New Cytogenetic Aspects of Myelodysplasia and Acute Leukemia

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The use of modern chromosomal banding techniques in preleukemia and leukemia has revealed the presence of nonrandom chromosome abnormalities, some of which have clear diagnostic and prognostic significance. Among these are translocations t(8;21), t(15;17), t(9;11), t(4;11), t(8;14), t(9;22); trisomies 4, 8, 12, 21, 1q; monosomies 5, 7, X, Y; deletions 5q-, 7q-, 9p-, 12p-, 20q- and some others [4]. According to our data nonrandom chromosome abnormalities were revealed in 35 of 47 patients (70%) with myelodysplastic syndromes and in 55 of 108 patients (51%) with acute leukemia.

The study has shown the pure noncomplicated chromosome changes in acute leukemia patients to occur infrequently, which is why the analysis of their role in pathogenesis and prognosis of leukemia is very difficult. Besides, most of them can disappear from the karyotype after cytostatic therapy. The majority of the above-mentioned chromosome abnormalities typical for acute leukemia are found at the stage of myelodysplasia. This evidence and the possibility of repeating investigations of karyotype make myelodysplasia a perfect object for studying many aspects of leukemia cytogenetics.

The accumulated information concerning the karyotypic abnormalities in patients with myelodysplastic syndromes is given in Table 1. A closer look at the material reveals a great variability of cytogenetic findings. The more frequent among them were monosomies and deletions of the long arms in chromosomes 5 and 7, followed by trisomies 8, 21 and 1q, as well as deletion 20q.

The best-known and most widespread anomaly is the 5q-anomaly, described by van den Berghe et al. [9]. The 5q-marker is formed as a result of interstitial or terminal deletion of a long arm of chromosome 5. It occurs in a quite characteristic clinicohematologic setting now termed the 5q- syndrome. This disorder typically develops in elderly female patients. Their anemia is macrocytic and is resistant to therapy. The other significant feature of the syndrome is a presence of normal or elevated platelets in spite of morphologically characteristic megakaryocyte abnormalities. Finally, it is worthwhile that the clinical course of 5q-syndrome is often mild. Transformation into acute leukemia is relatively rare, at least when 5q- is the only abnormality present at diagnosis. Among our patients it took place only once (patient no. 4), when karyotype at diagnosis was 47, XX, 5q-, + 21. On the other hand, growing experience shows that some patients with 5q- anomaly may reveal the nonclassical course of the disorder. For example, our first patient (49 years old, female), was treated at our clinic for 5 years. Initially she had only mild macrocytic anemia which was resistant to therapy and normal or slightly decreased platelet level. Later lymphocytic infiltration of stomach and moderate paraproteinemia had been revealed. However, serial cytogenetic studies did not show any additional nonrandom chromosome changes. For some time the patient was

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Table 1. Results of cytogenetic analysis of bone marrow cells from patients with myelodysplasias

Case no.	Age/sex	FAB class	Karyotype	Survival without AL (months)
1.	49/F	RA	46, XX, 5q−(q13, q33)	61
2.	78/M	RA	46, XX, 5q−(q12, q337	30+
3.	72/M	RAEB	46, XY, 5q−(q13, q34)	6+
4.	50/F	RA/RAEB	47, XX, 5q−(q13, q33), +21	12
5.	54/M	RAEB	45, XY, −7	3
6.	54/M	RAEB	43, X, −Y, −5, 7q−(q22), −12	1
7.	65/M	RAEB	48, XY, 5q−(q13, q33), 7q−(q22), +8, +9, 12p−(p12), 13q−(q14)	3
8.	80/F	RAEBT	46, XX, −7, +8, inv(9)	4
9.	21/F	RAEB	45, XX, −5, −6, −7, +der(11), t(11p, ?), +22q−(q11)	10
10.	28/F	RSA	46, XX, t(3; 3) (q21; q26)	108+
11.	37/M	RA	45, XY, −7, t(3; 3) (q21; q26)	
12.	62/M	CMML	46, XY, 3q−(q13, 3q23)	23
13.	58/F	RAEB	43, X, −X, 1q+, −3, −5	4
14.	73/F	RAEBT	46, XX, 20q−(q11)	4
15.	49/M	RAEBT	47, XY, −6, +der(6), t(2; 6) (p12; q25), 20−(q11), +20	28
16.	56/M	RAEB	47, XY, +8	10+
17.	68/M	RSA	46, XY, 11q−(q22)	4+
18.	56/F	CMML	47, XX, +11	20+
19.	65/F	RA	46, XX, −14, +i(14q)	5?
20.	18/F	RA	46, XX, −17+der(17), t(1; 17) (q21; p11)	68
21.	28/M	RA	46, XY, −2, +der(2), t(1; 2) (q21; q36)	20
22.	72/F	RA	46, XY, −5, +8, −9, +der(9), t(1; 9) (q11; q32)	36
23.	65F	RAEBT	49−53, XX, −5, +8, +11, +13, +14, −16, +19, +22, +22, +Mar1, +Mar2, +DM	?
24.	52/M	RAEBT	55, XX, +1, +2, −5, +6, +9, +10, +11, +14, −16, +21, +22, Mar1, Mar2	2

AL, acute leukemia; *F*, female; *M*, male; + means the available; patients are alive; ?, no complete information available; *RA*, refractory anemia; *RAEBT*, refractory anemia with excess of blasts; *RSA*, refractory sideroblastic anemia; *CMML*, chronic myelo-monocytic leukemia.

treated with blood transfusions, desferal, and steroids. She died 60 months later from serious bowel infection complicated by collapse. There were no signs of leukemia or lymphoma on autopsy. The case may be considered as an example of a real involvement of B-lymphocyte precursors into the pathological process in patients with 5q− syndrome.

