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CASE REPORT

# A Bleeding Puzzle: Unveiling Glanzmann's Thrombasthenia In Pediatric Patients With Normal Coagulation Profiles – A Case Series

**Dr. varshini[1], Dr. sugima[2], Dr. Supraja[3], Dr. G. V. Kumar[4]**

*[1]Post graduate student, dept of pediatrics, sri Siddhartha medical college and hospital, tumkur*
*[2]SNR district hospital, kolar*
*[3]Post graduate student, dept of pediatrics, sri Siddhartha medical college and hospital, tumkur*
*[4]Professor, dept of pediatrics, siddaganga medical college and research institute*

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**Corresponding Author:**

**Dr. varshini**
Post graduate student, dept of pediatrics, sri Siddhartha medical college and hospital, tumkur

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## ABSTRACT

**Background:** Glanzmann thrombasthenia (GT) is a rare inherited platelet function disorder characterized by mucocutaneous bleeding despite normal platelet counts and coagulation profiles. Early diagnosis remains challenging due to its rarity and often normal initial investigations.

**Case Series Summary:** We report three pediatric cases of GT with varied presentations—recurrent gum bleeding, post-circumcision hemorrhage, and menorrhagia. All patients had prolonged bleeding time with normal platelet counts and coagulation parameters. Platelet aggregation studies confirmed absent aggregation to ADP, collagen, and epinephrine, with preserved response to ristocetin, establishing the diagnosis.

**Methods**: This is a retrospective observational case series conducted at a tertiary care center over two years. Two patients were evaluated during inpatient admission, and one was assessed in the outpatient department. Clinical details and investigations were retrieved from hospital records.

**Conclusion:** This case series highlights the clinical variability of GT and emphasizes the importance of considering platelet function disorders in children with unexplained mucocutaneous bleeding. Early recognition and appropriate diagnostic workup are crucial for effective management and improved outcomes.

***Keywords****: Glanzmann thrombasthenia, platelet function disorder, mucocutaneous bleeding, platelet aggregation, consanguinity, pediatrichematology.*

## INTRODUCTION

Glanzmann thrombasthenia (GT) is a rare inherited platelet function disorder first described in 1918 by Swiss paediatrician Edward Glanzmann, who noted a form of purpura characterized by a normal platelet count and morphology, prolonged bleeding time, and absent or diminished clot retraction[1]. An autosomal recessive bleeding disorder caused by either a deficiency or dysfunction of the platelet glycoprotein (GP) IIb/IIIa complex, also referred to as integrin αIIbβ3[2]. Although the condition has a worldwide distribution, it is more frequently reported in populations with high rates of consanguinity, such as the French Romani, South Indian Hindus, Iraqi Jews, and Jordanian nomadic tribes[3].

Clinically, GT manifests as mucocutaneous bleeding of variable severity, including epistaxis, gingival bleeding, easy bruising, and, in females, menorrhagia. Refractory bleeding and platelet alloimmunization are common complications.[4] In addition, pregnant patients pose unique management challenges.

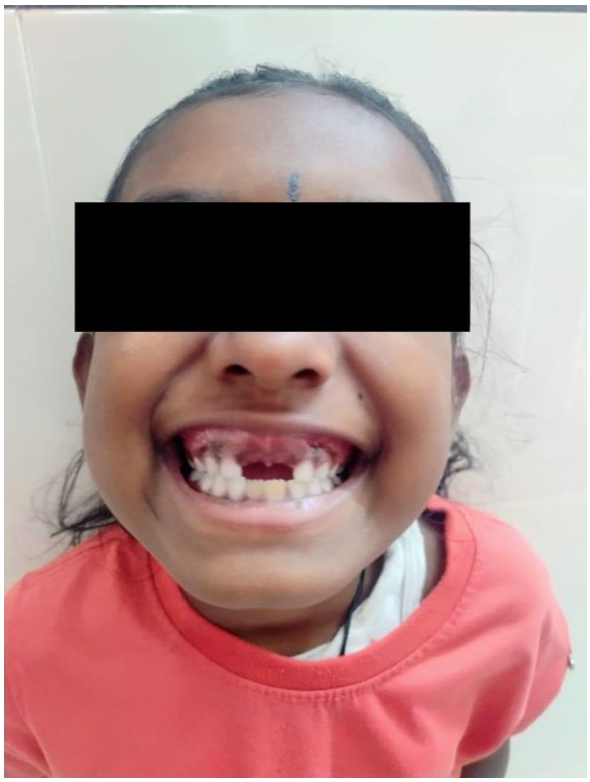
Due to its rarity and the presence of normal lab values in routine coagulation screening, diagnosis is often delayed. Here, we present a series of cases of Glanzmann thrombasthenia in pediatric patients from consanguineous families, all presenting with recurrent mucocutaneous bleeding, to emphasize the importance of early recognition and appropriate diagnostic workup in such settings.

