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The Pattern and Clinical Significance of Karyotypic Abnormalities in Patients With Idiopathic and Postpolycythemic Myelofibrosis

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Six of eight (75%) patients with postpolycythemic myelofibrosis (PPMF) and 11 of 20 (55%) patients with idiopathic myelofibrosis (MF), seen at the University of Chicago, had abnormal karyotypes in cells of bone marrow origin. The specific chromosomal findings and their clinical significance in these patients were analyzed. A review of the literature added the findings from abnormal karyotype studies in 10 patients with PPMF and 36 patients with MF to this series. The demonstration of an increased frequency of cytogenetic abnormalities after cytotoxic therapy in polycythemia vera (PV) implies that such therapy may have a role in the development of chromosomal changes seen in treated PV and PPMF. The cytogenetic abnormalities in MF appear to be unrelated to therapy except possibly for an association with partial or complete losses of chromosome 5 or 7. Trisomy 8 is the only finding that is more common in MF than in PPMF. Other abnormalities were more common in PPMF, particularly 20q−, loss of 7 or 7q−, and trisomy 9, and to a lesser extent trisomy 1q and 5q−. Cytogenetic abnormalities do not show a pattern that can be used to distinguish between PPMF and MF, nor are they useful in the prognosis of MF or in initial studies in PPMF. PPMF does appear to have a higher tendency toward leukemic transformation than does MF, and an evolution in karyotype appears to have serious prognostic implications in PPMF in regard to this transition.

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A SIGNIFICANT PROPORTION of patients with various chronic myeloproliferative states develop acute leukemia, including 5% to 6% of patients with polycythemia vera (PV) and 1% to 5% of those with idiopathic myelofibrosis (MF).[1-5] Clonal karyotypic abnormalities have been demonstrated in the bone marrow cells of some patients with these disorders. Because many of them have received therapy, the role of prior radiation or cytotoxic drug treatment in inducing these changes is uncertain. Several investigators have studied the possible prognostic significance of a clone of karyotypically abnormal cells in patients with these diseases. There are relatively few systematic cytogenetic studies of patients with idiopathic MF or undifferentiated myeloproliferative disease (UMPD), especially employing newer ing techniques. Previously the cytogenetic chan MF were thought to be inconsistent. Cytogenetic s in PV are more numerous.[6] About 15% to 30% tients with PV will develop a myelofibrotic state polycythemic myelofibrosis (PPMF) is consi some to be a part of the natural history of all PV whereas others believe it is related to previous therapy and carries with it an increased risk quent development of acute leukemia.

We present the results obtained from analy patients with PPMF and 20 individuals with idio MF or UMPD, in order to determine the frequen pattern of chromosome abnormalities in these di We compare MF and PPMF to see if they can be guished clinically or cytogenetically and examin relationship of chromosome changes to leukemic formation and other clinical parameters.

Materials and Methods

This report describes chromosomal analyses do bone marrow and peripheral blood samples be September 1965 and June 1980, at the Univers Chicago. Six of the eight patients with PPMF i series have been reported previously,[7] but are incl here for purposes of comparison with MF and UM

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TABLE 1. Clinical Characteristics, Treatment Status, and Causes of Death in Eight Patients With PPMF

Age Dx PV	Age Dx PPMF	Sex	Dx (date)	Rx	Cause of death (date)
48	55	F	PV(1/62); PPMF(1/69)	^{32}P, busulfan	DMF, infection (8/74)
49	64	F	PV(12/56); PPMF(1/72)	^{32}P, TEM	DMF, CHF (8/77)
52	61	M	PV(10/70); PPMF(1/80); ANLL(4/81)	None until 1/77, then busulfan	ANLL (4/81)
51	57	F	PV(1/69); PPMF(9/75); ANLL(7/79)	Busulfan	ANLL (7/79)
39	51	F	PV(1/61); PPMF(7/71)	^{32}P, busulfan	DMF, CHF (8/75)
63	73	M	PV(10/55); PPMF(9/65)	^{32}P, busulfan	Splenic rupture (8/68)
49		M	PV(7/67); PPMF(4/76)	Busulfan	DMF, CHF (8/77)
57	62	F	PV(4/70); PPMF(6/75)	None	Alive (1/83)

nts 1–6 are Cases 10, 17, 23, 19, 30 and 28, respectively, in *al.*[7]

iagnosis; PV polycythemia vera; PPMF postpolycythemic myelotibrosis; Rx: treatment; ANLL acute nonlymphocytic leukemia; TEM: triethylenemelamine; DMF deteriorating myelofibrosis; CHF congestive heart failure.

etic Procedures

hase chromosomes were obtained from bone or unstimulated peripheral blood. Recently, in s from whom an aspirate could not be obtained, a n of the bone core biopsy specimen was minced ltured for 24 to 48 hours to obtain dividing mye- ells. Chromosomes were examined with conven- Leishman-Giemsa stain, and, in 21 of 28 patients, ith the quinacrine banding technique.[8] For most s, chromosome counts were obtained from a um of 20 metaphase cells, 10 of which were pho- hed and analyzed in detail.

hods for the karyotypic analysis of patients with ological diseases have been described previously? nosomes are identified according to the ISCN,[10] aryotypes are expressed as recommended under stem.

ons of Disease Entities

lofibrosis (MF) has been defined by the Polycy- Vera Study Group.[11] Most importantly, none of ntifiable causes of secondardy MF should be Undifferentiated myeloproliferative disease D) includes the same constellation of findings as the absence of significant fibrosis (less than one the sectioned area shows fibrosis). Polycythemia V) is used as previously defined.[1] Postpolycythe- elofibrosis (PPMF) is defined similarly to MF but subsequent to documented PV.

riorating myelofibrosis (DMF) is similar to the e of agnogenic myeloid metaplasia as defined by nd Block.[1] There are increasing symptoms due to splenomegaly with progressive anemia, leuko- nd myeloid immaturity, and often thrombocy- The bone marrow shows a moderate to marked in the myeloid series with myeloblasts increased l below that diagnostic of acute nonlymphocytic ia.

