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Histomorphometry of bone marrow biopsies in chronic myeloproliferative disorders with associated thrombocytosis – features of significance for the diagnosis of primary (essential) thrombocythaemia *

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Summary. A histomorphometric analysis was performed on trephine biopsies of the bone marrow in 55 patients with chronic myeloproliferative disorders (CMPDs) and marked thrombocytosis (platelet count exceeding 600×10^9/l). This study aimed at discriminating primary (essential) thrombocythaemia (PTH) from the various other subtypes of CMPDs presenting with thrombocytosis. Following the diagnostic requirements postulated by the Polycythemia-vera-Study-Group for PTH and polycythaemia vera rubra (P.vera) and the generally accepted criteria for the establishment of chronic myeloid leukaemia (CML) and agnogenic myeloid metaplasia (AMM), our cohort of 55 patients was divided into the following subgroups: CML (16 cases), P.vera (11 cases), AMM (13 cases) and finally PTH (15 cases). Histomorphometric measurements revealed that PTH was distinguishable from the other subtypes of CMPDs with respect to several histological variables: patients with PTH had a normal amount of neutrophilic granulo- and erythrocytopoiesis as well as a non-increased content of reticulin (argyrophilic) fibers in contrast to the findings in CML, P.vera and of course AMM. Moreover, sizes of megakaryocytes and their nuclei were significantly greater in PTH and internalization of haematopoietic cells (emperipolesis) was more frequently encountered in comparison with the other subtypes of CMPDs. Deviation of the circular perimeter of megakaryocyte shape was most prominently expressed in CML and AMM, and consequently generated an increased number of a-nuclear cytoplasmic fragments. In contrast to this feature aberration of the nuclei from a circular outline occurred in a less pronounced way in CML, but was excessive in P.vera, AMM and PTH. Our morphometric evaluation demonstrates that certain histological features may serve as a valuable aid in discriminating PTH from the other occasionally thrombocythaemic subtypes of CMPDs.

Key words: Chronic myeloproliferative disorders – Thrombocytosis – Primary Thrombocythaemia – Granulo – Erythrocytopoiesis – Reticulin Fibers – Circular Deviation – Histomorphometry – Bone marrow biopsies

Introduction

In chronic myeloproliferative disorders (CMPDs) with the presenting clinical finding of thrombocytosis, discrimination into several subtypes may be biased by the common histological feature of a profound megakaryocytic growth in the bone marrow. Differentiation into the well-known clinical entities like chronic myeloid leukaemia (CML), polycythaemia vera rubra (P.vera), agnogenic myeloid metaplasia (AMM) or so-called primary osteomyelofibrosis with thrombocythaemic onset and finally primary (essential) thrombocythaemia (PTH), is often difficult. An unequivocal diagnosis can certainly be established by employment of the approach postulated by the Polycythemia-vera-Study-Group (PVSG) (Iland et al. 1983; Murphy et al. 1986). However, in contrast to these clinical criteria with their distinctive value, the diagnostic significance of corresponding histomorphological bone marrow lesions is still not settled. There are two controversial opinions expressed in the literature: that there are non-characteristic alterations

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with a trilineage growth or panhyperplasia resembling that of P.vera (Iland et al. 1983, 1987; Murphy 1983; Murphy et al. 1986) or a prodigious so-called monolinear megakaryocytic myeloproliferation without conspicuous abnormalities, termed chronic megakaryocytic myelosis (CMM) – the morphological equivalent of PTH (Georgii et al. 1984; Vykoupil et al. 1984; Burkhardt et al. 1986; Thiele et al. 1984, 1987). These conflicting reports concerning the histopathology in patients with PTH and allied disorders make a meticulous analysis of bone marrow features mandatory. Attempts to solve this problem must provide: – a non-selected group of patients with CMPDs presenting with a markedly elevated platelet count in excess of 600×10^9/l as the lower limit acceptable for the diagnosis of PTH required by the PVSG (Murphy et al. 1986), an initial and representative trephine biopsy of the bone marrow performed on admission, prior to any treatment, and a scrutinized histomorphometric evaluation of all components of the medullary tissue, i.e. neutrophilic granulo-, erythro- and megakaryocytopoiesis as well as the content of reticulin (argyrophilic) fibers.

Materials and methods

A total of 55 patients met the necessary requirements of an unequivocally established CMPD with thrombocythaemic onset (platelet count exceeding 600×10^9/l) and an initially taken biopsy of the bone marrow of a representative size (15.5 ± 6 mm^2) evaluable for histomorphometry. Recruitment was started in January 1975 and terminated December 31, 1985, with a time of observation ranging from 2.5–9.5 years (deadline April 15, 1987). Discrimination into several subtypes of CMPDs was possible by considering the relevant clinical findings significant for the diagnosis of CML (Goldman et al. 1982), P.vera (Berlin 1975; Berk et al. 1986), AMM (Geary et al. 1985) and PTH (Iland et al. 1983; Murphy et al. 1986). A survey of these patients enrolled in our study is given in Table 1 and the corresponding laboratory data on admission in Table 2. 20 specimens taken from patients (10 male/10 female-median age 54 years) without any haematological disease and a normal appearance of the bone marrow served as controls.

