

t(1;3)(p36;q21) in Acute Nonlymphocytic Leukemia: A New Cytogenetic–Clinicopathologic Association

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A number of specific chromosomal abnormalities have been associated with distinctive clinical and/or morphological subtypes of acute nonlymphocytic leukemia (ANLL) in recent years. We have studied three patients with ANLL and t(1;3)(p36;q21). Each had weakness as their major complaint, a moderately severe anemia and, for ANLL, a relatively high platelet count. All three demonstrated abnormalities of the megakaryocytic, erythroid and granu-

locytic lineages. Most striking was the dysmegakaryocytopoiesis. The blasts in all three patients showed relatively few azurophilic granules, one to four prominent nucleoli, and rare peroxidase positivity. No patient had Auer rods. No patient responded to standard chemotherapy regimens. The data suggest that t(1;3)(p36;q21) identifies a new cytogenetic–clinicopathologic subtype of ANLL.
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A NUMBER OF recurring chromosome translocations have been identified in acute nonlymphocytic leukemia (ANLL).¹⁻³ Often these have had characteristic hematologic and clinical features, including response to treatment and survival.²⁻⁴ Indeed, it appears that karyotype classified according to specific chromosome aberrations may be the most important prognostic factor in ANLL.³⁻⁵ Thus, recognition of new specific cytogenetic abnormalities is of considerable importance.

Moir et al recently identified a new translocation, t(1;3)(p36;q21), in three patients with myelodysplastic disorders.⁶ We here report three additional patients with the same translocation, all of whom had ANLL. The data suggest that patients with ANLL with this translocation comprise a relatively homogeneous morphological and clinical group.

MATERIALS AND METHODS

Following publication of the paper of Moir et al,⁶ the list of karyotypes from all bone marrows studied with banding at the University of Helsinki since 1972 was reviewed for cases that might have the t(1;3)(p36;q21); two were found, both with a diagnosis of ANLL. Consequently, the list of all 716 karyotypes from the Fourth International Workshop on Chromosomes in Leukemia⁴ was reviewed. Only three cases had translocations between chromosomes 1 and 3. Two involved 1p and 3q; both had the breakpoints reported by Moir et al; one was one of the cases from the University of Helsinki; the other was from the University of Melbourne. The bone marrow slides, karyotypes, and clinical histories of all three cases were reviewed.

Trypsin G-banded chromosomes were studied from bone marrow and blood at diagnosis in each patient.^{7,8} Marrow was prepared for patient 1 using a direct method⁷; for patient 2, methotrexate synchronization was used⁷; and for patient 3, an overnight culture was used.⁸ Blood was studied using phytohemagglutinin (PHA)-stimulated lymphocyte cultures.

RESULTS

Clinical features (Table 1). Patients 1 and 3 presented with de novo ANLL without a history of exposure to known toxins; patient 2 had secondary ANLL after six years of repeated treatment with radiation and multiple drugs. Each patient had weakness as their major complaint for periods of two to 12 months. Anemia was found in patients 1 and 2 two and three months, respectively, prior to the diagnosis of leukemia, but neither had bone marrow biopsies at the time. At diagnosis, physical findings were unremarkable in all patients, except for moderate splenomegaly in patient 1.

Patient 3 was first treated conservatively for five months with monthly blood transfusions. Once chemotherapy was initiated, all patients received intensive regimens that included an anthracycline and cytarabine. No patient had any significant response. Survival in all patients was moderately short.

Hematologic findings (Table 2). All three patients presented with moderately severe anemia. The platelet count was normal in the two patients who presented with leukopenia, and only modestly reduced in patient 1, who had marked leukocytosis. Two patients were classified as FAB M1; one was classified as M4.⁹ However, all had abnormalities in the megakaryocytic, erythroid, and granulocytic lineages. Most striking was the dysmegakaryocytopoiesis (Fig 1). Megakaryocytes were markedly abnormal, with hypolobulation and often only one or two nuclei, in all three patients. Patient 3 also had marked bone marrow dyserythropoiesis; erythropoiesis was very reduced in patients 1 and 2. Ringed sideroblasts were found in patients 2 and 3. Circulating nucleated erythrocytes were seen in patients 1 and 2.

