Hematologic Malignancies

Myeloproliferative Disorders

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Chronic Idiopathic Myelofibrosis

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Contents

Abstract. Chronic idiopathic myelofibrosis (CIMF) is a clinico-pathological entity characterized by a stem-cell-derived clonal myeloproliferation, extramedullary hematopoiesis, proliferation of bone marrow stromal components, splenomegaly, and ineffective erythropoiesis. It is the least common of the chronic myeloproliferative disorders and carries the worst prognosis with a median survival of only 4 years. Treatment for most cases is supportive, while androgens, recombinant erythropoietin, steroids and immuno-modulatory drugs are effective approaches for the management of anemia. Splenectomy and involved field irradiation may also be beneficial in carefully selected patients. Cure is only possible following bone marrow transplantation and a number of practical prognostic scores are available for identifying patients that would benefit from this approach. Recently, the use of low intensity conditioning has resulted in prolonged survival and lower transplant-related mortality. Finally, the recent reports of the association of CIMF with a gain-of-function JAK2 mutation opens the door to targeted therapies as well as molecular monitoring of treatment response.

15.1 Introduction

Chronic idiopathic myelofibrosis (CIMF), or myelofibrosis with myeloid metaplasia (MMM), is a chronic stem cell disorder characterized by bone marrow fibrosis, extramedullary hematopoiesis, splenomegaly, and a leuko-erythroblastic blood picture. It is an uncommon disorder, with a reported annual incidence ranging from 0.5 to 1.3 per 100,000 (Dougan et al. 1981; Mesa et al. 1997), with the highest rates being found among the Ashkenazi Jews in northern Israel (Chaiter et al. 1992). The etiology of CIMF is unknown, although environmental factors may be relevant as the disorder has been linked in a small number of patients to radiation (Andersen et al. 1964) and benzene exposure (Hu 1987). Although first described by Heuck in 1879, it was not until 1951, following Dameshek's seminal publication (Dameshek 1951), that the disease was regarded as one of the chronic myeloproliferative disorders. Recently, considerable progress has been made in understanding its pathogenesis, although this has yet to result in significant therapeutic advances. Indeed, its prognosis remains poor when compared to other *BCR-ABL*-negative chronic myeloproliferative disorders (Rozman et al. 1991), with death resulting from cardiac failure, infection, hemorrhage, and leukemic transformation.

15.2 Pathogenesis

15.2.1 Clonality

It has been appreciated for many years that CIMF is a clonal disorder and that the disease arises from the proliferation of malignant pluripotential stem cells. Such a conclusion was first suggested by early studies of the X-chromosome inactivation patterns of G-6-PD in patients who were heterozygous for this gene (Jacobson et al. 1978; Kahn et al. 1975). However, the low frequency of G-6-PD heterozygotes in the general population has led several groups to analyze the more informative X-linked genes, hypoxanthine phosphoribosyl transferase (HPRT) and phosphoglycerate kinase (PGK). In these studies, monoclonal hematopoiesis was documented in all patients irrespective of whether they had early cellular phase disease or more advanced myelofibrosis (Kreipe et al. 1991; Tsukamoto et al. 1994). Recently, Reeder and colleagues (2003), using fluorescent in situ hybridization (FISH), have provided evidence that both B and T cells can be involved, while karyotypic analysis has shown that the stromal proliferation is polyclonal, or reactive, and not part of the underlying clonal hematopoiesis (Jacobson et al. 1978; Wang et al. 1992). Involvement of the B and T lymphocytic lineage was also suggested by an earlier study that utilized N-*Ras* gene mutational analysis, again supporting the pluripotent stem cell origin of the disease (Buschle et al. 1988). An increased number of circulating hematopoietic precursors, including pluripotent (CFU-GEMM) and lineage restricted progenitor cells (BFU-E, CFU-GM, and CFU-MK), is a feature of CIMF (Carlo-Stella et al. 1987; Han et al. 1988; Hibbin et al. 1984) and is likely to result from the proteolytic release of stem cells from the marrow (Zu et al. 2005). It is also possible that the spleen and liver contribute to the circulating progenitor pool (Wolf and Neiman 1987) as splenectomy temporarily normalizes levels (Craig et al. 1991). The high level of circulating progenitor cells is reflected in the significantly increased peripheral blood $CD34^+$ cell count (Andreasson et al. 2002; Arora et al. 2004). Indeed, it has been proposed that not only can the absolute number of $CD34^+$ cells be used to differentiate CIMF from other Philadelphia (Ph)-negative CMPDs, but the levels may also predict evolution to blast transformation (Barosi et al. 2001). Increased sensitivity of committed erythroid progenitors to erythropoietin has been reported (Carlo-Stella et al. 1987), while CFU-MK may exhibit autonomous growth (Han et al. 1988; Taksin et al. 1999) and/or hypersensitivity to interleukin-3 (Kobayashi et al. 1993). Such findings, coupled with the fact that autonomous megakaryocyte growth is not related to *MPL* mutations or autocrine stimulation by Mpl-L (Taksin et al. 1999), suggest that events downstream from receptor-ligand binding are likely to be pathogenetically important (Taksin et al. 1999). Finally, indirect evidence for the involvement of the pluripotential stem cell is provided by the rare reports of acquired hemoglobin H disease (Veer et al. 1979), paroxysmal nocturnal hemoglobinuria (Nakahata et al. 1993; Shaheen et al. 2005), acquired Pelger-Huet anomaly and neutrophil dysfunction (Perianin et al. 1984), as well as many abnormalities of platelet function (Cunietti et al. 1981; Schafer 1982).

15.2.2 Cytogenetics

Cytogenetic studies have played a pivotal role in the elucidation of pathogenetically important oncogenes in many hematological malignancies although, until recently, the data for CIMF has been sparse and confusing. However, over the last 15 years the publication of three large studies, involving a total of 256 well-characterized patients, has helped to clarify the situation (Demory et al. 1988; Reilly et al. 1997; Tefferi et al. 2001a). All three studies, as well as a literature review of 157 abnormal cases (Bench et al. 1998), have revealed that deletions of 13q and 20q, trisomy 8 and abnormalities of chromosomes 1, 7, and 9 constitute more than 80% of all chromosomal changes in CIMF. Deletions of 13q are the most common cytogenetic abnormality, occurring in approximately 25% of cases with an abnormal cytogenetic analysis (Demory et al. 1988; Reilly et al. 1997). The genetic loss is large and involves the gene-rich region around RB-1, D13S319, and D13S25 (Sinclair et al. 2001). It is possible that more than one gene is involved on chromosome 13 since Macdonald and colleagues (1999) reported a case of CIMF with a t(4;13)(q25;q12) and provided evidence for the involvement of a novel gene located at 13q12. The second and third most common abnormalities are deletions of 20q and partial duplication of the long arm of chromosome 1, respectively (Demory et al. 1988; Reilly et al. 1997). Amplifications of 1q follow a nonrandom pattern and, although it may involve the whole of 1q, it always appears to include the specific segment, 1q23-1q32 (Donti et al. 1990). The inability to identify common breakpoints, or a preferential translocation site, suggests that an increase in gene(s) copy number located on 1q is more important than the position effect due to the juxtaposition of specific DNA sequences. In support of this view, Zanke and colleagues (1994) have demonstrated amplification and overexpression of a hematopoietic protein tyrosine phosphatase (HePTP) in patients with partial trisomy 1q. The underlying molecular consequences of 13q- and 20q- remain to be determined, although extensive mapping and mutational screening have not identified any candidate genes and suggest that haplo-insufficiency may be a mechanism (reviewed Reilly 2005). These three lesions, however, are not specific for CIMF and have also been reported in polycythemia vera, myelodysplastic syndrome, and other hematological malignancies. In contrast, the abnormality der(6)t(1;6)(q23-25;p21-22) has been recently identified as a possible marker for CIMF, although it is scarce, occurring in less than 3% of cases (Dingli et al. 2005). The incidence of chromosomal abnormalities in CIMF is significantly lower in younger patients (Cervantes et al. 1998), a fact that may explain their better prognosis. Indeed, normal cytogenetic findings are characteristic of pediatric cases, which, coupled with their long-term survival, suggests that they may have a different pathogenesis and require a more conservative management (Altura et al. 2000). Comparative genomic hybridization (CGH) studies have revealed that genomic aberrations are much more common than indicated by standard cytogenetic analysis and occur in the majority of cases. Gains of 9p appear to be the most frequent finding, occurring in 50% of cases, and suggests that genes on 9p may play a crucial role in the pathogenesis of CIMF (Al-Assar et al. 2005). A third of patients with CIMF possess an abnormal karyotype at diagnosis (Okamura et al. 2001; Reilly et al. 1994), although this increases to approximately 90% following acute transformation, a finding that supports the multistep process of leukemogenesis (Mesa et al. 2005; Reilly et al. 1994). The majority of leukemic transformations exhibit "high risk" cytogenetic changes, including -5/5q- and -7/-7q and, as a result, respond dismally to chemotherapy (Mesa et al. 2005).

