# Transformation of primary myelofibrosis into acute myeloblastic leukemia: clinical case

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**Abstract.** Primary myelofibrosis (PMF) is a disease from the group of Ph–negative myeloproliferative tumors, which is characterized by bone marrow fibrosis, splenomegaly and extramedullary hematopoiesis. The mean life in PMF ranges from 7.6 to 10 years and varies widely depending on the appearance of additional mutations and a higher degree of malignancy. Most patients have an indolent flow, and in some patients with PMF, the disease progresses rapidly with the development of acute myeloblastic leukemia. The international stratification system DIPSS-plus allows predicting the occurrence time of the PMF blast transformation phase. The article presents a case of early PMF transformation into acute myeloblastic leukemia in a patient with a heterozygous mutation in the JAK2 gene and an intermediate risk-2 established according to the International Prognostic Scoring DIPSS-plus. The patient received standard cytoreductive therapy.

## 1 Introduction

Primary myelofibrosis (PMF) according to the WHO classification (2016) is one of the benign Ph-negative myeloproliferative diseases. The article reports a rare case of early PMF transformation in a 53-year-old patient who ended fatally, despite the timely diagnosis of PMF with the detection of a heterozygous mutation in the JAK2 gene and the establishment of an intermediate risk-2 on the International Prognostic Scoring DIPSS-plus.

*The aim of the study* is to present a clinical observation of the early transformation of primary myelofibrosis into acute myeloblastic leukemia.

## 2 Materials and methods

*Description of the clinical case.*

Patient T., 53 years old, in December 2013, for the first time noticed heaviness and pain in the left hypochondrium, an increase in the volume of the abdomen, sweating and general weakness.

Patient appealed to the polyclinic at the place of residence, where doctors suspected a myeloproliferative disease, after which the patient was sent to a hematology hospital.

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Anamnesis reveals that the patient served in the missile forces in Afghanistan (1979–1980), suffered from Botkin's disease (1985), abused alcohol, and was registered at a gastroenterologist's dispensary with a diagnosis of Cirrhosis of the liver, class "B" according to Child-Pugh.

On examination, one could see the patient's condition of moderate severity. The skin and visible mucous membranes were pale, there were no hemorrhages. No pathology was detected from the cardiovascular and respiratory systems. The abdomen was enlarged in volume due to hepatosplenomegaly. There was no peripheral edema.

The complete blood count (CBC) dated 14.01.2014 shows: hemoglobin – 89 g/l; erythrocytes – $3{,}36x10^{12}$/l; leukocytes – $23{,}1x10^{9}$/l; banded neutrophils – 15%; segmented neutrophils – 50%; lymphocytes – 6%; monocytes – 4%; myelocytes – 18%; metamyelocytes – 4%; basophils – 3%, platelets – $679{,}0x10^{9}$/l; ESR – 38 mm/h. The biochemical blood test shows an increase in the level of lactate dehydrogenase (LDH), 2053 u/l.

The ultrasound of the abdominal cavity organs dated 15.01.2014 shows: the height of the right lobe of the liver is 176 mm, the thickness is 135 mm. The height of the left lobe of the liver is 103 mm, the thickness is 66 mm. The contours of the liver are smooth, the echostructure is homogeneous, and the echo density is increased. The portal vein is 13 mm. The gallbladder is oval. The bubble wall has no features. There are echogenic contents in the bladder cavity. The common bile duct is 4 mm. The pancreas is not enlarged, the contours are smooth, the echostructure is homogeneous. The echo density is average. The splenic vein is 9 mm. The spleen is enlarged, 200x78 mm. The contour is smooth. The echostructure is homogeneous. In the area of the spleen gate, an additional lobe with a diameter of 24 mm is detected. Conclusion: diffuse changes in the liver parenchyma. Hepatosplenomegaly. An additional portion of the spleen.

