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Myeloid Dysplasia: the Histopathology of Preleukemia*

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The clinical term "preleukemia" is understood as an alteration of the bone marrow and peripheral blood preceding overt acute myeloid leukemia (AML, review by Saarni and Linman 1973). However, in the majority of cases the diagnosis is only a retrospective one, derived from many mostly clinical and cytogenetic investigations (Fisher et al 1973; Dreyfus 1976; Linman and Bagby 1978; Pierre 1978). The aim of our study was to determine whether there are characteristic lesions of the bone marrow preceding obvious leukemia and if wether those lesions are similar in cases evolving AML or CML later on.

Among more than 15,000 biopsies of the bone marrow which were performed during the last 10 years 195 patients were selected whose examination of the bone marrow was initiated by the clinical assumption of a possible preleukemic state. This selection following the suggested clinical diagnosis of so-called preleukemia inherits a problem: there may be no clear cut separation between a preleukemic state of leukemia and a myeloproliferative disorder or CML in early stage or chronic megakaryocytic-granulocytic myelosis (CMGM, see Georgii 1979).

A re-evaluation of the semithin sections of these bone cylinders displayed two different categories of disorders: 62 patients had either nonneoplastic lesions (leukemoid reaction, 12; hyperergic myelitis (mostly rheumatic), 23; pernicious anemia, 11; panmyelophthisis, 3 and other diseases 13 or early stage CML 35 and oligoblastic leukemia 5. The remaining second category of 93 patients showed distinctive and identical morphological features of the bone marrow which probably correspond to hemopoietic dysplasia of Linman and Bagby (1978), but should be rather called myeloid dysplasia, MD, (Thiele et al. 1980a): Histopathology is characterized by a hypercellularity (Fig 1a) in most of the cases, a frequently occurring megaloblastoid and at least macrocytic differentiation of erythropoiesis (Figs. 1b, 2a). There are many sideroblasts of the granular type and a shift to the left of the neutrophilic granulopoiesis which displays the so called pseudo-Pelger-Huët anomaly of maturation (Figs. 2a,b). It should be emphasized that there is no increase in blasts along the peritrabecular generation zones of granulopoiesis. Megakaryocytes are not only increased but exhibit abnormal cells such as frequent naked nuclei, micromegakaryocytes, and too many immature forms (Figs. 1a, 2b). The myeloid stroma contains a patchy edema and often a remarkable perivascular plasmacytosis (Figs. 1a, 2c). Electron microscopy of these cell confirms these findings and extends our results of an abnormal cellular differentiation in MD (for details see Thiele et al. to be published a).

Of these 93 patients with the histomorphology of MD at the time of their first and initial biopsy, sequential corings of the iliac crest (up to five times in periods ranging from 2 months to 3½ years) as well as review of the clinical records revealed that 26 cases evolved obvious leukemia and the remaining 67 did not show apparent leukemia until now (Table 1).

Initial main clinical symptoms were mostly unspecific, ranging from fatigue, loss of weight, easy bleeding, and pallor to physical findings such as dermal hemorrhage, slight to moderate hepatomegaly, and minimal splenomegaly.

