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Case Report

# Diagnostic Wandering in a Case of Spontaneous Gingival Bleeding with Glanzmann's Thrombasthenia - A Case Report

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## Abstract

Glanzmann's thrombasthenia is an inherited platelet function disorder, which is rare in the global context but is relatively common in India, where consanguineous marriage is still prevalent. It presents with varied mucocutaneous bleeding manifestations. Many of the heterozygotic carriers are clinically asymptomatic. The reported case presented with gingival bleeding as the solitary manifestation of Glanzmann's thrombasthenia along with complex past medical history, which mimic those of coagulation disorders. There was a significant delay in the health seeking behavior of the patient causing undue delay in the diagnosis of the case, ultimately leading to several unexpected complications and prolonged hospital stay.

A case presenting with gingival bleeding secondary to undiagnosed underlying systemic condition is easily overlooked as plaque induced gingival changes by the clinician, because of lesser prevalence of such cases reporting to Periodontology Clinics. A careful recording of medical history of the patient is paramount. This case report exactly presents the systematic method of approach to a case of gingival bleeding associated with systemic conditions with an array of investigations, which led to the diagnosis of the case and prompt referral.

**Keywords:** Gingival bleeding; Glanzmann's thrombasthenia; Platelet function disorder

**Abbreviations:** GT: Glanzmann's Thrombasthenia, FDI: Federation Dentaire Internationale, Hb: Hemoglobin, FFP: Fresh Frozen Plasma

## Introduction

The approach to any patient needs a systematic assessment of the case in order to diagnose and lay a proper treatment plan. Due to heterogeneity and ramification of diseases, it is toilsome to diagnose and treat any disease condition that has progressed to a certain level that is simply unbeatable. When it comes to bleeding disorders affecting oral cavity the list of etiologies is vast. Inherited bleeding disorders affecting the platelet function is a rare disease condition. Glanzmann disease or Glanzmann Thrombasthenia (GT) is one such condition which is inherited in autosomal recessive pattern. GT usually manifests clinically since birth. The symptoms are manifested as repeated epistaxis, bruise formation, intraoral bleeding from the gingivae and petechiae. It can also

present with gastrointestinal bleeding, hematuria, significantly high menstrual bleeding and heavy postpartum hemorrhage. When the major symptoms are present, they are usually diagnosed at a very early age whereas presentation of the same with only gingival bleeding is often easily overlooked. Early diagnosis shall render the clinician with better options for management. This case report discusses the diagnostic gaps caused by delay in reporting to hospital and establishing the appropriate timely diagnosis.

## Case Report

A 13-year-old male patient who belonged to lower socio-economic status (As per Modified Kuppuswamy scale 2019) was brought to the Division of Periodontology in a tertiary care hospital by his mother with chief complaint of continuous bleeding from the gums for 2 months. The history of present illness revealed that the child was apparently asymptomatic 2 months back and presented only with gingival bleeding while brushing teeth initially and the bleeding gradually increased which occurred spontaneously over a period of time. The parents reported the appearance of rashes over chest which gradually involved lower limbs and entire body within 2 days. His past medical history revealed that he was diagnosed with Dengue Fever 1 month back and was hospitalized for 15 days after presentation with hemorrhagic symptoms. The patient was managed with oral tranexamic acid 250 mg for 7 days and thereafter bleeding occurred only intermittently. Post discharge, the patient developed recurrent gingival bleeding for next 2 weeks and was re-hospitalized for component support with 16 units of Fresh Frozen Plasma (FFP) and 4 units of platelet concentrates. After remission of gingival bleeding, he was discharged from the hospital. His antenatal, intrapartum and postnatal history was uneventful and the developmental milestones were normal for his age. The child also presented with history of easy bruising and swollen joints for the past 1 year and deliberately refused participate in physical activities due to easy fatigability. A single episode of prolonged bleeding from venipuncture site one year back was also reported. His family history revealed that his father had an episode of unexplained and undiagnosed excessive bleeding which manifested at 25 years of age. Family history revealed that there was third degree consanguineous marriage and he was the 'index case' and other four siblings were apparently healthy (Figure 1).

