

Myocardial infarction as a thrombotic complication of essential thrombocythemia and polycythemia vera

Éva Pósfai, Imelda Marton, Zita Borbényi, Attila Nemes

2nd Department of Medicine and Cardiology Centre, Medical Faculty, University of Szeged, Szeged-Hungary

ABSTRACT

Objective: Detailed analyses of clinical characteristics of myocardial infarction (MI) as an essential thrombocythemia (ET)- and polycythemia vera (PV)-related complication have been so far presented mostly as case reports. Therefore, the aim of this retrospective analysis was to evaluate the main cardiological and hematological characteristics for better understanding myocardial complications in ET/PV.

Methods: A retrospective analysis was carried out involving 263 patients diagnosed with ET or PV (155/108) between 1998 and 2014. Fourteen patients suffered MI during the hematological follow-up. Their clinical characteristics were compared to 162 patients (97 ET and 65 PV patients) who did not exhibit any major thrombotic complications (MI, stroke/transient ischemic attack, and venous events) before or after hematological diagnosis of ET/PV.

Results: Fourteen MI events occurred among the 263 patients (5.3%). Vascular risk factors were found in 92.9% (13/14) of analyzed cases. In all, 71.4% of the MI complications developed within 12 months after the diagnosis of ET/PV. The coronary angiography findings revealed ST-elevation MI in four cases and non-ST-elevation MI in 10. Significant stenosis of coronary arteries requiring percutaneous coronary intervention with a stent implantation was present in seven cases, while three had complex stenoses or previous grafts/stents. All of them had undergone coronary artery bypass graft operations.

Conclusion: The results of the present study suggest that early detection and consideration of individual management of vascular risk factors in ET/PV patients are also important. Furthermore, a better theoretic understanding of platelet activation and role of leukocytes in myeloproliferative neoplasm-related thrombosis could open new perspectives in thrombosis prediction and prevention. (*Anatol J Cardiol* 2016; 16: 000-000)

Keywords: essential thrombocythemia; polycythemia vera; myeloproliferative neoplasm; myocardial infarction; JAK2 V617F mutation; STEMI; NSTEMI

Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are listed by the World Health Organization as chronic Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs); these are characterized by increased levels of hemoglobin and red cell mass due to the proliferation of the erythroid lineage (PV) or the overproduction of circulating platelets in the periphery due to the excessive proliferation of megakaryocytes in the bone marrow (ET) (1–4). These patients are at a possible risk of the condition to progressing to myelofibrosis or/and acute myeloid leukemia. The reported 10-year risk of leukemic/fibrotic transformation is less than 1% in ET and 3%–10% in PV (4–6). In contrast, the incidence of thrombohemorrhagic complications, which are mostly responsible for the morbidity and mortality of ET/PV patients, is much higher, at an estimated 11%–39% (4–7).

MPN-related hemostatic abnormalities and the pathogenesis of the thrombosis seen in ET or PV are currently highlighted

topics. These conditions are complex and multifactorial, and besides the quantitative changes in the platelets, erythrocytes, or leukocytes, it is strongly suggested that the qualitative changes in them may initiate and contribute to the circulatory complications (8, 9).

The currently used thrombosis risk stratification is based on only two risk factors and classifies the patients into low-risk (age <60 years, without a prior thrombotic event) and high-risk (age >60 years and/or with a prior thrombotic event) categories (4, 10). An increasing number of publications have recently promoted the rethinking of the thrombosis risk stratification of ET/PV patients from a clinical aspect (4–6, 11–21). The impact of additional molecular or clinical risk factors that improve the prediction of ET/PV-related thrombotic complications has been reported, including the Janus kinase 2 (JAK2) V617F mutation (in ET/PV) and calreticulin mutational status (in ET) or thrombocytosis, leukocytosis, and atherosclerotic risk factors; however, no clear consensus has emerged (4–6, 13–25).

