Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of C-reactive protein and pentraxin 3

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ABSTRACT

We tested the hypothesis that levels of pentraxin high sensitivity C-reactive protein and pentraxin 3 might be correlated with cardiovascular complications in patients with essential thrombocythemia and polycythemia vera. High sensitivity C-reactive protein and pentraxin 3 were measured in 244 consecutive essential thrombocythemia and polycythemia vera patients in whom, after a median follow up of 5.3 years (range 0-24), 68 cardiovascular events were diagnosed. The highest C-reactive protein tertile was compared with the lowest (>3 *vs.* <1 mg/L) and correlated with age (P=0.001), phenotype (polycythemia vera *vs.* essential thrombocythemia, P=0.006), cardiovascular risk factors (P=0.012) and *JAK2*V617F allele burden greater than 50% (P=0.003). Major thrombosis rate was higher in the highest C-reactive protein tertile (P=0.01) and lower at the highest pentraxin 3 levels (P=0.045). These associations remained significant in multivariate analyses and indicate that blood levels of high sensitivity C-reactive protein and petraxin 3 independently and in opposite ways modulate the intrinsic risk of cardiovascular events in patients with myeloproliferative disorders.

Key words: essential thrombocythemia, polycythemia vera, C-reactive protein, pentraxin 3.

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Introduction

Management of polycythemia vera (PV) and essential thrombocythemia (ET) poses a significant challenge, and a risk-oriented therapeutic approach is recommended in order to avoid inappropriate exposure to potentially leukemogenic cytotoxic drugs on one side or suboptimal treatment on the other. Established risk factors for cardiovascular events are represented by older age and previous thrombosis. Low-risk subjects are younger (< 60 years) and asymptomatic patients, while older subjects and those with a history of thrombosis are categorized at high risk for major vascular events. There is now considerable interest in moving beyond these established risk factors, especially in the young or asymptomatic low- and intermediate-risk individuals not without risk of thrombosis.[1,2] Factors that might improve the vascular risk assessment in myeloproliferative neoplasms are now being examined in large observational studies with adequate follow up for vascular events. From these analyses, novel risk predictors have been recognized and, as in the general population,[3] white blood cell count is emerging as a new marker to predict future events.[4-6] It is important to note the observations that leukocytosis and leukocyte activation are sustained by *JAK2*V617F gene expression profile of neutrophils found to be similar to G-CSF activated granulocytes.[7]

Two other inflammatory biomarkers, belonging to the superfamily of pentraxins have been found to play a role as markers of thrombosis and atherogenesis in the general population. The first is the short pentraxin C-reactive protein, mainly produced in hepatocytes, following stimulation by cytokines, especially interleukin-6 (IL-6). The introduction of high sensitivity assays has allowed routine measurement

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and, based on epidemiological studies, high-sensitivity C-reactive protein (hs-CRP) has been incorporated into risk assessment for cardiovascular disease.[8] The second is the long pentraxin-3 (PTX3), an acute-phase reactant considered more closely related to cardiac injuries such as myocardial infarction than C-reactive protein.[9,10] However, whether PTX3 plays a role in the pathogenesis of thrombosis is still unclear. PTX3 is mainly produced by dendritic cells, macrophages, activated leukocytes and endothelial cells, and not by the liver, in response to primary inflammatory stimuli such as interleukin-1, tumor necrosis factor but not IL-6.[11]

We tested the hypothesis that blood levels of hs-CRP and PTX3 can be correlated with thrombotic complications in patients with essential thrombocythemia and polycythemia vera, and explored the relationship with *JAK2*V617F mutation.

