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Morphologic characterization of acute myeloid leukemia with cytogenetic or molecular evidence of t(8;21), t(15;17), inv(16) and 11q23 abnormalities

We reviewed the morphology of 110 acute myeloid leukemias (AML) with recurrent cytogenetic/molecular translocations. The t(8;21) cases had some pseudolymphoid blasts and severe dysgranulopoiesis. Acute promyelocytic leukemia showed atypical promyelocytes in peripheral blood and maturation of abnormal granulocytes. The atypical eosinophils were exclusive to inv(16). The cases with 11q23-abnormalities had blasts of monocytic appearance.

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The WHO classification[1] has divided AML into four categories, one of which includes the well established types of AML with recurrent cytogenetic/molecular translocations: AML with t(8;21), AML with t(15;17) and variants, AML with inv(16) and variants, and AML with 11q23 abnormalities. These AML have some degree of correlation with morphology, together with prognostic influence.[2-8] We reviewed the morphologic and laboratory characteristics of 110 cases of these AML subtypes diagnosed in seven hospitals in Catalonia from January 1994 to December 1999. The aim was to know whether the morphologic findings associated with these cytogenetic/ molecular abnormalities were as constant as stated in the literature. Table 1 shows the main clinical and laboratory data. Leukocytosis was significantly higher in 11q23 than in the other types. Cases with t(15;17) and M3 variant morphology had a mean (SD) leukocyte count of 28.5 (27.2) $\times 10^9$/L, higher than those with classical M3 [9.7 (24.8) $\times 10^9$/L], but the difference was of borderline significance (p=0.05). The percentage of blasts in peripheral blood (PB) was significantly higher in 11q23 than in the other types, and in bone marrow (BM), higher in 11q23 and t(15;17). Eosinophils in BM were present in an appreciable amount in inv(16) and in t(8;21). Table 2 shows the main morphologic data.

Twenty-two cases were AML-t(8;21), 4 M1 and 18 M2, coinciding with the FAB subtypes usually described.[1-3,9] Dysgranulopoiesis was severe in all cases, with constant abnormal nuclear segmentation (hyposegmentation or bizarrely segmented nuclei) and hypo or hypergranulation. Two types of blasts were observed in 9 (41%) cases in PB and 13 (59%) cases in BM, one type being of myeloid appearance, and the other one of pseudolymphoid appearance (high nuclear-cytoplasmic ratio, irregular nucleus, scant cytoplasm and moderate basophilia). Although the WHO review states that the small blasts are predominantly found in PB, we found them more frequently in BM. The myeloblasts had fine granulation, frequent Auer rods, and in some cases pseudo-Chediak granules, in agreement with the WHO report. Though uncommon in the other subtypes, cytoplasmic vacuolization was

Table 1. Comparison of the main clinical and laboratory results of the four types of AML. Results expressed as mean (SD).

Cytogenetic anomaly/ N. cases	*t(8;21) N=22*	*t(15;17) N=52*	*inv16 N=27*	*11q23 N=9*	*p*
Age (years)	48 (17)	42 (16)	41 (17)	58 (23)	0.04
Hemoglobin (g/L)	85 (25)	92 (23)	86 (22)	108 (32)	0.07
Platelets ($\times 10^9$/L)	39 (22)	45 (41)	50 (42)	61 (37)	0.4
Leukocytes ($\times 10^9$/L)	12.1 (7.1)	12.6 (25.6)	45.5 (49.2)	85.3 (53.4)	<0.001
Blasts in peripheral blood (%)	42.8 (25)	42.2 (34)	42.7 (33)	69.3 (32)	0.03
Blasts in bone marrow (%)	50.4 (19.9)	74.8 (17.3)	54.4 (19)	82.4 (14.8)	0.001
Eosinophils in bone marrow (%)	2.1 (2.9)	0.1 (0.5)	13 (9.6)	0.6 (1.7)	<0.001

Table 2. Main morphologic data in the four types of AML wih recurrent cytogenetic abnormalities.