Results

Patient Characteristics

PPMF (8 patients): The findings in this group are listed in Table 1. Patients 1 through 6 have been previously reported.[1] The median age at diagnosis of PV was 50 years, with a median interval to the development of PPMF of 9 years. Prior to the initial cytogenetic study, six of eight patients had been treated with either ^{32}P and an alkylating agent (four cases) or busulfan alone (two cases).

MF/UMPD (20 ***patients):*** The characteristics of this group are listed in Table 2. The median age at diagnosis was 62 years. There were no differences in the median age, initial physical findings, or hematologic parameters between the MF and UMPD groups. Of these 20 patients, only 5 had received alkylating agent or radiation therapy prior to cytogenetic analysis (Table 2).

Survival and Causes of Death

There have been seven deaths in the PPMF group, with a median interval of 3.5 years (range, 1–6 years) between the diagnosis of PPMF and death. The major causes of death are listed in Table 1 and include two cases of acute nonlymphocytic leukemia (ANLL).

There have been 17 deaths in the MF/UMPD group, with an average survival of 3 years (range, 1–18 years) (Table 2). There was one case of ANLL. Overall, 10 patients had complications of DMF that contributed to the cause of death. The causes of death were similar for the MF and UMPD subgroups, although the features of DMF were present in 8 of 10 MF patients (3 of whom died within 1 year of diagnosis) but in only 3 of 7 UMPD patients.

Results of Cytogenetic Studies

The cytogenetic findings are summarized in Table 3.

PPMF: Six of eight (75%) patients with PPMF had

TABLE 2. Clinical Characteristics, Treatment Status, and Causes of Death in 20 Patients With MF or UMPD

Case	Age/sex	Dx (date)	Rx	Cause of death (date)
9	74/F	MF (1971)	None	DMF, CHF (3/77)
10	48/M	MF (2/73)	NOM	DMF, splenic hemorrhage (11/74)
11	51/M	MF (1972)	Busulfan	DMF, COPD, resp failure (5/80)
12	69/M	MF (7/69)	None	DMF, hemorrhage (5/70)
13	69/M	MF (12/72)	None	DMF, CHF (5/74)
14	67/F	MF (3/75)	None	DMF, MI (5/80)
15	68/M	MF (3/75)	Busulfan	Alive (5/80)
16	62/M	MF (8/74)	None	Colon ca, met to liver (2/77)
17	65/M	MF (1/69)	NOM	MI (6/73)
18	61/M	MF (12/66)	None	DMF, intest infarct (1/70)
19	60/M	MF (5/65)	None	DMF, infection (I 1/66)
20	53/F	MF (4/80)	None	Alive (6/81)
21	47/F	UMPD (1948)	Splenic RT TEM	DMF, infection (6/77)
22	63/M	UMPD (7/70)	Splenex, Chloramb	DMF, CHF (3/74)
23	58/M	UMPD (7/69)	None	Thyrotoxicosis, CHF (I 1/72)
24	70/M	UMPD (1/75)	None	DMF, infection (10/78)
25	36/M	UMPD (11/74)	Splenex, busulfan	Alive (2/82)
26	73/F	UMPD (3/77)	None	Infection (1/80)
27	70/M	UMPD (9/68)	None	Pulm emb, lung Ca, splenic infarct
28	49/F	UMPD (8/72) MF (1/75) ANLL (4/76)	None	ANLL (5/76)

Dx: diagnosis; Rx: treatment; MF: idiopathic myelofibrosis; UMPD: undifferentiated myeloproliferative disease; ANLL: acute nonlymphocytic leukemia; RT: radiation therapy; TEM: triethylenemelamine; DMF: deteriorating myelofibrosis; COPD: chronic obstructive pulmonary disease; resp: respiratory; CHF: congestive heart failure; MI: myo infarction; Ca: carcinoma; met: metastases; intest: intestinal; infarction; Pulm emb: pulmonary embolism.

abnormal cytogenetic findings either initially or on subsequent examination (Table 3). Except for Case 3, all patients with abnormal karyotypes were previously treated with ^{32}P, cytotoxic drugs, or both. All six patients showed structural aberrations, usually deletions or translocations; unidentified markers were seen in two. Trisomy 1q and a 20q − were each seen in two cases. The two trisomy 1q cases included duplication of q21→qter and cen→qter. The two patients (Cases 6 and 7) with 20q− were both previously treated and both had del(q 11). Single instances of +8, +9, −9, −13, −X, 1q−, and 16p− were also seen.