## MATERIAL AND METHODS

A retrospective observational study was conducted at a tertiary care center over a period of two years in the Department of Pediatrics. Three pediatric patients diagnosed with Glanzmann thrombasthenia were included in the study. Of these, two were admitted for evaluation and management of bleeding symptoms, while one was evaluated in the outpatient department (OPD). Clinical history, physical examination findings, laboratory investigations, treatment details, and outcomes were obtained from hospital case records. The diagnosis in all three patients was confirmed by platelet aggregation studies. Data were compiled and analyzed to highlight the clinical presentation, diagnostic challenges, and management approaches in pediatric Glanzmann thrombasthenia.

### CASE 1:

An 8-year-old female child presented with a history of recurrent gum bleeding over the past three years, which was notably exacerbated by tooth brushing. She also had a history of prolonged bleeding on minor trauma. There was no history of bone painor prior blood transfusions.The child was born to consanguineously married parents, and there was no known family history of bleeding disorders. On physical examination, she appeared pale and had active gum bleeding. Her vital signs were stable, and systemic examination, including cardiovascular and respiratory systems, revealed no abnormalities.



Laboratory investigations revealed a hemoglobin level of 9 g/dL, total leukocyte count of 5600/mm³, with a differential count showing 74% polymorphs, 23% lymphocytes, and 3% eosinophils. The platelet count was 2.28 lakh/mm³. Red blood cell count was 2.82 million/mm³, with a hematocrit of 25.3%. Peripheral smear showed microcytic hypochromic red blood cells, normal white cell morphology with no immature cells, and adequate platelets with normal size and morphology.

Coagulation profile revealed normal activated partial thromboplastin time (28.7 seconds), prothrombin time (13.6 seconds), and INR (1.0). Clotting time was within normal limits; however, bleeding time was markedly prolonged (>15 minutes). Given the isolated prolonged bleeding time and clinical suspicion of a platelet function disorder, a platelet aggregation study was performed. The test demonstrated absent aggregation in response to ADP, collagen, and epinephrine, with preserved aggregation to ristocetin — findings diagnostic of Glanzmann's thrombasthenia.

She was managed conservatively with oral tranexamic acid and advised on strict bleeding precautions. She and her caregivers were counseled regarding lifestyle modifications, the importance of maintaining oral hygiene, and the avoidance of medications that may exacerbate bleeding.

### CASE 2:

A 6-month-old male infant was referred to the pediatric department with persistent bleeding following a routine circumcision performed earlier that day. The bleeding had continued for over 6 hours despite the application of local pressure and hemostatic measures. There was no history of trauma or prior bleeding episodes. The infant was born full-

term via an uneventful vaginal delivery to consanguineous parents. Antenatal and perinatal histories were unremarkable, and there was no known family history of bleeding disorders.

On physical examination, the infant was alert and hemodynamically stable. Local examination revealed continuous oozing of blood from the circumcision site. No petechiae, ecchymoses, hepatosplenomegaly, or lymphadenopathy were noted. There were no signs of joint or deep tissue bleeding.

Initial Laboratory investigations revealed a hemoglobin level of 10.2 g/dL and a total leukocyte count of 7,000/mm³. The platelet count was normal at 2.3 lakh/mm³. Coagulation parameters, including prothrombin time (13.4 seconds), activated partial thromboplastin time (28.5 seconds), INR (1.02), and clotting time, were all within normal limits. However, the bleeding time was significantly prolonged at more than 15 minutes. Peripheral smear showed normocytic normochromic red blood cells, adequate platelets with normal morphology, and no abnormal white cell forms. Given the isolated prolonged bleeding time with otherwise normal hematologic and coagulation parameters, a platelet function disorder was suspected.A platelet aggregation study was performed using standard agonists. Results revealed: Absent aggregation with ADP, collagen, and epinephrine. Normal aggregation with ristocetin

The infant was managed conservatively with platelet transfusion, after which the bleeding ceased. Topical haemostatic agents and sterile compression dressings were also applied. No further transfusions were needed during hospitalization, and the patient was discharged in stable condition with instructions for bleeding precautions and long-term follow-up.

