

Glanzmann Thrombasthenia Associated with Human Immunodeficiency Virus-positive Patient

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ABSTRACT

Glanzmann's thrombasthenia (GT) is an autosomal recessive inherited platelet function defect characterized by normal platelet count, prolonged bleeding time and abnormal clot retraction. This disease typically presents in infancy or early childhood and has proven to have very good prognosis. In this case study, a 22-year-old GT patient who also developed human immunodeficiency virus (HIV) infection after sometime is reported. The patient showed oral manifestations of gingival hyperplasia and petechial lesions. Unfortunately the detection of both thrombasthenia and HIV were done at considerably late stages which contributed to a poor prognosis. The patient died of cardiopulmonary arrest secondary to HIV, thrombasthenia and thrombocytopenia. The importance of early detection, supportive care and communication between the general and oral physician in management of the GT is also discussed.

Keywords: IIb/IIIa glycoprotein complex, gingival hyperplasia, Glanzmann thrombasthenia, human immunodeficiency virus, thrombocytopenia

INTRODUCTION

Glanzmann's thrombasthenia (GT) is an autosomal recessive inherited platelet functional defect characterized by normal platelet count, prolonged bleeding time and abnormal clot retraction.^[1] GT was first documented in 1918 by Dr. Eduard Glanzmann and described as "hereditary hemorrhagic thrombasthenia". GT occurs in a small fraction of the population; however, a high percentage persists in confined geographic areas within certain ethnic groups (Indians, Iranians, Iraqi Jews, French gypsies, Palestinians, Arabs and Jordanian Arabs) in which marriage is practiced among descendants of a common ancestor.^[1,2] GT is due to severe reduction in or absence of platelet aggregation in response to adenosine 5'-diphosphate (ADP), epinephrine, collagen, or thrombin because of abnormalities of platelet glycoprotein (GP) IIb and/or GPIIIa. The IIb-IIIa GP complex is an integrin receptor for fibrinogen, which helps in platelet aggregation. Such GPs form calcium-dependent complexes

that change conformation under activation and allow the fibrinogen binding necessary for this aggregation. The two genes, encoding for GPIIb (ITGA2B) and GPIIIa (ITGB3) are closely associated at chromosome 17q21.^[2,3] Patients with GT generally present in infancy or early childhood with the clinical complications of lifelong bleeding with easy bruising, gingival bleeding, epistaxis, menorrhagia, and gastrointestinal bleeding. Dental extractions and other invasive procedures are frequently complicated by excessive bleeding. Platelet aggregation in the presence of ristocetin and absence of platelet aggregation in the presence of ADP, epinephrine, collagen and thrombin will confirm the diagnosis of GT.^[1,4] Flow cytometry can also be used in GT to detect the presence of the IIB-IIIa GP complex, GPIIb (CD41), GPIIIa (CD61) and fibrinogen using monoclonal antibodies.^[1,5]

In this case study, a 22-year-old GT patient who also developed human immunodeficiency virus (HIV) infection after sometime is reported. The Patient showed oral manifestations of gingival hyperplasia and petechial lesions. Patient died of cardiopulmonary arrest secondary to HIV, thrombasthenia and pancytopenia.

The importance of early detection, supportive care and communication between the general and oral physician in management of the disease is discussed.

CASE REPORT

The present case report is about a 22-year-old Indian female patient who presented to the Department of Oral Medicine and Radiology with the complaints of enlarged, bleeding and bluish discolored gums and burning sensation in the mouth. Enlarged gums were first noticed approximately 4 weeks prior to presentation and progressed since then to the present state. The burning sensation in the mouth was present since 12-16 weeks while taking hot and spicy foods. The patient's medical history revealed recurrent episodes of epistaxis since 4 years after birth, recurrent episodes of menorrhagia since the age of 13 years, occasional petechiae over the mouth and lower limbs, gingival bleeding and continuous fatigue. At the age of 20, she was admitted to the Department of General Medicine, Nizam's Institute of Medical Sciences, Hyderabad, for the

treatment of menorrhagia. A diagnosis of GT was made and multiple blood transfusions were given to control menorrhagia. Patient was discharged after 5 days in stable condition and advised for follow-up every month. The patient visited a dental clinic at the same time and underwent oral prophylaxis and post oral prophylaxis bleeding was controlled by local application of Tranexamic acid paste. Personal history revealed patient was from a low socio-economic background and lack of education. Family history revealed she is the only child from her parent's non-consanguineous marriage.