Myelogram data dated 15.01.2014: blasts – 3%; neutrophilic myelocytes – 12.7%; neutrophilic metamyelocytes – 4%; banded neutrophils – 26.7%; segmented neutrophils – 42%; neutrophil maturation index 0.1 RU; eosinophils – 0.8%; basophils – 2.0%; monocytes – 0.2%; lymphocytes – 6.3%; all leukocyte cells – 94.7%; basophilic normocytes – 0.3%; polychromatophilic normocytes – 0.2%; oxyphilic normocytes – 1.8%; all erythroid cells – 2.3%; erythrokaryocyte maturation index – 1.1 RU; leukoerythroblastic ratio is 41:1 RU. Conclusion: bone marrow is cellular, polymorphic. The hematopoiesis type is normoblastic. The erythroid lineage is sharply narrowed. The myeloid lineage is hyperplastic due to mature forms of neutrophils. The basophils number has increased. Megakaryocytes are not detected. Histological study of the iliac trepan-biopsy No. 9695 dated 17.01.2014: There is no fat component in the biopsy. There is a significant narrowing of all lineages due to the growth of connective tissue (both in the form of fibrosis fields and in the form of cicatricial connective tissue). Single immature bodies of osteoid. A lot of megakaryocytes are medium-sized and smaller, with acceptable activity. Among the "white row" cells, granulocytes significantly predominate, metamyelocytes are found, there are many segmented cells; there are few lymphocytes. Conclusion: the morphological picture is characteristic of myeloid fibrosis (Fig. 1–4).

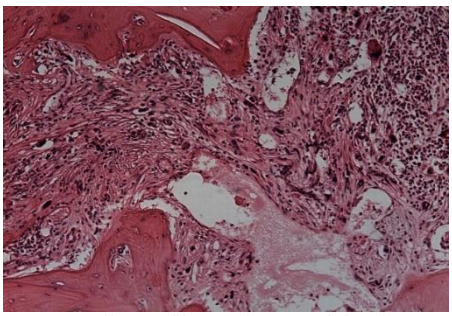

**Fig. 1**. Collagen fibrosis in one of the sinuses. Hematoxylin-eosin. Magnification x100.

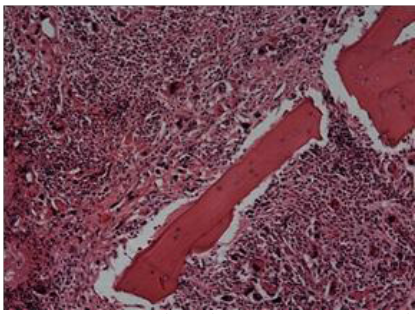

**Fig. 2.** Paratrabecular arrangement of megakaryocytes. Hematoxylin-eosin. Magnification x100.

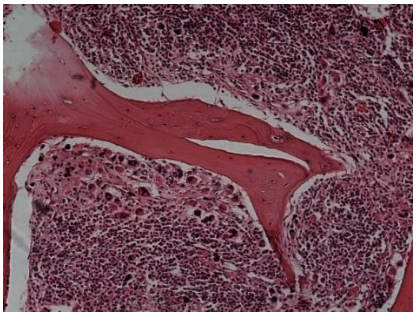

**Fig. 3.** Paratrabecular arrangement of large megakaryocytes in the form of a cluster. Hematoxylin-eosin. Magnification x100.

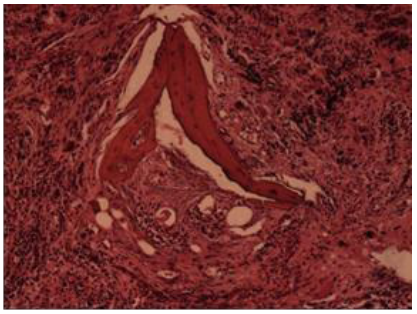

**Fig. 4.** The focus of osteomyelosclerosis. Hematoxylin-eosin. Magnification x100

Cytogenetic study of the bone marrow dated 26.01.14: no chromosomal pathology was detected in the examined bone marrow cells. However, a genetic study using the allele-specific polymerase chain reaction in real time to detect the V617F mutation in the JAK2 gene showed the presence of a heterozygous GT mutation (JAK2 gene, rs 77375493). This mutation is associated with an increased risk of thrombosis in the presence of myeloproliferative disease [29, 30].

Based on the obtained examination data, doctors drew the following diagnosis: “Primary myelofibrosis, chronic phase; intermediate risk-2 on the DIPSS-plus”. The therapy with hydroxyurea at a dose of 1500 mg/s was started. The patient was discharged in a satisfactory condition to continue treatment on an outpatient basis.

At discharge from the hospital, the blood counts were as follows: hemoglobin – 83 g/l; erythrocytes – 3,08x1012/l; leukocytes – 8,8x109/l; platelets – 493,0x109/l; myelocytes – 2%; banded neutrophils – 11%; segmented neutrophils – – 71%; basophils – 5%; eosinophils – 1%; monocytes – 1%; lymphocytes – 9%; normocytes – 5:100.