Address for correspondence: Éva Pósfai, 2nd Department of Medicine and Cardiology Centre
Medical Faculty, University of Szeged, H-6720 Szeged, Korányi fasor 6-Hungary
Phone: 36-62-545220 Fax: 36-62-544568 E-mail: evaposfay@gmail.com

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Among the major thrombotic complications, arterial thrombosis is responsible for the great majority of thrombohemorrhagic complications, including ischemic stroke, myocardial infarction (MI), and peripheral arterial occlusion (5). The incidence of MI has been reported in large multicenter studies, but detailed analyses of the associations and clinical characteristics of MI as an MPN-related complication are presented mostly in case reports (7, 26–33).

Our study aim was to add beneficial information that may contribute to the better understanding of myocardial infarction as a complication of ET/PV. The detailed aims of our retrospective analysis were to assess the incidence and the main cardiological characteristics of MI (type of MI, coronary angiography findings) as a severe MPN-related complication in a recent patient population and to compare their clinico-hematological characteristics (JAK V617F mutation, peripheral blood counts, vascular risk factors) with those of ET/PV patients who had never suffered from thrombotic complications [MI, stroke/transient ischemic attack (TIA), or venous complication events (deep venous thrombosis or pulmonary embolism thrombosis and cerebral sinus and venous thrombosis)] neither before the hematological diagnosis nor during the hematological follow-up period.

Methods

Patient population

Between 1998 and 2014, 263 patients were diagnosed with ET/PV in our academic center (mean age: 56.9 ± 15.5 years, range: 19–91 years). Through the use of the medical data files, all the hematological and cardiological results on these patients were reviewed with the approval of the Regional and Institutional Human Medical Biological Research Ethics Committee. The study was conducted in full accordance with the Declaration of Helsinki.

The following inclusion and exclusion criteria were used. Patients were selected retrospectively from the myeloproliferative neoplasm database established for scientific research at the 2nd Department of Internal Medicine and Cardiology Centre. Patients diagnosed with ET/PV during 1998–2014 were enrolled the study. The thrombotic events before and after clinical diagnosis of ET/PV were retrospectively collected for each patient, with focus on MI, ischemic stroke or TIA, and venous thrombotic events (such as deep venous thrombosis or pulmonary embolism thrombosis, and cerebral sinus and venous thrombosis). Patients who had MI during the hematological follow-up period were selected and compared with those of ET/PV patients who had never suffered from the aforementioned thrombotic complications—neither before the hematological diagnosis nor during/after the hematological follow-up period. Patients who reported other inherited or acquired thrombophilia at the time of the hematological diagnosis (such as increased lipoprotein A level) were excluded from the study.

The hematology management strategy was based on risk-oriented recommendations: anti-platelet therapy was administered

to low-risk patients in certain cases (aged <60 years and without a prior history of thrombosis), while the high-risk patients (aged ≥ 60 years, or/and with a prior thrombosis) received cytoreductive drugs (e.g., hydroxyurea) alone or in combination with anti-platelet medication. Phlebotomy was recommended for low-risk PV patients and before the cytoreductive treatment in high-risk PV patients, in order to reach the target hematocrit level below 0.45, respectively (10, 34).

Laboratory analysis

Routine blood analysis with automated blood count equipment was performed as part of the diagnostic protocol. DNA was isolated from EDTA-stabilized peripheral blood samples and screened for the JAK2 V617F mutation (35).

Statistical analysis

Continuous variables are expressed as mean values \pm standard deviation, and categorical variables are summarized as percentages. The unpaired t-test was used for comparing parameters of groups. A p value of <0.05 was considered statistically significant. All the analyses were performed with commercially available software (pl. Medcalc, Mariakerke, Belgium).

