# Successful allogenic bone marrow transplant post reduced-intensity conditioning chemotherapy in an adult patient with severe phenotype Glanzmann thrombasthenia: A case report

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**Research Article**

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# Abstract

*Background:* In patients with severe Glanzmann thrombasthenia (GT), a genetic platelet surface receptor disorder of glycoprotein IIb/IIIa (integrin αIIbβ3) that results in prolonged and chronic bleeding, hematopoietic stem cell transplantation (HSCT) is the only curative treatment option. Unfortunately, approximately 30% of all patients undergoing HSCT die from this toxic procedure, owing to the associated risk of infection or chronic graft-versus-host disease, with adults at a higher risk.

*Case presentation:* Herein, we describe the case of a 21-year-old woman from Saudi Arabia who had symptomatic GT for the past 15 years and underwent HSCT following a modified reduced-intensity conditioning (RIC) protocol. This is the fifth reported case of the use of HSCT for treating an adult patient with GT in which RIC HSCT has resulted in long term sustained chimerism with minimal toxicity. The patient was genetically confirmed to have GT since childhood. Owing to recurrent severe bleeding events, the patient had received multiple blood and platelet transfusions and hormonal therapy affecting her quality of life. In September 2019, the patient underwent allogeneic stem cell transplantation from her HLA-matched healthy brother, who was genetically negative for GT. A reduced-intensity conditioning chemotherapy regimen of anti-thymocyte globulin, fludarabine/busulfan (9.6 mg/kg), and a dose of $2.96 \times 10^6$ $CD34^+$ cells were administered. The patient experienced moderate mucositis with associated oral mucosal bleeding during HSCT, which was managed. Low cytomegalovirus viremia occurred 25 days after transplant and resolved with treatment. Neutrophil engraftment occurred on day +23, and platelet engraftment on day +27. A platelet aggregation test repeated after 1 year and 10 months was negative. At 24 months following HSCT, the patient was well and graft versus host disease-free, had no bleeding tendency, and discontinued all immunosuppressant therapy.

*Conclusion*: HSCT in adults with severe phenotype GT is possible if indicated, but careful consideration of different aspects of care should be considered and strictly followed for a successful outcome. Future research through more case reports or series utilizing similar reduced intensity conditioning HSCT is needed to fill the knowledge gap given the rarity of indication and the new protocol.


# Background

Glanzmann thrombasthenia is an autosomal recessive bleeding disorder characterized by either qualitative or quantitative abnormalities of integrin αIIbβ3 structure or function, as a result of gene mutations in *ITGA2B* and/or *ITGB3*. αIIbβ3 integrin is a critical mediator in platelet aggregation, and the genetic defects present in patients with GT result in integrin αIIbβ3 dysfunction, leading to increased bleeding [1]. Many patients with GT experience mild mucocutaneous bleeding; however, some patients present with recurrent life-threatening bleeding, and hypermenorrhea is a major debilitating symptom in women. Treatment may include local applications such as fibrin sealants, thrombin administered topically, or systematic agents such as antifibrinolytic agents. In severe cases of bleeding, the administration of platelet concentrates is a critical treatment option. However, the treatments described here may not be adequate for severe cases of GT, which may require the use of recombinant factor VIIa [2]; in such cases, the only cure for GT is allogeneic hematopoietic stem cell transplantation. While HSCT has been successfully performed in adult patients with GT, its application is more successful when administered during childhood [3, 4]. Considering the risks associated with HSCT among adults, Cid et al. [5] recommended that physicians and their patients complete a cost-benefit analysis to determine bleeding risks and the ability to control recurrent bleeding, prior to transplant approval for adults. Thus, we present a case report of HSCT administered to a 21-year-old woman with GT who presented with recurrent severe bleeding over a period of several years, affecting

her quality of life and daily activities medically, educationally, and socially. After careful consideration of all factors, including excellent compliance of the patient and family, the patient underwent successful HSCT via allogeneic bone marrow transplant (allo-BMT) using bone marrow obtained from a sibling.

