Three Cases of Translocation (8;16)(p11;p13) Observed in Acute Myelomonocytic Leukemia: A New Specific Subgroup?

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ABSTRACT: *In three cases of acute nonlymphocytic leukemia we observed a translocation (8;16)(p11;p13); in one case it was the sole karyotypic change and in the other two cases it was associated with other structural anomalies. All three cases were nonhyperleukocytic myelomonocytic leukemias with erythrophagocytosis by some blast cells and cytochemistry results consistent with leukemic proliferation of a common monocytic–granulocytic precursor. The importance of this translocation is discussed, and the implication of band 16p13 in myelomonocytic leukemia is stressed.*

INTRODUCTION

More accurate cytogenetic techniques have led to the discovery of a number of nonrandom structural chromosome abnormalities in acute nonlymphocytic leukemias (ANLL). Some are associated with rather specific cytologic pictures such as t(8;21)(q22;q22) [1, 2], inv(3)(q21q26) [3] and inv(16)(p13q22) [4], whereas, others define cytogenetic subgroups, such as t(9;11)(p21;q23) [5] and t(6;9)(p23;q34) [6].

We observed a t(8;16)(p11p13) in the bone marrow cells of three patients with acute myelomonocytic leukemia. This translocation, mentioned only once in the literature [7] to the best of our knowledge, defines a possible new cytogenetic subgroup of ANLL associated with some cytologic and cytochemical particularities.

MATERIALS AND METHODS

The karyotype status of 184 consecutive ANLL patients (from January 1981 to December 1985) was established on bone marrow cells after a 24-hour culture without stimulation. Chromosomes were analyzed, using R- and G-banding in some instances (case 2). Karyotypes were described according to the ISCN [8].

The diagnosis of ANLL (M1–M6) was made, according to morphologic criteria of the FAB study group [9]. Bone marrow and blood smears were stained with May–Grünwald–Giemsa and cytochemical tests were carried out: peroxidase [10], na-

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phtol-ASD acetate esterase with and without NaF [11], and, in some instances, combined esterase reaction on the same slide, using α-naphtyl-butyrate at first, followed by naphtol-ASD-chloroacetate staining [11].

RESULTS

Among the 184 ANLL patients, cytologic and cytochemical data showed 66 cases with a monocytic component. Using strict criteria, 41 cases were acute monocytic leukemias (M5) and 17 cases were acute myelomonocytic leukemias (M4). In the remaining eight cases, at least part of the bone marrow cells were difficult to classify as monocytic (monoblasts, promonocytes, monocytes) or granulocytic (myeloblasts or immature granulocytes): so these were classified as unusual acute myelomonocytic leukemias (unpublished data). Among these eight patients, three had a t(8;16).

Clinical Observations

The histories of the three cases with this translocation will be briefly presented below. Table 1 summarizes the main hematologic data.

Case 1 is a 13.5-year-old girl with acute leukemia. Clinical examination showed mild splenohepatomegaly and diffuse mild lymphadenopathy. There were no skin infiltrates and the cerebrospinal fluid was normal. Complete remission was induced with zorubicin (RBZ), cyclophosphamide (CPM) and cytosine arabinoside (ara-C), consolidation with thioguanin, ara-C, etoposide and mitoguazone, and maintenance therapy included a combination of ara-C and mercaptopurine. Remission is still present after 6 months; this patient is being considered for a bone marrow transplant.

Case 2 was a 29-year-old woman when she was hospitalized for a cerebral tumor (frontal glioblastoma). Successful treatment was achieved after 12 months with surgery, radiotherapy and chemotherapy including high doses of nitrosourea. Eleven months after the therapy she was readmitted for severe pancytopenia. Clinical examination showed fever, palor, and cutaneo-mucous bleeding. No splenohepatomegaly, lymphodenopathy, skin, or cerebral involvement was noted. Chemotherapy was started, using CPM, RBZ and Ara-C, but the patient died of infectious complications a few days later.

Case 3 is a 59-year-old woman with acute leukemia. Clinical examination showed no organ involvement, but important cutaneous bleeding. Complete remission was achieved after induction and consolidation with ara-C, RBZ, and teniposide, and maintenance therapy with AMSA and ara-C. The patient is still alive after 22 months.

