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Original Article

High rate of abnormal blood values and vascular complications before diagnosis of myeloproliferative neoplasms

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ABSTRACT

Background: Vascular complications occurring before the diagnosis of myeloproliferative neoplasms (MPN) in 612 patients from four centers in Sweden, Denmark and France were retrospectively studied.
Results: Vascular complications were observed in 151 (25%) of the 612 patients. Of these, 66% occurred during the two years preceding diagnosis. The majority of events were thromboembolic (95%), and included myocardial infarction ($n = 46$), ischemic stroke ($n = 43$), transient ischemic attack (TIA) ($n = 22$), deep vein thrombosis/pulmonary embolism ($n = 19$), splanchnic vein thrombosis ($n = 7$), and peripheral embolism ($n = 7$). Bleeding was observed in only 7 (5%) of the 151 patients with vascular events (3 with intracranial bleeding, 2 with epistaxis and 2 with gastrointestinal bleeding). Full blood counts obtained at least 3 months prior to the MPN diagnosis showed that 269 (44%) had abnormal blood values, fulfilling the diagnostic criteria for MPN. During the time from the abnormal blood test to the diagnosis of MPN, 50 patients suffered from a vascular complication.
Conclusion: We therefore conclude that a large proportion of MPN patients suffer severe thromboembolic complications prior to diagnosis. If MPN were diagnosed earlier, a large proportion of these events might be prevented. An MPN should always be suspected and ruled out in patients with unexplained elevated hematocrit, leukocyte and/or platelet counts.

1. Introduction

Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (MF) are Philadelphia chromosome-negative chronic myeloproliferative neoplasms (MPN) that carry an increased risk of arterial and venous thrombosis as well as hemorrhagic complications. All three entities are characterized by clonal expansion of hematopoietic stem cells, which in PV, ET and the early stages of MF, results in the overproduction of mature cells. In the advanced stages of MF, however, the production of mature blood cells is decreased due to progressive myelofibrosis. The pathogenesis of thrombosis in MPN patients is not fully elucidated, but various factors probably play a role [1]. Several risk factors for thrombosis, including a history of prior thrombosis and age > 60 years, have been identified [2,3]. Others, such as leukocytosis, a recognized risk factor for thrombosis in the general population, are still a matter of debate [3–5]. Several studies have also shown that cardiovascular risk factors, including smoking, hypertension, and diabetes mellitus, increase the risk of arterial thrombosis [3–5].

A thrombotic event can be the presenting clinical feature that leads to the diagnosis of an MPN, but thrombosis can also occur before diagnosis and during the course of the disease. Several studies have described the increased risk of thrombotic complications prior to and following MPN diagnosis [2,6]. The Italian Polycythemia Study Group retrospectively looked at the natural history of 1213 patients with PV and noted that 14% of these patients had a thrombotic event before diagnosis, with the highest incidence of thrombosis in the 2 years before diagnosis [7].

The role of the JAK2V617F mutation, as a risk factor for vascular complications, has been evaluated in many studies with variable results. According to three systematic literature reviews, the presence of JAK2V617F in ET patients indicated an increased risk of a thrombotic complication [8–10]. Several studies have shown that the risk of thrombosis in ET patients with the JAK2V617F mutation is higher than that in patients with calreticulin mutations [11,12]. The role of the allelic burden in PV patients has been a subject of debate in recent years. In

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one study, the results showed that a greater allelic burden of JAK2 V617F correlated with a higher risk of cardiovascular events [13], but other investigators have failed to find this correlation [14,15].

The aim of the present study was to describe vascular complications and to describe the extent of abnormal blood values in the pre-diagnostic phase in a large cohort of MPN patients recruited from four centers in three different European countries.

2. Patients and methods

2.1. Patients

Six hundred twelve patients with MPN, fulfilling the 2008 WHO-criteria [16], from Uddevalla, Sweden ($n = 211$), Luleå, Sweden ($n = 199$), Roskilde, Denmark ($n = 119$) and Dijon, France ($n = 83$) were included in this study. The patients were diagnosed between 1995 and 2013 with variations between the different participating centers, depending on differences in the local registries.

2.2. Methods

In this retrospective study, patients' data were retrieved from the local hospital registries. Medical charts were reviewed and laboratory data from the time of diagnosis were collected. Local hospital files and outpatient clinical files were searched for laboratory results prior to the diagnosis of MPN, and all laboratory findings were recorded for the individual patients. The following pre-diagnostic blood values were recorded: hemoglobin concentration (Hb), hematocrit (htc), platelet count (plt), white blood cell count (WBC) and the presence of blast cells. Hb > 18.5 g/dL in men or >16.5 g/dL in women, htc > 0.52 in men or >0.48 in women, plt > 450×10^9/L and/or WBC > 10×10^9/L were considered pathological. JAK2-analysis and the results of bone marrow biopsies, if present, were recorded.

