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RESEARCH ARTICLE

Clinical patterns and complete blood count parameters in young patients with primary myelofibrosis in the prefibrotic stage

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What is not yet known about the issue addressed in the submitted manuscript

The features of the prefibrotic stage of primary myelofibrosis in the young people and further evolution of the neoplasm.

The research hypothesis

The clinical and paraclinical features are the same for both stages of primary myelofibrosis in young patients.

The novelty added by the manuscript to the already published scientific literature

Determination of the characteristics of the prefibrotic stage of primary myelofibrosis will allow for further accurate detection of pathology in other patients in order to ensure better therapeutic management of these patients.

Abstract

Introduction. Primary myelofibrosis is a rare myeloproliferative neoplasm that affects 0.2-1.5 people per 100,000. As a rule, the diagnosis is confirmed after 60 years, but recently, hematologists around the world have encountered the problem of primary myelofibrosis in young people. The classic manifestations of myelofibrosis are characterized by splenomegaly, cytopenia, and bone marrow fibrosis, but in patients younger than 40 years, the diagnosis is most often made in the prefibrotic stage of the neoplasm. The aim of the paper is to identify and evaluate the clinical and hematological features of primary myelofibrosis in young patients in the prefibrotic stage.

Material and methods. A retrospective study was performed on clinical cases of primary myelofibrosis, registered at the Oncological Institute of the Republic of Moldova. The diagnosis was confirmed according to 2016 WHO criteria based on histological and molecular studies. We enrolled young patients under the age of 40 who had been diagnosed with prefibrosis in our study and analyzed them for clinical manifestations and complete blood count parameters. To optimize the analysis, all patients were divided into two groups according to their age: 18–29 and 30–40 years old.

Results. Changes in the complete blood count, manifested by thrombocytosis and leukocytosis, are the main laboratory patterns of primary myelofibrosis in young patients in the prefibrotic stage. The most relevant clinical features are splenomegaly and hepatomegaly, but no correlation between these manifestations has been found.

Conclusions. The classical clinical and hematological characteristics of primary myelofibrosis do not specify low- and intermediate-risk patients' management in the prefibrotic stage, as compared with the other chronic myeloproliferative BCR-ABL-negative neoplasms. The proliferation type of primary myelofibrosis is characteristic for young patients with pre-fibrotic stage. According to our results, the main manifestations in the prefibrotic stage are detected in a complete blood count and comprise anemia, leucopenia, leukocytosis, and thrombocytosis.

Key words: primary myelofibrosis, young patients, splenomegaly, thrombocytosis, bone marrow fibrosis.

Introduction

Myeloproliferative neoplasms are hemopathies with primary damage to the stem cell. In the case of polycythemia vera, there is a proliferation of all myeloid lineages in the bone marrow. The proliferation of only the megakaryocytic line is characteristic of essential thrombocythemia. The most interesting histological picture represents primary myelofi-

brosis with the proliferation of myeloid lines, the deformation of megakaryocytes with the formation of clusters with a terrible image, and collagenous fibrosis of various degrees [1]. The second important moment is the formation of foci of extramedullary hematopoiesis, with the most frequent involvement of the spleen and liver. Less commonly, the lungs, kidneys, central nervous system, and even peripheral lymph nodes are affected. The etiology is not known, which is why the inclusion of the word "idiopathic" in the name of this pathology is logical. It is assumed that causative factors may be chemicals, radiation, etc. Most cases are diagnosed in people over the age of 60 who are in the overtly fibrotic stage. For a long time, it was thought that primary myelofibrosis was a disease of the elderly. In recent years, there has been an increase in the number of articles published about primary myelofibrosis in young people, which is most diagnosed in the prefibrotic phase. The studies, observations, and analyses of these patients are few, which is why this neoplasm is of major interest to hematologists.

The aim of the manuscript was to identify and evaluate the clinical and hematological features of primary myelofibrosis in young patients in the prefibrotic stage.

Material and methods

The clinical aspects and the changes in the complete blood count of the disease were studied in 42 patients with NHL and primary myelofibrosis, aged between 18 and 40 years. The diagnosis was confirmed histologically and molecularly according to WHO criteria. The research was approved by the Research Ethics Committee of Nicolae Testemitanu State University of Medicine and Pharmacy (Protocol No. 1 of February 25, 2021).

The standard descriptive statistics kit was used for data analysis through Microsoft Excel and IBM SPSS Statistics 26.0. The use of the standard descriptive statistics kit facilitated the calculation of mean, median, and p value.

Results

Out of the 42 patients participating in the study, 9 (21.4%) were men and 33 (78.6%) were women. We divided the patients into two groups based on their ages: 18-29 and 30-40. There were 11 (26.2%) patients in the first group and 32 (73.8%) in the second.

