REVIEW ARTICLE

Progression of myeloproliferative neoplasms to myelofibrosis and acute leukaemia

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Abstract Bcr-abl-negative myeloproliferative neoplasms
(MPN), comprising polycythaemia vera (PV), primary
myelofibrosis (PMF) and essential thrombocythaemia
(ET), usually follow a biphasic course. From a phase which
is characterized by excess production of mature haemato-
poietic cells of one or more lineages, many, but not all
MPN, progress to haematopoietic insufficiency with cyto-
penia affecting two or three lineages. The latter may be the
result of either fibrosis, blastic transformation or both. An
intermediate stage of variable duration is called accelera-
tion. Unlike bcr-abl-positive chronic myeloid leukaemia
(CML), acceleration in MPN is not homogeneously
defined. Long-lasting PV may progress to a PMF-like
myelofibrosis, labelled spent phase. Less frequently, PV
develops into a myelodysplastic/myeloproliferative neo-
plasm (MDS/MPN) resembling either atypical CML or
chronic myelomonocytic leukaemia. Progression in PMF
and ET leads either to advanced osteomyelofibrosis or to
MDS/MPN with fibrosis. CML and bcr-abl-negative MPN
share the same definition for transformation with ≥20%
blasts in the blood or bone marrow. Transformation to blast
crisis can occur at any stage in MPN and is more likely in
PMF and PV than ET. There are different molecular
pathways to progression. In a subset of MPN, transforma-
tion is accompanied by the occurrence of a complex
karyotype.

Keywords Progression · Myeloproliferative neoplasm ·
Polycythaemia vera · Essential thrombocythaemia ·
Primary myelofibrosis

Introduction

The myeloproliferative neoplasms (MPN) according to the
WHO classification comprise eight different entities, which are
summarized in Table 1 [1]. Besides bcr-abl-positive chronic
myeloid leukaemia (CML), the most frequent diagnoses are
polycythaemia vera (PV), essential thrombocythaemia (ET)
and primary myelofibrosis (PMF). All four entities have in
common the fact that they may progress from a phase which
is characterized by excess production of mature haemato-
poietic cells of one or more lineages, to haematopoietic
insufficiency with cytopenia affecting two or three lineages.
The transition from overproduction of blood cells to
haematopoeitic insufficiency is called progression, and it is
caused by different underlying biological processes. One
mechanism is that neoplastic hyperproliferation with main-
tained capacity to differentiate is followed by loss of
differentiation during blast transformation. The second
mechanism, which may be combined with the first, is
progressive fibrotic obliteration of the bone marrow. Progres-
sion is intrinsic to CML, PV, PMF and ET, but the likelihood
and the type of progression differ between the four MPN
subtypes. The propensity for blastic transformation is highest
in CML and lowest in ET, whereas the probability of fibrosis
is high in PMF and low in ET and CML [1, 2].

Progression usually occurs in two steps with different
clinical manifestations, which in CML have been labelled

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Table 1 Myeloproliferative neoplasms (according to WHO [1])

- Chronic myelogenous leukaemia, *BCR-ABL1*-positive
- Chronic neutrophilic leukaemia
- Polycythaemia vera
- Primary myelofibrosis
- Essential thrombocythaemia
- Chronic eosinophilic leukaemia, not otherwise specified
- Mastocytosis
- Myeloproliferative neoplasms, unclassifiable

Table 2 Acceleration and transformation in MPN

	Acceleration	Transformation
Bcr-abl-positive CML [1]	Unresponsiveness to therapy:	$\geq$20% blasts in the bone marrow and/or peripheral blood
	-Persistent or increasing WBC >1×105/µl -Persistent or increasing thrombocytosis >1×106/µl	Extramedullary blast proliferation
	-Persistent or increasing splenomegaly	
	Thrombocytopenia <1×105/µl	
	$\geq$20% blood basophils	
	10–19% blasts in the bone marrow and/or peripheral blood	
PV	PMF-like (spent phase): Leucoerythroblastic blood smear	$\geq$20% blasts in the bone marrow and/or peripheral blood
	-Bone marrow fibrosis	
	-Decreasing blood cell counts and increasing splenomegaly MDS/MPN-like:	Extramedullary blast proliferation
	-aCML	
	-CMMoL	
	Blast increase:	
	-10–19% blasts in the bone marrow and/or peripheral blood	
PMF/ET	Stage 3 myelofibrosis/ osteoclerosis with high clinical risk scores MDS/MPN-like:	$\geq$20% blasts in the bone marrow and/or peripheral blood
	-MDS/MPN uc Blast increase:	Extramedullary blast proliferation
	-10–19% blasts in the bone marrow and/or peripheral blood	