One patient (Case 3) had two abnormal clones time of initial diagnosis of PV, as previously descri The hyperdiploid clone gradually disappeared w developed PPMF and then ANLL 9 and 10.5 yea respectively. No new abnormalities developed. tient in Case 7 had an abnormal karyotype (46,X initially (no prior therapy) but during a det DMF state after busulfan therapy, a second

TABLE 3. Summary of Cytogenetic Findings in PPMF (Cases 1–8), MF (Cases 9–20), and UMPD (cases 21–28)

Patient	Disease stage	Sample date	Sample source	Total no. of metaphases*	Percent abnormal†	Abnormal karyotype
PPMF Patients:						
1	PPMF	01/03/69	BM	28 (17)‡	0	
2	PPMF	09/09/74	PB	22 (11)	0	
	DMF	06/03/77	PB	2 (2)	100	48,XX,+8,−9,del(11)(q21?)14q+,+2
3	PV	10/26/70	BM	55 (37)‡	30‖	46,XY,−E17,+E-size mar/47,X,−Y,+ size acrocentric mar
	PV	07/20/71	BM	107 (26)‡	54‖	46,XY,−E17,+E-size mar/47,X,−Y,+ size acrocentric mar
	PV	08/25/71	BM	158 (28)‡	32‖	46,XY,−E17,+E-size mar/47,X,−Y,+ size acrocentric mar
	PV	07/26/72	BM	71 (71)	94	46,XY,t(12;17)(q13;p11)/ 47,X,−Y,+der(Y),t(Y;1)(q12;q21),+
	PV	01/21/71	BM	69 (27)	93	46,XY,t(12;17)(q13;p11)/47,X,- −Y,+der(Y),t(Y;1)(q12;q21),+9§
	DMF	01/09/80	BM	71 (37)	100	46,XY,t(12;17)(q13;p11)
4	PPMF	05/13/76	PB	11 (10)	/0	
	PPMF	07/09/76	BM	9 (6)	0	
	PPMF	07/12/77	PB	54 (18)	6	
	PPMF	10/12/78	PB	28 (17)	0	
	ANLL	07/25/79	PB, BM	20 (13)	40	47,X,−X,+2 or 3 mar

TABLE 3. *(Continued)*

Patient	Disease stage	Sample date	Sample source	Total no. of metaphases.	Percent abnormal†	Abnormal karyotype
	PPMF	07/02/73	PB	64 (34)	100	46,XX,t(2; 11)(p13;q21)¶/46,XX,−15,+der(1), t(1;15)(p1?;q1?),t(2; 11)(p13;q21), del(16)(p12)/51,XX,+3,+8,+8?, +C,−15,+19,+der(1),t(1;15)(p1?;q1?), t(2; 11)(p13;q21),del(16)(p12)
	PPMF	09/01/65	BM	6 (4)†	50	46,XY,Fq−
	DMF	11/27/67	BM	49 (10)	100	46,XY,del(20)(q11)
	PPMF	04/27/76	BM	18 (8)	25	46,XY,del(1)(q42?)
	DMF	07/29/77	BM	16 (13)	69	46,XY,del(1)(q42?)[8%]§/ 46,XY,del(20)(q11)[62%]
	PPMF	03/31/76	PB	27 (16)	0	
UMPD patients:						
	DMF	01/27/76	RM, PB	29 (20)	60	46,XX,−6,+der(6),t(1;6)(q25;p25?)
	DMF	05/08/74	PB	51 (37)	100	46,XY,del(12)(q14?q21)
	DMF	10/02/74	PB	36 (27)	100	46,XY,del(12)(q14?q21)[56%]/ 51,XY,+Y,+8,+8,+12,+19, del(12)(q14?q21)[44%]
	MF	03/28/77	PB	17 (14)	57	46,XY,−2,−6,+der(2),t(2;6)(q37?;q15?), +r(6)(p25?q15?)
	MF	07/29/69	PB	69 (21)‡	10	
	MF	01/26/73	PB	7 (6)	0	
	MF	03/02/77	PB	12 (9)	33	46,XX,del(13)(q11?q14?)
	MF	07/13/77	PB	11 (10)	50	46,XX,del(13)(q11?q14?)
	MF	10/24/79	PB	37 (15)	53	46,XX,del(13)(q11?q14?)
	MF	10/30/75	PB	28 (14)	100	47,XY,+8,del(5)(q31)
	MF	09/24/75	PB	21 (10)	100	46,XY,t(6;12)(6pter→6q23?::12q13?→ 12qter;12pter→12q13?:)
	MF	01/06/70	PB	30 (19)‡	0	
	MF	06/19/67	PB	9 (9)‡	0	
	MF	07/18/67	PB	48 (8)‡	0	
	MF	05/27/66	BM	57 (21)‡	0	
	MF	06/19/80	BM	22 (11)	27	47,XX,+20,dup(5)(pter → q33?::q22?→qter
	DMF (UMPD)	01/30/67	PB	108 (33)‡	100	46,XX,−A2,+mar#
	UMPD	07/19/72	BM	15 (3**)	0	
	UMPD	05/16/72	BM	36 (13)‡	92	47,XY,+D
	UMPD	08/24/72	BM	33 (31)	81	47,XY,+14
	UMPD	02/03/75	BM	15 (14)	93	45,X,−Y
	UMPD	03/31/77	BM	54 (21)	5	
	UMPD	04/04/77	BC, PB	31 (22)	5	
	UMPD	09/23/68	BM	34 (11)‡	0	
	UMPD	10/05/72	BM	17 (9)‡	78	47,XX,+G,Bq−
	UMPD	01/31/73	BM	21 (3)	100	46,XX,del(5)(q15)/47,XX,+21,del(5)(q15)§
	MF	08/04/75	PB	20 (6)	83	47,XX,+21,del(5)(q15)
	ANLL	04/19/76	PB	2 (2)	100	47,XX,+21,del(5)(q15)

...rs in parentheses indicate subtotal of metaphases examined in detail ... fluorescence, unless marked with#, in which case the subtotal is ...r of metaphases analyzed with conventional Giemsa stain.

