All About Myelofibrosis

What is myelofibrosis (MF)?

Myelofibrosis is a group of rare cancers of the bone marrow in which the marrow is replaced by scar tissue and is not able to make healthy blood cells. It is classified as a type of chronic leukemia and belongs to a group of blood disorders called myeloproliferative diseases. It may also be called primary myelofibrosis, chronic idiopathic myelofibrosis or myelosclerosis with myeloid metaplasia.

A myeloproliferative disorder is a disease in which the bone marrow produces either too many or too few of certain blood cells, most of which do not function properly (each disorder's name comes from the cells that are affected). Other diseases including chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET), chronic neutrophilic leukemia and chronic eosinophilic leukemia are related closely to MF. PV and ET can progress to myelofibrosis and account for 10-15% of myelofibrosis cases. Myelofibrosis can also progress to other, more aggressive, types of leukemia. The disease can have a variable prognosis with some patients living decades while others progress to much more aggressive forms.

What is bone marrow?

In order to understand myelofibrosis, it is helpful to understand how normal bone marrow functions. The bone marrow is a spongy area in the center of our bones. Its role is to produce blood cells.

- White blood cells (also called leukocytes) are the body's infection fighting cells.
- Red blood cells (also called erythrocytes) give blood its red color, but more importantly, carry oxygen from the lungs to the rest of the body and return carbon dioxide to the lungs as waste.
- Platelets (also called thrombocytes) help the body form blood clots to control bleeding.

Larger bones have more bone marrow, and therefore produce more blood cells. The larger bones include the femur (top part of the leg or thigh), the hip bones, and parts of the rib cage. The bone marrow contains hematopoietic stem cells (or blood stem cells), which are cells that can produce one type of blood cell over and over again. It also contains a small percentage of cells that are in development and are not yet mature. These immature cells are called blasts. Once the cell has matured, it moves out of the bone marrow and into the circulating blood. The body has mechanisms to know when more cells are needed and has the ability to produce them in an orderly fashion.

In the case of myelofibrosis, one blood stem cell acquires the ability to reproduce without regulation, producing large numbers of immature blood cells. When looked at under a microscope, these abnormally produced cells look different than the healthy cells and do not function properly. The body continues to produce these abnormal, non-functional cells, leaving little space for healthy cells. At the same time, these cells release chemicals that cause the bone marrow to become "fibrous" or fill with scar tissue, further interfering with the ability to produce healthy blood cells. In addition, these abnormal cells may be produced in other areas of the body, most often the spleen or liver, which results in an enlarged spleen or liver that can be felt by the healthcare provider.

What causes myelofibrosis and am I at risk?

Myelofibrosis is a rare diagnosis, though the exact incidence is not known. It is likely underestimated as less severe and/or asymptomatic disease may go undetected. However, estimates suggest the annual incidence in the United States population is 1.5 cases per 100,000 persons in the United States.

Aging is the major risk factor for developing myelofibrosis, as the disorder usually develops in people over age 50, with the
average age at the time of diagnosis being about 60 years old. About 15% of all patients diagnosed with myelofibrosis are under the age of 50 and about 6% under 40.

Environmental exposures to certain chemicals (benzene, toluene) and radiation may increase the risk of developing MF. Many cases of MF occur as a result of a genetic mutation in the bone marrow. The genes most frequently associated with MF are Janus kinase 2 gene (JAK2) and calreticulin gene (CALR). For some patients, the abnormality is found in the MPL gene, which is also involved in the pathway that signals for more blood cells to be produced. There may be other mutations associated with the development of MF. The underlying cause of the gene mutation is not known.

Myelofibrosis primarily develops without a known cause (called primary myelofibrosis); however, other myeloproliferative diseases can progress into myelofibrosis. Ten to fifteen percent of myelofibrosis cases have developed from a diagnosis of polycythemia vera or essential thrombocythemia (called secondary myelofibrosis). Though some families have a predisposition for the disease, it is not passed on or inherited. The disease is caused by a change in a gene that occurs during a person's lifetime. Perhaps this change is due to exposure to something in our environment (which family members may have in common).

**What screening tests are used for myelofibrosis?**

There is no known intervention to prevent myelofibrosis. Additionally, there is no screening test for the disease. However, routine blood work can be used as a screen to check the red and white blood cell counts as well as the platelet count. These tests can prompt further, more invasive testing, such as a bone marrow biopsy.

