JAK2-V617F Mutation is Associated with Clinical and Laboratory Features of Myeloproliferative Neoplasms

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A B S T R A C T

The aim of this study is to investigate the differences of clinical and laboratory parameters between patients with JAK2-V617F positive myeloproliferative neoplasms (MPNs) and JAK2 wild type MPNs. DNA was isolated from peripheral blood granulocytes of 106 patients treated at Rijeka University Hospital Center: 41 with polycythemia vera (PV), 43 with essential thrombocythemia (ET), 9 with primary myelofibrosis (PMF) and 13 with myeloproliferative neoplasm- -unclassifiable (MPN-u). The JAK2-V617F mutation was detected using allele specific PCR. Laboratory and clinical parameters were obtained from patient's medical records. The JAK2-V617F mutation was detected in 69% (73/106) patients with MPNs. The results revealed significantly different prevalence of JAK2-V617F mutation, between MPNs entities: 88% in PV, 58% in ET, 56% in PMF and 54% in MPNs-unclassified disorders. The JAK2-V617F mutation significantly correlated with higher leukocyte count and alkaline phosphatase score in ET group and with higher platelets count, leukocyte alkaline phosphatase score and serum lactate dehydrogenase in PV group. Vascular events were associated with elevated platelets count in whole MPNs group, with higher platelets and leukocyte count in ET and with splenomegaly in PV patients. Clinical and laboratory data revealed significant contribution of JAK2-V617F mutation to the development of clinical phenotype in patients with distinct subgroups of MPNs.

***Key words**: JAK2-V617F; essential thrombocythemia; polycythemia vera; primary myelofibrosis.*

Introduction

The classic Ph-negative myeloproliferative neoplasms (MPNs) include various disorders such as polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Their classification and the criteria for diagnosis have been recently updated by the Word Health Organization (WHO)[1]. The MPNs are clonal hematopoietic stem cell disorders characterized by proliferation of one or more myeloid cell lineages in the bone marrow[2–5]. The genetic cause of these diseases was unknown until 2005, when several independent groups demonstrated that most patients with PV, ET and PMF acquire a mutation affecting the gene for Janus tyrosine kinase 2. The mutation corresponds to a single-nucleotide change of JAK2 nucleotide 1849, in exon 14, resulting in a unique valine (V) to phenylalanine (F) substitution at amino acid position 617 of the protein (JAK2-V617F)[6–8].

This acquired mutation occurs in the pseudokinase domain of JAK2 in hematopoietic cells and is responsible for the constitutive activation of molecular signaling pathways leading to an uncontrolled phosphorylation of substrate molecules including signal transducers and activators of transcription (STAT proteins, so called JAK -STAT signaling). The result is cell proliferation independent of normal growth factor control[9]. JAK2-V617F mutation confirmed the presence of a clonal disorder and is an important diagnostic marker[10,11]. Thus, we investigated the prevalence of JAK2-V617F mutation in our MPNs patients treated at Clinical Hospital Center Rijeka. We have also examined the correlation of JAK2-V617F mutation with changes in hematologic and biochemical parameters and with incidence of splenomegaly and thromboembolic complications in MPNs patients.

Material and Methods

The study included 106 patients with a known or suspected myeloproliferative disorders treated at Department of Hematology, Internal Medicine Clinic, Clinical Hospital Center Rijeka. The diagnoses of PV, ET, PMF and MPN-u were made according to 2008 WHO criteria, based on peripheral blood counts and bone marrow histology. Bone marrow biopsy specimens, taken from iliac crests, have been fixed in Scheffer's fixative for 12 to 24 hours and decalcified in Osteodec (Bio-Optica Italy). Specimens were sectioned and stained using hematoxylin--eosin, Giemsa, PAS reaction, Gomory stain for reticular and iron staining. All slides were reviewed by two certified pathologists. Laboratory and clinical data included hemoglobin and hematocrit level, white blood cells and platelet count, leukocyte alkaline phosphatase score, serum lactate dehydrogenase, presence of splenomegaly and vascular events. The study was approved by the Ethical committee of the institutional review board of the Rijeka University Hospital Center. All the patients enrolled in this study signed consent form for anonymous use of laboratory and medical history data.

