BMJ Best Practice

Myelofibrosis

Straight to the point of care

Last updated: Apr 16, 2025

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Summary

Myelofibrosis is a reactive and reversible process common to many malignant and benign bone marrow disorders. It can present de novo as primary myelofibrosis (PMF), or as secondary (reactive) myelofibrosis if caused by another disorder, drug treatment, or toxic agent.

PMF (the focus of this topic) is a chronic progressive myeloproliferative neoplasm (MPN). Median survival is approximately 5 years, which is much shorter than that for other MPNs (polycythemia vera, essential thrombocythemia).

Bone marrow fibrosis, extramedullary hematopoiesis, leukoerythroblastosis, and splenomegaly are hallmarks of PMF.

Observation is appropriate for patients with asymptomatic, low-risk disease without hyperuricemia or a remedial cause for anemia.

Treatment with Janus kinase inhibitors (JAK) and hematopoietic stem cell transplant (along with supportive care) should be considered for patients with symptomatic and/or high-risk disease. Allogeneic hematopoietic stem cell transplant is the only treatment with curative potential.

Death is usually due to bone marrow failure (hemorrhage, anemia, or infection), transformation to acute leukemia, portal or pulmonary hypertension, heart failure, cachexia, or severe myeloid metaplasia with organ damage.

Definition

Myelofibrosis is a reactive and reversible process common to many malignant and benign bone marrow disorders. It is characterized by bone marrow fibrosis with increased reticulin deposits and in some cases increased collagen deposits. Depending on the underlying cause, patients may have abnormalities in blood production and associated extramedullary hematopoiesis.[1]

Myelofibrosis can present de novo as PMF, a chronic progressive MPN with its origin in a multipotent hematopoietic progenitor cell. The etiology of PMF is unknown, but it is commonly associated with somatic driver mutations in the Janus kinase 2 (JAK2), calreticulin (CALR), or myeloproliferative leukemia virus oncogene (MPL) genes. A specific clonal marker has not been identified.

Fibrosis in the bone marrow due to another disorder, drug treatment, or toxic agent is called secondary or reactive myelofibrosis.

This topic focuses on the diagnosis and management of primary myelofibrosis.

Epidemiology

In the US, incidence of primary myelofibrosis (PMF) is reported to be 0.44 per 100,000 person-years (data from 2002 to 2016).[4] In the UK, annual incidence of PMF is estimated to be 0.6 per 100,000, with an estimated 380 people newly diagnosed each year (data from 2010 to 2019).[5] In Europe, incidence is reported to be between 0.1 and 1 per 100,000 persons per year.[6]

PMF occurs more commonly in males (male to female rate ratio approximately 1.8 in the US, and 1.6 in the UK).[4] [5] Incidence in the US is reported to be highest among white people.[4] PMF more commonly affects older people (approximately 66% of patients in the US are age ≥65 years at diagnosis), but younger people may develop the disease.[4] Median age at diagnosis is 70 years in the US, and 73 years in the UK.[4] [5]

Etiology

The cause of primary myelofibrosis (PMF) is unknown, and a specific clonal marker has not been identified. Environmental and genetic factors may be involved in the development of PMF. However, there are no specific common risk factors identified in most patients with PMF.

Environmental factors

A high incidence of PMF has been reported in patients exposed to thorium dioxide-based radiographic contrast medium (used in x-ray diagnostics in the 1930s to 1950s), and in survivors of the Hiroshima atomic bomb.[7] [8] PMF was observed at 15 to 20 times the expected incidence rate in Hiroshima survivors (on average 6 years after the incident).[8]

Benzene, toluene, and many other aromatic solvents have been associated with hematologic malignancies, including PMF.[9]

Genetic factors

Chromosomal abnormalities with prognostic significance are present in 35% to 50% of patients with PMF.[10] These include cytogenetic abnormalities involving chromosomes 13 (del.13q), 20 (del.20q), +8 (trisomy 8), 1, 5 (-5/del5q), 7 (-7/del7q), +9 (trisomy 9), 12 (del12p), and 17.[10] Sole +9, del.13q, del.20q, and normal cytogenetics have the most favorable prognosis; sole +8, 5, 7, 12, 17, and complex mutations have a distinctly poorer prognosis.[10] [11] [12] [13]

Somatic driver mutations in the Janus kinase 2 (JAK2), myeloproliferative leukemia virus oncogene (MPL), or calreticulin (CALR) genes are commonly present in patients with PMF and other myeloproliferative neoplasms (MPNs, e.g., polycythemia vera, essential thrombocythemia).[14] [15] MPN driver mutation expression is not mutually exclusive, but patients typically only have one driver mutation that is clonally dominant. There may be a familial or germline predilection for acquiring MPN driver mutations, but this is subject to investigation.[16] [17]

The V617F mutation in the JAK2 gene (located on chromosome 9p) has been identified in approximately 58% of patients with PMF.[14] [15] The JAK2 V617F mutation causes an increase in production of normal leukocytes and platelets in many patients with PMF, but in some patients hematopoiesis is depressed.

Mutations in the MPL gene (on chromosome 1p) have been identified in approximately 8% of patients with PMF.[14] [15] The W515L/K/A mutations are the most frequently reported MPL mutations in PMF.[10] [18] MPL mutations can cause abnormal blood cells to grow and proliferate uncontrollably.

Patients with PMF with an MPL mutation have lower hemoglobin levels, higher platelet counts, and reduced bone marrow cellularity compared with their JAK2 V617F-positive counterparts. However, survival does not differ considerably between those with MPL mutations and those with JAK2 mutations.

Mutations in the CALR gene (on chromosome 19) have been identified in approximately 25% of patients with PMF.[15] Mutations in CALR are associated with improved overall survival compared with JAK2 V617F or MPL W515 mutations.[19] Type 1 CALR mutations (52-bp deletion) are more common, and have a more favorable impact on prognosis, than type 2 CALR mutations (5-bp insertion) in PMF.[20] [21]

The CALR gene encodes a multifunctional protein involved in protein folding and calcium homeostasis.[15] [22] Mutated CALR serves as a chaperone to the thrombopoietin receptor MPL, causing its activation.[23] CALR mutations (insertions or deletions) occur in exon 9 and cause a one base pair frameshift.

Approximately 10% of patients with PMF are negative for JAK2, CALR, and MPL mutations (i.e., triple negative); therefore, absence of these MPN driver mutations does not exclude the diagnosis.[24] Some triple-negative patients may have uncommon MPL mutations.[25] Triple-negative mutation status is associated with a worse prognosis in patients with PMF.[19] [26]

Potentially disease-modifying non-driver gene mutations are found in patients with PMF, including ASXL1, EZH2, SRSF2, TP53, IDH1, IDH2, and U2AF1. These are considered high-molecular-risk mutations, associated with shorter overall and leukemia-free survival.[26] [27]

Pathophysiology

Primary myelofibrosis (PMF) is a clonal hematopoietic stem cell disorder with its origin in a multipotent hematopoietic progenitor cell.[28] PMF is characterized by hyperplasia of morphologically abnormal megakaryocytes in the bone marrow in association with bone marrow fibrosis, osteosclerosis, marrow angiogenesis, extramedullary hematopoiesis, splenomegaly, and leukoerythroblastosis.

Bone marrow fibrosis in PMF is considered to be a secondary, reactive process.[29] The malignant clone stimulates marrow fibroblasts to proliferate and deposit reticulin and collagen fibers in the bone marrow.[28] [29][30] Condensation of interstitial reticulin fibers results in the formation of thick, continuous, and wavy bundles of reticulin fibers in the bone marrow. Sinusoidal basement membrane collagen fibers become continuous, leading to sinusoidal dilation and obliteration with an associated capillary neovascularization.

Megakaryocytic hyperplasia, dysplasia, and clustering are characteristic features of PMF. These cells release fibrogenic cytokines (e.g., platelet-derived growth factor and transforming growth factors) that promote marrow fibroblast proliferation and inhibit collagenase.[29] Transforming growth factors (e.g., TGF-beta) promote the synthesis of osteoprotegerin, which impairs osteoclast proliferation and promotes osteosclerosis. Increased levels of thrombopoietin in PMF also play a role in promoting bone marrow fibrosis.[31] [32]

Although bone marrow fibrosis is a key diagnostic feature of PMF, it is the malignant hematopoietic stem cell clone that impairs hematopoiesis and subsequently causes anemia, extramedullary hematopoiesis, and splenomegaly. Splenomegaly also contributes to anemia due to red cell sequestration and hemodilution. Folate deficiency (due to increased folate consumption from chronic myeloproliferation) may contribute to anemia.

Increased marrow angiogenesis is seen frequently in PMF. This is caused by abnormal angiogenic cytokine production (from dysfunctional megakaryocytes), marrow sinusoidal dilation, and intravascular

hematopoiesis.[28] Increased angiogenesis appears to be an early feature of PMF and correlates better with increased marrow cellularity than with marrow fibrosis.[33]

Classification

The 5th edition of the World Health Organization (WHO) classification of hematolymphoid tumors and International Consensus Classification (ICC) of primary myelofibrosis[2][3]

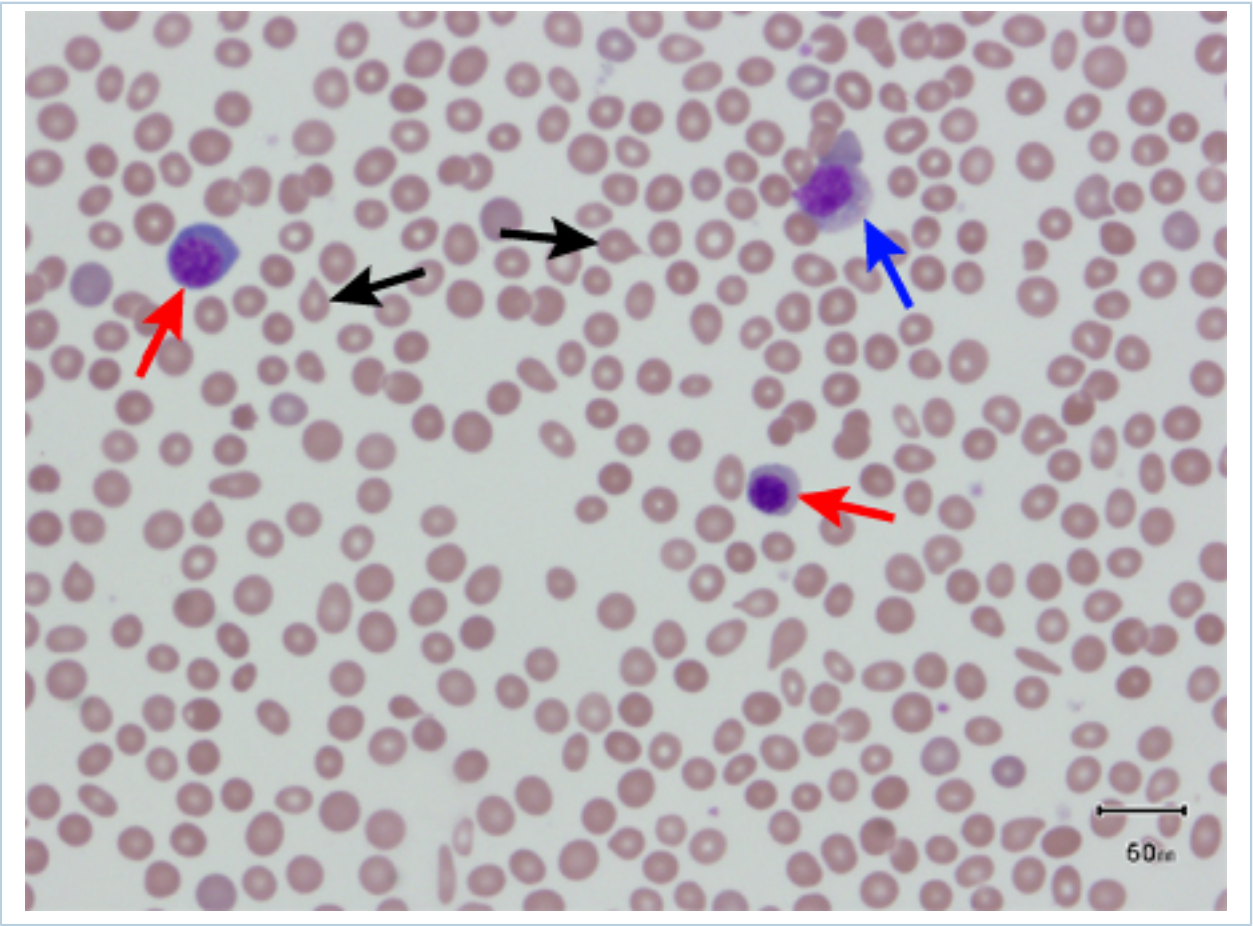
Primary myelofibrosis (PMF) is divided into the following two subclassifications (under the main classification of myeloproliferative neoplasms):

- Prefibrotic/early stage PMF (pre-PMF)
- Overt fibrotic stage PMF

Case history

Case history #1

A 67-year-old man, with a long-standing history of smoking (>100 pack-years), coronary artery disease, chronic renal insufficiency, hypertension, and chronic obstructive pulmonary disease, in his routine follow-up appointment is found to have a hematocrit of 19%. He had a hematocrit of 36% the previous year. He reports fatigue, night sweats, 4.5 kg (10 lb) weight loss, abdominal discomfort, and progressive dyspnea on exertion. He denies fever, chest pain, or upper or lower gastrointestinal bleeding. On exam, he is cachectic but not in acute distress. His conjunctivae are pale. He has mild-to-moderate hearing loss. There is no lymphadenopathy. Chest exam reveals distant heart sounds with bilateral expiratory wheezes. Cardiac exam reveals no murmurs. Abdominal exam reveals a moderately enlarged spleen without hepatomegaly. There is no peripheral edema or clubbing. Complete blood count shows a white blood cell count of 6240/microliter with an absolute neutrophil count of 2200/microliter, an absolute lymphocyte count of 2400/microliter, and 360 monocytes/microliter; a hemoglobin of 6 g/dL with a mean corpuscular volume of 86; and a platelet count of 96 × 10^3/microliter and a reticulocyte count of 0.6%, with an absolute reticulocyte count of 14.1 × 10^3/microliter. Peripheral blood smear shows occasional teardrop-shaped red blood cells, and erythroblasts and myelocytes.



Peripheral blood smear showing teardrop red blood cells (black arrows), 2 nucleated red blood cells (red arrows), and a myelocyte (blue arrow)
From the collection of A. Emadi and J.L. Spivak; used with permission

Lactate dehydrogenase is 245 U/L. Iron studies, serum B12, and red blood cell folate levels, as well as a serum and urine protein electrophoresis, are within normal limits. Computed tomographic scans of the chest, abdomen, and pelvis reveal moderate mediastinal lymphadenopathy and splenomegaly. Upper gastrointestinal endoscopy and colonoscopy are normal. A bone marrow aspirate is a "dry tap." Bone marrow biopsy reveals an entirely fibrotic marrow with a few scattered plasma cells, lymphocytes, and maturing myeloid cells. Megakaryocytes are scattered and sometimes clustered and atypical with large hyperchromic nuclei. Hemoglobin staining reveals a few erythrocyte precursors. A CD34 stain reveals no increase in blasts. Mutation testing is positive for MPL, but negative for JAK2 V617F and calreticulin (CALR).

Other presentations

Autoimmune phenomena (e.g., autoimmune thrombocytopenia) are characteristic of primary myelofibrosis.

Approach

The diagnosis of primary myelofibrosis (PMF) is one of exclusion because of the lack of a specific diagnostic marker. Once a diagnosis of PMF is made, it is important to carry out risk assessment to inform prognosis and to guide management.

History and physical exam

A careful history and physical exam should be performed to identify signs and symptoms associated with PMF, and to identify a reactive cause or another disorder that may suggest secondary myelofibrosis (e.g., polycythemia vera [PV], essential thrombocythemia [ET], systemic mastocytosis, acute leukemia, hairy cell leukemia, hyperparathyroidism, systemic lupus, drug treatment, or toxic agent).

Ruling out secondary myelofibrosis is essential because prognosis and management of other causes/conditions associated with myelofibrosis (e.g., post-PV and post-ET myelofibrosis) will differ.[34]

At diagnosis, PMF patients commonly present with signs and symptoms associated with anemia (e.g., fatigue, weakness, dyspnea, palpitations), and constitutional symptoms associated with a hypercatabolic state (e.g., weight loss, night sweats, low-grade fever, cachexia, fatigue, pruritus). Up to 30% of patients may be asymptomatic at diagnosis.[35]

Patients should be examined for splenomegaly, hepatomegaly, extramedullary hematopoiesis, portal hypertension, bleeding, bone and joint changes, and immune dysfunction.