**What are the signs of myelofibrosis?**

About one third of individuals with myelofibrosis have no symptoms, which can make the disease difficult to detect. As the number of abnormal cells increase and healthy cells decrease, symptoms tend to develop, most often related to a low red blood cell count (anemia) or enlarged spleen. Anemia commonly presents as paleness, generalized fatigue, and shortness of breath during activity. Approximately 50-70% of patients report fatigue at the time of diagnosis. People may also develop chest pain or dizziness as the heart has to work harder to get adequate oxygen to the brain and other organs when the red blood cell count is low. A minority of patients report "constitutional symptoms", which include weight loss, low-grade fever, and night sweats. Many patients will also experience intense itching, known as pruritis, caused by inflammation in the body.

Severe anemia, easy bruising or bleeding, and multiple infections can result because of the lack of healthy blood cells. An enlarged spleen (splenomegaly) and/or liver (hepatomegaly) may also occur. When the bone marrow scars, the liver and spleen try to make blood cells to compensate (called extramedullary hematopoiesis), causing these organs to swell. Approximately 25-50% of patients will have symptoms from an enlarged spleen at diagnosis, including pain with deep breaths, loss of appetite and feeling full after eating a small amount (called early satiety). Extramedullary hematopoiesis can also occur in other parts of the body (lymph nodes, spinal cord, lungs), causing swelling in these areas, leading to symptoms.

**How is myelofibrosis diagnosed?**

The diagnosis of MF is based on the results of a number of different tests:

**Complete Blood Count (CBC):** CBC is the most common blood test. It uses a machine to evaluate the number of red blood cells, platelets, and white blood cells circulating in the blood. The amount of hemoglobin, the substance which carries oxygen in red blood cells, is also assessed on a CBC. A low red blood cell count is known as anemia, which is common in this disease. Additionally, the platelet counts and white blood cells counts can either be elevated or low.

**Peripheral Blood Smear:** A small sample of blood can be smeared on a slide and examined under a microscope to count cells by hand as well as examine them for defects.

The body's normal response to anemia is to form new blood cells. Because this occurs poorly in myelofibrosis, immature blood cells are seen in the circulating blood. This is known as leukoerythroblastosis. Red blood cells frequently appear abnormal in myelofibrosis on a peripheral smear with unusual shapes and sizes, reflecting defective production of the red blood cells.
Defects in the appearance of the platelets and white blood cells can also be seen on a peripheral smear. Similar to red blood cells, immature platelets and white blood cells may be seen on a blood smear.

**Bone Marrow Biopsy:** A bone marrow biopsy is required for the diagnosis of myelofibrosis. Generally, this involves local anesthetic being injected into the buttock region and a small core of bone marrow taken out using a needle. A bone marrow aspiration, which is less invasive, is frequently unsuccessful because of the scarring. The scarring will cause the aspiration to be "dry", with no cells present.

In myelofibrosis, the bone marrow biopsy typically finds fibrosis, or scarring, of the marrow. Hyperplasia, which is an increase in the precursor cells (the cells that develop into mature red & white blood cells and platelets), is nearly always seen. This increase in precursor cells can be in one or multiple cell lines. For example an increase in the number of megakaryocytes, which will go on to form platelets in the blood, is known as megakaryocyte hyperplasia. These megakaryocytes may also appear abnormal under the microscope. Increased (thrombocytosis) or decreased (thrombocytopenia) platelets can be seen in the peripheral blood of individuals as well.

**Molecular Testing:** Testing for gene mutations including JAK2, CALR and MPL are also essential in the diagnosis of MF.

The World Health Organization (WHO) has developed the following criteria for the diagnosis of myelofibrosis. A patient must meet all 3 major criteria as well as 1 minor criteria for a diagnosis of primary myelofibrosis.

**Major Criteria**

- Proliferation and atypia of megakaryocytes accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 on a scale of 0-3
- Not meeting WHO criteria for ET, PV, BCR-ABL1 positive chronic myelogenous leukemia, myelodysplastic syndromes, or other myeloid neoplasm
- Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker or absence of reactive myelofibrosis

**Minor Criteria**

- Anemia not attributed to a comorbid condition
- Leukocytosis $\geq 11 \times 10^9/L$
- Palpable splenomegaly
- LDH increased to above upper normal limit of institutional reference range
- Leukoerythroblastosis

**What are the treatments for MF?**

Because there are very few curative options for myelofibrosis, most therapies are aimed at minimizing symptoms. Many patients do not meet criteria for aggressive therapies, and treatment is focused on palliation. The primary goal of palliative therapy is limiting the symptoms associated with the decreased blood counts, improving quality of life, and decreasing the risk of progression to acute leukemia. Generally speaking, patients that are not candidates for stem cell transplant (see below) and do not have symptoms are not treated until symptoms develop. Selecting the appropriate treatment for a patient is very important and a number of studies have demonstrated ways to determine which treatment is appropriate for a given person.

