

Glanzmann Thrombasthenia – A Rare Autosomal Recessive Bleeding Disorder



Medical Science

KEYWORDS: Thrombasthenia, Platelet aggregation, Receptor $\alpha_{Ib}\beta_3$, Factor VIIa.

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ABSTRACT

Glanzmann Thrombasthenia (GT) is a rare genetic autosomal recessive disorder of platelets in which the platelets have qualitative or quantitative deficiencies of the fibrinogen receptor $\alpha_{Ib}\beta_3$, resulting in impaired platelet aggregation. We present a case of Glanzmann thrombasthenia, who presented with gingival bleeding, the commonest presentation of GT. Bleeding was controlled by transfusion of platelet concentrates and supportive treatment was given with packed cell volume (PCV) to correct anaemia and patient was advised to maintain oral hygiene.

INTRODUCTION: ^{1,2}

Glanzmann Thrombasthenia (GT) is a rare autosomal recessive bleeding disorder, characterised by a quantitative or qualitative defect of platelet surface integrin $\alpha_{Ib}\beta_3$ (integrin $\alpha_{Ib}\beta_3$, previously known as GPIIb/IIIa), which leads to failure of platelets to bind fibrinogen. So, platelets cannot aggregate, which leads to increased bleeding. Till date, about 600 cases of GT are reported worldwide. Amongst them, incidence is high in the population with high consanguineous marriages. Most patients (>2/3) require blood and/or platelet transfusions at least once in their life. GT is therefore considered a severe hemorrhagic disorder. However, bleeding severity is much variable. Some patients have only minimal bruising/mucosal bleeding while others have frequent, severe, potentially fatal haemorrhages.

CASE REPORT:

A 15 years old Indian male presented to us with immediate spontaneous onset of gingival bleeding which followed each time after brushing of teeth since past 3 months. Patient also had history of repeated episodes of epistaxis and episodes of bleeding from lips and gums due to minor trauma. no positive history of iron-responsive anemia, history of transfusion or dietary habit or antibiotic use which might predispose to vitamin-K deficiency or other drug ingestion like anti-platelet/anticoagulant medications or herbal products. Other bleeding manifestations like hematuria, purpura, GI bleeding, haemarthrosis, etc. were also not present in our patient. Family history revealed that he was born of consanguineous marriage and other family members were not affected. On general examination, all vitals were normal. Other systemic examinations were normal. On oral examination patient had normal teeth and gums with minor bleeding from gum line. At present, no epistaxis, petechiae or superficial ecchymoses. Laboratory investigations revealed **hemoglobin 3.50 gm/dl, normal platelet count $421.00 \times 10^3/\text{cmm}$, PT 19.1 second, aPTT 37.40 second and bleeding time 6 minutes and 26 seconds. MCV was 58.30fl, and RBC count was decreased to $3.16 \times 10^6/\text{cmm}$.** Peripheral blood smear showed single isolated platelets without any platelet clumping in non-anticoagulated sample. The platelet aggregation test showed no agglutination with epinephrine, ADP and collagen in the previous report of the patient.

We infused three units of PCV and 7 units of platelet rich concentrate for active gum bleeding. After that gum bleeding stopped and patient's general condition improved. Periodontal treatment was advised. And patient was prescribed Tab tranex-

aemic acid for 2 days and 0.12 % chlorhexidine mouth rinses for 1 week. He was also advised to use soft bristle tooth brush and maintain oral hygiene. The treatment was successful and patient recovered fully. Thereafter he had weekly follow-up for 1 month. We also advised the patient to keep a long term follow-up and measures to prevent further bleeding episodes and **to avoid use of anti platelet drugs in future.** Patient was also advised to consult a physician immediately if he develops any kind of bleeding episode.



Fig⁶ :Patient presented with gum bleeding:

DISCUSSION: ^{3,4}

GT is a rare autosomal recessive disorder. Worldwide about 600 patients are reported and higher incidence is noted in countries like Iran, Israel, South-india and Jordan where families with consanguineous marriages are common. The genes encoding for GPIIb and GPIIIa are both situated on chromosome 17q 21-23 and a number of mutations are found in these genes which leads to either much reduced or no expression of the glycoprotein complex, resulting in platelet dysfunction.

A patient of GT can have following clinical history...

- excessive bleeding following dental extraction
- petechiae and ecchymosis
- menorrhagia often severe at menarche
- epistaxis
- gum bleeding (worse with poor dental hygiene)
- haematuria/ GI bleeding (less common)
- family history of a bleeding disorder may or may not be present
- haemarthroses (rarely)

Patient typically presents with mucocutaneous bleeding at birth or early in childhood, and incidence of bleeding episodes decreases with age. Bleeding episode may be severe in GT but if the patient is provided with appropriate timely treatment and supportive care, prognosis is generally good.

It may not be easy to diagnose and differentiate among many bleeding disorders with similar complains as GT. But if patient's platelet count is normal, PT/aPTT/clotting time - normal and Bleeding Time is prolonged, then, we have following Differential Diagnoses : 1. Von Willebrand disease 2.Autoantibodies to glycoprotein $\alpha_{IIb}\beta_3$ 3. Bernard Soulier Syndrome(BSS) 4. Acquired thrombasthenia 5. Glanzmann thrombasthaenia .

Normal agglutination of patient's platelets with addition of normal plasma indicates Von Willebrand Disease that can be confirmed by Von Willebrand factor antigen level test.

