

# Stroke, Carotid Thrombosis and Other Thrombotic Events in Essential Thrombocythemia Patient with a High Quantity of Micromegakaryocytes

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## Abstract

Essential thrombocythemia is a myeloproliferative neoplasm characterized by thrombocytosis and possible complications such as thrombosis, hemorrhage, splenomegaly, bone marrow failure and acute leukemia. In the myeloproliferative neoplasms, there is an increase number of dysplastic megakaryocytes, known as micromegakaryocytes and there is an association between the high expression of the *JAK2*<sup>V617F</sup> mutation and the presence of micromegakaryocytes in bone marrow. To date, reports and researches involving essential thrombocythemia and micromegakaryocytes are exceedingly scarce. We report a peculiar and unique case of a death of a 55-year-old man, due to stroke and carotid thrombosis, preceded by successive thrombotic events in a patient with essential thrombocythemia, *JAK2* positive, with no additional risk factor, who did not respond well to standard treatment and had a high amount of circulating micromegakaryocytes in peripheral blood. This case goes beyond the known prognosis of ET and raises the discussion of new prognostic markers, such as the quantification of micromegakaryocytes and reaffirms the importance of the *JAK2* mutation in the evolution of the disease. We also discuss the involvement of micromegakaryocytes in the probable mechanisms leading to our patient's thrombotic state.

**Keywords:** *JAK2* mutation; Thrombocytosis; Hematology; Thrombosis; Peripheral blood

others MPNs, has complications such as thrombosis, hemorrhage, splenomegaly, bone marrow failure and a possible course to acute leukemia [1]. In addition, there are reports of patients with ET that have developed from thrombosis of celiac and superior mesenteric arteries [2], thrombosis of cerebral venous sinuses [3] to pericarditis [4].

In MPNs, abnormal transient myelopoiesis and, more characteristically, myelodysplastic syndrome, there is an increase in the number of dysplastic megakaryocytes, known as micromegakaryocytes (mMK). The International Working Group on Morphology of MDS (IWGM-MDS) defined them as generally diploid, mononuclear cells with a nucleus similar in size to that of a myeloblast or promyelocyte and less than 30 µm in diameter [5].

In a study conducted by Pich, it was found that the high expression of the *JAK2*<sup>V617F</sup> mutation in patients with ET is associated with a higher presence of mMK in bone marrow biopsies [6]. However, little is known about the relationship between the presence of mMK in peripheral blood and the occurrence of such thrombotic events.

Here we present the case of a patient diagnosed with ET, who died after successive thrombotic events, both arterial and venous, with no additional predisposing factor, in a short period of time. The large amount of mMK and the presence of the *JAK2* mutation are the main peculiarities of the case.

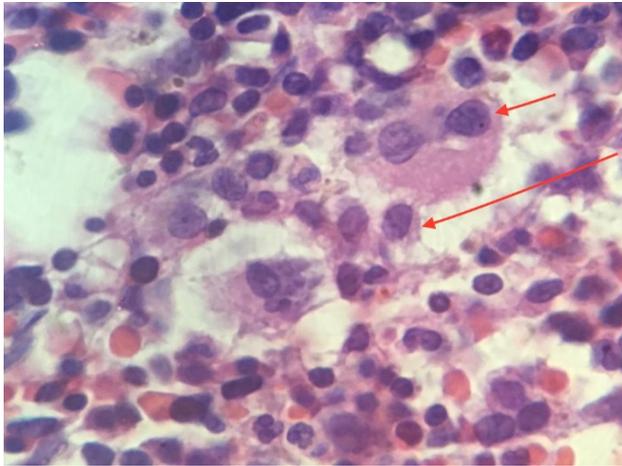
## Case Presentation

A 55-year-old white male was admitted in November 2012 to investigate a thrombocytosis detected on a routine exam. The patient had no symptoms or any other complaint. The possible cause of thrombocytosis was identified in 2013 when the diagnosis of ET was given. The patient's diagnosis complies with the WHO criteria, which are based on clinical and laboratory characteristics [7]. Their initial platelet count was

## Introduction

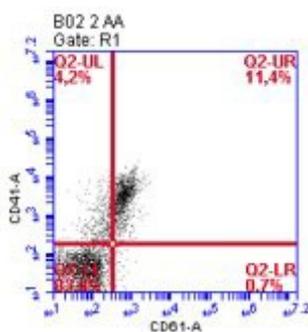
Essential Thrombocythemia (ET) is a Myeloproliferative Neoplasm (MPN) characterized by thrombocytosis and, like

greater than  $450 \times 10^9 /L$ , a bone marrow biopsy (BMB) confirmed the ET. The presence of the  $JAK2^{V617F}$  mutation was also evaluated (positive).