...ed as percentage of metaphases examined with fluorescence or, if ...s banding was not done, calculated as percentage of cells analyzed with ...l stain only.

...otype seen in only a single-banded cell from this sample.

...tage reflects only the clone with 47 chromosomes, since the abnormality ...ddiploid clone could not be accurately scored in many cells without ... techniques.

¶ A constitutional abnormality also observed in stimulated lymphocytes from this patient.

A metacentric B-size marker possibly resulting from a translocation between no. 2 and a C-group chromosome.

** Five other cells analyzed with conventional Giemsa only were all normal.

PPMF: postpolycythemia fibrosis; BM: bone marrow aspirate; PB peripheral blood (without phytohemagglutin); DMF: deteriorating myelofibrosis: PV polycythemia vera: ANLL: acute nonlymphocytic leukemia; MF: myelofibrosis; UMPD: undifferentiated myeloproliferative disorder; BC: bone core biopsy.

...onal abnormality appeared (46,XY,20q−). The ...in Case 4 had a normal karyotype on 4 occasions ...ars after the onset of PPMF but then developed ...mal clone (47,X,−X,+ 2 or 3 markers) coinci... transformation to ANLL. Therefore, both pa... with PPMF and subsequent ANLL (Cases 3 and 4) ...concomitant changes in their karyotypes.

UMPD Group: The results of cytogenetic studies ...oup are detailed in Table 3. Of the entire group of 20 patients, 11 *(55%)* had karyotypic abnormalities. In the MF and UMPD subsets, 7 of 12 *(58%)* and 4 of 8 (50%) patients were abnormal, respectively.

Three patients had abnormalities of 5q (Cases 15, 20, and 28); two involved a deletion with loss of the long arm distal to q15 or q31 (Figs. 1 and 2A). In the third case, there was a duplication of q22 to q33 (Fig. 2B). Three cases had a translocation involving no. 6; one *(Case* 9) affected the short arm and *two* (Cases 11 and 16) the long