- Splenomegaly: a hallmark of PMF and present in virtually every patient with PMF at diagnosis. If absent, other causes of the clinical abnormalities should be considered. The degree of splenomegaly varies but is frequently substantial. Because the rate of splenic enlargement is variable, spleen size cannot be used as an indication of disease duration.[36] Splenomegaly may result in early satiety, generalized abdominal discomfort, and left upper quadrant discomfort. Splenic infarcts, perisplenitis, or subcapsular hematoma may cause severe left upper quadrant or left shoulder pain.
- Hepatomegaly: present in 40% to 70% of patients at diagnosis.[37]
- Extramedullary hematopoiesis: a hallmark of PMF. Depending on the organ or site of involvement, it results in hemorrhage (gastrointestinal tract hemorrhage, cutaneous petechiae, hemoptysis, hematuria), spinal cord compression, focal seizures, symptoms related to increased intracranial pressure, ascites, pericardial or pleural effusion, pulmonary hypertension, and respiratory failure.
- Portal hypertension: can present without signs and symptoms, or manifest as ascites, esophageal and gastric varices, gastrointestinal bleeding, hepatic encephalopathy, and hepatic or portal vein thrombosis.
- Platelet dysfunction, acquired factor V deficiency, thrombocytopenia, and disseminated intravascular coagulation: may occur, contributing to bleeding.
- Joint and bone pain, symptoms of osteosclerosis, or gout: may be reported.
- Otosclerosis can cause hearing loss.
- Infections (most commonly pneumonia): may result from deficiencies in humoral immunity.

Initial investigations

A complete blood count (CBC) with differential, and peripheral blood smear, are the first tests to order. Bone marrow aspiration and biopsy are required to establish a diagnosis if history, exam, and initial blood tests suggest PMF.

CBC

A CBC is essential in patients thought to have PMF. Because of its origin in a multipotent hematopoietic progenitor cell, PMF affects all blood cell types but not in a predictable manner.

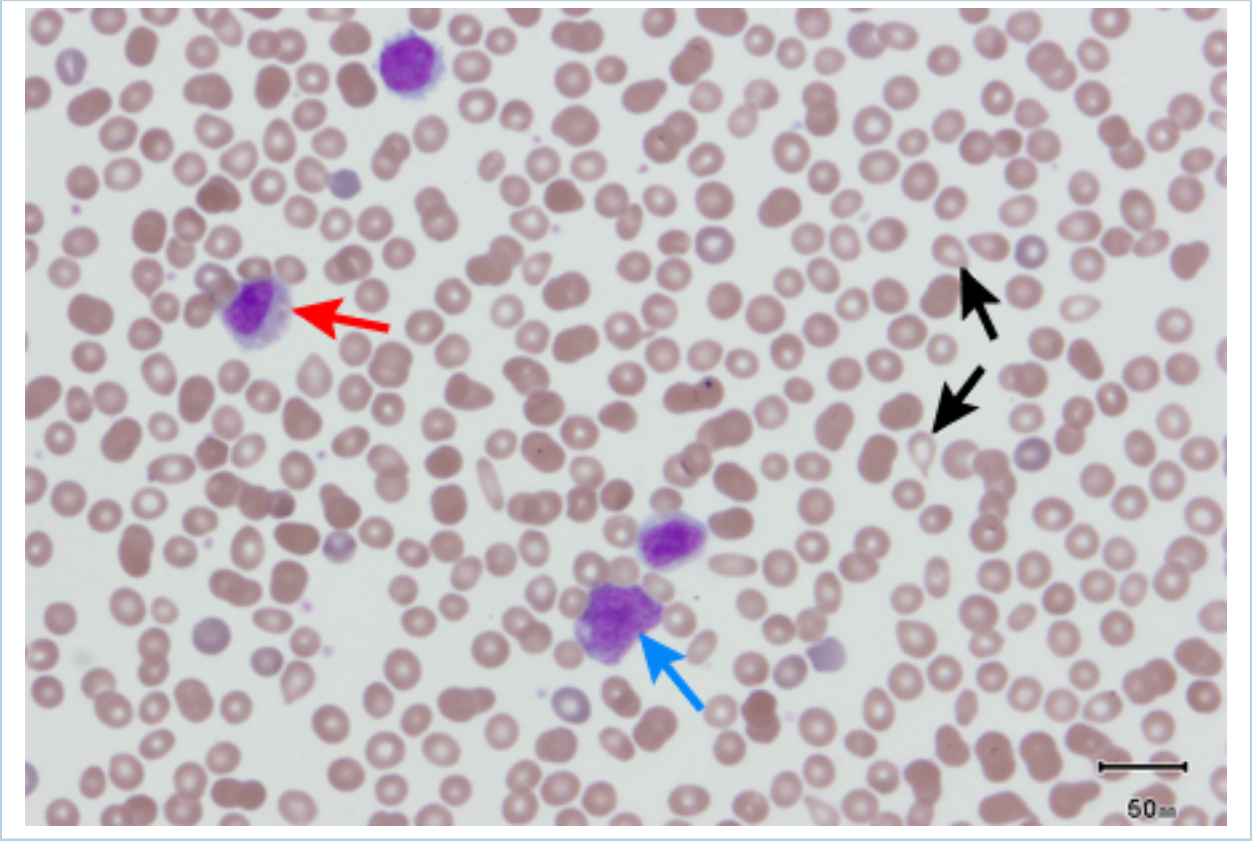
Anemia, usually mild, is present in most patients with PMF, with >60% having a hemoglobin concentration <10 g/dL. A normal hemoglobin or hematocrit in the presence of substantial splenomegaly should lead to immediate consideration of PV because the expanded plasma volume associated with splenomegaly can mask a substantial increase in the red blood cell (RBC) mass.

Leukocyte and platelet counts can be low, normal, or high without reference to spleen size.

The presence of blood count abnormalities should prompt a careful exam of a peripheral blood smear.

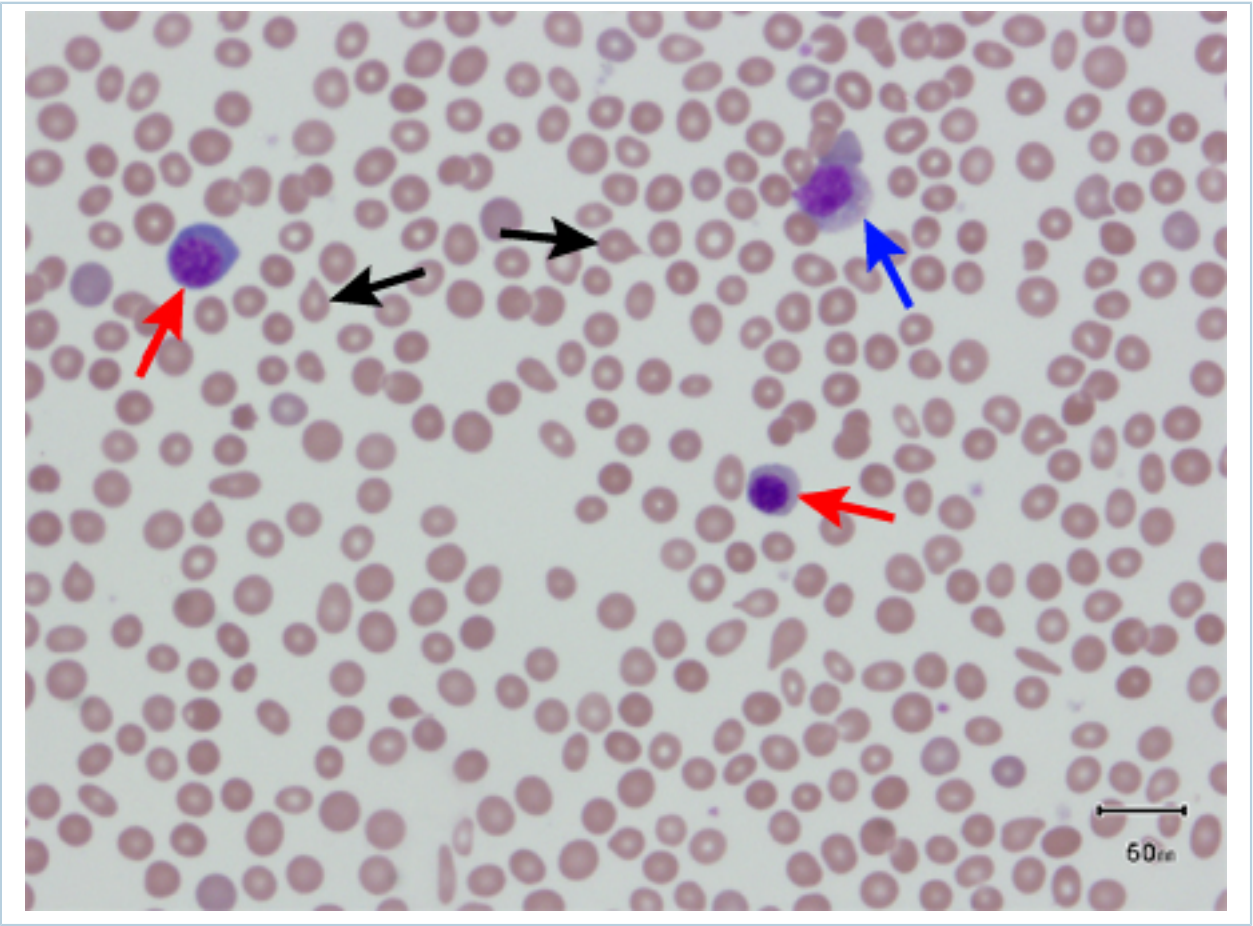
Peripheral blood smear

In patients with PMF, peripheral blood smear will usually show immature white cells (metamyelocytes, myelocytes, promyelocytes, myeloblasts), nucleated RBCs, and teardrop-shaped RBCs, as a result of extramedullary hematopoiesis. This leukoerythroblastic reaction is not specific for PMF, but it is a hallmark of PMF and its absence should challenge the clinical impression.



Peripheral blood smear showing leukoerythroblastic reaction: teardrop red blood cells (black arrows), myelocyte (red arrow), and promyelocyte (blue arrow)

From the collection of A. Emadi and J.L. Spivak; used with permission

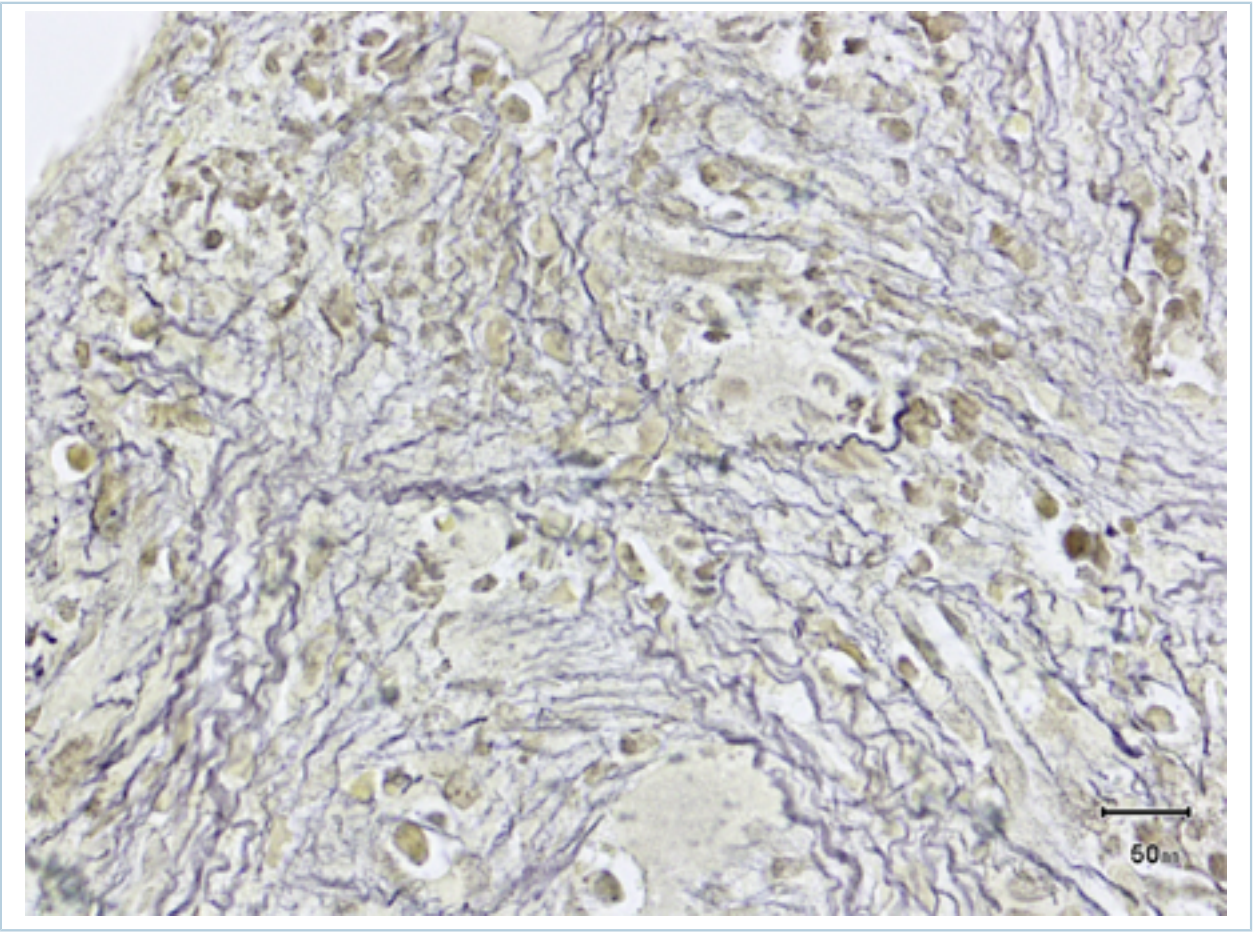


Peripheral blood smear showing teardrop red blood cells (black arrows), 2 nucleated red blood cells (red arrows), and a myelocyte (blue arrow)
From the collection of A. Emadi and J.L. Spivak; used with permission

Bone marrow aspiration and biopsy

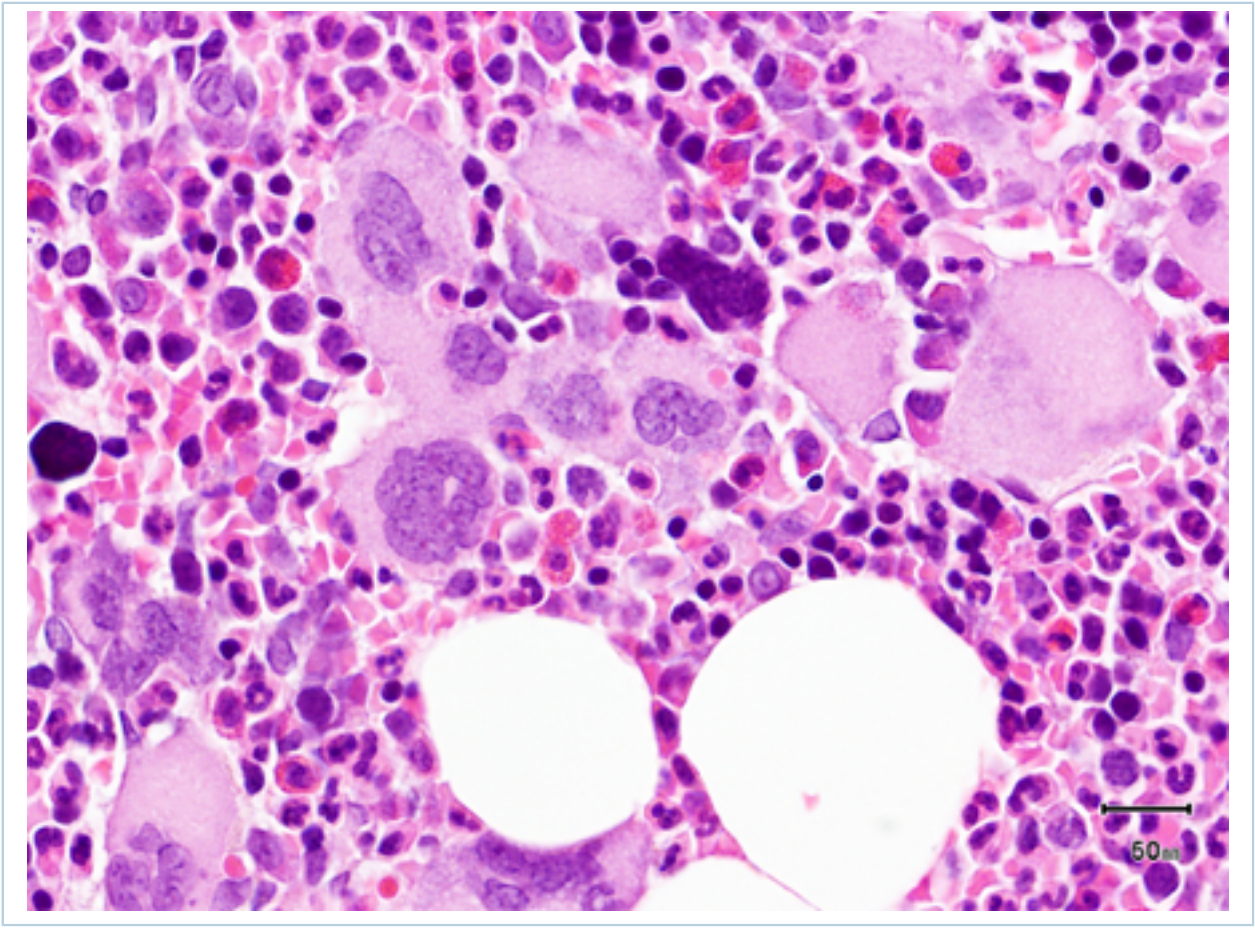
Essential for establishing a diagnosis. Bone marrow fibrosis is a hallmark of PMF. Its presence is mandated for the diagnosis of the overt fibrotic stage of PMF.[38] See Criteria .