DNA isolation and Polymerase Chain Reaction (PCR) method

Blood was drawn from 106 patients in collection tube for polymorphonuclear cells separation (Vacutainer CPT 4.0 mL Ficoll, BD, Franklin Lakes, USA). Genomic DNA was isolated from polymorphonuclear cells using Nucleo-Spin®Blood kit (Macharey-Nagel, Duren, Germany) according to the manufacturer's instructions. The JAK2--V617F mutation was determined using allele specific PCR as described previously[6]. Briefly, 1 μL of isolated genomic DNA was amplified in 35 cycle PCR reaction at annealing temperature of 58 °C with 1 μmol/L of common reverse primer (5'/ CTG AAT AGT CCT ACA GTG TTT TCA GTT TCA 3') and 0.5 μmol/L of two forward primers (forward specific 5/ AGC ATT TGG TTT TAA ATT ATG GAG TAT ATT 3' and forward internal control 5' ATC TAT AGT CAT GCT GAA AGT AGG AGA AAG 3'). First forward primer is specific for the mutant allele (a single-nucleotide G to T alteration at position 1849 of JAK2 gene), giving 203 bp product, and second amplifies 364 bp products from both mutant and wild type alleles and serves as internal PCR control. Described method is verified by using quality control JAK2 V617F DNA through collaboration with Laboratory for Molecular Pathology, Institute of Pathology, Medical University, Graz, Austria.

Statistical analysis

We used the t-test and Wilcoxon Mann-Whitney test for comparison of continuous variables and the two--tailed Fisher exact test for categorical variables. p values below or equal to 0.05 were considered significant and accepted only for statistical power of more then 0.8 for β_2 values. Statistical data were collected and organized using MS Excel and analyzed using R statistical software (The R Foundation for Statistical Computing).

Results

Clinical and laboratory findings of patients with MPNs and MPNs entities are shown in Table 1. Representative bone marrow biopsies of distinct MPNs entities are shown in Figure 1. The JAK2-V617F mutation was found in 73/106 (69%) patients with MPNs, 36/41 (88%) with PV, 25/43 (58%) with ET, 5/9 (56%) with PMF and 7/13 (54%) with MPN-u. The prevalence of JAK2-V617F mutation was significantly different between MPNs subtypes, ET and PV (p=0.003). Splenomegaly, vascular events, lactate dehydrogenase and leukocyte alkaline phosphatase were not significantly different within distinct MPNs subgroups, while the values of hemoglobin
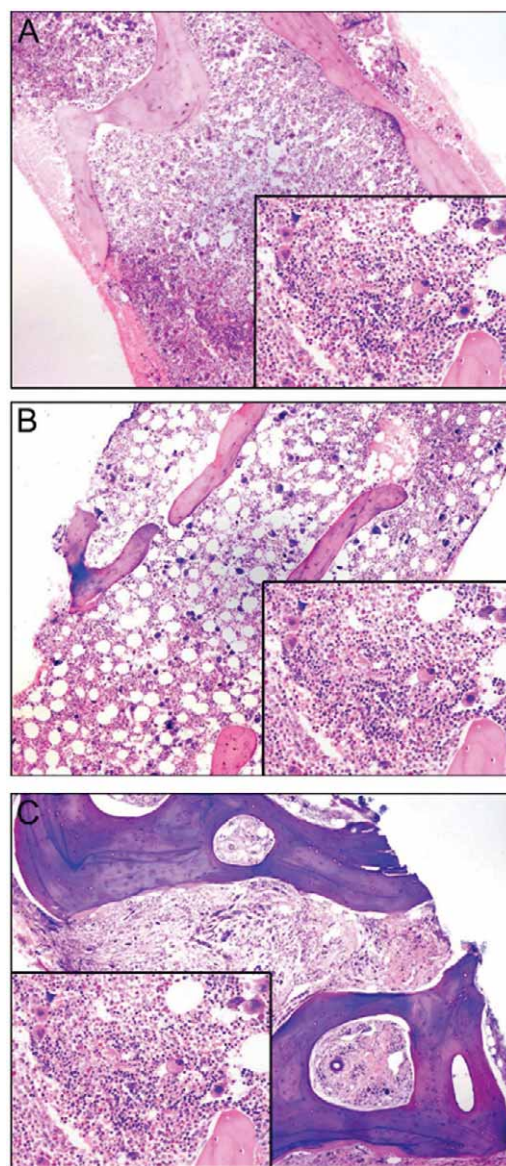