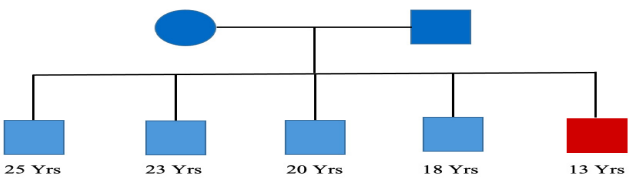



**Figure 1**: Family pedigree.

On general examination although the patient appeared ectomorphic, drowsy and weak, he was well oriented with no focal neural deficits. His BMI was 13.97 kg/m$^2$ with 3$^{rd}$ percentile classified as moderately underweight (30.6 Kg) from WHO chart with all other vitals within normal limits. The facial skin, palpebral conjunctiva, nail beds appeared pale with dry and with blood-stained and pursed lips. Numerous sparsely distributed petechiae were seen over the chest and flexor surfaces of the lower limb and *café-au-lait* spots were present near the left nipple (Figure 2). There was pitting edema over both the ankles. Extra-orally the child presented with mouth breathing and angular stomatitis (Figure 3). Intraoral examination, revealed an anterior deep bite, median fissured tongue with root stumps in relation to 36 and 46 (FDI notation) around which there was constant spontaneous mild oozing of blood (Figure 4). There was no abnormality reported in PA chest x-ray, lateral skull radiograph and ultrasound abdomen (Figure 5).