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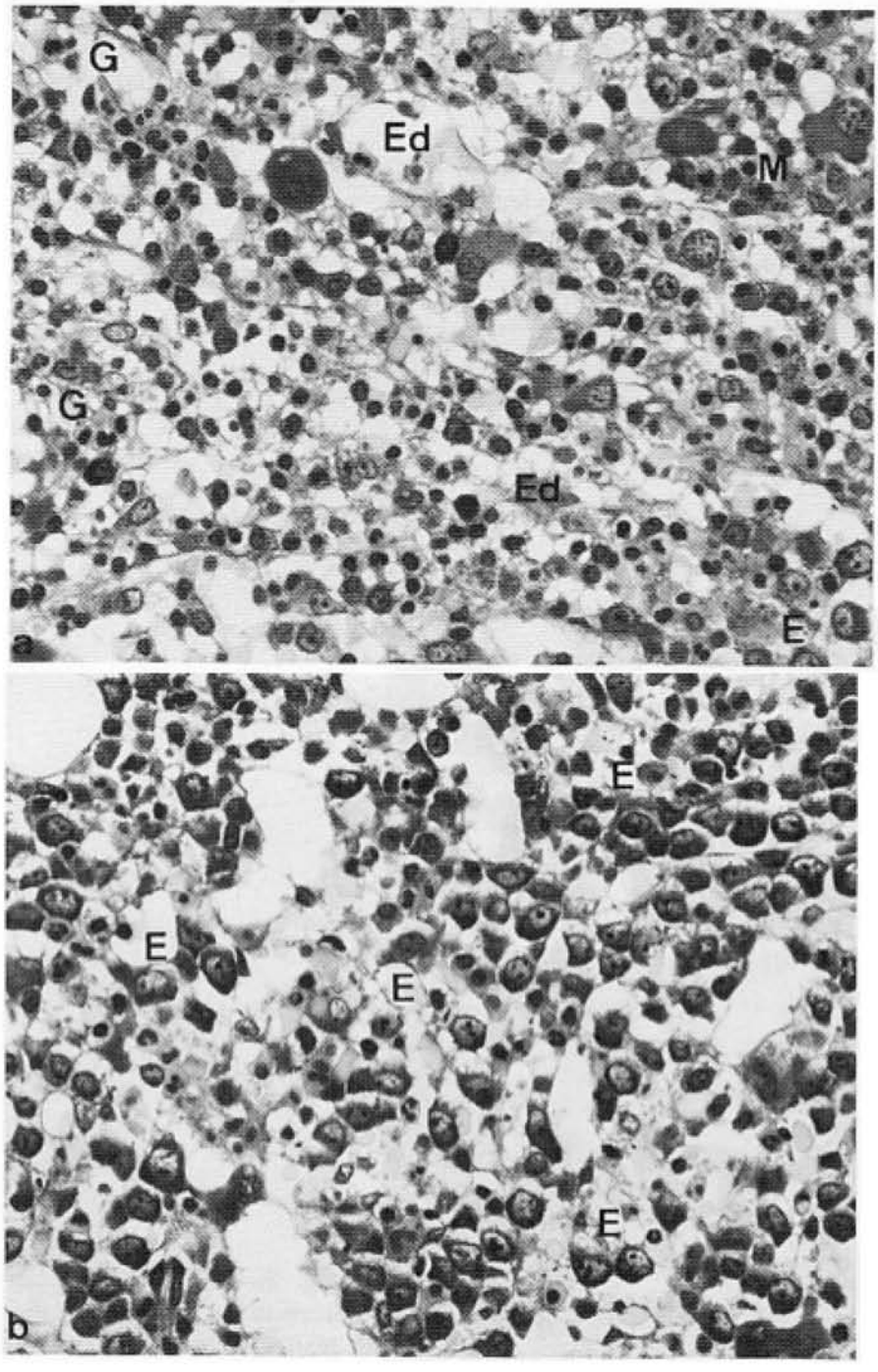

Fig. 1a,b. Survey of myeloid dysplasia in semithin sections of plastic embedded trephine biopsies. **a** Low magnification with patchy edema of the stroma *(Ed)*, a macrocytic/megaloblastoid erythropoiesis *(E)*, abnormal megakaryopoiesis *(M)* and dispersed neutrophilic granulopoesis *(G)*. **b** The higher magnification shows the prominent megaloblastoid differentiation of erythropoiesis *(E)*. a×234, b×256

Statistical evaluation of principle hematological data showed that median values of the retrospective group – regardless wether AML or CML was the evolving disease – and the prospective group showed no significant differences (for details see Thiele et al., to be published b). Median values of these data accompanying MD of 75 patients (retrospective and prospective group) are listed in Table 2.

Our results demonstrate that common morphological alterations exist in the bone marrow before onset of AML and CML and that they are associated with a normochromic anemia and a slight to moderate pancytopenia of the peripheral blood count. The clinical as well as statistical evaluation of our retrospective and prospective groups of patients confirms this statement (Thiele et al., to be published b). The term "preleukemia" should therefore be replaced by MD, which does not necessarily imply evolution towards leukemia in every case but refers also to CML. Hemopoietic dysplasia as proposed by Linman and Bagby (1978) only pertains to the hematopoietic cells and does not include the changes of the mesenchymal cells and stroma nor the development of chronic myeloproliferative disorders such as CML. The maturation defects of erythro- and granulopoiesis are in agreement with the megaloblastoid differention observed in aplastic or so-called iron refractory anemia or preleukemia (Saarni and Linman 1973;