Results

During the hematological follow-up period, MI events were reported in 14 (5.3%) of the enrolled 263 patients (five males, mean age: 65.7 years, range: 38–80 years). Most of the MI (10/14, 71.4%) complications appeared within 1 year after the hematological diagnosis of ET or PV. JAK V617F mutation positivity was also present in most of the cases (10/14, 71.4%). Vascular risk factors appeared in the majority of patients (13/14, 92.8%), and 8/14 (57.1%) exhibited two or more vascular risk factors.

In eight ET patients who suffered from MI, a tendency could be demonstrated in the decrease of mean peripheral platelet count between the hematological diagnosis and the time of the MI events, whereas the mean hemoglobin, mean hematocrit, and mean red blood cell count remained basically unchanged. The mean white blood cell count increased markedly (Table 1).

In the six PV patients who suffered from MI, the mean platelet count, mean hemoglobin, mean hematocrit, and mean red blood cell count showed similar reduction tendencies between the time of hematological diagnosis and the time of the MI event, although the mean white blood cell count increased (Table 1). Data on the patients who did not exhibit thrombotic complications earlier during the follow-up period are also given in Table 1. In both PV-AMI and ET-AMI groups, these aforementioned changes were not significant.

The mean hematocrit value was 44.8% and the mean hemoglobin value was 13.8g/L in the cases of ET patients without any thrombotic events (before the hematological diagnosis and during the follow-up hematological period). In the cases of PV pa-

Table 1. Comparison of clinical characteristics of patients without prior/follow-up thrombotic complications and patients who suffered MI during the follow-up period of ET/PV

Characteristics	ET/PV patients without prior/follow-up thrombotic complications (n=162)	ET patients with MI (n=8)	PV patients with MI (n=6)
Males, (%)	61, (38)	4, (50)	1, (17)
Age at diagnosis, mean years, range	57±16, 20–89	63±14, 38–80	70±5, 64–76
Hepatomegaly, n, (%)	30, (19)	1, (13)	2, (33)
Splenomegaly, n, (%)	30, (19)	0, (0)	1, (17)
Hepatosplenomegaly, n, (%)	15, (9)	3, (38)	1, (17)
Platelet counts			
Mean platelet count at ET/PV diagnosis, G/L	577±340	651±181	553±325
Mean platelet count at the time of the MI event, G/L	–	571±161	417±182
Hemoglobin			
Mean hemoglobin at ET/PV diagnosis, g/L	153±27	132±29	169±37
Mean hemoglobin at the time of the MI event, g/L	–	133± 27	161±44
Hematocrit			
Mean hematocrit at ET/PV diagnosis, %	47±28	40±9	53±9
Mean hematocrit at the time of the MI event, %	–	40±7	50±8
Red blood cell count			
Mean red blood cell count at ET/PV diagnosis, T/L	5.1±1.1	4.6±1.3	6.5±0.6
Mean red blood cell count at the time of the MI event, T/L	–	4.7±0.9	6.1±0.4
White blood cell count			
Mean white blood cell count at ET/PV diagnosis, G/L	10.8±12.5	11.3±2.6	11.3±5.7
Mean white blood cell count at the time of the MI event, G/L	–	17.8±9.9	13.5±5.8
Mutation			
JAK2 V617F-positive cases, n, (%)	126, (78)	5, (62.5)	5, (83)
Risk categories			
Low-risk cases	39, (24)	3, (37.5)	0, (0)
High-risk cases	123,(76)	5, (62.5)	6, (100)

ET - essential thrombocythemia; MI - myocardial infarction; PV - polycythemia vera

tients without any thrombotic complications, the mean hematocrit value was 50.9% and the mean hemoglobin value was 17.3g/L.

Following summarization of data of ET/PV patients with thrombotic events in order to compare them with that of ET/PV patients without thrombotic events, no significant differences was found between the groups (Table 1).

STEMI was diagnosed in four cases and NSTEMI in 10. Detailed angiographic results are presented in Table 2. Significant stenosis of coronary arteries requiring percutaneous coronary intervention with a stent implantation was present in seven cases, while three had complex stenoses or previous grafts/stents. All of them had undergone coronary artery bypass graft operations. Recanalization proved to be unsuccessful in one case. Coronary angiography showed only normal epicardial coronary artery arteries in one case, non-significant stenoses in one, and distal occlusion in one.