**Figure 1** Bone marrow biopsy of the patient (HE staining, original magnification 40x). The major arrow points to a micromegakaryocyte, while the smaller one, a binucleate megakaryocyte.

Therefore cytoreductive therapy with anagrelide (0.5 mg/2 × day), hydroxyurea (1.5 mg/day) and anti-aggregative with acetylsalicylic acid (100 mg/day) was started, which maintained his platelet count controlled. The patient did not report a history of alcohol or tobacco use and did not present any other comorbidities. However, within a few months, despite the standard therapy, the patient presented ulcers and thrombosis of both lower limbs, as well as ischemia of the fifth toe.



**Figure 2** Peripheral blood analysis of the patient by flow cytometry. The percentage of cells expressing double labeling for the CD41 and CD61 markers, which are indicative of micromegakaryocytes (mMK) is observed in the Dot plot.

In July 2016, another BMB confirmed the myeloproliferative disease, type ET, with mild fibrosis (grade 1). It was also excluded other myeloid malignancies and other causes of reactive thrombocytosis. Small, monolobular megakaryocytes with high nucleus/cytoplasm ratio were found on the slides, compatible with micromegakaryocytes (**Figure 1**).

In February 2017, the patient was recruited for a quantification study of mMK in peripheral blood using flow cytometry (**Figure 2**) and almost 7 times the amount of these cells was observed compared to a healthy person [8]. At the same time, their blood counts revealed LDH and platelet counts within the reference values, but red blood cell counts, lymphocytes, and leukocytes were reduced, as well as hemoglobin levels (**Table 1**). The patient died in June 2017 after an ischemic stroke associated with carotid thrombosis.

## Discussion

Hitherto it is unusual for a case to report so many thrombotic events in the same patient with ET and /or to relate them to the high amount of mMK in peripheral blood. However, the medical literature is rich in the collection of thrombo-hemorrhagic events. In a systematic review of Panayiotis D. Ziakas, thrombotic events were observed in 31.8% of cases positive for the  $JAK2$  mutation [9]. While in the analysis conducted by Lussana, such thrombotic events, whether arterial or venous, occurred in 32% of patients with the  $JAK2$  mutation [1]. In addition, the literature presents a greater number of cases of thrombosis in patients with ET and mutation carriers, splanchnic veins (including the hepatic portal vein) and deep venous system, with an incidence of 11% and 23%, respectively [10].

It is also worth mentioning that the current risk stratification for patients with ET is based on predictors of arterial thrombosis, such as age less than 60 years, history of thrombosis, cardiovascular risk factors (CV). In addition to the use of tobacco, hypertension or diabetes mellitus, leukocytosis ( $>11 \times 10^9 /L$ ) and the presence of the  $JAK2^{V617F}$  mutation [11].

The patient not only had deep vein involvement but also developed the curious event of carotid thrombosis associated with a stroke. Although there is no CV risk factor, no tobacco or alcohol use, no history of previous surgeries, splenomegaly, hypertension, overweight or diabetes mellitus, and did not have a leukometry lower than  $15,000/mm^3$ , indicated as an isolated risk factor for thrombosis [12]. A recent study revealed the association between monocytosis and deep venous thrombosis, but the patient did not present monocytosis at any time (**Table 1**) [13-17].

The patient survived a little more than 3 years after his diagnosis, not corresponding to the average survival of 33 years for patients with ET less than 60 years of age [13]. In addition, several thrombotic events occurred in this interval, even with the standard treatment for patients with high-risk

ET, which consists of systemic anticoagulation conjugated to a cytoreductive therapy, as already mentioned.

**Table 1** Table with results of laboratory tests of the patient. \*Note: Total white blood cell count (WBC), Red blood cells count (RBC), Lactate dehydrogenase (LDH).

Date	LDH (U/L)	Glucose (mg/dL)	WBC ( $10^3/\text{mm}^3$ )	Platelets ( $10^3/\text{mm}^3$ )	RBC ( $10^6/\text{mm}^3$ )	Haemoglobin (g/dL)	Lymphocytes ( $10^3/\text{mm}^3$ )	Monocytes ( $10^3/\text{mm}^3$ )
28-04-2017	216	88	8.80	730	2.93	11.00	1.76	0.44
17-02-2017			3.10	241	2.06	8.90	0.78	0.21
15-12-2016			3.60	254	2.23	9.90	0.86	0.18
20-10-2016			4.90	419	2.36	9.40	0.78	0.25
15-08-2016			8.80	638	2.52	9.70	0.74	0.50
09-06-2016	306	90	10.20	866	2.49	8.70	1.22	0.51
10-05-2016			5.20	555	2.04	6.80	1.04	0.26
19-04-2016			6.20	624	2.53	7.80	0.99	0.31
29-03-2016			9.10	1051	2.34	7.40	1.46	0.47
15-12-2015			9.90	874	2.37	8.00	1.19	0.49
03-08-2015			11.10	671	2.79	8.40	1.33	0.50
02-06-2015	453	78	13.70	934	2.90	9.80	1.51	0.23
19-09-2014			7.80	496	3.12	11.20	1.09	0.45
04-08-2014	243	92	6.40	372	2.93	10.50	0.83	0.34
25-04-2014		96	7.30	460	3.22	12.00	1.83	0.37
04-04-2014	256	87	5.90	428	3.20	12.20	1.00	0.35
10-03-2014	233	88	4.70	347	2.99	12.00	1.27	0.22
22-07-2013		90	7.40	352	3.25	12.40	1.55	0.37
25-03-2013			13.10	783	3.76	12.10	2.23	0.45
01-11-2012			9.70	563	3.38	11.70	1.55	0.40