Design and Methods

Patients

Permission was obtained from the Institutional Review Boards to review the medical records. Blood samples of 244 patients with essential thrombocythemia and polycythemia vera, diagnosed according to WHO 2008 criteria, were obtained from consecutive, well characterized patients, regularly followed-up in two Italian hematological centres (Bergamo and Florence). Blood samples were obtained at the last follow-up visit (median time from diagnosis 5.3 years, range 0-24 years). Cardiovascular risk factors at presentation were smoking, diabetes and hypertension. Sixty-eight major thrombotic events (myocardial infarction, stroke, peripheral arterial thrombosis and venous thromboembolism) were objectively documented as previously reported.[5] *JAK2*V617F mutation was carried out according to the already published assay[12] and classified as having low allele burden (<50%, heterozygous) or high allele burden (≥50%, homozygous).

Technical information

High sensitivity C-reactive protein

Hs-CRP was measured by a latex immunoassay (CardioPhase High Sensitivity C-Reactive Protein Siemens Healthcare Diagnostic Inc, Italy) based on anti-CRP antibody absorbed to latex particles. Agglutination resulting from interaction with C-reactive protein in plasma samples was read at 571 nm by means of an automatic analyzer. Normal values in 32 healthy controls ranged from 0.1 to 2.86 mg/L (median 0.57 mg/L).

PTX3

PTX3 plasma levels were measured by an in-house Sandwich ELISA as previously described.[9] Detection limit is 100 pg/ml and inter-assay variability is 8-10%. Briefly, ELISA plates (96 well; Nunc Immuno Plate, MaxiSorp; Nunc) were coated with 100 ng/well of rat monoclonal anti-PTX3 antibody (MNB4) diluted in coating buffer (15 mM carbonate, Na2CO3 + NaHCO3, buffer pH 9.6) by overnight incubation at 4°C. Washing buffer (Dulbecco's phosphate buffered saline (PBS) containing 0.05% Tween 20) was used to wash plates thoroughly after each passage. Non-specific binding to the plates was blocked with 5% dry milk in phosphate buffered saline for 2 h at room temperature before adding recombinant human PTX3 standards (100 pg/ml to 2 ng/mL) or unknown samples. After incubation for 2 h at 37°C, 25ng/well of biotin conjugated anti-PTX3 rabbit IgG were then added (1 h at 37°C) followed by the addition of 100 μL of streptavidin-peroxidase (BioSpa, Milan, Italy). Finally, 100 μL of ABTS chromogen (Pierce) were added and absorbance values were read at 450 nm in an automatic ELISA reader. Normal values in 32 healthy controls ranged from 0.45 to 2.9 ng/mL (median 1.74 ng/mL).

Statistics

Rounded tertiles of hs-CRP and PTX3 distribution were used as cut-offs for all the analyses. Univariate analysis compared patients in the first tertile with patients in the third tertile, using χ^2 test (or Fisher's exact test for cell frequencies less than 5) for categorical variables (sex, polycythemia vera or essential thrombocythemia, cardiovascular risk factors, *JAK2*V617F status and allele burden, treatments and thrombosis occurring at presentation or during follow up) and non-parametric K-sample test for equality of medians was used to analyze age. ANCOVA analysis was performed to test the difference in hs-CRP and PTX3 distributions between categories corrected by age as a covariate.

Multivariate models considered sex (male *vs.* female), age at sampling (≥ 60 years *vs.* < 60 years), disease at diagnosis (essential thrombocythemia *vs.* polycythemia vera), presence of almost one cardiovascular risk factor (yes *vs.* no), *JAK2*V617F allele burden (<50%, ≥50% *vs. JAK2* wild type) and hystory of hydroxyurea treatment (yes *vs.* no). Logistic unadjusted and sequentially adjusted multivariate models were performed to assess for effect modification.

Results and discussion

Patients' characteristics at presentation are shown in Table 1 and clearly reflect the variety of clinical features found in routine clinical practice of care of unselected essential thrombocythemia and polycythemia vera patients. As expected, there was a prevalence of females in essential thrombocythemia and a slight preponderance of males in polycythemia vera. *JAK2*V617F mutation was present in 97% (n=69) and in 63% (n=108) of polycythemia vera and essential thrombocythemia, respectively. Sixty-eight major thrombotic events were registered before blood sampling. Thirty-eight episodes (56%) were documented at diagnosis and 30 (44%) during follow up. Aspirin was prescribed

Table 1. Characteristics of patients participating in the study.