Repeated hospitalization after 10 months in December 2015 due to deterioration of the condition: faint, pain in the left hypochondrium, despite taking hydroxyurea. The CBC shows: hemoglobin – 89 g/l; erythrocytes – 2,7x1012/l; leukocytes – 4,3x109/l; banded neutrophils – 4%; segmented neutrophils – 62%; eosinophils – 3%; basophils – 3%; monocytes – 3%; lymphocytes – 25%; platelets – 365,0x109/l; ESR –18 mm/h.

Ultrasound of the abdominal cavity organs dated 25.12.2015 shows: diffuse liver changes. Splenomegaly (190x90x130 mm). Chronic cholecystitis. Nephroptosis on the left: shifted by 7–8 cm.

Myelogram dated 28.12.2015 shows: small-cell bone marrow. Counting per 100 cells: banded neutrophils – 4%; segmented neutrophils – 75%; lymphocytes – 20%; monocytes – 1%. Probably diluted with peripheral blood.

Histological study of the iliac trepan-biopsy No. 3381-83 dated 07.12.2015 shows: in the preparations, bone marrow with uneven growth of the fibroreticular stroma, in some places up to complete obliteration of the bone marrow space. The trabeculae of the bone are thickened, with uneven lines, glued together. Myeloid elements are at different stages of maturation, there are relatively many blast cells. The content of lymphoid elements is reduced. The number of megakaryocytes is increased, reaches 30-35 in the field of vision. They are visible both in sclerosed areas and in areas of low cell content. Their size is small, their shape is mostly rounded, the platelet lacing is small. Erythropoiesis is suppressed, but all intermediate growth cells are traced (Fig. 5, 6).

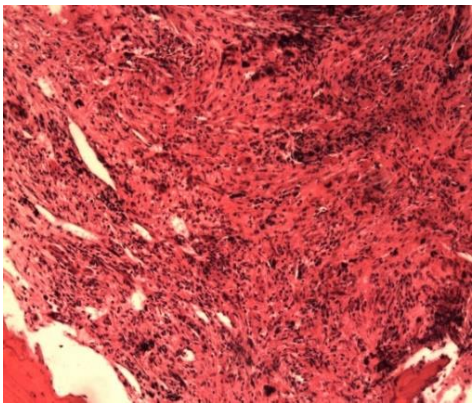

**Fig. 5.** Bone marrow cells are located among the collagen fibers. Hematoxylin-eosin. Magnification x100.

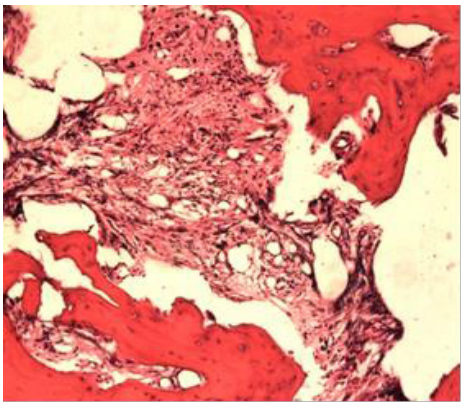

**Fig. 6.** Severe myelofibrosis. Hematoxylin-eosin. Magnification x100

Against the background of taking hydroxyurea at a dose of 1500 mg/day, disaggregant therapy (Trombo ASS 100 mg/s), the size of the spleen decreased to 14x10 cm, the hemoglobin level increased to 95 g/l; the number of leukocytes was $4,7x10^9$/l; thrombocytosis remained $408,0x10^9$/l.

After 9 months, patient was hospitalized again due to anemia (hemoglobin – 62 g/l, erythrocytes – 2,1x1012/l) and thrombocytopenia ($141,0x10^9$/l). The liver and spleen protrude from under the costal edge by 4 cm and 10 cm, respectively. A course of chemotherapy with small doses of cytosine-arabinoside (20 mg/s) s/c for 21 days, and hemotransfusion were started. Patient was discharged with a slight improvement and a recommendation to continue treatment with hydroxyurea at a dose of 1500 mg/day. Subsequently, frequent hospitalizations due to the steady progression of the disease, accompanied by severe anemia syndrome and dependence on blood transfusions.