Upon general physical examination, patient was of moderate built; had mild pallor of the skin and multiple (8-10) petechiae on the left lower limb; and all vital signs were in normal limits except for the increased radial pulse (88 beats/min). Extra oral examination showed palpable two rights and one left submandibular lymph nodes, all were measuring approximately 1 cm × 1 cm, mobile, firm and tender. Intraoral examination showed generalized pallor of the mucosa, two petechiae on the lower labial mucosa and generalized gingival enlargement [Figure 1]. Gingiva was blue in color, enlarged, soft to firm in consistency with spontaneous bleeding from the gingival sulcus. Generalized calculus and plaque accumulation was present. Hard tissue examination revealed multiple dental caries. Patient was subjected to laboratory studies. Laboratory findings were shown in Table 1 and peripheral smear showed red blood cells: Microcytic hypochromic and macrocytosis with few late normoblasts, white blood cells: Normal limits with no immature forms and platelets:



Figure 1: Clinical photograph of glanzmann thrombasthenia patient showing gingival enlargement and two petechiae on the lower labial mucosa

Table 1: Laboratory findings of glanzmann thrombasthenia patients at the time of dental visit

	Patients values	Normal range %
Bleeding time (ivy's method)	12 min	2-7 min
Hb%	3.3 g/dl	12-15 g/dl
Total WBC	9,800	4,500-11,000 c/c mm
Differential count		
Neutrophils	77	50-70
Lymphocytes	18	25-30
Eosinophils	3	2-6
Monocytes	2	2-8
Basophils	0	0-1
RBC	0.9	3.5-5.0 million/cu/mm
PCV	10	33-43
RDW	15	11-16
MCV	115	76-100
MCH	35	27-33
MCHC	30	33-37
Platelet count	10,000 cu/mm	1.5-4.5 lakh/cu/mm
Clot retardation	Decreased	

WBC=White blood cell, RBC=Red blood cell, PCV=Packed cell volume, RDW=Red cell distribution width, MCV=Mean cell volume, MCH=Mean cell Hemoglobin, MCHC=Mean corpuscular hemoglobin concentration, Hb=Hemoglobin

Decreased with no hemoparasites. Considering the past medical history, clinical examination and laboratory studies the patient was diagnosed as GT associated with gingival hyperplasia, dimorphic anemia and thrombocytopenia.

The patient was referred to department of general medicine, for further evaluation and definitive treatment. In addition to clinical examination, patient was subjected to further laboratory investigations. The liver function tests were normal except for the increased total bilirubin levels (4.2 mg/dl). Ultrasonography of the abdomen and pelvis showed mild splenomegaly (12.3 cm). Screening test (TRI-DOT) for HIV 1 and 2 was positive. Tests for hepatitis B, immunoglobulin M and immunoglobulin G for dengue and smear for malaria parasite were negative. Platelet aggregometry (Ristocetin) test was carried out using LABOR® aggregometer (Bad Homburg, Germany) Aggregometer, Hamburg, VI.2 version and results showed markedly diminished ADP, collagen and epinephrine induced and normal Ristocetin induced platelet aggregation

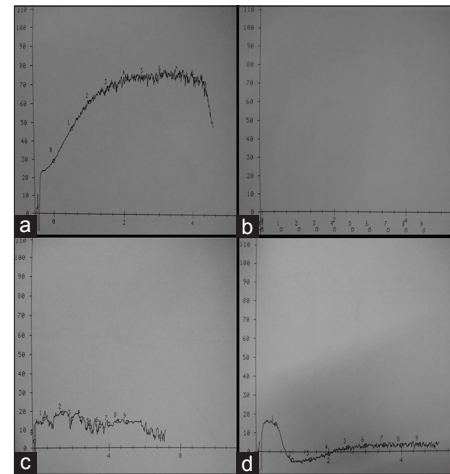


Figure 2: Platelet aggregometry test results of glanzmann thrombasthenia patient. (a) Platelet aggregation with ristocetin. (b-d) Markedly diminished adenosine 5'-diphosphate, collagen and epinephrine induced platelet aggregation