Retrospective group		Prospective group
26/93 evolved leukemia with the following histological categories:		0 / 67
AML	11	Deadline of this study was 1 February 1980; no leukemia among the 67 patients observed so far –
CML	9	
CML with blastic crisis	6	
	26	

Table 1. 93 patients who showed myeloid dysplasia (MD) in the first and initial biopsy of the bone marrow

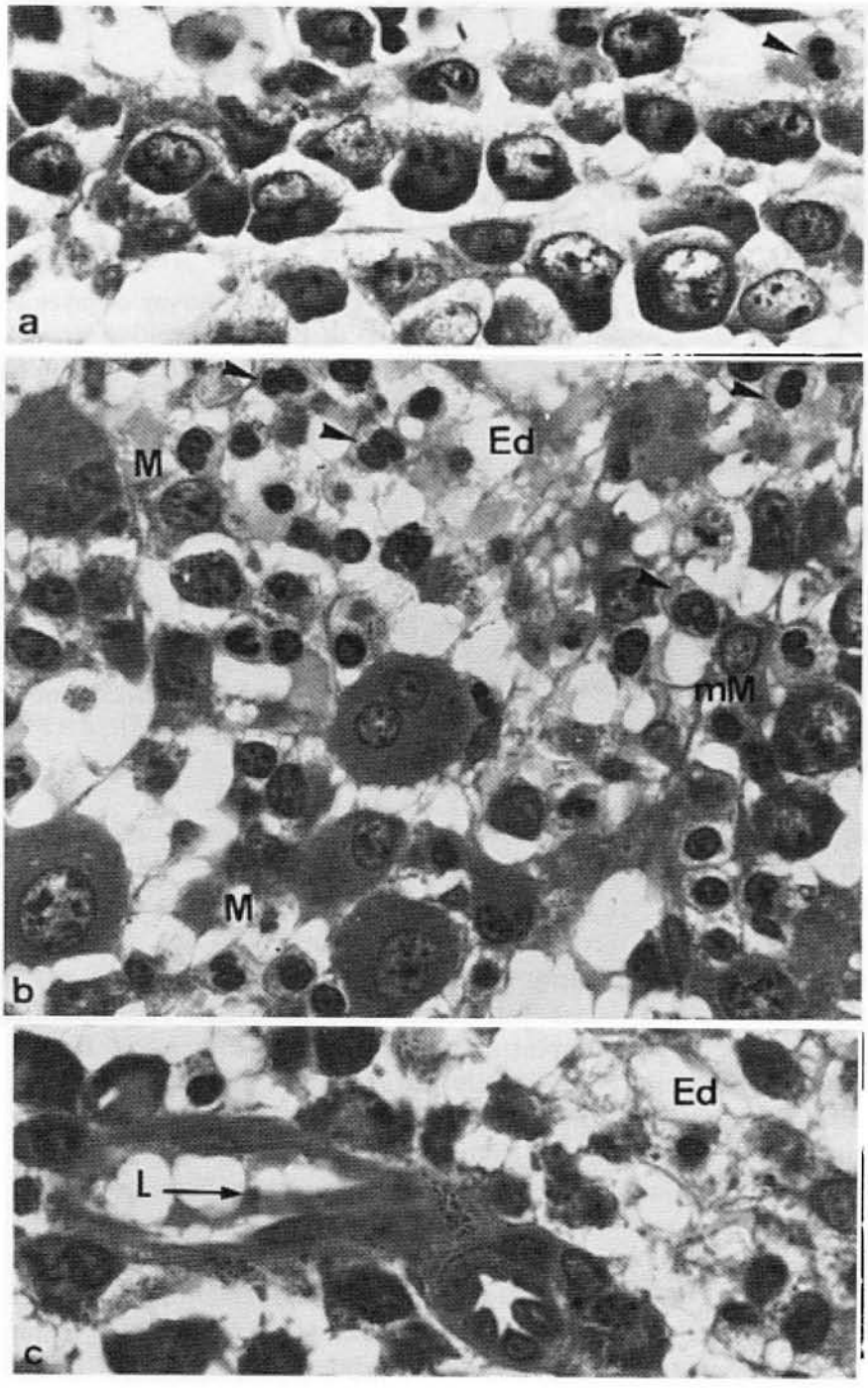

Fig. 2a–c. Conspicuous abnormalities in myeloid dysplasia. **a** Megaloblasts with linear deployment along a sinus wall and a so-called Pelger form of neutrophils *(arrow head,* see below). **b** Atypia of neutrophilic granulopoesis with hyposegmentation of nuclei associated with mature cytoplasm (pseudo-Pelgerforms, *arrow heads*). Megakaryopoiesis *(M)* with immature forms and micromegakaryocytes *(mM)*. There is also also a patchy edema of the stroma *(Ed)*. **c** Perivascular plasmacytosis along a marrow capillary with lumen *(L)* and prominent endothelial cells surrounded by edema *(Ed)*. a–c×792