All available medical charts were searched for thromboembolic events and bleeding complications prior to diagnosis. Events included acute myocardial infarction (AMI), peripheral arterial thrombosis, ischemic stroke, deep vein thrombosis (DVT), pulmonary embolism (LE), thrombosis of mesenterial and splanchnic veins and transient ischemic attacks (TIA). All hemorrhagic events, recorded in the hospital files, such as epistaxis, gastric bleeding and cerebral bleeding, were recorded.

2.3. Ethical approval

The study was approved by the Regional Ethical Committee in Gothenburg, Sweden, the Danish Data Protection Agency and the Danish Health and Medicines Authority.

2.4. Statistics

Descriptive statistics were used to describe the patients and the Mann–Whitney test was used to compare groups with and without vascular events. The Chi-square test was used when differences in frequencies between two groups were compared.

3. Results

Among the 612 MPN patients included in the study there were 272 with ET, 249 with PV and 91 with MF or MPN unclassified (uc). As expected, there was a female predominance in the ET cohort (57% of the patients). A slightly higher proportion of males were found in the PV and MF/MPNuc groups (53% and 52%, respectively). Also, the JAK2 V617F mutation status was in accordance with earlier studies: 95% in the PV group, 62% of the ET patients and 56% in the MF/MPNuc group had this mutation. The mean ages, hemoglobin concentrations, hematocrits, white blood cell counts and platelet counts at the time of diagnosis are presented in Table 1.

Vascular complications prior to the diagnosis of MPN were observed in 151 of the 612 patients (25%). Of these, 55% occurred <1 year, 12% 1–2 years, 11% 2–3 years and 21% >3 years before the diagnosis. The majority of events were thromboembolic (95%). Myocardial infarction (AMI) was reported in 46 patients, ischemic stroke in 43 patients, TIA in 22 patients, deep vein thrombosis (DVT)/pulmonary embolism (PE) in 19 patients, splanchnic vein thrombosis in 7 patients, and peripheral embolism in 7 patients. Only 7 (5%) of the 151 patients with vascular events had suffered from bleeding: 3 with intracranial bleeding, 2 with epistaxis and 2 with gastrointestinal bleeding. Only one of the patients with bleedings was treated with ASA. All peripheral emboli and DVT/PE were found in the ET and PV groups.

In the 272 ET patients, 164 had blood samples taken at least 3 months before the diagnosis, among which 153 (93%) were abnormal, with thrombocythemia and occasionally leukocytosis. In 26 of these patients, a vascular complication occurred in the period between the abnormal blood test and the diagnosis. The complications were 9 AMIs, 8 strokes, 3 TIA, 2 LE, 2 peripheral embolisms, 1 portal vein

Table 1
Age and laboratory findings at diagnosis of 612 MPN patients (mean values and standard deviations are given).

	Age years	Hemoglobin g/dL	Hematocrit %	WBC $\times 10^9$/L	Platelets $\times 10^9$/L	JAK2v617f Mutated/wild type
ET all $n = 272$	67 ± 15	13.7 ± 1.7	42 ± 5	10.2 ± 4.1	889 ± 355	106/65
ET male n = 117	66 ± 14	13.8 ± 1.5	42 ± 4	9.8 ± 3.6	892 ± 430	41/32
ET female $n = 155$	68 ± 15	13.7 ± 1.8	42 ± 5	10.5 ± 4.5	887 ± 291	65/33
PV all $n = 249$	69 ± 13	17.4 ± 2.1	54 ± 6	12.4 ± 6.6	579 ± 320	140/7
PV male $n = 131$	67 ± 13	17.4 ± 20	54 ± 6	12.6 ± 7.5	548 ± 271	71/4
PV female $n = 118$	69 ± 13	17.5 ± 21	54 ± 7	12.2 ± 5.4	614 ± 364	69/3
MF/MPNuc female $n = 44$	69,5 ± 11	11.4 ± 2.7	35 ± 7	13.6 ± 11.0	426 ± 336	17/17
MF/MPNuc all $n = 91$	71 ± 11	11.9 ± 2.8	37 ± 8	13.3 ± 9.6	517 ± 389	36/28
MF/MPNuc male $n = 47$	72 ± 11	12.3 ± 2.9	39 ± 8	13.1 ± 8.2	602 ± ±418	19/11

Abbreviations: MPN = myeloproliferative neoplasm, ET = essential thrombocythemia, PV = polycythemia vera, MF = myelofibrosis, MPNuc = myeloproliferative neoplasm unclassified.