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Acute Myeloid Leukemia with Myelodysplasia Related Changes

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Cite this chapter as: Shibusawa M, Tanimoto T. Acute Myeloid Leukemia With Myelodysplasia Related Changes. In: Li W. editor. *Leukemia*. Brisbane (AU): Exon Publications. Online first 05 Aug 2022.

Doi: https://doi.org/10.36255/exon-publications-leukemia-aml-mrca

Abstract: Acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) is one of the common subtypes of AML. It accounts for approximately 20% of newly diagnosed AML. The World Health Organization classification 2017 defines AML-MRC as acute leukemia with ≥20% blasts in the peripheral blood or bone marrow with morphological features of myelodysplasia, or occurring in patients with a prior history of myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN), with MDS related cytogenetic abnormalities, and the absence of specific genetic abnormalities of AML with recurrent genetic abnormalities. In diagnosing AML-MRC, there are three main criteria; the presence of (i) dysplasia; (ii) chromosomal abnormalities associated with AML-MRC; and (iii) a prior history of MDS or MDS/MPN. Therefore, AML-MRC is a heterogeneous disease, and the prognosis of each AML-MRC varies widely. AML-MRC is usually treated with chemotherapy, and

In: Li W (Editor). *Leukemia*. Department of Pathology and Laboratory Medicine, Children's Mercy Hospital, University of Missouri-Kansas City School of Medicine, Kansas City, USA. ISBN: 978-0-6453320-7-0. Doi: https://doi.org/10.36255/exon-publications-leukemia

hematopoietic stem cell transplantation is one of the treatment options. Prognostic factors should be considered in planning a treatment strategy for each case.

Keywords: acute leukemia; acute myeloid leukemia with myelodysplasia related changes; acute myeloid leukemia; myelodysplasia; myelodysplasia related changes

INTRODUCTION

Acute myeloid leukemia (AML) is a hematopoietic cell neoplasm which is characterized by expansion of leukemic cells in the bone marrow. The World Health Organization (WHO) classification 2017 classifies AML and related precursor neoplasms into subtypes as follows: AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes (AML-MRC), therapy-related myeloid neoplasms (t-AML), AML not otherwise specified (AML-NOS), myeloid sarcoma, and myeloid proliferations associated with Down syndrome (1).

The term of AML-MRC was first introduced by the WHO classification 2008. It included AML cases with a history of myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm (MDS/MPN), or with myelodysplasia-related cytogenetic abnormalities, or morphologic evidence of dysplasia in 50% or more of the cells in two or more myeloid lineages (2). In the revised WHO classification 2017, it defines AML-MRC as acute leukemia with ≥20% blasts in the peripheral blood or bone marrow with morphological features of myelodysplasia, or occurring in patients with a prior history of MDS or MDS/MPN, with MDS related cytogenetic abnormalities and the absence of specific genetic abnormalities characteristic of AML with recurrent genetic abnormalities (3). Therefore, there are three main criteria when patients are classified in this category: (i) those with the presence of dysplasia; (ii) those with MDS related cytogenetic abnormalities; and (iii) those with a prior history of MDS or MDS/MPN. According to a previous report (4), the reasons for AML-MRC diagnosis is as follows:(i) the majority of patients were diagnosed based on only one reason—20% for the presence of dysplasia, 56.8% for MDS related cytogenetics abnormalities, and 5.8% for a prior history of MDS or MDS/MPN; (ii) 16.8% of patients had two reasons—7.4% for MDS-related cytogenetics abnormalities and prior history of MDS or MDS/MPN, 7.4% for the presence of dysplasia and MDS related cytogenetics, and 2.1% for the presence of dysplasia and a history of MDS or MDS/MPN, and (iii) only 0.5% of patients had all three reasons.