Trephine biopsies of the bone marrow were taken from the posterior iliac crest (Jamshidi et al. 1971). Further processing included fixation in an aldehyde solution (2 ml 25% glutardialdehyde, 3 ml 37% formaldehyde and 1.58% calcium acetate

Table 1. Survey of 35 patients with CMPDs and thrombocytosis (exceeding 600 x 109/l) who entered this study. Time of observation ranged from 2.5 to 9.5 years (deadline April 15, 1987)

CMPD-subtypes	*n*	Sex (M/F)	Age (years)	Philadelphia-chromosome			dead/alive	Survival (months)
				yes	no	not determined		
CML	16	3/13	48	7	–	9	8/ 8	30±14
P.vera	11	2/ 9	60	–	–	11	2/ 9	61±25
AMM	13	4/ 9	72	–	4	9	2/11	41±21
PTH	15	4/11	50	–	15	–	0/15	–

Table 2. Haematological parameters of 55 patients with CMPDs and an elevated platelet count (exceeding 600×10^9/l)

Laboratory variables n	CML 16	P.vera 11	AMM 13	PTH 15
Thrombocytes $\times 10^9$/l	893±293	906±370	871±190	1517±562
Erythrocytes $\times 10^{12}$/l	4.07±0.9	7.0±1.0	4.28±0.74	4.5±0.4
Haemoglobin g/dl	12.2±2.7	17.9±2.3	11.8±1.9	13.1±1.0
Haematocrit %	38.0±4.1	54.6±6.7	37.0±5.1	40.0±3.4
Leukocytes $\times 10^9$/l	107.5±75.4	14.4±5.1	15.5±11	11.1±3.6
polymorphonuclear %	44.2	68.5	62.9	68.1
basophils %	6.1	1.5	1.4	1.1
promyelocytes %	2.1	0	0.2	0
myeloblasts %	2.3	0	1.4	0
normoblasts %	1.5	0	3.75	0
LAP[a] (score)	36±49	153±58	316±67	63±46
LDH U/l	723±358	380±126	4.32±129	323±118
Spleen size[b]	4.8±5.6	0.8±1.5	4.1±1.9	0.3±0.9
Liver size[b]	1.9±3.9	3.7±9.7	1.5±2.1	0.5±1.7

[a] normal score 10–80
[b] cm below costal margin

with aqua dest. ad 100 ml), decalcification in neutral buffered EDTA for three days and finally paraffin embedding (Schaefer et al. 1984). The following methods were employed on re-cut paraffin blocks taken from our files for the identification of certain histological features and morphometric analysis: Survey – Giemsa, megakaryocytes – periodic acid Schiff reagent (PAS), neutrophilic granulopoiesis (negative for erythropoiesis) – Naphthol-AS-D-chloroacetate esterase reaction, argyrophilic (reticulin) fibers – Gomori's silver impregnation.

Morphometric evaluation was done by a manual optic planimeter (MOP-A-MO1-Kontron) with a standard program set. Densities of neutrophilic granulocytes, erythrocytic precursors as well as megakaryocytes per square millimeter were measured at 500× magnification by calculation of the evaluable marrow area of the trephine biopsy and the total number of the corresponding cells. In case of the megakaryocytes, classification into nucleated forms, a-nuclear fragments or veil-like extensions of cytoplasm, naked (pyknotic, bare) nuclei, emperipolesis and mitoses was performed – see also Table 4. After dividing the total area of the trephine biopsy into 5 segments of approximately the same size, 20 randomly selected megakaryocytes were measured in each field at a magnification of 1250× with determination of area, diameter, circumference and circular deviation of certain cellular features as listed in Table 4. The circular deviation (CD) of the perimeter for megakaryocytes and their nuclei was defined as $CD = 4\pi A/C^2$ (C = circumference and A = area), giving the value -1- for a circle and a lower factor indicating an increased irregularity of shape. The reticulin fiber content was calculated in sections following silver impregnation (Gomori's stain) by counting the number of intersections (i) with the lines of a grid ocular at a magnification of ×500 in 20 randomly selected fields free of trabecular bone (equalling 1.14 mm^2). The area covered by fat cells was substracted and the reticulin fiber density distribution expressed as number of intersections per millimeter fat cell-free haematopoietic tissue (i/mm^2).

Results

Following the clinical establishment of certain subtypes of CMPD (Table 1) with relevant haematological findings (Table 2), the corresponding bone marrow lesions show a pronounced megakaryocytic proliferation with a dispersed or clustered growth pattern accompanied by various amounts of granulo- and erythrocytopoiesis (Fig. 1a–e). An overview of megakaryocytic morphology reveals prominent microforms in CML (Figs. 2a, 5a) and a mixture of small and large megakaryocytes with a pleomorphic appearance in P.vera (Fig. 2b). In AMM an abnormal differentiation of this cell line (Figs. 2c, 3d, 5b, d, f) is evident, thus contrasting PTH which shows groupings of apparently mature and large forms containing multi-lobulated nuclei (Figs. 2d, 5e). Occasionally megakaryopoiesis extends towards the endostal border of the trabecular bone (Fig. 2c, d). Neutrophilic granulopoiesis exhibiting many precursor cells is of course the predominant feature in CML (Fig. 2a). P.vera displays a prodigious proliferation of erythro- and, at a lesser degree granulocytic elements (Fig. 2b). Moreover, in AMM a normal to slightly reduced amount of granulo- and erythropoietic tissue is encountered (Fig. 2c).

