The Forgotten Myeloproliferative Disorder: Myeloid Metaplasia

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ABSTRACT

Myelofibrosis with myeloid metaplasia is a hematologic disorder currently classified with polycythemia vera and essential thrombocythemia as a chronic myeloproliferative disease. The median age at diagnosis is 60 years, and more than 90% of patients are diagnosed after age 40 years. Clinical manifestations include massive splenomegaly, progressive anemia, profound constitutional symptoms, and extramedullary hematopoiesis. The diagnosis is confirmed by bone marrow examination after other causes of myelofibrosis are ruled out. Median survival is 5 years and causes of death include leukemic transformation. Prognosis is adversely affected by the presence of anemia (hemoglobin <10 g/dl), leukopenia or leukocytosis (white blood cells >30,000/µl), circulating blasts, and hypercatabolic symptoms. Conventional treatment is palliative and does not improve survival. In this regard, androgen preparations, corticosteroids, and erythropoietin are useful for the treatment of disease-associated anemia. Symptomatic splenomegaly is best managed by cytoreductive therapy or surgical removal. Radiation therapy is most useful in the treatment of nonhepatosplenic extramedullary hematopoiesis. New treatment approaches include the use of thalidomide alone or in combination with prednisone and hematopoietic stem cell transplantation.

INTRODUCTION

Myelofibrosis with myeloid metaplasia (MMM), also known as agnogenic myeloid metaplasia or idiopathic myelofibrosis, was first described in 1879 [1]. Clinical manifestations include progressive anemia and extramedullary hematopoiesis (EMH) that results in marked hepatosplenomegaly, as well as the development, in some cases, of nonhepatosplenic EMH; hypercatabolic symptoms resulting in cachexia, bone marrow fibrosis, and osteosclerosis; and clonal evolution into acute leukemia [2]. The disease is rare, with an
incidence figure that ranges from 0.3-1.5/100,000 people [3, 4]. The median age at diagnosis is 60 years and approximately 10% of the patients are diagnosed before age 46 years [5]. There are well-documented cases of MMM in children although clinical course may be favorably different than that of adults with the disease [6]. Among clonal hematologic disorders, MMM is classified with polycythemia vera [7] and essential thrombocythemia [8] as a chronic myeloproliferative disease (CMPD) (Fig. 1). Among the CMPDs, MMM is the least prevalent as well as the most difficult to manage. As such, most cases are cared for by subspecialized hematologists, and the disease is infrequently seen by the community oncologist.

**PATHOGENESIS**

As is the case with most chronic myeloid disorders, MMM is a true stem cell disease with clonal involvement of neutrophils, monocytes, erythroid progenitors, CD34+ cells (myeloid progenitors), megakaryocytes, and both B and T lymphocytes [9]. However, MMM is unique among the CMPDs in displaying florid bone marrow stromal reaction including collagen fibrosis, osteosclerosis, and angiogenesis [10]. At present, the bone marrow stromal reaction in MMM is believed to be reactive and cytokine mediated. The evidence for this particular assumption stems from the demonstration of both polyclonality in bone marrow fibroblasts of patients with MMM [11] and increased cellular and extracellular concentrations of various fibrogenic and angiogenic cytokines including transforming growth factor-β (TGF-β), basic fibroblast growth factor, and platelet-derived growth factor (PDGF) [12]. The source of these cytokines might include both megakaryocytes and monocytes (Fig. 2) [13, 14].

Mice that are either chronically overexposed to thrombopoietin (TPO) [15] or carriers of a mutant GATA-1 gene (resulting in a phenotype with a reduced expression of a transcription factor that is important in the terminal differentiation of erythrocytes and megakaryocytes) display characteristic features of MMM, including megakaryocytic hyperplasia, bone marrow fibrosis/osteosclerosis, and EMH [16]. The stromal reaction in these experimental animals is believed to be directly related to megakaryocyte proliferation resulting from either the direct effect of TPO or impaired megakaryocyte differentiation associated with the GATA-1 gene mutation (Fig. 2). Furthermore, the development of TPO-induced bone marrow fibrosis in mice has been temporally associated with elevated TGF-β levels [17], while it was abrogated in TGF-β-knockout experiments (Fig. 2) [18]. These observations support the role of cytokines in the pathogenesis of MMM. However, it is currently not clear whether the aforementioned animal models of MMM involve pathogenetic mechanisms that are operating in the human form of the disease.

**DIAGNOSIS**

Striking splenomegaly that is secondary to EMH is the hallmark of MMM. However, there are many other conditions that are associated with a massive spleen size, and more than 80% of these involve hematologic disorders including chronic myeloid leukemia (CML), chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and hairy cell leukemia [19]. On the other hand, few patients with MMM may not display palpable splenomegaly. Additional clinical
features of MMM include progressive anemia, profound constitutional symptoms, and a spectrum of peripheral blood and bone marrow morphological changes.

