

CYTOGENETIC ANALYSIS IN PATIENTS WITH MYELODYSPLASTIC SYNDROME†

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Forty-six patients with myelodysplastic syndrome (MDS) were studied. Chromosomal abnormalities were observed in 20 of the 46 patients (43%). Abnormalities of chromosome No. 5 occurred in 6 patients (13%); four of them had a deletion of the long arm of this chromosome [del (5q)]. Four patients had monosomy 7 (8.6%), and six patients had trisomy 8 (13%). Our results suggest that chromosomal abnormalities, deletion (5q), monosomy 7 and trisomy 8, might play important roles in the pathogenesis of MDS.

Key words myelodysplastic syndrome; chromosomal abnormality; monosomy; deletion; trisomy

Primary myelodysplastic syndrome (MDS) comprises a group of acquired disorders of hematopoiesis, characterized by progressive cytopenia which reflects defects in erythroid, myeloid and megakaryocytic maturation (1). Up to 30% of cases eventually develop acute nonlymphocytic leukemia (ANLL) (2). The French-American-British (FAB) Cooperative Group proposed a morphological classification of these disorders, in which five subtypes are defined (3): refractory anemia (RA), RA with ring sideroblasts (RARS), RA with an excess of blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). These subtypes broadly represent the different stages of leukemogenesis. Patients with MDS who have a risk of leukemic change exhibit a variable clinical course. It has been suggested that the development of leukemia in patients with MDS may be related to chromosomal ab-

normalities (4, 5), and chromosomal abnormalities have been reported consistently in about 40 percent of patients with MDS (6). But in a recent series using high resolution chromosome banding techniques abnormalities were detected in 79 percent of cases (5). Karyotype assessment is the most important of all ancillary investigations since it is the only one which can confirm the diagnosis objectively. Moreover, the karyotype is an independent prognostic factor. Here we report the cytogenetic analysis of 46 patients with MDS, and the role of the cytogenetic changes is discussed.

PATIENTS AND METHODS

All of the 46 patients described here were first seen at the University of Chicago Medical Center, with a diagnosis of MDS confirmed by morphologic study of bone marrow specimens. There were 8 patients with RA, 6 with RAEB, 1 patient with RARS, and 5 patients with CMML. The diagnosis of MDS conformed to the criteria of the FAB classification (3). Cytogenetic analysis was performed using the trypsin-Giemsa

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banding technique on bone marrow cells in aspirate or biopsy specimens obtained at the time of diagnosis. The metaphase cells from direct preparations of 24- or 48-hour unstimulated cultures were examined. Chromosome abnormalities were described according to the International System for Human Cytogenetic Nomenclature (7). The criteria adopted at the First International Workshop on Chromosomes in Leukemia were used for the identification of abnormal clones (8).

RESULTS

Chromosomal abnormalities were observed in 20 of the 46 patients with MDS (43%). The results of cytogenetic analysis of the 20 patients with abnormal karyotypes are shown in Table 1. Abnormalities of chromosome No. 5 occurred in 6 patients; two had both a loss of one chromosome No. 5 and a translocation involving chromosome No. 5, t(2;5) (case 005) or t(5; 15) (case 020); four had a deletion of the long arm of this chromosome [del (5q)]. Two had a loss of part of the long arm of chromosome No. 7, and four patients (cases 001, 005, 012, 020) had monosomy 7. Trisomy 8 was observed in six patients. Patients 015 and 017 had deletions of the long arm of chromosome No. 11. Deletion of the short arm of chromosome No. 12 was noted in 2 patients (cases 011, 020) [del (12) (p11)]. Only one patient (case 020) had a deletion of the long arm of chromosome No. 20. In this study, the frequencies of alterations of six chromosomes, namely, No. 5, 7, 8, 11, 12, and 20, were 13% (6/46), 13% (6/46), 13% (6/46), 4% (2/46), 4% (2/46), and 2% (1/46) respectively. Loss of the Y chromosome was observed in one patient (case 004).