Discussion

The reported incidence of ET-related and PV-related MI complications was found to be 9.4% and 11.4%, respectively (31). The present cohort exhibited a lower incidence of MI both in ET (5.2%) and in PV (5.6%).

The JAK2 V617F mutation, an acquired gain-of-function mutation in exon 14 of the JAK2 gene, is present in some 50%–60% of ET patients and in almost all patients with PV (5, 14, 36). JAK2 mutation analysis has become a diagnostic criterion for ET/PV, but despite the association between the mutation and an enhanced tendency to major thrombotic complications, its prognostic value is limited (5, 14, 37). Our current analysis, focusing on MI complications, revealed a JAK2 V617F mutation-positive status in majority of the cases (10/14, 71.4%) and in all patients who suffered from other major arterial thrombotic complications, such as in ET-related stroke (38).

Table 2. Characteristics of ET and PV patients with MI

Case No. Age/Gender Date of diagnosis	Hematological diagnosis	Time between cardiological event and ET/PV diagnosis	Cardiovascular risk factors present at ET/PV diagnosis	JAK2 V617F mutation	Cardiological complications		Hematological treatment AFTER ET/PV diagnosis
					Cardiological presentation	Coronary angiography findings	
CASE 1 67/M/2011	ET	4 months	hyperlipidemia	negative	anterior STEMI	LAD-proximal critical and mid 40% stenosis (PCI-stent implantation) LCX-ostial 30% stenosis RC-normal	acetylsalicylic acid + clopidogrel
CASE 2 54/F/2011	ET	3 months	hypertension, smoking	negative	anterior STEMI	LAD- mid occlusion (PCI-stent implantation) LCX-proximal borderline stenosis RC-chronic total occlusion (PCI-stent implantation)	clopidogrel + hydroxyurea
CASE 3 38/F/2009	ET	1 months	smoking	positive	inferior STEMI	LAD-diagonal borderline stenosis LCX-normal RC-thrombotic subtotal occlusion (PCI-stent implantation)	acetylsalicylic acid + hydroxyurea
CASE 4 61/F/2011	ET	9 months	hypertension, obesity	negative	subacute inferior STEMI	LAD-normal LCX-normal RC-occluded (unsuccessful recanalization)	acetylsalicylic acid + hydroxyurea
CASE 5 55/M/1999	ET	139 months	none	positive	NSTEMI	LAD-20% stenosis in LM (due to LM dissection PCI-stent implantation) LCX-1. OM branch ostial critical stenosis RC-proximal significant stenosis	acetylsalicylic acid + hydroxyurea
CASE 6 73/F/2013	ET	9 months	hypertension	positive	NSTEMI	LAD-significant stenosis in ostium of 1. diagonal branch LCX-normal RC-proximal 80% stenosis (PCI-stent implantation)	acetylsalicylic acid
CASE 7 80/M/2013	ET	3 weeks	hypertension, hyperlipidemia	positive	NSTEMI	LAD-LM 20% stenosis + proximal LAD 80% stenosis + 1. diagonal significant stenosis LCX- 1. OM branch ostial critical stenosis RC-proximal significant stenosis (CABG)	acetylsalicylic acid + hydroxyurea
CASE 8 76/M/2012	ET	7 months	hypertension	positive	NSTEMI	LAD-stent in LM, ostial significant LAD stenosis, LIMA-LAD, SVG-diagonal LCX-proximal stent RC-SVG-CD (CABG)	acetylsalicylic acid + hydroxyurea
CASE 9 72/M/2005	PV	8 months	hypertension, hyperlipidemia, obesity	negative	NSTEMI	LAD-diagonal borderline lesion LCX-1. OM branch 20% stenosis RC-ostial 80% stenosis (PCI stent implantation)	acetylsalicylic acid + clopidogrel + venesection
CASE 10 63/F/2010	PV	15 months	hypertension	positive	NSTEMI	LAD-proximal 90% stenosis (PCI-stent implantation) LCX-normal RC-50% stent stenosis	acetylsalicylic acid + clopidogrel
CASE 11 74/F/2005	PV	41 months	hypertension, hyperlipidemia	positive	NSTEMI	LAD-proximal 40% stenosis LCX-normal RC-normal	hydroxyurea + venesection
CASE 12 76/F/2009	PV	13 months	hypertension, hyperlipidemia, obesity, diabetes mellitus	positive	NSTEMI	LAD-ostial occlusion, LIMA-LAD (normal) LCX-95% stenosis, proximal 70% stenosis of SVG-CX (stent in SVG) RC-proximal occlusion (CABG)	acetylsalicylic acid + venesection
CASE 13 64/F/2013	PV	8 months	hypertension, obesity	positive positive	NSTEMI NSTEMI	LAD-normal LCX-normal RC-normal	acetylsalicylic acid
CASE 14 68/F/2011	PV	4 months	hypertension, obesity, diabetes mellitus	positive	NSTEMI	LAD-normal LCX-normal RC-distal occlusion	acetylsalicylic acid + hydroxyurea

