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Cytogenetic Profile of Monosomal Karyotype in Adult Acute Myeloid Leukemia

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Abstract- Cytogenetic abnormalities at diagnosis are important prognostic indicators in acute myeloid leukemia (AML). AML is categorized into 3 risk groups according to cytogenetic abnormalities; favorable, intermediate, and unfavorable. A new cytogenetic risk group called the monosomal karyotype (MK) had been identified in AML in the unfavorable cytogenetic risk group. The MK was reported to be associated with a dismal prognosis. The objective of this retrospective study was to analyze the type of chromosomal abnormalities found in adult AML patients with MK at diagnosis. Conventional cytogenetic analysis using standard procedure was performed as a routine diagnostic test in all leukemia patients at presentation of the disease. We report here the cytogenetic profile of 11 adult AML patients (age: 24 to 77 years) with MK. The most frequent chromosome aberrations observed were -5 or/and del(5q) [54%], -7 (36%), and -16 (36%). Abn(17q) was observed in two out of 11 patients (18%). Out of 11 patients, nine had hypodiploidy (41-45 chromosomes), one had diploidy (46 chromosomes), and one had hyperdiploidy (47 chromosomes). Ten MK patients (91%) had complex karyotype with five to nine clonal abnormalities. MK+ AML patients have a very unfavorable outcome due to resistance against current treatment modalities. The diagnosis of MK in AML is important in the clinical management of these patients.

Index Terms- Monosomal karyotype (MK), Acute myeloid leukemia (AML)

I. INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous group of hematological neoplasm with regard to clinical, genetic and molecular features. Cytogenetic studies had shown that more than 50% of AML patients had an abnormal karyotype at diagnosis (1). Cytogenetic abnormalities at diagnosis are important prognostic indicators in determining response to therapy and outcome in AML. Based on cytogenetic abnormalities, AML can be categorized into three cytogenetic risk groups, favorable (20%), intermediate (50%) and unfavorable (30%). The favorable risk group include t(15;17), and core binding factor (CBF) AML with t(8;21), inv(16) or t(16;16). The intermediate risk group include the normal karyotype, t(9;11), del(9q), del(7q), del(20q), -Y, +8, +11, +13, and +21. The unfavorable risk group include complex karyotype (CK), inv(3) or t(3;3), t(6;9), t(6;11), t(11;19), del(5q), -5, and -7 (2). In the United States, CK is defined as the presence of a clone with at least three unrelated cytogenetic abnormalities. CK in the United Kingdom (UK) is defined as five or more chromosomal abnormalities. The UK Medical Research Council (MRC) group found that with each additional chromosomal abnormality, there was also an increase in the risk of failing to achieve a complete remission (hazard ratio [HR] = 1.42) as well as mortality (HR = 1.19) [3].

Breems *et al* (2008) [4] were the first to identify the monosomal karyotype (MK) in AML in the unfavorable cytogenetic risk group. MK is associated with a very unfavorable prognosis. In the unfavorable cytogenetic risk group, the 4-year overall survival (OS) of MK positive (+) patients with AML was 4% compared to 26% in the MK negative (-) patients. MK is defined as the presence of two or more distinct autosomal monosomies in the karyotype or a single autosomal monosomy in the presence of one or more structural chromosome abnormalities (in the absence of t(15;17) and CBF AML). Loss of X or Y chromosome is excluded. In AML the frequency of MK increases with age, 4% in patients below 30 years, 6–10% in patients less than 60 years, and 13-20% in patients above 60 years of age (5). The German-Austrian AML Study Group (6) revised the definition of MK (MK-R) to exclude cases with recurrent genetic abnormalities according to the World Health Organization (WHO) Classification of Myeloid Neoplasms and Acute Leukemia (7) and those with derivative chromosomes not leading to true monosomies. The MK-R group was also associated with a dismal prognosis. The prognostic significance of MK also depend on the treatment strategy used.

The objective of this study was to analyse the type of chromosome abnormalities found in adults with *de novo* AML having MK at presentation of the disease.

II. MATERIALS & METHODS

Patients

Cytogenetic studies are performed as a routine diagnostic test in our Cytogenetic Laboratory, Hematology Unit, Institute for Medical Research (IMR), Kuala Lumpur for all patients with hematological malignancies. The diagnosis of AML was according to the WHO classification. Patients with therapy-related AML (t-AML) and secondary AML after myelodysplastic syndrome (MDS) were excluded from this retrospective study. Eleven adult AML patients at presentation of the disease with MK were included in this study.