Aspiration (with a properly placed biopsy needle) usually results in a "dry tap" in patients with PMF. Biopsy will typically reveal marrow fibrosis (reticulin fibrosis) and megakaryocytic proliferation and atypia. Bone marrow cellularity may be increased, decreased, or hypoplastic.



Bone marrow biopsy showing increased reticulin deposition

From the collection of A. Emadi and J.L. Spivak; used with permission



Trephine bone marrow biopsy showing megakaryocytic hyperplasia and clustering

From the collection of A. Emadi and J.L. Spivak; used with permission

Bone marrow fibrosis alone is not sufficient to diagnose PMF because it can occur in other myeloproliferative neoplasms (MPNs, e.g., PV, ET, and chronic myeloid leukemia) and other hematologic disorders (e.g., systemic mastocytosis, hairy cell leukemia, myelodysplasia, primary marrow lymphoma, and acute leukemia). Distinguishing between PV/ET and early "prefibrotic" PMF may be difficult based on histologic findings, but accurate diagnosis is essential to optimize management.[33]

Confirming the diagnosis, assessing risk and prognosis

Additional tests (e.g., genetic mutation testing, cytogenetic analysis, imaging) may be required to:[26][39]

- exclude other disorders that can cause myelofibrosis
- confirm the diagnosis, and
- inform risk assessment and prognosis.

Cytogenetic and molecular testing

Fluorescence in situ hybridization (FISH) or multiplex reverse transcriptase PCR for BCR::ABL1 is required to exclude the diagnosis of chronic myeloid leukemia.

Somatic driver mutation analysis

All patients with suspected PMF should undergo molecular testing for the JAK2 V617F mutation initially. If negative, testing for MPL and CALR mutations should follow.[26] [39] Alternatively, a next-

generation sequencing panel comprising all three MPN driver mutations can be used, which also provides quantitative assessment of driver mutation allele burden.

Presence of JAK2 V617F, MPL, or CALR mutation indicates an MPN, but these driver mutations are not specific for PMF. Incidence of JAK2 V617F, MPL, and CALR mutation in PMF patients is reported to be approximately 58%, 8%, and 25%, respectively.[14] [15]

Approximately 10% of PMF patients are negative for JAK2, CALR, and MPL mutations (i.e., triple negative); therefore, absence of these MPN driver mutations does not exclude the diagnosis.[24] Some triple-negative patients may have uncommon MPL mutations.[25]

Although MPN driver mutations are not mutually exclusive, patients typically only have one driver mutation that is clonally dominant.

Testing for non-driver genetic mutations (e.g., ASXL1, EZH2, SRSF2, U2AF1 Q157, IDH1/2, SF3B1, TET2) should be carried out for prognostication and risk stratification following diagnosis.[24]

Bone marrow cytogenetic analysis

Chromosomal abnormalities, e.g., involving chromosomes 13 (del.13q), 20 (del.20q), +8 (trisomy 8), 1, 5 (-5/del5q), 7 (-7/del7q), +9 (trisomy 9), 12 (del12p), and 17 are commonly reported in patients with PMF.[12]

Chromosomal abnormalities are not diagnostic for PMF, but their identification can facilitate risk stratification and prognostication. Sole +9 (trisomy 9), 13 (del.13q), 20 (del.20q), and normal cytogenetics have the most favorable prognosis; sole +8 (trisomy 8), 5 (-5/del5q), 7 (-7/del7q), 12 (del12p), 17 (i(17q)), and complex mutations have a distinctly poorer prognosis.[10] [11] [12] [13]

Imaging

Imaging studies (ultrasound, radionuclide, computed tomography [CT], magnetic resonance imaging [MRI], echocardiogram) may be helpful in uncovering extramedullary hematopoiesis. MRI can readily identify spinal extramedullary hematopoiesis, and a technetium 99 (Tc 99m sulfur colloid) scan can uncover pulmonary extramedullary hematopoiesis. Echocardiogram can evaluate the presence of pulmonary hypertension, a manifestation of extramedullary hematopoiesis. Imaging studies should not routinely be used unless extramedullary hematopoiesis is suspected and the site needs to be identified for treatment.

Uric acid level

Hyperuricemia is a consequence of increased cell turnover and can cause kidney stones or gout, particularly with cytoreductive therapy. Serum uric acid levels may be >7 mg/dL in men and >6 mg/dL in women in cases of hyperuricemia.

Autoimmune phenomena

Autoimmune phenomena are characteristic of PMF.

Testing for autoreactivity can be carried out if clinically indicated (e.g., joint complaints, evidence of hemolysis, or unexplained thrombocytopenia). Results may reveal circulating immune complexes; complement activation; elevated antinuclear antibody, elevated rheumatoid factor titers; and/or a positive Coombs test in the absence of an overt connective tissue disorder.

History and exam

Key diagnostic factors

history of radiation exposure (common)

- A high incidence of primary myelofibrosis (PMF) has been reported in patients exposed to thorium dioxide-based radiographic contrast medium (used in x-ray diagnostics in the 1930s to 1950s), and in survivors of the Hiroshima atomic bomb.[7] [8]
- PMF was observed at 15 to 20 times the expected incidence rate in Hiroshima survivors (on average 6 years after the incident).[8]

history of industrial solvents exposure (common)

- Benzene, toluene, and many other aromatic solvents have been associated with hematologic malignancies, including primary myelofibrosis.[9]

symptoms of anemia (fatigue, weakness, dyspnea, palpitations) (common)

- In patients with primary myelofibrosis (PMF), the malignant hematopoietic stem cell clone impairs hematopoiesis and subsequently causes anemia, extramedullary hematopoiesis, and splenomegaly.
- Splenomegaly also contributes to anemia due to red cell sequestration and hemodilution.
- Increased folate consumption from chronic myeloproliferation may lead to folate deficiency, which may contribute to anemia.

constitutional symptoms (weight loss, night sweats, low-grade fever, cachexia, fatigue, and pruritus) (common)

- High cell turnover rate in primary myelofibrosis results in a hypercatabolic state that manifests as constitutional symptoms.

splenomegaly ± hepatomegaly (common)

- In patients with primary myelofibrosis (PMF), the malignant hematopoietic stem cell clone impairs hematopoiesis and subsequently causes anemia, extramedullary hematopoiesis, and splenomegaly.
- Splenomegaly is a hallmark of PMF and is present in virtually every patient with PMF at diagnosis. If absent, other causes of the clinical abnormalities should be considered. The degree of splenomegaly varies but is frequently substantial. Because the rate of splenic enlargement is variable, spleen size cannot be used as an indication of disease duration.[36]
- Splenomegaly may result in early satiety, generalized abdominal discomfort, and left upper quadrant discomfort. Splenic infarcts, perisplenitis, or subcapsular hematoma may cause severe left upper quadrant or left shoulder pain.
- Hepatomegaly may be present, invariably of a lesser extent than the splenomegaly (e.g., in 40% to 70% of patients).[37]

features of extramedullary hematopoiesis (uncommon)

- In patients with primary myelofibrosis (PMF), the malignant hematopoietic stem cell clone impairs hematopoiesis and subsequently causes anemia, extramedullary hematopoiesis, and splenomegaly.
- Extramedullary hematopoiesis is a hallmark of PMF.
- Depending on the organ or site of involvement, extramedullary hematopoiesis may result in hemorrhage (gastrointestinal tract hemorrhage, cutaneous petechiae, hemoptysis, hematuria), spinal cord compression, focal seizures, symptoms related to increased intracranial pressure, ascites, pericardial or pleural effusion, pulmonary hypertension, and respiratory failure.

Other diagnostic factors

features of portal hypertension (uncommon)

- May occur as a result of markedly increased splenoportal blood flow and decreased hepatic vascular compliance.
- Portal hypertension can present without signs and symptoms, or manifest as ascites, esophageal and gastric varices, gastrointestinal bleeding, hepatic encephalopathy, and hepatic or portal vein thrombosis.

joint and bone pain (uncommon)

- Manifestation of osteosclerosis or gout.

hearing loss (uncommon)

- Due to otosclerosis. An interesting but often nonelicited symptom.

bleeding (uncommon)

- Bleeding can occur due to extramedullary hematopoiesis and portal hypertension, and varies in severity from insignificant cutaneous petechiae to severe, life-threatening gastrointestinal bleeding. Platelet dysfunction, acquired factor V deficiency, thrombocytopenia, and disseminated intravascular coagulation may occur, contributing to bleeding.

infections (uncommon)

- Caused by deficiencies in humoral immunity. Pneumonia is the most common infection.

Risk factors

Strong

radiation exposure

- High incidence of primary myelofibrosis (PMF) has been reported in patients exposed to thorium dioxide-based radiographic contrast medium (used in x-ray diagnostics in the 1930s to 1950s), and in survivors of the Hiroshima atomic bomb.[7] [8]
- PMF was observed at 15 to 20 times the expected incidence rate in Hiroshima survivors (on average 6 years after the incident).[8]

industrial solvents exposure

- Benzene, toluene, and many other aromatic solvents have been associated with hematologic malignancies, including primary myelofibrosis.[9]

Weak

age ≥65 years

- Primary myelofibrosis more commonly affects older people (approximately 66% of patients in the US are age ≥65 years at diagnosis), but younger people may develop the disease.[4]
- Median age at diagnosis is 70 years in the US, and 73 years in the UK.[4] [5]

cytogenetic abnormalities

- Somatic driver mutations in the Janus kinase 2 (JAK2), myeloproliferative leukemia virus oncogene (MPL), or calreticulin (CALR) genes are commonly present in patients with primary myelofibrosis (PMF) and other myeloproliferative neoplasms (MPNs, e.g., polycythemia vera, essential thrombocythemia).[14] [15]
- The V617F mutation in the JAK2 gene (located on chromosome 9p) has been identified in approximately 58% of patients with PMF.[14] [15]
- Mutations in the MPL gene (on chromosome 1p) have been identified in approximately 8% of patients with PMF.[14] [15]
- Mutations in the CALR gene (on chromosome 19) have been identified in approximately 25% of patients with PMF.[15]
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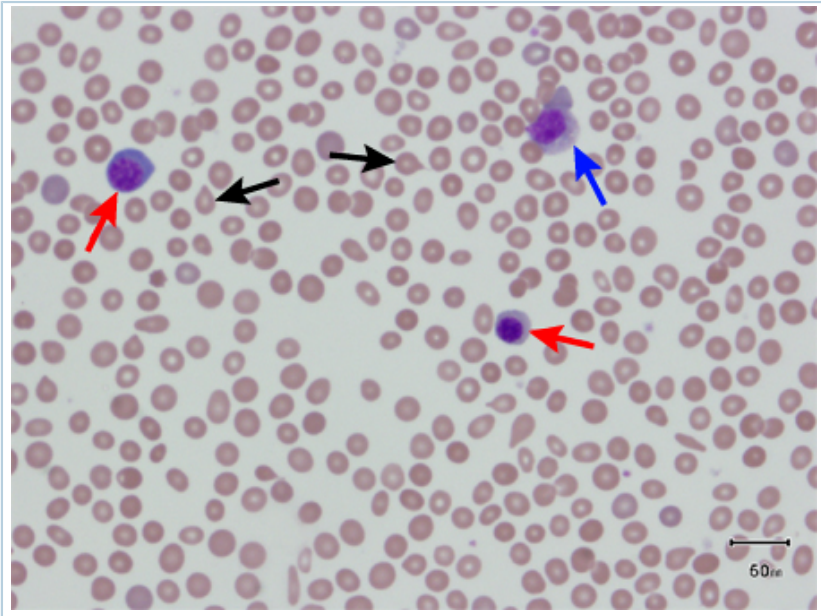
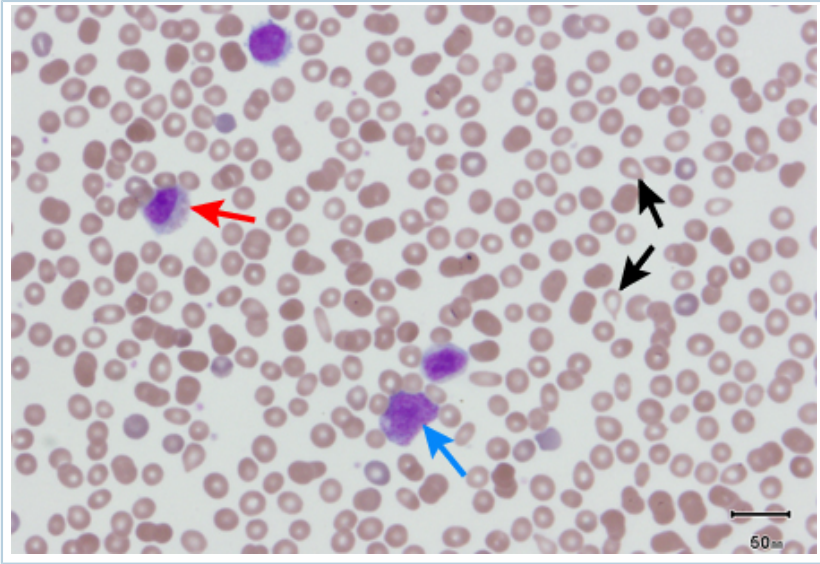
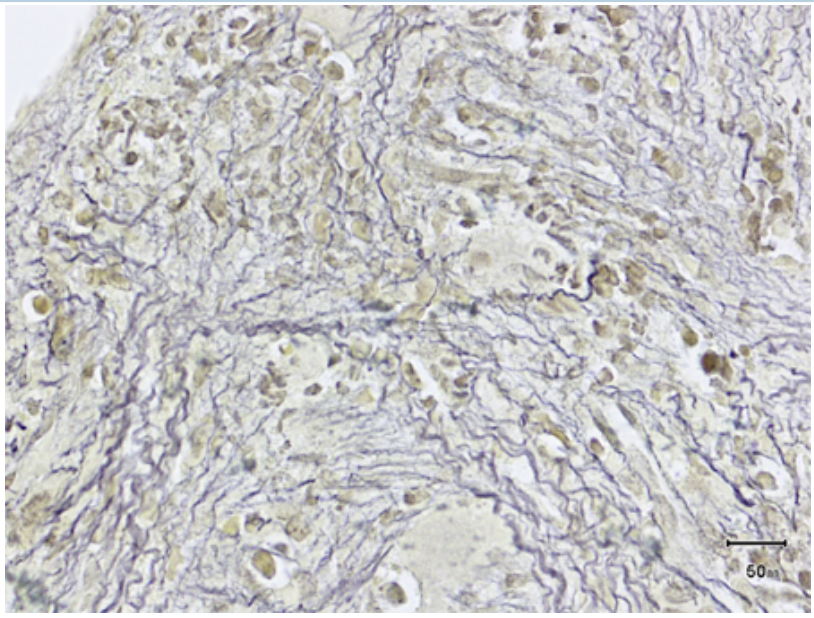
Tests