In the upcoming 5th edition of the WHO classification for myeloid and histiocytic/dendritic tumors (5), the name of AML-MRC has been changed to AML, myelodysplasia-related (AML-MR). Morphology alone as a diagnostic premise to make a diagnosis of AML-MR is removed. Since more detailed updates of this disease as seen in the printed 5th edition book won't be available until the end of 2022, the description in this chapter is mostly based on the revised 4th edition. This chapter describes the epidemiology, morphological and cytogenetic features, diagnosis, clinical features, treatment, prognosis, and predictive factors of AML-MRC.

EPIDEMIOLOGY

According to a report from the United States, the age-adjusted incidence of AML is 4.3 per 100,000 persons annually. Incidence increases with age, with a median age at diagnosis of 68 years. Males develop AML 1.2–1.6 times more likely than females (6). As for the AML-MRC, according to a previous report from China (4), it accounted for 22.2% of all newly diagnosed AML. The median age of AML-MRC patients was 61 years (range 16–87). In addition, comparing AML-MRC patients with AML-NOS patients, AML-MRC patients had significantly older ages ($p < 0.001$). AML-MRC was also male-predominant (male to female ratio, 1.79:1) (4).

MORPHOLOGICAL MANIFESTATIONS OF DYSPLASIA

The findings of dysplasia observed in MDS (7) are shown in Table 1. Diagnosing AML-MRC solely based on the presence of dysplasia requires the presence of dysplasia in ≥50% of the cells in at least two hematopoietic cell lineages (hematopoietic cell lineages are neutrophils and their precursors, erythroid cells, and megakaryocytes) (3). It should be noted that several factors, including deficiency of vitamin B12, folic acid, and copper, can cause morphological dysplasia and cytopenia (7). Even so, the findings of nuclear hyposegmentation (pseudo-Pelger anomaly) (Figure 1A), ring sideroblasts (Figure 1B), micromegakaryocytes (Figure 1C) correlate most strongly correlate with MDS (8).

TABLE 1 **Morphological manifestations of dysplasia observed in myelodysplastic syndrome**

Dysgranulopoiesis	Dyserythropoiesis	Dysmegakaryopoiesis
Small or unusually large size	Nuclear	Micromegakaryocytes
Nuclear hyposegmentation (pseudo Pelger Huët)	Nuclear budding	Nuclear hypolobation
Nuclear hypersegmentation	Internuclear bridging	Multinucleation
Decreased granules; agranularity	Karyorrhexis	
Pseudo Chédiak Higashi granules	Multinuclearity	
Döhle bodies	Megaloblastoid changes	
Auer rods	Cytoplasmic	
	Ring sideroblasts	
	Vacuolization	
	Periodic acid Schiff (PAS) positivity	

From Myelodysplastic syndromes in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th Edition; 2017. p.102, cited in.