Table 1 Hematologic data of the three patients at presentation

	Blood					Lysozyme (mg/L)		Bone marrow		
Case no.	WBC ($\times 10^9$/L)	Blasts (%)	Monocytes (%)	Hemoglobin (g/L)	Platelets ($\times 10^9$/L)	Serum (n = 5–15)	Urine (n < 2,5)	Density	Blasts (%)	Monocytes (%)
1	3.9	8	8	106	80	84	400	Rich	89	0.5
2	2.0	19	2	72	21	13	1	Rich	85	1.0
3	4.9	1	10	110	20	12	3	Rich	73	4.5

Cytologic and Cytochemical Observations

Morphology. The bone marrow cells in case 1 were morphologically homogeneous: large blast cells with low N:C ratio, round nucleus, and many azurophilic granules scattered in the cytoplasm and over the nucleus. In case 2, cells identical to those of case 1 were mixed with 30% blasts with a higher N:C ratio and fewer granules and 20% of cells having common cytologic features of promyelocytes and promonocytes. In case 3, 50% of the blasts displayed features of the high and low N:C ratio of the leukemic cells described above and the other 50% were slightly more mature and rather consistent with promonocytes (folded or twisted nucleus, vacuolated cytoplasm) though the granules were prominent and numerous. In no case were there any Auer rods of abnormal (or excess) eosinophils seen, though one common feature was conspicuous erythrophagocytosis by some of the immature cells, and to a lesser extent by more mature cells in cases 2 and 3.

The five other cytologically "unusual" cases were comparable with the three cases described above, but no phagocytosis was encountered. Careful research on the other monocytic leukemias showed occasional phagocytosing blasts in at least two cases of M5 type.

Cytochemistry. Results were summarized in Table 2, showing 71% and 65% dual esterase positivity in the blasts in cases 1 and 2 respectively, and strong peroxidase associated with positive fluoride-sensitive esterase in 100% of the cells in case 3.

Cytogenetic Observations

In the M5 and M4 leukemias followed by us, karyotypes are abnormal in 23 of 41 cases (56%) and in 11 of 17 cases (65%), respectively. The main numeric or structural abnormalities were comparable with those in the literature [12]; e.g., trisomy 8 (three in M4 and seven in M5), 11q23 abnormalities (six cases, all M5) and inv(16)(p13;q22) (four cases M4 with abnormal eosinophils) (unpublished data).

Among the eight cases that were more difficult to classify cytologically, one had a normal karyotype, two a hypodiploid clone, one a trisomy 8, and one a trisomy 8 and t(1;21). The cytogenetic findings of the three others are described in detail below.

For cases 1, 2, and 3 analysis of 26, 18, and 32 cells was performed, respectively. In case 1, the t(8;16) was the only abnormality found at diagnosis in most of the metaphases observed (Fig. 1); only one cell had a normal karyotype. In case 2, this translocation was associated with other structural alterations: t(1;6)(q32;q25), del(3)(q23q27?) (Fig. 2). In case 3, three cellular clones were present: normal cells (46,XX) (12 metaphases), 46,XX,t(8;16)(p11;p13) (five metaphases), and 46,XX,

Table 2 Cytochemistry of bone marrow blast cells in the three patients

Case number	Peroxidase (%)[a]	NASDA esterase +NaF (%)	Combined esterase (%)
1	100	100	71
2	38	60	65
3	100	100	NT[b]

[a]In each case peroxidase was moderate to strong, and dispersed.

[b]NT, not tested.