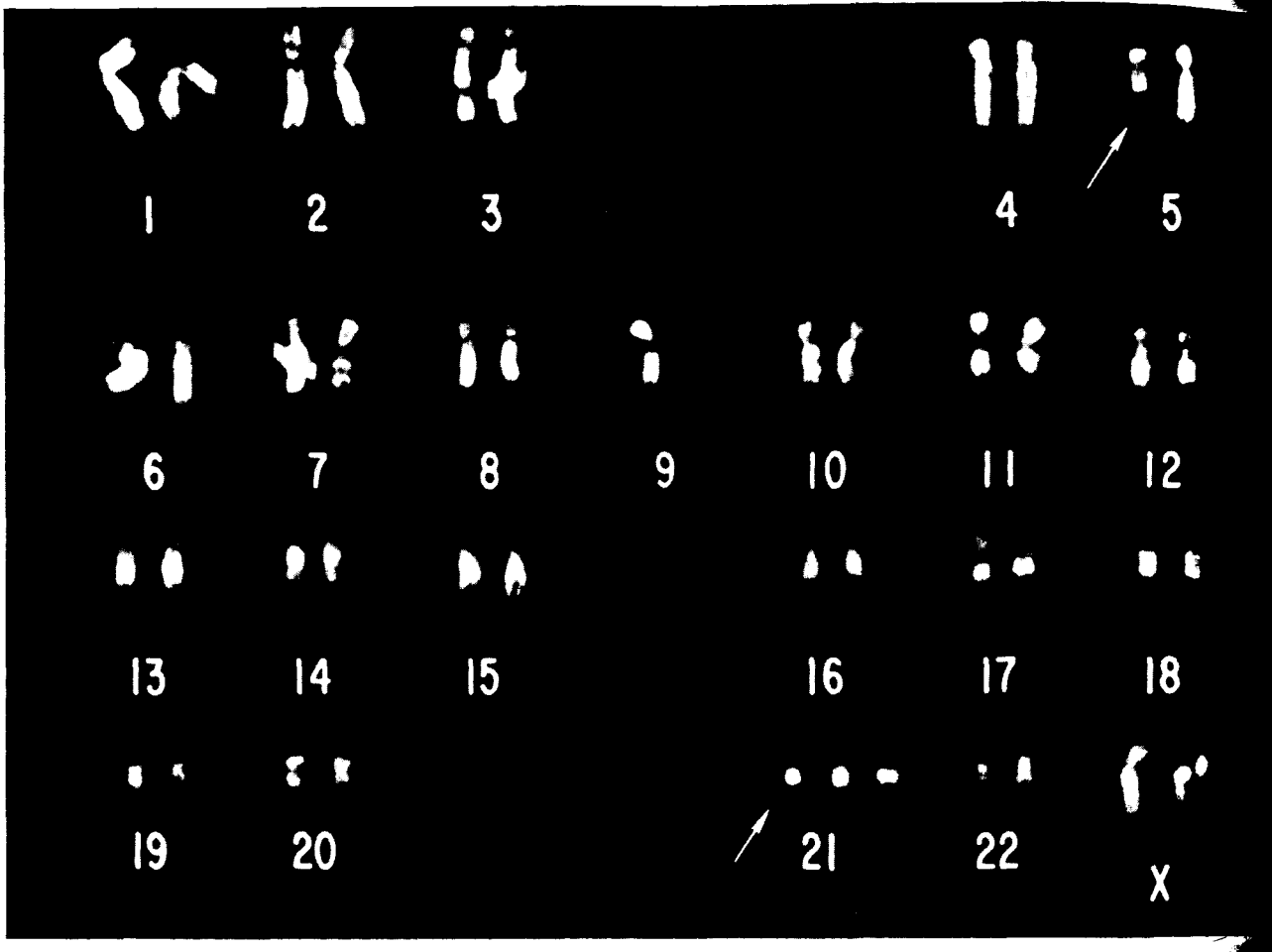


FIG. 1. **Karyotype of a Q-banded metaphase cell obtained from Patient 28. The cell contains a partial deletion of the long arm** of chromo del(5)(q15), **and an extra no. 21. There is** also **a loss** of **one no. 9, which was observed in this** cell only. **Chromosomal abnormalities identi arrows.**

arm (Fig. 3). In one patient (Case 16) it appeared that 6q23 to q terminal (qter) was missing; in another (Case 11), part of no. 6 was translocated to 2q and the remainder formed a ring chromosome. In both Cases 9 and 11, a break occurred in 6p25 with probable loss of 6p25 to 6pter. Two patients (Cases 10 and 16) had aberrations of 12q; one involved an interstitial deletion (q14?q21) and the other a translocation with a break in 12q13? (Figs. 4A and 4B). Due to the uncertainty of the breakpoints, these could be in the same band of no. 12. Trisomy for 1q (Fig. 3) and deletion of 13q were each noted in one case. A gain of No. 8 was noted twice, once (Case 10) as part of an evolution of the karyotype (Fig. 4). The latter patient was the only one whose karyotype evolved in this group, and this change was associated with a progressively deteriorating clinical course of DMF. A gain of 14, 20, or 21, and a loss of Y each were observed in single patients.

Clinical correlates: The survival, causes of death, and the proportion of patients developing DMF were generally similar for those with normal or abnormal karyotypes, although the single case of ANLL (French-American-British [FAB] classification M2) was seen in the abnormal group. The histologic division between MF and UMPD did not correlate with aneuploidy.

Only 5 of 20 patients with MF or UMPD had received toxic drug or radiation therapy prior to cytogenetic study. Only the patient in Case 9 was heavily pretreated, whereas the other four had relatively brief courses of alkylating agent therapy shortly before chromosome analysis. There was no correlation between prior treatment and the frequency of abnormal karyotype, with 8 of 15 (53%) of the untreated group and 3 of 5 (60%) of the treated patients being abnormal.

The one patient who developed clearcut ANLL (Case 28) was unusual in appearing initially with severe anemia and a marrow showing early MF but more strikingly a severe erythroid hypoplasia. Her initial cytogenetic sample and three additional ones over the next 3.5 years until her death showed the same abnormal karyotype (47,XX,+21,5q−) (Fig. 1). During this time, her marrow showed progressive fibrosis with increasing myel

negakaryocytic hyperplasia. She then developed topenia and one year later evolved into frank . She had never received any cytotoxic therapy.

Discussion

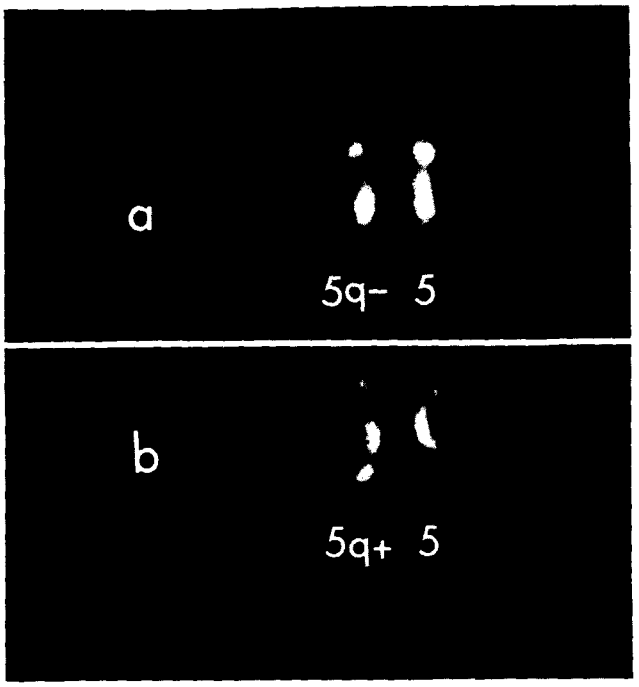
ical observations: The age distribution and clinitures of our PPMF group were indistinguishable those of our patients with MF or UMPD, and edge of the previous diagnosis of PV was essential rentiating between them. In our study, the overall ncy of ANLL in PV is **14% (5** of 36 **cases),'** s 2 of 8 patients **(25%)** in the subgroup with developed ANLL. These findings are in general nt with those of Silverman *et al.*,[2] who reported cidence of ANLL in patients with PV, whereas **5** 7%) in their PPMF series subsequently transo ANLL.

