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CASE REPORT

Glanzmann thrombasthenia complicated by frequent myeloproliferative neoplasm-related thromboembolism: thrombosis occurring regardless of αIIbβIII integrin deficiency

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Abstract

A patient with Glanzmann Thrombasthenia developed recurrent venous thrombosis with a *JAK2* positive myeloproliferative neoplasm. This indicates that the platelet aIIbβIII integrin has no role in venous thrombosis. We discuss the other potential mechanisms that are involved. In addition, we describe the successful use of dabigatran in this patient.

KEYWORDS

dabigatran, Glanzmann thrombasthenia, myeloproliferative neoplasm, platelet, venous thrombosis, αIIbβIII integrin

1 | INTRODUCTION

Glanzmann thrombasthenia (GT) is a rare autosomal recessive platelet disorder characterized by a lack of functional integrin αIIbβ3. The clinical phenotype is dominated by an increased mucocutaneous bleeding tendency.[1] The occurrence of venous thromboembolism (VTE) in these patients is very rare, but a total of 12 case reports have been published.[2,3] The causes in these cases were (flight) travel, inherited thrombophilia, or peripheral catheter insertion.

2 | CASE PRESENTATION

We describe a 74-year-old woman with GT caused by compound heterozygosity for a pathogenic missense mutation (c.1787T>C p.(Ile596Thr)) and a donor splice site mutation (c.2841+1G>T p.(?)) in the ITGA2B gene (Glanzmann thrombasthenia type 1). Her medical history is extensive, and her bleeding score (ISTH-BAT) was 22 in 2016. She suffered from hypertension for several years and smoked 5 cigarettes a day for over 20 years, but stopped smoking in 2011. She has had multiple episodes of mild microcytic anemia since 2014, for which she undergoes regular colonoscopies for surveillance of adenomas. In March 2016, she developed a superficial thrombophlebitis in her right calf after a long car drive, which was treated with 200mg celecoxib once daily for 4 weeks. In April 2016, she had angina pectoris with ischemic abnormalities on the electrocardiogram. An MRI-heart with adenosine showed baso-inferoseptal and baso-anteroseptal perfusion defects. She was treated with statins, metoprolol, and amlodipine, but platelet inhibitors were contraindicated due to her GT. Treatment was successful, and she remains free of cardiac complaints until today. In October 2017, she developed another thrombophlebitis in her left calf, for which treatment with celecoxib for 4 weeks was

started again. In February 2018, after a mild pneumonia, a deep vein thrombosis (DVT) was diagnosed in the right leg, extending from the popliteal vein to the distal external iliac vein. Her blood count at that time showed a mild microcytic anemia (hemoglobin 9.0 g/dL) with normal leukocyte and platelet counts. CT-thorax/abdomen showed no malignancies; antiphospholipid antibodies (lupus anticoagulant, anticardiolipin (IgM and IgG), and anti-beta2-glycoprotein I (IgM and IgG)) were negative. Treatment with 110mg dabigatran twice daily was started for 3 months. Two weeks after stopping dabigatran, an exacerbation of her microcytic anemia was detected that resolved after iron supplementation. In September 2018, a new DVT occurred in the left leg, for which dabigatran was restarted. After 3 months, dabigatran was reduced to once daily 110 mg for long-term use. She experienced no increase in bleeding tendency and is on dabigatran since. A year later, in October 2019, she had higher hemoglobin values than she was used to (hemoglobin 14.7 g/dL), her platelet count, which was always in the normal range, increased to 599×10^9/L, and a mild leukocytosis developed (11.9×10^9/L). A *JAK2* mutation was found (c.1849 G>T; p. Val617Phe, allele burden 33%) and the diagnosis of polycythemia vera was made. To prevent further thromboembolic disease, low-dose hydroxyurea treatment (500 mg daily) was started, and her blood count normalized within two weeks. Meanwhile, she showed slight progression of DVT in her leg, after which dabigatran was increased to twice daily 110 mg. A year later, in Dec 2020, she had progression of DVT, after which dabigatran was increased from twice daily 110mg to twice daily 150mg. To date, she is without complaints and tolerates both dabigatran and hydroxyurea very well.