Cytogenetic anomaly	*t(8;21) n (%)*	*t(15;17) n (%)*	*inv16 n (%)*	*11q23 n (%)*	*p*
Peripheral blood					
Granulocytes					
Abnormal granulation	17/18 (94)	5/30 (16)	16/23 (70)	1/7 (14)	<0.0001
Abnormal segmentation	18/18 (100)	3/30 (10)	17/23 (74)	3/7 (43)	<0.0001
Single Auer rods	0/18 (0)	1/30 (3)	3/23 (13)	0/7 (0)	ns
Hybrid eosinophils	0/22 (0)	0/50 (0)	8/27 (30)	0/9 (0)	0.008
Red cells					
Dysplasia	1/21 (5)	13/49 (26)	3/22 (13)	2/9 (22)	ns
Platelets					
Dysplasia	0/19 (0)	2/42 (5)	2/26 (7)	2/9 (22)	ns
Bone marrow					
Dyserythropoiesis	2/17 (12)	3/39 (7)	3/22 (13)	0/5 (0)	ns
Dysmegakaryopoiesis	2/15 (13)	0/17 (0)	2/18 (11)	0/5 (0)	ns
Granulocytes					
Abnormal granulation	21/21 (100)	22/30 (73)	19/24 (79)	1/6 (16)	<0.0001
Abnormal segmentation	21/21 (100)	14/30 (46)	17/24 (71)	0/6 (0)	<0.0001
Single Auer rods	5/21 (24)	2/30 (6)	5/24 (21)	0/6 (0)	ns
Vacuoles	8/21 (38)	1/30 (3)	1/24 (4)	0/6 (0)	0.001
Hybrid eosinophils	0/22 (0)	0/50 (0)	27/27 (100)	0/9 (0)	<0.001
Blast characteristics					
Irregular or bilobed nuclei	11/22 (50)	40/50 (80)	20/27 (74)	3/9 (33)	0.001
Fine granulation	15/22 (68)	8/50 (16)	18/27 (66)	5/9 (55)	0.0001
Large granulation	4/22 (18)	42/50 (84)	1/27 (4)	0/9 (0)	0.0001
Pseudo-Chediak granules	6/22 (27)	7/50 (14)	1/27 (4)	0/9 (0)	ns
Single Auer rods	16/22 (73)	8/50 (16)	7/27 (26)	2/9 (22)	0.002
Faggots	0/22 (0)	46/50 (92)	1/27 (4)	0/9 (0)	<0.0001

frequent and useful for raising suspicion. The presence of Auer rods in the mature granulocytes, referred in the WHO description as typical in this AML, was occasional, as in the other subtypes.

Fifty-two cases were AML-t(15;17)/PML/RARα (43 classical hypergranular M3, 8 hypogranular variant and 1 M1). Although the WHO report describes occasional leukemic promyelocytes in PB, we found them in 44 cases. In many cases, the most noticeable trait was the atypical maturation of white cell precursors further than the promyelocytic stage, which were identified by the presence of typical M3 granules and/or faggots. RT-PCR for PML-RARα was performed in 47 cases in a single laboratory, showing a bcr1 rearrangement in 23 and bcr2/bcr3 in 24. Contrary to the published data[5,10] we did not find any significant differences between the 2 types of rearrangement regarding atypical maturation, classical or variant morphology, hemoglobin level, leukocyte count or blast percentage. Although the mean (SD) leukocyte count was higher in cases with the bcr2/bcr3 isoform than with the bcrl one [15.4 (32.2) vs 7.2 (13)], the difference was not significant.

Twenty-seven cases were of the inv(16) category (6 M2, 2 M4, 18 M4Eo and 1 M5). Dysgranulopoiesis was frequent, but scanty hyposegmentation was observed (9/24). There were two types of blasts in 6 cases: 1 M2 and 5 M4. The presence of atypical eosinophils, which have been identified as part of the leukemic cell population,[7] was observed in BM in all cases and frequently in PB, a fact seldom described in the literature.[6] This was a constant and exclusive feature of this subtype of leukemia, irrespective of the FAB subtype.

Finally, 9 cases were adult primary AML with 11q23 abnormalities (1 M0, 2 M4, 5 M5a and 1 M5b). Although in all the reports 11q23 abnormalities are associated with M5 and M4 FAB subtypes,[1,8] few morphologic data are reported. The blasts of monocytic appearance were quite homogeneous, and no Auer rods or vacuolization were seen in the mature granulocytes.

In comparing the morphologic data among the groups, we found that dyserythropoiesis and dysmegakaryopoiesis were uncommon in all types. Dysgranulopoiesis was highly marked and statistically significant in t(8;21), marked in inv(16), intermediate in 11q23, and low in t(15;17). The irregular nuclear profile of the blasts showed statistical significance among the different types. The presence of atypical eosinophils was exclusive to inv(16). Despite the need for the new technologies to accurately diagnose and predict clinical outcome, morphologic aspects are still the first step in the evaluation of AML.

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Key words: acute myeloid leukemia, morphology, t(15;17), inv(16), t(8;21), 11q23.

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