Chromosomal abnormalities have been associated with a poor prognosis in several studies (Demory et al. 1988; Reilly et al. 1997), although the prognostic impact of specific cytogenetic lesions has been difficult to define. A recent report addressed this issue and indicated that only certain clonal abnormalities, such as trisomy 8 and deletion of 12p, carry an adverse prognosis, in contrast to the majority of changes which have little survival effect (Tefferi et al. 2001a). In addition, a number of rare karyotypic abnormalities, unrelated to therapy, have been associated with a poor outcome. Trisomy 13, a nonrandom aberration in myelofibrosis, confers a poor prognosis due to early blast transformation (Zojer et al. 1999), as appears also to be the case for del(1)t(1;9) (Rege-Cambrin et al. 1991) and t(6;10)(q27;q11) (Cox et al. 2001). Recently, Strasser-Weipel et al. (2004) reported the association of chromosome 7 deletions (-7/7q-) with an unfavorable prognosis, although surprisingly not with leukemic transformation. Finally, cytogenetic abnormalities have also been linked to treatment response, with anemia responding less well in patients with chromosomal abnormalities (Besa et al. 1982).

15.2.3 Molecular Studies

Recently, an acquired somatic point mutation in the *JAK2* gene (Val617Phe) has been reported in 49% of a total of 88 CIMF patients by four independent groups (Baxter et al. 2005; James et al. 2005; Kralovics et al. 2005; Levine et al. 2005). This mutation, which also occurs in approximately 90% of patients with polycythemia vera and 40% of patients with essential thrombocythemia, almost certainly contributes to the myeloproliferative state, as cellular expression has been shown to lead to growth factor independence (James et al. 2005) as well as myelofibrosis in a murine bone marrow transplant model (Wernig et al. 2006). Interestingly, 22% of CIMF cases are homozygous for the *JAK2* mutation, a feature that appears linked to loss of heterozygosity of 9p (Kralovics et al. 2005). Initial clinical studies suggest that CIMF patients possessing the *JAK2* mutation have a higher total white cell and neutrophil count, are less likely to require blood transfusions and have a poorer survival (Campbell et al. 2006). It is to be hoped that this novel finding will lead to the future development of targeted therapy for use in this group of related disorders. The molecular defects in the remaining cases remain essentially unknown. Intriguingly, STAT5 has been reported to be constitutively activated in the majority of CIMF $CD34^+$ cells and megakaryocytes (Komura et al. 2003), and suggests that STAT5 activation may occur by mechanisms other than by acquired *JAK2* mutations. However, mutational screening of candidate receptor tyrosine kinase (RTK) genes that activate JAK2, namely *c-KIT*, *c-FMS*, and *FLT3*, has been unhelpful (Abu-Duhier et al. 2003). A possible clue to alternative STAT5 activation mechanisms in CIMF is the reported overexpression of FK506 binding protein 56 (FKBP51) in megakaryocytes. This immunophilin is known to induce sustained activation of the JAK2/STAT5 pathway as well as being able to induce an antiapoptotic phenotype (Giraudier et al. 2002). Overexpression of FKBP51 may also have a role in the activation of NF-κB, a feature of CIMF megakaryocytes and circulating CD34 cells (Komura et al. 2005). The mechanism by which FKBP51 is upregulated in CIMF, however, remains to be determined. *RAS* mutations, predominantly affecting codon 12 of *N-RAS*, have been described, but appear rare, occurring in approximately 6% of patients in chronic phase (Reilly et al. 1994). Mutations involving *p53* and *p16* are also rare in the chronic phase of the disease, although they may be associated with transformation of a variety of BCR-ABL-negative chronic myeloproliferative disorders, including myelofibrosis (Gaidano et al. 1993; Tsuruni et al. 2002; Wang and Chen 1999). Kimura and colleagues (1997) reported *KIT* mutations (Asp52Asn) in two patients and suggested that this acquired abnormality resulted in enhanced sensitivity to KIT ligand. However, a detailed study did not confirm these findings, suggesting that such mutations are rare (Abu-Duhier et al. 2003). Loss of heterozygosity (LOH) studies have highlighted RARβ2 to be a candidate tumor suppressor gene in CIMF, although for most patients epigenetic changes rather than gene deletion may be the most significant determinant of reduced activity (Jones et al. 2004). Finally, a recent study, using oligonucleotide microarrays on purified $CD34^+$ cells, has highlighted the potential underlying complexity in CIMF by identifying 95 genes that were aberrantly expressed (Jones et al. 2005)

15.2.4 Role of Growth Factors

Myelofibrotic stroma has a complex structure, characterized by an increase in total collagen, that includes both the interstitial and basement membrane collagens, types I, III, IV, V, and VI (Apaja-Sarkkinen et al. 1986; Gay et al. 1984; Reilly, et al. 1985a, 1995b). In addition, there is an excessive deposition of fibronectin (Reilly et al. 1985a), laminin (Reilly et al. 1985b) tenascin (Reilly et al. 1995), and vitronectin (Reilly and Nash 1988) as well as a marked neo-vascularization and an associated endothelial cell proliferation (Mesa et al. 2000; Reilly et al. 1985b). Indeed, the hypervascularity and sinusoidal hyperplasia leads to a marked increase in bone marrow blood flow (Charbord 1986). The increased deposition of interstitial and basement membrane antigens is supported by the findings of raised serum markers for laminin and collagen types I, III, and IV, especially in patients with active disease (Hasselbalch et al. 1986; Reilly et al. 1995). These complex structural features and the wealth of stromal proteins are now believed to result from the abnormal release of growth factors, especially PDGF and TGF-β, from clonally involved megakaryocytes (Fig. 15.1).

15.2.4.1 Platelet-Derived Growth Factor

A number of observations support the concept that the megakaryocytic lineage plays a pivotal role in the pathogenesis of myelofibrotic stroma. Structural and matura-

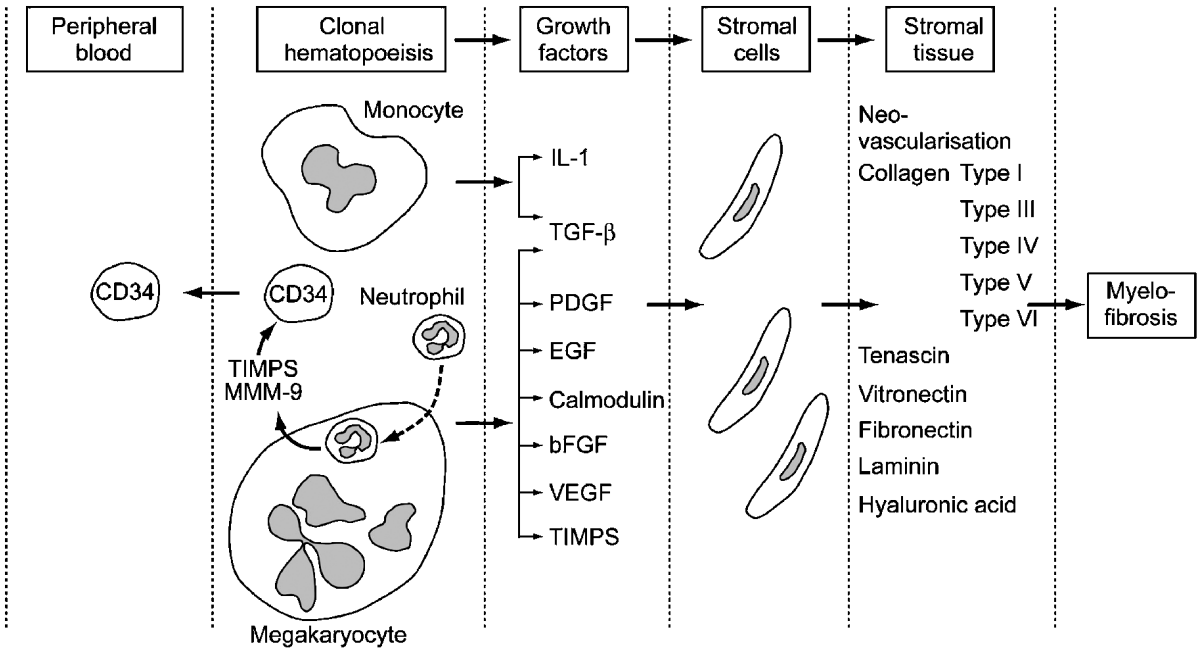

Fig. 15.1. The current pathogenetic model for the development of myelofibrotic stroma. bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; IL-1, interleukin-1; PDGF, Platelet-derived growth factor; TGF-*β*, transforming growth factor-*β*; TIMPs, Tissue inhibitors of metalloproteins; VEGF, vascular growth factor. (Modified from Reilly 1997, Blood Reviews 11:233–242)