3 | DISCUSSION

The hallmark of myeloproliferative neoplasms MPN is a dysregulation of cellular processes in bone marrow precursors. Thrombosis frequently occurs in MPNs. Well-known risk factors are age and prior thrombosis. In addition, hematocrit, leukocytosis, smoking, and hypertension all independently contribute to thrombotic risk in MPNs,[4,5] although they are not incorporated in the current thrombotic risk stratification model.

As the key finding in essential thrombocytosis (ET) is thrombocytosis, it is plausible that platelets contribute to thrombotic risk in MPNs. The efficacy of platelet inhibitors for primary prevention of thrombosis in MPNs further supports an important role for platelets in MPN-associated venous thrombosis. Nevertheless, there is no clear correlation between platelet count and thrombotic risk in ET,[5] although there are reports of altered platelet reactivity.[6-10] This case report clearly demonstrates that platelet aggregation through integrin αIIbβ3 does not contribute to venous thrombosis in MPNs. This is supported by the observation that platelet aggregates are not dominantly present in venous thrombi. Instead, platelets adhere directly either to the activated endothelium or to the adherent leukocytes, forming small heterotypic aggregates. Platelet recruitment to the venous thrombus depends on the interaction between GPIbα and exposed VWF.[11]

How then, would platelets contribute to thrombosis in MPNs?

The interplay between platelets and the coagulation system in thrombus formation appears to be pivotal. It has been demonstrated that αIIbβ3-deficient platelets aggregate if fibrin is formed allowed.[12] This fibrin-dependent platelet aggregation is thought to be mediated by glycoprotein VI (GPVI).[13] Indeed, GPVI has been identified as a promising antithrombotic target as GPVI deficiency protects against thrombosis while not interfering with normal hemostasis.[14] Activated platelets subsequently provide a surface on which the coagulation reaction can propagate. Moreover, they secrete both activated factor V and polyphosphates, greatly enhancing the coagulation reaction.

Platelet-leukocytes complexes also play a significant role in venous thrombosis. New evidence shows that CTL2 (choline transporter-like protein 2, also known as SLC44A2) on the surface of neutrophils drives neutrophil recruitment, activation, and NETosis in vivo and that CTL2 is directly bound by activated αIIbβ3 integrin on platelets in a flow-dependent manner in vitro.[15] Especially in MPN, exacerbated response to Toll-like receptor stimulation is suggested to promote platelet/leukocyte/endothelial interactions and secretion of inflammatory mediators, reinforcing the thromboinflammatory state.[16] However, the lack of αIIbβ3 integrin in GT suggests that platelet-leukocyte complexes do not play an important role in MPN-related VTE.

In this case, MPN was diagnosed after the occurrence of VTE. Hence, primary prevention was not an issue. However, if we would have found MPN before she developed VTE, we still would not have started antiplatelet therapy, in the assumption that her M. Glanzmann would provide a natural protection against VTE. We decided to treat the VTE with a direct oral anticoagulant (DOAC), as the superiority of DOACs over vitamin K antagonists in terms of safety is demonstrated.[17] We used a dose of 110 mg twice daily, as also recommended by the manufacturer in patients with an increased bleeding risk. Unfortunately, our patient had progression of VTE for which the dose of dabigatran was increased twice. She did not experience any bleeding episodes in 2 years of follow-up. We are not aware of other patients with GT currently treated with a

DOAC. We do like to point out that this is a unique case, where the procoagulant activity is pronounced, perhaps counterbalancing the bleeding risks with a DOAC here.

4 | CONCLUSION

In summary, this case shows that the platelet αIIbβ3 integrin is not involved in the pathogenetic mechanism of relapsing venous thrombosis in MPN. This might argue for further interest in the therapeutic role of GPVI inhibition.

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Informed consent was obtained from the patient.

CONFLICT OF INTEREST

RS and RU have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

RS and RU both wrote the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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