netic studies: Six of eight **(75%)** patients with had either initially or subsequently chromosomal malities. Only the abnormalities in Case 3 (triq and trisomy 9) were found without the backof prior therapy. Both of these findings have been ed in polycythemic phase PV patients.[13]

chromosome gains and losses in ten cases of with karyotypic abnormalities collected from a of the literature[14-21] are summarized in the histoin Figure 5. Eight of these ten individuals had une prior therapy. Table 4 summarizes the findings this review when added to those of the current (a total of 16 PPMF patients).

late finding of 5q− appears to be a frequent ability associated with the terminal stages of PV,[7,22] lly in association with other karyotypic abnors. We previously reported the appearance of 5q − patients, seen concomitant with transformation LL in three and as an evolutionary change in one tient after therapy.' However, three patients, all had significant prior treatment for PV, have been ted during DMF to have the late appearance of not followed by ANLL.[5]

vious studies in PV indicate that the incidence of typic abnormalities is higher in treated patients in newly diagnosed ones, and that the types of s differ between these two groups. Changes seen therapy involved hyperdiploidy, often due to of 8 or 9, whereas changes seen after extensive often involve structural rearrangement of chromes (20q −, trisomy 1q).[6,22,23] Our two patients nsformed to ANLL had karyotype changes assowith this event. This is consistent with earlier rehat the finding of karyotypic abnormalities in PV y is not necessarily a poor prognostic sign, but that bsequent deveiopment of abnormalities in inormal patients often carries a poor prognosis.[24,25]



FIGS. 2A AND 2B. (A) Chromosome pair no. 5 from a Q-banded metaphase cell from **Patient 15. There is a partial deletion of the long arm of one no. 5, del(5)(q31). (B) Chromosome pair no. 5 from a Q-bandedcell from Patient *20*. The 5q + is the result of a duplication of part of the long arm of no. 5, dup (5)(pter→q33?::q22?→qter).**

MF and UMPD

Clinical characteristics: Sixty percent of our patients had MF and 40% had UMPD. The initial clinical characteristics were not clearly different between the MF and UMPD subsets, although there was a suggestion that the MF subset developed DMF more frequently. The causes of death and the frequency of leukemic transformation (1 of 20 patients *(5%))* were similar to previous reports, in which 2 - 5% of patients with MF have developed ANLL.[3,4,26]

Cytogenetic findings in MF/UMPD: Eleven of our 20 patients *(55%)* with MF or UMPD had abnormal karyotypes. There were no clinical differences or prognostic significance associated with aneuploidy. These findings are in agreement with Whang Peng *et al.*, who reported an incidence of cytogenetic abnormality of **64%** upon initial study of patients with MF.[27]

Previous reports have presented a wide array of abnormal karyotypes in MF and UMPD. The chromosomal abnormalities in 36 cases of MF or UMPD collected from the literature are shown in the histogram of Figure 5.[13,14,16,17,20,21,24,25,27,28,28a-28h] Whenever possible the published karyotypes have been reviewed by us to identify the breakpoints of structural changes. Three cases of idiopathic thrombocythemia (IT), a disorder closely related to UMPD, are included. One patient with IT was found to have both trisomy 8 and trisomy 9, one was a 60-year-old man with loss of the Y chromosome,