CABG - coronary artery bypass grafting; ET - essential thrombocythemia; F - female; LAD - left anterior descending coronary artery; LCX - left circumflex coronary artery; LIMA - left internal mammary artery; LM - left main artery; M - male; NSTEMI - non-ST segment elevation myocardial infarction; OM - obtuse marginal artery; STEMI - ST segment elevation myocardial infarction; PV - polycythemia vera; RC - right coronary artery; SVG - saphenous vein graft

At least one vascular risk factors displayed by most of the patients with MI complications (13/14, 92.9%), and 8/14 (57.1%) of them exhibited two or more vascular risk factors, such as smoking, hypertension, diabetes, and hyperlipidemia. This draws attention to the controversial topic of whether cardiovascular risk factors have an important role in the thrombosis risk-guided management and stratification of MPNs (17, 39).

Our analyses revealed a decrease in elevated platelet count between the time of hematological diagnosis of ET and the time of cardiologic thrombotic complications, as well as corresponding decreases in the mean platelet, hemoglobin, hematocrit, and red blood cell count in PV. We presume that the applied hematological therapy is responsible for these changes. However, the results indirectly support the idea that besides the quantitative changes in the platelets and erythrocytes, qualitative changes in them might additionally contribute to the hemostatic changes (8, 9). Interestingly, in both ET and PV, the slightly elevated white blood cell count at the time of the hematological diagnosis was not decreased at the time of the MI, when the white blood cell count was even higher despite the hematological treatment. From a cardiologic point of view, the importance of the elevated white blood cell count and the relationship between the baseline white blood cell count and the degree of coronary artery disease in patients with acute coronary syndromes has already been established (40, 41). The relevant literature on MPNs reveals that the quantitative role of the white blood cell count in thrombotic complications and its predictive role in thrombosis stratification are still under consideration, and there have been few reports of the qualitative role of leukocytes, in which platelet-leukocyte interactions might be indicative of platelet activation in MPN (42–45).

Study limitations

A limitation of our study is its retrospective design.

Conclusions

It should be concluded that early diagnosis of MPNs is essential for the prognosis and subsequent therapy-related thrombosis risk stratification in ET/PV patients, with emphasis on MI as a major complication. The result of the present study could suggest that most of MI developed within 12 months following the diagnosis of ET/PV, with evident implications for the necessity of early detection and personalized management of vascular risk factors in this group of patients. Furthermore, better theoretic understanding of platelet activation and role of leukocytes in MPN-related thrombosis could open new perspectives in thrombosis prediction and prevention.

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