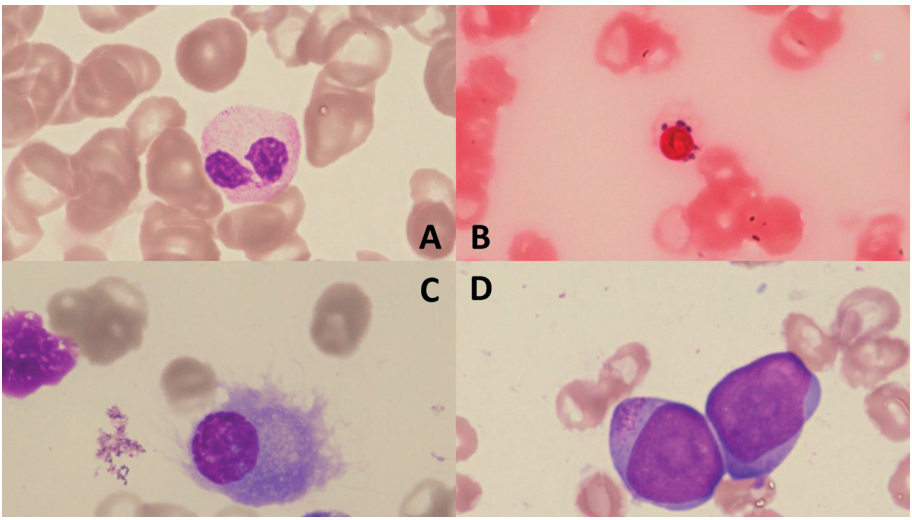

Figure 1. Microscopic picture of bone marrow smear. A: Nuclear hyposegmentation (pseudo-Pelger anomaly, Wright–Giemsa staining, ×1,000). The two lobes are joined by thin filaments and have coarse nuclear chromatin. **B:** Ring sideroblast (Iron stain, ×1,000). Iron granules are present in more than five and cover at least a third of the nuclear circumference. **C:** Micro megakaryocyte (Wright–Giemsa staining, ×1,000). Megakaryocyte has mononuclear and is less than promyelocytes in size. **D:** Blasts observed in acute myeloid leukemia with myelodysplasia-related changes (Wright–Giemsa staining, ×1,000). Blasts presented with loose reticular chromatin and a high nucleus-to-cytoplasm ratio. Some blasts showed cytoplasmic nucleoli and granules.

According to a previous report, among AML-MRC patients according to the WHO classification 2008, 31.9% of patients had the presence of dysplasia in one hematopoietic lineage. In 27.0% of patients, dysplasia was observed in two cell lineages, whereas trilineage dysplasia was found in only 8.8% of patients. In addition, multilineage dysplasia was observed in a higher frequency in cases with a history of prior MDS or MDS/MPN compared to those without (66.7% vs. 32.5%; P = 0.001) and also, cases with MDS related cytogenetic abnormalities compared those without (49.1% vs. 4.0%; P = 0.035), respectively (9).

ASSESSMENT OF THE PERCENTAGE OF BLASTS

Blasts in an AML-MRC case are shown in Figure D. Morphologically, the blasts found in AML-MRC vary from case to case, but it is important to know that pure erythroid leukemia (M6), according to the classical French-American-British classification, is associated with a prior history of MDS (7).There are several things to note in assessing the percentage of blasts. Firstly, the percentage of blasts in the peripheral blood may be higher than the percentage of blasts in the bone marrow. (10) Secondly, a bone marrow biopsy may be useful in assessing the percentage of blasts in the bone marrow. When a patient has myelofibrosis in the bone marrow, aspiration can be “dry tap”. In such a case, immunostaining of bone marrow biopsy is the only way to assess the percentage of blasts (11).

CHROMOSOME ABNORMALITIES

Cytogenetic abnormalities sufficient for the diagnosis of AML-MRC (3) are shown in Table 2. There are a few things to keep in mind in AML-MRC diagnosis. Firstly, trisomy 8, del(20q), and loss of Y chromosome are observed to be common in MDS patients, but these abnormalities are not considered to be specific to AML-MRC. Therefore, the presence of these chromosomal abnormalities is not sufficient for AML-MRC diagnosis. Secondly, AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) and AML with t(6;9)(p23;q34.1) may present with multilineage dysplasia. However, these cases should be classified as AML with recurrent genetic abnormalities (3). The percentages of cytogenetic abnormalities observed in AML-MRC patients as follows: complex karyotype in 77% of patients, monosomy 5 or del(5q) in 6%, monosomy 7 or del(7q) in 16%, concurrent chromosome 5 or 7 abnormalities in 1%, del(13q) in 1%, and i(17) in 0.5% (12).