This gross assessment of histopathology has also to include the bone marrow matrix, i.e. adipose tissue and reticulin (argyrophilic) fibers. An approximately normal content of fat cells is generally observable in the so-called (early) hyperplastic stages of AMM and PTH (Fig. 1b, d, e). However, in P.vera (Fig. 1c), but particularly in CML, a striking replacement of this compartment of the bone marrow by haematopoietic elements is always conspicuous (Fig. 1a, c). The amount of reticulin fibers is a histological variable, since in CML several cases without increase (Fig. 3a), but others with a slight to moderate fibrosis are recognizable. P.vera is characterized by a borderline or slight amount of argyrophilic elements (Fig. 3b). In PTH the majority of cases do not show any fibrosis, and only in a very few patients is a minimal increase in density of fibers seen. In comparison with these rather inconsistant findings AMM regularly presents either with a moderate (Fig. 3c) or markedly increased (Fig. 3d) amount of reticulin fibrosis, associated with an atypical megakaryocytic proliferation.

In addition to a remarkable increase in megakaryocytic proliferation (by 4–5 times in comparison with control cases), a survey of morphometric data demonstrates that the other components of the bone marrow reveal striking differences in the various subtypes of CMPDs (Table 3). A calculation of these different constituents composing the bone marrow space (Fig. 3) further shows that the total area of megakaryopoietic cells covering one square millimeter amounts to $1.7 \times 10\ mm^{-2}$ in CML and 3.8×10^{-2} mm in PTH (normal value 0.4×10^{-2} mm). This significant extension of megakaryocytic area is not due to disparate counts per square millimeter bone marrow (see Table 3), but to an increased size of all types of this cell line as shown in Table 4. Moreover, morphometric measurements (Fig. 4) confirm that the content of adipose tissue is not significantly different in AMM and PTH in comparison with the obvious decrease in P.vera and CML, when considering specimens of an age-matched normal population. As might be expected, in AMM the density of reticulin fibers is certainly greater than in the other subtypes of CMPDs, although at least some of the CML cases also exhibit a shift to a moderate myelofibrosis (Table 3, Fig. 4). However, it is conceivable that not only the proportions of marrow area occupied by megakaryopoiesis may be an essential feature of histopathology, but also the fine