	ET	PV
N	173	71
Age (years, median, range)	61 (21-96)	66 (34-94)
Sex M/F (%)	62/111 (36/64)	43/28 (61/39)
Cardiovascular risk factors* (%)	39 (22.5)	26 (37%)
*JAK2*V617F/ JAK2 wt	108/64 (63/37)	69/2 (97/3)
If *JAK2* mutated, <50% / >50%	101/6 (94/6)	47/22 (68/32)
Thrombosis any time, n (%)	44 (25)	24 (31)
AMI	14 (32)	5 (21)
Stroke - TIA	16 (36)	7 (29)
PAT	0 (0)	1 (4)
VTE	14 (32)	11 (46)
Follow up** (years, median, range)	5.36 (0.25-24.5)	5.05 (0.41-22.2)
Any treatment, Yes/No (%)	153/20 (88/12)	66/5 (93/7)
If yes, Aspirin	139 (80)	41 (58)
Phlebotomy	-	36 (51)
Myelosuppressive drugs	101 (59)	46 (65)

*AMI: acute myocardial infarction; TIA: cerebral transient ischemic attack; PAT: peripheral arterial thrombosis; VTE: venous thromboembolism. *Defined as presence of smoking and/or diabetes and/or hypertension **Time elapsed from diagnosis to blood sample (last follow up).*

in the large majority of cases and chemotherapy (hydroxyurea) was given in 59% and 65% of essential thrombocythemia and polycythemia vera cases, respectively.

Clinical and hematological variables associated with tertiles of hs-CRP and PTX3 concentrations are presented in Table 2.

The comparison between the third *versus* the first hs-CRP tertile (hs-CRP >3 *vs.* <1 mg/L) showed a significant correlation with age (P=0.001), with phenotype (PV *vs.* ET) (P=0.006), with presence of at least one cardiovascular risk factor (P=0.012) and with *JAK2*V617F allele burden greater than 50% (P=0.003). There was a significantly higher proportion of patients who needed chemotherapy when hs-CRP values were higher than 3 mg/L. The number of patients with major thrombosis progressively increased according to increments of hs-CRP values (P=0.01).

PTX3 values (<2.5; 2.5-4.5 and >4.5 ng/mL) showed a significant correlation with *JAK2*V617F allele burden greater than 50% (P=0.01) and in contrast to hs-CRP, thrombotic episodes and cardiovascular risk factors were less frequent in the third tertile than in the first (P=0.0085).

Online Supplementary Figure S1 provides box-plot analysis of hs-CRP and PTX3 values in patients with and without thrombosis both in essential thrombocythemia and polycythemia vera groups. A trend towards higher hs-CRP and lower PTX3 values in patients with thrombosis can be observed, despite a large overlap of values (P=0.021 and P=0.049, respectively). A comparison of patients treated *versus* those not treated with hydroxyurea corrected by age showed no difference in the distribution of these inflammatory proteins (ANCOVA analysis; *data not shown*).

Factors influencing thrombotic risk according to hs-CRP and PTX3 levels were tested in multivariate models (Table 3). For hs-CRP, a significant association with thrombosis was seen when the level exceeded 3.0 mg/L. Effect sizes for the intermediate tertile of hs-CRP (1 to 3 mg/L) were not significant (P values ranged from 0.06 to 0.23). In multivariate analysis sequentially adjusted for sex, age and essential thrombocythemia or polycythemia vera, cardiovascular risk factors, *JAK2* mutation and hydroxyurea treatment, the odds ratios remained significantly higher in patients with hs-CRP levels greater than 3 mg/L.

For PTX3, in unadjusted and progressively adjusted models, we found significant and independent association with thrombosis, but in contrast to hs-CRP, odds ratios (OR) estimates were significantly inferior to 1, indicating that the higher the levels the less frequent were the vascular events.