Another problem in diagnosing GT is to eliminate patients with acquired autoantibodies that block aggregation of platelets,although these patients would often be thrombocytopenic. If these antibodies are present in a patient, then the patient's bleeding would not be controlled effectively by platelet transfusion. These antibodies can be detected immunologically by their binding to $\alpha_{IIb}\beta_3$ of control platelets during incubation with the patient's serum. These autoantibodies can be ruled out clinically by effective response (control of bleeding) by platelet transfusion.

Normal ristocetin-induced platelet agglutination and normal platelet size clearly rule out BSS, a disorder of platelet adhesion.

Acquired thrombasthenia must be eliminated in the absence of a family history of the disease. Platelet $\alpha_{IIb}\beta_3$ deficiency and abnormal platelet aggregation have been reported in patients with acute promyelocytic leukemia. The etiology of this acquired disorder is probably a chromosome 15 to 17 translocation. Rarely acquired Glanzmann thrombasthenia, due to allo- or auto- antibodies to the platelet integrin $\alpha_{IIb}\beta_3$ can occur in a number of settings like Pregnancy, autoimmune conditions(e.g. SLE) and use of therapeutic antagonists of integrin $\alpha_{IIb}\beta_3$ (e.g. abciximab,eptifibatide). Clinical manifestations are similar to the inherited disorder.

In GT, the primary platelet aggregation response to ADP, epinephrine and collagen are decreased whereas response to ristocetin is normal with normal platelet morphology and single isolated platelet seen in non-anticoagulated peripheral blood smear examination. and this is how you can reach the diagnosis of GT. This disorder may also occur in combination with defects in leukocyte function in the disorder leukocyte adhesion deficiency III, and should be suspected in infants with concomitant leucocytosis, delayed separation of umbilical cord or severe bacterial infections. regarding **Management** aspects .

MANAGEMENT : 5

Table : General principles for management of GT patients.

Treatment	How to manage GT.
Conservative	only for minor bleeding (when applicable)
Primary measures	<ol style="list-style-type: none"> 1. Early treatment important . 2. Fibrin glue application to active bleeding sites. 3. Antifibrinolytic agents (mainly for mucosal bleeding) ϵ-aminocaproic acid: oral/intravenous 50–60 mg/kg q4h. Tranexamic acid : oral 10–25mg/kg q8h; intravenous 10–15 mg/kg q8h.

Platelet concentrate transfusions	<ol style="list-style-type: none"> 1. For severe bleeding or cases in which other management fails, for invasive procedures 2. HLA-compatible and leukocyte depleted platelets where available and possible. 3. One single donor aphaeresis unit ; in children 10–15 ml/kg are given. 4. Continue till bleeding stops and/or wound heals.
rFVIIa	<ol style="list-style-type: none"> 1. Early treatment is important 2. Use Priority: <ul style="list-style-type: none"> * history of anti-$\alpha_{IIb}\beta_3$ and/or anti-HLA antibodies together with history of platelet refractoriness; * prevention of development of iso-antibodies (e.g. women before and during fertile life) 3. Bolus injection: dosage: $\geq 80 \mu\text{g/kg}$ at interval of $\leq 2.5\text{h}$, for 3 or more doses for moderate or severe bleeding. After bleeding stops, additional consolidation dose may reduce recurrences. 4. Continuous infusion:- not effective to stop bleeding but it is effective to prevent surgical bleeding . 5. Antifibrinolytic agents can be used with rFVIIa. 6. If bleeding persists despite rFVIIa: higher dosage patients with platelet antibodies: plasmapheresis or immunoadsorption to remove antibodies, followed by platelet concentrate transfusion.
Hematopoietic cell transplantation.	Hematopoietic cell transplantation has been successfully employed in some patients with severe bleeding and/or development of antiplatelet antibodies.

Patient education : Life-style modification and preventive measures to avoid bleeding episodes. These include the avoidance of trauma and use of drugs interfering with platelet function (e.g. acetylsalicylic acid and non-steroidal anti-inflammatory drugs, NSAIDs),use of soft bristle brush,maintenance of dental hygiene and regular dental care to prevent gingival bleeding, and vaccination against hepatitis B. all bleeding episodes in GT does not require systemic therapy, as many minor bleedings can be managed by conservative measures. The latter are also effectively used in association with platelet transfusions and/or haemostatic agents.

Hormonal treatment : High-dose progesterone can be prescribed to control severe menorrhagia in female GT patients. Bleeding usually stops within 24 hours, and then the progesterone dose can be decreased and to be continued for several weeks. Menstrual bleeding will occur on withdrawal and is usually not severe. Maintenance treatment with oral contraceptive pills should then begin. More than one dose daily may be required to prevent breakthrough bleeding. Similar to von Willebrand disease, oestrogen-progesterone combinations have been reported for the management of bleeding angiodysplasia of the gut in some GT patients .

CONCLUSION:

1. Although Glanzmannthrombosthenia is one of the rare bleeding disorders, one should be aware of this condition while evaluating patients with spontaneous gum bleeding in the setting of normal platelet count.
2. Early diagnosis and effective treatment carries good prognosis.
3. Communities should be counselled to avoid consanguineous marriage and related hazards.
4. Patient should be advised for life style modification and measures to avoid bleeding episodes which includes avoidance of anti platelet drugs, avoid trauma and maintain oral hygiene and consult physician if patient develops bleeding episode.

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