acceleration and transformation. There is the same definition for transformation in bcr-abl-negative MPN ($\geq$20% blasts in the blood or bone marrow, extramedullary blast infiltrates), but acceleration in these diseases is not homogeneously defined. In CML, acceleration is characterized by resistance to therapy, thrombocytopenia, blood basophilia or blast increase in the marrow between 10% and 20%. Bone marrow fibrosis has been shown to precede blast transformation and therapy resistance [3], but it is not generally accepted as a marker of acceleration (Table 2).

Bone marrow fibrosis as a marker of progression

In order to stage fibrosis, a three-tiered system has been inaugurated [4]. Myelofibrosis stage 1 reveals a loose network of reticulin with intersections, especially in peripheral areas, but no collagenisation. In stage 2, diffuse increase in reticulin with extensive intersections and only focal bundles of collagen occur. When a diffuse and dense reticulin meshwork with extensive intersections with course bundles of collagen and significant osteosclerosis are present, the criteria for stage 3 are fulfilled [4] (Table 3). Typical examples for the different stages of myelofibrosis are depicted in Fig. 1.

Medullary fibrosis has negative prognostic impact not only in CML but also in myelodysplastic syndrome (MDS) [5]. It is not a specific feature of bcr-abl-negative MPN, but these diseases exhibit an intrinsic tendency to develop myelofibrosis. Some of the MPN, like ET, do only rarely progress to myelofibrosis. Besides PMF, post-PV and post-ET myelofibroses have been proposed as nomenclature to describe the fibrotic progression of MPN [6]. Despite its suggestive name, PMF does not generally show evolvement to full-blown fibrosis. The latter may remain on a low level for years or may not develop at all. In a study on 102 PMF patients with up to seven follow-up biopsies, 24.4% of patients did not develop myelofibrosis during an observation period of up to 6 years [7]. The majority of patients showed increase of fibre content in the marrow. Only a minor portion progressed from stage 2 to stage 3 [7]. In a

small subgroup, reduction of fibre content not related to therapy occurred (Table 4). The concept of obligatory progression to myelofibrosis in PMF starting from a prefibrotic stage has been developed by Thiele and co-workers [8] and was recently questioned by others, who found fibrosis also in ET [9].

Progressing myelofibrosis in MPN is associated with alterations of the haematologic and clinical status. A leucoerythroblastic blood picture usually occurs in fibrosis stages 2 and 3, and it is generally lacking when no fibrosis is present [7]. With increasing bone marrow fibrosis, thrombocyte counts normalize, or even thrombocytopenia

Table 3 Staging of myelofibrosis in MPN

| Myelofibrosis	MF 1	MF 2	MF 3
Description	Loose network of reticulin with intersections, especially in peripheral areas, no collagenization	Diffuse increase in reticulin with extensive intersections and only focal bundles of collagen. Hypercellular bone marrow	Diffuse and dense increased reticulin with extensive intersections with course bundles of collagen and significant osteosclerosis
Fibres	Reticulin	Reticulin plus collagen	Mostly collagen
Spread	Focal, patchy	Diffuse meshwork	Diffuse meshwork, scarring
Sinus		Sclerosis	Fibrosis, dilatation
Sinusoidal haematopoiesis	-	May be present	Prominent
Endophytic bone formation	-	May be present	Scant to prominent

occurs, and anaemia worsens. Leucocyte counts usually stay elevated. Splenomegaly also parallels the stage of myelofibrosis [7, 8].

Despite these clinical–pathologic correlations, myelofibrosis is not taken into account when clinical risk scores for assessment of prognosis are considered. It has been shown that the median survival with supportive therapy depends on several factors such as haemoglobin concentration (<10 g/dL), leucocyte counts, thrombocyte counts, blasts in the peripheral blood, the karyotype and B symptoms [10–13] (Table 5). The development of myelofibrosis does not correlate with the JAK2 allele burden [14] and cannot be linked to particular molecular features at present.