tional defects of megakaryocytes are well-recognized features, including conspicuous proliferation and clustering, and with accumulation of fibrotic tissue often being associated with necrotic and/or dysplastic megakaryocytes (Thiele et al. 1991). In addition, bone marrow fibrosis is a well-described feature of patients with megakaryocytic leukemia (Den Ottolander et al. 1979) and the rare Gray Platelet Syndrome (Jantunen et al. 1994), disorders that are thought to affect platelet alpha granule packaging. However, the first tangible evidence for the role of megakaryocytic-derived growth factors was provided by Castro-Malaspina and colleagues (1981), who demonstrated that megakaryocytic homogenates stimulated the proliferation of bone marrow fibroblasts and that this effect was the result of PDGF. Subsequently, decreased platelet PDGF levels (Bernabei et al. 1986; Dolan et al. 1991; Katoh et al. 1988) associated with increased plasma and urinary levels (Gersuk et al. 1989) were reported in patients, a finding thought to reflect an abnormal release and/or leakage of PDGF from bone marrow megakaryocytes. In addition, similar findings for platelet *β*-thromboglobulin and platelet factor 4 favor a platelet and/or megakaryocyte release mechanism (Romano et al. 1990; Sacchi et al. 1986). However, the release of PDGF, while undoubtedly inducing fibroblast growth, cannot account totally for the observed complexity of the stromal tissue. PDGF, for example, does not have angiogenic properties, nor does it increase the transcription of stromal proteins. Additional growth factors must play a role, the most important of which is probably transforming growth factor-*β*.

15.2.4.2 Transforming Growth Factor-*β* (TGF-*β*)

Like PDGF, TGF-*β* is synthesized by megakaryocytes, stored in platelet alpha granules and released at sites of injury (Fava et al. 1990). The pathological relevance of TGF-*β* lies in its ability to regulate extracellular matrix synthesis. It increases, for example, transcription of genes that code for fibronectin, collagens I, III and IV, and tenascin. It possesses powerful angiogenetic properties, with neovascularization occurring within 48 h of injection and, in addition, it can decrease the activity of metalloproteinases, enzymes that degrade extracellular stromal tissue (Overall et al. 1989; Roberts et al. 1986). In addition, TGF-*β* promotes endothelial cell migration, enhances stromal cell synthesis of vascular en-

dothelial growth factor (VEGF), and may also inhibit the production of antiangiogenic molecules (Harmey et al. 1998; O'Mahoney et al. 1998). The combined effect of these activities is the increased synthesis and accumulation of extracellular matrix. Evidence for a pathogenetic role in CIMF include the report of significantly increased intraplatelet TGF-β levels when compared to normal platelets (Martyr et al. 1991), the finding of active TGF-β synthesis by megakaryoblasts (Terui et al. 1990), and the finding of increased plasma concentrations in a case of acute micromegakaryocytic leukemia that correlated with enhanced stromal turnover (Reilly et al. 1993). In addition, TGF-β expression is increased in patients' peripheral blood mononuclear cells at the mRNA level and/or at the secreted protein level (Martyré et al. 1994). Megakaryocytes, however, may not be the only cellular source of TGF-β, since TGF-β deposition appears to correlate with fibrosis even in cases with normal or reduced megakaryocyte numbers (Johnson et al. 1995). Interestingly, macrophages are frequently increased in myelofibrosis (Thiele et al. 1992; Titius et al. 1994) as is serum M-CSF, a growth factor which regulates the survival, proliferation, differentiation, and activation of macrophages (Gilbert et al. 1989). Furthermore, it has been shown that circulating monocytes in CIMF may be preactivated and contain increased levels of cytoplasmic TGF-β and IL-1 (Rameshwar et al. 1994). It has also been hypothesized that extracellular matrix protein-adhesion molecule interactions, involving CD44, may induce overproduction of fibrogenic cytokines in CIMF monocytes and contribute to stromal fibrosis in the bone marrow (Rameshwar et al. 1996). However, TGF-β is known to negatively regulate the cycling status of primitive progenitor cells and yet CIMF is characterized by an increased number of circulating CD34+ cells. This apparent paradox has been addressed by Le Bousse-Kerdiles and colleagues, who suggest that the explanation may, in part, be due to an acquired reduction in TGF-β type II receptor expression on myelofibrotic CD34+ progenitor cells. This fact, coupled with increased expression of basic fibroblast growth factor (bFGF) on the same cells, could explain the impaired inhibition by TGF-β (Le Bousse-Kerdiles et al. 1996).

15.2.4.3 Additional Growth Factors and Cytokines

A number of additional growth factors have been implicated in the pathogenesis of myelofibrotic stroma, including the calcium binding protein calmodulin, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and the tissue inhibitors of metalloproteinases (TIMPS) (Fig. 15.1). Several facts suggest a role for extracellular calmodulin, including the finding of elevated urinary levels in CIMF, the knowledge that platelets are a rich source of calmodulin, and the fact that the protein acts as a fibroblast mitogen in the absence other growth factors (Dalley et al. 1996; Eastham et al. 1994). The finding of elevated plasma levels of VEGF in CIMF (Novetsky et al. 1997), coupled with the fact that megakaryocytes produce and secrete large amounts (Brogi et al. 1994), suggests that this multifunctional cytokine may also contribute to the pathogenesis of the characteristic neoangiogenesis. In addition, bFGF has been reported by Martyré and colleagues (1997) to be elevated in platelets and megakaryocytes from CIMF patients, while urinary excretion is similarly increased (Dalley et al. 1996). Megakaryocytes and platelets are also rich sources of releasable TIMPS, with serum levels being significantly higher than those found in plasma. These proteins may contribute to the induction of marrow fibrosis by inhibiting connective tissue breakdown by members of the matrix metalloproteinase family and by functioning as growth factors for marrow fibroblasts. Indeed, Murate and colleagues (1997) have shown that the combined effects of TIMP-1 and TIMP-2 are almost equal to the fibrogenic effects of TGF-β. Recently, Emadi and colleagues (2005) have provided evidence for the involvement of IL-8 and its receptors (CXCR1 and CXCR2) in the altered megakaryocytic proliferation, differentiation and ploidization characteristic of CIMF, while IL-6 is also likely to be involved (Wang et al. 1997). The study of the pathogenesis of osteosclerosis typical of advanced CIMF has been limited, but it may be related to the overproduction of osteoprotegerin (OPG) (Wang et al. 2004).

Finally, an underlying mechanism for megakaryocyte-derived growth factor release has recently been proposed, in addition to the standard model of dysplasia and defective alpha granule packaging. CIMF, for example, is characterized by enhanced neutrophil and eosinophil emperipolesis by megakaryocytes, with the latter expressing both abnormal amounts and distribution

of P-selectin, an important mediator of neutrophil rolling (Schmitt et al. 2002). Activation of the engulfed neutrophils results in release of their proteolytic enzymes leading both to death of cells and the release of megakaryocytic TGF-β and PDGF. This phenomenon could also underlie the increased neutrophil elastase and active MMP-9 present in CIMF which, as a result of their multiple proteolytic activities, may enhance the release of $CD34^+$ progenitor cells from the bone marrow (Schmitt et al. 2002; Xu et al. 2003) (Fig. 15.1).

15.2.5 Animal Models

Several mouse models support the pivotal role of megakaryocytes in the development of the stromal proliferation, or myelofibrosis, that characterizes CIMF. These models were originally developed to investigate the role of thrombopoietin (TPO) and its receptor (Mpl), as well as the transcription factor GATA-1, in the control of megakaryocytopoiesis (Vannuchi et al. 2004; Yan et al. 1996). It was noted, however, that mice that overexpressed TPO, or underexpressed GATA-1, developed a clinical state similar to myelofibrosis, with tear drop poikilocytosis, increased circulating progenitors, and extramedullary hematopoiesis. The linking event appears to be a block in megakaryocyte differentiation, associated with an abnormal localization of P-selectin, which leads to neutrophil emperipolesis and the eventual release of TGF-β1 from megakaryocytic alpha granules (Vannucchi et al. 2005). These animal models support clinical observations and imply that myelofibrosis may not have a single cause, but may be the consequence of any perturbation that leads to increased neutrophil emperipolesis within the megakaryocyte. Although such models do not provide any insight into the pathogenesis of the underlying clonal hematopoiesis, they do support the link between TGF-β and stromal tissue development and may be of value for identifying novel antifibrotic agents for use in reversing clinical myelofibrosis.