## Case Presentation

A 21-year-old woman diagnosed with GT at the age of 1 year, presented to our center at King Faisal Specialist Hospital & Research Center (General Organization), Jeddah, in March 2016, with signs of severe anemia. The patient was referred to us for consideration of HSCT, given her severe clinical phenotype and strong preference. The patient was diagnosed at another institution in 2001 following recurrent episodes of epistaxis (chronic mucocutaneous bleeding tendency). Her family history was relevant, revealing other members affected by the same syndrome. Laboratory tests revealed a normal complete blood count. Prothrombin time and partial thromboplastin time were normal. Bleeding time was prolonged. Platelet aggregation response to adenosine diphosphate, collagen, and epinephrine was impaired. She showed evidence of a remarkable reduction in platelet glycoprotein IIb/IIIa, which is consistent with GT. Management at that time was symptomatic, with frequent emergency room visits because of epistaxis requiring platelet transfusions and packed red blood cell (PRBC) transfusions for iron-deficiency anemia.

Following admission at our center, she received two units of PRBCs. The patient's initial diagnosis was confirmed by repeating all laboratory tests, and tranexamic acid (500 mg, three times a day) was administered orally. Since admission to our hospital, the patient had experienced frequent epistaxis, leading to severe anemia and requiring treatment with blood and platelet transfusions and levonorgestrel as hormonal therapy. For several years thereafter, she continued to require frequent blood and platelet transfusions.

The patient had an HLA-matched healthy brother who was genetically negative for GT. At baseline, the patient had an HSCT comorbidity index of 1 (depression and anxiety requiring consultation or treatment) with 21% non-relapse mortality at 1 year. She was diagnosed with depression but was not compliant with anti-depressant treatments. In September 2019, allogeneic stem cell transplantation from her brother was determined to be the best treatment option. A reduced-intensity conditioning chemotherapy regimen of anti-thymocyte globulin (ATG, fludarabine/busulfan, 9.6 mg/kg) was administered. The patient received a dose of $2.96 \times 10^6$ $CD34^+$ cells/kg. Graft-versus-host disease (GVHD) prophylaxis treatment included cyclosporine as well as prophylactic antifungal and antiviral coverage with fluconazole and acyclovir, respectively. Since it is contraindicated, we did not insert any Hickman line; instead, a peripherally inserted central catheter (PICC) line was used. Supportive care included daily platelet transfusion regardless of platelet count, starting from the day before line insertion and continuing throughout her transplant until engraftment. High-dose tranexamic acid was added, and factor VII was kept on standby but was not needed. The patient experienced moderate mucositis with associated oral mucosal bleeding, which was managed. Low cytomegalovirus viremia occurred 25 days after the transplant, but given that the patient had received ATG, she was treated with valganciclovir. Neutrophil engraftment occurred on day + 22, and platelet engraftment on day + 35. Peripheral blood chimerism was 100% myeloid and 84% lymphoid on day 28 post-HSCT. Subsequent chimerism testing continued to show near full donor chimera. A platelet aggregation test repeated after 1 year was negative. At 24 months following HSCT, the patient was well and GVHD-free, had no bleeding tendency, and had discontinued all immunosuppressant therapy for 1 year.

## Discussion And Conclusions

HSCT has become an essential procedure if indicated with curative intent for individuals with malignant/non-malignant, acquired, or congenital hematopoietic system disorders. Children with GT often present with severe epistaxis, requiring multiple transfusions. In this case report, the woman was 21 years old. Therefore, this discussion compares the present case report with four other adult reports of HSCT to cure GT, which will subsequently be referred to as cases 1, 2, 3, and 4. The details of these cases are reported in Table 1 for an easy comparison of the differences and similarities between each case. All four published cases received myeloablative conditioning HSCT. Case 1 involved a 44-year-old woman who received myeloablative HSCT conditioning and subsequently died as a result of GVHD and infection complications. Case 2 involved an 18-year-old patient who had grade 2 GVHD, while cases 3 and 4 involved a man and a woman, respectively, who developed extensive GVHD. All patients received peripheral stem cells except one.