Phenotypic transitions indicating acceleration

After a long duration, PV can undergo phenotypic changes which mimic either myelofibrosis or MDS/MPN. In the case of myelofibrotic progression, late-stage PV resembles fibrotic PMF with splenomegaly and anaemia. Fibrotic
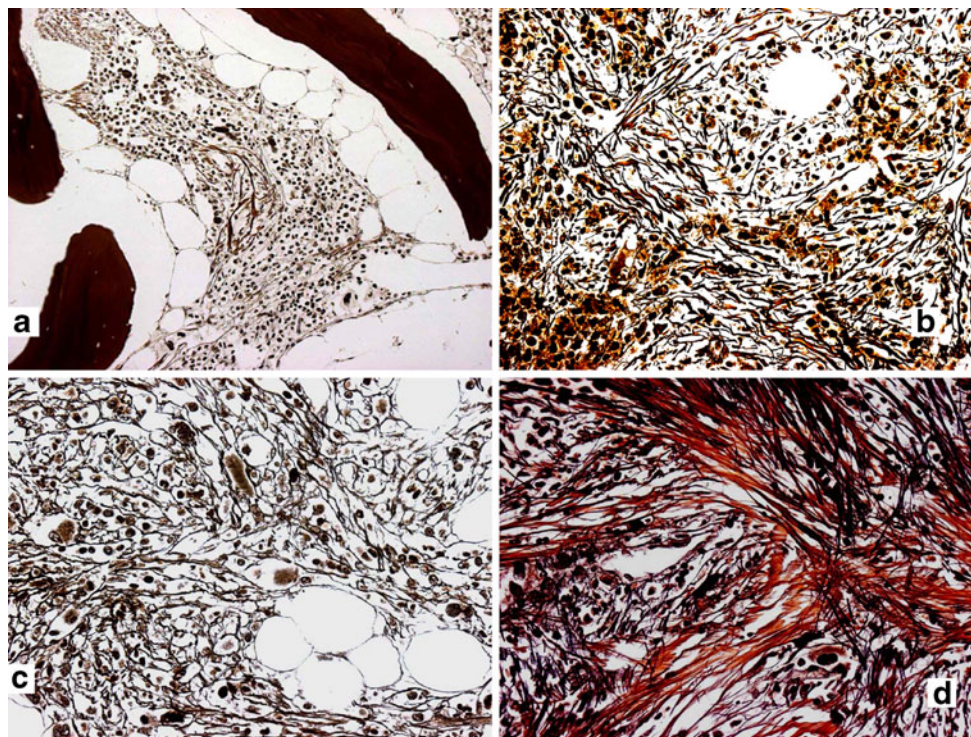
Fig. 1 Different stages of bone marrow fibrosis. In stage 1, there is only focal and loose increase of reticulin fibres, without collagenisation (**a**). In stage 2, reticulin fibres are diffusely increased with extensive intersections. A few bundles of collagen may be present (**b**, **c**). In stage 3, a diffuse and dense intensively intersecting reticulin meshwork is combined with course bundles of collagen and significant osteosclerosis. In Gomori silver stain, collagen reveals a brownish appearance (**d**). Collagen might also be highlighted by its birefringence

Table 4 Progression of myelofibrosis in a series of follow-up biopsies in primary myelofibrosis [7]

Initial fibrosis staging	No change ratio (%)	Increase ratio (%)	Decrease ratio (%)
MF 0	11/31 (35.5)	20/31 (64.5)	0 (0)
MF 1	7/24 (29.2)	15/24 (62.5)	2/24 (8.3)
MF 2	10/18 (55.6)	6/18 (33.3)	2/18 (11.1)
MF 3	11/12 (91.7)	0 (0)	1/12 (8.3)
Total	39/85 (45.9)	43/85 (50.6)	5/85 (5.9)

transition in PV has been labelled "spent phase" or post-PV myelofibrosis [1, 6, 15]. As an alternative mode of progression, PV can evolve to proliferative states which resemble MDS/MPN, in particular bcr-abl-negative CML and chronic myelomonocytic leukaemia (CMMoL).