The major interest represents the changes in the complete blood count. Starting with hemoglobin levels (Table 1), hemolytic anemia was found in both groups at 7.1%. In most cases (48.4%), the level of hemoglobin was perfectly normal. In 4 (36.4%) cases in the first group, there was anemia, and in 8 (25.8%) in the second group, according to WHO criteria for primary myelofibrosis. The elevated hemoglobin level in 6 (19.3%) patients aged 30 to 40 years, on the other hand, was quite surprising.

Table 1. Distribution of patients according to hemoglobin levels.

Laboratory patterns	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Hemolytic anemia	Number of patients	1	2	3
	%	9.1%	6.5%	7.1%
Normal range of hemoglobin	Number of patients	5	15	20
	%	45.6%	48.4%	47.6%
Low value of hemoglobin	Number of patients	4	8	12
	%	36.4%	25.8%	28.6%
Elevated level of hemoglobin (>160 g/l for men, >140 g/l for women)	Number of patients	1	6	7
	%	9.1%	19.3%	16.7%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The second parameter analyzed is leucocyte count (Table 2). Leucopenia was detected in 1 (9.1%) case in the first group and in 3 (9.7%) cases in the second group. The most interesting difference between these two groups is the normal range of white blood cells in patients younger than 30 years: 6 (54.5%) in the first group and 10 (32.3%) in the second group. Leukocytosis in the second age group was revealed in 18 (58.0%) cases and proved to be more common than in the first age group (36.4%, $p < 0.05$).

Table 2. Distribution of patients according to leukocyte count.

Laboratory patterns	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Leukopenia (< $4x10^9$/l)	Number of patients	1	3	4
	%	9.1%	9.7%	9.5%
Normal range (4-$9x10^9$/l)	Number of patients	6	10	16
	%	54.5%	32.3%	38.1%
Leukocytosis (>$11x10^9$/l)	Number of patients	4	18	22
	%	36.4%	58.0%	52.4%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The most important and interesting parameter of peripheral blood is platelets (Table 3). Patients with myeloproliferative neoplasms are more often diagnosed with thrombotic complications, especially those with primary myelofibrosis. Most patients are diagnosed with primary myelofibrosis due to elevated levels of platelets. 30 patients (71.4%) had thrombocytosis. Thrombocytopenia was found in 1 (9.1%) case from the first group and in 2 (6.5%) cases from the second group. Platelets were within the normal range in 36.4% of patients younger than 30 years old and 16.1% of patients older than 30 years old ($p < 0.05$).

Table 3. Distribution of patients according to thrombocyte count.

Laboratory patterns	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Low level of platelets (<150x10^9/l)	Number of patients	1	2	3
	%	9.1%	6.5%	7.1%
Normal range of platelets (150-400x10^9/l)	Number of patients	4	5	9
	%	36.4%	16.1%	21.4%
High level of platelets (>400x10^9/l)	Number of patients	6	24	30
	%	54.5%	77.4%	71.4%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The spleen is the primary organ involved in extramedullary hematopoiesis, and splenomegaly is always observed in the overt fibrotic stage. According to this analysis, 4 (36.4%) and 9 (29.0%) of patients, respectively, in the prefibrotic stage have severe splenomegaly (Table 4). But in 2 (18.2 %) of the first group and in 3 (9.7 %) of the second, the normal size of the spleen was found ($p < 0.05$).

Table 4. Distribution of patients according to the spleen sizes.

	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Normal size	Number of patients	2	3	5
	%	18.2%	9.7%	11.9%
Moderate splenomegaly	Number of patients	4	17	21
	%	36.4%	54.9%	50.0%
Severe splenomegaly	Number of patients	4	9	13
	%	36.4%	29.0%	31.0%
Splenectomy	Number of patients	1	2	3
	%	9.1%	6.5%	7.1%
Total	Number of patients	11	31	42
	%	100%	100%	100%

The last parameter that was analyzed was the size of the liver (Table 5). In most cases, in 8 (72.7%) patients from the first group and in 14 (45.1%) from the second, the size of the liver was in the normal range. But for the patients in the second group, moderate hepatomegaly occurred in 11 (35.5%) cases and severe hepatomegaly in 6 (19.4%) cases.

Table 5. Distribution of patients according to the liver sizes

	Number of patients / rates within the age category	Age		Total
		18-29 years	30-40 years	
Normal size	Number of patients	8	14	22
	%	72.7%	45.1%	52.4%
Moderate hepatomegaly	Number of patients	1	11	12
	%	9.1%	35.5%	28.6%
Severe hepatomegaly	Number of patients	2	6	8
	%	18.2%	19.4%	19.0%
Total	Number of patients	11	31	42
	%	100%	100%	100%

Discussion

The incidence of primary myelofibrosis is low. In the USA, primary myelofibrosis is detected in 0.5–1.5 cases per 100,000 [2], in Great Britain – 0.75, but in the Republic of Moldova, according to Ion Corcimaru's data from 2007, it is 0.2 per 100,000 [3]. Analyzing literature data, due to the diagnosis, a tendency towards an increase in the incidence and prevalence of 40–50% in the initial stage of primary myelofibrosis is observed. The pathology is seen in children only very rarely, being congenital and occurring in conjunction with other malformations. The peak incidence of primary myelofibrosis is between 50 and 70 years of age.