15.3 Diagnosis

Classical CIMF is characterized by bone marrow fibrosis, extramedullary hematopoiesis, splenomegaly, and a leuko-erythroblastic blood picture. However, in contrast to CML, there is no specific biological marker and many

Table 15.1. Conditions associated with bone marrow fibrosis

Malignant	Non-malignant
Chronic idiopathic myelofibrosis	Infections (e.g., TB, visceral leischmaniasis
Other chronic myeloproliferative disorders, histoplasmosis, HIV) (e.g., PV, CML, ET)	Renal osteodystrophy
Acute megakaryoblastic leukemia	Vitamin D deficiency
(Acute myelofibrosis)	Hypothyroidism
Myelodysplastic syndromes	Hyperthyroidism
Acute myeloid leukemia	Gray platelet syndrome
Acute lymphoblastic leukemia	Systemic lupus erythematosus
Hairy cell leukemia	Scleroderma
Hodgkin's disease	Radiation exposure
Non-Hodgkin's lymphoma	Benzene exposure
Multiple myeloma	Gaucher's disease
Systemic mastocytosis	Osteopetrosis
Metastatic carcinoma (e.g., breast, prostate, stomach)	

Table 15.2. Italian Consensus Diagnostic criteria

Necessary criteria
Diffuse bone marrow fibrosis
Absence of Ph-chromosome or *BCR-ABL*
Optional criteria
Splenomegaly of any grade
Aniso-poikilocytosis
Presence of immature circulating myeloid cells
Presence of circulating erythroblasts
Clusters of megakaryocytes and abnormal megakaryocytes in the bone marrow
Myeloid metaplasia

Diagnosis of CIMF is acceptable if the following combinations are present: the two necessary criteria plus any other two optional criteria when splenomegaly is present, or the two necessary criteria plus any other four criteria if splenomegaly is absent.

studies have included a heterogeneous population of patients. The inappropriate inclusion of cases with secondary myelofibrosis, postpolycythemic myelofibrosis, and myelodysplasia with myelofibrosis and related disorders (Table 15.1) may explain the discrepancies in the early literature relating to cytogenetic abnormalities, therapeutic response, and prognosis. To address these difficulties, the "Italian Consensus Conference on Diagnostic Criteria for Myelofibrosis with Myeloid Metaplasia" proposed a definition of CIMF that has >80% sensitivity and specificity (Barosi et al. 1999). The definition requires two necessary criteria, namely diffuse bone marrow fibrosis and the absence of the Ph chromosome or *BCR-ABL* rearrangement, as well as a number of optional criteria (see Table 15.2). However, although this definition of CIMF encompasses a wide spectrum of the disease, from the early stages with slight reticulin fibrosis to the late osteomyelosclerotic phase (CIMF-1 to 3), it fails to include the recently recognized initial prefibrotic stage (CIMF-0) (see Figs. 15.2–15.4).

The concept of a prefibrotic stage of classical CIMF, that is distinguishable from essential thrombocythemia, has been stressed by a number of European histopathologists (Buhr et al. 2003; Georgii et al. 1998; Thiele and Kvasnicka 2004; Thiele et al. 1999) with the result that prefibrotic CIMF has been incorporated in the WHO classification of hematopoietic and lymphoid tumors

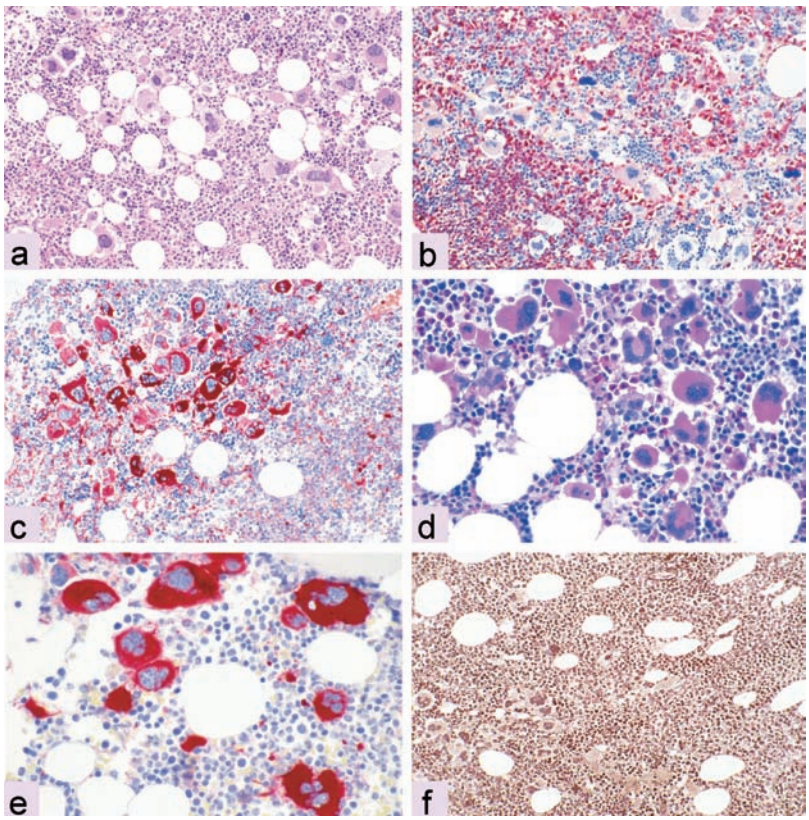

Fig. 15.2. Prefibrotic CIMF (CIMF-0). (**a**) An overall hypercellularity is evident including prominent growth of abnormally differentiated megakaryocytes (i.e., false ET). (**b**) There is a mixed neutrophil granulocytic and megakaryocytic proliferation with loose to dense clustering. (**c**) Atypias of megakaryopoiesis include histotopography (dense clustering) besides maturation defects revealing hypolobulated (bulbous) and hyperchromatic nuclei. (**d**) A prevalence of abnormal megakaryocytes with deviation of nuclear-cytoplasmic maturation is detectable. (**e**) Megakaryocytic abnormalities are highlighted by application of immunohistochemistry. (**f**) No increase in the reticulin fiber content may be observed. (**a**, **b**, **c**, **f**) ×70; (**d**, **e**) ×380; (**a**). hematoxylin-eosin, (**b**). AS-D-chloroacetate esterase, (**c**) and (**e**). CD61 immunostaining, (**d**). PAS (periodic acid Schiff reagent), (**d**). Silver immunostaining after Gomori (courtesy of Dr. Kvasnicka)

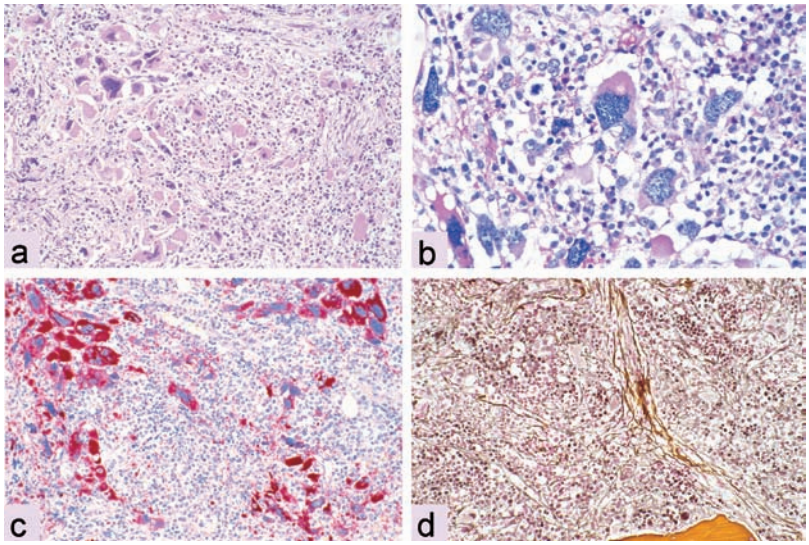

Fig. 15.3. Manifest CIMF. (**a**) In addition to a still slighty hypercellular bone marrow and a prominent granulopoiesis there are clusters of atypical megakaryocytes trapped in a fibrous meshwork. (**b**) Megakaryocytes show abnormal cloud-like (bulbous) nuclei and maturation defects (**c**) Dense clustering of atypical megakaryocytes is a conspicuous feature. (**d**) A dense increase in reticulin and some collagen fibers are characteristic. (**a**, **c**, **d**) ×170; (**b**) ×380; (**a**) Hematoxylin-eosin, (**b**) PAS. (**c**) CD61 immunostaining (**d**) Silver impregnation after Gomori (courtesy of Dr. Kvasnicka

(Thiele et al. 2001b). It has been estimated that approximately 25% of patients with CIMF initially present with a hypercellular bone marrow characterized by granulocytic and megakaryocytic proliferation and with little or no reticulin. The diagnosis requires careful examination of the bone marrow trephine and relies on the identification of morphologically atypical megakaryocytes, including dense clustering with hypolobulated (bulbous) and hyperchromatic nuclei. Other diagnostically important parameters include the frequency and shape of microvasculature (Kvasnicka et al. 2004), the level of $CD34^+$ progenitor cells (Thiele and Kvasnicka 2002), and abnormalities of cell kinetics (Kvasnicka et al. 1999). Prefibrotic CIMF is likely to have been misdiagnosed as essential thrombocythemia in many studies since it is characterized by thrombocythemia, borderline anemia, mild splenomegaly, and an absence of a leuko-erythroblastic blood picture (Thiele and Kvasnicka 2004; Thiele et al. 2001a). The natural history of prefibrotic CIMF remains unclear since prospective studies are lacking. However, preliminary data suggest that the rate of progression to advanced disease may depend on the degree of megakaryocytic dysplasia (Buhr et al. 2003; Thiele et al. 2003).

