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CASE REPORT

Apixaban for treatment of venous thromboembolism in an obese patient with Glanzmann thrombasthenia

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Abstract

Background: Glanzmann thrombasthenia (GT) is a rare congenital platelet function disorder associated with a severe bleeding diathesis. Thrombotic manifestations remain a rare condition. We report here the first case of recurrent venous thromboembolism (VTE) successfully treated with apixaban in a patient with GT. Our patient's morbid obesity was an additional challenge.

Key Clinical Question: The Key Clinical Question was to determine if direct oral anticoagulants are suitable for patients with both obesity and GT.

Clinical Approach: In our patient, the first episode of VTE occurred after the use of a low dose of activated recombinant factor VII for a minor procedure, whereas the second was unprovoked. Administration of rivaroxaban very quickly led to the appearance of bleeding symptoms and subsequently led to poor compliance and extension of deep vein thrombosis. The patient was switched to apixaban, with very good efficacy and safety over the cumulative 18 months of use.

Conclusion: The last updated guidelines now recommend the use of rivaroxaban and apixaban for management of VTE in patients with obesity. Regarding patients with GT, there is still insufficient data on the use of direct oral anticoagulants. Management of thrombotic manifestations in these patients remains a rare and complex condition and could be improved by the creation of a specific international registry.

KEYWORDS
apixaban, obesity, recombinant FVIIa, rivaroxaban, thrombasthenia, venous thromboembolism

Essentials

- Glanzmann thrombasthenia (GT) is a rare inherited bleeding disorder.
- Thrombotic manifestations, such as venous thromboembolism, are rare in patients with GT.
- We present an obese patient with GT and recurrent venous thromboembolism successfully treated with apixaban.
- The choice of the anticoagulant treatment to be given was a real challenge.

1 | INTRODUCTION

Glanzmann thrombasthenia (GT) is a rare congenital hemorrhagic platelet disorder in which quantitative or qualitative abnormalities of the αIIbβ3 complex are associated with a decrease or absence of platelet aggregation. GT is inherited in an autosomal recessive pattern. Bleeding diathesis may be severe and includes nosebleeds, bleeding from the gums and/or purpura, and susceptibility to easy bruising. Women with GT often also have unusually heavy menstrual bleeding and irregular uterine bleeding [1].

In case of bleeding, therapeutic management must include, if possible, local hemostatic procedures and/or administration of tranexamic acid. Transfusion of human leukocyte antigen (HLA)-matched platelet concentrates may be necessary if these measures are ineffective or to prevent bleeding during surgery. Administration of activated eptacog alfa (activated recombinant factor VII [rFVIIa]) is increasingly seen as a good therapeutic alternative, mostly for patients with platelet antibodies and/or a history of platelet refractoriness [2].

The current use of rFVIIa for surgical procedures in patients with GT seems to be quite safe, with only 1 thromboembolic event reported in the Glanzmann Thrombasthenia Registry [3]. In parallel, thrombotic complications are rare in these patients, as only a few cases have been reported in the literature [4–6]. We report here the first case, to our knowledge, of venous thromboembolism (VTE) successfully treated with apixaban in a GT patient. Our patient's morbid obesity was an additional challenge in this unique case of management. We reviewed the literature to evaluate if direct oral anticoagulants (DOACs) are suitable for patients with both obesity and GT.

2 | CASE REPORT

We report the case of a 40-year-old female patient with type I GT belonging to the French Romani population. GT was diagnosed during the neonatal period upon observation of significant oral mucosal bleeding. Her initial hemorrhagic phenotype was relatively moderate (International Society on Thrombosis and Haemostasis bleeding assessment tool score, 10). There was an absence of both platelet aggregation (with common physiologic agonists except ristocetin) and clot retraction. Flow cytometry showed an absence of αIIbβ3 expression on the platelet surface. She was found to be homozygous for the French Gypsy mutation (c.1544+1G>A substitution at the 5' splice donor site of intron 15 of the *ITGA2B* gene).