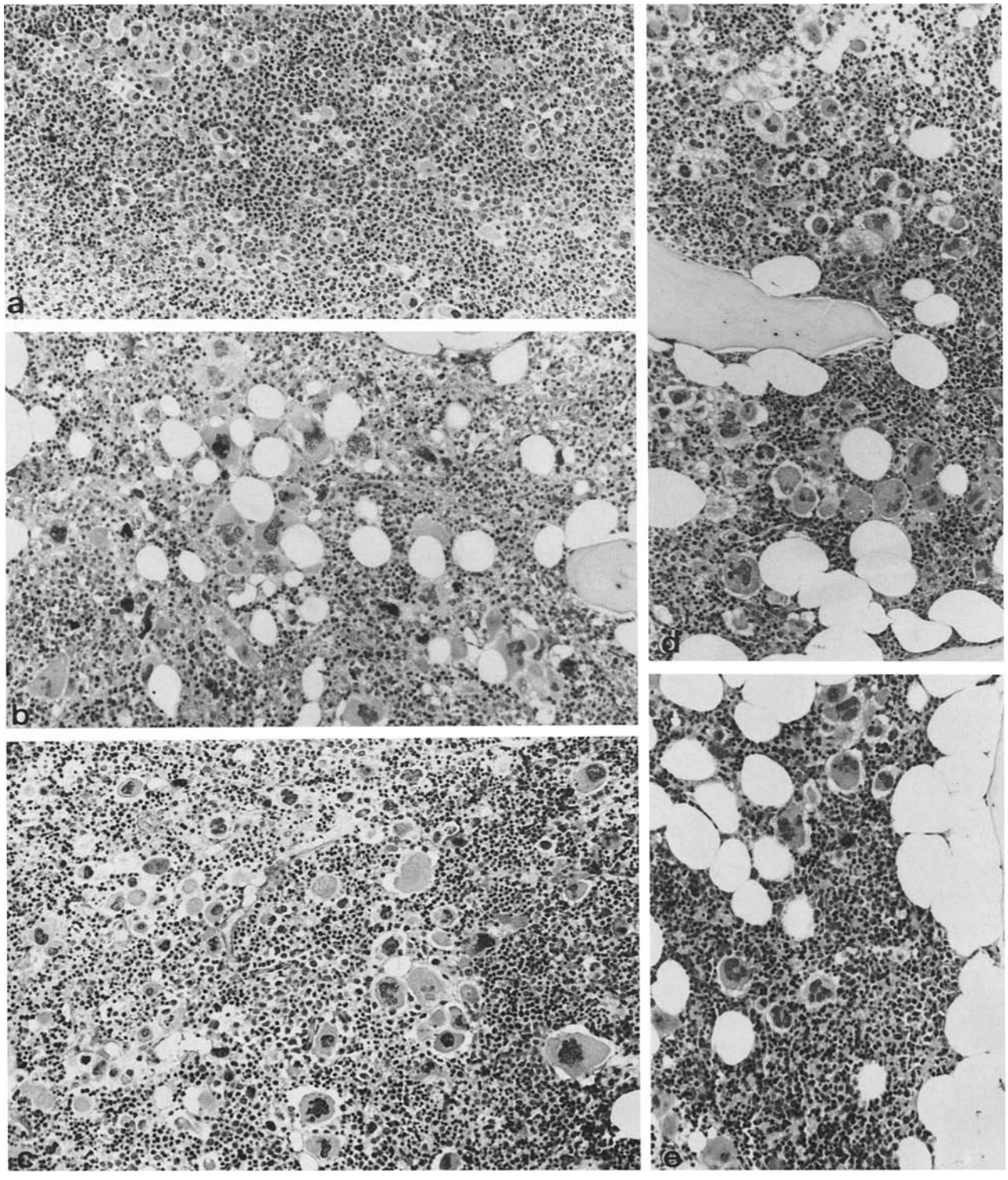

Fig. 1a–e. Survey of bone marrow trephine biopsies with CMPDs and thrombocytosis (see also Fig. 4). **(a)** CML with a mixed megakaryocytic- granulocytic myeloproliferation. **(b)** AMM initial hyperplastic stage with prominent clustering of megakaryocytes. **(c)** P.vera showing a trilinear erythro- granulo- and megakaryocytic growth. **(d, e)** PTH with predominance of either dispersed or focally clustered megakaryocytic proliferations, translocation towards the spongy trabeculae and residual adipose tissue. **(a–e** ×150), PAS stain

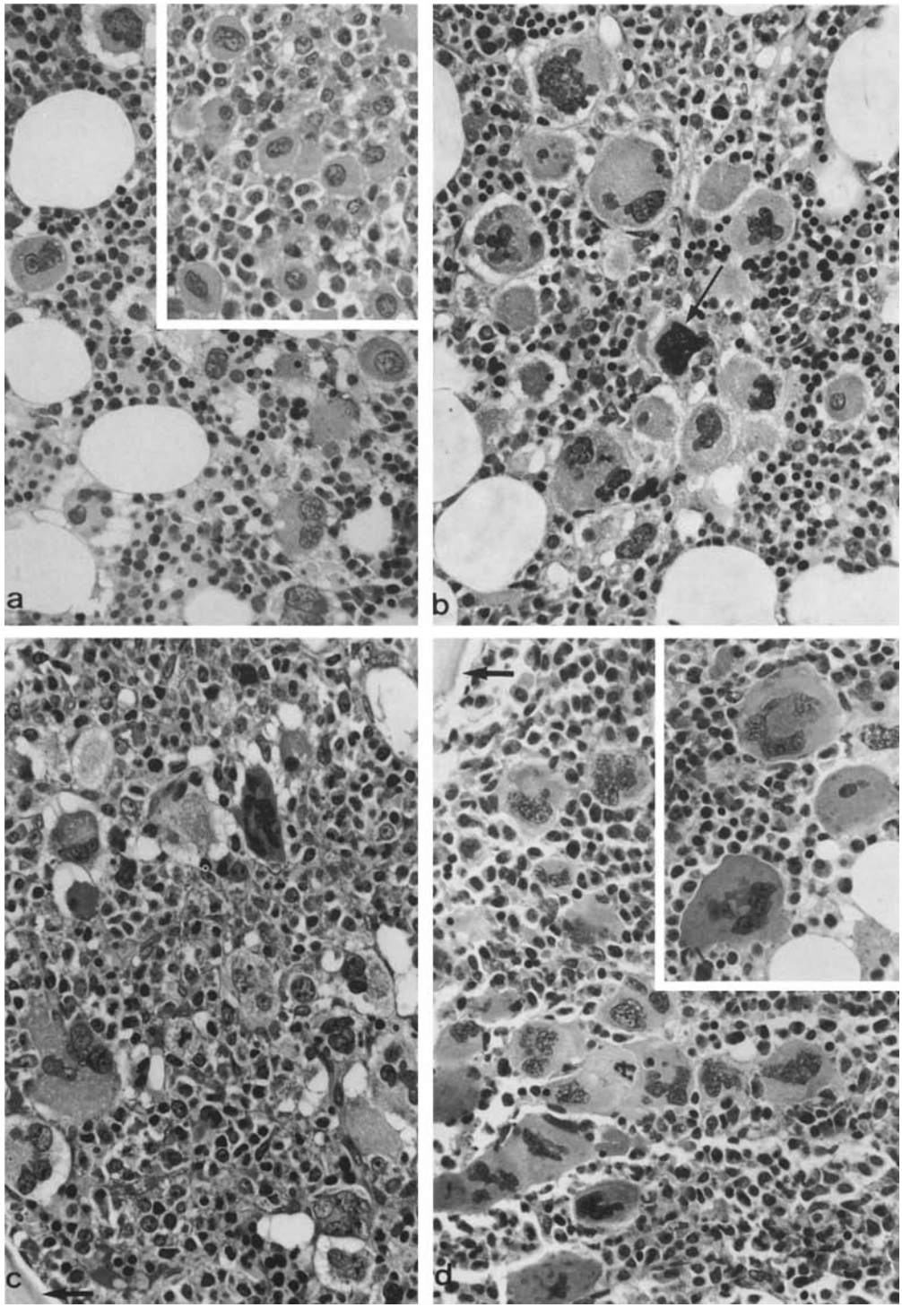

Fig. 2a–d. Megakaryopoiesis in the bone marrow of patients with CMPDs and thrombocytosis. (**a**) CML with an either dispersed or conspicuously clustered growth pattern of small to medium sized megakaryocytes containing uni- or bilobulated nuclei. (**b**) P.vera revealing a pleomorphic appearance of megakaryocytes with small to giant forms; the latter show extensively segmented nuclei; additionally there are large naked (*pyknotic*) nuclei (*arrow*). (**c**) AMM with groupings of atypical megakaryocytes of various sizes and shapes translocated towards the peritrabecular area of the spongious bone (*arrow*). (**d**) PTH displaying numerous megakaryocytes with predominance of large mature forms showing highly lobulated staghorn-like dense nuclei (*inset*). A dislocation of megakaryopoiesis towards the trabecular bone area (*arrow*) is obvious. (**a–d** × 350), PAS stain