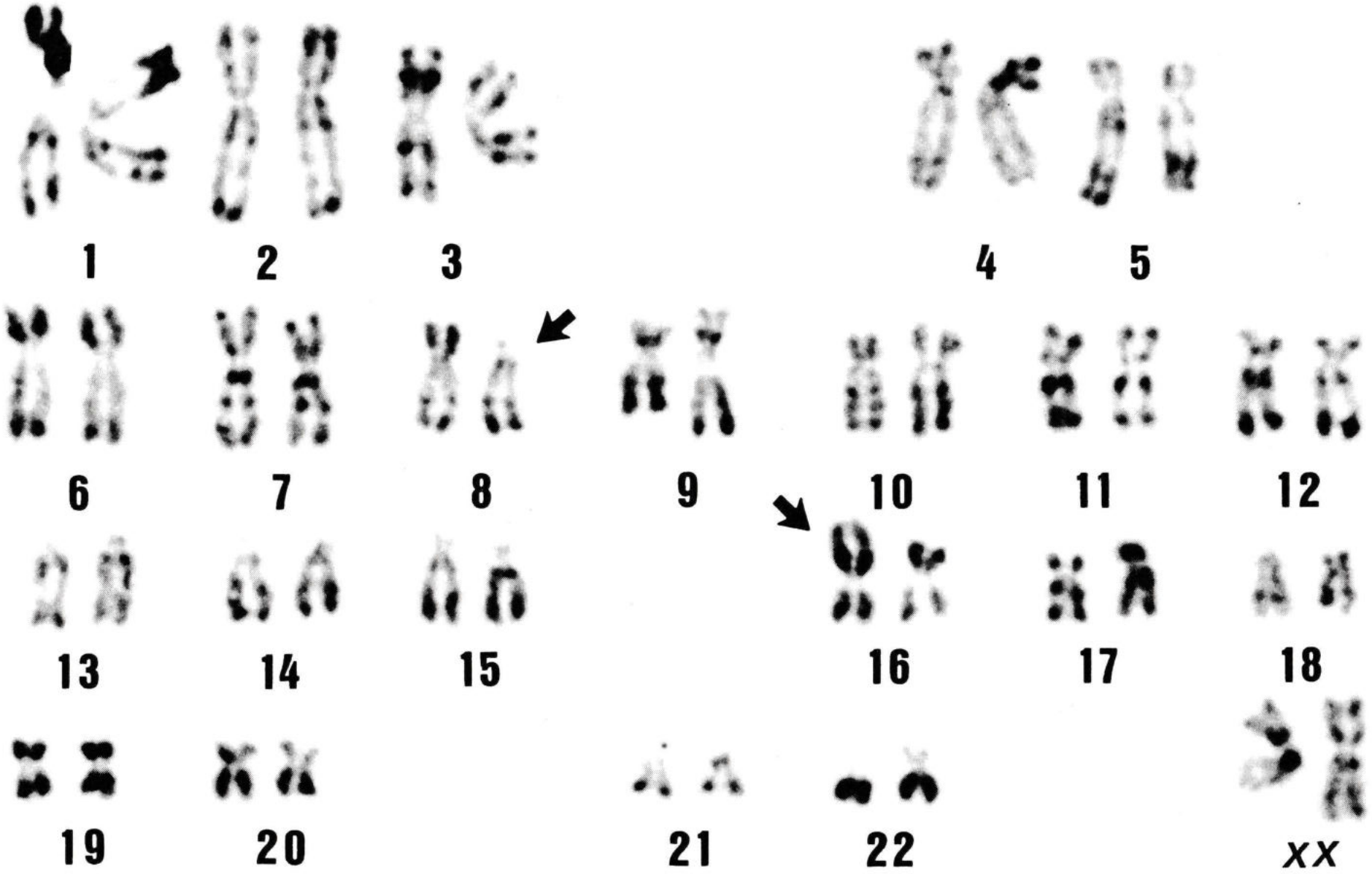


Figure 1 Representative karyotype from case 1: 46,XX,t(8;16)(p11;p13) (R-banding). Breakpoints are indicated by bold arrows.