**CASE 3:**
A 13-year-old female presented to the outpatient department with complaints of excessive menstrual bleeding since menarche at the age of 11. Her menstrual cycles were regular but prolonged, lasting 8–10 days, with heavy flow requiring frequent changes of sanitary pads. The excessive bleeding was accompanied by progressive fatigue and reduced exercise tolerance.

Further history revealed frequent episodes of epistaxisand easy bruising. The patient was the child of a consanguineous marriage.

On examination, the patient was pale, but vitally stable. There was no hepatosplenomegaly, joint swelling, or lymphadenopathy. Systemic examination was unremarkable.

Laboratory investigations revealed a hemoglobin level of 7.8 g/dL, indicating anemia. The total leukocyte count was 6,300/mm³, and the platelet count was within the normal range at 2.4 lakh/mm³. Peripheral smear showed microcytic hypochromic red blood cells, consistent with iron deficiency anemia, and platelets appeared normal in size and morphology. Coagulation studies revealed a normal prothrombin time (12.8 seconds), activated partial thromboplastin time (29.1 seconds), INR (1.0), and clotting time. However, bleeding time was markedly prolonged at over 15 minutes, suggestive of a platelet function defect.

Given the normal coagulation profile and platelet count, along with a history suggestive of a mucocutaneous bleeding disorder, a platelet aggregation study was performed. The results were as follows:No aggregation with ADP, collagen, and epinephrine. Normal aggregation with ristocetin. These findings were diagnostic of Glanzmann thrombasthenia
The patient was started on:Oral tranexamic acid during menstruation to reduce bleeding. Combined oral contraceptive pills for hormonal regulation and reduction of menstrual blood loss. Oral iron supplementation for correction of iron deficiency anemia. She and her family were counseled on the nature of the disease, bleeding precautions, and the importance of avoiding medications such as NSAIDs that may exacerbate bleeding.At follow-up, the patient reported reduced menstrual flow and improvement in energy levels.

**RESULT**
This case series includes three pediatric patients diagnosed with Glanzmann thrombasthenia (GT), each presenting with variable mucocutaneous bleeding symptoms but sharing a common diagnostic profile. All three patients had normal platelet counts, normal coagulation parameters, and prolonged bleeding time, with definitive diagnosis established via platelet aggregation studies.

Across all three cases, the platelet counts and coagulation profiles—including PT, aPTT, and INR—were within normal limits, while bleeding time was prolonged in each patient. Platelet aggregation studies consistently demonstrated absent aggregation in response to ADP, collagen, and epinephrine, with preserved aggregation to ristocetin, thereby confirming the diagnosis of Glanzmann thrombasthenia. All patients showed favorable responses to supportive management, which included antifibrinolytics, hormonal therapy where applicable, and platelet transfusion in one case. No major complications or recurrence of bleeding episodes were noted during follow-up, underscoring the effectiveness of timely diagnosis and individualized treatment.

These cases underscore the varied clinical presentations of Glanzmann thrombasthenia and emphasize the need for heightened clinical suspicion in patients with unexplained mucocutaneous bleeding. They also highlight the critical role of platelet aggregation studies in confirming the diagnosis, particularly when routine hematological and coagulation parameters are within normal limits.

**DISCUSSION**

Glanzmann thrombasthenia (GT) is a rare autosomal recessive platelet function disorder characterized by defective platelet aggregation despite normal platelet counts and coagulation profiles. This dysfunction arises from abnormalities in the platelet surface integrin αIIbβ3 (glycoprotein IIb/IIIa complex), which is essential for fibrinogen binding and platelet-platelet interaction during primary hemostasis[5,4].