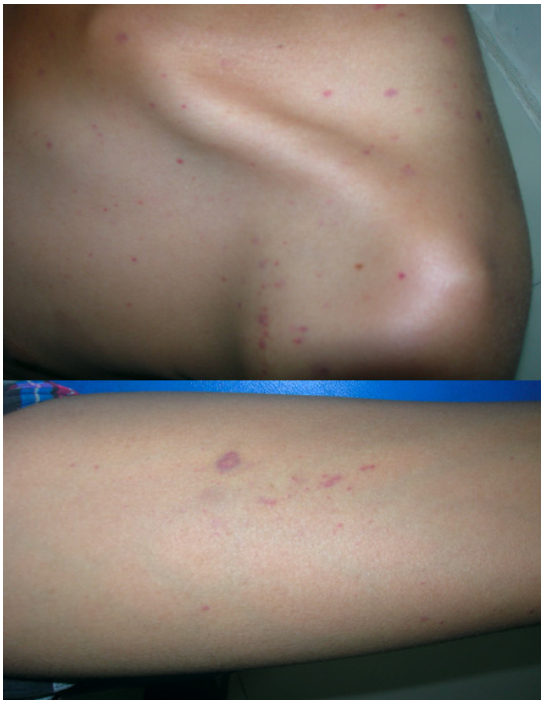


**Figure 2**: General examination

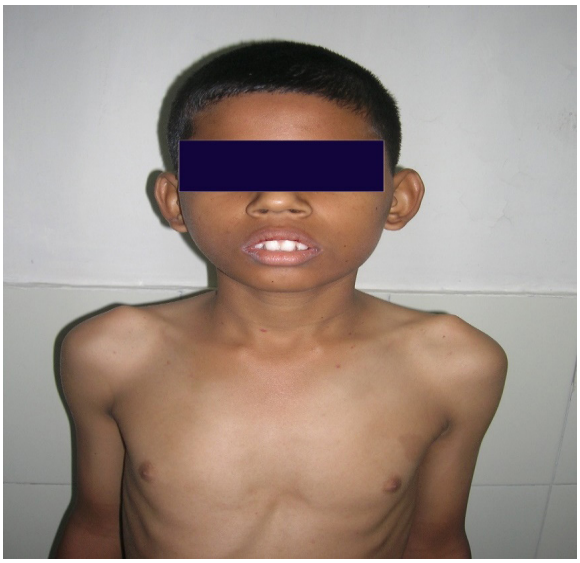


**Figure 3**: Extra-oral examination

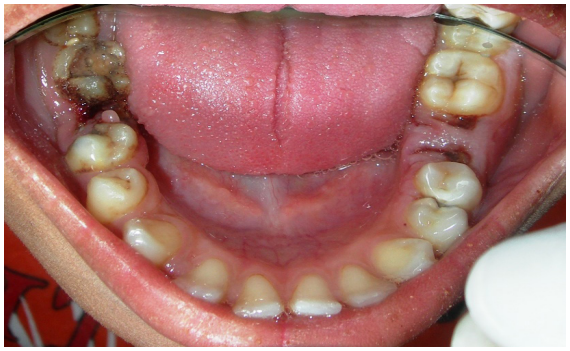


**Figure 4**: Intra-oral examination

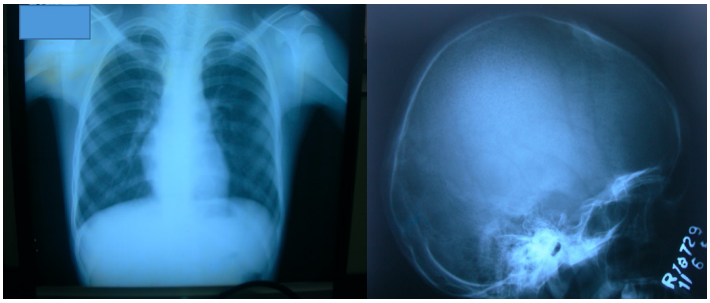


**Figure 5** : Radiographic examination

The significant finding in hematologic investigation was the reduced hemoglobin (Hb) of 5.2 g%. The high-performance liquid chromatography study for HbF (1.9%), HbA2 (2.4%), HbAo (87.4%) and unknown (0.3%) was within normal range. The peripheral smear revealed a dual picture of macrocytes and microcytes with hypochromicity, anisopoikilocytosis, pencil cells with normal platelet morphology. The platelet count was found to be within normal range but the coagulation workup revealed an International Normalized Ratio (INR) of 1.13. There was a mild increase in Prothrombin time (PT) 18s (Control 12s) and activated partial thromboplastin time (aPTT) 45s (Control 32s) after correction studies. The levels of factor VIII, factor IX, von Willebrand factor and liver function tests were found to be within normal limits with a negative Rumpel-Leede test. Based on the initial findings, patient was admitted for anemia investigation and for workup with Department of Immunohaematology & Paediatrics. His one-week diet chart revealed that he was consuming only 990 Cal/day (Required for age was 1740 Cal/day), hence he was maintained on 'O'-Diet. The patient was conservatively managed with Injection Vitamin K – 1 mL OD x 3 days and Oral Tranexamic acid 500 mg TDS x 7 days.

Further investigations included serum iron (56 mg/dl), total iron binding capacity (TIBC–379 mg/dl) and serum ferritin (5.0 mg/ml) which were within normal limits; however, occult blood in stool was positive. After one week of treatment with FFP, Hb raised to 12.7 g%. A provisional diagnosis of gingival bleeding secondary to bleeding diathesis was made. The differential diagnosis included idiopathic thrombocytopenic purpura (Post viral fever), vasculitis, lymphoproliferative malignancy, malabsorption syndrome, platelet type (Pseudo) von Willebrand disease (vWD), connective tissue disorder and functional platelet disorder.

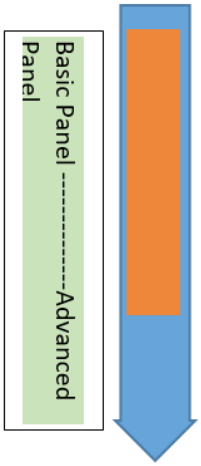
Further investigations were undertaken to reach a definitive diagnosis. The p-ANCA and c-ANCA, ds DNA, RA factor were negative. The platelet aggregation with Ristocetin assay was 22% and with collagen and ADP was absent. The platelet glycoprotein receptor flow cytometric analysis revealed that GpIb of 93.1%, Gp IX 94.52%, fibrinogen 49.3%, GpIIb-IIIa 0.04% clearly designating the diagnosis of GT. Based on these sequential investigations and analysis, the final diagnosis of gingival bleeding secondary to GT was arrived upon.

