

Myelofibrosis with Myeloid Metaplasia

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Introduction

Myelofibrosis with myeloid metaplasia (MMM) represents both agnogenic myeloid metaplasia (AMM) and the fibrotic stages of polycythemia vera (PV) and essential thrombocythemia (ET). The latter two conditions are also referred to as post polycythemic myelofibrosis (PPM) and post thrombocythemic myelofibrosis (PTM). MMM is currently classified under the broad category of chronic myeloid disorders (CMD). Classification of the CMDs is based on certain molecular, cytogenetic, morphologic, and clinical characteristics⁽¹⁾. In the context of a CMD, the demonstration of the *bcr/abl* genetic translocation between chromosomes 9 and 22 mandates a diagnosis of chronic myelocytic leukemia (CML). The *bcr/abl*-negative group may be divided into two major subgroups; the myelodysplastic syndromes (MDS) and the chronic myeloproliferative disorders (CMPD). MMM is classified under the latter group along with PV and ET.

Pathogenesis

In MMM, the monoclonality of the residing hematopoietic cells and the polyclonality of the neighboring fibroblasts has been well established⁽²⁾. Accordingly, the bone marrow fibrosis is a reactive process that may result from both kinetic and synthetic stimulation of fibroblasts by cytokines derived from clonal megakaryocytes and/or histiocytes^(3,4). The particular cytokines that have been implicated in the process include transforming growth factor-beta (TGF-beta), platelet derived growth factor (PDGF), and basic fibroblast growth factor (bFGF)⁽⁵⁻⁷⁾. These observations are further supported by the recent demonstration of an AMM-like syndrome in mice that were chronically exposed to high levels of thrombopoietin (TPO)^(8,9). It is currently believed that this process may be mediated by a cytokine excess (TGF-beta) that is associated with a TPO-induced expansion of megakaryocyte mass⁽¹⁰⁾.

Diagnosis

The peripheral blood smear provides the first clue to the diagnosis of MMM. The characteristic feature of myelophthisis includes the presence of teardrop-shaped red blood cells, nucleated erythrocytes, and granulocyte precursors (myelocytes, metamyelocytes, and blasts). However, a myelophthisic blood picture may also result from bone marrow infiltration by metastatic cancer or infectious granulomata. The bone marrow biopsy is required for establishing the diagnosis. However, several other causes of bone marrow fibrosis should be considered before the diagnosis of MMM is confirmed (**Table 1**).

Clinical Aspects

MMM is the least frequent among the CMPD; its incidence is estimated to be 1.3/100,000/year in Olmstead County, Minnesota⁽¹¹⁾. The median age at presentation is 60 years with a male to female ratio of 1.2:1. Approximately 5 and 17 percent of the patients are diagnosed before the age of 40 and 50 years, respectively⁽¹²⁾. Most patients present with anemia and marked splenomegaly. The marked splenomegaly in MMM is usually associated with early satiety and hypercatabolic symptoms including severe fatigue, low-grade fever, night sweats, and weight loss. Occasionally, a severe left upper quadrant pain may result from splenic infarction.

The major cause of hepatosplenomegaly in MMM is extramedullary hematopoiesis (EMH)⁽¹³⁾. Hepatomegaly is often associated with markedly elevated levels of alkaline phosphatase, a fraction of which comes from the bone as a result of associated osteosclerosis. EMH may involve many other organs including lymph nodes (lymphadenopathy), the peritoneum (ascites), pleura (pleural effusion), paraspinal and epidural spaces (cord compression), urinary bladder (dysuria), intestinal tract (polyps), the pulmonary parenchyma (respiratory distress), the pericardium (tamponade), and the brain (tumor).

Portal hypertension in AMM may develop as a result of either massive splenomegaly (increased splanchnic blood flow) or intrahepatic obstruction (presinusoidal EMH, portal fibrosis, thrombotic obliteration of small portal veins)⁽¹⁴⁾.

Table 1. Causes of bone marrow fibrosis.

Myeloid disorders

- Chronic myeloproliferative diseases
- Myelodysplastic syndrome
- Acute myelofibrosis
- Acute myeloid leukemia
- Mast cell disease
- Malignant histiocytosis

Lymphoid disorders

- Lymphomas
- Hairy cell leukemia
- Multiple myeloma

Non-hematologic disorders

- Metastatic cancer
- Connective tissue disease
- Infections
- Vitamin D-deficiency rickets
- Renal osteodystrophy
- Gray platelet syndrome

Regardless of the cause, portal hypertension may lead to variceal bleeding and ascites. Osteosclerosis that accompanies the bone marrow fibrosis in AMM may cause severe bone and joint pain that is difficult to treat.