The clinical manifestations of primary myelofibrosis are variable and unusual. The diagnosis can be established early on by performing some prophylactic control analyses until long-term manifestations appear over time.

The weakness is a clinical manifestation that is detected most often in patients with primary myelofibrosis, even in those without anemia, which must attract maximum attention from internists. The second key pathogenic moment in fatigue is the development of anemia with the onset of the anemic syndrome. Most patients complain of constitutional symptoms, such as general weakness, weight loss, profuse night sweats, and fever, which interfere with their daily activities. These complaints can be explained by the already-mentioned imbalance in cytokine homeostasis [4]. These manifestations are associated not only with a negative impact on the patients' quality of life but also with an unfavorable prognosis [5].

Extramedullary hematopoiesis affects the spleen most often and rarely the liver, manifesting clinically through discomfort and pain under the costal arch caused by the increase in size. Splenomegaly is the result not only of myeloid hematopoiesis but also of the sequestration of myeloid cells. In some cases, there are pronounced pains in the left flank, along with fever and the clinical picture of acute abdomen caused by a splenic infarction. Hepatomegaly occurs in 40-70%. The involvement of the liver in the tumor process results in its dysfunction, manifesting itself through coagulopathy and thrombosis of the portal, splenic, and mesenteric veins [6, 7].

Often, anemia [8, 9, 10] and thrombocytopenia are the first paraclinical manifestations of myelofibrosis. Decreased hemoglobin and low platelet count are prognostic scores [10-14] and leukopenia often portends a poor prognosis [15, 16, 17]. Another special feature of primary myelofibrosis is the clinical-paraclinical variety. It can be manifested by cytopenia (cytopenic phenotype) and by bone marrow hypercellularity and pancytosis (proliferative phenotype) [18, 19]. However, the cytopenic phenotype is characterized by a reserved prognosis.

An interesting paper was published in 2022 on the prognostic impact of cytopenia in primary myelofibrosis. Two groups of patients in the prefibrotic and overt fibrotic phases were evaluated. In both cohorts, cytopenia resulted in progressive and unfavorable evolution. The most important indices were thrombocytopenia and anemia. The published results further extend the characterization of cytopenic features in PMF with a new understanding of the differences between the prefibrotic and overt fibrotic stages [20]. Primary myelofibrosis is characterized by anemia, which is detected in 50% of cases. Anemia is caused by both ineffective erythropoiesis in the bone marrow due to bone and extramedullary fibrosis and erythrocyte sequestration in the spleen.

It was mentioned above that thrombocytopenia is an unfavorable prognostic factor in primary myelofibrosis, and thrombocytosis is part of the proliferative phenotype.

The most common manifestations of primary myelofibrosis were described in the introduction of this article, but they are more characteristic of the overt fibrotic stage. Therefore, the hematologist knows how to manage these complications or minimize the intensification of constitutional symptoms. Young patients with primary myelofibrosis or other myeloproliferative neoplasms are understudied, resulting in unresolved treatment management. The changes in the complete blood count (thrombocytosis and leukocytosis) that are characteristic of the proliferative type are described in this study. Leukocytosis is one of the minor criteria for confirmation of myelofibrosis, but an elevated level of platelets is less common. It is very important for effective management because all patients with primary myelofibrosis are predisposed to thrombotic complications. Timely preventive measures can provide a better quality of life. Organomegaly was detected in most cases, which corresponds to the clinical features, but in the prefibrotic stage, it is smaller. So, the elevated level of platelets and leucocytes can be explained by hyperproliferation in the bone marrow and extramedullary hematopoiesis. Nevertheless, no correlations were found between the cellularity of peripheral blood and the sizes of the spleen or liver.

Conclusions

1. The classical clinical and hematological characteristics of primary myelofibrosis do not specify low- and intermediate-risk patients' management in the prefibrotic stage, as compared with the other chronic myeloproliferative BCR-ABL-negative neoplasms.
2. The proliferation type of primary myelofibrosis is characteristic for young patients in the prefibrotic stage.
3. According to our results, the main manifestations in the prefibrotic stage are detected in a complete blood count and comprise anemia, leukopenia, leukocytosis, and thrombocytosis.

Authors' contribution

NSB studied the bibliographic reference sources, summarized, and systematized the data of published research, studies, and clinical recommendations, collected the data, and structured and drafted the article. The manuscript was conceptualized by VM, MR, LJ, LM, AD, CD, and EC, who also summarized and systematized data from published research and studies and revised the draft of the article. All authors read and approved the final version of the article.

Declaration of conflicting interests

The author declares no conflict of financial or non-financial interests concerning the data and information presented in the manuscript.

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