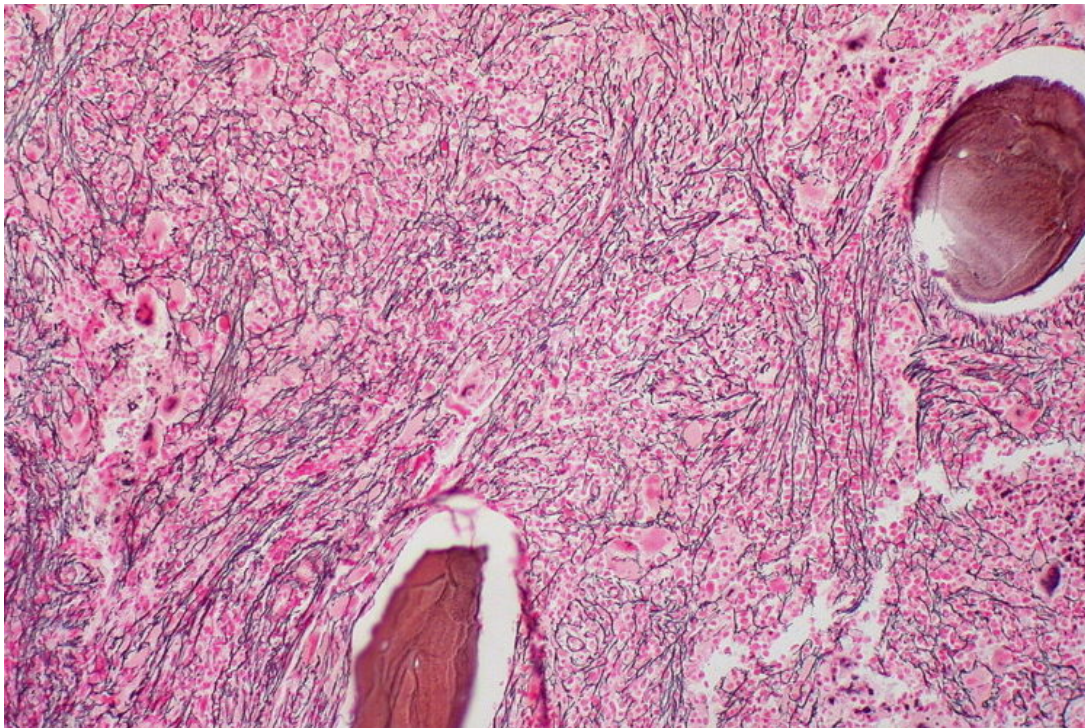


Myeloproliferative Disorder — Symptoms and Treatment

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Patients with myeloproliferative diseases can have chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia or myelofibrosis. Disease transformation from one type into another is common. Different tyrosine kinase genes mutations have been identified and found to be related to myeloproliferative diseases which include bcr-abl, JAK2, and CALR mutations. Treatment of proliferative diseases is usually symptomatic, but disease-specific treatments are also available.



Definition of Myeloproliferative Disease

Myeloproliferative diseases are a **group of blood disorders** that are characterized by an **increased number of one or more of the blood cell lines in the peripheral blood**, that are distinct from [acute leukemia](#).

Per this definition, myeloproliferative diseases can be classified into **four main diseases**:

1. **Chronic myelogenous leukemia**
2. **Polycythemia Vera**
3. **Essential thrombocythemia**

4. Primary myelofibrosis

Additionally, patients with one myeloproliferative disease are at risk of developing other myeloproliferative diseases or **acute leukemia**.

Epidemiology of Myeloproliferative Disease

The most common form of myeloproliferative diseases is **chronic myelogenous leukemia** (CML). CML is diagnosed in **more than 8,000** patients per year in the United States.

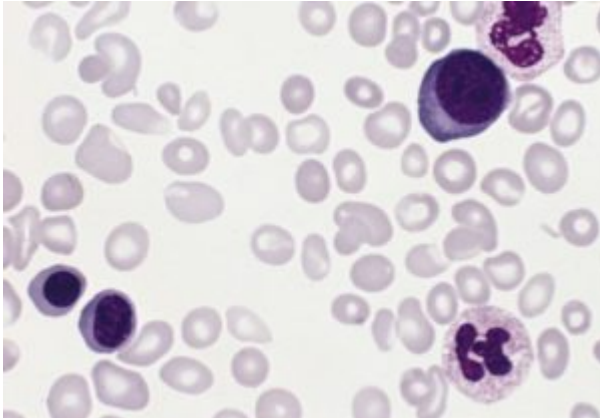


Image: "Blood smear in polycythemia vera." by The Armed Forces Institute of Pathology (AFIP) - PEIR Digital Library (Pathology image database). Image# 404905. License: Public Domain

The incidence of **polycythemia vera** in the United States is **5 per 1 million** per year. **Essential thrombocythemia** has an incidence of **1.5 per 100,000**, while **myelofibrosis** incidence is estimated to be around **0.9 per 100,000** per year.

