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IMPACT OF THE IMPARED IRON HOMEOSTASIS ON THE PATHOGENESIS OF ANEMIA IN PRIMARY MYELOFIBROSIS

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SUMMARY

Anemia is a well established prognostic factor in primary myelofibrosis (PMF). Recent data suggests that markers of abnormal iron homeostasis, which are known to be affected by both iron overload and inflammation, may be involved in the pathogenesis of anemia in PMF.

Aim: To evaluate the relation between anemia, bone marrow fibrosis, prognostic score, survival and parameters of iron metabolism.

Materials and methods: We studied 72 patients with PMF. The following parameters were analyzed: degree of bone marrow fibrosis, hemoglobin level, MCV, components of iron homeostasis (total iron binding capacity (TIBC), ferritin, serum iron). The prognostic score was determined according to IPSS and DIPSS. Statistical analysis was performed by SPSS version 19.

Results: We found significant correlation between the level of hemoglobin and degree of bone marrow fibrosis and prognostic score. The MCV was analyzed in 56 of the patients and was found low in 9,5 % of them. However, there was no significant correlation between degree of fibrosis and the lower MCV. We found significant straight correlation between degree of fibrosis, serum ferritin level (p=0.006) and TIBC (p=0.018). In univariate analysis, significant feedback correlation was established between hemoglobin and serum ferritin level.

Conclusion: Our results reveal the possible role of the impaired iron metabolism in the pathogenesis of anemia in PMF. Further studies are needed in order to elucidate the precise mechanisms of this process.

Key words: Primary myelofibrosis, anemia, iron metabolism.

INTRODUCTION:

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by stem cell-derived clonal myeloproliferation, abnormal cytokine expression, bone marrow fibrosis, anemia, splenomegaly, extramedullary hematopoiesis, constitutional symptoms, leukemia progression, and shortened survival [1]. Anemia is a well-established prognostic factor in PMF [2]. Prognosis in PMF is also influenced by increased levels of circulating inflammatory cytokines (e.g., interleukin [IL]-2 receptor [IL-2R], and/or IL-8), within specific DIPSS-plus risk categories. These data suggest that markers of abnormal iron homeostasis, known to be affected by both iron overload and inflammation, may be involved in the pathogenesis of anemia in PMF [3].Increased serum ferritin levels appeared adverse predictive value for overall survival independent of DIPSS. It reveals the severity of the erythropoietin defect in PMF, reflecting the marrow-suppressive effect of disease-related inflammation [4]. Microcytosis is a relatively frequent finding in primary myelofibrosis. Up to 28% patients with PMF can present with microcytic anemia as a result of chronic inflammation which is a hallmark of PMF [5].

Our aim was to evaluate the relation between anemia, bone marrow fibrosis, prognostic score, survival and parameters of iron metabolism.

PATIENTS AND METHODS:

We included 72 patients with PMF, 29 women and 43 men, with median of age 67,6. We analyzed the following parameters: degree of bone marrow fibrosis, hemoglobin level, MCV, components of iron homeostasis (TIBC, ferritin, serum iron).

The degree of bone marrow fibrosis was established according to the three-stage Hannover system -low, intermediate and high. Bone marrow samples were fixed in buffered neutral formalin for 12 - 48 hours. Slides were stained with Haematoxylin and Eosin and immunohistochemically for the evaluation of endothelial cells with FLEX Monoclonal Mouse Anti-Human CD34 Class II, Clone QBend 10 (DAKO). Visualization system was Envision High pH (Link) (Code K8000)

The prognostic score was determined according to IPSS and DIPSS. Statistical analysis was performed by SPSS version 19.

RESULTS:

We found significant correlation between degree of bone marrow fibrosis and level o hemoglobin. (p=0.026) (Fig. 1) According to DIPSS we divided patients in three groups: Intermediate 1 - 12 patients, Intermediate 2- 24 patients and High - 36 patients. We found statistically significant correlation between scoring system and severity of anemia (p=0.020) (Fig. 2). Blood transfusion dependence is significantly related to overall survival (OS) in the analyzing group (Fig. 3). The MCV was analyzed in 56 of the patients and was found low in 9,5% of them. However, there was no significant correlation between degree of fibrosis and the lower MCV (p=0,039). We found significant straight correlation between degree of fibrosis, serum ferritin level (p=0.006) and TIBC (p=0.018) (Table.1). In univariate analysis, significant feedback correlation is established between hemoglobin level and serum ferritin level (p=0.003) (Table.2).

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Fig. 1. Correlation between level of hemoglobin and degree of bone marrow fibrosis.