The first clue to the diagnosis of MMM is the presence of myelophthisis, also known as leukoerythroblastosis, in the peripheral blood smear (nucleated red blood cells, granulocyte precursors, tear-drop-shaped erythrocytes) (Fig. 3A). Myelophthisis suggests a bone marrow infiltrative process, and the differential diagnosis includes bone marrow fibrosis, metastatic cancer, granulomatous infection, and lymphoproliferative disorders. A bone marrow examination is critical in providing information that helps in distinguishing among the different causes of both myelophthisis and bone marrow fibrosis (Table 1). In MMM, peripheral blood myelophthisis is.

Figure 2. Pathogenesis of bone marrow fibrosis in myelofibrosis with myeloid metaplasia.

Figure 3. Peripheral blood myelophthisis (A), bone marrow fibrosis (B & C), and osteosclerosis/sinusoidal hematopoiesis (D) in myelofibrosis with myeloid metaplasia. Reproduced with permission [2].
associated with bone marrow megakaryocytic hyperplasia, collagen fibrosis, osteosclerosis, and intramedullary sinusoidal hematopoiesis (Fig. 3).

An experienced hematopathologist is key for the accurate diagnosis of MMM. However, it is the responsibility of the primary physician to provide the pertinent clinical information to the pathologist, as well as independently consider alternative diagnoses. In this regard, it is underscored that both CML and myelodysplastic syndrome (MDS) may mimic MMM in their presentation. Therefore, bone marrow examination in MMM should be accompanied by cytogenetic studies as well as peripheral blood fluorescent in situ hybridization for the \textit{bcr-abl} fusion gene in order to rule out the possibility of CML.

The distinction between MMM and MDS with myelofibrosis (MDS-\textit{f}) can sometimes be problematic and may require in-depth morphological and cytogenetic scrutiny. Clonal cytogenetic abnormalities occur in approximately 50% of patients with MMM and include 13q-, 20q-, 8, 9, and abnormalities of chromosomes 1, 7, and 12 [20]. Although some of these abnormalities are also found in MDS, some (13q-, abnormalities of chromosome 1) are relatively specific to MMM, while others (5q-) are rarely seen in MMM and their presence suggests MDS-\textit{f} instead.

Diagnostic accuracy also requires the recognition of cellular-phase MMM as well as the entity “acute myelofibrosis.”

In the former, the degree of bone marrow fibrosis may be minimal but intense bone marrow megakaryocytic hyperplasia, splenomegaly, myelophthisis, and elevated serum lactate dehydrogenase are often present. Acute myelofibrosis often behaves like acute leukemia and is characterized by the presence of constitutional symptoms, nonpalpable spleen, and increased circulating blasts. Some, but not all, cases of acute myelofibrosis are classified as acute megakaryocytic leukemia. The operational classification in this instance depends on whether one can demonstrate enough bone marrow or peripheral blood blast concentration to warrant designation as acute leukemia. To be subclassified as acute megakaryocytic leukemia, these blasts must express megakaryocyte-specific surface markers (CD61/CD41).

**PROGNOSIS**

Overall median survival in MMM is approximately 5 years but it varies substantially among patients based on the presence or absence of well-defined prognostic determinants [21]. The most important indicators of adverse prognosis are the presence of anemia (hemoglobin <10 g/dl), advanced age (>64 years), hypercatabolic symptoms (weight loss, profound fatigue, night sweats, low-grade fever), leukocytosis (>30,000/µl) or leukopenia (<4,000/µl), circulating blasts (≥1%), and high-risk cytogenetic abnormalities (+8, 12p-) [20-22]. Accordingly, patients might be categorized into a low-risk (absence of any poor prognostic factor or the presence of advanced age only), a high-risk (presence of two or more adverse features not including age), and an intermediate-risk (not classified as either a low- or high-risk) disease group. Median survival may exceed 10 years in low-risk disease but may be less than 2 years in high-risk disease.

**TREATMENT**

At present, only allogeneic hematopoietic stem cell transplantation (HSCT) offers a potentially curative treatment in MMM [23]. Both autologous HSCT and drug therapy are palliative and may not prolong survival. The same is true regarding splenectomy and radiation therapy in MMM. However, the majority of patients with MMM are of advanced age and therefore not good candidates for allogeneic HSCT, and such patients rely on palliative therapy to improve quality of life. There is substantial activity in regards to experimental therapy and some of the drugs being tested are already showing some promise.

**Hematopoietic Stem Cell Transplantation**

Current information does not allow definitive comments regarding the role of allogeneic HSCT in MMM. In a retrospective, multicenter study of 66 consecutive

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**Table 1. Causes of bone marrow fibrosis**

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patients, neutrophil engraftment was documented in 84% of the patients by day 30. Engraftment was faster in splenectomized patients and delayed in the presence of pretransplant anemia (hemoglobin <10 g/dl) and osteosclerosis [24]. Age was the major determinant of transplant outcome; 5-year survival was 62% in patients younger than 45 years of age and 14% in those that were older. Other investigators have reported better survival figures in patients older than 44 years [25], and preliminary data suggest that transplant-related morbidity (TRM) in older patients may be positively influenced by the use of reduced-intensity conditioning regimens [26]. The risk of TRM is further decreased with the use of autologous HSCT, which has been shown to alleviate anemia and splenomegaly in the majority of patients in the absence of leukemic transformation [27].

