

Review

Myelofibrosis in chronic myeloproliferative disorders - dynamics and clinical impact

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Summary. In chronic myeloproliferative disorders, presenting or evolving myelofibrosis (MF) is associated with significant morbidity and mortality. A systematically conducted evaluation of previous studies and data from our own material reveals a strikingly expressed heterogeneity of findings. Assessment of MF should be performed by a recently established semiquantitative scoring system regarding quantity and quality (reticulin versus collagen). It is important to differentiate between a fiber increase in bone marrow specimens and the clinical diagnosis that is explicitly based on extramedullary hematopoiesis (myeloid metaplasia). For this reason, prodromal stages of (reticulin) fibrosis are overlooked by the clinicians. Up to 30% of patients with chronic myelogenous leukemia show a minimal to advanced MF that is significantly associated not only with corresponding clinical parameters but more importantly with prognosis. In polycythemia vera about 20% of patients may display some degree of reticulin fibrosis at diagnosis, depending on stage of the disease. Transformation into (collagen) MF after more than 10 years is accompanied by clinical signs of myeloid metaplasia (spent phase). Essential thrombocythemia (ET) is characterised by the absence of increased reticulin at onset and an insignificant progression into MF, provided diagnosis is performed by the WHO criteria. Discrimination of prefibrotic and early stages of chronic idiopathic myelofibrosis (CIMF) from ET is relevant, especially concerning the rate and time usually required for the development of MF with myeloid metaplasia (full-blown CIMF).

In conclusion, more elaborate evaluations including standardized grading of MF is warranted by regarding bone marrow biopsy specimens in association with clinical parameters including follow-up examinations.

Key words: Myelofibrosis, Chronic myeloproliferative disorders, Incidence, Progression, Bone marrow biopsies

Introduction

In chronic myeloproliferative disorders (CMPDs) myelofibrosis is consistent with a fibrous effacement of the bone marrow spaces generating an increasing insufficiency of hematopoiesis. This phenomenon is clinically followed by cytopenias that are usually associated with significant morbidity and mortality, with only limited therapeutic options (Buhr et al., 2003; Thiele et al., 2003a, 2004b; Kreft et al., 2005). A conflict of opinion has repeatedly been expressed concerning the critical issue of a clear-cut diagnosis of myelofibrosis (MF), in particular since the diagnostic guidelines of CMPDs have recently been redefined by the World Health Organization (WHO) criteria (Vardiman, 2003). First of all, it has to be kept in mind that MF implicates an increase in the bone marrow (BM) fiber content without explicitly referring to the exact quantity or to quality (reticulin versus collagen). Accordingly a proper evaluation of this feature should not be based on the occurrence of an unsuccessful bone marrow aspirate (so-called dry tap as occasionally reported in the literature. Diagnosis and a more refined assessment of MF warrants the performance of BM biopsies, including follow-up examinations and an appropriate semiquantitative grading system. In the past, different methods of scoring have been applied that were mainly based on subjective evaluations by individual pathologists using a variety of techniques, including tissue processing (Bauermeister, 1971; Manoharan et al., 1979; Pasquale and Chikkappa, 1986; Beckman and Brown, 1990). The latter problem has been resolved by a consensus of hematopathologists (Thiele et al., 2005c) to circumvent the apparent difficulties resulting from a failure of standardization (Table 1). In this context it should be emphasized that following paraffin embedding of the BM biopsy samples and the preferred silver impregnation method after Gomori, quantity and quality (reticulin versus collagen) of the fiber content was determined only in areas of hematopoiesis by using a scoring system comprising four grades (Fig. 1 a-d).

In contrast to morphological assessment of BM

Table 1. Semiquantitative grading system regarding quantity and quality of myelofibrosis (MF) according to a consensus of European experts (Thiele et al., 2005c).

GRADING	DESCRIPTION
MF - 0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM
MF - 1	Loose network of reticulin with many intersections, especially in perivascular areas
MF - 2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF - 3	Diffuse and dense increase in reticulin with extensive intersections, often associated with focal bundles of collagen and/or focal osteosclerosis

*: fiber density should be assessed in hematopoietic (cellular) areas.

samples, clinical diagnosis of MF is closely related or even totally dependent on signs and symptoms of myeloid metaplasia (MMM) indicative for extramedullary hematopoiesis, i.e. increase in anemia and splenomegaly, leuko-erythroblastosis and tear drop erythrocytes (Laszlo, 1975; Barosi, 1999; Barosi et al., 1999; Cervantes et al., 2002). The salient point of difference between these two definitions is that early stages of MF with borderline to mild increase in reticulin are either not recognized or the rate of progression is significantly underestimated when totally relying on clinical findings (Thiele et al., 2001; Thiele and Kvasnicka, 2005a). Unfortunately, many clinical trials on CMPDs that were focused on the development of relevant complications like MF do not include a proper evaluation of repeatedly performed BM biopsies and thus fail to consider prodromal stages of MF and the stepwise evolution, i.e. dynamics of this feature. For this reason, the aim of this review is to collect relevant data from the pertinent literature and especially from our own clinicopathological investigations rendering a more scrutinized insight into this phenomenon which may be relevant at presentation and in follow-up examinations of patients.

