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Long-Term Disease Stability in Essential Thrombocythemia with Double Driver *MPL* and *CALR* Mutations: A Case Report

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Abstract

Myeloproliferative neoplasms (MPNs) are a group of hematologic disorders that are primarily associated with driver mutations in the Janus kinase 2 (*JAK2*), Calreticulin (*CALR*), and Thrombopoietin Receptor (*MPL*) genes. While these mutations were typically thought to be mutually exclusive, recent studies have reported particularly poor prognosis in cases with double driver mutations. We report the case of an 85-year-old woman diagnosed with Essential thrombocythemia (ET) over 30 years ago, with confirmed double driver *MPL* and *CALR* type 2 mutations. This patient has maintained a stable disease course on hydroxyurea, with no major adverse clinical events noted. This case report highlights the clinical variability and unpredictability that can occur in patients with double driver mutations and further emphasizes the ongoing need for additional research to better understand the complex interactions between double driver mutations and their impact on disease progression, treatment response, and prognosis.

Abbreviations

MPNs: Myeloproliferative neoplasms;
JAK2: Janus kinase 2;
CALR: Calreticulin;
MPL: Thrombopoietin receptor;
ET: Essential thrombocythemia;
PMF: Primary myelofibrosis;
PV: Polycythemia vera

Introduction

Philadelphia-negative myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematologic malignancies that include Essential thrombocythemia (ET), Polycythemia vera (PV), and Primary myelofibrosis (PMF). A hallmark of MPNs is the presence of driver mutations in the Janus kinase 2 (*JAK2*), Calreticulin (*CALR*), and Thrombopoietin receptor (*MPL*) genes [1,2]. Driver mutations in *JAK2*, *CALR*, and *MPL* lead to constitutive activation of the JAK2 signal transducer and activator of transcription 5 (STAT5) pathway, resulting in abnormal proliferation of myeloid precursor cells and dysregulated production of erythrocytes, leukocytes, or platelets [3]. MPNs are typically prognosticated using the International prognostic score for thrombosis in Essential thrombocythemia (IPSET) score, which assesses the risk of thrombosis based on factors including age, history of thrombosis, cardiovascular risk, and platelet count. It categorizes patients into low, intermediate, and high-risk groups for thrombotic events [4]. Management of ET often requires cytoreductive therapy for patients at higher risk of

thrombosis, and hydroxyurea is typically considered first-line [5].

CALR mutations in MPNs are predominantly gain-of-function frameshift mutations occurring in exon 9. Over 80% belong to one of two distinct mutation types [6]. The *CALR* type 1 mutation is a 52-bp deletion. The type 2 mutation is a 5-bp TTGTC insertion [6]. A previous study noted significantly higher platelet counts in individuals with a *CALR* type 2 mutation [7]. Notably, despite a higher platelet count, type 2 *CALR* mutations are associated with a lower risk of thrombosis and a more indolent clinical course [8].

It was initially thought that driver mutations in *JAK2*, *CALR*, and *MPL* occurred mutually exclusively in patients with MPNs. However, recent literature describes the co-occurrence of these mutations [9,10]. Diagnosis of an MPN with double driver mutations occurs in approximately 0.5% of patients, typically in older individuals with elevated platelet counts compared to those with single mutations [10]. Due to the rarity of this clinical entity, little information is otherwise known regarding the long-term clinical outcomes of patients with MPNs and double driver mutations.

We present a case of a patient with ET diagnosed over 30 years ago, with both *MPL* and *CALR* type 2 mutations, who has had a stable disease course with no major adverse events. This case adds valuable information to the literature, given the long-standing follow-up period in a patient with double-driver mutations. Additionally, we provide further data regarding the clinical course of a patient with a *CALR* type 2 mutation.