Fig. 1. Representative bone marrow biopsy specimens from iliac crests. (A) polycithemya vera, (B) essential thrombocytosis, and (C) idiopathic myelofibrosis. Larger microphotographs magnification x100, smaller microphotographs magnification x400.

TABLE 1
CLINICAL AND LABORATORY PARAMETERS IN MYELOPROLIFERATIVE NEOPLASMS (MPNS) AND DISTINCT ENTITIES, ESSENTIAL THROMBOCYTHEMIA (ET), POLYCYTHEMIA VERA (PV), PRIMARY MYELOFIBROSIS (PMF) AND MYELOPROLIFERATIVE NEOPLASM UNCLASSIFIED (MPN-U)

	MPNs (No=106)	ET (No=43)	PV (No=41)	PMF (No=9)	MPN-u (No=13)	p values
JAK2-V617F						
Positive, N (%)	73 (69)	25 (58)	36 (88)	5 (56)	7 (54)	0.005
Negative, N (%)	33 (31)	18 (42)	5 (12)	4 (44)	6 (46)	0.003[*]
Hemoglobin (g/L) ($\overline{X}$±SD)	149.3±31.5	135±20.5	175.9±13.9	124.4±24.9	122.5±43.2	<0.001[*]
Hematocrit ($\overline{X}$±SD)	0.5±0.1	0.4±0.1	0.6±0.1	0.4±0.1	0.4±0.1	<0.001[*]
Platelets (x10⁹/L), median (range)	602 (80–2692)	682 (423–2692)	520 (135–1224)	560 (80–1776)	403 (91–915)	<0.001
>1000×10⁹/L, N (%)	19 (18)	12 (28)	3 (7)	1 (11)	0	0.021[*]
<1000×10⁹/L, N (%)	86 (82)	31 (72)	38 (93)	8 (89)	12 (100)	
WBC (×10⁹/L), median (range)	10.6 (4.1–31)	9.4 (4.1–29)	11 (5.8–18.5)	10.1 (4.3–16.7)	14.4 (6.4–31)	0.098
>10×10⁹/L, N (%)	56 (53)	17 (40)	27 (66)	2 (22)	8 (62)	0.018[*]
<10×10⁹/L, N (%)	49 (47)	26 (60)	14 (34)	7 (78)	5 (38)	
Alkaline phosphatase (U/L), median (range)	61.5 (0–338)	68 (0–332)	82 (5–338)	34 (19–41)	40.5 (2–108)	0.444[*]
Lactate dehydrogenase (U/L), median (range)	238 (68–1463)	225.5 (90–546)	248 (68–984)	433 (220–1463)	215.5 (77–575)	0.557[*]
Splenomegaly (>3 cm)						
Yes, N (%)	36 (34)	12 (28)	14 (34)	2 (22)	8 (62)	0.151
No, N (%)	70 (66)	31 (72)	27 (66)	7 (78)	5 (38)	0.638[*]
Vascular events						
Yes, N (%)	26 (25)	11 (26)	13 (32)	1 (11)	1 (8)	0.313
No, N (%)	80 (75)	32 (74)	28 (68)	8 (89)	12 (92)	0.631[*]

[*] indicate p values of differences evaluated by Fisher exact test between MPNs subtypes, essential thrombocythemia (ET) and polycythemia vera (PV). In the platelets and WBC columns the total number of patients is not exact (106) because some data are missing.