Myelofibrosis at presentation of patients

In the Philadelphia chromosome (Ph) -positive and -negative CMPDs a strikingly expressed disparity in the incidence and extent of reticulin and collagen MF is encountered at first presentation of patients (Table 2) representing the four main subtypes (Vardiman, 2003): chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and chronic idiopathic myelofibrosis (CIMF).

In CML our results (Table 2) are generally in keeping with the current literature where a minimal reticulin (MF-1) to advanced collagen fibrosis (MF-3) is reported to be present on admission in up to 30% of patients (Georgii et al., 1990, 1998; Buhr et al., 1993; Thiele et al., 1999c; Buesche et al., 2003). As shown in Table 3, clinical findings reveal that significant differences exist between the majority of patients that

Table 2. Relative rate (%) of myelofibrosis (MF) at presentation of 1,843 patients with CMPDs according to a consensus semiquantitative grading system (Thiele et al., 2005c).

	No. OF PATIENTS	MF - 0	MF - 1	MF - 2	MF - 3
CML	584	71	19	6	4
PV	227	84	14	2	0
ET	167	0	0	0	0
CIMF	865	27	38	17	18

present with no BM fibrosis (MF-0) compared to those with more advanced reticulin/collagen fibrosis (MF-2/3). More elaborate morphometric evaluations provided persuasive evidence concerning a striking relationship between density of argyrophilic fibers (reticulin and collagen) with relevant clinical parameters (Thiele et al., 1999c, 2000d). Moreover, quantity of the atypical small (dwarf) megakaryocytes characterising CML (Fig. 2a) revealed a close correlation with the presence of MF (Lazzarino et al., 1986; Buhr et al., 1992a; Thiele et al., 1993, 1999c, 2000d). It is noticeable that MF was further associated with a reduction of nucleated erythroid precursor cells (Thiele et al., 1999c; Kvasnicka et al., 2001b). Even in initial stable phase CML with a peripheral blast count of less than 10% and no extensive blood basophilia or persistent thrombopenia/thrombocytosis, few patients may show overt collagen fibrosis (Table 3). For this reason, acceleration and blastic crisis (Muehleck et al., 1984; Faderl et al., 1999) may not necessarily be associated with a higher degree of BM fibrosis. Regarding the search for prognostic factors, a mild to overt increase in MF (Lazzarino et al., 1986; Dekmezian et al., 1987; Thiele et al., 1998; Kvasnicka et al., 2001b) was reported to exert an unfavorable influence in retrospectively performed clinical observational studies. Including multivariate risk classifications these studies revealed that the predictive value can be significantly improved by the inclusion of morphological parameters (Kvasnicka et al., 2001a) following standard therapeutic strategies. Moreover,