DISCUSSION

In this study, we confirmed that MDS is characterized by the presence of abnormalities of chromosomes No. 5, 7 and 8. We detected breakpoints in the long arm of chromosome No. 5 in 13% of our patients. A deletion of chromosome No. 5 was found in 4 of the 6 patients with abnormalities of chromosome No. 5. Partial deletion of chromosome No. 5 was usually interstitial but could also be terminal. The proximal breakpoints varied from 5q11 to 5q23, and the distal from 5q22 to 5q35 (9, 10). The breakpoints in the 4 patients with del (5q) were from 5q13 and from 5q31 to 5q35 (Fig 1). The

breakpoints of chromosome No. 5 in two patients with translocations were 5q22 and 5q13. All the 6 patients having a breakpoint on chromosome No. 5 developed other chromosomal abnormalities (e.g. case 020, Fig 2) since the first cytogenetic study. The results suggest that most of these patients were in the late stage of the disease. It is of interest that 66% of the MDS patients reviewed by Van den Berghe et al (4) with 5q- as the only alteration at diagnosis had RA, whereas 66% of the patients with 5q- plus other alterations at diagnosis had RAEB or MDS. However, it is also possible that heterogeneity of this marker and the different patterns of presentation may be correlated with the morphologic classification of the disease. Recent observations concerning the 5q- abnormality may offer a clue to the underlying molecular mechanisms (11, 12). By fusing human bone marrow cells from del (5q) patients with rodent cells, Nienhuis et al (11) found that c-fms (McDonough feline sarcoma virus) sequences were incorporated within the deleted segment of chromosome No. 5. The distal breakpoint on chromosome 5 was thought to be proximal to band q34. Using *in situ* chromosomal hybridization, Le Beau et al (12) have localized the c-fms gene to band q33; GM-CFS (granulocyte-monocytic colony stimulating factor) has been localized to somewhere between 5q23 and 5q31 (12). Both of these genes were deleted in several patients with del (5q) (12). Thus, the products of the c-fms and GM-CSF genes may play an important role in the proliferation and differentiation of cells of the mononuclear-phagocytic lineage. Four patients (cases 001, 005, 012, 020) who had chromosome 7 monosomy and two patients (cases 014, 010) with partial deletion of chromosome 7 have been found. The proto-oncogene C-erb B (avian erythroblastosis virus) and the transforming sequence met are located on chromosome No. 7. The former gene has recently been shown to code for a protein that is a truncated form

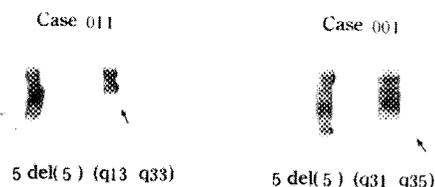


Fig 1. Partial karyotypes illustrating the terminal deletion of chromosome 5 in patients 011 and 001.

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Table 1. Cytogenetic results of twenty patients with MDS

| Case No. | FAB classification | Age at diagnosis | Specimen | No. of metaphase cells | Karyotype |
|----------|--------------------|------------------|----------|------------------------|---|
| 001 | RA | 59 | BC | 22 | 46, XY, del (5) (q31q35) (5%)/45, XY, -7, del (5)(q31q35)(95%) |
| 002 | MDS | 78 | BM | 21 | 46, XY (95%)/ SCA: 46, XY, del (20) (q11 q13) (5%) |
| 003 | CMML | 72 | BM | 20 | 46, XY (85%) / 46, XY, del (15) (q13 q15) (15%) |
| 004 | RAEB | 70 | BM | 22 | 46, XY (68%) / 45, X, -Y (32%) |
| 005 | RAEB | 79 | BM | 33 | 46, XY (67%) / 45, XY, -5, -7, -9, -13, -17, -19, +i (3q), t (2;5) (q14; q13), + der (9) t (1;9) (q21; q21), + mar1, + mar2, + mar 3 (33%) |
| 006 | MDS | 81 | BM | 22 | 46, XY, (9%)/48, XY, +y, +8 (91%) |
| 007 | CMML | 65 | BM | 21 | 46, XY, inv (10) (p21 q21) (10%) / 47, XY, +8, inv (10) (90%) |
| 008 | MDS | 60 | BM | 23 | 46, XY (13%)/ 47, XY, + 8 (87%) |
| 009 | MDS | 83 | BM | 26 | 46, XX (88%)/ 47, XX, + 8 (12%) |
| 010 | RA | 59 | BM | 22 | 46, XX, del (5) (q14 q33.3) (100%) |
| 011 | MDS | 92 | BM | 21 | 47, XX, +8, del (5) (q13 q33) (29%)/ 47, XX, +8, del (5), del (12) (p11 p12) (67%)/ SCA: 48 XX, +8, +12, del (5), del (12), t (1;12) (q42; q22) (5%) |
| 012 | RAEB | 54 | BM | 30 | 46, X, t (X; 17) (q28;q21) (53%) / 46, X, t (X; 17), -7, + der (1) t (1;7) (p11; p11) (47%) |
| 013 | MDS | 75 | BM | 38 | 46, XY (84%)/46, XY, inv (3) (q23;q25) (16%) |
| 014 | MDS | 52 | BM | 22 | 46, XX (77%)/ 46, XX, del (7) (q22 q32) (23%) |
| 015 | MDS | 31 | BM | 23 | 46, XX (87%)/ 47, XX, +6 (9%) / SCA: 46, XX, del (11) (q13 q21) (4%) |
| 016 | MDS | 70 | BC | 9 | 46, XY (89%) / SCA: 46, XY, del (13) (q14 q22) (11%) |
| 017 | RA | 81 | BM | 19 | 46, XY, del (11) (q13 q23) (100%) |
| 018 | MDS | 88 | BM | 24 | 46,XX (17%)/45,X,-X,del (5) (q14 q33) (79%) / SCA: 46, XX, del (7) (p12 p22) (4%) |
| 019 | RAEB | 68 | BM | 21 | 46,XY, idic(14)(p11)(100%) |
| 020 | RAEB | 79 | BM | 21 | 46, XX (19%) / 48, XX, -5, +6, -7, +8, del (12*) (p11), t (12*; ?) (q22; ?), del (17) (p11), + der (7) t (7; 11) (q21; q21), + mar 1 (5%) / 47, XX, same as clone 1, -4 (29%)/47, XX, same as clone 2, -5, del (3) (q27 q29), inv (6*) (p12 q25), t (6*; ?) (p25; ?), + der (5) t (5;15) (q22; q15) (48%) |