1st test to order

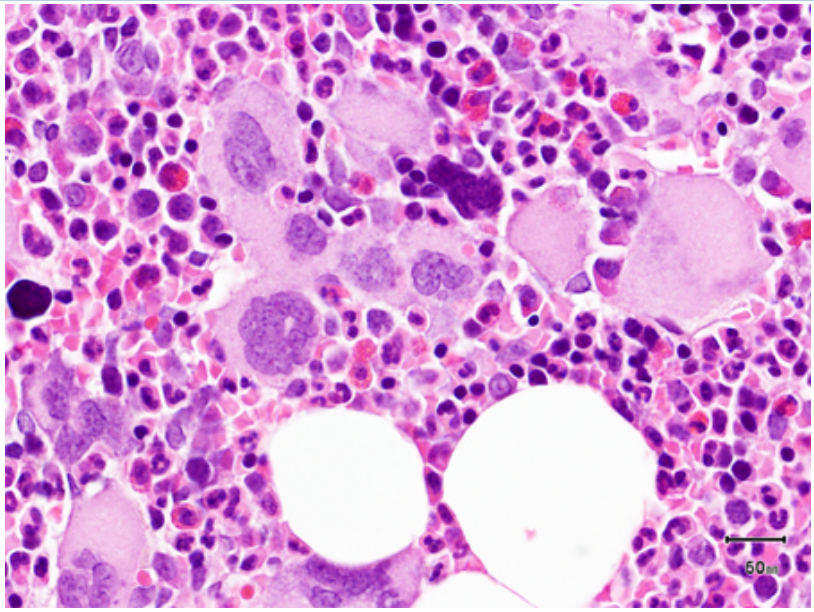
Test	Result
CBC with differential • A first test to order if primary myelofibrosis (PMF) is suspected. • The presence of blood count abnormalities should prompt a careful exam of peripheral blood smear. • Because of its origin in a multipotent hematopoietic progenitor cell, PMF affects all blood cell types but not in a predictable manner. • Anemia, usually mild, is present in most patients with PMF, with >60% having a hemoglobin concentration <10 g/dL. • Leukocyte and platelet counts can be low, normal, or high without reference to spleen size. Thrombocytosis is more common than thrombocytopenia. Disseminated intravascular coagulation is observed in 15% of patients and can manifest as thrombocytopenia, decreased clotting factors, and increased fibrin degradation products.	**anemia; leukocyte and platelet count normal or abnormal**
peripheral blood smear • A first test to order if primary myelofibrosis (PMF) is suspected. • In patients with PMF, peripheral blood smear will usually show immature white cells (metamyelocytes, myelocytes, promyelocytes, myeloblasts), nucleated red blood cells (RBCs), and teardrop-shaped RBCs, as a result of extramedullary hematopoiesis. This leukoerythroblastic reaction is not specific for PMF, but it is a hallmark of PMF and its absence should challenge the clinical impression.  *Peripheral blood smear showing teardrop red blood cells (black arrows), 2 nucleated red blood cells (red arrows), and a myelocyte (blue arrow)* *From the collection of A. Emadi and J.L. Spivak; used with permission*	**presence of metamyelocytes, myelocytes, promyelocytes, myeloblasts; nucleated RBCs; and teardrop-shaped RBCs in the circulation**

Test	Result
 *Peripheral blood smear showing leukoerythroblastic reaction: teardrop red blood cells (black arrows), myelocyte (red arrow), and promyelocyte (blue arrow)* *From the collection of A. Emadi and J.L. Spivak; used with permission*	
bone marrow aspiration • Bone marrow aspiration and biopsy are essential for establishing a diagnosis. • Bone marrow fibrosis is a hallmark of primary myelofibrosis (PMF). Its presence is mandated for the diagnosis of the overt fibrotic stage of PMF.[38] See Criteria . • Bone marrow aspiration (with a properly placed biopsy needle) usually results in a "dry tap" in patients with PMF.	**unable to aspirate marrow ("dry tap")**
bone marrow biopsy • Bone marrow aspiration and biopsy are essential for establishing a diagnosis. • Bone marrow fibrosis is a hallmark of primary myelofibrosis (PMF). Its presence is mandated for the diagnosis of the overt fibrotic stage of PMF.[38] See Criteria . • Biopsy will typically reveal marrow fibrosis (reticulin fibrosis) and megakaryocytic proliferation and atypia. • Bone marrow cellularity may be increased (with trilineage hyperplasia and erythroblastic and megakaryocytic islands), or decreased (with scattered areas of hyperplastic marrow embedded in a collagenous matrix), or hypoplastic (with intense osteomyelosclerosis and residual megakaryocytic islands).	**marrow fibrosis; megakaryocytic proliferation and atypia; increase or decrease bone marrow cellularity**

Test	Result



Bone marrow biopsy showing increased reticulin deposition
From the collection of A. Emadi and J.L. Spivak; used with permission



Trephine bone marrow biopsy showing megakaryocytic hyperplasia and clustering
From the collection of A. Emadi and J.L. Spivak; used with permission

- Bone marrow fibrosis alone is not sufficient to diagnose PMF because it can occur in other myeloproliferative neoplasms (e.g., polycythemia vera, essential thrombocythemia, chronic myeloid leukemia) and other hematologic disorders (e.g., systemic mastocytosis, hairy cell leukemia, myelodysplasia, primary marrow lymphoma, and acute leukemia). Distinguishing between PV/ET and early "prefibrotic" PMF may be difficult based on histological findings, but accurate diagnosis is essential to optimize management.[33]
- Further cytogenetic and molecular testing is required to exclude other disorders that can cause myelofibrosis.

Test	Result
fluorescence in situ hybridization (FISH) or multiplex reverse transcriptase PCR • For the presence of BCR::ABL1 fusion gene. Required to exclude chronic myeloid leukemia.	**negative for Philadelphia chromosome (BCR::ABL1 fusion gene)**
genetic mutation analysis • All patients with suspected PMF should undergo molecular testing for the JAK2 V617F mutation initially. If negative, testing for CALR and MPL mutations should follow.[26] [39] Alternatively, a next-generation sequencing panel comprising all three MPN driver mutations can be used, which also provides quantitative assessment of driver mutation allele burden. • Presence of JAK2 V617F, MPL, or CALR mutation indicates a myeloproliferative neoplasm (MPN), but these mutations are not specific for primary myelofibrosis (PMF). • Incidence of JAK2 V617F, MPL, or CALR mutation in PMF patients is reported to be approximately 58%, 8%, and 25%, respectively.[14] [15] • Approximately 10% of PMF patients are negative for JAK2, CALR, and MPL mutations (i.e., triple negative); therefore, absence of these MPN driver mutations does not exclude the diagnosis.[24] Some triple-negative patients may have uncommon MPL mutations.[25] • Although MPN driver mutations are not mutually exclusive, patients typically only have one driver mutation that is clonally dominant. • Testing for non-driver mutations (e.g., ASXL1, EZH2, SRSF2, U2AF1 Q157, IDH1/2, SF3B1, TET2) should be carried out for prognostication and risk stratification following diagnosis.[24]	**may be positive for MPN driver mutation (JAK2 V617F, CALR, or MPL) and/or non-driver mutations (e.g., ASXL1, EZH2, SRSF2, U2AF1 Q157, IDH1/2, SF3B1, TET2)**

Other tests to consider

Test	Result
bone marrow cytogenetic analysis • Chromosomal abnormalities, e.g., involving chromosomes 13 (del.13q), 20 (del.20q), +8 (trisomy 8), 1, 5 (-5/del5q), 7 (-7/del7q), +9 (trisomy 9), 12 (del12p), and 17, are reported in approximately 45% of patients with primary myelofibrosis (PMF).[12] • Chromosomal abnormalities are not diagnostic for PMF, but their identification can facilitate risk stratification and prognostication. • Sole +9 (trisomy 9), 13 (del.13q), 20 (del.20q), and normal cytogenetics have the most favorable prognosis; sole +8 (trisomy 8), 5 (-5/del5q), 7 (-7/del7q), 12 (del12p), 17 (i(17q)), and complex mutations have a distinctly poorer prognosis.[10] [11] [12] [13]	**may reveal cytogenetic abnormalities, e.g., involving chromosome 13 (del.13q), 20 (del.20q), +8 (trisomy 8), 1, 5 (-5/del5q), 7 (-7/del7q), +9 (trisomy 9), 12 (del12p), or 17**
echocardiogram • May be helpful in uncovering pulmonary hypertension, a manifestation of extramedullary hematopoiesis. • Imaging studies should not routinely be used unless extramedullary hematopoiesis is suspected and the site needs to be identified for treatment.	**enlarged main pulmonary artery**
ultrasound of suspected site • May be helpful in uncovering extramedullary hematopoiesis. • Imaging studies should not routinely be used unless extramedullary hematopoiesis is suspected and the site needs to be identified for treatment.	**evidence of extramedullary hematopoiesis**
technetium 99 scan • May be helpful in uncovering pulmonary extramedullary hematopoiesis. • Imaging studies should not routinely be used unless extramedullary hematopoiesis is suspected and the site needs to be identified for treatment.	**evidence of extramedullary hematopoiesis**
CT of suspected site • May be helpful in uncovering extramedullary hematopoiesis. • Imaging studies should not routinely be used unless extramedullary hematopoiesis is suspected and the site needs to be identified for treatment.	**evidence of extramedullary hematopoiesis**
MRI of suspected site • May be helpful in uncovering spinal extramedullary hematopoiesis. • Imaging studies should not routinely be used unless extramedullary hematopoiesis is suspected and the site needs to be identified for treatment.	**evidence of extramedullary hematopoiesis**
serum uric acid • Serum uric acid levels may be >7 mg/dL in men and >6 mg/dL in women in cases of hyperuricemia. • Hyperuricemia is a consequence of increased cell turnover and could cause kidney stones or gout, particularly with cytoreductive therapy.	**normal or elevated**

Test	Result
antinuclear antibodies • Autoimmune phenomena are characteristic of primary myelofibrosis (PMF). • Testing for autoreactivity can be carried out if clinically indicated (e.g., joint complaints, evidence of hemolysis, or unexplained thrombocytopenia). • Results may reveal circulating immune complexes; complement activation; elevated antinuclear antibody, elevated rheumatoid factor titers; and/or a positive Coombs test in the absence of an overt connective tissue disorder.	**may be elevated**
rheumatoid factor titer • Autoimmune phenomena are characteristic of primary myelofibrosis (PMF). • Testing for autoreactivity can be carried out if clinically indicated (e.g., joint complaints, evidence of hemolysis, or unexplained thrombocytopenia). • Results may reveal circulating immune complexes; complement activation; elevated antinuclear antibody, elevated rheumatoid factor titers; and/or a positive Coombs test in the absence of an overt connective tissue disorder.	**may be elevated**
complement levels • Autoimmune phenomena are characteristic of primary myelofibrosis (PMF). • Testing for autoreactivity can be carried out if clinically indicated (e.g., joint complaints, evidence of hemolysis, or unexplained thrombocytopenia). • Results may reveal circulating immune complexes; complement activation; elevated antinuclear antibody, elevated rheumatoid factor titers; and/or a positive Coombs test in the absence of an overt connective tissue disorder.	**may reveal complement activation**
Coombs test • Autoimmune phenomena are characteristic of primary myelofibrosis (PMF). • Testing for autoreactivity can be carried out if clinically indicated (e.g., joint complaints, evidence of hemolysis, or unexplained thrombocytopenia). • Results may reveal circulating immune complexes; complement activation; elevated antinuclear antibody, elevated rheumatoid factor titers; and/or a positive Coombs test. • PMF should be suspected with a positive Coombs test in the absence of an overt connective tissue disorder.	**may be positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Polycythemia vera	• Aquagenic pruritus (itching after a shower), plethora.	• Peripheral blood smear: absence of leukoerythroblastosis. • CBC: erythrocytosis; red blood cell mass and plasma volume elevated.
Essential thrombocythemia	• Erythromelalgia, ocular migraine. • Splenomegaly and hepatomegaly less frequent (10% to 20%).[40] [41]	• Peripheral blood smear: absence of leukoerythroblastosis. • CBC: absence of anemia or leukocytosis.
Chronic myeloid leukemia	• May be no differences in signs and symptoms.	• Fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR): positive for Philadelphia chromosome (BCR::ABL1 fusion gene).
Myelodysplastic syndrome (MDS)	• Absence of splenomegaly.	• Bone marrow aspiration and biopsy with flow cytometry and cytogenetic analysis: dysplastic bone marrow with variable degrees of peripheral blood cytopenia (with or without monocytosis) suggests MDS.
Mast cell disease (systemic mastocytosis)	• Dermatographia or skin rash.	• Serum tryptase level: elevated.
Malignant histiocytosis	• May be no differences in signs and symptoms.	• Bone marrow aspirate and biopsy: infiltration by malignant histiocytes.
Acute myeloid leukemia	• Symptoms (constitutional, bleeding, infections) are more acute. Moderate to massive splenomegaly is less common than in primary myelofibrosis.	• Bone marrow aspiration and biopsy: bone marrow hypercellularity and infiltration by blasts; blasts >20%, Auer rods, morphologic description of type of blast. • Immunophenotyping and molecular studies: blasts express surface antigens and molecular markers that help to identify their specific lineage. • Peripheral blood smear: blasts on blood film, presence of Auer rods.

Condition	Differentiating signs / symptoms	Differentiating tests
Acute lymphoblastic leukemia	• Symptoms (constitutional, bleeding, infections) are more acute. Moderate to massive splenomegaly is less common than in primary myelofibrosis.	• Bone marrow aspiration and biopsy: bone marrow hypercellularity and infiltration by lymphoblasts. • Immunophenotyping and molecular studies: blasts express surface antigens and molecular markers that help to identify their specific lineage. • Peripheral blood smear: leukemic lymphoblasts.
Hairy cell leukemia	• May be no differences in signs and symptoms.	• CBC: lymphocytosis and absence of monocytes. • Bone marrow aspiration and biopsy: presence of hairy cells in the bone marrow. • Flow cytometry: reveals a B-cell phenotype lacking CD5 and CD23, while expressing CD103 and cyclin D1. • Immunohistochemical analysis: may reveal BRAF-V600E mutation. • Peripheral blood smear: presence of hairy cells.
Hodgkin lymphoma	• Lymphadenopathy more common in lymphomas.	• Lymph node biopsy: Hodgkin cells within an appropriate background cellular milieu.
Non-Hodgkin lymphoma	• Lymphadenopathy more common in lymphomas.	• Lymph node biopsy: positive for non-Hodgkin lymphoma.
Multiple myeloma	• Symptoms of hyperviscosity and bone pain.	• Serum and urine protein electrophoresis: serum M-protein (IgG or IgA) ≥3 g/dL; urine monoclonal protein ≥500 mg/day; hypogammaglobulinemia. • Serum and urine immunofixation assay: paraprotein band (IgG, IgA, IgM, IgD, or IgE; and kappa or lambda light chain). • Serum free light-chain assay: increased concentration of free light chains. • Bone marrow aspirate and biopsy: monoclonal plasma cell infiltration in the bone marrow ≥10%.

Condition	Differentiating signs / symptoms	Differentiating tests
		• CT scan and skeletal survey: osteolytic lesions and/or pathologic fractures.
Hyperparathyroidism	• May be no differences in signs and symptoms.	• High-normal to elevated calcium; decreased vitamin D; high-normal to elevated parathyroid hormone (PTH).
Renal osteodystrophy	• May be no differences in signs and symptoms.	• BUN, creatinine: elevated. • Radiographic studies: osteopenia.
Vitamin D deficiency	• May be no differences in signs and symptoms.	• Decreased vitamin D levels.
Systemic lupus erythematosus (SLE)	• Skin, joint, and mucosal manifestations of SLE.	• Anti-double-stranded DNA.
HIV infection	• Opportunistic infections.	• Anti-HIV antibody: positive. • CD4 count: decreased CD4 count. • Presence of HIV viral load.
Tuberculosis	• Cough and hemoptysis.	• Positive tuberculin skin testing; abnormal chest x-ray; positive microbiologic tests.
Metastatic cancer in the bone marrow	• May be no differences in signs and symptoms.	• CT scans, bone survey, tumor markers: indicate metastatic spread.

Criteria

Several diagnostic criteria for primary myelofibrosis (PMF) have been proposed.

The 5th edition of the World Health Organization (WHO) classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms[2]

The WHO classification divides PMF into prefibrotic/early stage PMF and overt fibrotic stage PMF, and each has a different diagnostic criteria.

Prefibrotic/early stage PMF requires meeting all of the following major criteria and at least one minor criterion (confirmed in 2 consecutive determinations):

- Major criteria:

1. Presence of megakaryocyte proliferation and atypia, without reticulin fibrosis grades 2 or 3*, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis.
2. Not meeting the WHO criteria for BCR::ABL1# chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), myelodysplastic syndromes (MDS), or other myeloid neoplasms.
3. Presence of JAK2, CALR, or MPL mutation; or in the absence of these mutations, presence of another clonal marker (e.g., ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) or absence of minor (grade 1) reactive bone marrow reticulin fibrosis (e.g., secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic [chronic] myelopathies).