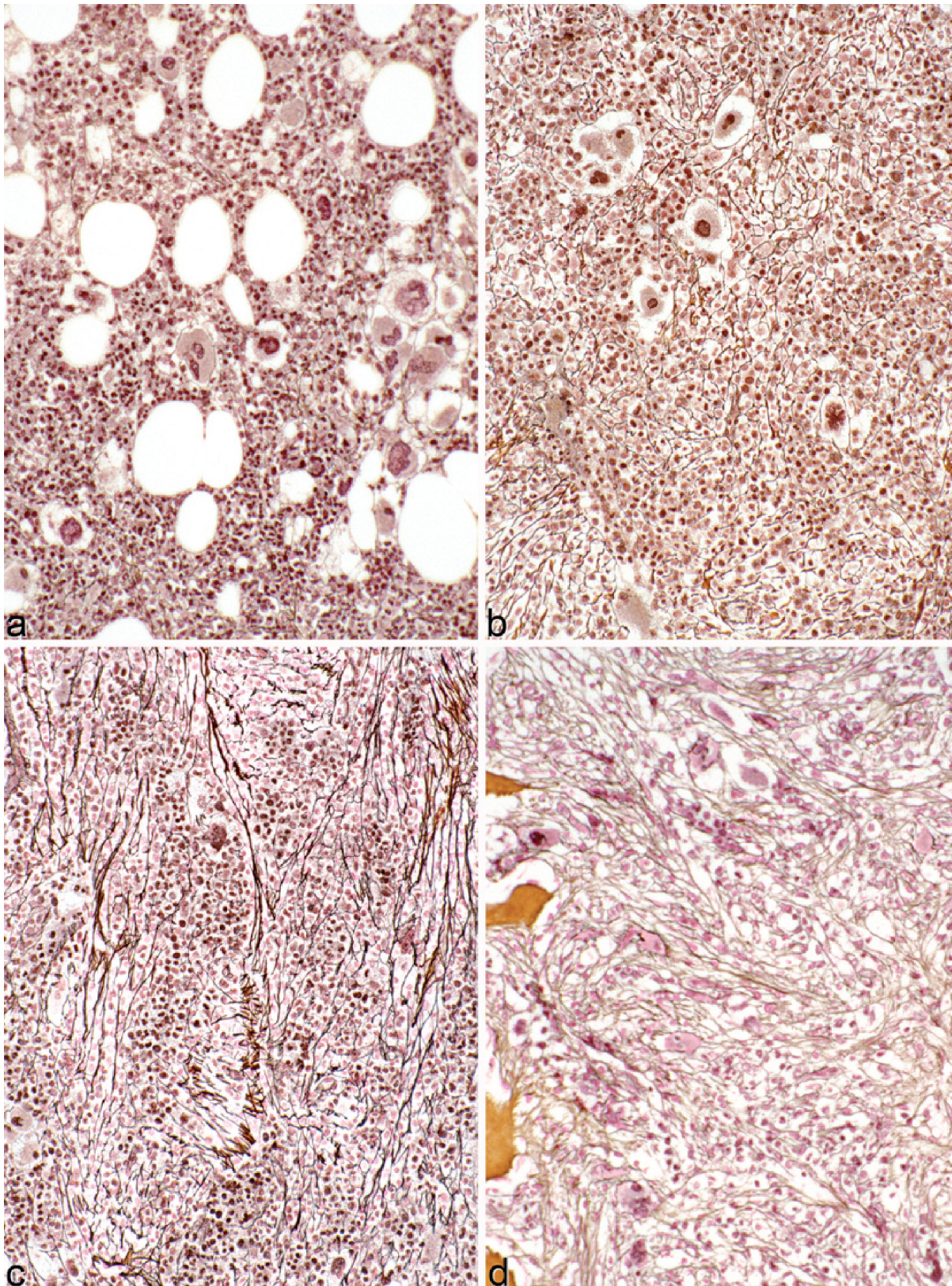


Fig. 1. Semi-quantitative grading of myelofibrosis (MF) in bone marrow biopsy sections (compare with Table 1) derived from patients with chronic idiopathic myelofibrosis. **a.** No increase in fibers (MF-0). **b.** Minimal to mild increase in reticulin (MF-1), **c.** Marked reticulin and slight collagen fibrosis (MF-2). **d.** Advanced reticulin and collagen fibrosis with initial osteosclerosis (MF-3). Gomori's silver impregnation, x 180