Chronic myelogenous leukemia is associated with a significant risk of **mortality**. **Ashkenazi Jews** are at an increased risk of developing polycythemia vera compared to other races and ethnicities. The most common age group for the presentation of myeloproliferative diseases is **40 - 60 years**. These disorders are **related to aging**; hence, are rarely seen in young adults or children.

Pathogenesis of Myeloproliferative Disease

Several experimental designs to study myeloproliferative diseases have shown that the first step in the pathogenesis is to **acquire an activation mutation in tyrosine kinase genes**. For instance, the bcr-abl tyrosine kinase gene is found to be over-expressed and activated in patients with chronic myelogenous leukemia.

Philadelphia chromosome, which is a translocation between chromosomes 9 and 22, is responsible for the activation of this oncogene in a significant number of patients with chronic myelogenous leukemia.

Patients with other forms of myeloproliferative diseases usually have a **mutation in the Janus kinase (JAK2) gene**. Mutations in the JAK2 gene are responsible for **hypersensitivity** to the **endogenous hormone erythropoietin** which induces red blood cell maturation and proliferation.

The majority of the patients with primary myelofibrosis have an **acquired mutation in**

the CALR gene instead of JAK2 mutations. CALR mutations are also responsible for at least 60% of the cases of essential thrombocythemia.

Once a mutation in one of these genes is acquired, **clonal expansion** happens, which ensures the proliferation of the affected cells and, eventually, the development of the myeloproliferative disease.

Due to the overlap in the genetic mutations associated with the different myeloproliferative diseases, it becomes evident why **transformation from one disorder into another** is possible.

Presentation of Myeloproliferative Disease

Patients with myeloproliferative diseases share some **common symptoms** regardless of the exact type of the disease which includes **tiredness, weight loss, anorexia** and **splenomegaly** that causes abdominal discomfort and early satiety.

Patients can develop **easy bruising** or **thrombosis**, especially in essential thrombocythemia. Due to the **overload of uric acid** from the breakdown of large numbers of peripheral blood cells, patients are at risk of developing **gouty arthritis**.

Leukostasis may lead to priapism, tinnitus, and stupors. However, most of the patients are **asymptomatic**, and the diagnosis is usually incidental due to an abnormal blood count or peripheral blood smear.

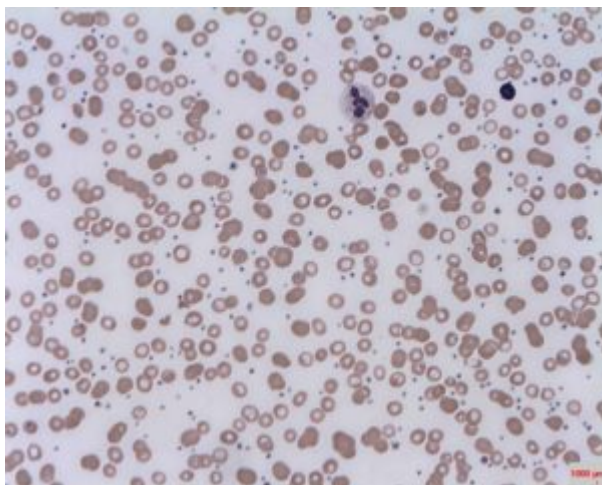


Image: "Thrombocytosis or thrombocythemia is the presence of abnormally high platelet counts." by Erhabor Osaro (Associate Professor) - Own work. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

A physical examination can reveal certain signs in a myeloproliferative disease that are not specific but can decrease the physician's threshold to suspect the condition. **Pallor** or **plethora** are common in patients with polycythemia vera.

Patients with chronic myelogenous leukemia and polycythemia vera might develop **splenomegaly**, hence an **abdominal examination** is essential to exclude this common finding. Patients can develop a **fever** and a **painful maculopapular rash**, which is known as **acute febrile neutrophilic dermatosis**.

Diagnostic Work-up for Myeloproliferative Disease

Laboratory investigations are the first diagnostic tests to be ordered in a patient suspected to have the myeloproliferative disease.

A **complete blood count with differential counts**, sometimes combined with **microscopic examination of peripheral blood smear**, is indicated. It is usually possible to identify the expansion of a single cell line or more commonly multiple cell lines. **Leukocyte alkaline phosphatase testing** is indicated to differentiate between CM and other forms of [leukemia](#).

The **detection of the bcr-abl gene** is helpful in differentiating between CML and other myeloproliferative disorders; therefore, a **polymerase chain reaction** is indicated to confirm the presence of this gene.

As we have explained, patients with myeloproliferative disease are at an increased risk of developing hyperuricemia and gouty arthritis; therefore, **serum uric acid levels** should be checked in patients with the myeloproliferative disease.

Patients with **isolated splenomegaly** or **hepatosplenomegaly** might need **ultrasonography** and **other imaging studies** to evaluate the size of these two organs and plan possible **surgical intervention** if needed.