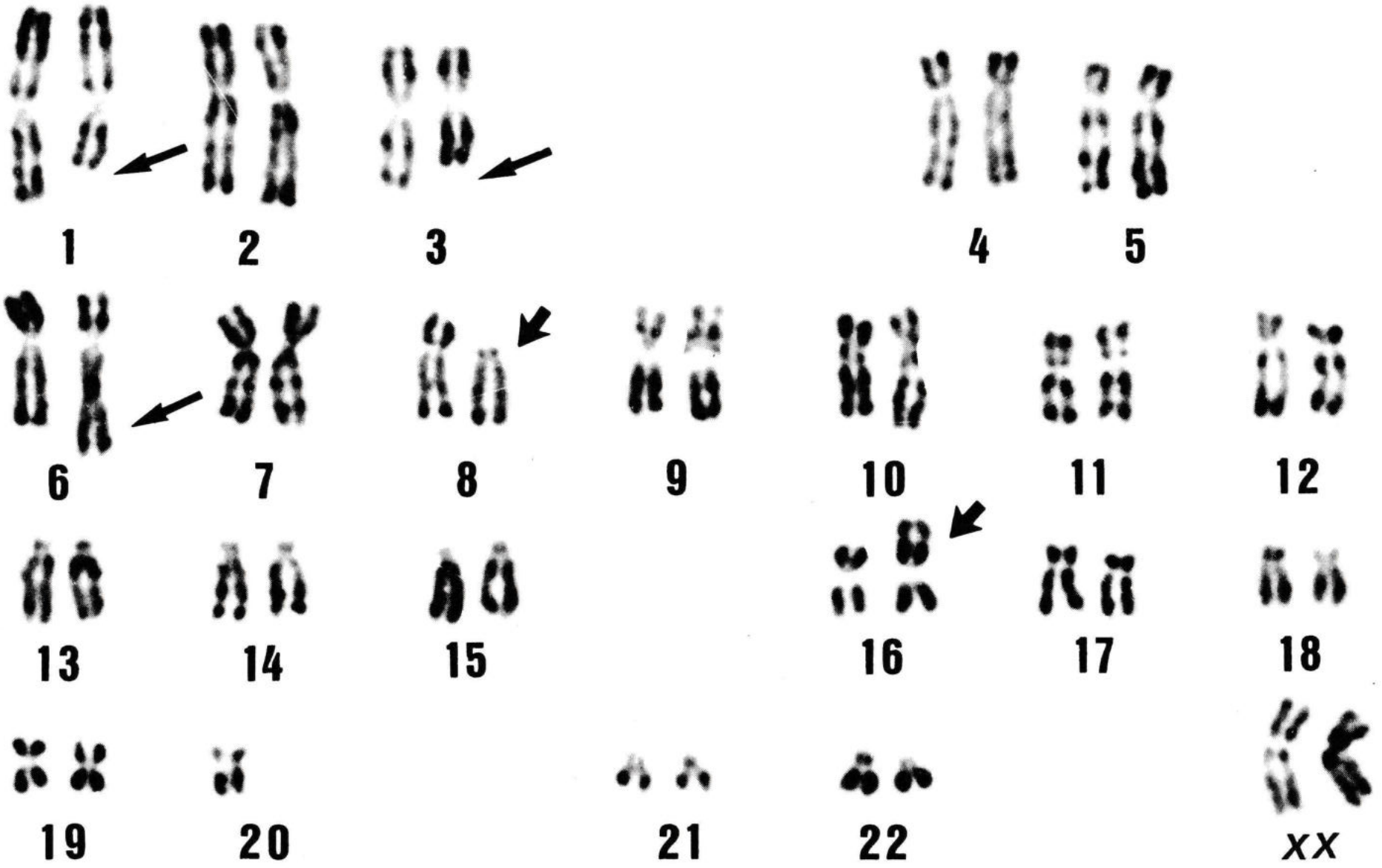


Figure 2 Representative karyotype from case 2: 46,XX,t(8;16)(p11;p13),t(1;6)(q32;q25),del(3)(q23q27?) (R-banding). Breakpoints are indicated by bold arrows, other structural anomalies by thin arrows.