Under physiological conditions, αIIbβ3 remains in a low-affinity state until activated by agonists or endothelial injury. Activation triggers "inside-out" signaling involving key molecules such as protein kinase C (PKC), CalDAG-GEFI (RASGRP2), and phosphoinositide 3-kinase (PI3K), resulting in a conformational change that enables high-affinity binding to fibrinogen. Fibrinogen then acts as a bridge between adjacent platelets, facilitating aggregation. Subsequent "outside-in" signaling initiates cytoskeletal reorganization, platelet spreading, secretion of granules, and clot retraction. Talin and kindlin-3 are critical intracellular mediators that regulate and stabilize integrin activation.[6,7]

GT results from either a quantitative or qualitative defect in αIIb or β3 subunits. These defects may be due to mutations that impair protein folding, post-translational processing, or membrane transport, leading to reduced or absent surface expression of the integrin complex. [8] The causative genes—ITGA2B and ITGB3—are located on chromosome 17q21.31 and 17q21.32, respectively, and encode the αIIb and β3 subunits. Pathogenic variants in either gene may result in GT, though mutations in ITGA2B are more frequently observed, likely due to its larger gene size. Despite differing genetic origins, the clinical phenotypes are indistinguishable.[9]

Clinically, Glanzmann thrombasthenia (GT) commonly presents in early childhood with mucocutaneous bleeding manifestations such as epistaxis, gingival bleeding, easy bruising, and, in females, menorrhagia. Less commonly, patients may present in infancy, as in our case of post-circumcision hemorrhage. While spontaneous joint bleeding is not typical (unlike hemophilia), significant bleeding after trauma or surgery is frequent. The mean age of diagnosis is around 1 year, though approximately 15% of patients are diagnosed after age 14.[10]

All three patients in our series presented with characteristic features of GT—with recurrent mucosal bleeding and normal platelet counts and coagulation profiles. Platelet aggregation studies are central to diagnosis, typically revealing absent aggregation in response to ADP, collagen, and epinephrine, while aggregation to ristocetin remains intact. Flow cytometry can confirm reduced or absent expression of the GPIIb/IIIa complex [11]. Genetic diagnosis involves sequencing all 45 exons and splice sites of the ITGA2B and ITGB3 genes, with confirmation of pathogenic variants using a second DNA sample. This not only provides a definitive diagnosis but also aids in family counseling and prenatal diagnosis. [11,12] Management of GT is largely supportive. Antifibrinolytics such as tranexamic acid were effective in controlling mucosal bleeds in all three patients. In the infant with post-circumcision bleeding, platelet transfusion was effective, with no recurrence. The adolescent girl with menorrhagia improved with antifibrinolytics, hormonal therapy and iron supplementation. These interventions illustrate the tailored approach needed depending on the patient's age and clinical manifestations.

While platelet transfusions remain the cornerstone of treatment during major bleeding or preoperative preparation, repeated transfusions may lead to alloimmunization against HLA antigens or the αIIbβ3 complex, resulting in platelet refractoriness. In such scenarios, recombinant activated factor VII (rFVIIa) has been shown to be effective. [11] Hormonal therapy remains a valuable option for adolescent females with menorrhagia. Hematopoietic stem cell transplantation (HSCT) is the only curative option but is reserved for severe, refractory cases due to its associated risks and resource limitations. [13]

Our case series emphasizes the clinical variability of GT, ranging from early infancy to adolescence, and highlights the importance of recognizing this disorder in patients with unexplained mucocutaneous bleeding and normal initial laboratory findings. The presence of consanguinity in two of the three cases further supports the need for heightened awareness in populations with high rates of consanguineous marriages. Prompt diagnosis not only guides appropriate treatment and reduces morbidity but also prevents unnecessary investigations and delays in care.

Education regarding bleeding precautions, medication avoidance (particularly NSAIDs and antiplatelet agents), and oral hygiene is essential to reduce bleeding episodes. Although a multidisciplinary approach was not employed in our cases, integration with hematology, pediatrics, and genetic counseling services can enhance long-term outcomes in these patients.

## CONCLUSION

Glanzmann thrombasthenia is a rare but important inherited platelet function disorder that should be suspected in patients with recurrent mucocutaneous bleeding and normal platelet counts and coagulation profiles. This case series highlights the clinical variability of GT, ranging from post-surgical bleeding in infancy to menorrhagia in adolescence. Early recognition and diagnosis through platelet aggregation studies are essential to avoid unnecessary interventions and ensure timely, supportive management. Patient education, bleeding precautions, and individualized treatment plans play a critical role in improving outcomes. Greater awareness among clinicians is especially important in populations with a high prevalence of consanguineous marriages, where the risk of autosomal recessive conditions is increased.

**Conflict of Interest:**
The authors declare that there are no conflicts of interest regarding the publication of this case series.

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