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Abstract

Philadelphia-negative myeloproliferative neoplasms (MPNs), essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), are rare clonal hematopoietic stem cell disorders accompanied by a strong inflammatory milieu which is directly responsible for constitutional symptoms associated with the disease, such as fever, weight loss or night sweats. Non-hematologists sometimes (and often wrongly) consider the fever in a MPN patient to be a simptom of an underlying disease, which may have devastating consequences. Serum procalcitonin (PCT) is a circulating biomarker commonly used to improve the diagnostic accuracy of bacterial infections and to guide antibiotic therapy. The aim of this study was to test whether PCT could aid the clinician in the early diagnosis of bacterial infections in MPNs. We investigated PCT in 41 ambulatory MPN patients (13 ET, 13 PV and 15 MF) who had no signs of infection and compared it to 10 MPN patients with microbiologically and/or serologically documented bacterial infections. Median PCT in MPN patients was 0.02 ng/mL (range 0.01-0.09). No difference in PCT was found between ET, PV and MF patients ($p=0.993$), whereas MPN patients with documented bacterial infections had significantly higher PCT [median PCT 2.45 (range 0.90-5.40 ng/mL)] when compared to MPN patients with (median PCT 0.03 ng/mL) or without constitutional symptoms (median PCT 0.02 ng/mL; $p<0.001$ for both analyses). These results clearly show that PCT should not be considered as a disease biomarker in MPNs and careful clinical assessment for the signs of infection is needed when MPN patients present with fever and high PCT.

Keywords; procalcitonin; myeloproliferative neoplasm; essential thrombocythemia; polycythemia vera; myelofibrosis

Introduction: Philadelphia-negative myeloproliferative neoplasms (MPNs), essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), are characterized by clonal myeloproliferation and a strong inflammatory milieu. MPN patients show elevated levels of various proinflammatory cytokines, including interleukin (IL)-1, IL-8, IL-6, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP), which are directly responsible for many of the inflammation-linked debilitating symptoms associated with the disease, such as fever, fatigue, weight loss, or night sweats [1,2]. In everyday clinical practice, non-hematologists sometimes (and often wrongly) consider the fever in MPN patients to be a simptom of an underlying disease, which may have devastating consequences. Furthermore, traditional biomarkers of inflammation, such as elevated leukocyte and granulocyte counts, have a limited utility for the diagnosis of bacterial infections in these patients, as they can be a feature of the disease.

Serum procalcitonin (PCT), synthesized by neuroendocrine cells in different tissues, is a circulating biomarker widely used to improve the diagnostic accuracy of bacterial infections and to guide antibiotic therapy [3]. However, PCT can also be slightly elevated in various inflammatory disorders, as well as in different cancers, and the cut-off value of PCT >0.5 ng/mL is usually used to differentiate between the suspected bacterial infection and the exarcerbation of the underlying disease [4,5]. In this study, we aimed to investigate PCT in MPNs and to test whether this blood test might aid the clinician in the early diagnosis of bacterial infections.

Patients and methods: We included consecutive ambulatory MPN patients without any signs of infection and diagnosed according to World Health Organization 2016 criteria [6]. Patients' demographic and clinical characteristics were recorded. Constitutional symptoms were defined as presence of fever ≥37.5ºC, fatigue, night sweats or weight loss ≥ 10% in the preceding 6 months. Blood samples for measurement of PCT, blood counts and CRP were taken at the time

of study enrollment. PCT was measured using the automated electrochemiluminescent immunoassay Elecsys BRAHMS Procalcitonin (Roche Diagnostics, Mannheim, Germany) on Cobas 6000 modular analyzer series (Roche Diagnostics, Mannheim, Germany). The reference value of PCT for adults was <0.02 ng/mL, as supplied by the manufacturer. Through the medical chart review, we have also retrospectively extracted the data about PCT, CRP and blood cell counts in MPN patients with microbiologically (blood, urinary and sputum cultures) and/or serologically (rapid urinary test for Streptoccoccus pneumoniae and Legionella antigens) documented bacterial infections.

Statistical analyses were performed with MedCalc Statistical Software®, version 19.1.7. (MedCalc Software Ltd, Ostend, Belgium). Categorical variables were compared using the χ^2 test, while the differences between independent samples were assessed with Mann-Whitney or Kruskal-Wallis test, as appropriate. Spearman correlation coefficients were calculated to assess the correlations between PCT and different laboratory variables. Significant p-value was set at <0.050 for all analyses. The study was performed in accordance to the Declaration of Helsinki and approved by the General Hospital of Šibenik-Knin County's Ethics Commitee.