The myeloblasts in the bone marrow were greatly increased in number in all three patients, ranging from 66% to 84% at time of treatment. In patients 1 and 2, they were morphologically similar, being of median size, with a high nuclear-cytoplasmic ratio, pale blue cytoplasm, few azurophilic granules, a generally round to oval nucleus and one to four prominent nucleoli (Fig 1). In patient 3, the blasts were slightly larger, with a lower nuclear/cytoplasmic ratio, a few more azurophilic granules, and a less round nucleus. Sudan black B or peroxidase positivity was seen in only a small

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Table 1. Summary of Clinical Course of Three Patients With t(1;3)(p36;q21) and ANLL

	Patient 1	Patient 2	Patient 3
Age/sex	36/M	47/F	61/M
Prior exposure history	Primary school teacher; building home prior 2 yr	Breast cancer for 6 yr; extensive radiotherapy and chemotherapy	Worked in brick factory for 24 yr
Symptoms at diagnosis			
Fever	—	—	—
Bleeding	—	—	—
Weakness	+	+	+
Duration (mo)	2	3	12
Physical findings			
Lymphadenopathy	—	—	—
Splenomegaly	+	—	—
Hepatomegaly	—	—	—
Gingival hypertrophy	—	—	—
Skin infiltrates	—	—	—
CNS leukemia	—	—	—
Treatment and response	ADPx4 → NR VAMP → NR	TAD → NR	AAAdVPx2 → NR TAD → NR
Survival (mo)	6	6	16

ANLL, acute nonlymphocytic leukemia; A, cytarabine; D, daunorubicin; P, prednisone; Ad, Adriamycin; V, vincristine; T, 6-thioguanine; VAMP, vincristine, 6-mercaptopurine, methotrexate, prednisone; NR, no response.

percentage of cells in each case, and Auer rods were not found. In each case, neutrophils that showed Pelger-Huët-like changes were found.

Cytogenetic findings (Table 3). In each patient, the initial chromosome study of the bone marrow demonstrated

only abnormal metaphases with a single abnormal clone containing t(1;3)(p36;q21) (Fig 2). In patients 1 and 2, there was also an interstitial deletion of the long arm of chromosome 5, but the breakpoints in 5q differed. Case 1 had a near-metacentric 5q- chromosome, in which the banding

Table 2. Summary of Pretreatment Hematologic Findings

Hematologic Parameter	Patient 1 at Dx	Patient 2 at Dx	Patient 3	
			at Dx	at Rx
Hemoglobin (g/dL)	8.0	9.4	7.0	7.5
Platelets ($\times 10^9/L$)	95	233	220	195
WBC ($\times 10^9/L$)	96.0	2.4	2.8	3.3
Blasts (%)	96	39	Rare	42
Normoblasts	2/300	2/100	0	0
Bone marrow				
Cellularity	Increased	Increased	Increased	Increased
Erythropoiesis	Reduced, slightly megaloblastoid	Reduced	Dyserythropoiesis	Dyserythropoiesis
Ringed sideroblasts	No	2%	27%	No
Megakaryocytes				
Number	Decreased	Normal	Normal	Normal
Morphology	Abnormal	Abnormal	Abnormal	Abnormal
Myeloblasts	84%	66%	28%	80%
Nucleoli	2–4 per cell	1–2 per cell	1–4 per cell	1–4 per cell
Peroxidase	Negative	ND	Few positive	ND
Sudan black B	Positive	7% positive	ND	ND
Nonspecific esterase	ND	Negative	15% nucleated cells weakly positive	ND
Auer rods	—	—	—	—
Pelger-Huët-like changes	+	+	+	+
FAB classification	M1	M1	M4	M4

Dx, diagnosis; Rx, treatment; ND, not done.

*Within two months, the patient demonstrated 25% circulating blasts. Bone marrow was first repeated five months after diagnosis.