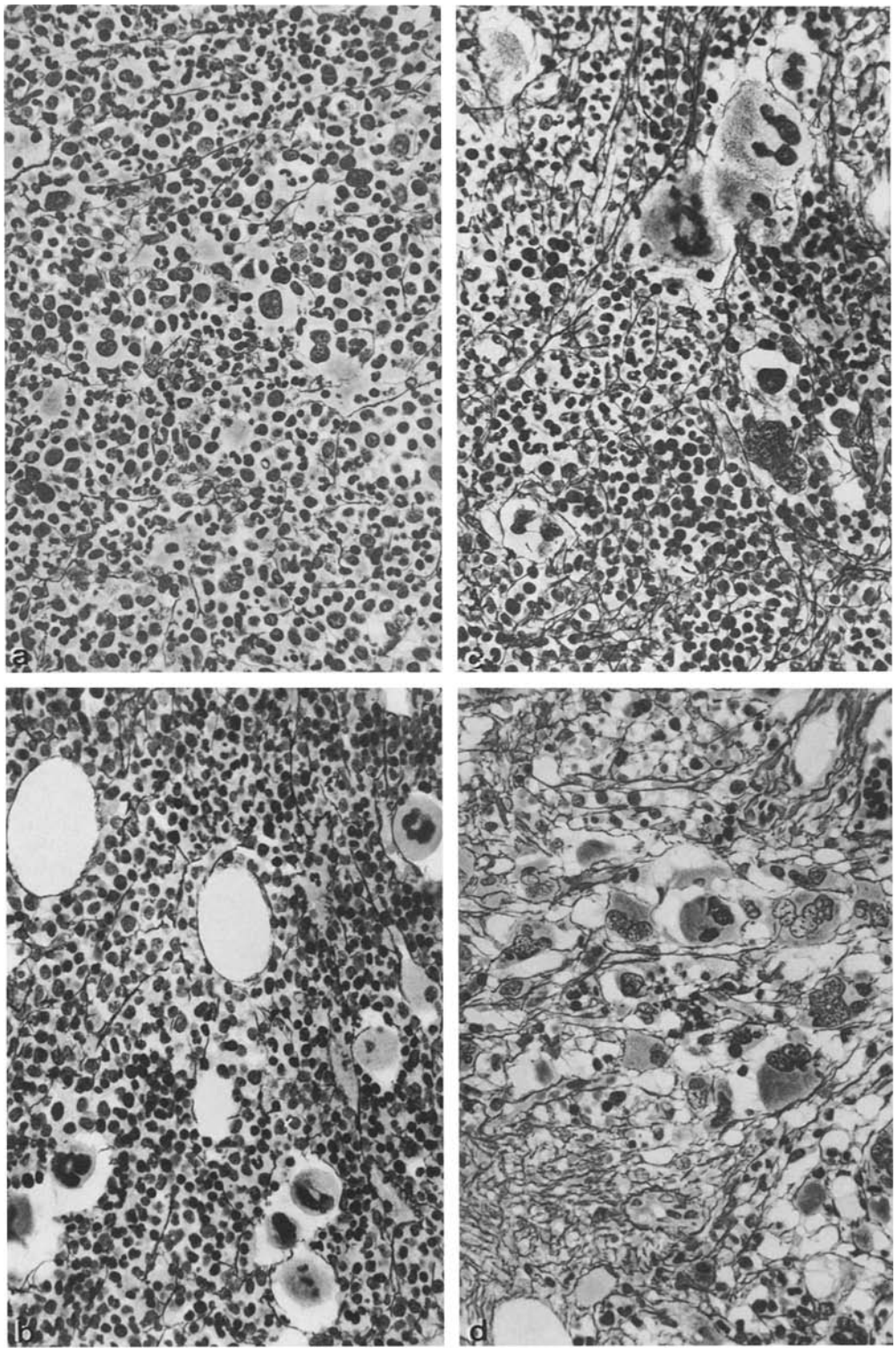

Fig. 3a–d. Argyrophilic (reticulin) fibers in CMPDs with thrombocytosis (normal content 16×10^2 i/mm^2). (**a**) CML with no remarkable increase (18×10^2 i/mm^2), (**b**) P.vera showing a borderline (20×10^2 i/mm^2) density, (**c and d**) AMM with either a moderate (c- 45×10^2 i/mm^2) or marked (d- 92×10^2 i/mm^2) fibrosis associated with an atypical megakaryocytic myeloproliferation. (**a–f** $\times$ 350), Gomori's silver impregnation