Total	75	Hb_E	30.3 pg
Sex	33M/42F	Leukocytes	3.9×10^3 µl
age	66 years	Neutrophils	47%
ESR	28/89 (Westergren)	Monocytes	3%
Erythrocytes	3.0×10^6/µl	Platelets	141×10^3 µl
Hemoglobin	9.1g/dl		

Table 2. Clinical findings in 75 patients with myeloid dysplasia (MD) at the time of their first biopsy (median values)

Maldonado et al. 1976) as well as the frequent pseudo-Pelger forms (Linman and Bagby 1978), results which in the majority are derived from aspirates of the bone marrow. These morphological atypia account for the functional disturbances of colony formation and iron metabolism as demonstrated in "preleukemic" states by several authors (Golde and Gline 1973; Senn et al. 1976; Hast and Reizenstein 1977; Koeffler 1978). Cytogenetic studies may be of a major value to establish or confirm the diagnosis of a possible preleukemic condition as shown by Pierre (1978) and our findings of a Philadelphia-chromosome occurring before obvious CML in four cases (Thiele et al., 1979).

References

Dreyfus B (1976) Preleukemic states. I. Definition and classification. II. Refractory anemia with a excess of myeloblasts in the bone marrow (smoldering acute leukemia). Blood Cells 2:33–55 – Fisher WB, Armentrout SA, Weisman R, Graham RC (1973) "Preleukemia" A myelodysplastic syndrome often terminating in acute leukemia. Arch Intern Med 132:226–232 – Georgii A (1979) Histopathology of bone marrow in human chronic leukemias. In: Neth, R (eds) Modern trends in human leukemias III. Berlin Heidelberg New York, Springer, pp 60–70 – Golde DW, Cline MJ (1973) Human preleukemia. Identification of a maturation defect in vitro. N Engl J Med 28821:1083–1086 – Hast R, Reizenstein P (1977) Studies on human preleukaemia. I. Erythroblast and iron kinetics in aregenerative anaemia with hypercellular bone marrow. Scand J Haematol 19:347–354 – Koeffler HP, Golde DW (1978) Cellular maturation in human preleukemia. Blood 52:355–361 – Linman JW, Bagby GC (1978) Preleukemic syndrome (hemopoietic dysplasia). Cancer 42:854–864 – Maldonado JE, Maigne J, Lecoq D (1976) Comparative electronmicroscopic study of the erythrocytic line in refractory anemia (preuleukemia) and myelomonocytic leukemia. Blood Cells 2:167–185 – Pierre RV (1978) Preleukemic syndromes Virchows Arch [Cell Pathol] 29:29–37 – Saarni, MI, Linman, JW (1973) Preleukemia. The hematologic syndrome preceding acute leukemia. Am J Med 55:38–48 – Senn JS, Price GB, Mak TW, McCulloch EA (1976) An approach to human preleukemia using cell culture studies. Blood Cells 2:161–166 – Thiele J, Vykoupil KF, Georgii A (1979) Präleukämien: Knochenmarks- und Chromosomenbefunde zum Versuch einer Definition. Verh. Dtsch Ges Path f 63:372–379 – Thiele J, Vykoupil KF, Georgii A (1980a) Myeloid dysplasia (MD): A hematological disorder preceding acute and chronic myeloid leukemia. A morphological study on sequential core biopsies of the bone marrow in 27 patients. Virchows Arch, A, [Pathol Anat] 389:343–367 – Thiele J, Vykoupil KF, Perschke B, Babilas J, Török M, Krmpotic E, Bodenstein H, Georgii A (to be published b) Preleukaemic lesions of the bone marrow or myeloid dysplasia (MD): Morphological and clinical features in a combined retro- and prospective study of 93 patients.