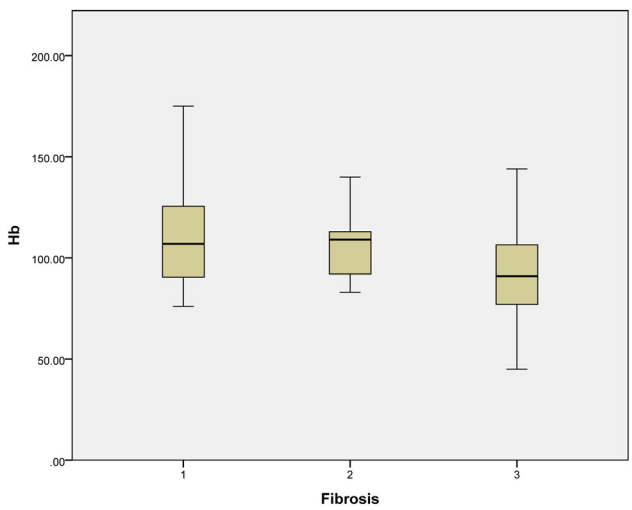

Fig. 2. Correlation between level of hemoglobin and risk stratification according to DIPSS

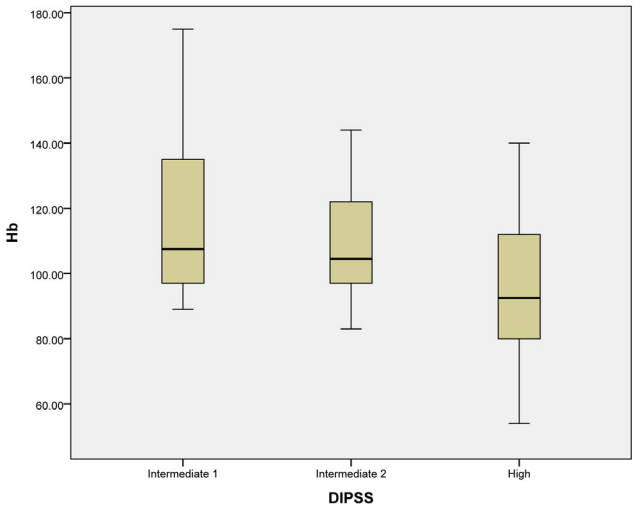

Fig. 3. Transfusion needs and OS

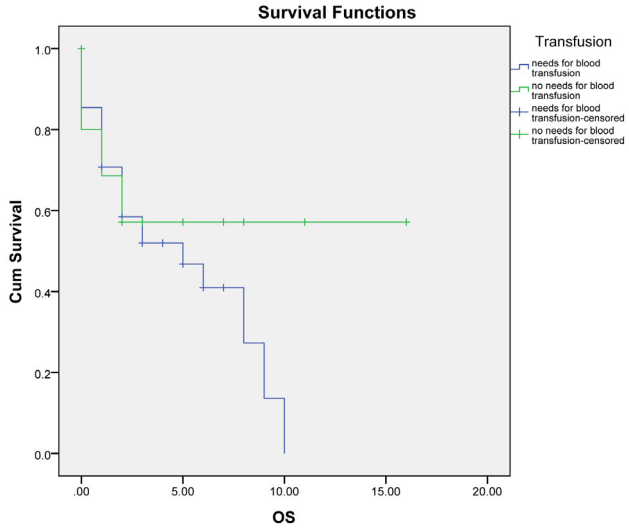

Table. 1. Correlation between degree of fibrosis and parameters of iron metabolism (Independent component: degree of fibrosis)

AVONA

		Sum of Squares	df	Mean Square	F	Sig
Feritin	BetweenGroups	7762607.818	2	3881303.909	9.069	.006
	Within Groups	4279947.310	10	427994.731		
	Total	12042555.128	12			
Capacity	BetweenGroups	464.925	2	232.462	6.186	.018
	Within Groups	375.778	10	37.578		
	Total	840.703	12			

Table. 2. Correlation between serum ferritin level and hemoglobin level.

Correlations

		Hb	Feritin
Hb	Pearson Correlation	1	-.706**
	Sig. (2-tailed)		.003
	N	15	15
Feritin	Pearson Correlation	-.706**	1
	Sig. (2-tailed)	.003	
	N	15	15

**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION:

Anemia and its clinical manifestations is the main indicator of risk stratification in diagnosis and follow-up in PMF. Bone marrow fibrosis is a key pathogenetic factor leading to hematopoietic insufficiency. We determined negative correlation between hemoglobin level in patients in different stage of the disease and degree of bone marrow fibrosis and prognostic score.

Blood transfusion needs are closely associated with the severity of anemia and influence the overall survival in patients with PMF. In the present study we found significantly lower OS in transfusion dependent patients in comparison to those who do not need blood transfusion.

The influence of new pathogenetic mechanisms, related to pathological expression of cytokines and their participation in processes like myeloproliferation, neoangiogenesis, myelofibrosis and osteosclerosis already suggested. Dysregulation of cytokine expression leads to changes in levels of serum hepcidin and disbalance in iron homeostasis, examined by level of serum ferritin as a independent prognostic factor for OS [4]. Our study shows negative correlation between hemoglobin level, serum ferritin and TIBC. The change in serum ferritin level is an indirect sign of significance of hepcidin and interleukins levels for severity of anemia in patients with PMF.

Our results reveal the possible role of the impaired iron metabolism in the pathogenesis of anemia in PMF. Further studies are needed in order to elucidate the precise mechanisms of this process.

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