# IDIOPATHIC MYELOFIBROSIS CLINICAL-LABORATORY DIAGNOSIS AND TREATMENT METHODS

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Idiopathic or primary myelofibrosis is characterized by the development of bone marrow fibrosis (myelofibrosis) following pathological proliferation of myeloid cells.

The excessive proliferation of myeloid cells stimulates the production of collagen by the stromal cells (fibroblasts) in the bone marrow, which is influenced by the release of various humoral factors. These factors, including collagen types I, III, V, VI, fibronectin, and vitronectin, lead to the deposition of collagen in the bone marrow. Therefore, the abnormal expansion of hematopoiesis in the proliferative phase of idiopathic myelofibrosis is accompanied by its replacement with fibrotic tissue.

Clinical presentation. Idiopathic myelofibrosis has distinct clinical manifestations. The disease is usually asymptomatic in the early stages and only requires monitoring for the development of splenomegaly. Characteristic features of extramedullary hematopoiesis can be seen in the peripheral blood, such as nucleated red blood cells, myelocytes, and promyelocytes. Initially, the disease may present with erythrocytosis, which can progress to anemia. The number of leukocytes and platelets can be normal, decreased, or increased. Obtaining a bone marrow biopsy for diagnosis of myelofibrosis of any etiology is often challenging. The activity of leukocyte alkaline phosphatase and plasma alkaline phosphatase is usually elevated. The activity of leukocyte alkaline phosphatase is either normal, decreased, or increased. Physical examination may reveal splenomegaly and hepatomegaly. Osteosclerosis is a typical finding on X-ray examination.

Stages of idiopathic myelofibrosis. The disease progression is divided into two distinct phases:

- Chronic phase;
- Terminal phase or blast transformation phase.

The chronic phase is the initial phase of idiopathic myelofibrosis and accounts for the majority of newly diagnosed patients (over 90%). The most characteristic features of this phase are the changes in the complete blood count (gradual shift towards immature forms in the neutrophil and erythroid series), increase in liver and spleen size, and signs of intoxication (fever, weight loss, night sweats).

The blast phase is defined by the presence of >20% blast cells in the peripheral blood and bone marrow, indicating terminal progression of the disease.

From a morphological perspective, the following stages are distinguished:

- Profibrotic/early stage;
- Fibrotic stage.

Differential diagnosis between these stages is based on the histological examination of bone marrow trephine biopsy.

The transition from the profibrotic/early stage to the fibrotic stage occurs within 4.2 years in 65% of cases; progression to overt leukemia occurs in 5-30% of cases. However, the profibrotic/early stage of idiopathic myelofibrosis can persist for more than ten years without progressing to the fibrotic stage.

According to the WHO classification, the diagnosis of idiopathic myelofibrosis relies on the combination of clinical, morphological, molecular, and cytogenetic features (Table 1).

The overall survival of patients with idiopathic myelofibrosis is lower compared to individuals of the same gender and age, with a 31% reduction. The average survival is about 5 years, but younger patients may live longer.

Table 1. Criteria for idiopathic myelofibrosis

| Large criteria* | Small criteria |
|---|---|
| 1. Proliferation and atypical** megakaryocytes are combined with reticulin and / or collagen fibrosis of the bone marrow. In the absence of pronounced reticulin fibrosis, increased bone marrow cellularity with the reproduction of granular cells and invasiveness of erythropoiesis (profibrotic cell phase of primary myelofibrosis) | 1. Increase LDG Activity |
| 2. Lack of criteria forother myeloproliferative diseases (politsiemia, BCR-ABL1 + chronic myeloid leukemia, myeloid plastic syndrome). | 2. Palpable Divorce |
| 3. Detection of clonal markers (MPLW515K/L, JAK2V617F) or lackof symptoms of reactive myelofibrosis (infections, autoimmune diseases, chronic inflammation, hairy cell leukemia, other lymphoproliferative diseases, solidtumor metastases, toxic myelopathies) | 3. Leukoeritroblastosis |
| | 4. Anemia |
| | 5. Constitutional symptoms (strong night sweat, weight loss >10%<br>Unprovoked fever for 6 months >37.5°C or diffuse bonepain) |

** Idiopathic or primary myelofibrosis requires three large and two small bone marrow samples for diagnosis.

*** According to the JSST classification, small bone marrow samples only take 1-4 samples within themselves.

Diagnostic methods. The diagnostic procedure for patients with idiopathic myelofibrosis includes the following medical services:

- Initial general medical examination (observation, consultation);
- Complete blood count, including platelets and reticulocytes;
- Determination of alkaline phosphatase level in the blood;
- Determination of total protein level in the blood;
- Determination of ALT and AST levels in the blood;

 Determination of sodium, potassium, and calcium levels in the blood plasma;
 Determination of creatinine, urea, and uric acid levels in the blood plasma;
 Determination of LDG level in the blood;
 Serologic reaction to various infections and viruses;
 Molecular genetic analysis of peripheral blood (for the presence of JAK2 gene V617F mutation, using qualitative PCR, and if absent, determination of CALR and MPL gene mutations);
 Determination of iron, ferritin, transferrin, folic acid, vitamin B12, and erythropoietin concentration in the blood plasma;
 PCR analysis of BCR-ABL gene (qualitative) (transcripts p210, p190);
 Obtaining and analyzing bone marrow cytologic preparations;
 Examination of the chromosomal apparatus (karyotype);
 Obtaining and examining a histological sample of bone marrow tissue;
 Ultrasonography of the liver and spleen;
 Cytological examination of bone marrow preparations using cytochemistry;
 Immunophenotyping of bone marrow cells.