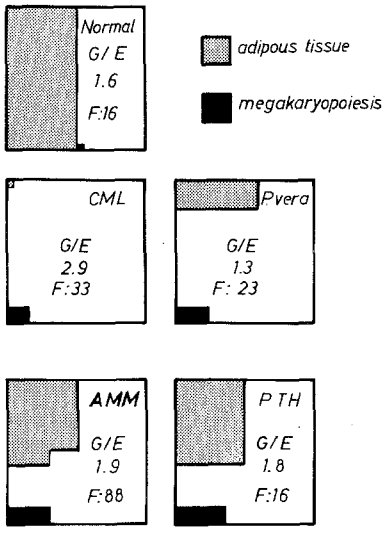

Fig. 4. Schematic presentation of one square millimeter bone marrow area showing the proportions for adipous tissue, the extension of megakaryopoiesis, the ratios of granulo-/erythrocytopoiesis (G/E) and the density of argyrophilic (*reticulin*) fibers ($F \times 10^2$ i/mm^2) for normal controls and patients with CMPDs and thrombocytosis (see also Fig. 1a–e). Additionally this square millimeter bone marrow area contains a varying number of plasma and mast cells, erythrocytes, lymphocytes, monocytes and histiocytic reticulum cells and is further occupied by interstitial edema and vascular structures (sinusoids, capillaries, arterioles)

structure or various elements composing this cell lineage (Fig. 5a–f). Amongst these, size and frequency of nucleated megakaryocytes, a-nucleated cytoplasmic fragments or extensions, naked (pyknotic) nuclei and the deviation from a circular shape of perimeter (shapes of cell and nucleus) may reveal a characteristic pattern which is of diagnostic value for the recognition of the different subtypes of CMPDs with thrombocytosis (Fig. 6).

Discussion

Morphometric analysis of the various elements composing haematopoietic tissue and bone marrow matrix in patients with CMPDs and thrombocytosis reveals significant differences when considering certain sets of histological features. It should be emphasized that these sets of morphological differences shown by morphometry (Tables 3, 4) can be appreciated in the majority of cases with confidence by an educated observer using a light microscope and a representative, adequately processed trephine biopsy. For this reason our results are not consistent with the assumption of a non-characteristic histomorphology in PTH and allied disorders (Iland et al. 1983, 1987; Murphy et al. 1986). Consequently a number of distinctive findings of diagnostic value for this subtype of CMPDs are emphasized (Figs. 4 and 6), and the statement of a panhyperplasia similar to P.vera (Murphy 1983; Murphy et al. 1986; Iland et al. 1987) should be discarded. This critical standpoint is further underlined when taking into consideration the selection of our patients. Cases with P.vera and PTH were recruited by following the rigid diagnostic requirements of the PVSG (Berlin 1975; Murphy et al. 1986; Berk et al. 1986). Moreover, all patients, but particularly those showing the clinical signs and symptoms of P.vera, presented with an elevated platelet count greater than 600×10^9/l. This platelet count was chosen as the lower acceptable limit for PTH (Murphy et al. 1986). The finding of a non-specific histopathology in PTH (so-called trilineage hyperplasia) and the inability to distinguish this disorder from P.vera without (Iland et al. 1983; Murphy et al. 1986) or with marked thrombocytosis (Iland et al. 1987) on morphological grounds alone, may possibly be due to the methods employed for bone marrow examination. Apparently, in a number of cases no trephine biopsies, but only clot sections of small marrow particles were available and were evaluated by the authors together with smears of aspirates (Iland et al. 1983). These samples should not be regarded as representative specimens for an analysis of bone marrow histopathology. This statement is supported by the failure to demonstrate an increased number of megakaryocytes in bone marrow aspirates in more than 50% of 94 patients with PTH

Table 3. Histomorphometry of bone marrow components in 55 patients with various subtypes of CMPDs presenting with an elevated platelet count (exceeding 600×10^9/l). Features of significance for diagnosis have been underlined – for further details, see Fig. 4

Morphometric variables *n*	CML 16	P.vera 11	AMM 13	PTH 15	Controls 20
Megakaryopoiesis per mm^2	63.3± 4.2	44.7±8.8	54.1±14.9	66.0±7.8	13.5± 2.9
Neutrophilic granulocytopoiesis $\times 10^2$/mm^2	83.6±12.6	71.9±7.6	34.7± 8.3	48.2±6.0	46.4± 6.2
Erythrocytopoiesis $\times 10^2$/mm^2	29.2± 5.7	53.9±3.7	21.9±11.1	27.7±4.5	29.4± 5.4
Argyrophilic fibres (density) $\times 10^2$ per i/mm^2	32.8±25.8	23.3±9.9	87.9±34.0	15.9±7.0	16.1±88

Table 4. Histomorphometric features of megakaryopoiesis in the bone marrow of patients with CMPDs and thrombocytosis (exceeding 600×10^9/l). – Features of significance for diagnosis have been underlined – for further details see Figs. 5a–f, 6