We tested the interaction between hs-CRP and PTX3 in relation to the number of thrombotic events in a multivariate model (*Online Supplementary Table S1*). Patients with low hs-CRP (< 3 mg/L) and high PTX3 (≥ 4.5 ng/mL) levels were chosen for the reference category (n=51, OR=1). The intermediate categories in which we sequentially added low PTX3 or high hs-CRP doubled this risk (OR=1.82, P=0.18 and OR=2.13, P=0.18, respectively). The most potent and significant correlation with thrombosis was registered in the category with high hs-CRP and low PTX3 values (OR=2.66, P=0.045).

To our knowledge, this is the first study examining hs-CRP and PTX3 blood values and their association with vascular events in essential thrombocythemia and polycythemia vera.

In the general population, hs-CRP blood levels below 1, from 1 to 3, and above 3 mg/L denote lower, average, and higher relative risk for future vascular events. In our essential thrombocythemia and polycythemia vera series, most patients (n=170, 70%) had hs-CRP values much greater than normal concentrations (> 1mg/L).

Likewise, PTX3 plasma levels were significantly higher than the median level of our healthy controls and normal population.[13] There have still been no large population studies to determine the epidemiological association of plasma PTX3 and thrombosis.

In this paper, we have found that levels of these biomarkers in essential thrombocythemia and polycythemia vera patients were significantly associated with the number of major thrombotic events but the effects of this association were completely different for hs-CRP and PTX3. For hs-CRP, odds ratios were between 2.61 and 2.27 in all categories, indicating that the highest levels doubled the risk of thrombosis. This novel finding in myeloproliferative neoplasms is consistent with results of several prospective studies showing that hs-CRP levels in the general population are strongly associated with myocardial infarction, stroke and venous thrombosis[14] so that this inflammatory marker is currently recommended to recognize individuals at high cardiovascular risk and to quantify the efficacy of interventions.[15] For PTX3, we found that the higher the levels, the

Table 2. Meaningful variables associated with values of hs-CRP and PTX3.

	hs-CRP*				PTX3*			
	<1	1 - 3	> 3	P†	< 2.5	2.5 - 4.5	> 4.5	P‡
N=244	73	93	78		75	84	85	
Age, years (median, range)	56 (21-89)	61 (33-89)	73 (30-96)	<0.0001	62 (21-87)	62 (30-96)	66 (24-94)	0.43
Sex M/F (%)	28/45 (38/62)	39/54 (42/58)	38/40 (49/51)	0.20	34/41 (45/55)	37/47 (44/56)	34/51 (40/60)	0.50
ET/PV (%)	59/14 (81/19)	67/26 (72/28)	47/31 (60/40)	0.006	46/29 (61/39)	68/16 (81/19)	59/26 (69/31)	0.28
CV risk factors yes/no, n (%)	10/63 (14/86)	31/62 (33/67)	24/54 (31/69)	0.012	27/48 (36/64)	23/61 (27/73)	15/70 (18/82)	0.0085
*JAK2*V617F / *JAK2* wild type, n (%)	52/21 (71/29)	69/23 (75/25)	56/22 (72/28)	0.94	56/19 (75/25)	58/25 (70/30)	63/22 (74/26)	0.94
If *JAK2* mutated, <50% / >50%	48/4 (92/8)	62/7 (90/10)	38/17 (69/31)	0.003	51/5 (91/9)	52/6 (90/10)	45/17 (73/27)	0.01
Any treatment, yes/no (%)	65/8 (89/11)	82/11 (88/12)	72/6 (92/8)	0.49	64/11 (85/15)	77/7 (92/8)	78/7 (92/8)	0.20
If yes, Aspirin	58 (79)	66 (71)	56 (72)	0.27	47 (63)	70 (83)	63 (74)	0.12
Phlebotomy	8 (11)	12 (12)	16 (21)	0.15	12 (16)	10 (12)	14 (16)	0.96
Myelosuppressive drugs	38 (52)	53 (57)	56 (72)	0.01	46 (61)	48 (57)	53 (62)	0.89
Thrombosis	13 (17)	27 (28)	28 (36)	0.01	29 (39)	18 (21)	21 (25)	0.045