15.4 Clinical Manifestations

CIMF characteristically occurs after the age of 50, with a median age at diagnosis of approximately 60 years. About 25% of patients are asymptomatic at diagnosis and are identified following routine examination. The most common symptoms in classical CIMF are the consequence of anemia, namely fatigue, weakness, dyspnea, and palpitations. Splenomegaly is characteristic and when massive can lead to a variety of complaints including abdominal discomfort and early satiety (Fig. 15.5). Splenic infarction, due to the inability of the blood supply to match organ growth, usually produces transient discomfort although rarely can result in severe abdominal pain simulating an abdominal emergency (Fig. 15.6). Hepatomegaly occurs in approximately 70% of cases and portal hypertension may result from increased hepatic blood flow or intrahepatic obstruction (Tsao et al. 1989; Wanless et al. 1990). Nonspecific symptoms may dominate the clinical picture in CIMF, including low-grade fever, night sweats, and weight loss, and are associated with a poor prognosis (Cervantes et al. 1998). Patients may also complain of bone pain, especially in the lower extremities. Bleeding may complicate the clinical course and although often mild, manifesting

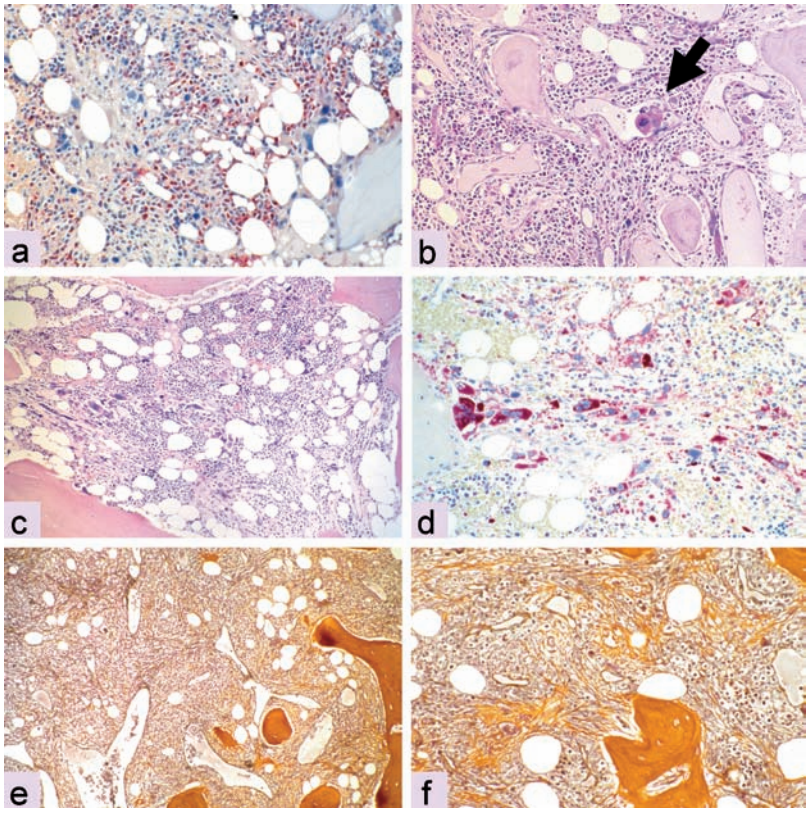

Fig. 15.4. Advanced CIMF. (**a**) Patchy hematopoiesis shows megakaryocyte clusters besides a reduction of granulo- and erythropoiesis and bundles of fibers. (**b**) Prominent dilated sinuses with intraluminally dislocated megakaryopoiesis (*arrow*) may be observed. (**c**) In addition to differences in cellularity there are initial plaque-like osteosclerotic changes and a meshwork of fibers. (**d**) Megakaryocytes reveal abnormalities of histopography (endosteal translocation and clustering) apparently in close association with bud-like endophytic bone formation – osteosclerosis may usually be found. (**a**, **b**, **d**) ×170; (**c**, **e**, **f**) ×80; (**a**) AS-D-chloroacteta esterase, (**b**) PAS, (**c**) Haematoxylin-eosin, (**d**) CD61 immunostaining; (**e**, **f**) Silver impregnation after Gomori (courtesy of Dr. Kvasnicka)

as petechiae and ecchymoses, can be life threatening due to massive gastrointestinal hemorhage. The hemorrhagic diathesis may result from a combination of thrombocytopenia, acquired platelet dysfunction, and low-grade disseminated intravascular coagulation.

Extramedullary hematopoiesis (EMH), or myeloid metaplasia, may result in a bewildering array of symptoms which depend on the specific organ involved. EMH, for example, may affect the central nervous system and result in spinal cord compression (Horwood et al. 2003; Price and Bell 1985), delirium (Cornfield et al. 1983), diabetes insipidus (Badon et al. 1985), serious headaches and exophthalmos due to meningeal infiltration (Ayyildiz et al. 2004; Landolfi et al. 1988), as well as raised intracranial hypertension with papilledema and ultimately coma (Cameron et al. 1981; Ligumski et al. 1979; Lundh et al. 1982). Involvement of lymph nodes can lead to generalized and marked lymphadenopathy (Williams et al. 1985). Pleural infiltration may result in hemothoraces (Kupferschmid et al. 1993) and pleural effusions (Jowitt et al. 1997) (Fig. 15.7), while massive ascites may result from ectopic implants of peritoneal or mesenteric extramedullary hematopoiesis (Yotsumoto et al. 2003). The effusions often contain a variety of hematopoietic elements, including megakaryocytes, immature myeloid cells, and erythroblasts. The gastrointestinal tract may be involved and this results in abdominal pain and intestinal obstruction (Mackinnon et al. 1986; Sharma et al. 1986), while infiltration of the kidneys (Fig. 15.8), prostate, and gallbladder have been reported to result in chronic renal failure, bladder outlet obstruction, and chronic cholecystitis, respectively

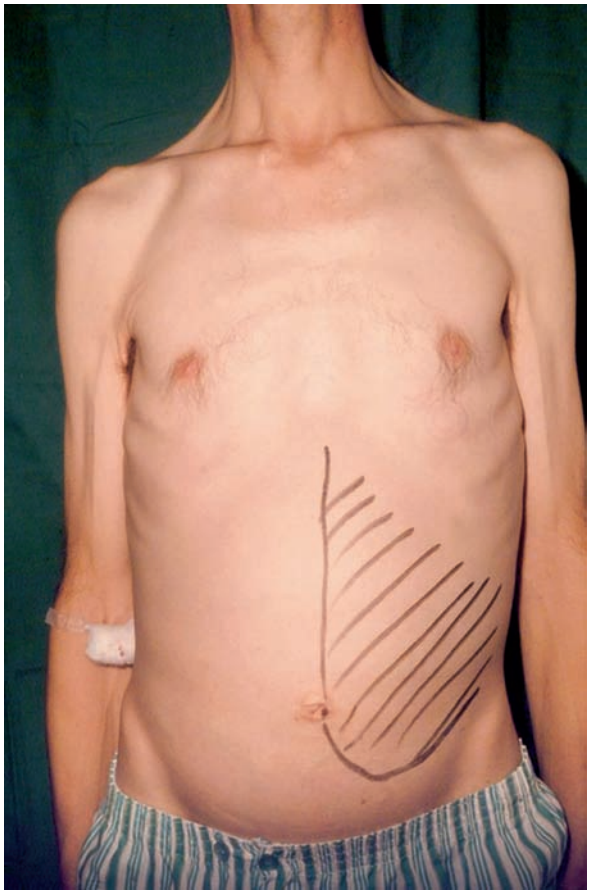

Fig. 15.5. Gross splenomegaly (extending 22 cm below the left costal margin) and associated cachexia

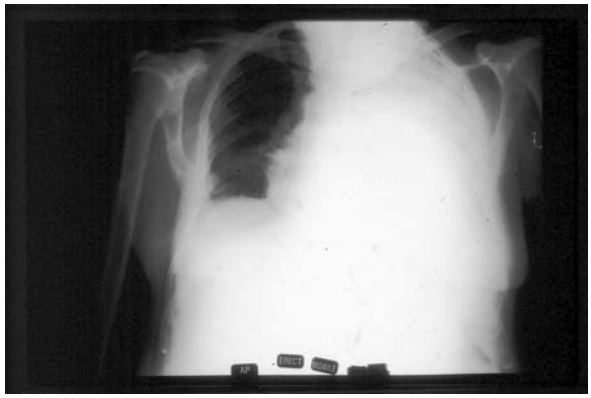

Fig. 15.7. Pleural effusion in a patient with myelofibrosis and extramedullary hematopoiesis involving the pleura