(p<0.001), hematocrit (p<0.001), platelets (p=0.021) and leukocytes counts (p=0.018) were significantly different between ET and PV. At diagnosis, JAK2-V617F positive MPNs patients were characterized by higher values of hemoglobin, hematocrit, leucocytes counts and leukocyte alkaline phosphatase score (in all cases p< 0.001; Table 2). There was no significant correlation between JAK2-V617F mutation and splenomegaly and vascular events (p=0.188 and p=0.342, respectively) in whole group of MPNs patients. ET patients with JAK2--V617F mutation demonstrated significantly higher leukocyte count and alkaline phosphatase score (p=0.005, p<0.001), while PV patients with this mutation were characterized with higher platelets counts, higher alkaline phosphatase and lactate dehydrogenase score (p= 0.006, p=0.059, p=0.03). Thromboembolic and bleeding complications were present in 26/106 (25%) patients with MPNs or more specifically in 32% with PV, 26% with ET, 11% with PMF and 8% with MPN-u (Table 1). Majority of those patients were JAK2-V617F positive (20/26; 77%; Table 2.). Vascular events were associated with platelets count (p=0.006) in whole MPNs group, with platelets and leukocyte count in ET (p=0.033, p=0.014, respectively), and with splenomegaly in PV patients (p=0.017), as shown in Table 3.

Discussion and Conclusion

Results from our study showed that a single somatic activating mutation JAK2-V617F was identified in most patients with PV and in about half of patients with ET or PMF. PV, ET and PMF share common clinical features and belong to clonal disorders of multipotent progenitors, underlying many similarities between these disorders. Literature data revealed that prevalence of JAK2-V617F mutation in PV ranges from 65 to 100%, in ET from 28 to 80%, in PMF from 33 to 85% and in MPN-u from 38 to 75%[12]. These differences could be explained with variable number of analyzed cases and the differences in sensitivity and specificity of methods applied for detection of JAK2- V617F mutation[13,14].

Our study revealed that the patients carrying JAK2--V617F mutation displayed leukocytosis and higher level of hemoglobin and hematocrit than mutation negative patients, as it was reported by previously published studies[15–18]. Furthermore, we demonstrated that higher leukocyte count, elevated serum lactate dehydrogenase and alkaline phosphatase score are associated with presence of JAK2-V617F mutation, a finding that indicates activated myelopoiesis, which is also suggested in several previous published studies[17,19]. Although some studies

TABLE 2
CLINICAL AND LABORATORY PARAMETERS ACCORDING TO THE PRESENCE OF JAK2-V617F MUTATION IN MYELOPROLIFERATIVE NEOPLASMS (MPNS) AND TWO MAJOR ENTITIES, ESSENTIAL THROMBOCYTHEMIA (ET) AND POLYCYTHEMIA VERA (PV)