- Minor criteria:
  - Anemia not attributed to a comorbid condition
  - Leukocytosis ≥11 × 10^9/L
  - Palpable splenomegaly
  - LDH increased to above upper normal limit of institutional reference range

Overt fibrotic stage PMF requires meeting all of the following major criteria and at least one minor criterion (confirmed in 2 consecutive determinations):

- Major criteria:
  1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*.
  2. Not meeting WHO criteria for ET, PV, BCR::ABL1# CML, MDS, or other myeloid neoplasms.
  3. Presence of JAK2, CALR, or MPL mutation; or in the absence of these mutations, presence of another clonal marker (e.g., ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1), or absence of reactive myelofibrosis (e.g., bone marrow fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic [chronic] myelopathies).
- Minor criteria:
  - Anemia not attributed to a comorbid condition
  - Leukocytosis ≥11 × 10^9/L
  - Palpable splenomegaly
  - LDH increased to above upper normal limit of institutional reference range
  - Leukoerythroblastosis

*Reticulin fibrosis grade 2: diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis. Reticulin fibrosis grade 3: diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis.

International Consensus Classification of myeloid neoplasms and acute leukemias[3]

The International Consensus Classification (ICC) divides PMF into early/prefibrotic stage PMF and overt fibrotic stage PMF, and each has a different diagnostic criteria.

Early/prefibrotic stage PMF requires meeting all of the following major criteria and at least one minor criterion (confirmed in 2 consecutive determinations):

- Major criteria:
    1. Bone marrow biopsy showing megakaryocytic proliferation and atypia, bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
    2. JAK2, CALR, or MPL mutation, or presence of another clonal marker (e.g., ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2, and TET2 mutations), or absence of reactive bone marrow reticulin fibrosis (e.g., minimal reticulin fibrosis [grade 1] secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic [chronic] myelopathies)
    3. Diagnostic criteria for BCR::ABL1-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met.
- Minor criteria:
    - Anemia not attributed to a comorbid condition
    - Leukocytosis ≥11 × 10^9/L
    - Palpable splenomegaly
    - Lactate dehydrogenase level above the reference range

Overt fibrotic stage PMF requires meeting all three major criteria and at least one minor criterion confirmed in two consecutive determinations:

- Major criteria:
    1. Bone marrow biopsy showing megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grades 2 or 3
    2. JAK2, CALR, or MPL mutation, or presence of another clonal marker (e.g., ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2, and TET2 mutations), or absence of reactive myelofibrosis (e.g., minimal reticulin fibrosis [grade 1] secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic [chronic] myelopathies)
    3. Diagnostic criteria for ET, PV, BCR::ABL1-positive CML, myelodysplastic syndrome, or other myeloid neoplasms are not met.
- Minor criteria:
    - Anemia not attributed to a comorbid condition
    - Leukocytosis ≥11 × 10^9/L
    - Palpable splenomegaly
    - Lactate dehydrogenase level above the reference range
    - Leukoerythroblastosis

Approach

The treatment approach for patients with primary myelofibrosis (PMF) is based on a variety of considerations, including the presence of symptoms and risk factors.

Enrollment in a clinical trial should be considered for all patients with PMF.

The goals of treatment include relieving symptoms, improving blood counts, and preventing or delaying progression to advanced disease or leukemia. Splenectomy or splenic irradiation are no longer widely used in the management of PMF.

Allogeneic hematopoietic stem cell transplant is the only treatment with curative potential.

Symptom assessment and risk stratification

Assessing symptoms and risk factors (for prognosis and risk stratification) are key to guiding treatment in patients with PMF.

Symptoms and their severity/burden should be assessed at diagnosis and at each clinical review using a validated tool, such as the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS).[39] [44]

The following validated scoring systems can be used for prognostication and risk stratification:

- International Prognostic Scoring System (IPSS)[45]
- Dynamic International Prognostic Scoring System (DIPSS)[11]
- Dynamic International Prognostic Scoring System-plus (DIPSS-plus)[46]
- Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis (MIPSS70)[47]
- Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis (MIPSS70-plus)[13]
- Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis (GIPSS)[48]

IPSS is validated for assessing risk and prognosis at the time of diagnosis only, whereas DIPSS is validated for assessing risk and prognosis at any time during the disease course.

DIPSS uses the following risk factors to determine if a patient is low risk (DIPSS score 0), intermediate-1 risk (DIPSS score 1 or 2), intermediate-2 risk (DIPSS score 3 or 4), or high risk (DIPSS score 5 or 6):

- Age >65 years
- Hemoglobin <10 g/dL
- Leukocyte count >25 × 10^9/L
- Circulating blasts ≥1%
- Constitutional symptoms

DIPSS-plus is a modified version of DIPSS that incorporates the following additional risk factors:

- Platelet count
- Need for red blood cell transfusion
- Unfavorable chromosome abnormalities

MIPSS70, MIPSS70-plus, and GIPSS all incorporate genetic mutations and should be used if molecular testing has been carried out.

The Myelofibrosis Transplant Scoring System (MTSS) may be helpful in assessing risk and optimizing patient selection when considering stem cell transplant in a patient with PMF.[26] [49] [50]

Lower risk: asymptomatic patients

Up to 30% of patients may be asymptomatic at diagnosis.[35]

Asymptomatic lower-risk patients (e.g., DIPSS score ≤2; MIPSS70 score ≤3) without hyperuricemia or a remedial cause of anemia require no therapy. Observation is recommended.[26] [51] Patients should be monitored closely for signs and symptoms of disease progression.

A trial of oral folic acid may be reasonable for patients with anemia.

Asymptomatic leukocytosis with a normal serum uric acid level or thrombocytosis requires no therapy.

Lower risk: symptomatic patients

Symptomatic lower-risk patients (e.g., DIPSS score ≤2; MIPSS70 score ≤3) may require treatment with ruxolitinib (a Janus kinase [JAK] inhibitor) or peginterferon alfa-2a.[26] [42] [51]

- Ruxolitinib: for the treatment of symptomatic splenomegaly and constitutional symptoms (e.g., due to thrombocytosis or leukocytosis)
- Pegylated interferon: to reduce marrow fibrosis and symptomatic splenomegaly, and improve blood counts[52]

Alternative JAK inhibitors are useful in specific circumstances, or when a patient is resistant to, or intolerant of, ruxolitinib:[24] [26] [51]

- Pacritinib: a JAK2 and FMS-like tyrosine kinase-3 (FLT3) inhibitor; can be used for patients with a platelet count <50 × 10^9/L.[53] [54]
- Momelotinib: a JAK1/2 and activin A receptor type 1 (ACVR1) inhibitor; may be considered for patients with anemia.[26] [55] [56] [57] [58] [59]
- Fedratinib: a JAK2/FLT3 inhibitor; an option for patients with a platelet count ≥50 × 10^9/L and splenomegaly.[60] [61] [62] [63] Serious and fatal cases of encephalopathy have been reported with fedratinib.[64] If Wernicke encephalopathy is suspected, fedratinib should be discontinued immediately and parenteral thiamine initiated. Fedratinib should not be used in patients with thiamine deficiency.[63] Before starting fedratinib, assess thiamine levels and correct deficiency. During treatment with fedratinib, give prophylactic oral thiamine supplementation to all patients and monitor thiamine levels.[51] [63]

Hydroxyurea is not generally of use in treating PMF (although it is sometimes used for cytoreduction in an emergency). It should be considered with caution as it is teratogenic and leukemogenic.

Evaluation for allogeneic HSCT may be considered for selected lower-risk PMF patients with a DIPSS intermediate-1 score or MIPSS70 intermediate score.[26] Transplantation-related morbidity and mortality are high; decisions should be individualized.

Higher-risk: patients suitable for stem cell transplant

Higher-risk patients (e.g., with DIPSS score >2; MIPSS70 >3) should be considered for allogeneic hematopoietic stem cell transplant (HSCT), if eligible.[26][51]

Allogeneic HSCT is the only treatment with a curative potential for PMF.[50][65]

Following HSCT, regular driver mutation monitoring is recommended to detect and treat early relapse with donor lymphocyte infusion.[50]

Prospective studies are required to establish the most effective conditioning regimen, the optimal timing for transplantation, and which patients would benefit most from this procedure.

Identifying HSCT candidates

Patients must be fit enough to undergo the procedure (e.g., based on age and performance status), have manageable comorbidities, and have an acceptable human leukocyte antigen (HLA)-matched donor (HLA-matched sibling donors are preferred).[50] [51]

High survival rates have been reported for stem cell transplant performed in younger patients (i.e., <50 years of age) with a matched related donor.[65] [66] [67]

In patients ages over 70 years, allogeneic HSCT should be considered on an individual basis, balancing patient preferences and disease-associated and patient-associated features.[50] Studies report promising outcomes for older patients with good performance status after allogeneic HSCT with a suitable donor.[68] [69]

Pre-transplant JAK inhibitor

Larger spleen size is associated with higher rates of relapse following transplant. Patients who are candidates for allogeneic HSCT with symptomatic splenomegaly or splenomegaly >5 cm below the left costal margin should receive a JAK inhibitor to reduce spleen size and manage symptoms prior to transplant.[50] [70]

Patients already taking a JAK inhibitor should continue treatment. JAK inhibitor therapy should be gradually stopped before, or shortly after, starting conditioning.[26] [50]

Conditioning regimens for HSCT

Reduced-intensity conditioning and myeloablative conditioning are both options for patients with myelofibrosis. A reduced-intensity nonmyeloablative conditioning regimen is recommended for older patients, and patients with significant comorbidities. For younger patients with good performance status, a myeloablative conditioning regimen should be considered.[50] [71]

Higher-risk: patients not suitable for stem cell transplant

Higher-risk patients (e.g., with DIPSS score >2; MIPSS70 >3) who are not suitable for stem cell transplant or for whom transplant is not currently possible should undergo treatment to manage symptomatic splenomegaly and/or constitutional symptoms (e.g., due to thrombocytosis or leukocytosis).

Splenomegaly is very common and often the most distressing complication of PMF, leading to mechanical discomfort, inanition (severe weakness and wasting), splenic infarction, portal and pulmonary hypertension, and blood cell sequestration.

Patients with thrombocytosis (nonpregnant)

- Ruxolitinib: recommended for controlling organomegaly and blood counts in PMF.[26] [51] It is approved for use in intermediate-risk or high-risk patients. Ruxolitinib is effective in reducing splenomegaly and constitutional symptoms in these patients.[72] [73] [74] [75] [76] Early initiation

may improve outcomes, including durable spleen reduction and overall survival.[77] Ruxolitinib is given continuously. It should be started at a low dose and slowly escalated. When discontinuing ruxolitinib (e.g., due to lack of response) the dose should be tapered to minimize the risk of withdrawal symptoms, rebound leukocytosis and thrombocytosis, and cytokine storm. Abrupt discontinuation should be avoided.

- Fedratinib: can be used to control organomegaly and blood counts in PMF.[26] [51] It is approved for use in adult patients with intermediate-2 or high-risk primary or secondary (postpolycythemia vera or postessential thrombocythemia) myelofibrosis. Fedratinib is effective in reducing splenomegaly and symptom burden in patients with myelofibrosis who are JAK-inhibitor-naive, or resistant or intolerant to ruxolitinib.[61][62] [63] [78] Serious and fatal cases of encephalopathy have been reported with fedratinib.[64] If Wernicke encephalopathy is suspected, fedratinib should be discontinued immediately and parenteral thiamine initiated. Fedratinib should not be used in patients with thiamine deficiency.[63] Before starting fedratinib, assess thiamine levels and correct deficiency. During treatment with fedratinib, give prophylactic oral thiamine supplementation to all patients and monitor thiamine levels.[51] [63]
- Momelotinib: recommended for symptomatic PMF patients (splenomegaly and constitutional symptoms) with anemia.[26] [51] [55] [56] [57] [58] [59] It is approved for use in patients with intermediate-risk or high-risk PMF and disease-related anemia. Momelotinib may be considered if ruxolitinib or other JAK inhibitors are ineffective or not tolerated.[26] [51]
- Pacritinib: may be considered if other JAK inhibitors are ineffective or not tolerated.[26] [53]

If initial treatment is unsuccessful, an alternative, untried JAK inhibitor or enrollment into a clinical trial should be considered.

Patients without thrombocytosis (nonpregnant)

- Pacritinib: preferred option for higher-risk patients without thrombocytosis.[26] It is approved for the treatment of intermediate- or high-risk PMF in patients with a platelet count <50 × 10^9/L. Pacritinib is effective in reducing splenomegaly and symptom burden in patients with myelofibrosis (including those with severe cytopenias).[54]
- Momelotinib: may be considered as an alternative option for higher-risk patients without thrombocytosis.[26]

If initial treatment is unsuccessful, an alternative, untried JAK inhibitor or enrollment into a clinical trial should be considered.

Higher-risk PMF refractory to pharmacologic agents

Nonpharmacologic measures, such as splenectomy or splenic irradiation, are no longer widely used.

- Splenectomy may be an option if pharmacologic agents are ineffective in patients with severe symptomatic splenomegaly (e.g., with splenic abdominal pain, symptomatic portal hypertension, frequent red blood cell transfusions).[24] [51] [79] Splenectomy may also be used in some patients with extreme splenomegaly prior to transplant.[26] [51] [79] Splenectomy is a high-risk procedure with potential complications such as bleeding (the greatest risk), postoperative thrombosis, infection, abdominal hernia, and difficult-to-control myeloproliferation with hepatomegaly; therefore, the decision to perform splenectomy requires careful consideration. Splenectomy for patients with PMF is associated with high mortality and morbidity rates (approximately 9% and 30%, respectively) with limited survival benefit.[24] [80]

- Splenic irradiation (e.g., with external-beam radiation therapy) can be effective at alleviating splenic pain and temporarily reducing spleen size.[81] [82] However, its use should be restricted to patients unsuitable for splenectomy because there is an unpredictable risk of severe cytopenias.

Pregnant patients

PMF in pregnancy is rare. Patients who become pregnant should be under the joint care of a hematologist and an obstetrician experienced in high-risk care. Treatment should be individualized.

- Peginterferon alfa-2a may be considered for pregnant patients with PMF.[51] Use can be limited by its induction of leukopenia or thrombocytopenia, but it can decrease splenomegaly. There is a lack of data for the use of peginterferon alfa-2a in pregnancy; it should be used only if the benefits outweigh the potential risk to the fetus.[26]
- JAK inhibitors, hydroxyurea, and thalidomide are contraindicated in pregnancy.

Adjunctive treatments

Transfusion may be needed for short-term symptomatic relief and while optimizing treatment.[26] [51]

Patients with anemia

Momelotinib is recommended for symptomatic PMF patients (splenomegaly and constitutional symptoms) with anemia.[26] [55] [56] [57] [58] [59]

Further options for anemia, which can be used in combination with a JAK inhibitor, include:

- Erythropoiesis-stimulating agents (e.g., epoetin alfa, darbepoetin alfa) for patients with serum erythropoietin (EPO) levels <500 mU/mL.[26] [83] Erythropoiesis-stimulating agents are effective and well tolerated when used in combination with ruxolitinib.[84] However, they can cause a reversible increase in splenomegaly or hepatomegaly. Response rate is approximately 50%; patients most likely to respond are those with a low baseline serum EPO level (<125 mU/mL) and low transfusion requirement.[83] [85]
- Danazol for patients with serum EPO levels ≥500 mU/mL.[26] [86] [87] Luspatercept is being evaluated as an option for these patients.[88] [89] Danazol and luspatercept are contraindicated in pregnancy.
- Immunomodulatory agents, such as thalidomide or lenalidomide, combined with prednisone.[26] Thalidomide and lenalidomide are contraindicated in pregnancy.

Patients with hyperuricemia

- Allopurinol is given to patients with hyperuricemia.
- In patients who are pregnant, allopurinol should be considered if the benefit of treating the hyperuricemia outweighs the risk of hyperuricemia to the mother and child and no other safe alternatives are available.

Patients with extramedullary hematopoiesis

- Local irradiation is appropriate for the management of nonpregnant patients with symptomatic extramedullary hematopoiesis in tissues and organs other than the spleen.[24]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
lower risk: asymptomatic		
	1st	observation
	adjunct	folic acid
lower risk: symptomatic		
	1st	Janus kinase (JAK) inhibitor or peginterferon alfa
	adjunct	management of anemia
	adjunct	allopurinol
	2nd	evaluation for stem cell transplant
higher risk: younger stem cell transplant candidate without comorbidities		
	1st	myeloablative stem cell transplant
	adjunct	pretransplant Janus kinase (JAK) inhibitor
higher risk: stem cell transplant candidate >70 years or younger stem cell transplant candidate with comorbidities		
	1st	nonmyeloablative stem cell transplant
	adjunct	pretransplant Janus kinase (JAK) inhibitor
higher risk: not stem cell transplant candidate		
with thrombocytosis: nonpregnant	1st	Janus kinase (JAK) inhibitor
	adjunct	management of anemia
	adjunct	allopurinol
	adjunct	local irradiation
without thrombocytosis: nonpregnant	1st	Janus kinase (JAK) inhibitor
	adjunct	management of anemia
	adjunct	allopurinol
	adjunct	local irradiation

Acute			(summary)
		2nd	splenectomy or splenic irradiation
	pregnant	1st	individualized care
		adjunct	management of anemia
		adjunct	allopurinol

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

lower risk: asymptomatic

1st **observation**

» Symptoms and their severity/burden should be assessed at diagnosis and at each clinical review using a validated tool (e.g., Myeloproliferative Neoplasm Symptom Assessment Form total symptom score [MPN-SAF TSS]).[39] [44]

» A validated scoring system can be used for prognostication and risk stratification (e.g., International Prognostic Scoring System [IPSS]; Dynamic International Prognostic Scoring System [DIPSS]; Dynamic International Prognostic Scoring System-plus [DIPSS-plus]; Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis [MIPSS70]; Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis [MIPSS70-plus]; Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis [GIPSS]).[11] [13] [45] [46] [47][48]

» Up to 30% of patients may be asymptomatic at diagnosis.[35]

» Asymptomatic lower-risk patients (e.g., DIPSS score ≤2; MIPSS70 score ≤3) without hyperuricemia or a remedial cause of anemia require no therapy. Observation is recommended.[26] [51] Patients should be monitored closely for signs and symptoms of disease progression.