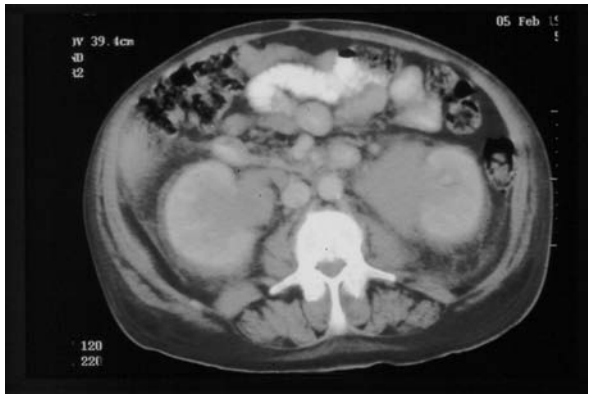

Fig. 15.8. Extramedullary hematopoiesis involving both kidneys

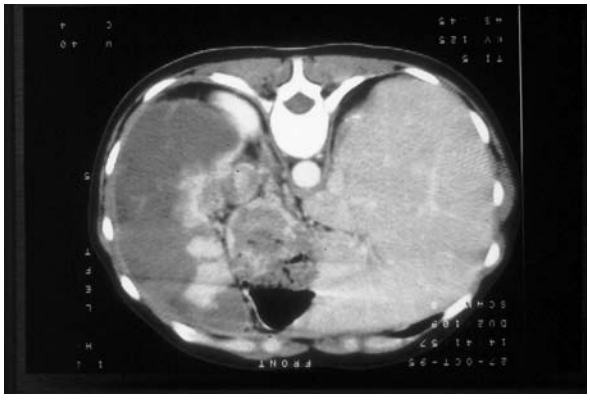

Fig. 15.6. Massive splenic infarction necessitating splenectomy

(Humphrey and Vollmer 1991; Schnuelle et al. 1999; Thorns et al. 2002). Involvement of breast tissue may mimic carcinoma (Martinelli et al. 1983), while urethral infiltration has been reported to masquerade as a caruncle (Balogh and O'Hara 1986) and synovial involvement can give rise to arthritis (Heinicke et al. 1983). Skin manifestations are rare and include erythematous plaques (Fig. 15.9), nodules, diffuse or papular erythema, ulcers, and bullae (Loewy et al. 1994). Rarely, the development of CIMF can be preceded by the presence of neutrophilic dermatosis, or "Sweet's syndrome" while pyoderma gangrenosum and leukemic infiltrations have been reported (Gibson et al. 1985).

The major causes of death are infection, hemorrhage, cardiac failure, and acute leukemic transformation. The latter, which occurs in approximately 15% of patients (Silverstein et al. 1973) are commonly myeloblastic or myelomonoblastic, but may involve the megakaryocytic (Reilly et al. 1993), erythroid (Garcia et al. 1989), lymphoid (Polliak et al. 1980), and basophilic

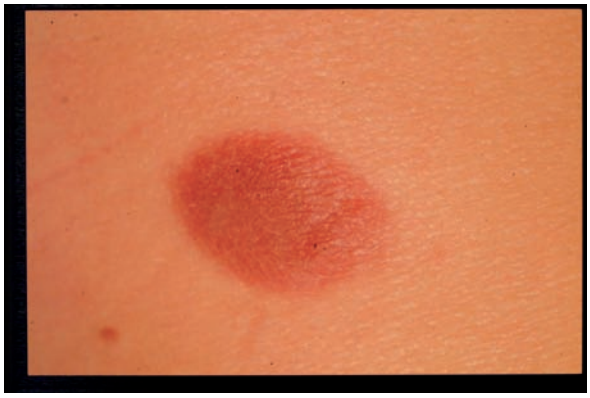

Fig. 15.9. Cutaneous extramedullary hematopoiesis

lineages (Sugimoto et al. 2004). Hernandez and colleagues (1992) have described the occurrence of mixed myeloid (myeloblastic-erythroid-megakaryocytic) or hybrid (myeloid-lymphoid) phenotypes in up to a third of cases, a fact that reflects the pluripotent stem cell origin of the disease. Localized granulocytic sarcomas, or chloromas, can develop in a wide variety of sites, including bone, lymph nodes, and skin and on occasion precede the diagnosis of leukemia.

15.5 Laboratory Features

A normocytic normochromic anemia is characteristic of classic CIMF, as is anisocytosis, poikilocytosis, and teardrop-shaped cells (dacrocytes). The origin of dacrocytes is uncertain but they are thought to be the sine qua non of extramedullary hematopoiesis. Nucleated red cells are present in the peripheral blood of nearly all cases and there is frequently a mild reticulocytosis. The major cause of anemia is ineffective erythropoiesis but other causes may include iron deficiency, red cell sequestration, and hemodilution due to plasma volume expansion as a result of splenomegaly. Hemolysis can be significant and, although frequently direct antiglobulin test (DAT) negative, may be autoimmune in etiology (Bird et al. 1985).

Immunological abnormalities, other than anti-red cell antibodies, are common and include the development of antinuclear and rheumatoid antibodies, lupus-type anticoagulants, antiphospholipid antibodies (Rondeau et al. 1983), hypocomplementemia (Gordon et al. 1981), and increased nodules of lymphoid cells in the bone marrow (Caligaris Cappio et al. 1981). Lewis and Pegrum (1972) described immune complexes on leukocytes while, more recently, antibodies directed against stromal proteins, for example anti-Gal antibodies, have been demonstrated that appear to correlate with disease activity. Interestingly, galactosidic determinants are thought to be expressed by fibroblasts and megakaryocytes in patients with CIMF raising the possibility of an autoimmune pathogenesis (Leoni et al. 1993). A number of these abnormalities are likely to be epiphenomena, resulting from impaired reticulo-endothelial system clearance, but immunological mechanisms have been postulated for the induction and/or maintenance of the disease (Caligaris Cappio et al. 1981); for example, immune complexes could result in platelet activation and additional growth factor release. Interestingly, Gordon and colleagues (1981) noted a correlation between circulating immune complexes and disease activity as manifested by increased transfusion requirements, bone pain, and fever. The immunological hypothesis for myelofibrosis is supported by reports of successful immunosuppressive therapy, including low-dose dexamethasone (Jack et al. 1994), prednisolone (Mesa et al. 2003) and cyclosporin A (Pietrasanta et al. 1994), as well as the reports of myelofibrosis associated with systemic lupus erythematosus (Kaelin and Spivak 1986) and polyarteritis nodosa (Connelly et al. 1982).

15.6 Prognosis

The overall median survival of classical CIMF varies from series to series but is approximately 4 years (Demory et al. 1988; Reilly et al. 1997; Rupoli et al. 1994; Varki et al. 1983), although individual survival may range from 1 to over 30 years. This is considerably lower, however, than the 14-year median survival of age- and sex-matched controls (Rozman et al. 1991). As a result, many groups have used univariate or multivariate analysis to identify clinical and laboratory features that predict survival. Despite the bewildering number of prognostic factors highlighted, most studies agree on the predictive value of anemia (Barosi et al. 1988; Cervantes et al. 1991; Dupriez et al. 1996; Ivanyi et al. 1984; Kreft et al. 2003; Njoku et al. 1983; Reilly et al. 1997; Rupoli et al. 1994; Visani et al. 1990), age at diagnosis (Barosi et al. 1988; Cervantes et al. 1997; Kvasnicka et al. 1977; Reilly et al. 1997; Varki et al. 1983), karyotype (Dupriez et al. 1996; Reilly et al. 1997; Tefferi et al. 2001), and the percentage of immature granulocytes and/or circulating myelo-

blasts (Barosi et al. 1988; Cervantes et al. 1991; Visani et al. 1990). The data regarding the prognostic value of absolute peripheral blood CD34+ counts, however, are less clear. Several groups, for example, have suggested that, in addition to a possible diagnostic role, elevated CD34+ counts are an important adverse prognostic marker (Barosi et al. 2001; Passamonti et al. 2003; Sagaster et al. 2003). In contrast, Arora and colleagues (2004), although finding that counts above 0.1×10^9/L correlated with shortened survival, noted that this significance was lost on multivariate analysis. Finally, the degree of angiogenesis (Mesa et al. 2000), in contrast to the extent of collagen fibrosis or osteosclerosis (Dupriez et al. 1996; Kvasnicka et al. 1997; Rupoli et al. 1994), has been shown to be a significant and independent risk factor for overall survival.