Complete blood count: hemoglobin - 162 g / l; erythrocytes - 5.0x1012 / l, hematocrit - 47%, MCV - 100 fl, MCH - 31 pg, leukocytes - 28×109/l. Leukocyte differential count: eosinophils - 2%, basophils - 1%, myelocytes - 5%, metamyelocytes - 14%, band neutrophils - 10%, segmented neutrophils - 58%, lymphocytes - 15%, monocytes - 5%, platelets - 645×109/l, ESR 15 mm/hour.

Table 2. Differential diagnosis of idiopathic myelofibrosis

| Diagnostics | Chronic myeloid leukemia | Idiopathic myelofibrosis | Real polities |
|---|---|---|---|
| Divorce | Increased | Significant increase | Small or powerful increase |
| Number of L ecocities | $50x10^9$/l and high | $20–30x10^9$/l | $10–20x10^9$/l |
| Number of platelets | normal, high | Normal, high or low | Normal, high or low |
| Ph-chromosome | Bow | No | No |
| embarrassment of the JAK2 V617F gene | No | Discovered in '40<br>In 50% of cases | discovery<br>in 90-95% of cases |
| Alkali phosphatase content in leukocytes | Low, insome cases normal or increased | Rises,rarely normal or decreases | Increased |
| $B_{12}$Vitamin composition in the bloodstream | Top | Normal or<br>slightly increased | normal or high |
| Milgram | Bone marrow cells are rich in elements, unfulfilled forms of granulopoiesis, red self-cells decrease | Decreases in cellular elements, superiority of mature forms of granulopoiesis | The enlargement of all cells of hematopoiesis |

| | | | |
|---|---|---|---|
| Trepanations | Myeloid hyperplasia with the superiority of undefeated granulocytes | Polymorphous. megacaryotsitosis. Focal fibrosis, low-cell bone marrow, megakaryocytes. Diffuse myelofibrosis, with the compression of the active bone marrow. combination of osteosclerosis with myelofibrosis | The enlargement of all cells of hematopoiesis |

Treatment. Currently, various methods are used in the treatment of idiopathic myelofibrosis, and they can be divided into several groups:

- allogeneic transplantation of hematopoietic stem cells;
- drug therapy;
- surgical treatment (splenectomy, portal hypertension correction);
- radiation therapy;
- blood component therapy;
- symptomatic treatment (antiplatelet and anticoagulant drugs). Drug therapy is considered the main method of treating idiopathic diseases. This therapy, even if it does not cure the disease, can stop its progression, preserve the quality of life for patients, and increase life expectancy. Traditional drugs are used for the treatment of primary myelofibrosis. The purpose of using these drugs is to control the proliferation of fibrous tissue and to monitor blood parameters to prevent complications. It is preferable to prescribe doses selected based on individual tolerance, which allows monitoring of blood volume. As monotherapy, the following drugs are usually used in low doses:

- hydroxyurea - 10-30 mg/kg per day;
- mercaptopurine - 2 mg/kg per day;
- cytarabine - 10-20 mg/m2 per day for a course of 10-14 days per month;
- busulfan - 0.5-4 mg per day, total dose up to 200 mg.

In patients under 60 years old with early-stage idiopathic myelofibrosis without massive splenomegaly, interferon alpha therapy may be recommended as a first-line treatment. The dose and administration method are also chosen individually, taking into account the patient's tolerance: 1.5-3 million IU are administered under the skin every day. Combining interferon alpha with cytostatic drugs can improve the effectiveness of treatment and allow for reducing the dose of each drug with improved tolerance.

To stop and reduce anemia, drugs that stimulate erythropoiesis can be used.

So far, only dreamlining has been approved for the use of JAK2 inhibitors. The drug may also be considered as a treatment for patients who need rapid reduction of spleen size and/or relief of symptoms of hypersplenism before allogeneic hematopoietic stem cell transplantation (Table 5.8).

Follow-up care. Patients need to visit their doctor every month.

3rdadval. Preparations used to treat idiopathic myelofibrosis

| International Non-Proprietary Name | Markup Frequency | Calculated Daily Dose | Equivalent term worker dose |
|---|---|---|---|
| Dori tools thataffect the blood vesselsystem, dose of exposure | | | |
| Heparin sodium | 0,5 | 24 000ED | 240000ED |
| Clopidogrel | 0,03 | 75mg | 525mg |
| Pentoxifylline | 0,05 | 1500mg | 10 500mg |
| Preparations for the treatment of analgesics, non-steroidal inflammatory drugs, rheumatoid arthritis and podagra | | | |
| Acethylsalitsil acid | 1.0 | 100mg | 500mg |
| Allopurinol | 0,8 | 300mg | 3000mg |
| Drugs that affect the endocrine system | | | |
| non-sex hormones, synthetic substances and antihormones | | | |
| Prednisolone | 0.3 | 30 mg | 900 mg |
| For the treatment and acquisition of infections | | | |
| Antiviraldrug tools | | | |
| Interferon alpha 2b | 0,5 | 5 mln IU | 1825 million IU |
| Antitumor, immunosuppressivedrug tools | | | |
| Hydroxymochevina | 1.0 | 15,000 mg | 9000 mg |
| Mercaptopurine | 0.2 | 1 mg | 60 mg |
| Busulfan | 0.2 | 2 mg | 200 mg |

They need to be examined by a hematologist with monitoring of general blood tests and biochemical indicators every 2-3 months.

Instructions for hospitalization.

- Newly diagnosed idiopathic myelofibrosis;
- Febrile neutropenia;
- Hemorrhagic syndrome.

The need to continue the chemotherapy regimen is considered for hospitalization.

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