

Management of Post-circumcision in Glanzmann'S Syndrome: Case Report and Review of Literatures

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Abstract

Background: Fatal bleeding episodes due to spontaneous mucocutaneous bleeding are common in Glanzmann's Syndrome (GT). Control of such bleeding with imperative approaches remains challenging. The unanticipated rare genetic GT hematological disorder of platelet function is life-threatening particularly from the surgical interventions. It is regularly controlled by medical therapies (including; systemic recombinant factor VIIa, local anti-fibrinolytic agents and blood/platelet transfusions) and surgical therapies (including; electrocautery, laser coagulation, and embolization).

Case Description and Management: We describe here, for the first time in country, an uncircumcised 10-years old Saudi boy with GT diagnosed during a regular circumcision surgical intervention for relieving phimosis due to edematous enlarged glans penis with bluish skin coloration. The post circumcision life-threatening bleeding - that necessitated redoing the surgery with deep suturing - was confirmed upon hematological consultation to be a GT bleeding disorder. Repeated transfusion of packed red blood cells reaching 8 units significantly induced effective cessation of bleeding within 24 hours, discharge within 72 and complete wound healing without complications within a week.

Conclusions: Although very rare, GT should be anticipated upon surgical intervention with secured packed red blood cells, concentrated platelets and rFVIIa (the latter two were available for our case). This case report represents the first description for successful treatment of life-threatening hemorrhage in a GT patient in Saudi Arabia and molecular investigations are planned since his sisters gave a history of profuse menstruation.

Keywords: Glanzmann's syndrome; Bleeding disorder; Platelet function; Profuse menstruation

Introduction

Glanzmann's thrombasthenia (GT) is the most frequent congenital platelet function disorder [1]. GT is an autosomal recessive disorder that is caused by abnormal quantitative/qualitative platelet function due to mutation in the genes for glycoproteins IIb/IIIa that disturb the structure and signaling function of integrin α IIb β 3 on the surface of platelets. These protein platelet membrane receptors function as fibrinogen receptor. Dysfunctional platelets do not aggregate properly at the site of injury and prolonged blood clotting time and liability for easy bleeding [2-4]. The disease usually is associated with mild bleeding, but severe fatal hemorrhage may occur [5]. Rarely an acquired form of the disease could be caused by inhibitory effect of autoantibodies against glycoprotein IIb/IIIa [6].

GT was first described by Swiss pediatrician Eduard Glanzmann in 1918. Patients typically present before 6 years of age with purpura, gingival bleeding, epistaxis, and bruisability. However, chief complaints of gastrointestinal bleeding may also be reported [7-12]. GT has an incidence of about 1/1.000.000 but is more common in populations where consanguineous marriage is common. Two types of GT have been identified; the more-severe type I has no glycoprotein IIb/IIIa receptor complex, and the less-severe type II has varied amounts of the receptor molecules [9].

The diagnostic criteria for GT include: 1) Normal prothrombin time (PT), 2) Normal partial thromboplastin time (PTT), 3) Normal absolute platelet count, 4) Normal platelet size on peripheral smear, 5) Prolonged bleeding time, and, 6) Absence of platelet aggregation on peripheral smear. Management includes medical and surgical options - with various degrees of success. In particular, control of hemorrhage has been a frequent and challenging problem for patients with GT. Clinical researchers recently reported that ~82% of bleeding events in patients with GT involved the nasal cavity, i.e., epistaxis [10]. Recent literature reports describe medical therapies that use systemic recombinant factor VIIa, local anti-fibrinolytic agents, or platelet transfusions (with or without red blood cells) to control bleeding [4,10-15]. Those medical therapies are often used in a neo-adjuvant or concurrent fashion with surgical techniques. Surgical therapies including; electrocautery, laser coagulation, and embolization). The degree of therapeutic success, whether medical, surgical, or combined, varies from very low to very high with respect to recurrence rates [11].

Case Presentation

An uncircumcised 10-years old Saudi boy was brought to Emergency Department, Gurayat General Hospital, 22nd of Aug. 2015 with the history of sever penile pain. The boy's father gave an informed consent for anonymously reporting the case. It was started incidentally associated with a swelling in anterior shaft of penis. The patient had no history of fever, trauma or bleeding. On physical examination, the boy was found to be irritable, anxious and other vital signs were normal.

There was no bruising. External genitalia and scrotum looked normal but penis glans was edematous with slightly bluish color and the skin was constricted around it. On examination, the abdomen was soft, lax and no organomegally. On further investigation, the patient was diagnosed with phimosis and prepared for an emergency operation after failed conservative treatments.

Laboratory tests such as Complete Blood Count (CBC), blood biochemistry, PT, PTT, INR and platelets count were within the normal range. Circumcision was performed and compressing dressing was done post-circumcision around the wound in order to prevent bleeding. Later in recovery room, an oozing was noticed around the wound dressing which was cleaned and tough dressing was done. After the patient felt normal, he was transferred to the ward. After five hours, patient was inspected for any hematoma and bleeding through the dressing site. A big hematoma was identified once the dressing was removed. Patient was directly operated for exploration and circumcision redo. At the time of operation, one unit of packed red blood cells (PRBC) was kept ready for urgent transfusion.