TABLE 2 **Cytogenetic abnormalities sufficient for the diagnosis of acute myeloid leukemia with myelodysplasia-related changes**

Complex karyotype	**≥3 abnormalities**
Unbalanced abnormalities	Loss of chromosome 7 or del(7q)
	del(5q) or t(5q)
	Isochromosome 17q or t(17p)
	Loss of chromosome 13 or del(13q)
	del(11q)
	del(12p) or t(12p)
	idic(X)(q13)
Balanced abnormalities	t(11;16)(q23.3;p13.3)
	t(3;21)(q26.2;q22.1)
	t(1;3)(p36.3;q21.2)
	t(2;11)(p21;q23.3)
	t(5;12)(q32;p13.2)
	t(5;7)(q32;q11.2)
	t(5;17)(q32;p13.2)
	t(5;10)(q32;21)
	t(3;5)(q25.3;q35.1)

From Acute myeloid leukaemia with myelodysplasia-related changes. in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th; 2017. p.151, cited in.

GENETIC MUTATIONS

The frequency of genetic mutations (present in >10% of patients) detected in AML-MRC patients according to the WHO classification 2017 is as follows: the most frequent mutation was TP53 (39%), followed by ASXL1 (20%), NRAS (17%), DNMT3A (16%), SRSF2 (14%), TET2 (14%) and U2AF1 (14%) (12). In the diagnosis of AML-MRC, the following should be noted that AML cases with NPM1 and/or FLT3 mutations or mutations of CEBPA may present with multilineage dysplasia. However, these AML cases should be classified as AML with recurrent genetic abnormalities (3).

DIAGNOSIS

The diagnostic criteria for AML-MRC are shown in Table 3. Diagnosing AML-MRC requires taking a history of the presence or absence of a prior history of MDS or MPN. In addition, it also requires taking a history of the presence or absence of prior use of anticancer drugs and having radiation therapy to rule out t-AML. Furthermore, evaluation of microscopic findings and chromosomal analysis are necessary. Finally, the detected chromosomal abnormalities must be confirmed that they are not chromosomal abnormalities, which should be classified as AML with recurrent genetic abnormalities.

CLINICAL FEATURES

According to a retrospective analysis of Chinese patients (4), laboratory data of AML-MRC patients were as follows: white blood cell count (WBC), 7.5 × 10^9/L (range 0.3–375.9); hemoglobin level (Hb), 71 g/L (range 30–146); platelet

TABLE 3 Diagnostic criteria of acute myeloid leukemia with myelodysplasia-related changes

1	≥20% blood or marrow blasts	
2	Any of the following	History of myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm
		Myelodysplastic syndrome related cytogenetic abnormality
		Mutilineage dysplasia
3	Absence of both of the following	Prior cytotoxic or radition therapy for an unrelated disease
		Recurrent cytogenetic abnormality as discribed in acute myeloid leukemia with recurrent genetic abnormalities

The diagnosis of acute myeloid leukemia with myelodysplasia-related changes requires the three of the above criteria to be met. From Acute myeloid leukaemia with myelodysplasia-related changes. in WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th; 2017. p.150, cited in.

count, 44 × 10^9/L (range 1–458); and lactate dehydrogenase (LDH) level, 387 IU (range 86–5986) (4). According to the 2017 European leukemia Net (ELN) criteria, 80.4% of cases were assigned to the intermediate-risk group. The remaining 19.6% of cases were classified into the unfavorable risk group. It is noteworthy that there were no patients assigned to the favorable risk group (4). Furthermore, in the study comparing 190 AML-MRC patients and 667 AML-NOS patients, AML-MRC patients had significantly older age ($p < 0.001$), lower Hb level ($p < 0.001$), and lower WBC count ($p < 0.001$), and higher male-to-female ratio ($p = 0.006$). As for clinical outcomes, AML-MRC patients had significantly lower complete remission (CR) rates (65.3% vs. 76.2%; $p = 0.005$) (4).

TREATMENT

There is no established standard of care for AML-MRC. AML-MRC is usually treated with chemotherapy, and hematopoietic stem cell transplantation is one of the treatment options.