** Rounded tertiles used as cut-offs. † Tests comparing values of h-CRP >3 mg/L in ET and PV patients with those who had values <1 mg/L of the same distribution. ‡ Tests comparing values of PTX3 > 4.5 ng/mL in ET and PV patients with those who had values < 2.5 ng/mL of the same distribution.*

Table 3. Unadjusted and sequentially multivariable adjusted risk of thrombosis associated to different hs-CRP and PTX3 levels.

	1.0 to 3.0 mg/L hs-CRP			More than 3.0 mg/L hs-CRP			2.5 to 4.5 ng/mL PTX3			More than 4.5 ng/mL PTX3		
	OR*	95% CI	*P*	OR*	95% CI	*P*	OR*	95% CI	*P*	OR*	95% CI	*P*
Unadjusted	1.89	0.89-3.99	0.10	2.59	1.21-5.51	0.014	0.43	0.22-0.87	0.019	0.52	0.26-1.00	0.049
Adjusted for+ age	1.82	0.86-3.86	0.12	2.27	1.04-4.95	0.039	0.42	0.21-0.85	0.016	0.51	0.26-1.00	0.050
+ sex	1.83	0.86-3.91	0.12	2.36	1.08-5.18	0.032	0.41	0.20-0.84	0.015	0.49	0.25-0.98	0.043
+ disease	1.80	0.84-3.85	0.13	2.25	1.02-4.96	0.045	0.44	0.21-0.90	0.025	0.50	0.25-1.00	0.050
+ CV risk factors	2.11	0.97-4.59	0.06	2.61	1.17-5.83	0.020	0.41	0.20-0.85	0.017	0.42	0.21-0.87	0.018
+ *JAK2*V617F	1.85	0.84-4.09	0.13	2.47	1.07-5.69	0.034	0.43	0.20-0.92	0.033	0.33	0.14-0.76	0.009
+ hydroxyurea treatment	2.16	0.91-5.10	0.08	2.92	1.18-7.27	0.021	0.41	0.18-0.93	0.030	0.39	0.18-0.83	0.015

**Reference categories: hs-CRP < 1.0 mg/L; PTX3 < 2.5 ng/m.*

fewer the patients with cardiovascular risk factors and thrombotic events. The explanation for this hitherto unknown effect in humans may be offered by recent experimental observations showing that, in mouse models, PTX3 released from activated leukocytes has anti-thrombotic effects, likely through a regulatory role of inflammation.[16] This protective action consists in an attenuation of neutrophil recruitment at sites of inflammation[17] through a PTX3 binding to P-selectin on activated endothelial cells and platelets.[18,19]

Blood values of hs-CRP and PTX3 were correlated with *JAK2*V617F allele burden (P=0.003) suggesting that this production may be due to the effect of gene transcription in the case of the *PTX3* gene which is transcribed by dendritic cells, macrophages, activated leukocytes and endothelial cells, and may be the consequence of high levels of circulating inflammatory cytokines, such as IL-6, in the case of C-reactive protein.[11] These experimental observations prompted us to examine the interaction between these two pentraxins and thrombotic events. The most frequent association with vascular events was detected when the lowest PTX3 tertile interacted with the highest C-reactive protein values. This would indicate that high PTX3 level antagonizes the C-reactive protein thrombotic association likely through a reduction of vascular inflammation. Even though our study has some limitations, such as the retrospective design and the limited number of thrombotic events, nevertheless, it offers further evidence that thrombosis in myeloproliferative neoplasms are associated with a constitutive inflammatory component.

Authorship and Disclosures

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