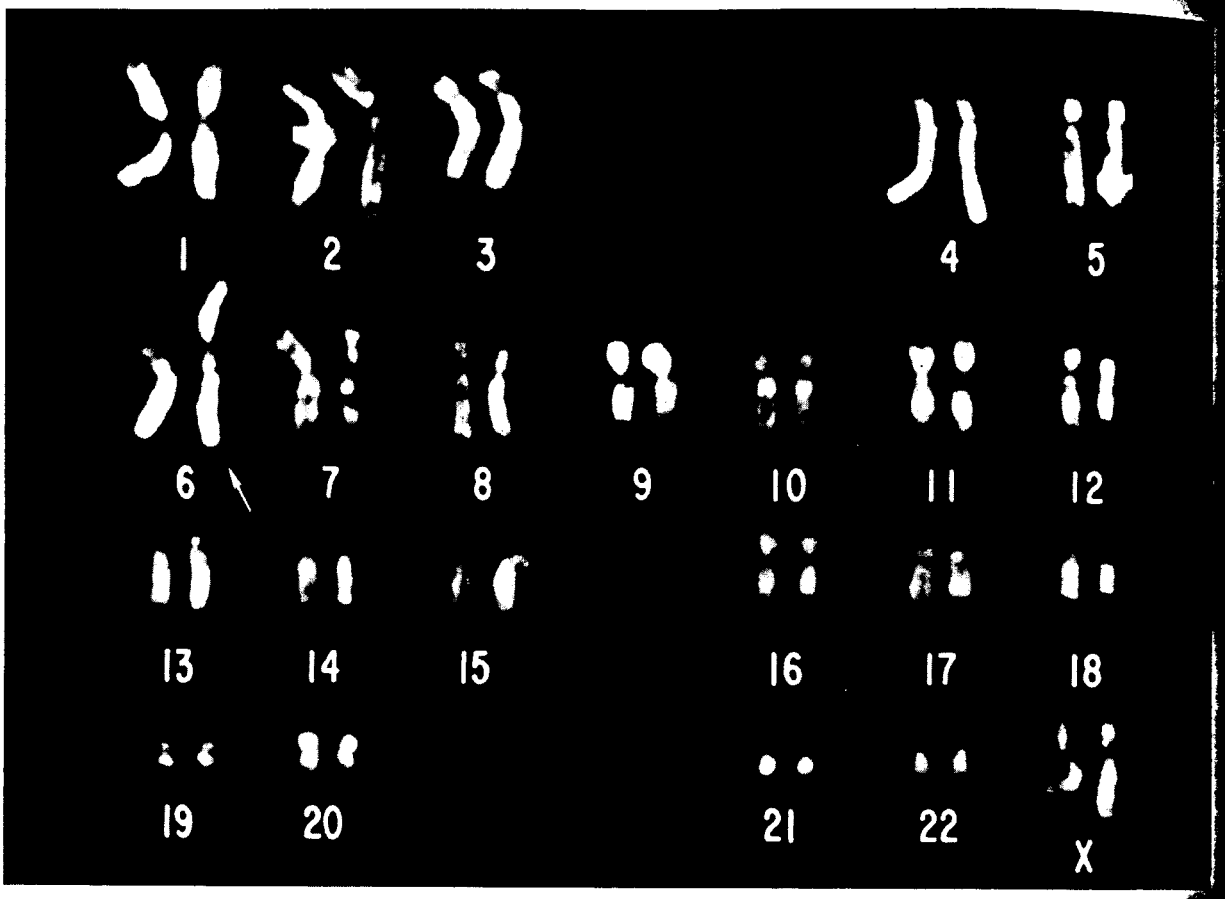


FIG. 3. **Karyotype of a Q-banded metaphase cell obtained from patient 9. There is a rearrangement (arrow) between chromosomes resulting in trisomy of a portion of Iq. [46,XX,-6,+ der(6),t(1;6)(q25;p25?)].**

and the third had a rearrangement of the long arm of No. 5 leading to 5q−. When the results of our current study (11 aneuploid patients) are added to these 36 cases, the following abnormalities (with at least 2 cases of each) were found in order of decreasing frequency: trisomy 8 (10 cases), trisomy 1q (8 cases), loss of 5 or 5q− (5 cases) or 5q+ (1 case), loss of 7 or 7q− (5 cases, 1 of which is both −7 and 7q−), trisomy 9 (4 cases), trisomy 21 (4 cases), loss of Y (4 cases), 15q−, (3 cases), 20q− (3 cases), 6p− (3 cases, all involving a translocation leading to trisomy 1q) and 17p+ (2 cases).

In the current series, the loss of the Y chromosome was found in the initial study of a 70-year-old man who never developed ANLL. The loss of the Y chromosome in elderly males may be unrelated to hematologic disease.[29,30] Our review of the literature revealed three additional MF cases with loss of the Y chromosome in previously untreated males who tended to be younger than previously noted (ages of 49, 60, and 61 years, respectively).

Of the 36 cases collected from the literature, 27 had no prior treatment, 3 had received prior cytotoxic therapy, and the status of 6 could not be ascertained from the data provided. Only 3 of the 11 patients from the current series had received prior cytotoxic therapy. O there was no apparent correlation of karyotypi malities with prior cytotoxic treatment. How analyzed more closely those patients with los 5q− and/or loss of 7 or 7q−, since recently the genetic findings have been reported to be as strongly with either previous cytotoxic therapy vious occupational exposure to chemical solvents ticides, or other potential mutagens, and the subs development of preleukemic syndromes or ANL Although only 9 of 47 patients (19%) with MF or U shown in Table 4 had partial or total losses of chr somes 5 or 7, 4 of these 9 (44%) had prior exposu either radiotherapy (2 cases: 1 for prostatic carcin and 1 for Hodgkin's disease[25]), busulfan (one pat Case 15), or benzene and other petroleum solvent case)[27]. Of the 38 MF/UMPD patients with karyot abnormalities other than losses of chromosomes 5 o only 6 (16%) had prior cytotoxic therapy or chem exposure. This suggests an association of prior the with the occurrence of these specific karyotypic ab malities in patients with MF or UMPD.

Trisomy 1q of various derivations is a frequent find in MF and UMPD (Fig. 5). Nowell[14] described tris

4A AND 4B. (A, top) Karyotype of a G-banded metaphase cell obtained from the initial peripheral blood sample from Patient 10. The cell 12q−, del(12)(q14?q21). (B, bottom) Partial karyotype of a Q-banded cell from a subsequent peripheral blood sample. In addition to the there are several evolutionary changes (+Y,+8,+8,+12,+19). The partially deleted chromosome 12 in each metaphase cell is identified by ow.

two patients with MF. Hsu *et al.* have reported a al trisomy 1q (46,XX,−6,+der(6),t(1;6)(q25;p22) patient with deteriorating **MF** without frank ,[16] a cytogenetic finding similar to that in our Case hrton *et* al. also reported a similar abnormality Y,−6,+der(6),t(1;6)(q25;p21) in a patient with ho rapidly evolved into ANLL without radiother- cytotoxic drugs ever having been given.[28] Ger- *et al.* described three individuals with DMF (one idiopathic and two with **PPMF),** all of whom had trisomy 1q and monosomy 7q with identical translocations between chromosomes 1 and 7.[20]