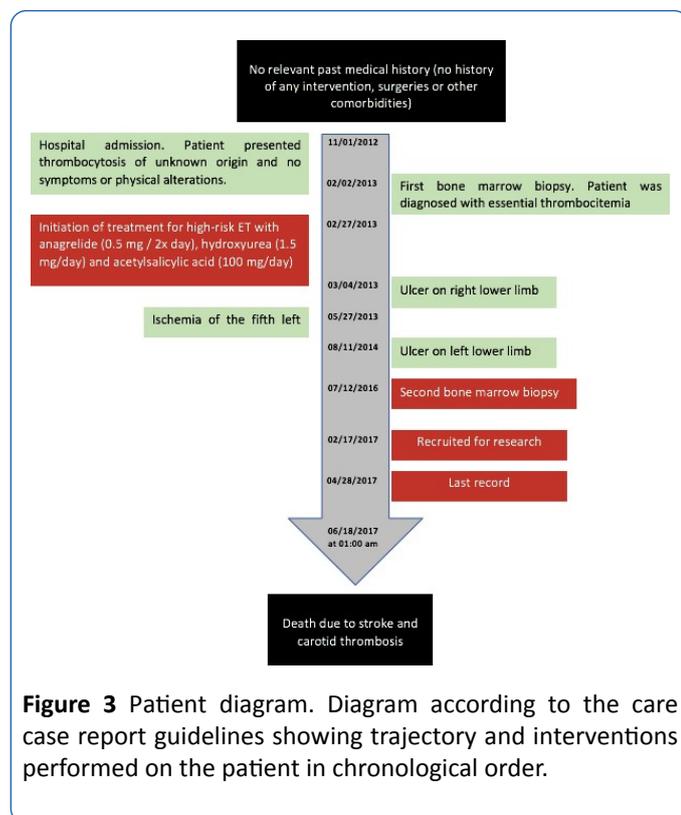
The uniqueness of the case is attributed to the *JAK2*<sup>V617F</sup> mutation and a high number of mMK observed in the peripheral blood of the patient. The pathogenesis of vascular thrombosis associated with *JAK2*<sup>V617F</sup> mutations is still not well understood. However, the cause appears to be associated with increased heparanase activity under the *JAK2* mutation, which would directly increase Tissue Factor concentration (TF) and

decrease Tissue Factor Pathway Inhibitor (TFPI) activity leading to increased factor Xa and subsequent activation of the coagulation cascade. This situation implies an increased thrombosis [14,15].

In addition to this evidence, there are studies in animal models with the *JAK2* mutation, showing that megakaryocytes become hypersensitive to fibrinogen, thrombopoietin and

other endogenous stimulant compounds. Thus, this alteration in the physiology of megakaryocytes could be related to thrombocytosis and to thrombotic events due to a higher reactivity also of platelets to thrombin [16,17].

The patient on this case had mMK-compatible cells in the bone marrow while demonstrating an increase in the number of these cells in the circulation. In this way, what would be the influence of the large amount of mMK? Can mMK be associated with a greater predisposition to thrombotic events? Since they could respond in the same or similar way to normal megakaryocytes in the condition of the *JAK2* mutation (**Figure 3**), we need to analyze what is the impact on patient survival?



## Conclusion

The presentation and outcome of the case did not correspond to many of the proposed paradigms for essential thrombocythemia and raised questions about the role of mMK in the pathogenesis of the disease. Therefore, there is a need for more related studies in order to prove the importance of the quantification of mMK in peripheral blood of patients with ET. Perhaps in the future, we will use quantification of mMK in the clinic, with new perspectives for the prognosis of these patients.

## Author's Contributions

MAP wrote the case report and was the principal investigator; SN was responsible for the acquisition of data and drafting the manuscript; BP recruited the patient and elaborated the consent form; HK evaluated critically and

designed the manuscript. All authors read and approved the manuscript.

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## Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Competing Interests

The authors declare that they have no competing interests.

## Compliance with Ethical Standards

The manuscript has been read and approved by all qualified authors.

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