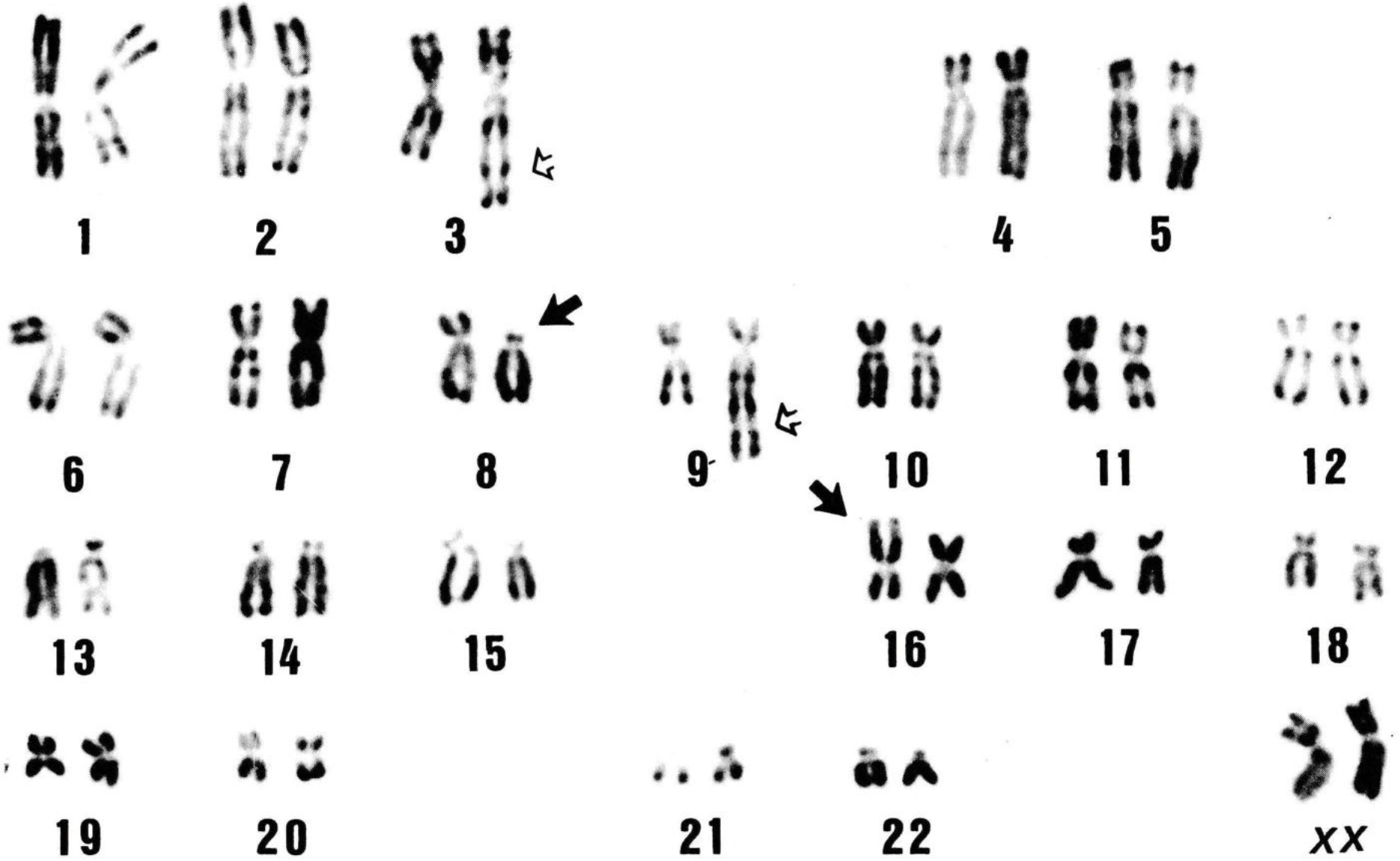


Figure 3 Representative karyotype from case 3: 46,XX,t(8;16)(p11;p13), − 3, + der(3)t(3;11)(q27;q13), − 9, + der(9)t(1;9)(q24;q34) (R-banding). Breakpoints are indicated by black arrows, other structural anomalies by white arrows.

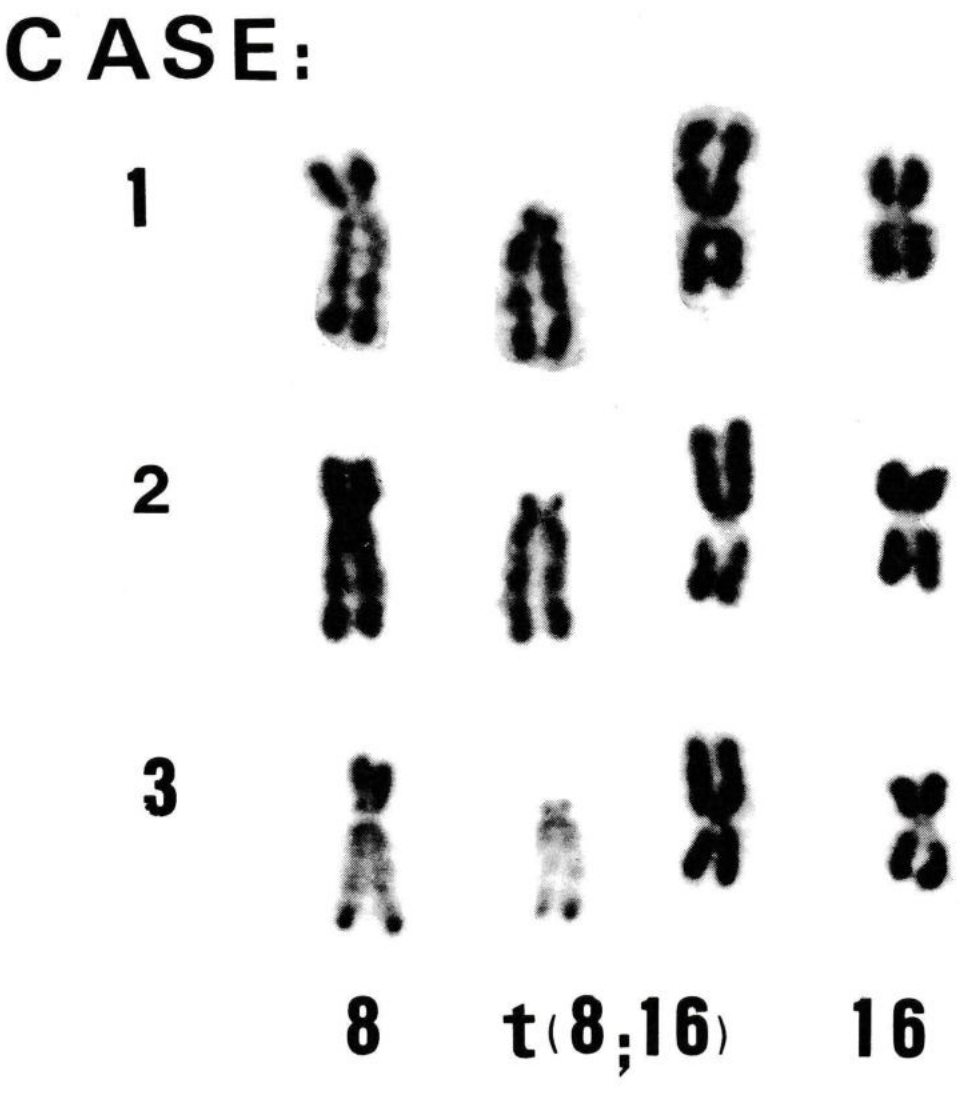
t(8;16)(p11;p13), − 3, + der(3)t(3;11)(q27;q13), − 9, + der(9)t(1;9)(q24;q34) (15 metaphases) (Fig. 3). In all three cases a t(8;16) was discovered with the breakpoints thought to be 8p11 and 16p13 (Fig. 4).