## Discussion

Bleeding and thrombotic disorders of congenital origin are classified as vascular wall alterations, disorders of platelet function and thrombocytopenias. Gingival bleeding is usually suspected to be of inflammatory in origin induced by plaque formation. It is alarming to the patient as well as the clinician, when the bleeding is spontaneous and continuous which even impairs the routine oral hygiene measures. The history and presentation of a case similar to the one reported here brings suspicion of an undiagnosed, potentially life threatening underlying hemostatic defect. Intraorally, gingival bleeding can be the only initial symptom in many bleeding disorders, which can be easily overlooked, without a proper systemic history and sequential investigations. The hemostatic system is highly organized which initially started with the 'WATERFALL CASCADE' theory which involves a complex interaction of various proteins and cells mainly the endothelial

cells and platelets, which in strict sense are not true cells. The mechanisms of coagulation are highly interrelated to each other with mechanisms of vasoconstriction, formation of platelet plug and simultaneous complex steps leading to formation of a clot to arrest the bleeding and finally the dissolution of clot [1]. Any mismatch in this complex process can lead to bleeding / clotting disorders. Evaluation of a case with any form of unusual bleeding history should involve a complete physical examination and a thorough family history, drug history and array of investigations.

The systematic investigative approach of a suspected case of bleeding / clotting disorder should include testing each step of the hemostatic pathway as follows:




| Step of Coagulation | Diagnostic Test |
|---|---|
| Vascular phase | Bleeding Time |
| Platelet plug formation | Quantitive - Platelet Count<br>Qualitative - Platelet aggregation assays,<br>Fluorescence assorted cell sorting (FACS) |
| Intrinsic pathway | aPTT |
| Extrinsic pathway | PT & INR |
| Common pathway | PT, INR, Clotting Time |
| Isolated aPTT changes | Mixing coagulation studies and repeat the aPTT and search for specific factor deficiencies |
| Specific factor assays | Factor VIII and Factor IX assay, vWF assay |
| Excess fibrin / FDPs | Thrombin time |

There should be a systematic method to rule out various conditions affecting coagulation mechanism from basic to advanced level panel [2].

The conditions affecting the platelet quantity are easily diagnosed with platelet count. On the other hand, qualitative defects affecting the platelets are relatively difficult to diagnose at first hand as in GT, vWD, Bernard-Soulier disease, uremia and drug-induced platelet defects [3]. Qualitative defects affecting platelets can be congenital, familial or acquired and have been placed under the broad head "Thrombocytasthenias". There is a wide array of diseases under the term 'familial thrombasthenia' or Glanzmann's disease or GT, first described by Glanzmann in 1918 [4]. The condition is familial and affects both genders equally. The prevalence of GT in India was found to be similar to the western world with 8.3% prevalence rate [5]. Spontaneous gingival hemorrhage is a frequent finding along with hemarthroses and purpuric hemorrhages of the skin. The onset of menarche in girls can often lead to fatal bleeding episodes [6]. Platelets play a very significant role in the initial stages of hemostasis by forming the platelet plug to physically seal the breach in endothelial integrity. The interaction of platelets with the exposed collagen underlying the vascular endothelium is complex and involves a series of reactions. The initial interaction of the platelets with the fibrinogen is through glycoprotein IIb and IIIa receptors (Gp IIb-IIIa). A defect of these glycoproteins leads to failure of platelet aggregation causing excessive and spontaneous bleeding at various sites (Figure 6). The property of aggregation is used as a line of diagnosis of GT with agents like adenosine diphosphate, epinephrine, collagen and thrombin.

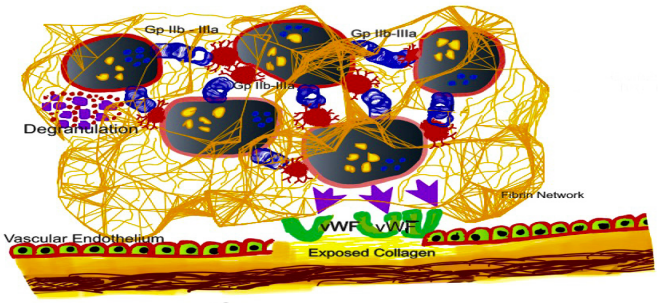



**Figure 6**: Schematic diagram of GpIIb-IIIa interaction

Although there is no racial predilection for this exceedingly rare disease, literature has reported the same in Gypsy families of Manouche tribe. In India, it has been reported in 42 families and all of them showed a strong predilection to consanguineous marriage as reported in this case as well [7]. The spectrum of clinical presentation varies from an asymptomatic stage to epistaxis, gingival hemorrhages, gastric bleeding, excess bleeding after trauma, excessive menorrhaghia in women and rarely hematuria. It has been reported that such recurrent bleeding may lead to reduced red blood cell count alongwith iron deficiency [8]. The presentation of severe anemia is common in girls with GT who present with severe menstrual blood loss. This case uniquely