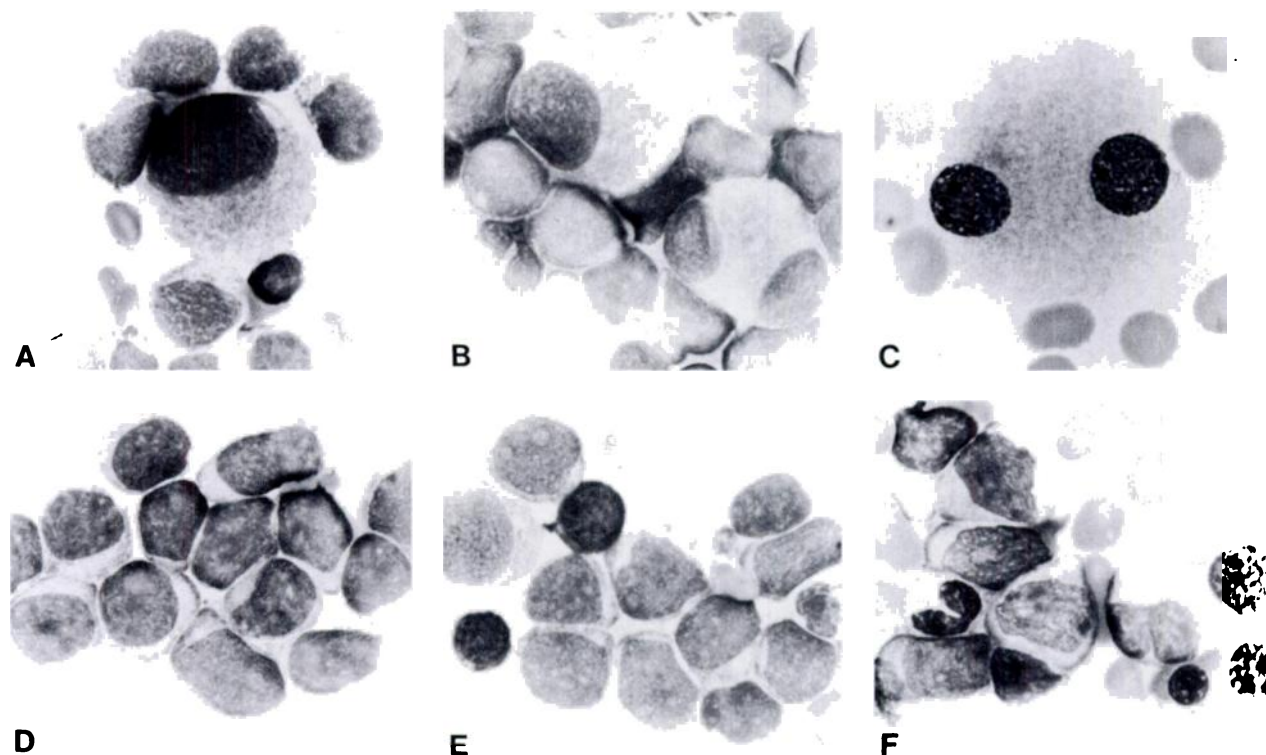


Fig 1. Representative abnormal megakaryocytes (A through C) and myeloblasts (D through F) in the initial bone marrow aspirates from three patients with the t(1;3)(p36;q21). Patient 1 (A,D); patient 2 (B,E); patient 3 (C,F). (May-Grünwald-Giemsa stain, original magnification $\times 1,250$; current magnification $\times 750$).

suggested del(5)(q12q32). In case 2, the 5q- chromosome was only slightly shorter than normal, with probable del(5)(q31q32).

Bone marrow from patients 1 and 3 was studied a second time, in patient 3 prior to chemotherapy, and in patient 1 after two cycles of induction therapy. Neither case showed clonal evolution. PHA-stimulated blood in each patient showed normal metaphases, although the abnormal clone was also present in a proportion of cells in patients 2 and 3.

DISCUSSION

Several specific chromosome abnormalities in ANLL identify patients with characteristic clinical and morphologi-

cal features.²⁻⁴ Here, we seem to have another cytogenetic-clinical type of ANLL that is defined by the t(1;3)(p36;q21). It is characterized clinically by a history of weakness as the major symptom at diagnosis, initial anemia with a relatively normal platelet count, and poor response to therapy. Morphologically, it is characterized by marked dysmegakaryocytopoiesis, little peroxidase positivity, absence of Auer rods, and blood or marrow evidence of dyserythropoiesis.¹⁰

To our knowledge, only three patients with t(1;3)(p36;q21) had previously been reported⁶; each had the t(1;3) as their sole karyotypic abnormality. Each had a myelodysplastic disorder that was not easy to classify, but