Case Presentation

An 85-year-old female currently followed in our Hematology clinics was initially diagnosed with ET in 1987 after admission to the hospital for a radical mastectomy for a new diagnosis of breast cancer. She was noted to have incidental thrombocytosis, which ultimately led to a clinical diagnosis of ET. At the time of referral to our clinic, her comorbidities included hypertension, hyperthyroidism, gastroesophageal reflux disease, and breast cancer. During her follow-up, she developed dementia, macular degeneration, squamous cell carcinoma, depression, and anxiety. The earliest laboratory values noted in our system were in 2003, at which time her hemoglobin was 133 g/L, MCV was 87 fL, RDW was 15.4 L/L, and platelet count was 979 x 10^9/L, prior to initiation of cytoreductive therapy. Other diagnostic results include normal ferritin levels ranging from 46 µg/L to 174 µg/L, from 2010 to present. Peripheral blood films from 2008 to present have shown isolated moderately increased platelets without other abnormalities. In 2011, Polymerase Chain Reaction (PCR) testing for the typical *JAK2 V617F* mutation was negative but subsequent myeloid Next Generation Sequencing (NGS) panel revealed type 2 *CALR*: c.1154_1155insTTGTC, p.(Lys385Asnfs*47) (49%) and *MPL*: c.1771T>G, p.(Tyr591Asp) (44.5%) mutations.

Due to initial concerns about side effects, the patient had refused treatment until 16 years after diagnosis, when she started hydroxyurea 500 mg orally twice daily. Since the initiation of treatment, the patient has remained stable without any adverse events or need for therapies beyond hydroxyurea and aspirin. She has had hydroxyurea dose adjustments over the years to maintain her platelet counts below a target of 600 × 10^9/L, but has been clinically well on a daily oral dose of 1000 mg since 2021. She was briefly on aspirin 81 mg orally daily in 2010, but she discontinued it due to epistaxis. It was reintroduced in 2023. She has also had brief periods off hydroxyurea, again due to concerns about side effects (potential hair loss) and social stressors. Her platelet counts have varied over the years, with levels above 600 × 10^9/L, but hydroxyurea uptitration has been limited due to patient reluctance and macrocytic anemia. Her platelet counts over time are outlined in Figure 1. Despite varying platelet counts and periods without treatment, the patient has not experienced any thrombotic or other adverse clinical events secondary to ET.