Myeloablative conditioning chemotherapy should be generally avoided in non-malignant diseases. Substantial evidence confirms that RIC can lead to similar disease response outcomes with much less toxicity, and that stable mixed chimera can cure the disease and prevent its symptoms. The 21-year-old woman treated in the present case received a combination of fludarabine/busulfan 9.6 mg/kg ATG (BU/FLU). The patient in case 1 received myeloablative BU/FLU conditioning and subsequently died as a consequence of post HSCT complications [7–10].

Our patient received $2.96 \times 10^6$ $CD34^+$ cells/kg during the transplant from the bone marrow source. In non-malignant disorders, the use of peripheral stem cells is not advised, as they carry a higher risk of GVHD. GVHD effect is seen more with peripheral harvest and is not required in benign diseases, as illustrated in multiple studies [11–14].

An evaluation of the previous cases reported in the literature and the above case highlights the following points. First, iron deficiency should be screened and treated prior to transplantation. Second, we recommend judicious prophylactic use of hemostatic measures such as tranexamic acid and fibrin sealants. Third, a daily platelet transfusion should be administered once chemotherapy starts, regardless of platelet count. Fourth, we should ensure the availability of factor VII before transplantation to treat any severe bleeding event. Finally, the central line insertion should be avoided; instead, the PICC line placement should be prioritized as a safe procedure with a low incidence of bleeding.

HSCT in adults with GT is rarely indicated. Careful consideration of the patient's condition, disease, and transplant factors in the pre-, peri- and post-HSCT phases are of extreme importance to ensure better outcomes for adult patients who may be at higher risk of transplant-related morbidities and mortality.

**Table 1: Case details from published case reports of adult patients with GT treated with HSCT**

| Checklist Item | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| **Author, publication year** | [5] | [6] | [7] | [3] |
| **Patient age** | 44 years | 18 years | 52 years | 16 years |
| **Conditioning chemotherapy** | Myeloablative BU/FLU regimen | Myeloablative Busulfan and Cyclophosphamide regimen | Myeloablative 12 Gy total body irradiation<br><br>and cyclophosphamide regimen | Myeloablative Busulfan and Cyclophosphamide |
| **GVHD prophylaxis regimen** | Prednisolone and Cyclosporine | Cyclosporine and short-term methotrexate | Tacrolimus and short-term methotrexate | Cyclosporine and methotrexate |
| **Stem cell source and dose** | Peripheral blood with partial T-lymphocyte depletion and positive CD34+ selection | 4.2 × 108/kg body weight non-manipulated peripheral blood mononuclear cells (5.8 × 106/kg CD34+ cells) | HLA-matched unrelated donor | HLA-identical sibling bone marrow transplant (3.55 × $10^8$ nucleated cells/kg) |
| **Complications** | - Chronic GVHD and urinary tract infections<br><br>- Frequent outpatient visits | - Stage 2 skin GVHD (Chronic GVHD) | - Grade 3 acute GVHD of the skin and intestine | - Moderate (grade II mucosal toxicity)<br><br>- Skin and intestinal grade II acute GVHD<br><br>- Extensive chronic GVHD<br><br>- CMV Antigenemia |
| **Notes** | | | Transfusions were performed to maintain a platelet count between 30,000 and 40,000/L. | A central venous line was inserted |

Abbreviations: BU, busulfan; CMV, cytomegalovirus; FLU, fludarabine, GVHD, graft-versus-host disease

# Abbreviations

anti-thymocyte globulin, ATG

busulfan, BU

cytomegalovirus, CMV

fludarabine, FLU

Glanzmann thrombasthenia, GT

graft-versus-host disease, GVHD

hematopoietic stem cell transplantation, HSCT

packed red blood cell, PRBC

peripherally inserted central catheter, PICC

reduced-intensity conditioning, RIC

# Declarations

*Ethics approval and consent to participate*

This case report was approved by the KFSHRC Jeddah IRB committee with reference number: IRB 2022-CR-11

*Consent for publication*

The patient consented to participate/publish her condition in educational journals.

*Availability of data and materials*

The data supporting the conclusions of this article will be made available by the authors, without undue reservation.

*Competing interests*

The authors declare that they have no competing interests.

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*Authors' contributions*

WQ designed the article, interpreted the data, and wrote the paper manuscript. NJ supervised, reviewed, and edited the article. All authors read and approved the final manuscript.

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