	JAK2-V617F		p value
	Positive	Negative	
MPNs (No=106)			
Hemoglobin (g/L) ($\overline{X}\pm$SD)	156.8±27.9	133.2±33.4	<0.001[*]
Hematocrit ($\overline{X}\pm$SD)	0.5±0.1	0.4±0.1	<0.001[*]
Platelets (x10⁹/L) median (range)	616.5 (80-2692)	548 (91-1512)	0.192[†]
>1000x10⁹/L, N (%)	14 (19)	5 (15)	0.786[‡]
<1000x10⁹/L, N (%)	58 (81)	28 (85)	
WBC (x10⁹/L), ($\overline{X}\pm$SD)	11.8±4.2	9.5±5	<0.001[†]
>10x10⁹/L, N (%)	46 (64)	10 (30)	<0.001[‡]
<10x10⁹/L, N (%)	26 (36)	23 (70)	
Alkaline phosphatase (U/L), median (range)	88 (2-338)	21.5 (0-108)	<0.001[†]
Lactate dehydrogenase (U/L), median (range)	245 (68-984)	220 (77-1463)	0.905[†]
Splenomegaly (>3 cm)			
Yes, N (%)	28 (38)	8 (24)	0.188[‡]
No, N (%)	45 (62)	25 (76)	
Vascular events			
Yes, N (%)	20 (27)	6 (18)	0.342[‡]
No, N (%)	53 (73)	27 (82)	
ET (No=43)			
Hemoglobin (g/L) ($\overline{X}\pm$SD)	140.7±21	131.2±19.1	0.138[*]
Hematocrit ($\overline{X}\pm$SD)	0.4±0.1	0.4±0.04	0.3[*]
Platelets (x10⁹/L) (median, range)	721 (423-2692)	651 (476-1512)	0.118[†]
>1000x10⁹/L, N (%)	9 (36)	3 (17)	0.911[‡]
<1000x10⁹/L, N (%)	16 (64)	15 (83)	
WBC (x10⁹/L), ($\overline{X}\pm$SD)	12.1±5.7	8.1±2.3	0.005[†]
>10x10⁹/L, N (%)	14 (56)	3 (17)	0.013[‡]
<10x10⁹/L, N (%)	11 (44)	15 (83)	
Alkaline phosphatase (U/L), median (range)	97 (28-332)	15 (0-85)	<0.001[†]
Lactate dehydrogenase (U/L), median (range)	228 (96-417)	220 (90-546)	0.963[†]
Splenomegaly (>3 cm)			
Yes, N (%)	9 (36)	3 (17)	0.191[‡]
No, N (%)	16 (64)	15 (83)	
Vascular events			
Yes, N (%)	9 (36)	2 (11)	0.086[‡]
No, N (%)	16 (64)	16 (89)	
PV (No=41)			
Hemoglobin (g/L) ($\overline{X}\pm$SD)	177±13.9	168.4±12.5	0.21[*]
Hematocrit ($\overline{X}\pm$SD)	0.6±0.1	0.5±0.1	0.386[*]
Platelets (x10⁹/L), (median, range)	546.5 (135-1224)	185 (173-307)	0.006[*]
>1000x10⁹/L, N (%)	3 (8)	0	1[‡]
<1000x10⁹/L, N (%)	33 (92)	5 (100)	
WBC (x10⁹/L), ($\overline{X}\pm$SD)	11.6±2.9	8.9±2.3	0.064[†]
>10x10⁹/L, N (%)	25 (69)	2 (40)	0.317[‡]
<10x10⁹/L, N (%)	11 (31)	3 (60)	
Alkaline phosphatase (U/L), median (range)	96.5 (5-338)	19 (14-69)	0.059[†]
Lactate dehydrogenase (U/L), median (range)	257.5 (68-984)	148 (137-170)	0.03[†]
Splenomegaly (>3 cm)			
Yes, N (%)	13 (36)	1 (20)	0.645[‡]
No, N (%)	23 (64)	4 (80)	
Vascular events			
Yes, N (%)	10 (28)	3 (60)	0.304[‡]
No, N (%)	26 (72)	2 (40)	

[*]Student t-test; [†]Mann-Whitney Wilcoxon test; [‡]Fisher exact test

TABLE 3
CLINICAL AND LABORATORY PARAMETERS ACCORDING TO THE VASCULAR EVENTS IN MYELOPROLIFERATIVE NEOPLASMS (MPNS) AND TWO MAJOR ENTITIES, ESSENTIAL THROMBOCYTHEMIA (ET) AND POLYCYTHEMIA VERA (PV)