Prognosis

Reported median survival times in MMM vary substantially with average figures between 3 to 5 years⁽¹⁵⁻¹⁷⁾. According to a recent study, risk factors for decreased survival were advanced age (> 60 years), hepatomegaly, weight loss, anemia (hemoglobin < 10 gm/dL), leukocytosis (white count > 30,000/ μ L), leukopenia (white count < 4,000/ μ L), circulating blasts \geq 2%, male sex, thrombocytopenia (platelet count < 150,000/ μ L) and abnormal karyotype⁽¹⁵⁾. In contrast, splenomegaly and the degree of bone marrow fibrosis did not affect survival. Accordingly, a scoring system was applied and identified a low-risk group (hemoglobin \geq 10 gm/dL and a white count between 4 and 30,000/ μ L) with a median survival of 8 years. In contrast, the anemic patients with leukocytosis or leukopenia had a median survival of only one year. Patients with either anemia or leukocytosis/leukopenia had an intermediate median survival of approximately 2 years. The general findings in this particular study are consistent with those reported by others⁽¹⁶⁻¹⁸⁾.

Treatment

At present, only allogeneic hematopoietic stem cell transplantation (HSCT) has a "curative" potential in MMM. Earlier studies had raised some concern regarding successful engraftment of stem cells in a fibrotic marrow. However, more recent studies have demonstrated the lack of an adverse effect on stem cell engraftment of bone marrow fibrosis⁽¹⁹⁾ and the curative potential of allogeneic HSCT in both AMM⁽²⁰⁾ and PPMM/PTMM⁽²¹⁾. A recent collaborative study of 55 patients with AMM that underwent allogeneic HSCT reported an engraftment rate of 91% and a 5-year survival rate of 47%⁽²²⁾. However, the substantial risk of mortality and morbidity associated with the procedure limits its use to poor risk patients⁽¹⁵⁾.

The combination of an androgen preparation (fluoxymesterone, Halotestin, 10 mg orally twice a day) and a corticosteroid (prednisone 30 mg orally) improves anemia in approximately 25% of the patients. After 1 month of therapy, treatment with fluoxymesterone is continued in responding patients and the corticosteroid is tapered. All patients treated with androgens should have periodic monitoring of liver function tests and male patients should be screened for prostate cancer (digital rectal examination and measurement of PSA) before initiating therapy. Similarly, some patients with anemia may respond to danazol therapy (200-800 mg/day). In our experience, treatment with EPO has not been successful in alleviating anemia associated with MMM⁽²³⁾.

Hydroxyurea (starting dose 500 mg PO BID) may result in reduction of spleen size and control of thrombocytosis and leukocytosis in some patients. Unfortunately, anemia may get worse on HU therapy and thrombocytopenia

may develop. When HU fails to control splenomegaly associated complications (mechanical discomfort, hypercatabolic symptoms, portal hypertension), surgical removal of the spleen is considered. At experienced centers, the mortality rate with the procedure should be less than 10%. Postsurgical complications include intra-abdominal bleeding, subphrenic abscess, sepsis, large vessel thrombosis, extreme thrombocytosis, and accelerated hepatomegaly. Laboratory evidence of disseminated intravascular coagulation, before splenectomy, may increase the risk of perioperative bleeding, and it is recommended that the operation be postponed until the abnormalities correct.

After splenectomy, almost all patients experience improvement in hypercatabolic symptoms and portal hypertension. In addition, approximately one-third of the patients with refractory anemia may benefit from splenectomy. The thrombocytosis and hepatomegaly that develop following splenectomy may transiently be controlled with HU (starting dosage 500 mg orally 3 times a day) or 2-chlorodeoxyadenosine (2-hour intravenous administration of 0.14 mg/kg/day x 5 days)⁽²⁴⁾.

In poor surgical candidates, the alternative to splenectomy is splenic irradiation (200 to 300 cGy delivered in 10-15 daily fractions), which usually provides a transient (3 to 6 months) benefit⁽²⁵⁾. Radiation therapy is most useful in the management of extramedullary hematopoiesis⁽²⁶⁾.

Current investigational therapeutic approaches in MMM include allogeneic HSCT, autologous HSCT, and the use of a variety of anti-fibrotic and anti-angiogenic drugs. Preliminary results from some of these treatment trials will be available within the next year.

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