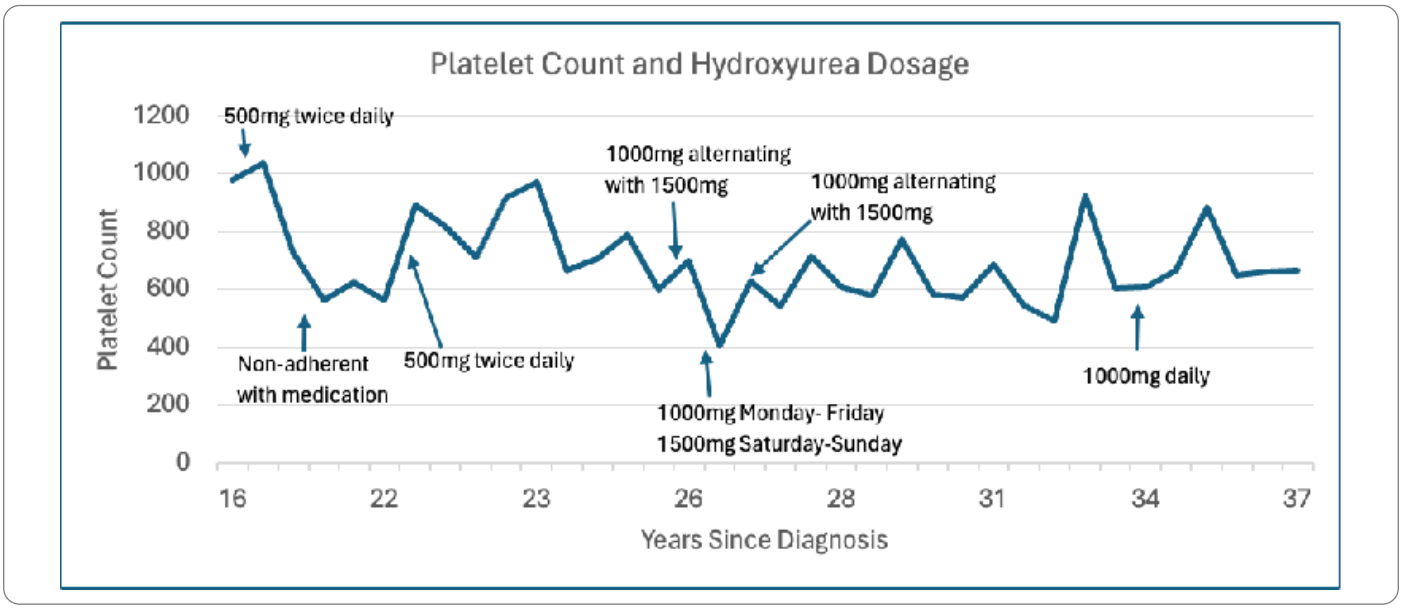

Figure 1 : Platelet Count and Hydroxyurea Dosage

Discussion

This case report offers insight into the clinical phenotype of ET patients with double driver mutations and highlights differences between *CALR* type 1 and type 2 mutations. We follow an 85-year-old female with ET, carrying *MPL* and *CALR* type 2 mutations, to examine her decades-long, stable disease progression with hydroxyurea, despite intermittent adherence.

Building on these observations, studies comparing clinical outcomes between patients with *CALR* type 1 versus type 2 mutations have reported variable results. Type 1 mutations, involving a 52-bp deletion at the C-terminal domain, are generally associated with a more favorable prognosis, such as lower risk of thrombosis and better overall survival, whereas type 2 mutations, defined by a 5-bp insertion, tend to be linked to higher platelet counts and may be associated with different clinical features. Functionally, mutant *CALR* binds to the thrombopoietin receptor *MPL* and facilitates abnormal activation of JAK2 and STAT5 signaling, leading to uncontrolled megakaryocyte proliferation [11].

A 2014 study of 51 *CALR* type 1 and 44 *CALR* type 2 patients reported higher platelet counts in type 2 despite similar IPSET scores [7]. Larger studies show type 1 mutations more often lead to myelofibrosis and higher thrombotic risk [8,12,13]. Our patient has had a lower platelet count over time compared to median values for *CALR* type 2 in those studies, yet a more indolent disease course, aligning with these findings. Direct comparisons remain challenging due to the presence of an additional driver mutation. These findings highlight the need to further explore how specific mutations influence patient outcomes.

The Table 1 summarizes previous case reports that followed patients diagnosed with ET and double driver mutations. Our literature search to identify case reports of patients with ET and double driver mutations revealed only one case of a patient with *MPL* and *CALR* type 2 mutations [14]. The case was a 67-year-old female with *MPL* and *CALR* type 2 mutations who experienced transformation of her disease 3.5 months after diagnosis, and death within 2 years, despite aggressive treatment [14]. As the disease progressed, the *CALR* type 2 mutation was no longer present, suggesting that the *MPL* mutation may have been the more dominant clone. These findings contrast our patient with the same double driver mutations, who has remained stable for over 30 years.

A previous case report discusses a 57-year-old male with *MPL* and *CALR* type 1, who has been well managed on aspirin and herbal remedies [15]. Another report of a 69-year-old female with the same driver mutations, who faced disease progression into acute myeloid leukemia, despite undergoing various treatments [16]. This difference in disease progression may be attributed to additional mutations or clonal evolution, highlighting the variability that can occur. Other studies on patients with *JAK2 V617F* and *CALR* exon 9 type 1 mutations showed comparable disease progression, with no thrombotic nor hemorrhagic events noted [17,18]. Theoretical mechanisms for the differences in disease progression in patients with double driver mutations may involve the presence of two distinct clones, each harboring a different mutation. Such clonal coexistence could allow for independent contributions to pathogenesis, leading to complex disease behavior and varied treatment responses [19]. The dominant mutation may significantly influence clinical outcomes, underscoring the importance of identifying co-occurring mutations for prognosis and treatment planning.

Limitations to this case study include our lack of access to the patient's initial laboratory results and presenting symptoms, both of which would have enhanced our understanding of her disease progression. Additionally, the lack of a bone marrow biopsy limits the comprehensiveness of our evaluation. It is not known whether the patient had both driver mutations present at the time of diagnosis, more than 37 years ago, as molecular diagnostic tests for *JAK2 V617F* and myeloid Next Generation Sequencing (NGS) were not available at our institution until 2007 and 2018, respectively. Thus, we cannot determine which driver mutations occurred first or which represents the dominant clone. Further, single-cell sorting techniques are not available to us to distinguish between the presence of a single clone with both mutations versus two distinct clones, each with its own mutation.