DISCUSSION

Among 184 karyotypes in ANLL, we observed t(8;16)(p11;p13) in three instances, each being a peculiar form of acute myelomonocytic leukemia. Two were de novo leukemias and the third was a possible secondary leukemia. This structural abnormality has been listed once in a recent review [7] as occurring in ANLL, but without more details; in another instance a t(8;16)(p11;q13) was reported in a case of acute myeloid leukemia [13].

Structural changes of chromosome #8 involve essentially its long arm: band 8q24 in Burkitt-type ALL [14] and band 8q22 in a subgroup of acute myeloblastic leukemia with maturation (M2) [1]; the short arm may also be affected in t(8;9)(p11;q34) encountered in myeloproliferative disorders [7] and in t(8;16)(p11;q13) of one case of acute myeloid leukemia [13]; in these two latter translocations the breakpoint on chromosome #8 was the same as in our three cases. Chromosome #16 is implicated in the above mentioned t(8;16)(p11;q13) [13], and in the following structural changes: del(16)(q22)[15],inv(16)(p13q22) [4]

Figure 4 Representative partial karyotypes of the three cases showing t(8;16)(p11;p13) (R-banding).



or t(16;16)(p13;q22) [16], all three conditions described occurred in acute myelomonocytic leukemia with abnormal eosinophils, suggesting the presence in 16q22 of genetic sequences of importance for eosinophil differentiation [4, 16]. It is to be noted that 16p13 may also be involved, as in our observations, and perhaps this fragment corresponds to a myelomonocytic specificity in at least some acute monocytic leukemias. To our knowledge, no oncogene has been described yet in or near 8p11 and 16p13.

Acute myelomonocytic leukemia, as described by the FAB group (M4) [9], is associated with myeloblasts, granulocytic maturation, and an excess of promonocytes and monocytes; in our observations, the results of the combined esterase reaction (and peroxidase plus specific esterase both positive) point to the proliferation of leukemic cells bearing monocytic and granulocytic markers. Among all our monocytic leukemias, only eight cases (12%), including the presented ones, were slightly different from true M4 and M5: comparable exceptions exist, mentioned as occurring preferentially in leukemias evolving from a preleukemic phase [17], and may represent up to 20% of all monocytic leukemias [18]. In no instance were cytogenetic data evaluated.

Erythrophagocytosis is a known but rather uncommon nonspecific finding in acute monocytic leukemia [19–21]. In our cases, it was a constant and very easily observable phenomenon.

Too few observations exist to enable us to draw definite conclusions, but the importance of band 16p13 in acute monocytic leukemias is to be stressed; more cases with this easily detectable translocation are necessary in order to a) check the presence of a unique cytologic or cytochemical (or functional?) picture and b) determine the role of chromosome #16 in the pathophysiology of the granulomonocytic system.

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