Results: We measured PCT in 41 ambulatory MPN patients (13 ET, 13 PV, and 15 MF). The median age was 65 (range 45-89), and 20 patients (48.7%) were female. JAK2-V617F mutation was detected in all PV (100%), 9 ET (69.2%) and in 8 MF (53.3%) patients. Fifteen (36.6 %) patients (2 ET, 5 PV and 8 MF) had constitutional symptoms, and 8 (19.5%) patients (2 PV and 6 MF) had low-grade fever (37.5-38ºC) at blood sampling. Twenty-eight patients (68.3%) used hydroxycarbamide. Median absolute leukocyte and granulocyte count was $7.9x10^9$/L (range 4.9-55.3) and 5.5 $x10^9$/L (range 2.4-35.7), respectively, whereas the median CRP level was 2.45 mg/L (range 0.4-30.4).

Ten MPN patients (4 ET, 2 PV and 4 MF) with documented bacterial infections (6 with pneumonia, 3 with urosepsis and 1 patient with biliary sepsis) served as controls. Median leukocyte count in this patient group was $13.2x10^9$/L (range 5.6-65.6) and $6.2x10^9$/L (range 4.2-40.2), respectively. There was no difference in absolute leukocyte (p=0.141) and granulocyte counts (p=0.249) between MPN patients with or without infections. On the other hand, MPN patients with infections had higher CRP [median 84.1 (range 40.5-256.3 mg/L] when compared to MPN patients without infections (p<0.001).

Median PCT of MPN patients without infection was 0.02 ng/mL (range 0.01-0.09) and 20 patients (48.7%) had PCT above the laboratory reference range (>0.02 ng/mL). There was no difference in PCT between ET [median PCT 0.03 (range 0.01-0.04 ng/mL)], PV [median PCT 0.03 (range 0.01-0.06 ng/mL)] and MF patients [median PCT 0.02 (range 0.02-0.09 ng/mL); p=0.993]. MPN patients with constitutional symptoms had a trend towards higher median PCT (0.03 ng/mL vs 0.02 ng/mL; p=0.063), whereas MPN patients presenting with fever had statistically significantly higher median PCT (0.02 vs 0.03 ng/mL; p=0.019). MPN patients with documented bacterial infections had higher PCT [median PCT 2.45 (range 0.90-5.40 ng/mL)] when compared to MPN patients without infections (p<0.001), as shown in Figure 1. Similarly, MPN patients with infections had significantly higher median PCT when compared to MPN patients with constitutional symptoms (p<0.001). There was no difference in PCT with regard to hydroxycarbamide treatment (p=0.223). In MPN patients without infections, PCT positively correlated with total leukocyte count (rho=0.529, p<0.001), but not with granulocytes (rho=0.158, p=0.323), erythrocytes (rho=-0.239, p=0.131) and platelets, nor with hemoglobin (rho=-0.249, p=0.130) and CRP levels (rho=-0.172, p=0.299). On the other hand, in MPN patients with bacterial infections, PCT correlated positively with total leukocyte (rho=0.837, p=0.002) and granulocyte counts (rho=0.775, p=0.008), as well as with CRP (rho=0.790, p=0.006).

Discussion: Several studies have investigated PCT in hematological malignancies and different cancers. In these studies, high PCT has been shown to correlate with the presence of bacterial infections, with lower PCT being been mostly attributed to tumor- or drug-associated fevers [7-9]. However, the majority of hematological patients included in these studies suffered from acute leukemias, myelodysplastic syndromes or lymphomas. We identified only one case report describing exceedingly high PCT in a patient suffering from post-PV MF that presented with recurrent episodes of systemic inflammatory response syndrome (SIRS). In that case, a simultaneous elevation in serum TNF-α levels were also noted. After the potential infection was excluded, the patient was successfully treated with cytarabine and prednisolone [10]. Therefore, authors have suggested that this "inflammatory" paraneoplastic phenomenon (SIRS) might have been potentially caused by JAK2-V617F-driven increased production of TNF-α [1]. On the other hand, our results show that MPN patients generally have normal or discretely elevated PCT (Figure 1). Even though the subset of MPN patients with constitutional symptoms had slightly higher PCT, probably cytokine-driven by chronic inflammation underlying these disorders [1,10], these data indicates that PCT should not be considered as a disease biomarker in MPNs. Limitations of this study are small number of patients included, retrospective inclusion of MPN patients with documented bacterial infections which might have caused patient selection bias, and the absence of other (atypical) bacterial, viral, or protozoal infections in the control group. In addition, a substantial proportion of MPN patients included in our study used hydroxycarbamide at blood sampling, which influenced the blood cell counts, and possibly the PCT and CRP values. Nevertheless, our results indicate that careful clinical assessment for the signs of infection is needed when MPN patients present with fever and high PCT.

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Figure 1. Serum procalcitonin (PCT) in essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF) patients in comparison to Philadelphia-negative myeloproliferative neoplasm (MPNs) patients who had documented bacterial infections. The Kruskall-Wallis test was used.