In summary, this case report provides valuable insights into the clinical variability of ET in patients with double driver mutations, particularly *MPL* and *CALR* type 2 mutations. The patient's stable disease course over three decades contrasts with poorer clinical outcomes reported in similar cases, emphasizing the heterogeneity of disease progression. These findings highlight the importance of considering the interplay between multiple mutations and the potential for individualized disease trajectories, underscoring the need for further research into the mechanisms driving these differences and their implications for treatment strategies.

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Authors' Contribution

Conceptualization: Jessie Sanghe, Emily Wildman, Cyrus Hsia; Data curation: Jessie Sanghe, Emily Wildman, Cyrus Hsia, **Analysis:** Jessie Sanghe, Emily Wildman, Cyrus Hsia;
Project administration: Cyrus Hsia;
Resources: Cyrus Hsia;
Visualization: Jessie Sanghe;
Writing- original draft: Jessie Sanghe;
Writing- review & editing: Emily Wildman, Benjamin Chin-Yee, Cyrus Hsia;
Senior authors: Cyrus Hsia, Benjamin Chin-Yee
Ethical Conduct Approval – Helsinki – IACUC: As per institutional guidelines from London Health Sciences Center, ethics approval

was not required for the publication of this case report. Informed consent was obtained from the patient for publication.

Informed Consent Statement: All authors and institutions have confirmed this manuscript for publication.

Data Availability Statement: All are available upon reasonable request.

Competing of Interest

No competing interests were disclosed.

Table 1 : Previous Case reports that followed patients with ET and double driver mutations.

Previous Case Reports						
	References	***Age (years)***	***Gender***	***Mutations***	***Treatment***	***Outcome***
1	Wang et al. (2023)[14]	67	Female	*MPLS204P* and Type 2 *CALR* As the disease progressed, *CALR* mutation was no longer present.	Hydroxyurea and aspirin after diagnosis. Disease progression occurred in the first 3.5 months and treatment switched to decitabine, cytarabine, aclarubicin hydrochloride and granulocyte colony-stimulating factor	After refusing additional treatment the patient died from disease progression.
2	Kelkar et al. (2019)[15]	57	Male	*MPL* exon 10 and type 1 *CALR*	Aspirin and herbal remedies	Well managed
3	Cleyrat et al. (2017)[16]	69	Female	*CALR* type 1 and *MPL W515R*	Hydroxyurea and erythropoietin in 2008, trial of ruxolitinib from 2010–2014. No response to a B-catening/wnt pathway inhibitor in 2014. Continued with ruxolitinib in 2015.	Progressed to acute myeloid leukemia in 2016.
4	McGaffin et al. (2014)[17]	79	Female	*JAK2V617F and CALR* exon 9 type 1	The discovery of the *CALR* mutation did not change initial treatment that was prescribed when only the *JAK2* mutation was known.	Patients is being managed well with no previous thrombosis, bleeding or cerebrovascular disease
5	Xu et al. (2014)[18]	63	Female	*JAK2V617F* and *CALR* exon 9 type 1	Hydroxyurea and interferon alfa	Complete hematologic remission. No history of thrombosis, bleeding or cerebrovascular disease.
6	Rashid et al. (2016)[20]	55	Female	*JAK2V617F* and *CALR*	Continued with previous warfarin treatment and received hydroxyurea treatment from 2011–2012	Remission in 2014.
7	Jang et al. (2020)[21]	57	Male	*JAK2V617F* and *MPL*	Hydroxyurea and aspirin	Discharged from hospital and monitored with follow up.
8	Pennisi et al. (2023)[22]	57	Female	*JAK2V217F* and *MPL*	-	-
9	Wang et al. (2023)[10]	68	Female	*JAK2V617F* and *CALR* type 1	Treated with aspirin and hydroclopidogrel hydrochloride. A month later admission due to fracture and sustained continued thrombocytosis. Hydroxyurea and interferon was administered.	Remission not achieved at time of report.
10	Boddu et al. (2018)[23]	61	Female	*JAK2* and Type 1 *CALR*	Hydroxyurea and aspirin	-

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