In Fig. 2, a case of a 66-year-old male is shown, who was known to have PV for 25 years and was treated with hydroxyurea. At the time of bone marrow biopsy, he had an elevated leucocyte count of 84×10^9/l, basophilia (1.4×10^9/l) and immature precursors in the peripheral blood. The presentation resembled CML, but no bcr-abl rearrangement was detectable, whereas 85% of JAK2^{V617F} alleles were present. Similar cases have been described by others [16–19]. Besides bcr-abl-negative CML, transitions with Philadelphia chromosome positivity have been reported [20–23]. With regard to the co-existence between bcr-abl-positive and JAK2-mutated diseases, it is likely that two independent stem cell clones proliferate in parallel [24]. Only rarely, a progression of PV can be observed which resembles CMMoL (Fig. 3).

Phenotypic transition in PMF resembles MDS/MPN with myelofibrosis. In particular, megakaryocytes reveal a different phenotype and those found in MDS. In contrast to the megakaryocytes found in the chronic phase of the disease with large cloud-like nuclei and a broad rim of cytoplasm, megakaryocytes in these cases are small with hypolobulated and small nuclei. Still, cluster formation can be observed (Fig. 4). This effect can, however, also be mimicked by hydroxyurea treatment. Usually, the phenotypic transition from PMF to MDS/MPN with fibrosis is accompanied by thrombocytopenia.

With the acquisition of MDS-like properties, the likelihood of blast increase in the bone marrow increases. An accelerated stage is diagnosed when more than 10% but less than 20% blasts are present. Immunohistochemical staining may be useful to detect blasts (Fig. 5). As a caveat, it has to be kept in mind that blasts may be CD34 negative (Fig. 5). In addition, dysplastic megakaryocytes display a spectrum of maturation, and some more mature forms may also be labelled, which cannot be considered as blasts (Fig. 5). Because a try tap is frequent in progressed PMF, bone marrow smears may not be available, and blast determination may completely rest on their morphological identification in CD34-negative cases.

Table 5 Risk scores in primary myelofibrosis

	Lille Score [8]	DIPSS plus Score [9]	International Score [10]	Mayo Score [11]
Haemoglobin	<10 g/dL	<10 g/dL	<10 g/dL	<10 g/dL
Leucocytes	<4 or >30 G/L	–	>25 G/L	<4 or >30 G/L
Blasts in peripheral blood	–	≥1%	≥1%	–
Thrombocyte count	–	<100 G/L	–	<100 G/L
Monocyte count	–	–	–	>1 G/L
Constitutional symptoms	–	+	+	–
Red cell transfusion need		+		
Age	–	>65 years	>65 years	–
Cytogenetic aberrations	–	Complex karyotype or sole or two abnormalities that include +8,-7/7q-,i(17q), -5/5q-,12p-, inv(3), or 11q23 rearrangement	Only in intermediate risk, when combined with anaemia	–
Score, low	0	0	0	0
Score, intermediate	1	1, 2–3	1, 2	1
Score, high	2	≥4	≥3	≥2
Median survival, low risk (months)	93	180	135	173
Median survival, intermediate risk (months)	26	Intermediate 1, 63 Intermediate 2, 33	Intermediate 1, 95 Intermediate 2, 48	61
Median survival, high risk (months)	13	16	27	26
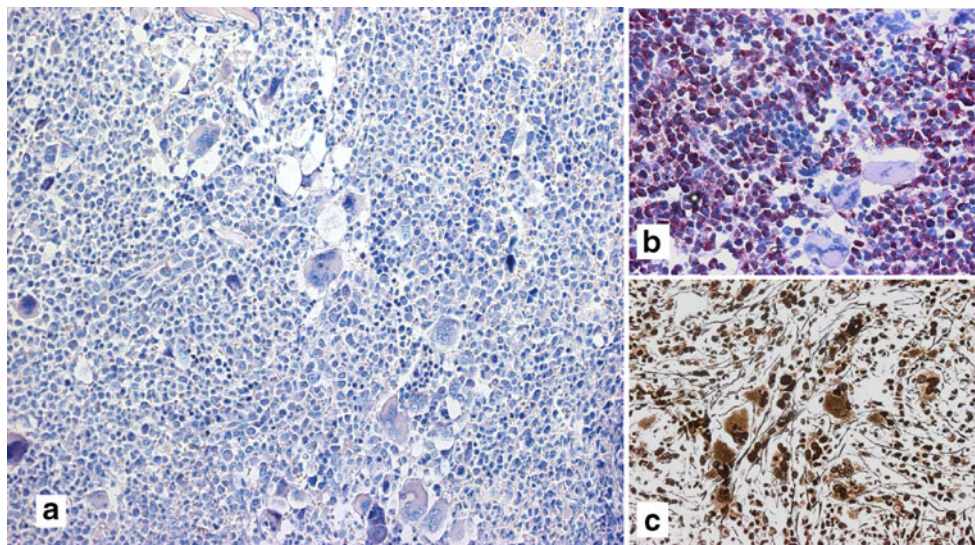
Fig. 2 Atypical CML-like acceleration in a case of PV. After 25 years of PV treated with phlebotomy and hydroxyurea, a 66-year-old male presented with a leucocyte count of 84×10^9/l; basophils, 1.428×10^9/l; pathologic left shift; erythrocytes, 6.85×10^{12}/l; haemoglobin, 17.1 g/dll; thrombocytes, 573×10^9/l; LDH, 1,362 U/l and spleen enlargement. JAK2^{V617F} was found in 85% of alleles, and bcr-abl was negative. Bone marrow biopsy revealed a relative reduction of erythropoiesis and a tremendous increase of granulopoiesis (**a**). Increased granulopoiesis is highlighted by chloroacetate esterase staining (**b**). There was slight increase of reticulin fibres (**c**)