» Asymptomatic leukocytosis with a normal serum uric acid level or thrombocytosis requires no therapy.

» Enrollment in a clinical trial should be considered for all patients with PMF.

adjunct **folic acid**

Treatment recommended for SOME patients in selected patient group

Primary options

» folic acid (vitamin B9): 1 mg orally once daily

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» A trial of oral folic acid may be reasonable for patients with anemia.

lower risk: symptomatic

1st **Janus kinase (JAK) inhibitor or peginterferon alfa**

Primary options

» ruxolitinib: 5-25 mg orally twice daily
Starting dose, dose adjustments, and maximum dose depend on platelet count. Consult product literature for further information.

OR

» peginterferon alfa 2a: consult specialist for guidance on dose

Secondary options

» pacritinib: 200 mg orally twice daily

OR

» momelotinib: 200 mg orally once daily

OR

» fedratinib: 400 mg orally once daily

» Symptoms and their severity/burden should be assessed at diagnosis and at each clinical review using a validated tool (e.g., Myeloproliferative Neoplasm Symptom Assessment Form total symptom score [MPN-SAF TSS]).[39] [44]

» A validated scoring system can be used for prognostication and risk stratification (e.g., International Prognostic Scoring System [IPSS]; Dynamic International Prognostic Scoring System [DIPSS]; Dynamic International Prognostic Scoring System-plus [DIPSS-plus]; Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis [MIPSS70]; Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis [MIPSS70-plus]; Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis [GIPSS]).[11] [13] [45] [46] [47][48]

» Symptomatic lower-risk patients (e.g., DIPSS score ≤2; MIPSS70 score ≤3) may require

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treatment with a Janus kinase (JAK) inhibitor or peginterferon alfa-2a.[26] [42] [51]

» Ruxolitinib (a JAK 1/2 inhibitor) can be used to treat symptomatic splenomegaly and constitutional symptoms (e.g., due to thrombocytosis or leukocytosis).

» Ruxolitinib is given continuously. It should be started at a low dose and slowly escalated. When discontinuing ruxolitinib (e.g., due to lack of response) the dose should be tapered to minimize the risk of withdrawal symptoms, rebound leukocytosis and thrombocytosis, and cytokine storm. Abrupt discontinuation should be avoided.

» Pegylated interferon can be used to reduce marrow fibrosis and symptomatic splenomegaly, and to improve blood counts.[52]

» Alternative JAK inhibitors are useful in specific circumstances, or when a patient is resistant to, or intolerant of, ruxolitinib.[24] [26] [51]

» Pacritinib, a JAK2 and FMS-like tyrosine kinase-3 (FLT3) inhibitor, can be used for patients with a platelet count <50 × 10^9/L.[53] [54]

» Momelotinib, a JAK1/2 and activin A receptor type 1 (ACVR1) inhibitor, may be considered for patients with anemia.[26] [55] [56] [57] [58] [59]

» Fedratinib, a JAK2/FLT3 inhibitor, is an option for patients with a platelet count ≥50 × 10^9/L and splenomegaly.[60] [61] [62][63] Serious and fatal cases of encephalopathy have been reported with fedratinib.[64] If Wernicke encephalopathy is suspected, fedratinib should be discontinued immediately and parenteral thiamine initiated. Fedratinib should not be used in patients with thiamine deficiency.[63] Before starting fedratinib, assess thiamine levels and correct deficiency. During treatment with fedratinib, give prophylactic oral thiamine supplementation to all patients and monitor thiamine levels.[51] [63]

» Enrollment in a clinical trial should be considered for all patients with PMF.

adjunct **management of anemia**

Treatment recommended for SOME patients in selected patient group

Primary options

» epoetin alfa: consult specialist for guidance on dose

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OR

» darbepoetin alfa: consult specialist for guidance on dose

OR

» danazol: consult specialist for guidance on dose

Secondary options

» luspatercept: consult specialist for guidance on dose

OR

» thalidomide: consult specialist for guidance on dose
-or-
» lenalidomide: consult specialist for guidance on dose

--AND--

» prednisone: consult specialist for guidance on dose

» Transfusion may be needed for short-term symptomatic relief and while optimizing treatment.[26] [51]

» Further options for anemia, which can be used in combination with a Janus kinase inhibitor, include erythropoiesis-stimulating agents, danazol, luspatercept, or an immunomodulatory drug (e.g., thalidomide, lenalidomide).

» Erythropoiesis-stimulating agents (e.g., epoetin alfa, darbepoetin alfa) are recommended for patients with serum erythropoietin (EPO) levels <500 mU/mL.[26] [83] Erythropoiesis-stimulating agents are effective and well tolerated when used in combination with ruxolitinib.[84] However, they can cause a reversible increase in splenomegaly or hepatomegaly. Response rate is approximately 50%; patients most likely to respond are those with a low baseline serum EPO level (<125 mU/mL) and low transfusion requirement.[83] [83]

» Danazol can be considered for patients with serum EPO levels ≥500 mU/mL.[26] [87] [86]

» Luspatercept is being evaluated as an option for these patients.[88] [89]

Acute

» Immunomodulatory agents, such as thalidomide or lenalidomide, combined with prednisone, may be a further option.[26]

adjunct **allopurinol**

Treatment recommended for SOME patients in selected patient group

Primary options

» allopurinol: 300-800 mg/day orally given in 1-3 divided doses

» Allopurinol is given for 2-3 days to patients with hyperuricemia.

2nd **evaluation for stem cell transplant**

» Evaluation for allogeneic hematopoietic stem cell transplantmay be considered for selected lower-risk PMF patients with a DIPSS intermediate-1 score or MIPSS70 intermediate score.[26]

» Transplantation-related morbidity and mortality are high, so decisions should be individualized.

» The Myelofibrosis Transplant Scoring System (MTSS) may be helpful in assessing risk and optimizing patient selection when considering stem cell transplant.[26] [49] [50]

higher risk: younger stem cell transplant candidate without comorbidities

1st **myeloablative stem cell transplant**

» Allogeneic hematopoietic stem cell transplant is the only treatment option with curative potential.[50] [65]

» Symptoms and their severity/burden should be assessed using a validated tool (e.g., Myeloproliferative Neoplasm Symptom Assessment Form total symptom score [MPN-SAF TSS]).[39] [44]

» A validated scoring system can be used for prognostication and risk stratification (e.g., International Prognostic Scoring System [IPSS]; Dynamic International Prognostic Scoring System [DIPSS]; Dynamic International Prognostic Scoring System-plus [DIPSS-plus]; Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis [MIPSS70]; Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis [MIPSS70-plus]; Genetically

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Inspired Prognostic Scoring System for Primary Myelofibrosis [GIPSS]).[11] [13] [45] [46] [47][48]

» The Myelofibrosis Transplant Scoring System (MTSS) may be helpful in assessing risk and optimizing patient selection when considering stem cell transplant.[26] [49] [50]

» Higher-risk patients (e.g., DIPSS score >2; MIPSS70 >3) should be considered for allogeneic hematopoietic stem cell transplant, if eligible.[26] [51]

» Patients must be fit enough to undergo the procedure (e.g., based on age and performance status), have manageable comorbidities, and have an acceptable human leukocyte antigen (HLA)-matched donor (HLA-matched sibling donors are preferred).[50] [51]

» Reduced-intensity conditioning and myeloablative conditioning are both options for patients with myelofibrosis. For younger patients with good performance status, a myeloablative conditioning regimen should be considered.[50] [71]

» High survival rates have been reported for stem cell transplant performed in younger patients (i.e., <50 years of age) with a matched related donor.[65] [66] [67]

» Following transplant, regular driver mutation monitoring is recommended to detect and treat early relapse with donor lymphocyte infusion.[50]

» Enrollment in a clinical trial should be considered for all patients with PMF.

adjunct **pretransplant Janus kinase (JAK) inhibitor**

Treatment recommended for SOME patients in selected patient group

Primary options

» ruxolitinib: 5-25 mg orally twice daily
Starting dose, dose adjustments, and maximum dose depend on platelet count. Consult product literature for further information.

Secondary options

» fedratinib: 400 mg orally once daily

OR

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» momelotinib: 200 mg orally once daily

OR

» pacritinib: 200 mg orally twice daily

» Larger spleen size is associated with higher rates of relapse following transplant. Patients who are candidates for allogeneic hematopoietic stem cell transplant (HSCT) with symptomatic splenomegaly or splenomegaly >5 cm below the left costal margin should receive a JAK inhibitor to reduce spleen size and manage symptoms prior to transplant.[50] [70]

» Bridging therapy with ruxolitinib appears to improve post-transplant outcomes among patients who experience clinical improvement with this JAK inhibitor.[90] [91] Fedratinib, pacritinib, momelotinib have shown efficacy in reducing splenomegaly, although there is a lack of evidence on their use before transplantation.[50]

» Patients already taking a JAK inhibitor should continue treatment. JAK inhibitor therapy should be gradually stopped before, or shortly after, starting conditioning.[26] [50]

» Ruxolitinib should be started at a low dose and slowly escalated. When discontinuing ruxolitinib the dose should be tapered to minimize the risk of withdrawal symptoms, rebound leukocytosis and thrombocytosis, and cytokine storm. Abrupt discontinuation should be avoided.

» Serious and fatal cases of encephalopathy have been reported with fedratinib.[64] If Wernicke encephalopathy is suspected, fedratinib should be discontinued immediately and parenteral thiamine initiated. Fedratinib should not be used in patients with thiamine deficiency.[63] Before starting fedratinib, assess thiamine levels and correct deficiency. During treatment with feratinib, give prophylactic oral thiamine supplementation to all patients and monitor thiamine levels.[51] [63]

higher risk: stem cell transplant candidate >70 years or younger stem cell transplant candidate with comorbidities

1st **nonmyeloablative stem cell transplant**

» Allogeneic hematopoietic stem cell transplant is the only treatment option with curative potential.[50] [65]

Acute

» Symptoms and their severity/burden should be assessed using a validated tool (e.g., Myeloproliferative Neoplasm Symptom Assessment Form total symptom score [MPN-SAF TSS]).[39] [44]

» A validated scoring system can be used for prognostication and risk stratification (e.g., International Prognostic Scoring System [IPSS]; Dynamic International Prognostic Scoring System [DIPSS]; Dynamic International Prognostic Scoring System-plus [DIPSS-plus]; Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis [MIPSS70]; Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis [MIPSS70-plus]; Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis [GIPSS]).[11] [13] [45] [46] [47][48]

» The Myelofibrosis Transplant Scoring System (MTSS) may be helpful in assessing risk and optimizing patient selection when considering stem cell transplant.[26] [49] [50]

» Higher-risk patients (e.g., DIPSS score >2; MIPSS70 >3) should be considered for allogeneic hematopoietic stem cell transplant, if eligible.[26] [42]

» Patients must be fit enough to undergo the procedure (e.g., based on age and performance status), have manageable comorbidities, and have an acceptable human leukocyte antigen (HLA)-matched donor (HLA-matched sibling donors are preferred).[50] [51]

» In patients ages over 70 years, allogeneic HSCT should be considered on an individual basis, balancing patient preferences and disease-associated and patient-associated features.[50] A reduced-intensity nonmyeloablative conditioning regimen is recommended for older patients, and patients with significant comorbidities.[50] [71]

» Studies report promising outcomes for older patients with good performance status after allogeneic HSCT with a suitable donor.[68] [69]

» Following transplant, regular driver mutation monitoring is recommended to detect and treat early relapse with donor lymphocyte infusion.[50]

» Enrollment in a clinical trial should be considered for all patients with PMF.

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adjunct **pretransplant Janus kinase (JAK) inhibitor**

Treatment recommended for SOME patients in selected patient group

Primary options

» ruxolitinib: 5-25 mg orally twice daily
Starting dose, dose adjustments, and maximum dose depend on platelet count. Consult product literature for further information.

Secondary options

» fedratinib: 400 mg orally once daily

OR

» momelotinib: 200 mg orally once daily

OR

» pacritinib: 200 mg orally twice daily

» Larger spleen size is associated with higher rates of relapse following transplant. Patients who are candidates for allogeneic HSCT with symptomatic splenomegaly or splenomegaly >5 cm below the left costal margin should receive a JAK inhibitor to reduce spleen size and manage symptoms prior to transplant.[50] [70]

» Bridging therapy with ruxolitinib appears to improve post-transplant outcomes among patients who experience clinical improvement with this JAK inhibitor.[90] [91] Fedratinib, pacritinib, momelotinib have shown efficacy in reducing splenomegaly, although there is a lack of evidence on their use before transplantation.[50]

» Patients already taking a JAK inhibitor should continue treatment. JAK inhibitor therapy should be gradually stopped before, or shortly after, starting conditioning.[26] [50]

» Ruxolitinib should be started at a low dose and slowly escalated. When discontinuing ruxolitinib the dose should be tapered to minimize the risk of withdrawal symptoms, rebound leukocytosis and thrombocytosis, and cytokine storm. Abrupt discontinuation should be avoided.

» Serious and fatal cases of encephalopathy have been reported with fedratinib.[64] If Wernicke encephalopathy is suspected,

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fedratinib should be discontinued immediately and parenteral thiamine initiated. Fedratinib should not be used in patients with thiamine deficiency.[63] Before starting fedratinib, assess thiamine levels and correct deficiency. During treatment with fedratinib, give prophylactic oral thiamine supplementation to all patients and monitor thiamine levels.[51] [63]

higher risk: not stem cell transplant candidate

with thrombocytosis: nonpregnant

1st

Janus kinase (JAK) inhibitor

Primary options

» ruxolitinib: 5-25 mg orally twice daily
Starting dose, dose adjustments, and maximum dose depend on platelet count. Consult product literature for further information.

OR

» fedratinib: 400 mg orally once daily

OR

» momelotinib: 200 mg orally once daily

Secondary options

» pacritinib: 200 mg orally twice daily

» Symptoms and their severity/burden should be assessed at diagnosis and at each clinical review using a validated tool (e.g., Myeloproliferative Neoplasm Symptom Assessment Form total symptom score [MPN-SAF TSS]).[39] [44]

» A validated scoring system can be used for prognostication and risk stratification (e.g., International Prognostic Scoring System [IPSS]; Dynamic International Prognostic Scoring System [DIPSS]; Dynamic International Prognostic Scoring System-plus [DIPSS-plus]; Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis [MIPSS70]; Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis [MIPSS70-plus]; Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis [GIPSS]).[11] [13][45] [46] [47][48]

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» Higher-risk patients (e.g., with DIPSS score >2; MIPSS70 >3) who are not suitable for stem cell transplant or for whom transplant is not currently possible should undergo treatment to manage symptomatic splenomegaly and/or constitutional symptoms (e.g., due to thrombocytosis or leukocytosis).

» Splenomegaly is very common and often the most distressing complication of PMF, leading to mechanical discomfort, inanition (severe weakness and wasting), splenic infarction, portal and pulmonary hypertension, and blood cell sequestration.

» Ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, is recommended for controlling organomegaly and blood counts in PMF.[26] [51] It is approved for use in intermediate-risk or high-risk patients. Ruxolitinib is effective in reducing splenomegaly and constitutional symptoms in these patients.[72] [73] [74] [75] [76] Early initiation may improve outcomes, including durable spleen reduction and overall survival.[77]

» Ruxolitinib is given continuously. It should be started at a low dose and slowly escalated. When discontinuing ruxolitinib (e.g., due to lack of response) the dose should be tapered to minimize the risk of withdrawal symptoms, rebound leukocytosis and thrombocytosis, and cytokine storm. Abrupt discontinuation should be avoided.