confirming GT [Figure 2]. By considering the past medical history, hematological investigations and platelet aggregometry (Ristocetin) test, the final diagnosis of GT with pancytopenia was given. Patient was admitted and given intravenous (IV) fluids, 40 units of human leukocyte antigen matched platelet transfusions on day 1, 10 units of AB + whole blood transfusions on day 2 and 40 units of platelet transfusions plus 10 units of whole blood transfusions on day 3. The patient's blood picture was monitored regularly; there was no improvement in the platelet (30,000/cu/mm) and red cell (0.9 million/cu/mm) counts. Patient developed fever (101 F) and was given oral paracetamol (650 mg 3 times daily) on day 4. The next day patient developed cough, vomiting and cutaneous clots and was given IV antibiotic augmentin (1.2 g twice daily), IV ondansetron (2 mg 3 times daily), IV ceftriaxone sodium (2 g twice daily), oral paracetamol (650 mg 3 times daily) and combination of heparin 5000iu and benzyl nicotinate 0.2 g/100 g topical application along with platelet and whole blood transfusions on day 5 and 6. Patient developed hypoxia secondary to pancytopenia with no response to therapy and expired due to cardio-pulmonary arrest on day 7.

DISCUSSION

GT patient who also developed HIV infection after sometime is reported. The Patient showed oral manifestations of gingival hyperplasia and

petechiae. GT is an extremely rare bleeding disorder. From 1956 to 2011, 353 cases of GT were published in the English literature. GT is seen relatively high in populations with consanguineous marriages whereas in the present case she is the only child from parent's non-consanguineous marriage. George *et al.* divided the GT Patients into three groups based on the platelet fibrinogen content and clot retraction; Type 1: With <5% GPIIb/IIIa and absent clot retraction; Type 2: With 10-20% GPIIb/IIIa and minimal clot retraction; and Type 3: A variant form of qualitative platelet defects, with abnormal function despite normal or near-normal levels of GPIIb/IIIa.^[6] The present case is classified as Type 2 GT 1 with values of GPIIb-IIIa was measured between 9.1 and 14.5% respectively. Some clinical observations have shown no correlation between the amounts of platelet GPIIb-IIIa and the severity of hemorrhage disease.^[4] The present case showed severe clinical symptoms with relatively mild degree of GPIIb-IIIa deficiency (Type 2). However a report of patients presenting with neonatal purpura had severe GPIIb-IIIa deficiency (Type 1), so the degree of GPIIb-IIIa abnormality appears to be related to severity of clinical symptoms.^[6] Several authors reported extensive gingival bleeding in GT and used local hemostatic measures to control post-operative hemorrhage. Bleeding is exaggerated due to presence of local irritants in GT patients rather than spontaneous bleeding.^[2,3] In the present case, there was a bluish colored gingival hyperplasia and no such presentation is presently reported in the literature. This gingival hyperplasia in the present case could be attributed to exaggeration due to poor oral health.

A single case of GT with HIV infection in 1996 was reported in the English literature from 1956 to 2011, in which the patient exposed to blood transfusions from 20 donors as supportive treatment for his bleeding episodes who were HIV-negative. The source of HIV transmission was identified as one of the donor who developed anti-HIV 3 months later, attributing to a large inoculum of HIV virus in the "window period" of infectivity of the newly infected donor.^[7] Patient in the present case is unmarried with no history of sexual contact. The source of HIV transmission could be attributed probably to prior blood transfusions given to control menorrhagia. Hematological abnormalities such

as anemia, thrombocytopenia and pancytopenia are commonly observed in HIV infected people.^[8,9] In the present case, hematological abnormalities were attributed to HIV infection.

In GT patients, epistaxis continues in adulthood and is the most common cause for bleeding of clinical significance.^[4,10] At present, there is no known cure and has proven to have very good prognosis for GT. Supportive care and platelet transfusions before invasive procedure or in cases of heavy bleeding episodes are critical in management of GT patients.^[3,10] In the present case, the clinical significance of recurrent episodes of epistaxis, seen since the age of 4 years and recurrent episodes of menorrhagia, seen since its onset at the age of 13 years was neglected by her parents owing partly to their lack of education and access to healthcare facilities. Diagnosis of GT was made only at the age of 20 years when patient visited the hospital for the management of menorrhagia. Post diagnostic critical supportive care as a part of the GT treatment was not followed. Patient visited the dental clinic with petechiae on the labial mucosa and gingival enlargement. Patient also had continuous fatigue, and pancytopenia. In spite of being referred to critical care unit, patient developed cardio-pulmonary arrest resulting in her death, signifying the importance of early diagnosis and regular supportive care in GT patients.

CONCLUSIONS

In this study, a case of delayed diagnosis of GT subsequently complicated by HIV infection after sometime is reported. The importance of awareness, early detection and appropriate supportive care in the management and prognosis of GT is discussed.

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