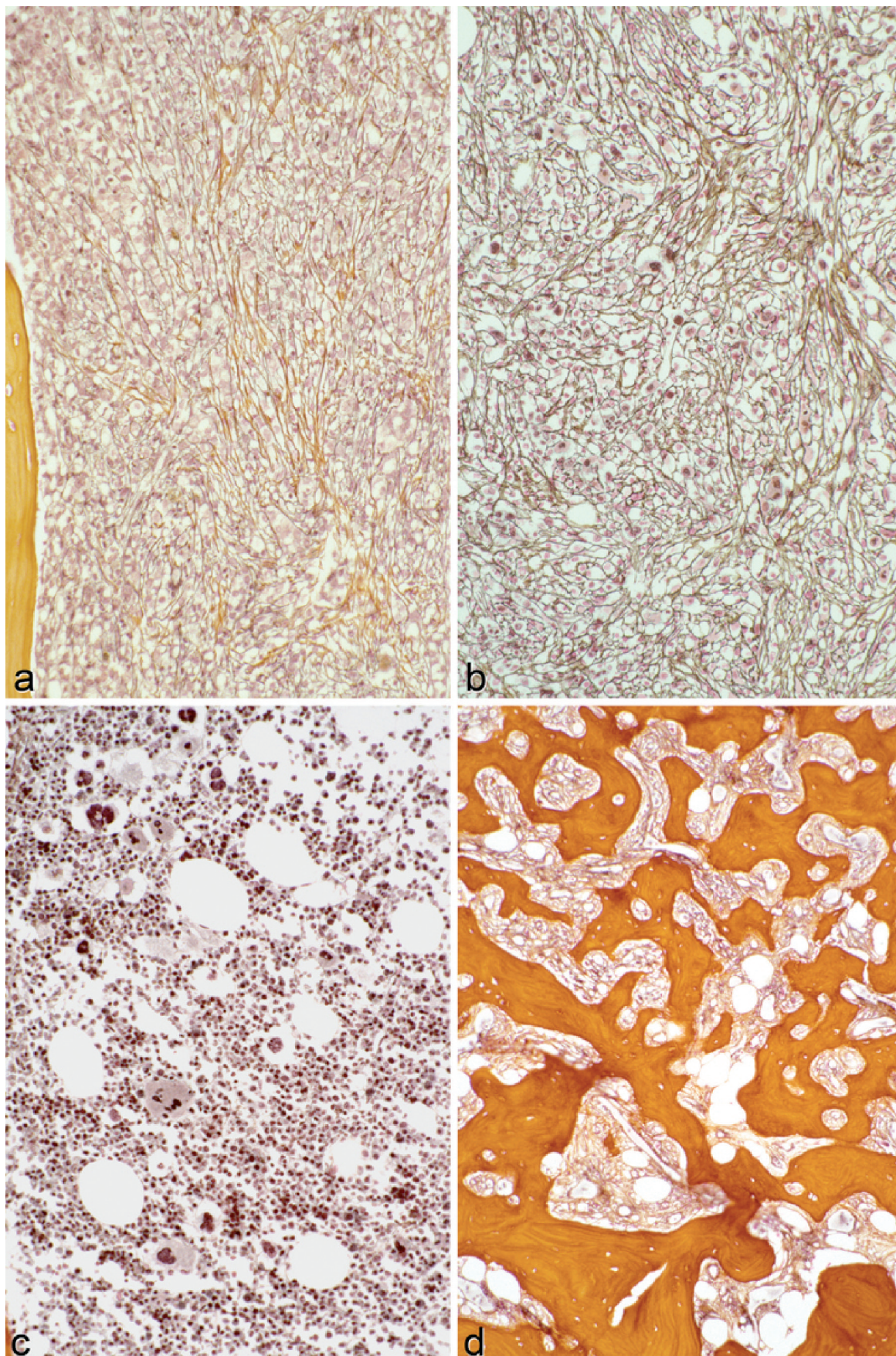


Fig. 2. Myelofibrosis in different subtypes of chronic myeloproliferative disorders. **a.** In chronic myelogenous leukemia a close association between atypical small megakaryocytes and increase in reticulin is observed. **b.** Late stage polycythemia vera is often characterised by a marked myelofibrosis. **c** In essential thrombocythemia no increase in reticulin is seen at the beginning. **d** Advanced - terminal stage of chronic idiopathic myelofibrosis reveals a conspicuous osteosclerosis in addition to collagen fibers corresponding with so-called myelofibrosis with myeloid metaplasia. Gomori's silver impregnation. x 180

regarding bone marrow transplantation, a delayed or failing reconstitution of hematopoiesis was significantly associated with an increase in reticulin in the pretransplant specimens (Thiele et al., 2000a). Although due to their retrospective nature, these evaluations may give rise to discussion and controversy, arguments are resolved because all these data have later been confirmed in a controlled prospective randomized clinical trial (Buesche et al., 2003).

Regarding PV, depending on the progression of disease, a minimal (Fig. 2b) to overt reticulin fibrosis (Table 2) may be seen in about 20% of patients in initial examinations (Bartl et al., 1993; Buhr et al., 1993; Georgii et al., 1998; Thiele et al., 1999d, 2005b; Kreft et al., 2005; Thiele and Kvasnicka, 2005b). Several lines of evidence have implied that the significantly higher degree of MF (36%) in pretreatment biopsies reported by the Polycythemia vera Study Group (Ellis et al., 1986) may be due to a later entry of patients and/or performance of the BM biopsies. However, contrasting CML histopathological factors that predict progression are not well defined and it has not been established yet that MF alone exerts an influence on survival (Ellis et al., 1986; Thiele et al., 2005b; Kvasnicka and Thiele, 2006).

In ET usually no relevant reticulin fibrosis is detectable (Table 2) in initial pretreatment BM biopsy specimens (Fig. 2c) (Buhr et al., 1993; Georgii et al., 1998; Thiele et al., 1999d, 2000e, 2006; Imbert et al., 2001; Michiels and Thiele, 2002; Kreft et al., 2005). If a substantial amount of reticulin or bundles of collagen fibers are present, a differentiation from early stage CIMF is warranted (Buhr et al., 1992b; Thiele et al., 1996, 2001; Thiele and Kvasnicka, 2003b).