To treat mainly menometrorrhagia, the patient received platelet transfusions in adolescence. She presented with iatrogenic amenorrhea for a decade on leuprorelin (a gonadotropin-releasing hormone analog) and has not reported any other significant bleeding. Since 2010, all of the surgeries (several dental treatments and 1 gastroscopy) were performed under activated eptacog alfa (rFVIIa), without any particular complications. The patient has smoked an estimated one pack of cigarettes per day for more than 30 years. She suffers from morbid obesity associated with eating disorders (snacking, night eating, and binge eating).

In early 2018, with a body mass index (BMI) of 50 kg/m^2 (weight of 150 kg) and increasingly disabling musculoskeletal disorders, preparation for bariatric surgery began in our university hospital center. In May, a gastroscopy was performed under rFVIIa (2 injections of 90 μg/kg at 2-hour intervals).

One week later, the patient reported calf pain. A Doppler ultrasound revealed a thrombosis of the popliteal vein. The angiologist prescribed rivaroxaban (15 mg twice daily for 3 weeks then 20 mg once daily). The peak concentration was checked at steady state and was considered to be satisfactory (170 ng/mL on day 7, 3 hours after intake), knowing that the patient had normal kidney and liver functions. At the same time, the D-dimer level was 1670 μg/L (normal value [NV], <500).

One month later, the laboratory tests revealed iron-deficiency anemia with hemoglobin at 9.8 g/dL (vs 11.6 g/dL at the initiation of treatment), iron at 4.2 μmol/L (NV, 9-30), ferritin at 7 μg/L (NV, 10-291), mean corpuscular volume at 78.1 fL (NV, 80-100), and mean corpuscular hemoglobin at 22 pg (NV, 27-32). A Doppler ultrasound reassessment of the thrombosis showed persistence of the initial popliteal thrombosis, with extension to the superficial femoral vein. The D-dimer level was 10,140 μg/L. The patient admitted to taking rivaroxaban only occasionally during the last 3 weeks due to the onset of menometrorrhagia.

Therefore, the patient was switched to apixaban (10 mg twice daily for 7 days and then 5 mg twice daily). The treatment was maintained 12 months. In this case, the efficacy (regression then disappearance of thrombosis), clinical tolerance (absence of noticeable bleeding), and compliance with the treatment were perfect. There were no abnormalities in the thrombophilia assessment.

The bariatric surgery was finally performed in November 2019 and consisted of a sleeve gastrectomy. The procedure was performed under treatment with 2 pooled platelet concentrates given 1 hour before and 12 hours after the procedure and rFVIIa (1 injection of 90 μg/kg). Thromboprophylaxis with enoxaparin (6000 IU once daily) was prescribed for 10 days. No thrombotic or bleeding complications were observed after the procedure. The patient rapidly lost weight (−50 kg in 8 months).

A new popliteal thrombosis was diagnosed 12 months after the surgery, this time without a triggering factor. The situation rapidly evolved positively under apixaban (same dosage as during the first VTE) with regression and disappearance of the thrombosis. The clinical tolerance was again perfect, and the anticoagulant treatment was interrupted after 6 months. Today (ie, 21 months after cessation of anticoagulation), the patient is in good general condition with a BMI of 25 kg/m^2 and has not presented any new thrombotic recurrences.

3 | DISCUSSION

Since the creation of the Haemophilia Centre in Strasbourg 20 years ago, 45 patients with GT have been treated. Among them, we documented 3 patients with venous thrombosis (VT). All of these events occurred after the use of a large dose of rFVIIa during major

procedures. In this case, the first episode of a deep vein thrombosis (DVT) occurred after the use of a low dose of rFVIIa for a minor procedure, whereas the second episode was unprovoked.

