1*       | M/41    | M6  | 3.6           | 9.4       | 30           | 42;XY,2,-5,-7,der(17)(q14;17)(q12;p13),der(18)(q11.2;q11.2),del(9)(q22) | NA      | -/-/NA              | 7.7         | Dead†             |
| 2*       | F/42    | M0  | 23.8          | 6.1       | 162          | 46;XXadd(5)(q35)t(9;22)(q34;q11.2)(t(21;19);q(11.2) | e1a2    | -/-/NA              | 89.4        | Alive‡            |
| 3*       | M/28    | M1  | 77.5          | 10.4      | 22           | 49;XY,t(9;22)(q34;q11.2)(t(21;19);q17) | b3a2    | -/-/NA              | 62.5        | Alive‡            |
| 4†       | M/38    | M7  | 5.2           | 7.5       | 86           | 46;XXinv(9)(p12q13)t(9;22)(q34;q11.2)(20) | b3a2    | -/-/NA              | 62.3        | Alive‡            |
| 5†       | M/54    | M4  | 288.1         | 9.1       | 84           | 46;XXt(9;22)(q34;q11.2)(20) | b3a2    | -/-/NA              | 33.4        | Alive‡            |
| 6†       | M/70    | M2  | 71.4          | 12.7      | 100          | 46;XXt(9;22)(q34;q11.2)(20) | b3a2    | -/-/NA              | 2.7         | FU loss           |
| 7†       | M/71    | M0  | 2.0           | 9.1       | 158          | 46;XXinv(9)(p12q13)(20) | e1a2    | -/-/NA              | 14.3        | FU loss           |

Categorized as MRC*, RGA†, and ND‡, respectively, based on the 2008 WHO criteria; *Cases that underwent allogeneic hematopoietic stem cell transplantation.

Abbreviations: M, male; F, female; FAB, French-American-British; WBC, white blood cell; PLT, platelet; NA, not available; ITD, internal tandem duplication; CEBPA, biallelic CEBPA; FU, follow-up; m, month; MRC, AML with myelodysplasia-related changes; RGA, AML with recurrent genetic abnormalities; ND, AML with subcategory not determined.

**DISCUSSION**

According to the revised 2016 criteria, the 2008 criteria-defined patients with AML were most commonly categorized as RGA (65.7%), followed by MRC (24.1%), NOS (20.0%), TR (3.9%), ND (3.8%), MDS (2.1%), and DS (0.3%). The discrepancy rate between the two criteria was 6.6%. The RGA to NOS (35.9% of discrepancy) recategorization was the most common and represented cases with *CEBPA* mutation. The MRC to MDS (25.6%) recategorization represented erythroleukemia cases and the MRC to RGA (23.1%) recategorization represented recurrent genetic abnormalities showing myelodysplasia features. Patients with *NPM1* or *CEBPA* mutations within the MRC to RGA recategorization were characterized by a high agreement rate, categorization under MRC by the previous criteria in some cases, and identification of cases with a prior history of MDS or MDS/MPN. We demonstrated that patients with secondary AML and gene mutations had a worse prognosis than those presenting MLD or del(9q). Patients harboring del(9q) were characterized by three quarters of the agreement rate and enrichment in core binding factor AML or cases with *CEBPA* mutations. The vast majority of erythroleukemia was recategorized as MDS, with only 10.7% of cases remaining as an AML entity.