Concerning CIMF, a wealth of data has been accumulated in the last two decades that precursor stages exist without clinical signs and symptoms of relevant myeloid metaplasia (extramedullary hematopoiesis) or BM collagen fibrosis (Fig. 1a, b) (Thiele et al., 1989b, 1999a, 2001, 2006; Buhr et al., 2003; Thiele and Kvasnicka, 2004; Kreft et al., 2005). The recognition of a stepwise occurring evolution of the disease process including a prodromal phase (Table 2) has significantly

altered the diagnosis of ET (Thiele and Kvasnicka, 2006b), because of the prevalent thrombocytosis in many of these patients with early stage CIMF. When following the PVSG criteria (Pearson, 1998; Murphy, 1999) these cases were usually regarded as ET (Thiele et al., 2000e; Thiele and Kvasnicka, 2003a). Correlating grade of MF with corresponding clinical data in a large series of patients significant differences are revealed between the extreme endpoints, i.e. MF-0 versus MF-3 (Table 4). These differences in clinical data have been previously re-evaluated (Thiele et al., 1989b, 2005b; Buhr et al., 1992b, 2003) and are in keeping with a progression of the disease process closely associated with a fibrous effacement of BM hematopoiesis including osteosclerotic changes (Fig. 1b, c, 2d) and evolving myeloid metaplasia (Thiele and Kvasnicka, 2005a).

Progression of myelofibrosis

In CML dynamics of MF is significantly influenced by therapeutic modalities, because significant effects of treatment on the BM fiber content were reported. Among others these included a stabilization or regression during hydroxyurea (HU) medication (Thiele et al., 2000b,c; Buesche et al., 2003), but especially following tyrosine kinase inhibition (imatinib mesylate) a relevant fibrolysis occurred (Beham-Schmid et al., 2002; Hassserjian et al., 2002; Thiele et al., 2004a). Discussion arises when addressing the influence of IFN- α on the development or reversal of BM fibrosis. Although there seems to be a consensus that busulfan exerts no fibrolytic properties, but rather stimulates MF in CML, a conflict of opinion persists about the corresponding effects of IFN- α (Wilhelm et al., 1998; Thiele et al., 2000b; Buesche et al., 2003). In contrast to a more favorable effect of HU in CIMF, a similar improvement could not be achieved by IFN- α treatment alone (Parmeggiani et al., 1987; Barosi et al., 1989). Similarly, in CML following an application of this drug, an apparent failure to ascertain a regression of MF was reported (Thiele et al., 1995; Facchetti et al., 1997). On the other hand, two studies were unable to

Table 3. Clinical data (median values) in 584 patients presenting with stable phase CML according to their degree of myelofibrosis (MF).

	MF-0	MF-1	MF-2	MF-3
No. of patients	357	171	36	20
Hemoglobin (g/dl)	12.9	12.3	11.3	10.2
Leukocytes ($\times 10^9/l$)	63.7	98.6	104.2	70.3
Thrombocytes ($\times 10^9/l$)	380	434	537	498
Basophils	3.2	3.9	5.4	9.8
Peripheral blasts	2.0	2.5	3.5	4.5
Palpable spleen (cm below costal margin)	1.5	2.5	3.5	12.0

Table 4. Clinical data (median values) in 865 patients presenting with CIMF according to their degree of myelofibrosis (MF), i.e. stages of disease.

	MF-0	MF-1	MF-2	MF-3
No. of patients	232	333	146	154
Hemoglobin (g/dl)	13.9	13.2	12.3	10.9
Leukocytes ($\times 10^9/l$)	10.8	11.2	10.1	9.7
Thrombocytes ($\times 10^9/l$)	854	825	593	276
Peripheral erythro-myeloblasts (%)	0.0	3.0	1.5	2.9
Palpable spleen (cm below costal margin)	0.0	1.0	2.0	5.0

confirm a fibrogenic capacity of this agent but recorded the opposite finding of a resolution of MF (Straetmans et al., 1996; Wilhelm et al., 1998). These strikingly disparate results may be explained by the study design, in particular differences in therapeutic modalities. In the latter trials, IFN- α treatment was combined with HU and cytarabine (Straetmans et al., 1996), or it was given following the therapeutic recommendations for the management of CML by this group (Giralt et al., 1995; Kantarjian et al., 1995). Accordingly, patients were referred within three months from diagnosis already having received initial HU therapy (Wilhelm et al., 1998). Finally, in a more recently published study (Buesche et al., 2003) no differences regarding the resolution and stabilization of MF could be found between patients receiving either IFN- α or HU. It has to be taken into account that the BM samples were derived from the German CML Study Group trial (Hehlmann et al., 1994) where a relevant fraction of so-called cross-over patients were included. Considering the fiber-stabilizing or even -reducing effect of HU in CIMF (Lofvenberg et al., 1990; Hasselbalch and Lisse, 1991; Thiele et al., 2000b; Buesche et al., 2003), combination regimens certainly will lead to an improvement of MF, and, therefore, the discordant results are understandable.