presented with severe iron deficiency anemia in a 13-year-old boy child. The reported case was initially managed as a case of severe anemia by the physician and was referred to Periodontology clinic for the management of bleeding gums, which was the only persistently clinical symptom. The causes of spontaneous gingival bleeding are exhaustive and is a common presentation in most of the disorders affecting hemostatic pathway. When gingival bleeding of systemic origin is suspected, a thorough diagnostic workup has to be formulated.

The key approach to the GT patient and family includes deliberation of proper health information, genetic counselling and a 'preventive life style' approach to avoid bleeding emergencies. Oral and periodontal surgical procedures can be taken up in known cases of GT after exercising due precautions and surgical chairside preparedness to manage complications. It should noted that a similar clinical presentation occurs with a rare inherited disorder Bernard-Soulier syndrome and the differential diagnosis of the same is based on the normalcy of aggregation assays with epinephrine, ADP and collagen [9]. Based on Gp IIb-IIIa activity, GT is classified as Type I with less than 5%, Type II with 5-20%, and Type III with more than 20% of levels of the protein. There is no correlation between the amount of the protein with severity of hemorrhaghic diathesis [10]. Hence the later classifications are only based on the mere presence or absence of glycoprotein as GT° or $GT^+$ [11]. Earlier GT is diagnosed better is the prognosis, unlike other inherited platelet disorders [12].

Since there is no permanent cure for this disease, patient education and discharge of health information to the family members was made. Oral hygiene instructions were reinforced and patient was encouraged to do brushing gently with a soft toothbrush. The patient was issued an 'Health Card' with details of GT and was instructed to carry the same, whenever he visited any clinic further for any treatment. Oral hematinics were prescribed in consultation with the Pediatrician and the hematological assessment after three months revealed restitution of hemogram within normal range. In such case, establishment of a supportive care is of utmost importance. Local anaesthesia can safely be administered in GT. In compromised patients, antifibrinolytics like epsilon amino caproic acid, tranaexamic acid, desmopressin can be useful if administered pre-operatively. In severe cases and in emergency scenario, the only life saviors are the platelet concentrates. In preventive periodontal practices, 0.2% Chlorhexidine gluconate rinses are indicated to keep the gingival inflammation to a minimum [13]. Patients must be advised not to take medications that can prolong bleeding and use of aspirin and other NSAIDs must be avoided after dental treatment. Newer treatment modalities like recombinant VIIa therapy and bone marrow transplantation which started in 1984 is still restricted in routine practice because of licensing and cost factor issues in developing countries like India [14]. Every possible effort should be taken to avoid invasive surgical procedures and more emphasis should be given to personalized periodontal approach [15]. The overall prognosis of GT patients is generally good and with an average lifespan, but there always exists a theoretical risk of a bleeding emergency which may become fatal rarely. With the high prevalence of 97.51% periodontal diseases in India, any random patient in the periodontal clinic may have an undiagnosed potentially underlying systemic illness, which definitely mandates thoroughness in history taking and clinical examination as was made in this case report [16].

## Conclusion

A careful and thorough history taking, pedigree analysis, family history and complete systemic and oral examination will provide the necessary clues for diagnosis. Early detection and prompt treatment offers best chance for better quality of life. An interdisciplinary approach with a team of Paediatrician and Immunohematologist eases the path of diagnosis. Any undue delay in diagnosis, as happened with the reported case may even cause to endangering fatal life episodes. The early diagnosis of any such condition can speed up the process of appropriate treatment and therefore improve the prognosis. This also requires the patient to seek medical /dental care as soon as any presenting symptoms do appear. Every dental practitioner should keep in this mind while examining such cases and formulate a well-planned diagnostic evaluation. From periodontal point of view, personalized periodic oral health examination is a mandate in all cases of GT. A preventive oral hygiene education with atraumatic oral hygiene practices is necessary to avoid unwarranted emergencies and to lead a safe life.

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