Thrombotic events are rare in patients with GT. Twelve cases of VTE have been described in the literature to date, and 9 were associated with triggering circumstances (catheter insertion, surgery, cancer, air flight, immobilization, and use of rFVIIa). Cases of unprovoked thrombosis are exceptional [3–6]. Furthermore, arterial thromboses (ATs) are even less frequent than VTs. Unlike VTs, ATs are highly dependent on platelet activation. Patients with GT benefit from the protective effect of the absence of integrin αIIbβ3, which prevents the aggregation of platelets upon stimulation [7].

The data reported in the Glanzmann Thrombasthenia Registry suggests that rFVIIa is safe for surgical procedures in patients with GT: of the 206 procedures performed in 96 patients, only one VTE was reported [3]. This is in contrast to the higher rate of thromboembolism, and in particular of AT when rFVIIa is used off-label in patients without a bleeding disorder [8]. Furthermore, although the thrombophilia assessment result was negative, our patient had a first-degree family history (unprovoked pulmonary embolism at the age of 39 years in the mother) and was an active smoker with morbid obesity. The relative risk of VT in patients with a positive family history (ie, first-degree relative affected before the age of 50 years), active smokers, and obesity is 2.7, 1.23, and 2.5, respectively, with a linear relationship between BMI and risk of VTE [9–11].

The choice of the anticoagulant treatment to be given was a real challenge, given the combination of a major risk of bleeding inherent in GT and morbid obesity. Although there was only 1 previously reported experience among cases of VTE in patients with GT and limited clinical data available for patients with obesity, the choice was made to treat with direct oral factor Xa inhibitors in light of their safety and ease of use and because there was no need to adjust the posology for the weight. It should be noted that only rivaroxaban and apixaban are available in France.

Patients with morbid obesity are poorly represented in clinical trials, but the latest data on these molecules nevertheless confirm that the pharmacokinetics, efficacy, and safety are comparable to those seen in nonobese patients [12,13]. Moreover, the last updated guidance of the International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation now recommends the use of rivaroxaban or apixaban for management of VTE in patients with a BMI of >40 kg/m^2 or weight of >120 kg, and dabigatran is not recommended due to unconvincing data. Regarding patients who have undergone bariatric surgery, the same guidance document suggests not using DOACs in the acute setting. If necessary, their use may be considered after at least 4 weeks of parenteral treatment [14].

The use of DOACs has been reported in 2 patients with GT. The first patient was successfully treated with dabigatran for recurrent DVTs in the context of a JAK2-positive myeloproliferative neoplasm [5]. The second patient received rivaroxaban for recurrent unprovoked DVTs. However, the patient developed more bleeding manifestations and was consequently put back on prior antithrombotic therapy (ie, low molecular weight heparin) [6].

In our patient, rivaroxaban very quickly led to the appearance of abnormal uterine bleeding and subsequently to poor compliance and extension of the DVT. This was unlike apixaban, the efficacy of which was very good and which was not associated with any bleeding over the cumulative 18 months of use for the 2 episodes of VTE. In a recent review, the relative risk of abnormal uterine bleeding for rivaroxaban, apixaban, and dabigatran compared with warfarin was 2.10, 1.18, and 0.53, respectively [15]. Also, although there is insufficient evidence, the superiority of apixaban over rivaroxaban in VTE in terms of efficacy and safety was observed recently in cohort studies [16,17].

In conclusion, management of thrombotic manifestations in patients with GT, whether arterial or venous, remains a rare and complex condition, requires multidisciplinary collaboration, and could be improved by the creation of a specific international registry.

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ETHICS STATEMENT

The authors followed the CARE (CAse REports) guidelines.

AUTHOR CONTRIBUTIONS

L.S. and D.D. designed the study, analyzed the data, and wrote the paper. L.S., J.W., A.H., A.-C.G., O.F. and D.D. contributed to acquisition and interpretation of the data and critically reviewed the manuscript. All authors approved the final version.

RELATIONSHIP DISCLOSURE

O.F. reports personal fees from Bayer, Pfizer, and BMS Pfizer. L.S., J.W., A.H., A.-C.G., and D.D. declare no conflict of interest in relation to the submitted work.

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