Abbreviations: i: isochromosome; t: translocation; del: deletion; der: derivative chromosome; inv: inversion; dic: dicentric; BM: bone marrow; BC: bone core biopsy; SCA: single cell abnormality.

*two aberrations in the same chromosome.

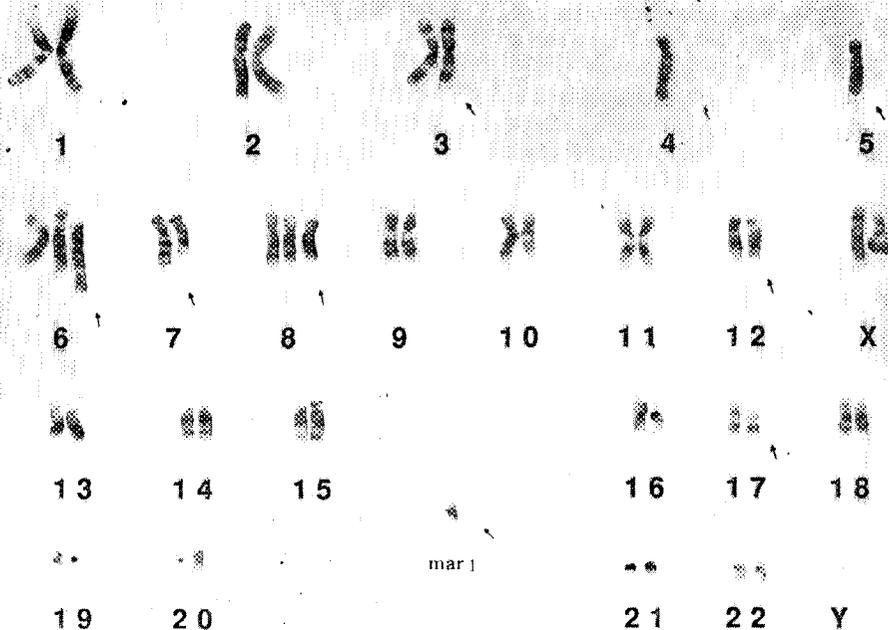


Fig 2. Bone marrow cell from patient 020 with karyotype 47, XX, -4, -5, +, +8, +der (5) t (5; 15) (q22; q15), +der (7) t (7; 11) (q21; q21), +mar 1, del (3) (q27 q29), inv (6*) (p12 q25), t (6*; ?) (p25; ?), del (12*) (p 11), t (12*; ?); (q22; 7), del (17) (p11).

of the receptor for epidermal growth factor (13). C-erb B has been located to 7p or proximal 7q (14). Met has been localized to 7q (15).

We have found two different clones in 12 of the 46 patients: clones with 5q- and clones with trisomy 8. These data strongly suggest a non-random association between the clones and MDS, although we do not know the meaning of this phenomenon.

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