Amongst the various BM changes related to tyrosine kinase inhibitors (imatinib mesylate) regression of MF has been particularly emphasized (Beham-Schmid et al., 2002; Hasserjian et al., 2002; Bueso-Ramos et al., 2004; Thiele et al., 2005d). In this context, persuasive evidence was repeatedly provided that megakaryocytes are the principal mediators of fibrillogenesis in CMPDs, acting through abnormal release of transforming growth factor- β and PDGF (Kimura et al., 1994; Yang et al., 1997; Le Bousse-Kerdiles and Martyre, 1999; Martyre, 2003). However, a more critical evaluation of the BM samples and their fiber content (grade 3-4 reticulin fibrosis consistent with grade 2-3 according to our scoring) showed that in one series, 15 of 21 patients (71%) actually revealed a reduction after a median follow-up of 37 weeks (Hasserjian et al., 2002). This figure supports the findings of a partial regression of MF and the maintenance of a stable state in most patients, although after long-term treatment a progression may be encountered in those cases developing a resistance to this agent (Thiele et al., 2005d). Resolution of MF after imatinib medication in the majority, but not all patients (Hasserjian et al., 2002; Bueso-Ramos et al., 2004) accompanied by a normalisation of megakaryopoiesis could be related to a direct anti-PDGF receptor effect of this agent (Buchdunger et al., 2000). According to previous findings derived from morphometry after CD61 immunostaining there is a significant decline in the quantity of atypical small micromegakaryocytes characteristic of CML (Thiele et al., 1992; Bartl et al., 1993; Georgii et al., 1998) and a return of a large, normally appearing cell fraction. It should be noticed that according to morphometry not only size and shape

(form factor) of megakaryocytes and their nuclei were retrieved and achieved almost normal features, but also the nuclear-cytoplasmic ratio. This normalisation of the megakaryopoietic cell lineage after tyrosine kinase inhibitors monotherapy is in line with corresponding findings (Beham-Schmid et al., 2002; Hasserjian et al., 2002) and is often associated with a simultaneously occurring regression of fibrosis. It has been recently shown that according to FISH analysis these changes of megakaryocyte morphology are significantly associated with a drastic regression of bcr/abl+ labelling (Thiele et al., 2004c).

In PV, progression with evolution of MF is frequently documented in the relevant clinico-pathological studies (Ellis et al., 1986; Buhr et al., 1993; Najean and Rain, 1997; Tatarsky and Sharon, 1997; Georgii et al., 1998; Petti et al., 1998; Kreft et al., 2000; Passamonti et al., 2000; Kiladjian et al., 2003; Thiele and Kvasnicka, 2006c). Following an observation time between 3 to 5 years, the risk of developing various degrees of MF ranged between 15-20% (Ellis et al., 1986; Buhr et al., 1993; Georgii et al., 1998; Kreft et al., 2005). This transformation was found to be not significantly altered by IFN- α or chemotherapy (Kreft et al., 2000). In this context it should not be overlooked that a certain degree of MF may be present for months to years before the clinical onset of spent-phase PV (Ellis et al., 1986). Moreover, because a relevant fraction of patients may already show an increase in reticulin at diagnosis (Table 2), the dynamics of fibrosis is only calculable when estimating the increase to obtain a more elaborate insight into the grade of progression (Table 5). Unfortunately, this indicator (so-called myelofibrosis progression index), including also the very different intervals between the repeatedly performed BM biopsies, were either not or only insufficiently regarded in the pertinent literature (Thiele et al., 1999a).

As in the other CMPD subtypes, a prevalent problem concerning the clear-cut diagnosis of myelofibrotic transformation in ET is the failure or incomplete involvement of BM biopsy evaluations to accomplish an accurate classification. This important limitation of the UK-PT1 trial, the first randomized prospective study on ET (Harrison et al., 2005), has been explicitly mentioned in the corresponding editorial (Barbui and Finazzi, 2005). Regarding this well-known study on hydroxyurea (HU) versus anagrelide (ANA) therapy in patients with

Table 5. Dynamics of myelofibrotic transformation (relative rates) in 76 patients with PV after a median follow-up of 34 months according to a consensus semiquantitative grading system (Thiele et al., 2005c).