» Fedratinib, a JAK2 and FMS-like tyrosine kinase-3 (FLT3) inhibitor, can be used to control organomegaly and blood counts in PMF.[26] [51] It is approved for use in adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. Fedratinib is effective in reducing splenomegaly and symptom burden in patients with myelofibrosis who are JAK-inhibitor-naive, or resistant or intolerant to ruxolitinib.[61][62][63] [78]

» Serious and fatal cases of encephalopathy have been reported with fedratinib.[64] If Wernicke encephalopathy is suspected, fedratinib should be discontinued immediately and parenteral thiamine initiated. Fedratinib should not be used in patients with thiamine deficiency.[63] Before starting fedratinib, assess thiamine levels and correct deficiency. During treatment with fedratinib, give prophylactic oral thiamine supplementation to all patients and monitor thiamine levels.[51] [63]

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» Momelotinib, a JAK1/2 and activin A receptor type 1 (ACVR1) inhibitor, is recommended for symptomatic PMF patients with anemia.[26] [51] [55] [56] [57] [58] [59] It is approved for use in patients with intermediate-risk or high-risk PMF and disease-related anemia. Momelotinib may be considered if ruxolitinib or other JAK inhibitors are ineffective or not tolerated.[26] [51]

» Pacritinib may be considered if ruxolitinib and fedratinib are ineffective.[26] [53]

» If initial treatment is unsuccessful, an alternative, untried JAK inhibitor or enrollment into a clinical trial should be considered.

adjunct **management of anemia**

Treatment recommended for SOME patients in selected patient group

Primary options

» epoetin alfa: consult specialist for guidance on dose

OR

» darbepoetin alfa: consult specialist for guidance on dose

OR

» danazol: consult specialist for guidance on dose

Secondary options

» luspatercept: consult specialist for guidance on dose

OR

» thalidomide: consult specialist for guidance on dose
-or-
» lenalidomide: consult specialist for guidance on dose
--AND--
» prednisone: consult specialist for guidance on dose

» Transfusion may be needed for short-term symptomatic relief and while optimizing treatment.[26] [51]

» Further options for anemia, which can be used in combination with a Janus kinase inhibitor,

Acute

include erythropoiesis-stimulating agents, danazol, luspatercept, or an immunomodulatory drug (e.g., thalidomide, lenalidomide).

» Erythropoiesis-stimulating agents (e.g., epoetin alfa, darbepoetin alfa) are recommended for patients with serum erythropoietin (EPO) levels <500 mU/mL.[26] [83] Erythropoiesis-stimulating agents are effective and well tolerated when used in combination with ruxolitinib.[84] However, they can cause a reversible increase in splenomegaly or hepatomegaly. Response rate is approximately 50%; patients most likely to respond are those with a low baseline serum EPO level (<125 mU/mL) and low transfusion requirement.[83] [85]

» Danazol can be considered for patients with serum EPO levels ≥500 mU/mL.[26] [86] [87]

» Luspatercept is being evaluated as an option for these patients.[88] [89]

» Immunomodulatory agents such as thalidomide or lenalidomide, combined with prednisone, may be a further option.[26]

adjunct **allopurinol**

Treatment recommended for SOME patients in selected patient group

Primary options

» allopurinol: 300-800 mg/day orally given in 1-3 divided doses

» Allopurinol is given for 2-3 days to patients with hyperuricemia.

adjunct **local irradiation**

Treatment recommended for SOME patients in selected patient group

» Local irradiation is appropriate for the management of nonpregnant patients with symptomatic extramedullary hematopoiesis in tissues and organs other than the spleen.[24]

without thrombocytosis: nonpregnant

1st **Janus kinase (JAK) inhibitor**

Primary options

» pacritinib: 200 mg orally twice daily

Secondary options

» momelotinib: 200 mg orally once daily

» Symptoms and their severity/burden should be assessed at diagnosis and at

Acute

each clinical review using a validated tool (e.g., Myeloproliferative Neoplasm Symptom Assessment Form total symptom score [MPN-SAF TSS]).[39] [44]

» A validated scoring system can be used for prognostication and risk stratification (e.g., International Prognostic Scoring System [IPSS]; Dynamic International Prognostic Scoring System [DIPSS]; Dynamic International Prognostic Scoring System-plus [DIPSS-plus]; Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis [MIPSS70]; Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis [MIPSS70-plus]; Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis [GIPSS]).[11] [13][45] [46] [47][48]

» Higher-risk patients (e.g., with DIPSS score >2; MIPSS70 >3) who are not suitable for stem cell transplant or for whom transplant is not currently possible should undergo treatment to manage symptomatic splenomegaly and/or constitutional symptoms (e.g., due to thrombocytosis or leukocytosis).

» Splenomegaly is very common and often the most distressing complication of PMF, leading to mechanical discomfort, inanition (severe weakness and wasting), splenic infarction, portal and pulmonary hypertension, and blood cell sequestration.

» Pacritinib, a JAK2/FLT3 inhibitor, is the preferred option for higher-risk patients without thrombocytosis.[26] It is approved for the treatment of intermediate- or high-risk PMF in patients with a platelet count <50 × 10^9/L. Pacritinib is effective in reducing splenomegaly and symptom burden in patients with myelofibrosis (including those with severe cytopenias).[54]

» Momelotinib, a JAK1/2 and activin A receptor type 1 (ACVR1) inhibitor, may be considered as an alternative option for higher-risk patients without thrombocytosis.[26] Momelotinib is recommended for symptomatic PMF patients (splenomegaly and constitutional symptoms) with anemia.[26] [58] [59]

» If initial treatment is unsuccessful, an alternative, untried JAK inhibitor or enrollment into a clinical trial should be considered.

adjunct **management of anemia**

Acute

Treatment recommended for SOME patients in selected patient group

Primary options

» epoetin alfa: consult specialist for guidance on dose

OR

» darbepoetin alfa: consult specialist for guidance on dose

OR

» danazol: consult specialist for guidance on dose

Secondary options

» luspatercept: consult specialist for guidance on dose

OR

» thalidomide: consult specialist for guidance on dose
-or-
» lenalidomide: consult specialist for guidance on dose
--AND--
» prednisone: consult specialist for guidance on dose

» Transfusion may be needed for short-term symptomatic relief and while optimizing treatment.[26] [51]

» Further options for anemia, which can be used in combination with a Janus kinase inhibitor, include erythropoiesis-stimulating agents, danazol, luspatercept, or an immunomodulatory drug (e.g., thalidomide, lenalidomide).

» Erythropoiesis-stimulating agents (e.g., epoetin alfa, darbepoetin alfa) are recommended for patients with serum erythropoietin (EPO) levels <500 mU/mL.[26] [83] Erythropoiesis-stimulating agents are effective and well tolerated when used in combination with ruxolitinib.[84] However, they can cause a reversible increase in splenomegaly or hepatomegaly. Response rate is approximately 50%; patients most likely to respond are those with a low baseline serum EPO level (<125 mU/mL) and low transfusion requirement.[83] [85]

Acute

» Danazol can be considered for patients with serum EPO levels ≥500 mU/mL.[26] [86] [87]

» Luspatercept is being evaluated as an option for these patients.[88] [89]

» Immunomodulatory agents such as thalidomide or lenalidomide, combined with prednisone, may be a further option.[26]

adjunct **allopurinol**

Treatment recommended for SOME patients in selected patient group

Primary options

» allopurinol: 300-800 mg/day orally given in 1-3 divided doses

» Allopurinol is given for 2-3 days to patients with hyperuricemia.

adjunct **local irradiation**

Treatment recommended for SOME patients in selected patient group

» Local irradiation is appropriate for the management of nonpregnant patients with symptomatic extramedullary hematopoiesis in tissues and organs other than the spleen.[24]

2nd **splenectomy or splenic irradiation**

» Nonpharmacologic measures, such as splenectomy or splenic irradiation, are no longer widely used for PMF.

» Splenectomy may be an option if pharmacologic agents are ineffective in patients with severe symptomatic splenomegaly (e.g., with splenic abdominal pain, symptomatic portal hypertension, frequent red blood cell transfusions).[24] [51][79] Splenectomy may also be used in some patients with extreme splenomegaly prior to transplant.[26] [51] [79]

» Splenectomy is a high-risk procedure with potential complications such as bleeding (the greatest risk), postoperative thrombosis, infection, abdominal hernia, and difficult-to-control myeloproliferation with hepatomegaly; therefore, the decision to perform splenectomy requires careful consideration. Splenectomy for patients with PMF is associated with high mortality and morbidity rates (approximately 9% and 30%, respectively) with limited survival benefit.[24] [80]

Acute

» Splenic irradiation (e.g., with external-beam radiation therapy) can be effective at alleviating splenic pain and temporarily reducing spleen size.[81] [82] However, its use should be restricted to patients unsuitable for splenectomy because there is an unpredictable risk of severe cytopenias.

pregnant — **1st** — **individualized care**

Primary options

» peginterferon alfa 2a: consult specialist for guidance on dose

» PMF in pregnancy is rare. Patients who become pregnant should be under the joint care of a hematologist and an obstetrician experienced in high-risk care. Treatment should be individualized.

» Peginterferon alfa-2a may be considered for pregnant patients with PMF.[51] Use can be limited by its induction of leukopenia or thrombocytopenia, but it can decrease splenomegaly. There is a lack of data for the use of peginterferon alfa-2a in pregnancy; it should be used only if the benefits outweigh the potential risk to the fetus.[26]

» Janus kinase (JAK) inhibitors, hydroxyurea, and thalidomide are contraindicated in pregnancy.

adjunct — **management of anemia**

Treatment recommended for SOME patients in selected patient group

Primary options

» epoetin alfa: consult specialist for guidance on dose

OR

» darbepoetin alfa: consult specialist for guidance on dose

» Erythropoiesis-stimulating agents (e.g., epoetin alfa, darbepoetin alfa) may be considered for pregnant patients with serum erythropoietin (EPO) levels <500 mU/mL.

» Specialist consultation is advised in pregnant women.

adjunct — **allopurinol**

Treatment recommended for SOME patients in selected patient group

Acute

Primary options

» allopurinol: 300-800 mg/day orally given in 1-3 divided doses

» Allopurinol should be considered if the benefit of treating the hyperuricemia outweighs the risk of hyperuricemia to the mother and child and no other safe alternatives are available.

» Given for 2-3 days.

Patient discussions

Advise patients to contact their physician with constitutional symptoms such as fever, night sweats, and weight loss; or with change in abdominal girth, abdominal or joint or bone pain, dyspnea, and peripheral edema.

Monitoring

Monitoring

Repeat bone marrow exam and cytogenetic or imaging studies are only appropriate if there is a change in symptoms, signs, or blood counts. There is no set time for outpatient follow-up. The frequency and interval of follow-up visits depend on the degree of cytopenia and blood products transfusion.

Complete blood count with differential and lactate dehydrogenase (LDH)

- Patients should be closely monitored for transformation to acute leukemia. This may be heralded by a fall in the platelet count <100 × 10^3/microliter, or peripheral blood blasts increasing to >10%, or cytogenetic evolution, or increasing LDH.

Antibiotic prophylaxis

- Antibiotic, antiviral, and antifungal prophylaxis may be indicated for some patients with neutropenia. Patients taking chronic corticosteroids may need prophylaxis against *Pneumocystis jirovecii* .

Monitoring of adverse effects of treatment modalities

- Patients receiving cytoreductive therapy must be monitored closely for adverse effects.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
myeloid metaplasia due to extramedullary hematopoiesis	**long term**	**high**
Most common in the spleen and liver. Can occur at any site and compromise organ or tissue function. Peritoneal involvement can lead to ascites. Epidural involvement can cause spinal cord compression. Retroperitoneal involvement can lead to obstructive uropathy or portal hypertension. Pulmonary extramedullary hematopoiesis will cause pulmonary hypertension. The reason why myeloid metaplasia is more aggressive in some patients than in others is unclear.		
anemia	**variable**	**high**
Due to ineffective erythropoiesis, hemodilution due to an expanded plasma volume associated with splenomegaly, iron deficiency due to gastrointestinal blood loss, folic acid deficiency due to the increased demands of hematopoiesis, hemolysis due to autoimmune phenomena or hypersplenism, and, rarely, pyridoxine deficiency. In some patients, erythropoietin production may be inappropriately low for the degree of anemia, but in this instance hemodilution also needs to be excluded. Momelotinib is recommended to treat symptomatic PMF patients (splenomegaly and constitutional symptoms) with anemia.[26] [51] [55] [56] [57] [58] [59] Further options for anemia, which can be used in combination with a Janus kinase inhibitor, may include an erythropoiesis-stimulating agent (if serum erythropoietin levels <500 mU/mL) or danazol (if serum erythropoietin levels ≥500 mU/mL).[26] [83][86] [87]		
hemorrhage	**variable**	**high**
Due to thrombocytopenia and platelet dysfunction.		
infections	**variable**	**high**
Due to leukopenia.		
complications secondary to splenomegaly	**variable**	**high**
Splenic enlargement is inevitable and can lead to splenic infarction, malnutrition due to easy satiety, plasma volume expansion, hypersplenism, portal hypertension, splanchnic vein thrombosis, extreme discomfort due to its mass, and eventually cachexia.		

Complications	Timeframe	Likelihood
portal hypertension	**variable**	**high**
Hepatomegaly is associated with splenomegaly. Impaired hepatic function is usually a consequence of extramedullary hematopoiesis, which can lead to hepatic fibrosis and portal hypertension.		
acute leukemia/myelodysplasia	**variable**	**medium**
Diagnosis of leukemic transformation in primary myelofibrosis (PMF) is often difficult, primarily because abnormal cell counts and immature cells in the peripheral blood are part of the disease process, bone marrow aspirate is often "dry tap," and bone marrow biopsy may not reveal clear evidence of leukemia.[97] In a large case series, acute leukemic transformation was diagnosed in about 4% of PMF patients; all instances were myeloid in origin.[97] Circulating blasts ≥3% and platelet count <100,000/microliter at the time of diagnosis have been shown to be independent predictors of leukemic transformation. Overall survival after leukemic transformation is dismal, with a median survival of 2.6 months (range: 0-24 months).[97] The extent to which therapeutic intervention with mutagenic drugs such as hydroxyurea, alkylating agents, or irradiation predisposes PMF patients to progress to acute leukemia is unknown. For unknown reasons, splenectomy seems to be a predisposing factor for the development of acute leukemia.		
hyperuricemia-related gout	**variable**	**medium**
Hyperuricemia is a consequence of increased cell turnover. It can provoke acute gout if left untreated. Allopurinol is given for 2-3 days to patients with hyperuricemia.		
hyperuricemia-related renal stone formation	**variable**	**medium**
Hyperuricemia is a consequence of increased cell turnover. It can provoke renal stone formation if left untreated. Allopurinol is indicated in the management of patients with signs and symptoms of uric acid lithiasis.		