The frequency of discrepancy (approximately 7%) was not high between the two classification systems because the revision largely inherited the concept of the previous criteria and incorporated...
rated clinical features, morphology, immunophenotyping, cytogenetics, and molecular genetics to define the disease entities of clinical significance. This frequency is largely in line with the discrepancy frequency (89%) of a recent study that performed categorization using two classification systems in 610 patients [8]. The RGA to NOS and MRC to MDS recategorizations were anticipated consequences. However, further discussion is required regarding the MRC to RGA recategorization. This is partly due to the result of classifying the newly-introduced subtype, AML with BCR-ABL1 in the revised criteria. This was added to recognize this disease as distinct from blast-phase chronic myeloid leukemia that benefits from tyrosine kinase inhibitors and hematopoietic stem cell transplantation [15, 16]. However, categorization of cases with gene mutations (NPM1 or CEBPA) using the revised criteria is not straightforward. MLD and del(9q) have no adverse prognostic significance in these patients and their presence does not exclude a case from AML with gene mutations, whereas cases co-occurring with myelodysplasia-associated cytogenetic abnormalities should be diagnosed under the MRC category. In the present study, a subset of patients with gene mutations was classified in the MRC category using the previous criteria. However, rather than remaining in the MRC category, a larger number of these patients were recategorized into other categories by the revised criteria. This is an example of an effort to minimize diagnostic ambiguity based on clinical significance. Despite refinement, the MRC to RGA recategorization can be complicated by a complexity of priority rules in patients with gene mutations. In particular, there are no clear guidelines regarding the categorization of patients with recurrent gene mutations as well as a history of MDS or MDS/MPN. Schnittger et al. [17] observed that NPM1 mutation was identified in 13.1% of 283 patients with secondary AML. These authors argued that this mutation might contribute to the transformation of MDS to AML; however, they found no survival benefit in their secondary AML cohort [17]. These data suggest that the NPM1 mutation could reflect differently in de novo and secondary AML. This is in line with our observations that, within the MRC to RGA recategorization, patients with a prior history of MDS or MDS/MPN showed worse outcomes than those with MLD or del(9q). In this context, a recent expert review suggested that the diagnosis of MRC is appropriate in AML patients with a history of MDS and NPM1 mutation, particularly when supported with molecular genetic findings [18]. Nonetheless, large studies are required to confirm the prognostic influence of NPM1 or CEBPA mutants in secondary AML cohorts.

Del(9q) is a recurrent cytogenetic abnormality in AML and accounts for approximately 2% of unselected cases [19]. It is enriched in core binding factor AML, particularly in (8;21), or patients with CEBPA mutation [19, 20]. These findings are consistent with our observations that 3.0% of cases harbored del(9q) and nearly half of them had recurrent (cytogenetic abnormalities, particularly (8;21) and CEBPA mutations. A previous study delineated many genes in the commonly deleted region of del(9q) and the leukemogenic role of haploinsufficiency of TLE1 and TLE4 adjacent to this region by overcoming the negative survival and anti-proliferative effects of AML1-ETO fusion protein on myeloid progenitors and allowing preleukemic stem cells to expand into AML [21, 22]. Other investigators confirmed the low expression of TLE4 in AML with del(9q) and showed strong associations with DNMT3A and NPM1 mutations [23]. Naarmann-de Vries et al. [24] recently reported that the mRNA expression of the HNRNPK gene in the 9q21.32-9q21.33 region was enhanced to a normal karyotype level in a group of del(9q)/CEBPA-mutated patients, indicating a molecular relationship of CEBPA and the del(9q) CDR genes. Thus, del(9q) might contribute to leukemogenesis by the haploinsufficiency of tumor suppressor genes in CDR or a regulatory interaction between CEBPA and HNRNPK. Thus, AML with del(9q) could be a candidate for an anti-leukemogenic strategy by blocking the effect of HNRNPK or other CDR gene products on CEBPA expression, which could improve the outcomes of del(9q) AML.

A vast majority of erythroleukemia cases were recategorized as MDS in the present study. This finding is consistent with a recent study in which 30 (88.2%) of 34 de novo erythroleukemia cases were reclassified as MDS [7]. The present study found that approximately 10% of erythroleukemia cases had an NPM1 mutation and these cases were all reclassified as MDS using the revised criteria. Montalban-Bravo et al. [25] recently demonstrated that the frequency of NPM1 mutations among 1,900 patients with newly diagnosed MDS or MDS/MPN was 1.6%. Most cases (61%) were classified as MDS with excess blasts, and patients treated with chemotherapy had better clinical outcomes than those treated with hypomethylating agents [25]. Thus, NPM1 mutations are rarely detected in MDS and these patients might benefit from chemotherapy compared to MDS-based treatment approaches.
As RUNX1 mutation had not been systematically tested before the use of NGS in our laboratory, we only considered mutations in NPM1 and CEBPA as the defining drivers of AML in the present study. Exclusion of RUNX1 mutation data from the analysis resulted in a slight increase in the NOS category during recategorization. We have previously demonstrated that RUNX1 mutations were detected in approximately 15% of patients in the NOS category [26]. Thus, integration of RUNX1 mutation data is expected to shift some cases from the NOS category to the RGA category. Our actual data showed that RUNX1 mutation was detected in 11 (11.2%) of 98 patients with NGS results. Among these, 2 (2.0%) were diagnosed with AML with mutated RUNX1 according to the revised criteria (Supplemental Data Fig. S2). Comprehensive and high-throughput mutational analysis using NGS has replaced the Sanger sequencing-based stepwise approach of the mutational assay in patients with AML. Future studies should thus focus on mutation profiling and genotype-phenotype correlation, and their clinical relevance in myeloid neoplasms and acute leukemias in the context of categorization using the revised WHO criteria.