Cytogenetic studies

Conventional cytogenetic analysis was performed on the blood/ bone marrow aspirate of patients with hematological malignancies according to standard procedures. The chromosomes were G-banded and karyotype designation was

according to the International System for Human Cytogenetic Nomenclature (ISCN, 2009) [8] at the time of cytogenetic analysis. Abnormalities were considered clonal when at least two metaphases had the same type of aberration for a structural abnormality or an additional chromosome. For loss of a chromosome, it had to be present in at least three metaphase cells to be considered a clonal monosomy. CK was defined as the presence of a clone with three or more unrelated cytogenetic aberrations.

III. RESULTS

The cytogenetic findings of the 11 adult AML patients with MK are shown in Table 1. The age of the 10 patients with MK ranged from 24 to 77 years (median age: 62 years). Eight out of 11 patients with MK were elderly (age 60 years and above). The most frequent chromosome abnormalities observed were -5 or/and del(5q) [54%], -7 (36%), and -16 (36%). Abn(17p) [abnormal (17p)] was observed in 2 out of 11 patients (18%). Eight out of 11 patients (73%) had two or more monosomies, as well as two or more structural aberrations. Out of 11 patients, 9 had hypodiploidy (41 – 45 chromosomes), one had diploidy (46 chromosomes) and one had hyperdiploidy (47 chromosomes). Ten MK patients (91%) had CK as well with five to nine clonal cytogenetic abnormalities. Patient 11 did not have CK. Patient no.1 and Patient No. 5 had trisomy 3 and tetrasomy 8 respectively. Fig.1 shows the karyotype of a MK+ AML patient (Patient No. 6) with multiple cytogenetic abnormalities.

IV. DISCUSSION

In our study the most frequent chromosome abnormalities observed in MK+ AML patients were -5 or/and del(5q) [45%], -7 (36%), and -16 (36%). Abn(17p) was observed with a frequency of 18%. The most frequent autosomal monosomies reported in MK are -7, -5, -17, and -18. The six most frequent chromosome abnormalities reported in AML with MK were (in order of decreasing frequency) -5 or del(5q) [55%], -7 (45%), abn(17p) [41%], abn(12p) [24%], -20 or del(20q) [19%], and -18 or del(18q) [19%] (6). Deletions or mutations at 17p (which is frequently found in MK and CK) are associated with the loss or dysfunction of the tumor suppressor gene (TSG), *TP53* (9). These findings have led many to speculate the presence of TSGs on chromosomes 5 and 7, and that deletion of part or all of chromosomes 5 or/and 7 results in the pathogenesis of AML. However, no specific TSG has been identified and no simple explanation is available for the frequent losses involving these two chromosomes. Abn(17p), abnormalities in chromosomes 5 and 7, CK, and MK are found more frequently in t-AML than *de novo* AML (10). About 91% of our MK+ AML patients had CK, which was also similar to the study by Voutiadou *et al* (2013) [11].

MK is also found in MDS and primary myelofibrosis, and is associated with a very poor prognosis. MK is associated with prior chemotherapy or history of abnormal blood counts. Compared to MK- AML patients, MK+ AML patients were older in age, had lower hemoglobin levels, lower median white counts, lower percentage of blasts in bone marrow and peripheral blood. AML with MK has a poor outcome in patients in any age group, with a poor complete remission (CR) rate and survival estimate, and is even worse in elderly patients. The poor prognosis of MK+ AML is due to resistance against conventional chemotherapy, thus resulting in a low CR rate. High and early relapse rates were seen in patients achieving CR after conventional induction chemotherapy with anthracyclin-cytarabine. (12). The 4-year OS after allogeneic hematopoietic stem cell transplantation (HSCT) was 52% for MK- AML patients with poor-risk cytogenetics while for AML MK+ patients it was only 28%. However, the outcome of HSCT was considerably better than conventional chemotherapy for MK+ AML patients. Clinical trials using high-dose cytarabine led to superior disease free survival and OS in patients with favorable-risk cytogenetics but not for patients with intermediate- or unfavorable-risk cytogenetics (10). The diagnosis of MK in AML which have a dismal prognosis is important in the clinical management of these patients. The development of suitable novel therapies is greatly warranted for MK+ AML patients.