Transformation to blast crisis

In contrast to bcr-abl-positive CML, blast transformation in PV, PMF and ET is less frequent and provides a rather late event, occurring after many years of disease duration. The diagnosis of blast transformation rests on the demonstration of ≥20% blasts in the bone marrow or peripheral blood. Alternatively, an extramedullary blast infiltration is considered to represent transformation.

Blast crisis in PV, PMF and ET usually reveals a myelomonocytic or myeloid phenotype (Fig. 6). Only rarely does a lymphoblastic phenotype occur [25]. The blast infiltration in the bone marrow appears diffuse in most instances. Sometimes, focal and nodular infiltrates can be seen (Fig. 6). A blast crisis may be the result of clonal evolution which is obvious from a complex karyotype (Fig. 7). The phenotypic transition to an MDS/MPN phenotype preceding transformation often is paralleled by the development of a complex karyotype which is typical for secondary AML (Figs. 6d, 7). In other cases, a cytogenetic study does not reveal any abnormalities, and the persisting megakaryocytes still exhibit the typical PMF morphology (Fig. 6c).

Interestingly, in a considerable proportion of cases, the JAK2 mutation is lacking in the blast cells. Therefore,

Fig. 3 Progression to a CMMoL-like MDS/MPN in a case of PV. A 76-year-old male with a long duration of PV and erythrocyte count of 6.3×10^{12}/l; leucocytes, 22×10^9/l; thrombocytes, 283×10^9/l and an enlarged spleen (16×7 cm) showed monocytosis in the peripheral blood (5.940×10^9/l). Bone marrow smears (**a**) as well as histology (**b**) revealed an increase of monocytes like in CMMoL. JAK2^{V617F} was present in 18% of alleles. A wild type was found for CBL and N-ras, respectively, and bcr-abl was negative
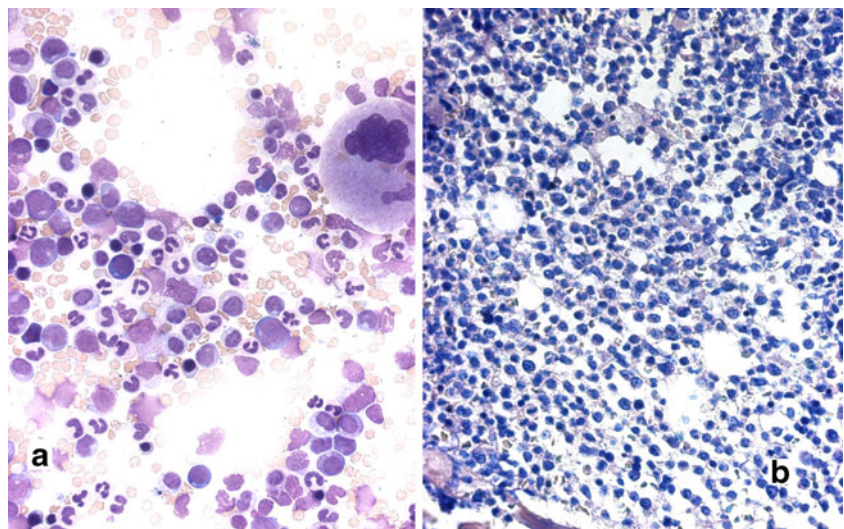
Fig. 4 PMF with MDS/MPN-like features during acceleration. Many PMF cases progress from thrombocytosis to thrombocytopenia. This may be accompanied by the appearance of MDS-like features. Megakaryocytes are hypolobulated and dysplastic as in MDS and do not resemble the large variants usually found in PMF (a, b). CD42 immunohistochemistry decorates atypical megakaryocytes which still show increased formation of prothrombocytes (c). Usually there is prominent myelofibrosis (d)
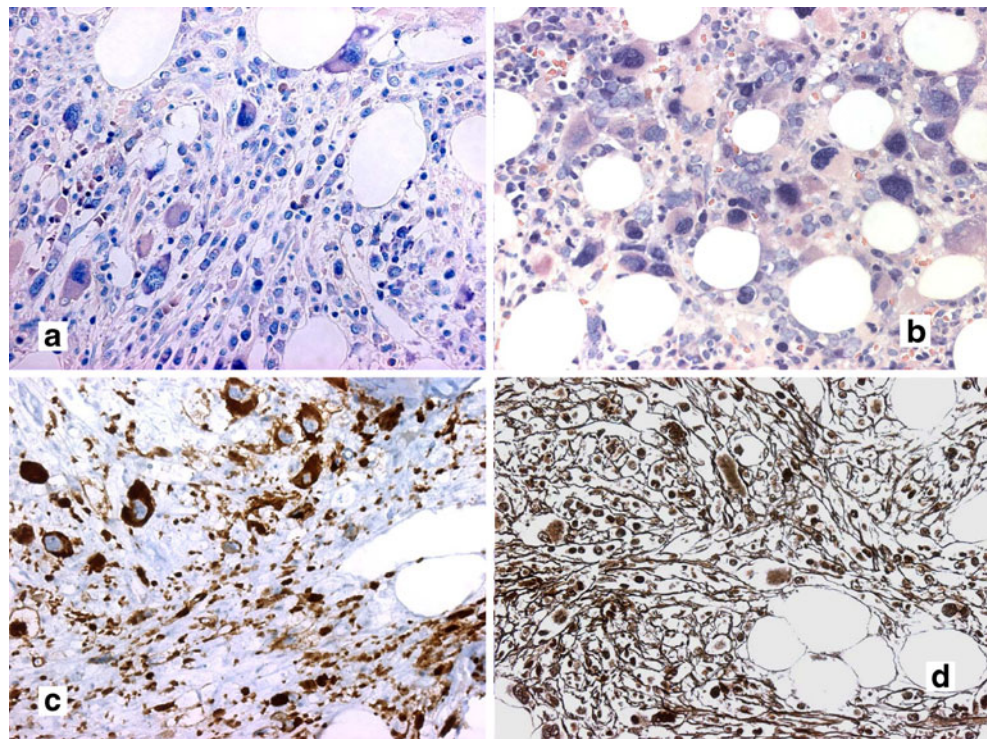

different routes to leukaemic transformation in JAK2-mutated MPN have been suggested [26]. Blast crisis may evolve from an independent hematopoietic stem cell clone, which is not related to the JAK2 or MPL mutated clone. Second, the MPN and blast clone may have a common ancestor with a shared mutation, e.g. of the TET2 gene. The third scenario of blast progression in MPN resembles that of CML with clonal evolution of blasts from the JAK2 or MPL mutated stem cell clone [26]. Loss of $JAK2^{V617F}$ mutation due to mitotic recombination could also be possible but was