	MF - 0	MF - 1	MF - 2	MF - 3
Relative difference (%) to degree of myelofibrosis (MF) at presentation	- 30	- 2	+19	+13

ET at high risk for vascular events, in at least one third, prior cytoreductive treatment precluded the evaluation of a BM biopsy sample at diagnosis. Moreover, there was no information provided about the incidence of non-representative or unclassifiable biopsy specimens at entry of the patients into this study or during follow-up. Repeatedly performed BM examinations after a median of 39 months were available in only 12 of the 21 cases with confirmed progression to myelofibrosis (Harrison et al., 2005), and clinical diagnosis followed the modified Italian criteria consistent with MMM (Barosi, 1999; Barosi et al., 1999). In another large retrospective cohort of 195 ET patients evolution into myelofibrosis, MMM occurred in only 13 cases after a median of 8 years from diagnosis (Cervantes et al., 2002). A significant shortcoming of this study was the lack of clear-cut data concerning the systematic evaluation of BM biopsies at onset, and it seems likely that sequential trephines were only performed when patients already developed clinical signs and symptoms of MMM (Cervantes et al., 2002). For this reason, the early stages of (reticulin) fiber increase were not recognized and, consequently, neither were precursor stages of CIMF (Thiele et al., 1999a; Michiels and Thiele, 2002; Thiele and Kvasnicka, 2003a, 2004, 2005a). As has been reported by different groups (Buhr et al., 1992b; Georgii et al., 1996, 1998; Thiele et al., 1996, 1999b, 2000e; Kreft et al., 2005) discrimination of ET from early stage CIMF can be definitely accomplished on the basis of standardized parameters (Thiele et al., 2000e, 2005a; Thiele and Kvasnicka, 2003b). In true ET according to the WHO classification (Imbert et al., 2001) progression into myelofibrosis is neglectable up to 5 years after diagnosis (Buhr et al., 1993; Georgii et al., 1998; Thiele et al., 2002a; Kreft et al., 2005). It has to be emphasized that MMM according to clinical definition (Laszlo, 1975; Barosi, 1999; Barosi et al., 1999) is only detectable in patients with more advanced stages of CIMF mimicking ET. Concerning the fraction of so-called high-risk ET patients (Harrison et al., 2005) in a large series that received either supportive therapy or HU and IFN- α but no ANA, after more than 5 years MF was observable in BM specimens (Table 6). This result is contrasting relevant data on the development of MF in (true) ET, but fits well with corresponding results derived from prefibrotic and early stage CIMF with thrombocytosis (Buhr et al., 1993; Thiele et al., 2002a; Kreft et al., 2005). The relatively high incidence (about 2.6%) of this feature in the British study (Harrison et al., 2005) after

slightly more than 3 years of observation may possibly be related to several facts working either alone or in concert. Amongst these, a late stage of disease at diagnosis or delayed entry of already pretreated patients into this study, as well as the inclusion of a significant fraction of early CIMF cases (false ET) into this trial may be a relevant feature (Kvasnicka and Thiele, 2006; Thiele and Kvasnicka, 2006a).

The dynamics of the disease process in CIMF have been significantly elucidated in the last two decades by conducting clinicopathological investigations based on a careful comparative analysis of sequential BM biopsy specimens with corresponding laboratory data. According to the results derived from these studies, progression of CIMF is stepwise and, thus, the wide spectrum of clinical changes observed is paralleled by the evolving features seen in the BM biopsy (Thiele et al., 1989b, 2003a; Georgii et al., 1998; Buhr et al., 2003; Thiele and Kvasnicka, 2005a).

Approximately 25% of patients with CIMF initially present with a hypercellular stage (CIMF-0) characterized by prominent granulocytic and abnormal megakaryocytic proliferation accompanied by reduction and/or partial maturation arrest of erythroid precursors, with no or only a borderline increase in the amount of reticulin (Buhr et al., 1993; Georgii et al., 1996, 1998; Thiele et al., 1999a, 2001, 2002b, 2003a, 2006; Thiele and Kvasnicka, 2004; Kreft et al., 2005). Clinical findings in cases of CIMF-0 often demonstrate only borderline to slight leukocytosis, therapy-refractory mild anemia, minimal to modest splenomegaly, and frequently mild to marked thrombocytosis (Table 4), mimicking ET. As has been repeatedly demonstrated (Thiele et al., 1999a, 2002b, 2003a; Buhr et al., 2003; Kreft et al., 2005), there is a significant probability of progression from a prefibrotic-early stage to full-blown CIMF (Table 7), the latter conforming with the classical diagnostic criteria for MMM (Laszlo, 1975; Cervantes et al., 1998b; Barosi, 1999; Barosi et al., 1999; Tefferi, 2000; Dingli et al., 2004). In this context, clinical parameters that indicate evolution of MF and therefore progressive disease in these early stages of CIMF (including anemia, splenomegaly, and the development of a leukoerythroblastic blood picture) usually occur in about 30% of cases in the first 5 years of observation (Buhr et al., 2003; Thiele et al., 2003a).

