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Case Report

A Case of Glanzmann's Thrombasthenia - Diagnosed During Evaluation of Post-Surgery Bleeding

Mafruha A[1], Md Ibrahim Khalil[2], Tahmid -E-R Khairul Koron[3], Abu Z Md. Saleh[4], Imtiaz Faruk[5]

Abstract:

Glanzmann's thrombasthenia (GT) is a very rare inherited autosomal recessive bleeding disorder due to platelet dysfunction. Clinical presentations and severity of bleeding are heterogeneous. Bleeding pattern is usually muco-cutaneous ranging from mild bruising to potentially life threatening bleeding, although severe internal organ bleeding is rare except in trauma or post surgery without precaution. Genetic defect of GT is associated with mutations in gene encoding platelet membrane glycoprotein GPIIb/IIIA leading to lack of platelet aggregation due to reduced expression or complete absence of GPIIb/IIIA.

Here we report a case of GT who was diagnosed first time at 20 years of age after emergency surgery without proper evaluation and precaution in a resource limited situation. However she was managed by platelet transfusion and antifibrinolytic therapy.

Keywords: Glanzmann's thrombasthenia, GPIIb/IIIA

1. Assistant Professor of Hematology & Bone Marrow Transplantation. Department of Hematology and BMT, Dhaka Medical College & Hospital. Dhaka, Bangladesh. email: mafruha673@ gmail.com
2. Assistant Professor, Department of Surgery, Dhaka Medical College & Hospital.
3. Indoor medical officer, Department of Surgery, Dhaka Medical College & Hospital.
4. Assistant registrar, Department of surgery, Dhaka Medical College & Hospital.
5. Professor, Department of surgery, Dhaka Medical College & Hospital.

Correspondence to: Dr. Mafruha Akter, Asstt. Professor of Hematology & Bone Marrow Transplantation. Department of Hematology and BMT, Dhaka Medical College & Hospital. Dhaka, Bangladesh. email: mafruha673@ gmail.com

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Introduction:

Glanzmann's thrombasthenia is an autosomal recessive platelet functional disorder. The disease is named after Dr. Eduard Glanzmann (1887-1959), the Swiss pediatrician who originally described it in 1918.[1]

First it was described as "hereditary hemorrhagic thrombasthenia" as this syndrome is characterized by mucocutaneous bleeding with a variable clinical presentation since childhood.[2]

The incidence is very rare, approximately one per 1,000,000 individuals worldwide.[3] Although it is distributed in all parts of world but comparatively seen more in certain ethnic region eg, India, Arab and Israel.[4] Consanguinity of parents may be a reason. The number of platelets is normal in GT but

In normal person a single platelet membrane is covered with approximately 50,000 copies of the GPIIb/IIIa integrin complex that allow binding principally with fibrinogen and to lesser extent to Von Willebrand Factor, fibronectin, and vitronectin.[5]

The binding of fibrinogen to this complex allows bridging two platelets to initiate platelet aggregation. Platelet aggregation is impaired when any component of the complex is mutated or the complex is deficient.

There are two genes, encoding GPIIb (ITGA2B) and GPIIIa (ITGB3) are closely located at chromosome 17q21.

Classically GT is divided into three types adapted to molecular understanding of the disease. In type I disease, very negligible amount (<5% of normal) GPIIIa/GPIIb is detectable on the platelet surface, while in type II GT their number is variable 10-20% of normal.[2],[6] Additionally the third type is very rare, type III is dysfunctional integrins expressed in normal or subnormal number.[2],[6]

Case Report:

A 20 year female patient was referred from a remote area of Bangladesh. She had an emergency appendicectomy in a local remote hospital and need 5 units of blood transfusion during and after surgery. The post surgery period was complicated by acute abdomen again and exploratory laparotomy was done there that revealed hematoma and blood collection in peritoneal cavity. Then she was referred to a government tertiary hospital in the capital city, Dhaka for better management. She was in hemorrhagic shock during admission in surgery department of Dhaka medical college hospital. After initial management and resuscitation, she was referred to Hematologist for bleeding evaluation.