	Vascular events		p value
	Positive	Negative	
MPNs (No=106)			
Hemoglobin (g/L) ($\overline{X}\pm$SD)	158.2±30.2	146.4±31.6	0.099*
Hematocrit ($\overline{X}\pm$SD)	0.5±0.1	0.5±0.1	0.78*
Platelets, median (range)	719 (173-1527)	565 (80-2692)	0.017†
>1000x10⁹/L, N (%)	10 (38)	9 (11)	0.006‡
<1000x10⁹/L, N (%)	16 (62)	70 (89)	
WBC($\overline{X}\pm$SD)	12.3±4.8	10.8±4.5	0.108†
>10x10⁹/L, N (%)	17 (65)	39 (49)	0.179‡
<10x10⁹/L, N (%)	9 (35)	40 (51)	
Alkaline phosphatase (U/L), median (range)	76 (14-295)	53 (0-338)	0.075†
Lactate dehydrogenase (U/L), median (range)	257.5 (68-627)	230 (77-1463)	0.980†
Splenomegaly (>3 cm)			
Yes, N (%)	12 (46)	24 (30)	0.156‡
No, N (%)	14 (54)	56 (70)	
JAK2 V617			
Positive, N (%)	20 (77)	53 (66)	0.342‡
Negative, N (%)	6 (23)	27 (34)	
ET (No=43)			
Hemoglobin (g/L) ($\overline{X}\pm$SD)	139.8±24.6	135.5±19.4	0.624*
Hematocrit ($\overline{X}\pm$SD)	0.4±0.1	0.4±0.04	0.833*
Platelets, median (range)	1020 (573-1527)	661 (423-2692)	0.033†
>1000x10⁹/L, N (%)	7 (64)	5 (16)	0.005‡
<1000x10⁹/L, N (%)	4 (36)	27 (84)	
WBC ($\overline{X}\pm$SD)	13.5±6.6	9.3±3.8	0.016†
>10x10⁹/L, N (%)	8 (73)	9 (28)	
<10x10⁹/L, N (%)	3 (27)	23 (72)	0.014‡
Alkaline phosphatase (U/L), median (range)	77 (33-177)	44 (0-332)	0.285†
Lactate dehydrogenase (U/L), median (range)	277 (134-412)	212 (90-546)	0.085†
Splenomegaly (>3 cm)			
Yes, N (%)	4 (36)	8 (25)	
No, N (%)	7 (64)	24 (75)	0.467‡
JAK2-V617F			
Positive, N (%)	9 (82)	16 (50)	
Negative, N (%)	2 (18)	16 (50)	0.086‡
PV (No=41)			
Hemoglobin (g/L) ($\overline{X}\pm$SD)	177.8±18	175.1±11.8	0.628*
Hematocrit ($\overline{X}\pm$SD)	0.6±0.1	0.6±0.1	0.852*
Platelets, median (range)	603 (173-1224)	498 (135-1177)	0.363†
>1000x10⁹/L, N (%)	2 (15)	1 (4)	
<1000x10⁹/L, N (%)	11 (85)	27 (96)	0.232‡
WBC ($\overline{X}\pm$SD)	11.6±3.05	11.1±3	0.604†
>10x10⁹/L, N (%)	9 (69)	18 (64)	
<10x10⁹/L, N (%)	4 (31)	10 (36)	1‡
Alkaline phosphatase (U/L), median (range)	99 (14-295)	82 (5-338)	0.94†
Lactate dehydrogenase (U/L), median (range)	212 (68-336)	253.5 (124-984)	0.16†
Splenomegaly (>3 cm)			
Yes, N (%)	8 (62)	6 (21)	
No, N (%)	5 (38)	22 (79)	0.017‡
JAK2-V617F			
Positive, N (%)	10 (77)	26 (93)	
Negative, N (%)	3 (23)	2 (7)	0.304‡

*Student t-test; †Mann-Whitney Wilcoxon test; ‡Fisher exact test

found correlation between JAK2-V617F mutation and splenomegaly others failed to find such association[20–22]. Our results are in agreement with those studies which were not able to confirm this association.