**Targeted Therapies**

The discovery of JAK2 mutations in 2005 opened the door to development of a targeted therapy for people with myelofibrosis. Ruxolitinib is currently the only medication with FDA approval specifically for the treatment of MF. Other medications in this class are currently being studied in clinical trials.

Other medications called immunomodulators, including lenalidomide and thalidomide, are also used in the treatment of symptomatic myelofibrosis.

Interferon is an immune therapy that works by reducing the overabundance of unhealthy blood cells and reduces the cytokines...
that lead to fibrosis in the marrow. It appears to work best in those with early myelofibrosis secondary to PV or ET. Interferon has significant side effects that can be difficult to tolerate.

**Stem Cell Transplant**
Currently, the only curative treatment is allogeneic stem cell transplant (where the bone marrow comes from a donor). Stem cell transplants have risks related to complications. For this reason, they are generally reserved for people in good health, who are younger than 60 and have a "matched" donor. Current guidelines recommend stem cell transplant only in young patients with high risk disease.

**Supportive Care**
Given that most people present with MF at an older age and that MF is a chronic disease, supportive care is extremely important to limit symptoms and maintain a high quality of life. Supportive care treatments include the following:

- **Androgen therapy** (oxymetholone, danazol), a synthetic version of male hormones can be used to improve anemia.
- **Erythropoietin** is a medication that stimulates the body to make red blood cells and has been shown to improve anemia in 30-50% of patients.
- **Hydroxyurea**: is a medication that is thought to interfere with the synthesis of DNA and is used in the treatment of other blood disorders. It has been shown to decrease the size of the spleen and help control platelet and WBC counts.
- **Cladribine**: is a medication that may be able to prevent cells from reproducing by inhibiting DNA synthesis.
- **Splenectomy**: Because the enlarged spleen can be a source of discomfort, its removal can alleviate symptoms. Surgical removal is associated with risks as the spleen has an important role in infection fighting. Indications for splenectomy in patients who continue to have splenomegaly despite drug therapy include thrombocytopenia, frequent red cell transfusions and symptomatic portal hypertension. One study of splenectomy in 314 patients with myelofibrosis found that 75% benefited from the procedure with resolution of severe thrombocytopenia and becoming transfusion-independent. In this study, the benefit lasted for a median of 1 year. If surgical removal of the spleen is not possible, a short course of radiation therapy to the spleen can be given to transiently improve symptoms.

**Clinical Trials**
Clinical trials are extremely important in furthering our knowledge of this disease. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your healthcare provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

**Follow Up Care and Survivorship**
Because of the complexity of treating and monitoring MF, patients with MF will see their healthcare providers for physical examination and lab testing on a frequent basis (sometimes monthly). Your healthcare team will monitor your blood counts and symptoms for signs of progression as well as the need for supportive care treatment interventions.

Fear of recurrence, relationship challenges, the financial impact of cancer treatment, employment issues and coping strategies are common emotional and practical issues experienced by MF survivors. Your healthcare team can identify resources for support and management of these practical and emotional challenges faced during and after cancer.

Cancer survivorship is a relatively new focus of oncology care. With some 15 million cancer survivors in the US alone, there is a need to help patients transition from active treatment to survivorship. What happens next, how do you get back to normal, what should you know and do to live healthy going forward? A survivorship care plan can be a first step in educating yourself about navigating life after cancer and helping you communicate knowledgeably with your healthcare providers. Create a survivorship care plan today on OncoLink.

**Resources for more information**
MPN Research Foundation
Started by patients, an advocacy organization that promotes research funding in pursuit of new treatments – and eventually a cure – for myeloproliferative neoplasms (MPNs)

http://www.mpnresearchfoundation.org/Primary-Myelofibrosis

MPN Education Foundation

Run by volunteer MF patients, offers MPN-Net online support group with approximately 3000 members from around the world

http://www.myelofibrosis.org/

Leukemia and Lymphoma Society

Provides disease information and support resources.

http://www.lls.org/

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