Other nonrandom karyotype changes of the patients with myelodysplasias were monosomy 7 or deletion 7q. They were revealed mainly in refractory anemias with or without blasts and were often combined with some other chromosome abnormalities, including monosomy 5 or deletion 5q. It is noteworthy that three of the patients (cases 5, 6, and 9) had

previous exposure to radiotherapy or cytotoxic drugs. According to our data, pure monosomy 7 was found only in a 54-year-old patient (patient no. 5) who had survived without leukemia for 3 months only. It should be kept in mind that the time of survival without acute leukemia in three other patients of this group (cases 6–8) did not exceed 4 months. It was longer only in two younger patients (nos. 9 and 11), who had additional numerical and structural chromosome rearrangements, including classical translocation t(3;3)(q21;q26). Of particular interest is the patient with t(3;3) associated with monosomy 7, who had no elevated platelet count in spite of the predisposing chromosome rearrangement. Furthermore, there were very few megakaryocytes in the patient's bone marrow. On the contrary, the presence in karyotype of translocation t(3;3)(q21;q26) alone which was revealed in a patient with acquired idiopathic sideroblastic anemia (no. 10) was associated with thrombocytosis and with prolonged (more than 9 years) survival without leukemia. It is worth noting that recently Caroll et al. [3] found the same translocation t(3;3)(q21;q26) in a similar patient with acquired idiopathic sideroblastic anemia and thrombocytosis.

The next nonrandom chromosome abnormality found in two patients with refractory anemia with excess blasts in transformation was deletion 20q. In one of the patients (no. 14) it was a sole rearrangement while in the other (no. 15) the karyotype was complicated by the other chromosome abnormalities. Yet the survival time was shorter in the first case which may be ascribed to her old age.

The results presented in Table 1 show part of the chromosome changes revealed to be associated with increasing cellular genetic material. First of all it concerns trisomies 8 or 11 as well as partial trisomy for the long arm of chromosome 1. The best-known chromosome anomaly among these is trisomy 8, which has been shown repeatedly to be connected with all famous types of myelodysplastic syndromes besides chronic myelomonocytic leukemia. As in our case 16, trisomy 8 may be a sole karyotypic change. However, its combinations with other chromosome abnormalities are more frequent (cases 8, 22, and 23).

The other common chromosome change in patients with myelodysplasia and leukemia [6] is a partial trisomy for 1q. The mechanisms through which trisomy 1q has arisen are translocations t(1;2), t(1;9), t(1;17). The latter took place in a young (18-year-old) woman who was under observation for 5 years [5]. She presented in 1984 with stomatitis, leukopenia and pseudo-Pelger-Huët anomaly. Bone marrow aspirate showed normal cellularity with clear morphologic dyshemopoiesis of all three lineages. Serial cytogenetic studies of the bone marrow cells revealed the cellular clone with t(1;17) and partial trisomy 1 which showed no changes until death. A diagnosis of myelodysplastic syndrome was made. The course of the disease was severe because of many infections which had not been properly controlled by antibiotics. She demonstrated neither clinical nor morphological features of leukemia. Autopsy confirmed the diagnosis of myelodysplasia. The case is interesting in several aspects. First, it demonstrates a new variant of partial trisomy of the long arm of chromosome 1 in a patient with myelodysplasia. Second, it shows that this translocation predisposes the formation of pseudo-Pelger-Huët anomaly. This conclusion is based on recent data illustrating close correlation between deletion 17p and the above-mentioned anomaly in chronic myelocytic leukemia [8]. As for survival time, it was comparatively long in a group of patients with additional genetic material. Thus, the prognosis of myelodysplasia patients, including leukemia risk, is apparently not influenced by the presence of clone with pure trisomy 1q and partial monosomy 17p. On the other hand, the presence of karyotypes with multiple abnormalities is concomitant with unfavor-

able prognosis, including an increased risk of leukemia (cases 24 and 25).

In general, the role of certain chromosome changes at the stage of transformation of myelodysplasia into acute leukemia depends on the character of the abnormality. Some of them, especially monosomy 7 or deletion 7q, are associated with particularly bad prognosis and frequent transformation into acute leukemia. In contrast, such numerical chromosome changes and structural arrangements as trisomy 8, deletion 5q, partial trisomy 1q and translocation t(3;3) can persist in the cells tested from 1 to 9 years. On the basis of these data the conclusion may be drawn that influence of the above-mentioned chromosome abnormalities on prognosis of myelodysplasia patients and on its transformation into acute leukemia is minimal.