Upon repeat surgery, the suturing was removed, hematoma was cleaned and deep bites of sutures were done. Foly's catheter was inserted and in recovery room patient was observed for more than one hour then transferred to his bed in the ward. On first day post-operation, there was some bleeding observed around the glans which came out through the dressing without clotting (Figure 1). Blood transfusion was done with one unit PRBCS because of his low hemoglobin of 8 gm/dL.



Figure 1: 10-years old Saudi boy diagnosed with Glanzmann's thrombasthenia causing penis glans hematoma after first circumcision (A) and after redoing the operation (B).

To rule out any undiscovered bleeding disorders after 8 units of PRBCS transfusion, a hematologist was consulted. Hemophilia A and B, factors II, V, VII, X, XII and von Wilbrand's factor deficiencies were excluded upon investigations. Platelet aggregation test was abnormal. Therefore, the boy was diagnosed to have GT. To follow up patients' prognosis, patient was given around eight units of concentrated platelet. After two days of observation, bleeding got stopped completely.

Patient was discharged oral treatments (Antibiotics(amoxicillin) and paracetamol) and complete bed rest was recommended. Aspirin and non-steroidal anti-inflammatory and popular traditional local herbs with anticoagulant activities (e.g., Cardamom) were advised to be strictly avoided. After one week on his next visit for follow up in urology clinic, he was looking very well with dry wound where Foly's catheter was removed (Figure 2). He was advised to visit hematology clinic with his family. Upon detailed investigation, it was found that his sister also is affected with the same disease.



Figure 2: 10-years old Saudi boy diagnosed with Glanzmann's thrombasthenia with dry healed penis shaft circumcision wound.

Discussion

The Glanzmann Thrombasthenia Registry prospectively collected worldwide information on the effectiveness and safety of platelet transfusion, recombinant activated factor VII and/or anti-fibrinolytics for the treatment of bleeds in patients with Glanzmann thrombasthenia. Data relating to 829 non-surgical bleeding episodes were entered into the Glanzmann Thrombasthenia Registry (severe/moderate: 216/613; spontaneous/post-traumatic: 630/199; [16]. Currently, developed understanding of coagulation physiology permits advanced therapeutic interventions. Impaired cytoskeletal remodeling caused by reduced surface expression (due to enhanced internalization) and constitutive activation of integrin $\alpha\text{IIb}\beta\text{3}$ is the main effector of platelet dysfunction and macrothrombocytopenia and of bleeding, in dominant Glanzmann Thrombasthenia variants caused by gain-of-function deletion mutations of ITGB3 or ITGA2B [1,15].

Other than the molecular and inheritance pattern analyses, the diagnosis of GT depends on identifying the dysfunction of the platelets with bleeding assessment tools, light transmission aggregometry using different adhesion surfaces and other techniques such as whole blood impedance Multiplate analyzer and And labeled surface protein expression flowcytometry analysis for subtyping [17-19]. Fatal bleeding episodes due to spontaneous mucocutaneous bleeding are common in GT. Control of such bleeding remains challenging with imperative approaches. The latter include; local anti-fibrinolytic therapy along with platelet transfusions. Treating and preventing GT hemorrhage with a good clinical safety profile achieved advancements with injection of human recombinant factor VIIa (rFVIIa) [2,20,21]. For GT, noninvasive medical therapies such as anti-fibrinolytic agents, replacement or supplementation of coagulation factors, and platelets transfusion offer potential benefit, but are not without complications. For example, most patients receive frequent red blood cell and/or platelet transfusions that could elicit isoantibodies against platelet integrin complex. Once formed, the antibodies are a formidable barrier to subsequent transfusion therapies, platelet aggregation is blocked and platelets are rapidly removed by the immune system [8]. Standard treatment for Glanzmann thrombasthenia is platelet transfusion. Recombinant activated factor VII has been shown to be successful in patients with Glanzmann thrombasthenia with platelet antibodies or who are refractory to platelet transfusions [1,22]. The efficacy of anti-fibrinolytic agents and coagulation factors is an ongoing area of research that requires refinement before standardized approaches can be implemented. Topical application of the herbal hemostatic agent Ankaferd Blood Stopper that is independent of the clotting factors was not tried in similar cases before despite being successful with other presentations of GT [10,12]. Surgical interference approaches vary and

there is no a special technique has been shown to have a greater efficacy than another [8]. Therefore, a therapeutic dilemma exists as to the most effective intervention with the least risk of side effect [11]. As an envisioned future promise, gene therapy and stem cell transplantation could help cure GT [2]. Allogeneic hematopoietic stem cell transplant is the only curative method of treatment [5,23,24]. The present case and his family required molecular genetic diagnosis and dissection of the nature of mutations they suffer, current planned for – after which such stem cell approaches could be thought of.

Conclusion

The very rare inherited GT should be anticipated upon surgical intervention with secured packed red blood cells, concentrated platelets and rFVIIa (the latter were not available for our case). This case report represents the first description for successful treatment of life-threatening hemorrhage in a GT patient in Saudi Arabia and molecular genetic investigations were planned since his sisters gave a history of profuse menstruation.

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