Fig. 5 CD34 stain for blasts in MPN. CD34 may be helpful in detecting and quantifying blasts in the bone marrow of accelerating MPN (a). However, care has to be taken that micro-megakaryocytes and normal megakaryocytes may also be labelled by anti-CD34 staining (b). In cases as shown in (b), a more or less arbitrary discrimination has to be made when CD34 blasts are quantified. Furthermore, in MPN, unambiguous blasts by morphology (c) may be completely negative for CD34 (d)
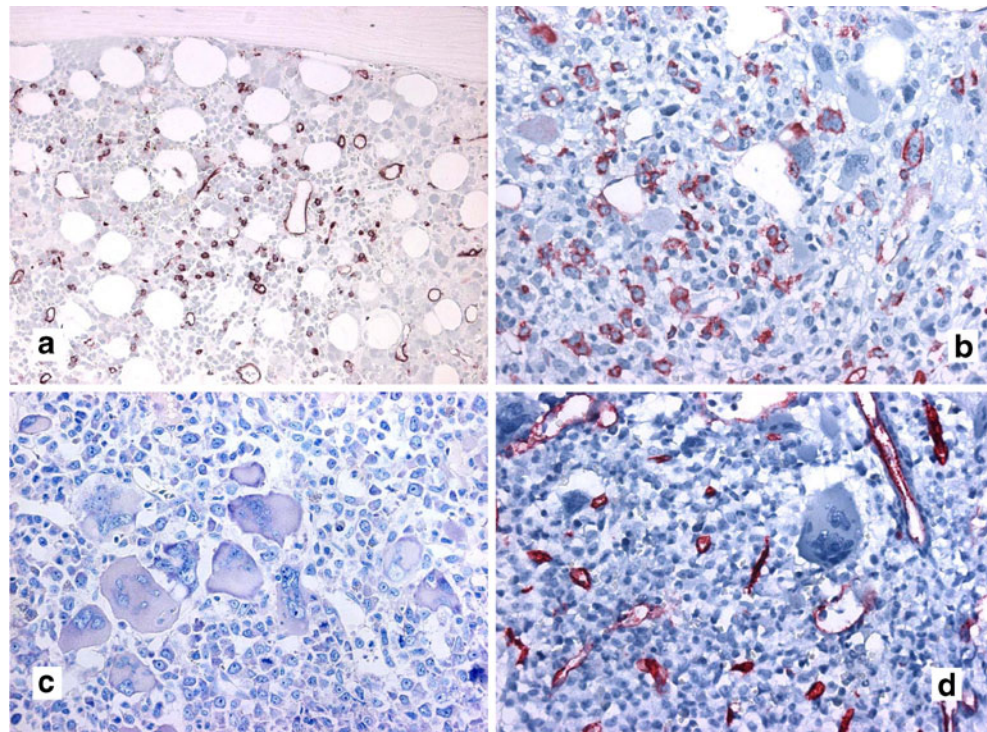
Fig. 6 Transformation to AML in MPN. Blast infiltrates may be diffuse with complete efface- ment of haematopoiesis (**a**). Alternatively, the blast increase may be focal with persisting maturing haematopoiesis outside of the blast infiltrates, which might escape cytologic detection (**b**). Blast crisis may be manifest already at presentation with high thrombocyte counts, no fibrosis and large megakaryocytes typical for PMF (**c**). In contrast, **d** shows a blast crisis which develops in progressed myelofi- brosis with dysplastic megakar- yocytes with MDS-like features. Most blast crises display a myelomonocytic phenotype as shown in (**e**) where focal CD68- positive blast infiltrates are shown. The blasts in (**a**) were negative for Jak2V617F which was, however, found in the preceding MPN
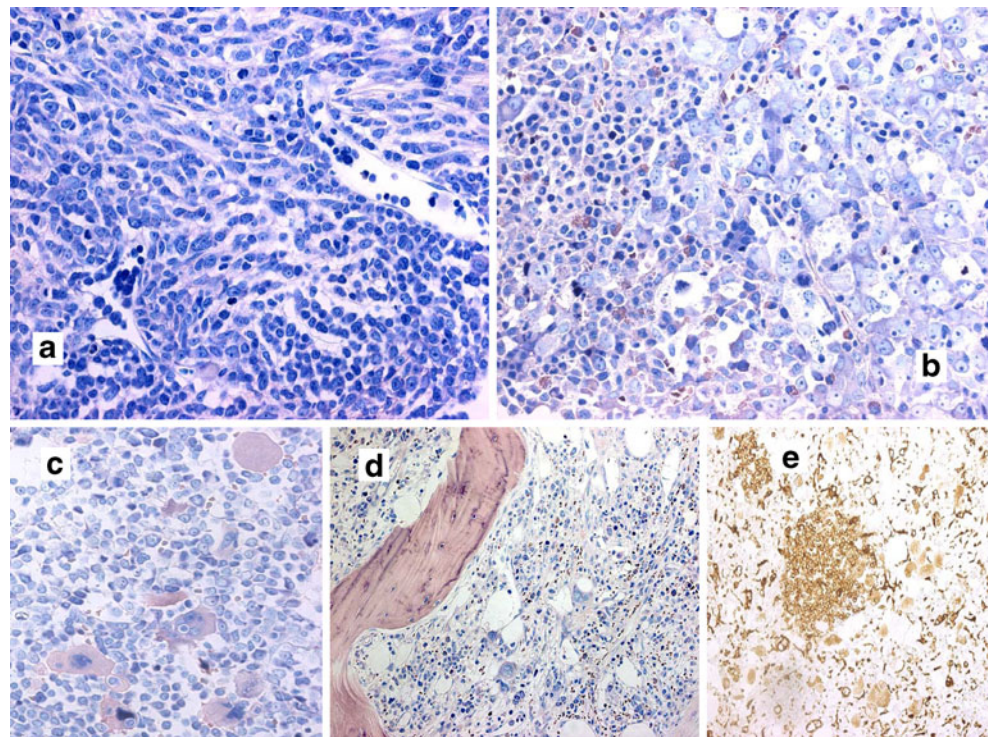