Megakaryocyte features	CML	P.vera	AMM	PTH
n	16	11	13	15
Subtypes				
nucleated forms – %	73.8	75.5	62.5	65.7
a-nucleated fragments	18.0	14.3	23.8	15.1
bare (pyknotic) nuclei	6.6	6.5	11.1	13.9
emperipolesis	1.6	2.9	2.1	4.3
mitosis	–	0.8	0.5	0.9
Diameter (nucleated forms)	19.3±2.4	24.8±1.8	27.8±1.8	30.2±2.3
Area				
megakaryocytes (total) – μm^2	114.2±52.7	434.6±58.8	433.9±171	584.4±92
nuclei	53.8±12.0	104.7±16.7	101.1± 36	138.0±27
a-nucleated fragments	178.1±39.4	310.7±46.8	352.0±102	411.9±61
bare (pyknotic) nuclei	79.7±25.6	123.3±14	124.0± 36	169.8±34.1
Circular deviation (factor)				
megakaryocytes	0.79±0.06	0.85±0.03	0.77±0.05	0.82±0.02
nuclei	0.65±0.06	0.47±0.05	0.51±0.06	0.47±0.05
Nuclear-cytoplasmic ratio	0.25±0.03	0.25±0.02	0.25±0.03	0.24±34.1

following the diagnostic criteria of the PVSG (Bellucci et al. 1986). In a recent paper about the differences between PTH and P.vera with concomitant thrombocytosis Iland et al. (1987) were hardly able to calculate distinctive values for bone marrow features (p-values ranging between >0.5 and <0.03) when comparing both entities by univariate statistical analysis. However, assessment of histological variables was performed by a semiquantitative scaling method, and there is no reference to the specimens employed, i.e. trephine biopsies or clot sections of marrow particles, sizes of evaluated marrow area or embedding techniques (paraffin or plastic).

An increase in reticulin (argyrophilic) fibers at presentation is not usually an initial feature of PTH (Georgii et al. 1984; Vykoupil et al. 1984; Burkhardt et al. 1986; Thiele et al. 1987), and is therefore not corroborated by our findings (Table 2). In contrast with this result, a slight to moderate fibrosis was reported by semiquantitative gradings in a considerable number of cases (Bellucci et al. 1986; Iland et al. 1983, 1987; Murphy et al. 1986). Hypercellularity and a decreased amount of adipose tissue similar to P.vera have been found as characteristic changes in PTH (Murphy 1983; Iland et al. 1987). Again this is not in agreement with our findings of an only slightly reduced content of fat cells in PTH in comparison with P.vera (Fig. 5).

Generally our histomorphometric analysis of the bone marrow in CMPDs with concomitant thrombocytosis extends some of the former results which were not based on the assessment of all marrow components and had been performed by different methods (morphometry on biopsies and/or smears, cytophotometry). In this regard our study evaluates for the first time the entire spectrum of marrow constituents in CMPDs by employment of trephine biopsies and morphometry. The fine structure of megakaryocytes was investigated in patients with the clinical signs of thrombocytosis (Vykoupil et al. 1984) and PTH (Georgii et al. 1984; Burkhardt et al. 1986) by an elaborate technique (plastic embedding). A semiquantitative calculation revealed that in the mature type or CMM, corresponding with the clinical diagnosis of PTH, megakaryocytes showed conspicuous giant forms with a dispersed growth or cluster formation (Burkhardt et al. 1986). This finding confirms earlier morphometric data on this lineage (Thiele et al. 1984), and is in congruence with results derived from paraffin embedded bone marrow biopsies in patients with the clinical diagnosis of PTH (Thiele et al. 1987). However, the method of calculation applied in the present study has to be noticed. Counts for megakaryocytes, neutrophilic granulo- and erythrocytopoiesis per square millimeter bone marrow area, were all measured by semiautomatic planimetry of the total biopsy (ranging from 10 to 32 mm^2). In comparison with the counts made by an ocular grid (Thiele et al. 1987), or the point-counting method (Kendrup et al. 1980) following a random selection of certain marrow fields, this