A **bone marrow aspiration with cytogenetic testing** is indicated to confirm the diagnosis of myeloproliferative disease. **PCR testing of the bone marrow aspirate** can differentiate between CM and other forms of myeloproliferative diseases by detection of bcr-abl, JAK2 or CALR genes.

A **histologic examination of the bone marrow aspiration** is also helpful in providing more clues about the diagnosis. Hypercellularity of a single blood cell precursor stem-cells or multiple is a common finding. Patients with myelofibrosis show bone marrow fibrosis activated fibroblasts and excess reticulin in the extracellular media.

Treatment of Myeloproliferative Disease

Treatment of myeloproliferative diseases is specific to the exact type of disease the patient has.

Treatment of polycythemia vera

Polycythemia vera is a condition that is not associated with a significant risk of increased mortality; therefore, treatment is mainly **supportive**. Patients benefit from **routine phlebotomies** which **decrease iron overload on body organs**.

Patients with a previous history of **thrombosis**, those **older than 69** years of age, and those who become **resistant to phlebotomies** are possible candidates for hydroxyurea. **Hydroxyurea** is a **potent bone marrow suppression therapy** that decreases the production of red blood cells.

JAK2 mutations are commonly identified in polycythemia vera and **ruxolitinib** is a biologic drug available to inhibit the JAK1/JAK2 pathways. Currently, it is recommended to use ruxolitinib only in patients who fail to respond to hydroxyurea.

Treatment of essential thrombocythemia

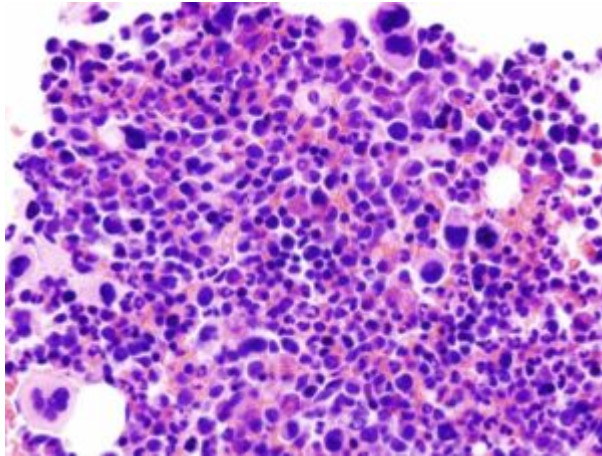


Image: "Histopathological image representing a bone marrow aspirate in a patient with essential thrombocythemia." by No machine-readable author provided. KGH assumed (based on copyright claims). – No machine-readable source provided. Own work assumed (based on copyright claims). License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Patients with essential thrombocythemia are at an increased risk of either **thrombosis** or **bleeding** due to **dysfunctional platelets**. The mainstay treatment of essential thrombocythemia aims to lower the number of produced platelets in the peripheral blood.

Anagrelide and **hydroxyurea** are the most commonly used drugs to inhibit platelet production. **Anticoagulation therapy**, along with **Aspirin** and **other antiplatelet therapy** should be tailored to the individual case and be not routinely used.

Treatment of myelofibrosis

Patients with myelofibrosis can be either asymptomatic or symptomatic. **Asymptomatic** patients should be **closely monitored** until they develop symptoms.

Symptomatic patients should be treated according to their main symptoms as there are currently no definitive treatments for myelofibrosis.

Anemia can be corrected by the administration of **erythropoiesis-stimulating drugs** or **immunosuppression**. The transfusion is usually needed in terminal illness. Patients with **massive splenomegaly** benefit from **splenectomy**. The only possible curative treatment for these patients is **allogeneic hematopoietic stem cell transplantation**.

JAK1/JAK2 inhibitor ruxolitinib is highly recommended in any patient with myelofibrosis and massive splenomegaly.

Treatment of chronic myelogenous leukemia

Patients with CML commonly have the **bcr-abl gene mutation**. **Imatinib**, which is a bcr-abl tyrosine kinase inhibitor, was found to be highly effective in the treatment of chronic myelogenous leukemia with complete response in up to 76% of the cases.

Interferon-alpha is indicated in patients with **blast crisis**, **accelerated phase CML** and **chronic phase CML**. It can induce remission in a significant number of patients. In the case of interferon-alpha failure, treatment with **Imatinib** is indicated. Patients, who report side effects with interferon-alpha, can be started on **hydroxyurea** and, if no

response could be identified, switched to Imatinib.

Unfortunately, a few patients with CML develop **resistance to Imatinib**. In these patients, **other tyrosine kinase inhibitors**, such as **Dasatinib** or **Nilotinib**, should be used. Younger patients might be possible candidates for **hematopoietic stem cell transplantation**.

Unfortunately, the prognosis remains very bad for patients with CML who progress to the **blast stage**.

References

[Myeloproliferative disorders](#) via nih.gov

[Myeloproliferative Disease](#) via medscape.com

[The chronic myeloproliferative disorders: clonality and clinical heterogeneity](#) via nih.gov

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