A more detailed analysis of the region of 1q that is trisomic in the 7 patients with **PPMF** and in the 8 patients with MF/UMPD shows that all 15 are trisomic for bands 1q25 to 1q32, in accord with the observations of Rowley.[23] One patient is trisomic for all of No. 1, and 12 patients are trisomic for part of no. 1 as the result of an unbalanced translocation of no. 1 from the breakpoint (p22 to q25) to the end of the long arm. Two other

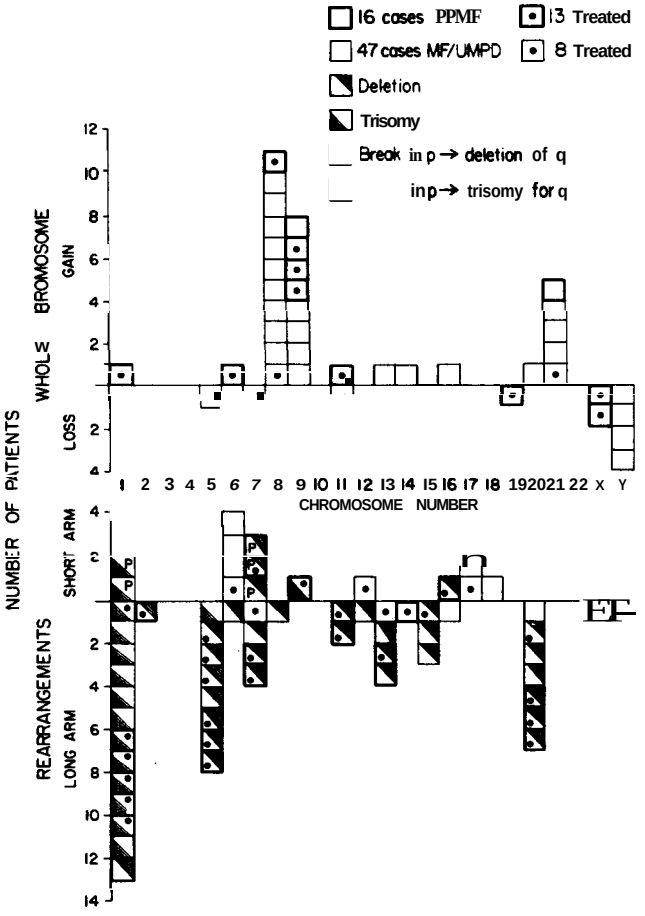


FIG. 5. Histogram of clonal karyotypic changes (gains, losses, and rearrangements) seen in 16 PPMF and 47 MF/UMPD patients. Each box represents a clonal change seen in a single patient.

patients (both with MF) have an internal rearrangement of no. 1 resulting in a duplication of the same segment, namely 1q21 to 1q32.

Although 20q − appears to be more frequent in PPMF (Table 4), three groups have reported del(20)(q11) in patients with MF. One case with early DMF showed the deletion after 5 years of busulfan therapy." Findley et *al.*[36] and Kondo et *al.*[37] each described a 20q − in patients who had never received any cytotoxic therapy. No ANLL developed during follow-up in either patient.

Comparison of the *PPMF* and *MF/UMPD Gro*

Although in many instances the chrom changes in PPMF as well as in MF and UMPD a be nonrandom, specific chromosome abnorma diagnostic patterns that clearly distinguished th eases were not apparent (Table 4). The cyto changes associated with MF seem to be more distributed among the various chromosomes tha seen in PPMF.

Some differences in the frequency of specific are seen, however. Trisomy 8 is the only finding more common in MF/UMPD than in PPMF. T incidence of trisomy 8 in PPMF (usually ju treated) and in secondary ANLL[31] are unexpec may imply that prior therapy is not related to the ance of trisomy 8 in these disorders. This also ap be true in our series with MF/UMPD. Trisomy 9 to be more common in all phases of PV (unt 23%;[22] PPMF—31% (Table 4); leukemic 23%[22]) than in MF/UMPD (9%, Table 4). Other malities were also more common in PPMF, partic 20q −, loss of 7 or 7q −, and, to a lesser extent, trisо and 5q−.

Cytogenetic abnormalities do not provide a diag pattern or prognostic usefulness in MF/UMPD initial studies in PPMF. Partial or complete lo chromosomes, particularly nos. 5 or 7, are asso with prior therapy or chemical exposure in MF/U PPMF does appear to have a higher tendency leukemic transformation than does MF, and an tion in karyotype appears to have serious prognos plications in PPMF in regards to this transition.

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TABLE 4. Common Clonal Karyotypic Abnormalities in PPMF (16 Cases) and MF/UMPD (47 Cases)

	Chromosome aberrations					
	No. of patients (percent)					
Disease	+1q	−5/5q−	−7/7q−	+8	+9	20q−
PPMF (16 cases)	7 (44%)	3 (19%)	5 (31%)	1 (6%)	5 (31%)	3 (19%)
MF/UMPD (47 cases)	8 (17%)	5 (11%)	5 (11%)	10 (21%)	4 (9%)	3 (6%)

PPMF postpolycythemia myelofibrosis; MF/UMFD: myelofibrosis/undifferentiated myeloproliferative disorder.

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