Comparison of basic chromosome abnormalities in myelodysplasia and in acute nonlymphoblastic leukemia patients whos their similarity (Table 2). In general, all chromosome changes revealed in myelodysplastic syndromes are now found in leukemia too. On the other hand, some of the most important and constant acute nonlymphoblastic leukemia arrangements – t(9;11), t(15;17), t(9;22) and inv(16)(p13q22) – are not seen in myelodysplasia. This fact indicates that patients with the chromosome abnormality mentioned above pass through a very brief phase pf myelodysplasia, if at all.

Analysis of the cytogenetic changes uncommon to both diseases showed that the most frequent among them were t(9;11), t(9;22), and t(15;17). The first abnormality was associated with M5a subgroup of actue myeloid leukemia (AML) (Table 3). The breakpoints clustered to two regions: 11q22–q24 and the more proximal 11q14 [1]. In most observations including our series the arrangements of the long arm of chromosome 11 were interpreted as reciprocal translocation between 9 and 11 chromosomes. In general, chromosome abnormalities in patients with acute monoblastic leukemia

Table 2. Comparison of basic chromosome abnormalities in myelodysplasia and acute nonlymphoblastic leukemia patients

Chromosome abnormalities	Myelo-dysplasia	Acute leukemia
1q+	+	+
t (3; 3)	+	+
5q−/−5	+	+
7q−/−7	+	+
+8	+	+
+11	+	+
11q−	+	+
12p−	+	+
20q−	+	+
t (6; 9)	−	+
t (9; 11)	−	+
t (15; 17)	−	+
t (9; 22)	−	+
inv (16)	−	+

(M5 variant according to the French-American-British Working Group for Leukemia Classification (FAB) criteria) were more complex than in those with acute myelomonocytic leukemia (M4 variant). It concerned both the number of patients with normal karyotype and the character of chromosome changes. Thus, the group of the patients with M5 variant of AML revealed many nonrandom chromosome abnormalities and the absence of normal karyotypes. In contrast, the karyotype of the cells tested in 8 of 13 patients with M4 variant of AML was normal while the others revealed only moderate chromosome abnormality. A possible explanation for this difference may be the presence in the bone marrow from patients with acute myelomonocytic leukemia of certain granulocytic and/or erythroid elements with unchanged chromosomes.

Another frequent abnormality is the Ph′ chromosome. In our series it was found in ten patients with acute lymphoblastic leukemia. One of them (37-year-old woman) had karyotype, showing duplication of Ph′ chromosome and partial trisomy for the long arm of chromosome 1. The latter arised trough

Table 3. Comparison of nonrandom chromosome changes in patients with M4 and M5 variants of acute nonlymphoblastic leukemia

Karyotype	Number of cases	Type of leukemia	
		M4	M5
46, XX or 46, XY	8	8	–
46, XX, inv. (9)	1	1	–
46, XX, 9q−(q21; q22)	1	1	–
46, XY, t (8, 17) (q22; q23)	1	1	–
46, XY, t (8, 21) (q22; q22)	1	1	–
46, XY/46, XY, DM (7%)	1	1	–
46, XY, t (9; 11) (p22; q23)	1	–	1
46, XX, t (9; 11) (p22; q23)	1	–	1
46, XX, t (9; 11) (p22; q23) /the same +t (12; 18) (q13; p11)	1	–	1
47, XX, +8, t (9, 11) (p22; q24)	1	–	1
47, XY, −4, −5, +Mar1, +Mar2, +Mar3	1	–	1
43, XY, 5q−, −7, −12, −14, +der (7), t (7; 14), −15, −22, +der (22), t (18; 22)	1	–	1
48, XY, +11, +21	1	–	1
55, XX, +1, +2, −5, +6, +9, +10, +11, +14, −16, +21, +22, +Mar1, +Mar2	1	–	1

translocation of part of a long arm of chromosome 1 to the short arm of chromosome 14. Furthermore, the cells tested had lost one chromosome 16 and revealed additionally marker 19p+ which remained unrecognized. In spite of massive cytostatic and hormonal therapy which continued for 2 years, complete remission was not achieved and the patient expired. A similar situation occurred in six more patients with Ph′ positive acute lymphoblastic leukemia where it was impossible to control the expansion of leukemic clone by cytostatics. The current literature indicates that the average survival for Ph′ positive AML patients was about 10 months [7]. Similar prognostic features were also characteristic for Ph′ positive acute lymphoblastic leukemia in which the rate of remission was very slow [2].

Taken together, these data show that rearrangements of chromosomes found in myelodysplasia and acute leukemia play the significant role in pathogenesis and prognosis of these disorders. Furthermore, the breaks of such loci as 3q26, 11q22–24, 16q22, and 17p11 are related to the formation thrombocytosis, monocytosis, eosinophilia, and Pelger-Huët anomaly.

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