In November 2016, patient was hospitalized for emergency indications. The CBC dated 05.11.2016 shows: hemoglobin – 53 g/l; erythrocytes – $1,6x10^{12}$/l; leukocytes $2,6x10^9$/l; platelets – $67,0x10^9$/l; ESR – 25 mm/h. Microscopy: blasts – 3%; myelocytes – 4%; metamyelocytes – 1%; banded neutrophils – 13%; segmented neutrophils – 56%; eosinophils – 1%; basophils – 1%; monocytes – 5%; lymphocytes – 16%. Again, the hospital carried out a course of treatment with cytosine-arabinoside at a dose of 30 mg/s (No. 11), transfusion of erythrocyte mass. They noted a positive effect in the form of a spleen size reduction from +16 to +8 cm; the liver – from +6 cm to +3 cm. Maintenance chemotherapy was continued with hydroxyurea at a dose of 1500 mg per day. In February 2017, another course of chemotherapy with small doses of cytosine-arabinoside was carried out, after which the patient did not apply for seven months, and only in October 2017 was hospitalized in a serious condition with profound anemia and severe splenomegaly occupying the entire left half of the abdominal cavity (+21 cm). Upon admission the CBC shows: hemoglobin – 45 g/l;

erythrocytes – $1,5x10^{12}$/l. leukocytes – $1,5x10^{9}$/l; blasts – 6%; metamyelocytes – 1%; banded neutrophils – 12%; segmented neutrophils – 38%; eosinophils – 1%; basophils – 3%; monocytes – 8%; lymphocytes – 31%, erythro-normoblasts – 1:100, platelets – $20,0x10^{9}$/l; ESR – 60 mm/h.

Due to the threatened rupture of the spleen and severe blood transfusion dependence, a splenectomy was performed (23.11.2017). Macropreparation: 45x20x10 cm, dense, uneven. Weight – 2600 mg. The operation was complicated by parietal thrombosis of the portal and splenic veins. Anticoagulant, disaggregant and supportive chemotherapy with hydroxyurea was performed at a daily dose of 1500 mg.

At this stage of observation, the doctors established the blast phase of primary myelofibrosis, the high-risk group 3 according to DIPSS-plus. Condition after splenectomy. Complications: Post-transfusion iron overload. Parietal thrombus of the portal and splenic veins.

Since December 2017, alpha-interferon has been added to hydroxyurea therapy for 3 million units 3 times a week.

In March 2018 – urgent hospitalization due to severe anemia (Hb – 51 g/l) and thrombocytosis ($589,0x10^{9}$/l). The number of leukocytes – $13,6x10^{9}$/l; ESR – 45 mm/h; microscopy: blasts – 5%; metamyelocytes – 3%; banded neutrophils – 3%; segmented neutrophils – 27%; eosinophils – 1%; monocytes – 6%; lymphocytes – 55%.

USDG of the liver vessels dated 05.04.18: Hepatomegaly. The blood flow in the portal vein is not disturbed. No hemodynamic stenoses or thrombosis were detected. They performed transfusions of erythrocyte mass, alpha-interferon million units 3 times per week. Patient was discharged with recommendations to continue therapy with hydroxyurea and intron A.

Since July 2018 until January 2019, the patient was on outpatient observation and received combination therapy with hydroxyurea and alpha interferon. Due to the deterioration of condition, patient was repeatedly hospitalized in the hematology department of a multidisciplinary hospital. The CBC dated 08.01.2019 shows: hemoglobin – 69 g/l; leukocytes – $13,0x10^{9}$/l; platelets – $67,0x10^{9}$/l, ESR – 39 mm/h. Microscopy: blasts – 30%; myelocytes – 34%; banded neutrophils – 3%; segmented neutrophils – 13%; eosinophils – 1%; basophils-1%; monocytes-8%; lymphocytes-10%; normocytes 476:100. In connection with the transformation of primary myelofibrosis into acute myeloblastic leukemia, treatment courses with decitabine (dacogen 34,5 mg) were started monthly against the background of hemotransfusion and chelation therapy with exjade 500 mg 2 times per day. A total of 12 courses of decitabine chemotherapy were performed. Only clinical improvement was achieved: the size of the liver, sweating and weakness decreased slightly. During a break from the treatment course, they performed supportive chemotherapy with hydroxyurea (500 mg 1 time per day).