On careful history taking it was evident that she had easy bruising and muco cutaneous bleeding (gum bleeding, epistaxis) since childhood and had heavy menstrual bleeding since menarche. Her parents had consanguineous marriage but no other siblings of her had similar excessive bleeding, although her mother had moderate menorrhagia previously. The patient had also excessive per vaginal bleeding after normal vaginal delivery at 19 years that had been managed with 6 units of whole blood transfusion. But these bleeding episodes were never addressed before properly.

She was having persistent bleeding from appendicectomy wound for weeks.

On routine CBC the number of platelets was normal 377x109/L with apparently normal morphology, although less clumps of platelets were noticed. The screening test for bleeding disorder eg. PT, APTT were normal. But bleeding time was prolonged (11 min) and no (0%) clot retraction in 24 hours. Platelet aggregometry test revealed that no aggregation with ADP, Collagen and Epinephrine. Platelet aggregation with ristocetin was not checked due to lack of reagent. Platelet flow cytometry and mutation analysis were not done, because these are not available in this centre.

Von Willibrand factor was normal 149% and RiCof was normal. Fibrinogen and FVIII were within normal level.

Finally, diagnosis of Glanzmann's thrombasthenia was established based on abnormal platelet aggregometry, normal platelet count and very suggestive history of bleeding disorder and family history.

Her acute bleeding was managed with apheretic platelet transfusions and injection tranexamic acid and DDAVP nasal spray in addition to surgical management for wound and hemoperitoneum.

Clinical features and clue to diagnosis:

Patients with GT typically present with gum bleeding, epistaxis, easy bruising, purpura and excessive bleeding following trauma. The symptoms start in infancy or early childhood. Consanguinity of marriage between parents may lead to give birth homozygous GT if both of them are heterozygous.

Bleeding symptoms may vary from mild bleeding or asymptomatic in heterozygous subject but usually moderate bleeding in homozygous subjects. In a large cohort of 177 GT patients George et al stated that most patients present within 5 years of age and the commonest clinical features are purpura, epistaxis, gum bleeding in both sexes and additionally menorrhagia in female.[2] Females also face increased risk of

bleeding during pregnancy and delivery. Although serious internal organ bleeding is uncommon spontaneously, but may be due to trauma or surgery if proper precautions are not taken. Gastrointestinal bleeding, hematuria are less common and intracranial bleeding and hemarthrosis are unusal.[7]

In contrast to acquired thrombocytopenia or drug induced platelet dysfunction there are long history of bleeding since childhood and family history of bleeding disorder are important clue to diagnose any inherited bleeding disorder.

Laboratory diagnosis:

GT is typically associated with normal platelet count and morphology, prolong bleeding time, absent or decreased clot retraction and normal aggregation with ristocetin but absent aggregation with other agonist eg ADP, Collagen, Epinephrine and Arachidonic acid. Absent platelet aggregation with these agonists is due to dependence of these factors on fibrinogen attachment to platelet for aggregation whereas independence of ristocetin to this attachment.[8]

The definitive laboratory diagnosis of GT is made with flow cytometric analysis for GPIIb (CD 41) and GPIIIA (CD61).[9] Although it is an effective test for detecting homozygous or heterozygous states of GT, it is highly expensive and not available in many coagulation laboratories.

Finally through genomic DNA sequencing of the 45 exons comprising the GPIIb/IIIA unit, GT can be detected but these are not available in all centres.[3]

Treatment and Discussion:

There is no definite treatment for GT patients except supportive. They usually do not need regular daily therapy as the symptoms are heterogeneous. But they require treatment during spontaneous or traumatic bleeding and before surgical procedures.

The current standard of treatment of GT patients with active bleeding is the use of local measures alone or in conjunction with anti-fibrinolytic therapy, followed by platelet transfusion if needed. In severe persisting bleeding rFVIIa may be used.