Two simple and practicable schemas have been reported that allow the identification of patients with limited life expectancy, for whom more aggressive therapeutic approaches might be appropriate (Dupriez et al. 1996; Reilly et al. 1997). The most widely used is the Lille scoring system (Table 15.3) which is based on two adverse prognostic factors, namely hemoglobin <10g/dL and a total white count <4 or $>30\times10^9$/L, and which separates patients into three groups with low (0 factor), intermediate (1 factor), and high risk (2 factors) disease, associated with median survivals of 93, 26, and 13 months, respectively (Dupriez et al. 1996). The Sheffield schema (Table 15.4), by combining age, hemoglobin concentration, and karyotype, identifies patient groups with median survival times that vary from 180 months (good risk) to 16 months (poor risk) (Reilly et al. 1997). However, there are two important caveats that apply to these and many other studies. Firstly, only a few groups have included the full spectrum of the disease, from the early prefibrotic phase to the advanced full-blown osteomyelosclerotic state. This is important as the early prefibrotic stages of CIMF show a more favorable outcome than the advanced stages of disease (Kvasnicka et al. 1997). Secondly, most studies have included very few young patients, a fact that could potentially limit the schema's utility when attempting to identify cases suitable for bone marrow transplantation. This deficiency has been addressed by Cervantes and colleagues (1999), who reported a large collaborative study of 116 patients below the age of 55 years and concluded that, by using a combination of hemoglobin, constitutional symptoms, and percentage of blasts, patients with low- and high-risk disease could be identified. Importantly, the median survival in this cohort was 128 months which is significantly better than that reported for studies of unselected patients.

Table 15.3. The LILLE scoring system

No. of adverse prognostic factors	Risk group	Cases (%)	Median survival (months)
0	Low	47	93
1	Intermediate	45	26
2	High	8	13

Adverse prognostic factors; Hb <10g/dL, WBC <4 or $>30\times10^9$/L. (Reproduced from Dupriez et al. 1997 with permission).

Table 15.4. The SHEFFIELD schema for predicting survival (reproduced from Reilly et al. 1997 with permission)

Age (years)	Hb (g/dl)	Karyotype	Median survival (months) (95% CI)
<68	<10	N	54 (46, 62)
		A	22 (14, 30)
	>10	N	180 (6, 354)
		A	72 (32, 112)
>68	<10	N	44 (31, 57)
		A	16 (5, 27)
	>10	N	70 (61, 79)
		A	78 (26, 130)

Demonstrating median survival times in months with associated 95% confidence intervals in parenthesis;
N, normal; A, abnormal.

15.7 Management

15.7.1 Medical Therapy

15.7.1.1 Cytotoxic Therapy

Cytotoxic chemotherapy has a definite role in the management of CIMF patients. Hydroxyurea, the most widely used agent (Lofvenberg et al. 1990; Manoharan 1991), can reduce the degree of hepatosplenomegaly, decrease or eliminate constitutional symptoms, reduce thrombocytosis and, in some cases, lead to an increase in hemoglobin. Hydroxyurea may also be useful in individuals who develop compensatory hepatic myeloid metaplasia following splenectomy and it has also been shown to improve bone marrow fibrosis (Lofvenberg et al. 1990). The use of busulfan has been reported in the proliferative phase of the disease (Manoharan and Pitney 1984), but the risks of prolonged cytopenias are significant. Responses are often short-lived, lasting a median of only 4.5 months (Silverstein 1975). Low-dose melphalan (starting at 2.5 mg three times a week) may be an alternative option (Petti et al. 2002) but again hematological toxicity is common. 2-chlorodeoxyadenosine (2-CdA) may have a palliative role in controlling the extreme thrombocytosis and leukocytosis, as well as the accelerated hepatomegaly that can occur post splenectomy. Responses were observed in about half of patients and occurred in most cases by the second course (Faoro et al. 2005; Tefferi et al. 1997).

15.7.1.2 Androgens

Anemia, usually normochromic normocytic, is a common problem in CIMF, with 20–25% of presenting cases being symptomatic. Iron deficiency, ineffective hematopoiesis, erythrocytic sequestration, hemodilution secondary to plasma volume expansion, and hemolysis are recognized mechanisms. Patients with normal red cell masses and marked increase in plasma volume have a dilutional form of anemia that does not require treatment. Androgen therapy, including nandrolone, fluoxymesterolone, and oxymetholone, improves marrow function in approximately 40% of patients (Besa et al. 1982; Brubaker et al. 1982; Hast et al. 1978), with optimal responses seen in patients lacking massive splenomegaly and in those with a normal karyotype (Besa et al. 1982). Danazol (400–600 mg/day), a synthetic attenuated androgen, may give similar results with the added benefit of correcting thrombocytopenia and reducing the degree of splenomegaly in some patients (Cervantes et al. 2000, 2005; Levy et al. 1996). Androgen therapy should be continued for a minimum of 6 months and once a response is obtained, it should be reduced to the lowest maintenance dose. Pretreatment variables associated with response to danazol include lack of transfusion requirement and higher hemoglobin concentration at commencement of treatment (Cervantes et al. 2005). Side effects include fluid retention, increased libido, hirsutism, abnormal liver function tests, and hepatic tumors. All treated patients should have regular monitoring of liver function tests and periodic abdominal ultrasound investigation to detect liver tumors. In addition, male patients should be screened for prostate cancer prior to therapy.

15.7.1.3 Erythropoietin

Human recombinant erythropoietin (EPO) has been shown by several groups to be an effective and safe therapy in CIMF, although the number of reported cases remains small (Aloe-Spiriti et al. 1993; Bourantas et al. 1996; Hasselbalch et al. 2002; Tefferi and Silverstein 1994). Hasselbalch et al. (2002), for example, reported that 90% (9 of 10 evaluable cases) attained a favorable response, which was maintained in the majority of patients. Importantly, most responding individuals exhibited inappropriately low serum EPO levels for the degree of anemia. More recently, Cervantes et al. (2004) confirmed these findings and showed that 45% of patients responded favorably to a dose of 10,000 U three times a week. In addition, those with a serum EPO level <125 U/L and those that were transfusion independent had a more favorable outcome. It can be concluded from these studies that EPO is a well-tolerated therapy for the anemia in CIMF but that its use should be restricted to cases with inappropriately low serum EPO levels. It should be noted, however, that the majority of patients have appropriate levels for the degree of anemia (Barosi et al. 1993a). The dose may be doubled if there has been no response after 1–2 months and the treatment discontinued if there has been no response after 3–4 months.

15.7.1.4 Interferon

Parmeggiani et al. (1987) reported the use of α-interferon (α-IFN) for the treatment of painful splenomegaly in CIMF. Splenic pain and pressure symptoms resolved with a decrease in spleen size, although peripheral

counts deteriorated. Pegylated IFN, a polyethylene glycol formulation of α-IFN that is administered once a week, is currently undergoing clinical trials in CIMF and may have the advantage of being better tolerated (Verstovsek et al. 2003).

15.7.1.5 Thalidomide

Recently, thalidomide has been advocated as a therapy for controlling angiogenesis in several neoplastic and inflammatory diseases. The marked neo-vascularization that characterizes CIMF bone marrow (Mesa et al. 2000, Reilly et al. 1985b) suggested that thalidomide might be beneficial in this disease and has led to several small studies. A pooled analysis of the latter indicated that thalidomide can ameliorate anemia, thrombocytopenia, and splenomegaly in some cases, but that most patients were intolerant of standard doses (200–800 mg/day), with nearly 50% of cases withdrawing from the studies by the third month (Barosi et al. 2002). As a result, the combination of low-dose thalidomide (50 mg/day) and prednisolone at 0.5 mg/kg/day slowly tapered over the course of 3 months was evaluated and shown to be associated with a higher response rate and lower toxicity (Mesa et al. 2003). A meaningful improvement in anemia was demonstrated in 62% of all patients, while a 70% response rate was obtained for those cases that were transfusion dependent. However, although thrombocytopenia and splenomegaly improved in 75% and 19% of cases, respectively, there was no apparent decrease in extramedullary hematopoiesis or angiogenesis, suggesting that thalidomide's activity may not be due to its antiangiogenic properties. Following the discontinuation of prednisolone, the improvement in anemia and thrombocytopenia was lost in over a third of cases. The role of steroids in this study supports earlier data that indicated the benefit of low-dose dexamethasone (Jack et al. 1994). A recent European study (Marchetti et al. 2004) confirmed the usefulness of single agent low-dose thalidomide (50 mg/day) in a cohort of 63 patients with advanced stage disease and concluded that it was effective especially for transfusion-dependent and/or thrombocytopenic patients and for those requiring control of progressive splenomegaly. A combination of thalidomide and erythropoietin has been shown to correct the anemia in some cases in which both drugs have previously failed as single agents (Visani et al. 2003). Lenalidomide (CC-5013, Revlimid), a more potent drug with less neurotoxicity than thalidomide, has recently been shown to have clinical activity in approximately 20% of patients (Cortes et al. 2005; Tefferi et al. 2005). It should be stressed however, that most patients will become refractory to medical therapies and consequently will require life-long transfusions with resulting iron overload.