not found in a series of blast crisis [26]. Aberrations which discriminate the chronic from the acute phase of MPN affect the genes for WT1, p53, CBL, N-ras, TET2, as well as IDH1 and IDH2 [26, 27] indicating a potential role in clonal evolution. Chromosomal gains and losses were found with a threefold higher frequency in the blast phase in comparison to the chronic phase [28]. Besides trisomy 8, losses of 7q and 17p were observed [18]. Altered chromosomal regions were found on 16q, 19p and 21q [28]. Obviously, blast progres- sion in MPN is the result of a number of different genetic events during clonal evolution. At present, it is not possible to sort out which of the aberrations can be linked to genotoxic therapy such as hydroxyurea, which is commonly applied in MPN. Because AML also occurs in treatment- naive patients [15], there is little doubt that blast progression belongs to the natural history of MPN.
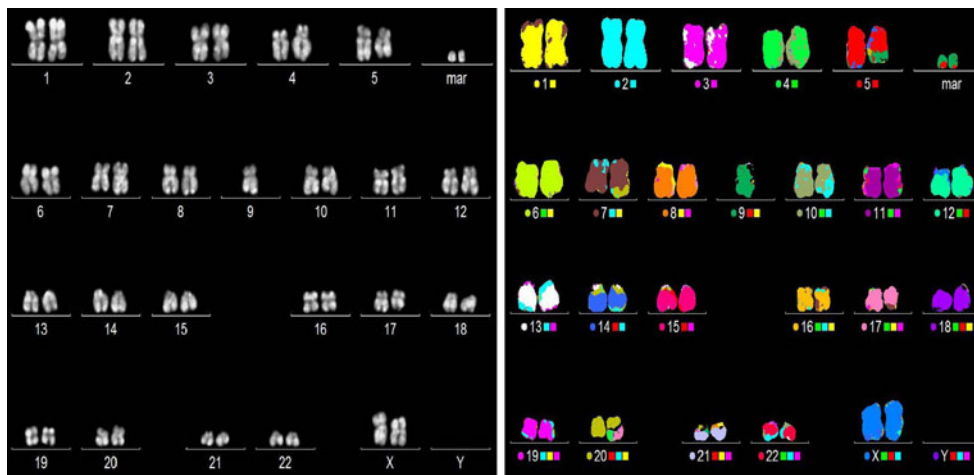
Fig. 7 Karyotypic evolution in a case of ET progressing to blast crisis. A complex karyotype was seen in a 55-year-old male who was diagnosed with ET 12 years ago. He had acquired pancytopenia, and the corresponding bone marrow trephine is shown in Fig. 6d. At presentation, no aberrations were present. The complex karyotype could be resolved by chromosomal painting as: 45~47,XX, der(5)t(5;9)(q14; q?), t(7;17;20)(q31;q22;q12), -9, +1-2 mar[cp19]/46,XX[1].nuc ish 5p15.2(5p15.2x2), 5q31(EGR1x1[85/100], cen7(CEP7x2), 7q31 (D7S486x2). 11q23(MLLx2),12p13(TELx2),20q12(D20S108x2)[100]

Conflict of interest The authors declare that they have no conflict of interest.

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