In conclusion, the present study highlights that applying the revised 2016 WHO criteria identified discrepancies in categorization of acute myeloid leukemia using the revised criteria. The study demonstrated that these discrepancies were due to the introduction of new entities, changed definitions, and refined subcategorization. Further refinement could be considered for the next version of the WHO criteria, including the precedence of a history of MDS over NPM1 mutation as a criterion for classifying the MRC category as well as potential new subtypes such as AML with del(9q), or MDS and MDS-related disorders with mutated NPM1.

요 약

배경: 2016년 개정된 WHO 기준과 2008년 WHO 기준에 따라 AML을 분류하면 일부 불일치하는 경우가 부각된다. 본 연구에서 는 불일치 사례의 변도, 분류 패턴, 특성을 분석하고, 개정된 기준에 의해 주요 변화를 보인 AML의 아형들을 특화하였다.

방법: 기존 및 개정된 WHO 기준에 따라 환자군을 다음 7가지 범주로 나누었다: 변복유전자이상 AML (AML with recurrent genetic abnormalities, RGA), 골수형성이상관련 AML (AML with myelodysplasia-related changes, MRC), 치료관련 AML, 상세분명 AML (AML not otherwise specified, NOS), 다운증후군관련 AML, 야행미결정 AML, 그리고 MDS.

결과: 총 1,185례의 AML 증례를 검토하였다. 두 기존 사이의 일치율은 93.4%이었다. 78례의 병별이 사례 중 가장 흔한 패턴 3개는 RGA에서 NOS, MRC에서 MDS, 그리고 MRC에서 RGA였으며, 각각 CEBPA 단일 돌연변이, 적백혈병(erythroleukemia), 그리고 골수형성이상을 보이는 백복유전자이상으로 인한 불일치였다. MDS 위주 치료보다 항암화학요법으로 임상적 이득을 취할 수 있는 NPM1 돌연변이 동반 적백혈병이 3례에서 확인되었다. 그리고 발견된 유전자의 환배수부전(haploinsufficiency) 혹은 유전자 사이의 상호작용을 통해 백혈병을 유발할 수 있는 9번 염색체 장환의 결실이 환자의 3%에서 확인되었다.

결론: 본 연구를 통해 AML 환자의 약 7%에서 새로운 질환의 도입, 변경된 정의, 그리고 정립한 하위범주화로 인해 다른 범주로 재 분류됨을 확인하였다. 이에 따라 다음 개정 사례는 추가적인 세밀한 개선이 고려되어야 할 것이다.

Conflicts of Interest

None declared.

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Supplemental Data Fig. S1. Influence of other (cyto)genetic abnormalities on overall survival in cases of AML harboring del (9q). Kaplan-Meier plots for the overall survival of patients with del (9q) alone (N=5), in combination with biallelic CEBPA mutation (N=5) or de novo t(8;21) (N=9).
Supplemental Data Fig. S2. Pattern and frequency of categorization for patients with AML harboring a RUNX1 mutation. The NOS to NOS represented patients with AML harboring mutated RUNX1 when considering the application of RUNX1 mutation in recategorization according to the revised criteria. The RGA case was based on the presence of t(3;3)(q21;q26).

Abbreviations: MRC, AML with myelodysplasia-related changes; NOS, AML not otherwise specified; RGA, AML with recurrent genetic abnormalities.