Prognosis

Developments in the management of primary myelofibrosis (PMF) have resulted in improved survival.[93] [94]

Median overall survival (all ages) for patients with PMF was 4.0 years, based on registry data for 3689 PMF patients diagnosed between 2001 and 2015 (median follow-up 5.8 years).[95] Retrospective data from a single center reported an improvement in median overall survival from 48 months (95% CI, 42-54 months) in patients diagnosed in between 2000 and 2010, to 63 months (95% CI, 55-71 months) in patients diagnosed between 2011 and 2020.[94] The study population comprised 844 patients; median age at new diagnosis of

myelofibrosis was 66 years. Those treated with ruxolitinib had a median overall survival of 84 months (95% CI, 70-94 months).[94]

Among a cohort of 361 patients diagnosed with a myeloproliferative neoplasm between 1967 and 2017, median overall patient survival from time of diagnosis (stratified by age) was estimated to be:[96]

- 20 years (age ≤40 years)
- 8 years (age 41-60 years)
- 3 years (age >60 years)

Adverse prognostic factors

Include age at onset (>64 years), anemia (Hb <10 g/dL), constitutional symptoms, white blood cell count abnormalities (<4000/microliter or >12,000/microliter), thrombocytopenia, circulating blast cells (>1%), and certain cytogenetic abnormalities (-5/del5q, -7/del7q, trisomy 8, 12p-).[11] [45]

Mutations in CALR are associated with better overall survival compared with JAK2 V617F or MPL W515 mutations.[19] Type 1 CALR mutations (52-bp deletion) are more common, and have a more favorable impact on prognosis than type 2 CALR mutations (5-bp insertion) in PMF.[20] [21]

Triple-negative mutation status (negative for JAK2, CALR, or MPL mutations) is associated with a worse prognosis in patients with PMF.[19] [26]

ASXL1, EZH2, SRSF2, TP53, IDH1, IDH2, and U2AF1 mutations are considered high-molecular-risk mutations, associated with shorter overall and leukemia-free survival.[26] [27]

Diagnostic guidelines

International

NCCN clinical practice guidelines in oncology: myeloproliferative neoplasms (https://www.nccn.org/guidelines/category_1) [26]

Published by: National Comprehensive Cancer Network **Last published:** 2025

Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines) [42]

Published by: European Society for Medical Oncology **Last published:** 2015

The use of genetic tests to diagnose and manage patients with myeloproliferative and myeloproliferative/myelodysplastic neoplasms, and related disorders (https://b-s-h.org.uk/guidelines/guidelines) [43]

Published by: British Society for Haematology **Last published:** 2021

Diagnosis and evaluation of prognosis myelofibrosis: a British Society for Haematology guideline (https://b-s-h.org.uk/guidelines/guidelines) [39]

Published by: British Society for Haematology **Last published:** 2023

Treatment guidelines

International

NCCN clinical practice guidelines in oncology: hematopoietic cell transplantation (HCT) (https://www.nccn.org/guidelines/category_3) [92]

Published by: National Comprehensive Cancer Network **Last published:** 2025

NCCN clinical practice guidelines in oncology: myeloproliferative neoplasms (https://www.nccn.org/guidelines/category_1) [26]

Published by: National Comprehensive Cancer Network **Last published:** 2025

Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: updated recommendations by the EBMT/ELN International Working Group (https://www.ebmt.org/research/publications) [50]

Published by: European Society for Blood and Marrow Transplantation/ European LeukemiaNet **Last published:** 2023

Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines) [42]

Published by: European Society for Medical Oncology **Last published:** 2015

The management of myelofibrosis: a British Society for Haematology guideline (https://b-s-h.org.uk/guidelines/guidelines) [51]

Published by: British Society for Haematology **Last published:** 2023

Key articles

- Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 May;98(5):801-21. Full text (https://onlinelibrary.wiley.com/doi/10.1002/ajh.26857) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36680511?tool=bestpractice.bmj.com)
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: myeloproliferative neoplasms [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)
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- Kröger N, Bacigalupo A, Barbui T, et al. Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: updated recommendations by the EBMT/ELN International Working Group. Lancet Haematol. 2024 Jan;11(1):e62-74. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38061384?tool=bestpractice.bmj.com)
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Images

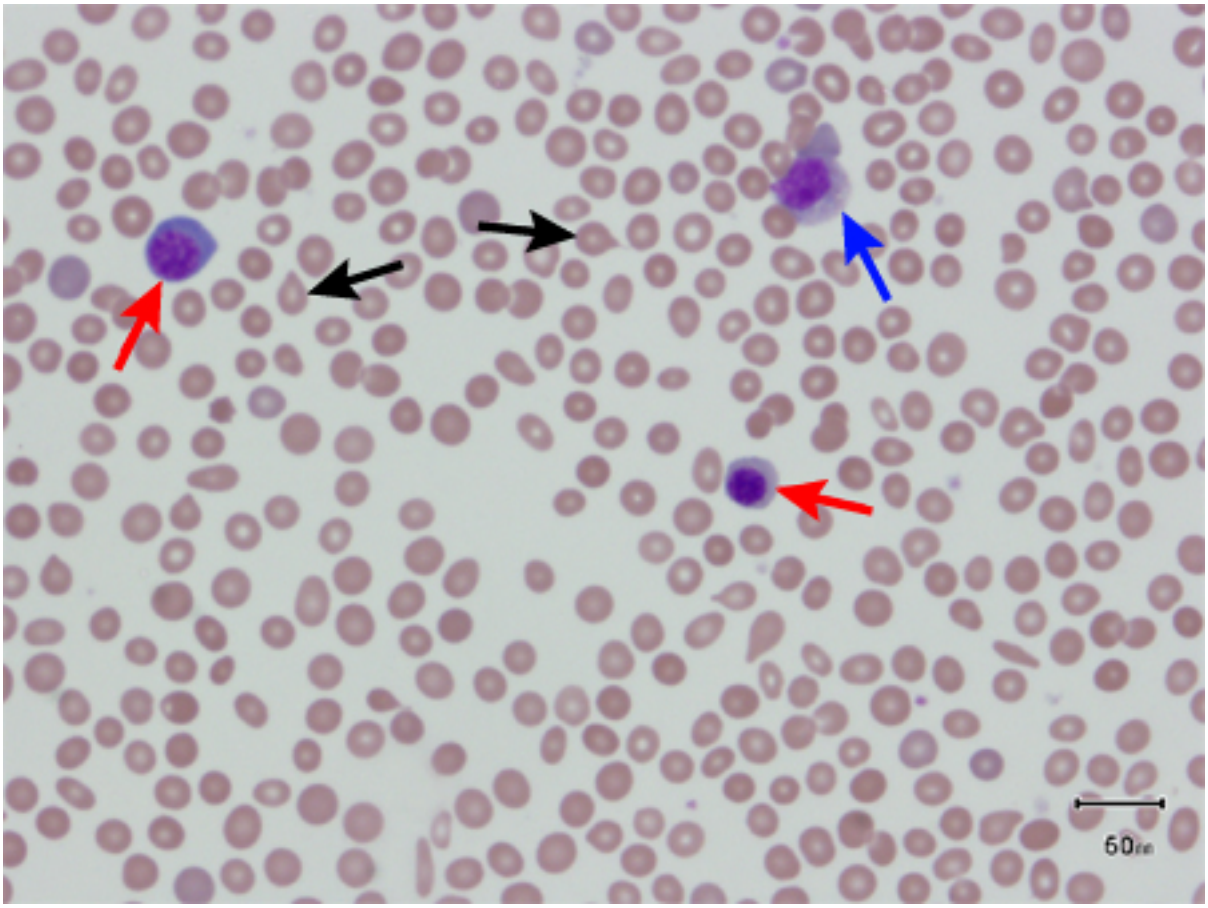

Figure 1: Peripheral blood smear showing teardrop red blood cells (black arrows), 2 nucleated red blood cells (red arrows), and a myelocyte (blue arrow)

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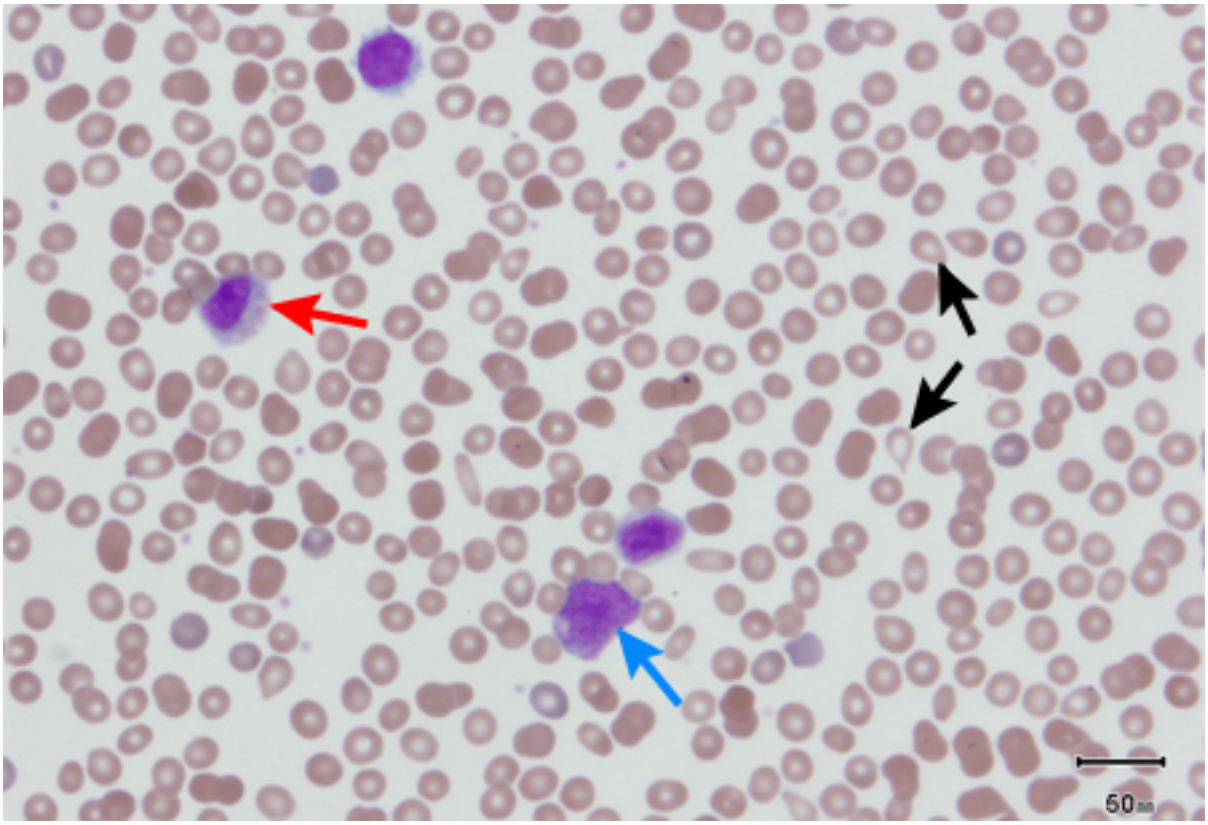

Figure 2: Peripheral blood smear showing leukoerythroblastic reaction: teardrop red blood cells (black arrows), myelocyte (red arrow), and promyelocyte (blue arrow)

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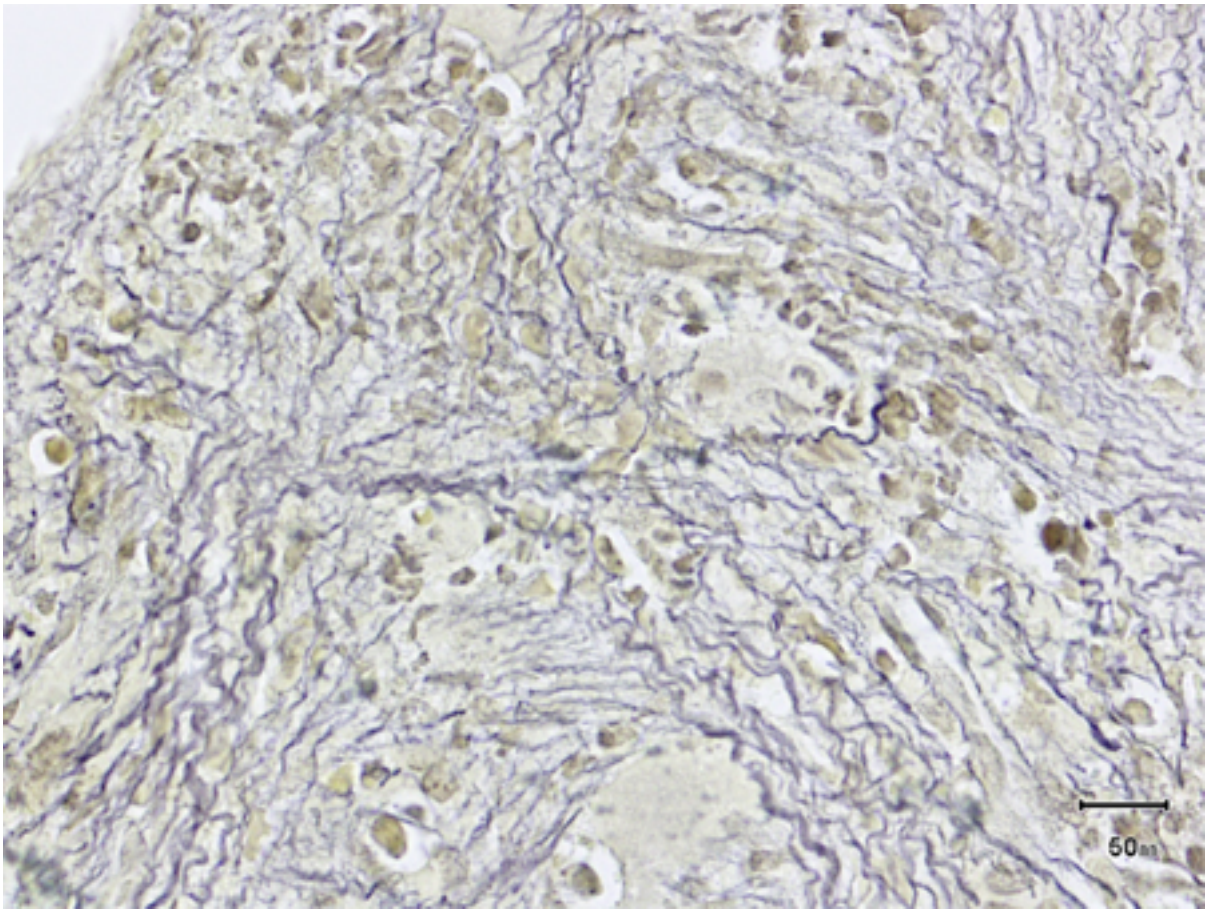

Figure 3: Bone marrow biopsy showing increased reticulin deposition

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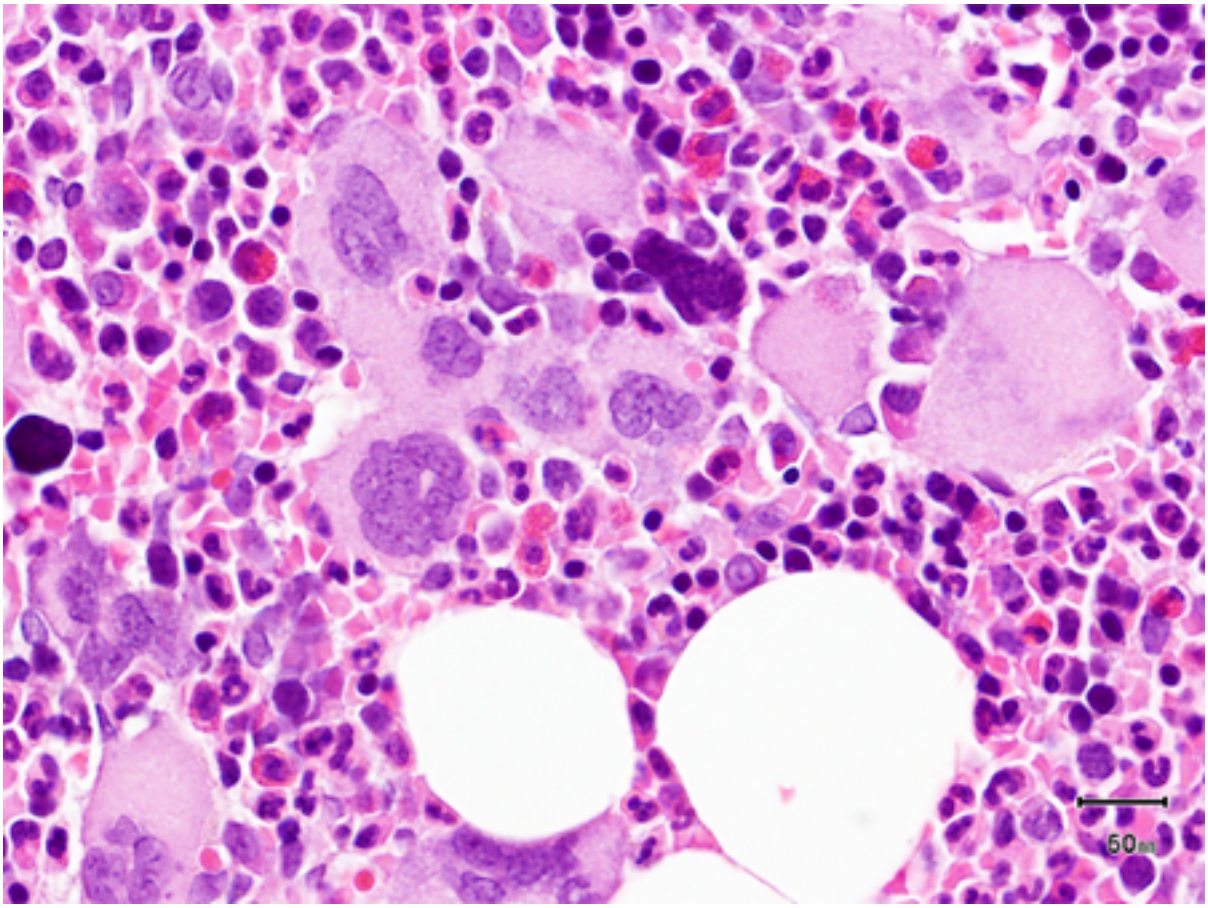

Figure 4: Trephine bone marrow biopsy showing megakaryocytic hyperplasia and clustering

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Figure 1 – BMJ Best Practice Numeral Style

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DISCLOSURES: JLS is an author of several references cited in this topic and has been reimbursed by GSK for a consultation.

// Acknowledgements:

Professor Jerry Spivak would like to gratefully acknowledge Dr Ashkan Emadi, a previous contributor to this topic.
DISCLOSURES: AE declares that he has no competing interests.

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DISCLOSURES: JTR is an author of several references cited in this topic.

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