Table 3. Summary of Cytogenetic Studies

Patient No.	Date	Prior Rx	Tissue	No. of Cells Studied			Karyotype
				Total	Normal	Abnl	
1	11/22/76	-	BM	15	0	15	46,XY,t(1;3)(p36;q21),del(5)(q12q32)
	11/22/76	-	BLD	15	15	0	46,XY
	12/17/76	+	BM	9	0	9	46,XY,t(1;3)(p36;q21),del(5)(q12q32)
	12/17/76	+	BLD	4	4	0	46,XY
2	11/27/80	-	BM	10	0	10	46,XX,t(1;3)(p36;q21),del(5)(q31q32)
	11/27/80	-	BLD	43	14	29	46,XX/46,XX,t(1;3)(p36;q21),del(5)(q31q32)
3	12/09/80	-	BM	10	0	10	46,XY,t(1;3)(p36;q21)
		-	BLD	34	17	17	46,XY/46,XY,t(1;3)(p36;q21)
	04/30/81	-	BM	10	2	8	46,XY/46,XY,t(1;3)(p36;q21)

Rx, treatment; BM, bone marrow; BLD, blood; Abnl, abnormal.

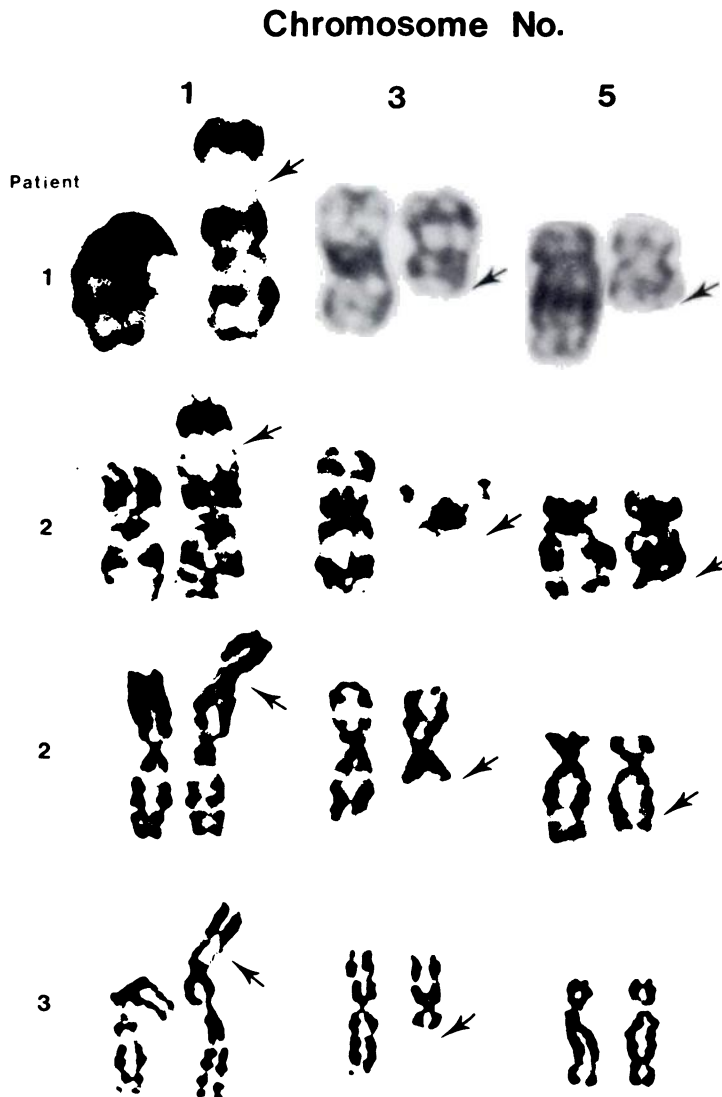


Fig 2. Partial karyotypes from bone marrow at diagnosis showing chromosomes 1, 3, and 5 in the three patients. To show the abnormality in chromosome 5 better, two cells are shown from patient 2. The normal chromosome of each pair is on the left. Each patient showed the same translocation between chromosomes 1 and 3. Arrows indicate the breakpoints at 1p36 and 3q21. In addition, patient 1 shows a $\text{del}(5)(\text{q}12\text{q}32)$ and patient 2 a $\text{del}(5)(\text{q}31\text{q}32)$ as indicated by the arrows. Both chromosomes 5 were normal in patient 3.

was described by the authors for case 1 as between refractory anemia with exam of blasts and chronic myelomonocytic leukemia, for case 2 as refractory anemia, and for case 3 as probable acute myelomonocytic leukemia.^{9,10} The first two patients had prolonged courses of three years and 6 months and seven years, respectively. Our patients had more acute courses, with only one having any symptoms for as long as one year; moreover, each probably had ANLL at diagnosis. Although our patient 3 had only 28% myeloblasts and 7% promyelocytes in the bone marrow when initially examined, within two months the number of circulating blasts had increased from rare to 25%; the second marrow, five months later, showed 80% blasts.