The last hospitalization due to the deterioration of the condition occured on 10.05.2019, the symptoms included the pain in the bones, dyspnea, palpitations and pronounced weakness. The ambulance team was taken to the emergency room of a multidisciplinary hospital. The CBC shows: hemoglobin – 60 g/l; platelets – $42,0x10^{9}$/l; leukocytes – $37,7x10^{9}$/l; blasts – 66%; banded neutrophils – 5%; segmented neutrophils – 21%; monocytes – 2%; lymphocytes – 6%; ESR – 52 mm/h. Due to the severity of the condition, patient was urgently hospitalized to the hematology department. On examination, the condition is extremely serious. The skin is pale earthy in color. Respiration rate – 24 per min. Auscultation in the lungs is vesicular breathing, wet wheezing in the posterior-lower parts of the chest. Saturation without oxygen is 85%, on oxygen – 97%. Heart tones of weakened sonority, tachycardia heart rate – 120 per minute, blood pressure 80/50 mm Hg. The abdomen is increased in volume due to hepatomegaly and ascites. On 11.05.2019 at 18:55, due to increasing cardiovascular and respiratory insufficiency, patient was transferred to the

intensive care unit. Fibrobronchoscopy dated 11.05.2019 shows indirect signs of pulmonary edema. The condition after the rehabilitation of the bronchial tree.

The patient's condition progressively worsened, and, despite intensive resuscitation manipulations, cardiac arrest occurred, biological death was pronounced at 19:40.

## 3 Results

The interest of the presented clinical case is that the transformation into acute myeloblastic leukemia in patient T., 53 years old, occurred quite early (from the date of PMF diagnosis within four years), despite the timely diagnosis of the disease with the detection of a heterozygous mutation in the JAK2 gene and the establishment of an intermediate risk-2 in accordance with the DIPSS-plus scoring.

## 4 Discussion

Primary myelofibrosis (PMF) refers to Ph-negative myeloproliferative diseases in accordance with the WHO classification (2016). Myeloproliferative diseases (MPD) are clonal tumors that occur at the level of a hematopoietic stem cell and are characterized by the proliferation of one or more myelopoiesis cell lines in the bone marrow with signs of preserved terminal differentiation [1, 3]. The discovery of the JAK2 V617F mutation (2005) contributed to the revision of the diagnostic criteria for MPD. 90% of patients with PMF have a point mutation in the januskinase gene (JAK) – a rearrangement of the erythropoietin receptor JAK2 V617F [17, 22, 25].

The clinical picture of PMF is characterized by a variety of manifestations. In most patients, the initial period of the disease may be asymptomatic for many years [1, 2, 4–6, 8, 9, 21, 24]. During the first years of the disease, the main manifestation is an increased risk of developing thrombosis and thromboembolism against the background of existing cardiovascular pathology and atherosclerosis.

With a prolonged course of the disease and the development of myelofibrosis, symptoms of tumor proliferation and intoxication may appear associated with the secretion of cytokines, the release of myeloid precursors into the peripheral blood with the appearance of extramedullary foci of hematopoiesis in the liver and spleen, the development of cachexia [2, 16, 21, 23]. Prolonged proliferation of the tumor clone leads to the acquisition of additional mutations and a higher degree of malignancy. This process ends with a blast transformation with the development of the terminal stage of the disease – the blast phase (BF), which is observed in 1–2,5% of patients during the first 10 years of PMF and in 5–8% of patients with a longer duration of the disease [29–31].

BF, along with tumor proliferation and intoxication, is characterized by the presence of 20% or more blast cells in the peripheral blood or in the bone marrow [22–24].

The most characteristic BF indicators are changes in the hemogram (leukoerythroblastemia, a shift in the neutrophil and erythroid series to young cell elements with the presence of intermediate maturation forms), an increase in the size of the liver and spleen, the presence of tumor intoxication symptoms (fever, weight loss, profuse sweats).

Depending on the severity of bone marrow fibrosis, according to the biopsy, there are prefibrotic and fibrotic stages of the disease [10–14]. The transformation of the prefibrotic stage into the fibrotic one is observed in 65% of patients within 4.2 years, the transformation into acute leukemia is noted in 5–30% of cases [8]. The mean life expectancy is 5 years, although younger patients may live longer [1, 17–20].

## 5 Conclusion

Primary myelofibrosis (PMF) is one of the benign Ph-negative myeloproliferative diseases [1, 2, 7, 12]. The presented clinical case of early PMF transformation in a 53-year-old patient who ended fatally indicates that the current treatment methods of patients with this pathology are aimed only at curbing the progression of the disease, preventing complications, and relieving the symptoms of the disease. The only radical method of therapy for patients with PMF is allogeneic hematopoietic stem cell transplantation, the use of which is associated with a high risk of mortality and complications [15, 25–28].

To choose the optimal treatment tactics and improve the survival rate of patients with primary myelofibrosis, molecular genetic verification of the disease and stratification of patients using the International Prognosis Scoring DIPSS-plus is necessary.

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