The clinical course of the MPNs is characterized by thrombotic and hemorrhagic events that significantly impact prognosis and quality of life. It is generally accepted that MPNs are a risk factor for thrombosis[21–23]. Although epidemiologic and clinical studies identify the MPNs as thrombophilic conditions, the pathogenesis of thrombosis in MPNs is not elucidated because it is multi-factorial and complex disorder[21]. Portal vein thrombosis can be the first and only sign, presenting latent or masked MPNs[24]. The incidence of thrombosis and hemorrhage at diagnosis for PV varies in average, from 5% to 39% and for ET, between 11% and 37%[22]. Our study has shown that 25% of patients with MPNs demonstrate vascular events. From 26 patients with thromboembolic complications 77% were JAK2-V617F mutation positive making this mutation the strongest possible predictor for thrombosis. Vascular events were associated with higher platelets count in whole MPNs group. Patients with ET demonstrated high platelets and leukocyte counts and 82% of patients were positive for JAK2-V617F mutation. The meta-analysis of large number of ET cases, with thrombosis, showed JAK2-V617F positive patients to be at a two-fold higher risk of developing thrombosis[25].

Our study revealed that splenomegaly was significantly associated with thromboembolic complications in 62% of PV patients. JAK2-V617F mutation was present in 77% patients suffering from thrombosis. There is no final agreement on the role of JAK2-V617F mutation in overall risk of thrombosis or bleeding in MPNs patients[20–23]. In a large study of 1213 patients with PV, thrombosis (both arterial and venous) occurred in 41% of patients and splenomegaly was present in approximately 70% of patients with PV[26]. Harrison suggested that progressive or symptomatic splenomegaly revealed high risk of thrombosis in patients with PV[27].

Recently, Carobbio et al. and Tefferi and Elliott, reported that leukocytosis, but not thrombocytosis, has been identified as a potential risk factor for thromboembolic complications in PV and ET[24,28]. Although the pathogenetic background leading to hypercoagulability is not clearly defined, it is suggested that the activated neutrophils may play a central role in thrombogenesis[29].

In conclusion, the JAK2-V617F mutation was frequently detected in our patients with MPNs in accordance with literature data, and therefore should be incorporated into the clinical work up of patients with suspected MPNs. Furthermore, analysis should focus on JAK2-V617F allele burden (copy number) as well as mutation genotype (gene dosage) to determine genetic background necessary to evaluate disease phenotype.

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MUTACIJA JAK2-V617F JE POVEZANA S KLINIČKO-LABORATORIJSKIM OBILJEŽJIMA MIJELOPROLIFERATIVNIH NEOPLAZMI

S A Ž E T A K

Cilj ovog rada je istražiti razlike između kliničkih i laboratorijskih parametara bolesnika s JAK2-V617F pozitivnim mijeloproliferativnim novotvorinama (MPN) i bolesnika s MPN-om bez JAK2-V617F mutacije. DNA je izolirana iz granulocita periferne krvi 106 bolesnika liječenih u KBC Rijeka: 41 bolesnik s policitemijom verom (PV), 43 s esencijalnom trombocitemijom (ET), 9 s primarnom mijelofibrozom (PMF) i 13 s neklasificiranom mijeloproliferativnom novotvorinom (MPN-u). JAK2-V617F mutacija je analizirana pomoću alel specifičnog PCR-a. Laboratorijski i klinički parametri dobiveni su iz medicinske dokumentacije bolesnika. JAK2-V617F mutacija je utvrđena u 69% (73/106) bolesnika s MPN-om. Rezultati su pokazali statistički značajnu razliku u prevalenciji JAK2-V617F mutacije kod bolesnika s različitim MPN entitetima: 88% u PV, 58% u ET, 56% u PMF-u i 54% u neklasificiranom MPN-u. JAK2-V617F mutacija statistički značajno korelira s leukocitozom i povišenom alkalnom fosfatazom kod ET oboljelih, a s trombocitozom i povišenom razinom leukocitne alkalne fosfatze i serumske laktat dehidrogenaze u oboljelih od PV-a. Vaskularni događaji su povezani s povišenim brojem trombocita u cijeloj skupini oboljelih od MPN-a, s povišenim brojem trombocita i leukocita u oboljelih od ET-a i sa splenomegalijom u bolesnika s PV-om. Klinički i laboratorijski podaci su pokazali značajnu povezanost JAK2-V617F mutacije s razvojem kliničkog fenotipa bolesnika u različitim podskupinama MPN-a.