Platelet concentrates should be single-donor apheretic source and preferably HLA-matched as there is risk of developing alloantibodies against the platelet glycoproteins, αIIbβ3, and/or the HLA antigens with repeated transfusions. In developing countries eg Bangladesh HLA- matched platelet are not readily available. Apheretic single donor platelets are only available in few centres in Bangladesh, mostly patients are dependent on random donor platelets that often are complicated with platelet refractoriness due allo-antibodies. In this reported case we used both single donor and random donor platelets for one week after admission to our hospital and she responded well with that in addition to antifibrinolytic treatment and DDAVP nasal spray. Usually in severe active bleeding platelet transfusions should be continued for 48 hours after the cessation of bleeding and until wound healing in post surgery.[3]

Anti-fibrinolytic drugs are good for mild to moderate muco¬cutaneous bleeding, during dental procedures and in menorhhagia to control bleeding. Commonly used anti fibrinolytic drugs are tranexamic acid and e-amino caproic acid. They can be used both oral or intravenous. Precaution must be taken to avoid these drugs if patient is associated with hematuria as there is risk of clot in urinary tract. Drugs affecting platelet function, such as NSAIDS or aspirin, should be avoided.

Desmopressin (DDAVP) causes the release of VWF, FVIII, and tissue plasminogen activator into the plasma. Although DDAVP has no direct effect on platelets, but it showed few efficacy in other platelet disorder as well as GT.10

Local measures include compression, gelatin sponges or tropical thrombin and fibrin sealants. Superficial wound compression with e-aminocaproic acid-soaked cotton as a local measure is often practiced in Bangladesh, specially in gum bleeding or nasal bleeding.

Female patients with GT having menorrhagia are usually managed with tranexamic acid alone or progesterone and /or with estro¬gen preparations. Pregnancy cases are associated with increased risk of bleeding. So they should be managed with special care with multidisciplinary approach. Platelet transfusions and antifibrinolytics are good options as treatments during delivery as advocated in several articles. Postpartum hemorrhage is

evidenced more in those who did not receive platelet transfusion as prophylaxis than those who received (63% Vs 38%).11 It is also important to monitor for platelet alloantibodies throughout pregnancy.

However in severe persisting bleeding can be controlled by rFVII as reported in few case reports.[12]

rFVIIa is being increasingly used in GT patients in last two decades. Through a tissue factor-independent mechanism rFVII increases thrombin generation through increase activation of factor IX and X. The increased amount of thrombin promotes platelet adhesion and aggregation, including those lacking GPIIb/IIIa.[12] This agent was first reported as a successful treatment in a child with GT with intractable epistaxis.[13] Several other authors also have documented its efficacy in controlling heavy bleeding at doses ranging from 120 to 300 µg/kg.[13-15]. It has also efficacy in platelet refractory patients though disadvantage is its high cost and thrombosis. In Bangladesh rFVII is available but due to high cost patients often unable to receive that.

Hematopoietic stem cell transplantation (HSCT) offers a curative treatment for severe GT patients, although currently no clear defined guideline for transplantation in GT. To date very few cases have been reported as transplanted successfully with stem cells from either matched family donor, unrelated donor or from umbilical cord blood using mostly busulphan and cyclophosphamide as conditioning.[16]

Conclusion:

Glanzmann's thrombasthenia is a very rare autosomal recessive disease that has association with consanguinous marriage as in other recessive diseases. Patients have bleeding problems in spite of normal platelet count. The clinical severity and prognosis vary according to underlying pathology either quantitative or qualitative dysfunction of the surface integrin GPIIb/IIIa. Although there is no specific therapy, mild to moderate cases can be treated with antifibrinolytic, DDAVP and platelet transfusions. These are the widely available treatments worldwide. In addition to supportive ones, several new medication are being explored in last two decades eg rFVII. Allogeneic HSCT is only curative treatment. Gene therapy has gained significant attention in the last decade.

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