At present, it is reasonable to consider allogeneic HSCT (related or unrelated) in high-risk patients who are younger than age 45 years. In the older age group with high-risk disease, it is reasonable to consider alternative transplant options including reduced-intensity allogeneic and autologous HSCT. In contrast, the risk of any type of HSCT may not be justified for good-risk patients. In all other instances, the decision regarding transplantation should be individualized with input from both the disease and procedure specialists.

Drug Treatment

Conventional drug therapy for anemia includes a combination of an androgen preparation (fluoxymesterone [halotestin] 10 mg bid and prednisone [0.5 mg/kg/day]) [28], exogenous erythropoietin (Epo) administration (40,000 units weekly s.c. injections) in the presence of an endogenous Epo level of less than 100 mU/ml [29], and danazol (200-800 mg/day) [30]. In addition, cytoreductive treatment to control splenomegaly may be combined with Epo administration in hopes of offsetting drug-induced anemia. Hydroxyurea is the drug of choice for controlling splenomegaly, leukocytosis, or thrombocytosis [31]. Other drugs that have been used in a similar setting include busulfan [32], melphalan [33], and 2-chlorodeoxyadenosine [34]. In contrast, alfa interferon has limited therapeutic value in MMM [35].

Surgical Treatment

Splenectomy in MMM is indicated in the presence of drug-refractory mechanical discomfort, portal hypertension, severe hypercatabolic symptoms, and heavy red blood cell transfusion requirements (Fig. 4). Operative mortality is approximately 9%, and 25% of patients may experience post-splenectomy thrombocytosis and progressive hepatomegaly. The majority of splenectomized patients derive benefit in terms of quality of life (decreased discomfort, weight gain, improved stamina), and approximately 25% might achieve durable remissions from their anemia (Fig. 4) [36]. Portal-systemic shunt surgery may be performed in conjunction with splenectomy for the treatment of symptomatic portal hypertension [37].

Radiation Treatment

Sclenic irradiation (100-500 cGy in 5-10 fractions) may be considered as an alternative treatment to splenectomy in poor surgical candidates [38]. However, the benefit (reduction of spleen size) of splenic irradiation is transient (median response duration is 6 months), and the procedure may be associated with more than 10% mortality rate resulting from treatment-associated cytopenias. In contrast, low-dose irradiation is effective for the treatment of paraspinal/epidural EMH (1,000 cGy in 5-10 fractions) as well as EMH resulting in pleural and peritoneal effusions (100-500 cGy in 5-10 fractions) [39, 40].

Symptomatic pulmonary hypertension that is not secondary to a thromboembolic process has been associated with MMM and is believed to arise from diffuse pulmonary EMH [41]. Diagnosis is confirmed by a technetium-99m sulphur colloid scintigraphy, which shows diffuse pulmonary uptake, and treatment with single-fraction (100 cGy) whole-lung irradiation has been shown to be effective [42].

Investigational Treatment

In the past decade, our group at the Mayo Clinic has been engaged in several exploratory treatment trials in MMM. The drugs that were shown to be ineffective include imatinib (inhibits PDGF receptor-associated tyrosine kinase activity) [43], alpha interferon (nonspecific

Figure 4. In a retrospective study of 223 splenectomies performed in patients with myelofibrosis with myeloid metaplasia, the average spleen weight was 2.7 kilograms (range, 380 grams to 7.7 kilograms).
myelosuppressive agent) [35], anagrelide (interferes with terminal differentiation of megakaryocytes and platelet production) [44], pirfenidone (impairs fibroblast proliferation and collagen synthesis) [45], and suramin (inhibits TGF-β binding on fibroblasts) [46]. The drugs that showed promise of activity include thalidomide (has antiangiogenic activity and also inhibits tumor necrosis factor [TNF]-α production) [47] and etanercept (a soluble TNF-α receptor) [48]. Thalidomide treatment at an average dose of 200 mg/day resulted in clinically relevant improvement of anemia (20%), splenomegaly (23%), and thrombocytopenia (71%) [47]. However, approximately 20% of patients experienced a myeloproliferative reaction consisting of thrombocytosis and leukocytosis [49]. The use of low-dose thalidomide (50 mg/day) in combination with a tapering dose of prednisone (0.5 mg/kg/day) has been associated with both a higher rate of response in anemia (62%) and a better toxicity profile [50]. Treatment with etanercept was most useful in alleviation of constitutional symptoms [48]. The mechanism of action of these two drugs is currently unknown. However, the lack of drug-induced reversal in bone marrow microvessel density suggests a mechanism of action that is independent of angiogenesis but possibly related to changes in TNF-α activity.

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