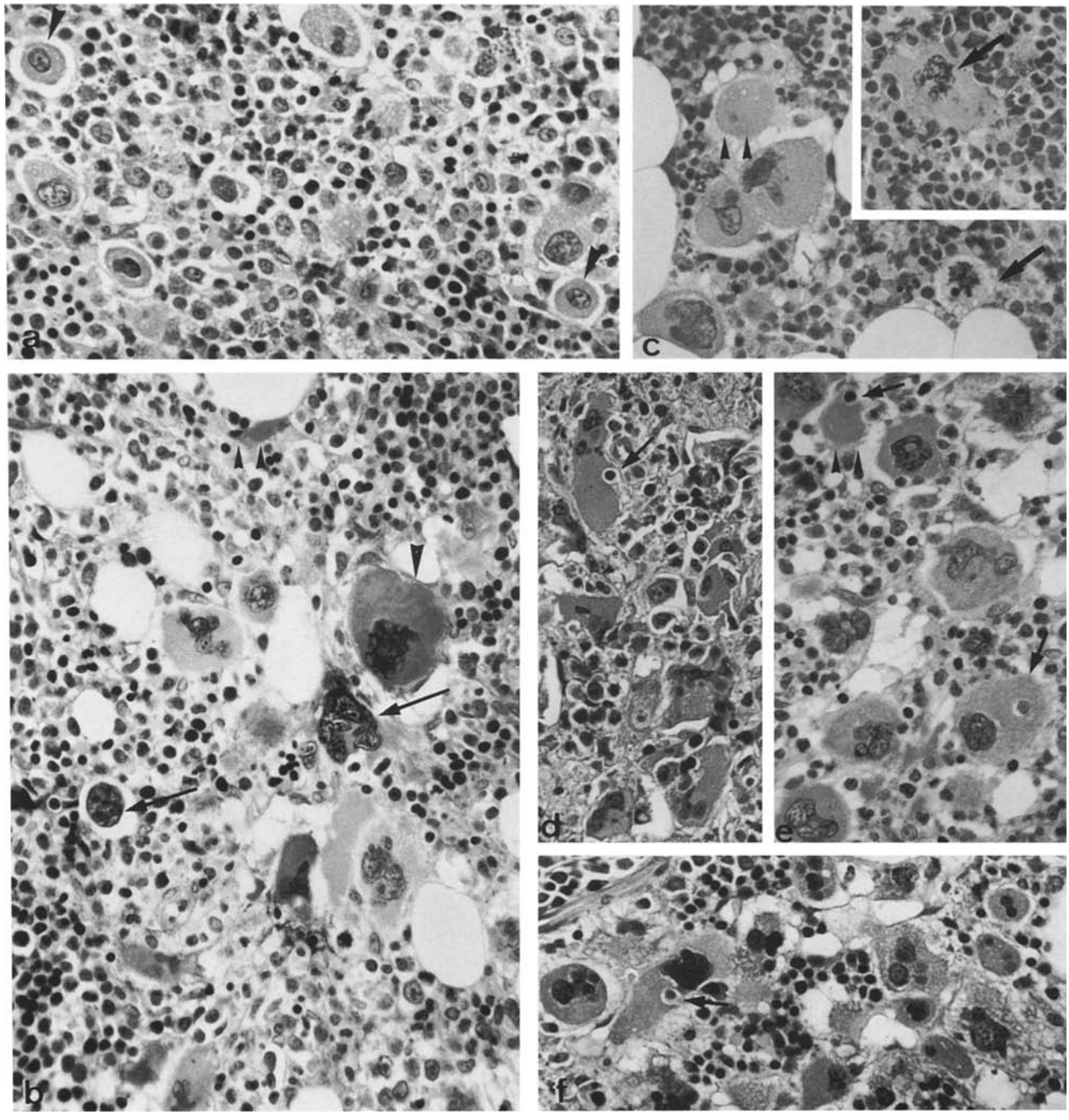

Fig. 5a–f. Histomorphometric features of megakaryocytes in CMPDs with thrombocytosis. Without regard to sizes, circular deviation of cytoplasmic perimeters reveal an almost perfectly round shape in micromegakaryocytes and giant forms (**a, b** – *arrow heads* – factor 0.85) in contrast to irregular ameboid outlines (**d** – factor 0.78). Naked (*bare*) pyknotic nuclei of different sizes and forms (**b** – long *arrows*) and also a-nucleated cytoplasmic fragments of megakaryocytes (**b, c, e** – *double arrow heads*). Complete (**e** – *short arrow*) and partial internalization or emperipolesis of haematopoietic cells – normoblasts (**e, f** – *short arrows*) and mitotic figures (**c**; *inset – thick arrows*). (**a–f** × 350), PAS stain

technique seems to be more accurate, but inevitably leads to lower values.

Usually megakaryocytes in the normal bone marrow display a 16 N ploidy class in two thirds of their population (Penington 1979). Consequently the obvious shift to microforms in CML (Albrecht and Fülle 1974; Franzen et al. 1961; Trautmann 1961; Kutti et al. 1973; Thiele et al. 1983; Wiesneth et al. 1980) implies a prevalence of 4–8 N ploidy classes (Lagerlöf 1972). Since sizes

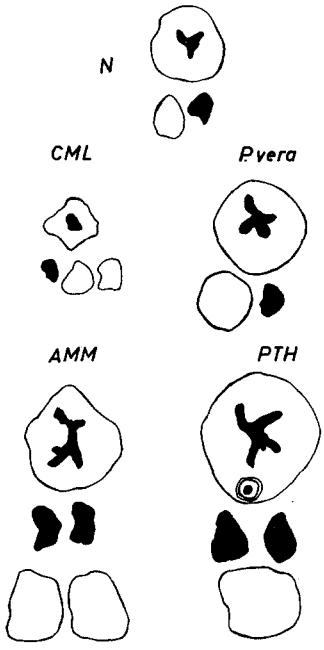

Fig. 6. Schematic presentation of distinctive histomorphological features of megakaryocytes for the discrimination of the various subtypes of CMPDs with the initial clinical finding of a markedly elevated platelet count (see also Fig. 5a–f and Table 4) in comparison with control specimens (*N*)

of megakaryocytes and lobulation of their nuclei are correlated and conversely linked with the different ploidy classes (Levine et al. 1982), the giant megakaryocytes observable in P.vera (Lundin et al. 1972; Branehög et al. 1975; Ellis and Peterson 1979; Franzen et al. 1961; Georgii et al. 1984; Burkhardt et al. 1986; Thiele et al. 1982, 1984) or PTH (Branehög et al. 1975; Thiele et al. 1984) represent an alteration of ploidy pattern with predominance of higher values (Queisser et al. 1976; Lagerlöf 1972). This shift to the right in distribution of sizes and associated ploidy classes in P.vera and PTH is presumably the result of an increased endomitotic activity of this cell lineage.

Our histomorphometric analysis on trephine biopsies of the bone marrow in patients presenting with various subtypes of CMPDs and marked thrombocytosis reveals significant differences in each group, but particularly also in PTH, which may contribute to an improvement of histological diagnosis in these conflicting disorders.

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