All six reported cases with the $\text{t}(1;3)$ share a number of features. All presented with moderate or severe anemia (4.8 to 9.4 g/dL) and blood or marrow evidence of dyserythropoiesis.¹⁰ Five patients initially had relatively high platelet counts (96 to $567 \times 10^9/\text{L}$). All three of our patients and the one previous patient with ANLL were relatively resistant to treatment. Unfortunately, megakaryocyte and blast mor-

phology, peroxidase positivity, and presence or absence of Auer rods in the prior cases were not described.

In two of our cases, the $\text{t}(1;3)(\text{p}36;\text{q}21)$ was associated with a deletion of 5q. A 5q- in ANLL has been associated with a poor prognosis, and, in some patients, with a pancytopenia.⁴ We believe the 5q- is unlikely to be the primary explanation of the findings in our patients, since all patients had similar features whether they had a deletion of 5q or not. Moreover, only 14% of ANLL patients with 5q- have had M1 (but both of our patients did), and ANLL patients with 5q- have rarely had such high percentages of blood or marrow blasts or such high platelet counts initially.⁴

Although we found no reports of other cases with $\text{t}(1;3)(\text{p}36;\text{q}21)$, karyotypes from several patients with myelodysplastic syndromes or acute leukemia previously published may have had the same abnormality.¹¹⁻¹³ One of these patients also had a missing chromosome 5.¹³ In addition, although there are no published reports of $\text{t}(1;3)(\text{p}36;\text{q}21)$ in lymphoma, we have recently seen the same translocation in two patients, both of whom had multiple other karyotypic

abnormalities. Similarly, other specific recurring chromosome rearrangements seen in ANLL, such as the del(16)(q22), t(9;22), and abnormalities of 11q23, have been found occasionally in lymphoma.^{14,15}

Several recurring chromosome abnormalities in ANLL are associated with characteristic morphological features.²⁻⁴ Of particular interest relative to t(1;3)(p36;q21), two rearrangements of chromosome 3 involving band q21—inv(3)(q21q26) and ins(3;3)(q26;q21q26)—have been associated with striking dysmegakaryocytopoiesis and normal to increased platelet counts at presentation.^{16,17} These findings are similar to those we see in our cases with t(1;3); it is possible that the t(1;3)(p36;q21) represents a variant form of rearrangement affecting band 3q21 analogous to the variant t(2;8)(p12;q24) and t(8;22)(q24;q11) seen in Burkitt's lymphoma. However, if the t(1;3) is a variant rearrangement, it may differ in having more significant red cell abnormalities, since cases of ANLL with inv(3) or ins(3;3) have not been reported to have dyserythropoiesis, nor have they uniformly had significant anemia, as in all six patients reported with the t(1;3). It will be of interest to see if patients with ANLL with

other chromosome rearrangements involving 3q21 have dysmegakaryocytopoiesis, with or without dyserythropoiesis. Abnormalities of 1p36 have not previously been associated with specific hematologic or clinical findings in ANLL.

Recent data suggest that karyotype defined by specific chromosome abnormalities may be one of the most important prognostic factors in ANLL.⁴ The t(1;3)(p36;q21) appears to be associated with a type of ANLL that is resistant to standard chemotherapy; none of our patients achieved even a partial remission. Patients with inv(3)(q21q26) and ins(3;3)(q26;q21q26) have similarly been reported to be unresponsive to treatment and have had short survivals. Whether the break at 3q21 is primarily responsible for the poor responses in our patients is unknown. Moreover, we can not exclude that the deletion of 5q may have also contributed to the poor response in two of our patients. However, both the ANLL patient of Moir et al⁶ and our one patient with only the t(1;3) had poor responses to standard chemotherapy. More cases with t(1;3)(p36;q21) as the only karyotypic abnormality must be studied to demonstrate its relation to prognosis convincingly.

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