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Table 1: Chromosome abnormalities in acute myeloid leukemia (AML) patients with monosomal karyotype

AML Patients			Types of Chromosome Abnormalities			Total No. of Chromosomes
No	**Age (Years)**	**Sex**	**Autosmal Monosomy/ monosomies**	**Structural abnormality/ abnormalities**	**Gain of whole chromosome/ chromosomes**	
1	75	M	-8, -17	del(1p), +abn(2q), del(4q), abn(12), abn(15q),	+3	46
2	62	F	-7,-9, -16,-17	del(5q), add(12p), abn(19p)	-	42
3	64	M	-5,-7,17,-18	abn(14q), abn(20), +ring chr	-	42
4	59	F	-13, -18	+del(4p), del(5q), del(6p), del(7p), +abn(9q), abn(17p), abn(22p)	-	45
5	67	M	-15	del(6q), del(7q)	+8,+8	47
6	60	F	-9,-12,-16,-18,-20	t(5;7), abn(5q), abn(17p)	-	41
7	77	F	-13, -16, -21, -21	+del(3q),+del(5q)	-	44
8	76	M	-7, -16	add(1p), +ring chr	-	45
9	60	M	-4,-12,-20	del(4p), del(5q), add(7q),del(8q)	-	43
10	35	M	-3	del(5q), del(7q), del(11q), del(12p)	-	45
11	24	F	-7	t(3;3)	-	45

Legend

abn : Abnormal
add : Additional chromosome material
chr: Chromosome
del : Deletion
F: Female
M : Male
minus sign (-) : Loss of part or whole chromosome
plus sign (+) : Gain of part or whole chromosome
p : Short arm of chromosome
q : Long arm of chromosome
t : Translocation

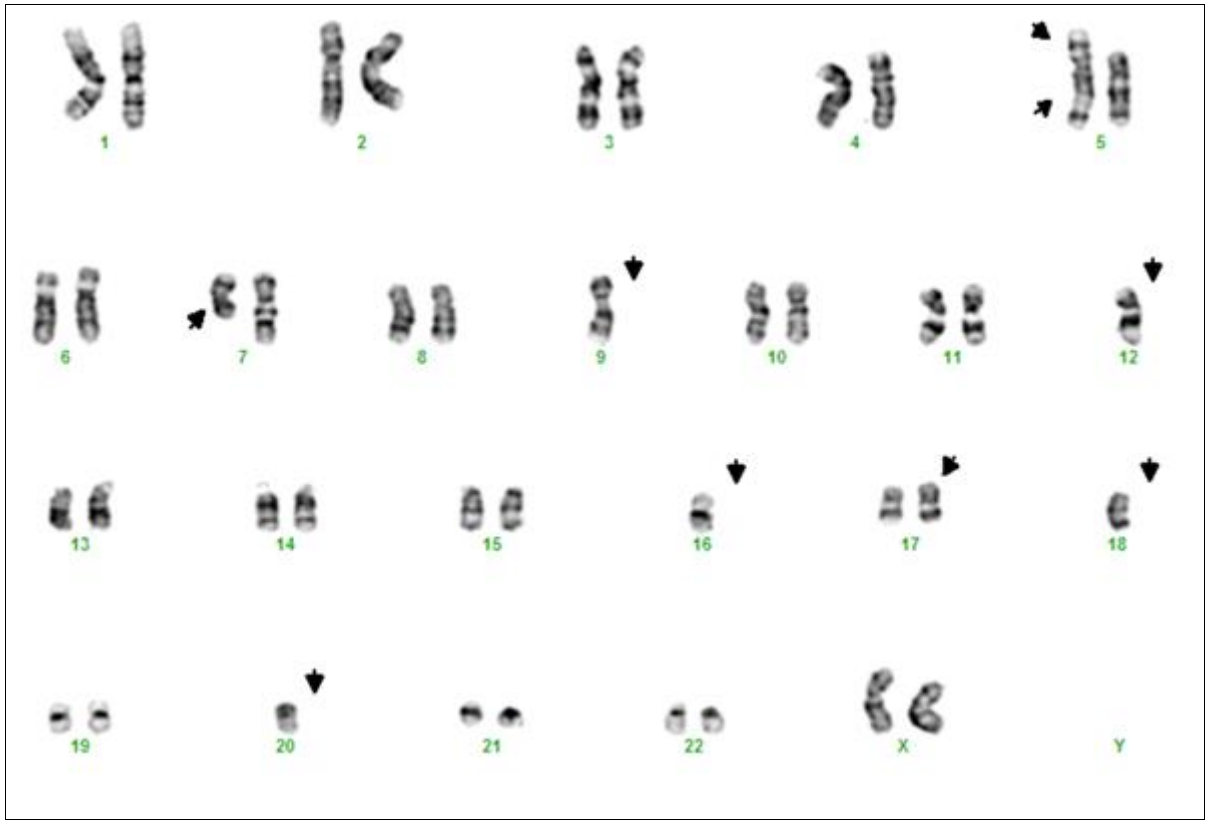

Fig. 1 41,XX,-9,-12,-16, 18,-20,t(5;7)(p13;q11.2),abn(5q),abn(17p)

Monosomal karyotype in AML showing monosomies of chromosomes 9,12,16,18,20; translocation between chromosomes 5 & 7; abnormal 5q and abnormal 17p