Chemotherapy

Outcomes of chemotherapy treatment for AML-MRC have been reported. AML-MRC patients aged 60–75 years were treated in three ways (4): (i) an idarubicin and Ara-C (IA/DA) group; (ii) decitabine, aclarubicin, Ara-C, and granulocyte colony-stimulating factor (DAC+CAG) group; and (iii) supportive care. Among patients classified as the intermediate risk group based on the 2017 ELN criteria, CR rate of IA/DA group and DAC+CAG group were 60% and 63.6%, respectively, and overall survival (OS) of both groups were 6 and 6.5 months, respectively. In the patients classified as the unfavorable risk group, the CR rate of the IA/DA group and the DAC+CAG group were 52.2% and 59.3%, respectively. OS of the IA/DA group and the DAC+CAG group were 4.5 and 6.2 months, respectively (4). Outcomes of Liposomal Daunorubicin-Cytarabine (CPX-351) treatment for AML-MRC have also been reported. 188 AML patients including 131 patients with AML-MRC, 53 patients with t-AML, and 2 patients with other subtype of AML were treated with CPX-351. CR rate was 47%. After a median follow-up of 9.3 months, the median OS was 21 months, and 1 year OS rate was 64%. In multivariate analysis, complex karyotype predicted lower response ($p = 0.0001$), while pretreatment with hypomethylating agents ($p = 0.02$) and adverse risk (based on ELN 2017) ($p < 0.0001$) were associated with lower OS (13).

Allogenic hematopoietic stem cell transplant

A previous study reported the treatment outcome of 60 AML-MRC patients (according to the WHO classification 2008) who had undergone allogeneic hematopoietic stem cell transplantation (allo-HSCT). In the patients' characteristics, there were no significant differences between the AML-MRC group and AML-NOS group in age, gender, performance status, hematopoietic cell transplantation comorbidity index, conditioning regimen, and

graft-versus-host disease prophylaxis, but the AML-MRC group had a higher frequency of non-CR disease status at allo-HSCT (48% vs. 27%, p = 0.01), unfavorable cytogenetic risk (40% vs. 9%, p < 0.0001), and underwent bone marrow transplantation (92% vs. 78%, p = 0.04) from HLA matched unrelated donor (75% vs. 41%, p = 0.0002). Despite the above differences in the patients' characteristics, there were no significant differences in the 2-year OS, cumulative incidence of relapse (CIR), and non-relapse mortality (NRM) between the two groups (2-year OS, 48% vs. 59%; 2-year CIR, 37% vs. 35%; 2-year NRM, 19% vs. 13%) (14). Thus, allo-HSCT is considered a treatment option for AML-MRC.

Prognosis

Among AML-MRC cases, according to the WHO classification 2017, the median OS was 7.6 months (95% confidence interval, 5–10.6 months) (15). As prognostic factors, age, LDH (4), the presence of MDS related cytogenetic abnormalities, monosomal or complex karyotype, and history of MDS or MDS/MPN (15) have been reported. However, it should be noted that the presence of dysplasia is not a prognostic factor. Actually, there were no significant differences in OS and event-free survival among AML-MRC patients having dysplasia in zero vs. one vs. two vs. three hematopoietic cell lineages. (16)

CONCLUSION

AML-MRC is one of the common subtypes of AML and accounts for approximately 20% of newly diagnosed AML. Diagnosing AML-MRC requires taking a history regarding the presence or absence of prior MDS or MDS/MPN and prior anticancer drug/radiotherapy treatment. There are three main criteria for AML-MRC diagnosis:the presence of dysplasia, chromosomal abnormalities associated with AML-MRC, and a prior history of MDS or MDS/MPN. AML-MRC is a heterogeneous disease, and the prognosis varies widely among patients. AML-MRC is usually treated with chemotherapy, and HSCT is one of the treatment options. In a planning treatment strategy, prognostic factors should be considered individually for each case.

Conflict of Interest: TT reports personal fees from Medical Network Systems Inc., and Bionics co., ltd, outside the submitted work. Dr. Shibusawa declares no conflicts of interest.

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