15.7.1.6 Experimental Therapy

Etanercept, a recombinant form of the extracellular domain of tissue necrosis factor (TNF) receptor linked to the Fc fragment of human IgG, inhibits TNF-α, a key mediator of malignancy-associated fever, cachexia, and other constitutional symptoms. Two pilot studies have reported its use in CIMF. Steensma and colleagues (2002) observed a 60% reduction in severity of constitutional symptoms, while 20% experienced reduction of splenomegaly and/or improvement of cytopenias. Imatinib mesylate has been evaluated in CIMF on the basis that it inhibits the receptors PDGFR and KIT (Tefferi et al. 2002). However, the drug demonstrated limited efficacy and side effects led to the withdrawal in many patients. R115777, a farnesyl transferase inhibitor, has in vitro antiproliferative activity for CIMF progenitor cells. In a small study, R115777 produced improvement in anemia and splenomegaly in 25% of cases, with responses correlating with high VEGF levels (Cortes et al. 2003). Paradoxically, however, the VEGF tyrosine kinase inhibitor SU5416 possesses minimal therapeutic activity in CIMF (Giles et al. 2003). Studies evaluating the efficacy of new drugs including thalidomide analogues, proteasome inhibitors and VEGF neutralizing antibodies are currently underway.

15.7.2 Surgery and Radiotherapy

15.7.2.1 Splenectomy

The role of splenectomy in the management of myelofibrosis is now fairly well defined (Barosi et al. 1993; Mesa et al. 2004; Tefferi et al. 2000). In contrast to earlier reports, which suggested that the operation be performed in every patient at diagnosis, it is now clear that the procedure should be restricted to carefully selected cases with refractory hemolysis and/or thrombocytopenia, symptomatic splenomegaly, significant splenic infarction, and severe portal hypertension. Splenectomy does not prolong survival and even in the best units is asso-

ciated with morbidity and mortality rates of approximately 31% and 9%, respectively (Tefferi et al. 2000). The main postoperative complications include bleeding, thromboembolism, subphrenic abscess, and pulmonary atelectasis. In addition, compensatory hepatic myeloid metaplasia leading to rapid hepatic enlargement is an unusual but well-recognized complication, while an unexpectedly high rate of leukemic transformation has been documented (Barosi et al. 1998; López-Guillermo et al. 1991). The explanation for the increased blast transformation is unclear, but it is possible that the procedure could accelerate a pre-existing hyperproliferation state, especially as this complication has not been reported in healthy individuals. A significant postoperative thrombocytosis is observed in approximately 20% of patients and carries an increased thrombotic risk (Barosi et al. 1993a). Once a patient is considered a candidate for splenectomy, an extensive preoperative evaluation is required to determine if the cardiac, hepatic, renal, metabolic, and hemostatic risks are acceptable. The importance of the frequently associated coagulopathy needs to be stressed. Defective platelet aggregation is common and many patients have a prolonged bleeding time. In addition, some cases have laboratory evidence of disseminated intravascular coagulation, which may only become clinically apparent following surgical intervention, while others have a prolonged prothrombin time due to associated liver dysfunction, an isolated factor V deficiency, or the presence of circulating anticoagulants. Surgical expertise is essential, since the operation is often difficult as the spleen may be adherent to adjacent serosal surfaces as well as possessing numerous collateral vessels and dilated spleno-portal arteries and veins. Individuals operated on for portal hypertension and bleeding varices should have dynamic circulatory studies performed during the procedure, since portal hypertension due to splenomegaly is corrected by splenectomy (Silverstein and ReMine 1979), whereas cases secondary to intrahepatic obstruction require a portal-systemic shunt (Tefferi et al. 1994).

15.7.2.2 Radiotherapy

Radiotherapy should be considered as an alternative to splenectomy in those patients who are unfit for surgery. Several studies have reported symptomatic relief, with mild to moderate reduction in spleen size, which lasts for approximately 6 months (Bouabdallah et al. 2000; Elliot et al. 1998). A significant percentage of patients, however, suffer unpredictable, life-threatening cytopenias, resulting in an overall mortality rate of 13%. The transient response, together with the high mortality rate for patients requiring subsequent splenomegaly, suggests that such therapy should not be regarded as an alternative to splenectomy in surgical candidates. Low-dose irradiation, however, remains the treatment of choice for peritoneal and pleural extramedullary hematopoiesis that results in ascites and pleural effusions, respectively (Bartlett et al. 1995; Leinweber et al. 1991), as well as for myeloid metaplasia of vital organs, including the lung, central nervous system, and liver (Price and Bell 1985; Steensma et al. 2002; Tefferi et al. 2001b).

15.7.3 Stem Cell Transplantation

15.7.3.1 Standard Allo-SCT

Currently, allogeneic hematopoietic stem cell transplantation (allo-SCT) is the only curative modality for patients with CIMF. Recently, two large studies have attempted to clarify the issues surrounding patient selection and outcome. Guardiola et al. (1999), in a retrospective multicenter study, reported the results of HLA-identical SCT in 55 patients (median age at transplantation 42 years, range 4–53). The 5-year probability of survival was 47% ± 8% for the overall group, and 54% ± 8% for patients receiving an unmanipulated HLA-matched related transplant. The 1-year probability of transplant-related mortality was 27% ± 6%. Hemoglobin (< 10 g/dL), osteosclerosis, and a high-risk score at the time of transplantation were associated with a worse survival, whereas older age, karyotypic abnormalities, and lack of grade II–IV acute GVHD were associated with treatment failure. Deeg and colleagues (2003) reported the results in 56 patients treated at a single institution with conventional allo-SCT. The median age at transplantation was 43 years (range 10 to 66) with median disease duration of 33 months (range 3 to 312). Fifty-three patients achieved engraftment, while two died from relapse/progressive disease and 18 from other causes. The probability of surviving 3 years was 58%, with patients having lower Lille scores, higher platelet counts, less severe marrow fibrosis, and normal karyotypes doing better than those with more advanced disease. The role of pretransplant splenectomy is unclear. Guardiola and colleagues (1999) reported that although splenectomy was associated with a faster hematopoietic recovery, there was no associated survival benefit. A

pragmatic approach, therefore, in view of the mortality and morbidity of splenectomy, would be to restrict the procedure to patients where engraftment might be significantly delayed, for example in cases of osteomyelosclerosis or massive splenomegaly.

15.7.3.2 Reduced Intensity Allo-SCT

Evidence for a graft-versus-myelofibrosis (GvMy) effect has provided the rationale for exploring the role of reduced-intensity, or nonmyeloablative, allo-SCT in CIMF. Guardiola and colleagues (1999), for example, reported that absent or minimal GvHD in the context of conventional allo-SCT correlated with treatment failure, while the infusion of donor lymphocytes in patients failing allo-SCT may lead to disease eradication (Byrne et al. 2000; Cervantes et al. 2000). The initial reports of reduced-intensity allo-SCT were retrospective registry studies with patients receiving a range of conditioning regimes. Nevertheless, encouraging 1-year survival rates of 54% and 90% were reported (Hessling et al. 2002; Rondelli et al. 2003). Recently, the first prospective study using reduced-intensity conditioning has been published (Kröger et al. 2005). This series demonstrated that a busulphan- and fludarabine-based regimen, followed by allo-SCT from either a related or unrelated donor, is a feasible and effective therapeutic option with a low treatment-related mortality. Complete donor chimerism was seen in 95% of cases on day 100 with acute GvHD grades II–IV and III/IV occurring in 48% and 19% of cases respectively, while 55% developed chronic GvHD. The estimated overall and disease-free survival at 3 years was 84%, with no treatment failure, as defined by recurrence or progression of myelofibrosis, being observed after a median follow-up of 22 months. Importantly, despite in vivo T-cell depletion, no relapses were reported. In addition, the results from unrelated donors compared favorably with the outcome of the few cases of unrelated SCT reported using standard conditioning. In the largest series of the latter, for example, seven patients were transplanted from unrelated donors, but only one survived (Guardiola et al. 1999). It should be stressed, however, that the overall experience of reduced-intensity allo-SCT remains limited and crucial questions such as the impact of prior splenectomy, the influence of karyotype and the effect of the degree of fibrosis on outcome, remain unclear. As a result, the use of reduced-intensity conditioning should be restricted to patients aged 45–70 years with high-risk disease.

15.7.3.3 Autologous SCT

The risks of allo-SCT have led clinicians to investigate the palliative option of autologous-SCT, especially for the older patient or for those without a stem cell donor. The feasibility of this approach was demonstrated by Anderson and colleagues (2001) who reported a multicenter retrospective analysis of 21 patients, conditioned using single agent busulphan at a dose of 16 mg/kg. At 2 years the actuarial survival was 61%, with six patients having died of infection, graft failure, or progressive disease. Following transplantation, 15 of 21 patients showed evidence of significant clinical improvement that lasted up to 4 years, including ten of 17 cases with anemia, 7 of 10 patients with symptomatic splenomegaly, and 6 of 8 cases with thrombocytopenia. G-CSF priming was recommended since, although CIMF patients have high circulating CD34+ cell counts, most peripheral CD34+ cells are likely to lack the capacity to maintain long-term hematopoiesis. The mechanism for response is unclear but may include the restoration of intramedullary hematopoiesis as a result of reduced fibrosis, reduced sequestration of nonclonal cells following improvement in the degree of splenomegaly, and the restoration of normal hematopoiesis secondary to a reduction of malignant cells.

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