Evolution into the full-blown (classical), grossly fibro-osteosclerotic stage is associated with a pronounced increase of reticulin (MF-2) and collagen

Table 6. Time (months, median values 95% CI) to develop a myelofibrotic transformation in 539 high risk patients with ET (Harrison et al., 2005) diagnosed according to the PVSG criteria (Pearson, 1998; Murphy, 1999).

Histopathology features	Clinical features (MMM)	Overall
63 (48-78)	121 (93-135)	81 (69-93)

Table 7. Myelofibrotic transformation (months, median values 95% CI) in CIMF including prefibrotic and early stages during follow-up.

	Histopathology features	Clinical (MMM) features	Overall
CIMF - 0	80 (67-93)	121 (99-148)	80 (65-95)
CIMF - 1	44 (29-59)	108 (79-137)	54 (36-72)

(MF-3), and in these phases of disease BM cellularity becomes more variable, with areas of patchy hematopoiesis that may be separated by fatty marrow. These advanced stages regularly show coarse bundles of collagen fibers with an optional development of focal osteosclerosis (Thiele et al., 1989a; Dickstein and Vardiman, 1993; Georgii et al., 1996, 1998; Buhr et al., 2003; Thiele et al., 2003a,b, 2006). Additional histological findings seen in corresponding BM tissue include the presence of dilated marrow sinuses (Wolf and Neiman, 1985; Thiele et al., 1989b; Kvasnicka and Thiele, 2004) with a prominent intraluminal hematopoiesis. These late stages of CIMF, consistent with MMM, are characterized by the constant finding of significant collagen fibrosis of the BM (Fig. 1d, 2d). The peripheral blood typically shows leukoerythroblastosis and poikilocytosis with many teardrop-shaped erythrocytes accompanied by anemia and pronounced splenomegaly, corresponding with full-blown CIMF or MMM (Dickstein and Vardiman, 1995; Cervantes et al., 1998a,b; Barosi, 1999; Dingli et al., 2004).

Therapy-induced changes in MF have occasionally been reported in CIMF (Parmeggiani et al., 1987; Barosi et al., 1989; Lofvenberg et al., 1990; Hasselbalch and Lisse, 1991). There seems to be agreement that following conventional treatment modalities (HU, IFN- α), no significant interference with the overall progressive nature of MF is observable and the rate of fiber regression ranges between 10% and 15% (Buhr et al., 2003; Thiele et al., 2003b, 2004b). Concerning prognosis the prefibrotic and early fibrotic stages of CIMF are characterized by a prolonged survival (Thiele and Kvasnicka, 2005a; Kvasnicka and Thiele, 2006; Strasser-Weippl et al., 2006). However, as overall factors of predictive value age at diagnosis, hemoglobin level, peripheral blood precursor cells, and leukocytosis or thrombocytosis remain the most important determinants (Barosi et al., 1988; Visani et al., 1990; Hasselbalch, 1993; Rupoli et al., 1994; Dupriez et al., 1996; Cervantes et al., 1997; Kvasnicka et al., 1997, 1999; Reilly, 1997; Okamura et al., 2001; Kreft et al., 2003; Kvasnicka and Thiele, 2006; Strasser-Weippl et al., 2006).

In conclusion, MF shows a wide spectrum of clinical and morphological aspects at presentation of patients as well as during follow-up. A close relationship with clinical data, prognosis and exact subtyping of CMPDs is encountered and also a variety of therapy effects. For this reason, a more scrutinized evaluation including standardization of this phenomenon is warranted by carefully regarding BM biopsy morphology and corresponding clinical parameters.

Acknowledgements. This work (grading of myelofibrosis) was partially supported by a grant from the European Union - EUMNET project (QLG1-CT 2002-01123). We are greatly indebted to Prof. V. Diehl, First Clinic of Medicine, University of Cologne, Germany, and his associates for providing the clinical data of their patients. Moreover, the skillful assistance of Mr. G. Simons is acknowledged.

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Accepted July 25, 2006