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Traumatic Hyphema Successfully Treated with Recombinant Factor VIIa in Glanzmann Thrombasthenia with Platelet Refractoriness

Trombosit Refrakterliği Olan Glanzmann Trombastenili Hastada Travmatik Hifemanın Rekombinan Faktör VIIa ile Başarılı Tedavisi

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ABSTRACT

Glanzmann thrombasthenia (GT) is a congenital disorder of platelet aggregation characterized by a lifelong bleeding tendency. Standard therapy consists of platelet transfusions; however repeated transfusions may result in antiplatelet antibodies and platelet refractoriness. Recombinant activated factor VII (rFVIIa) is an effective alternative therapy in GT patients, particularly in those with antiplatelet antibodies and/or platelet refractoriness. Ocular manifestations of GT are very rare. Here we report a case of GT with traumatic hyphema who was successfully treated with rFVIIa.

Key Words: Glanzmann thrombasthenia, Hyphema, Platelet refractoriness, Recombinant factor VIIa

ÖZET

Glanzmann trombastenisi (GT) yaşam boyu kanamaya yatkınlıkla karakterize olan trombosit agregasyonunun kalıtımsal bozukluğudur. Glanzmann Trombastenisinin göz bulgularıyla nadiren karşılaşılır. Standart tedavi trombosit transfüzyonudur; bununla birlikte tekrarlanan transfüzyonlar trombosite karşı antikor oluşumu ve trombosit refrakterliği ile sonuçlanmaktadır. Rekombinan aktif faktör VIIa (rFVIIa) trombosit antikoru ve/veya trombosit refrakterliği olan GT hastalarda efektif alternatif bir tedavidir. Burada rFVIIa ile başarılı bir şekilde tedavi edilen travmatik hifeması olan GT'li bir hastayı sunduk.

Anahtar Sözcükler: Glanzmann trombastenisi, Hifema, Trombosit refrakterliği, Rekombinan faktör VIIa

INTRODUCTION

Glanzmann thrombasthenia (GT) is an autosomal recessive disorder characterized by defects in the platelet membrane glycoprotein (GP) IIb/IIIa complex (1,2). Platelets have normal appearance, number and adherance to damaged endothelium but fail to aggregate when activated. Common symptoms are mucocutaneous bleeding such as purpura, petechiae, gingival bleeding, epistaxis and menorrhagia. Patients also frequently bleed after dental extraction, surgery, and trauma. When bleeding occurs, platelet transfusion is the main treatment. However, repeated platelet transfusions may result in alloimmunization and platelet refractoriness (3). Previous studies have demonstrated successful use of recombinant activated factor VII (rFVIIa) in these situations (4). In this report, we present a case of traumatic hyphema that was refractory to platelet transfusions but which responded well to treatment with rFVIIa.

CASE REPORT

A 10-year-old boy with a previous diagnosis of GT was admitted to our hospital with headache, decreased vision and pain in his left eye after contusion trauma to the forehead. He was the second child of a consanguineous marriage. The family history was unremarkable and his parents and older sibling were healthy. He had frequent episodes of epistaxis treated with repeated doses of platelet concentrates but no clinically relevant bleeding history.

On admission he had conjunctival bleeding and hyphema in his left eye (Figure 1). The visual acuity was light perception in his eye. Unfortunately, intraocular pressure could not be measured on admission. Neurological examination was unremarkable. Cranial tomography revealed no signs of intracranial or retrobulbar hemorrhage. On his laboratory evaluation, the hemoglobin was 14.6 g/dl, the white blood cell count was

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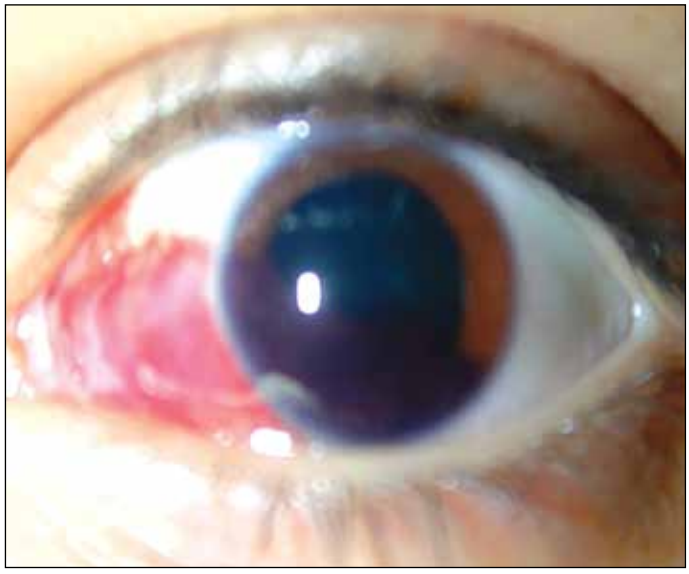

Figure 1: Hyphema and conjunctival bleeding in patient's left eye.

7.53x10^9/L, and the platelet count was 229x10^9/L. Bleeding time measured by the Ivy method was 15 minutes (normal: 2-7 minutes). Collagen ADP and collagen epinephrine closure times which were measured with platelet function analyzer-100 (PFA-100, Dade-Behring, Deerfield, IL, USA) were >240 sec (normal: 71-118 sec) and >240 sec (normal: 85-165 sec) respectively.

He was immobilized and prescribed topical prednisolone acetate, cyclopentolate, and betaxolol. After receiving 3 units of thrombocyte suspensions, his visual acuity was hand motions in the left eye but bleeding time was still 15 minutes, collagen ADP >244 sec (71-118 sec), and collagen epinephrine >277 sec (85-165 sec). Platelet refractoriness was considered and he was given three doses of rFVIIa (90µg/kg) at two-hour intervals. After given rFVIIa, his conjunctival bleeding and the fibrin clot in the anterior chamber decreased in size. Intraocular pressure of the left eye was measured as 48 mmHg and oral acetazolamide was added to the topical betaxolol and cyclopentolate therapy. On follow up, his intraocular pressure decreased and visual acuity improved.

DISCUSSION

Glanzmann thrombastenia is a very rare autosomal recessive platelet function disorder characterized by qualitative and quantitative defects of the platelet GPIIb/IIIa, the platelet integrin receptor. It mediates platelet adhesion to fibrinogen and von Willebrand factor (vWF). Both platelet adhesion and aggregation are markedly impaired in the absence of functional platelet integrin receptor. Glanzmann thrombastenia is characterized by a normal platelet count and morphology with prolonged bleeding time and prolonged closure times with testing PFA-100. Thrombasthenic platelets do not aggregate in response to agonists, such as ADP, collagen, thrombin and adrenaline, but do agglutinate in the presence of ristocetin. Definitive diagnosis is made by flow cytometry using antibodies to GPIIb (CD41) and GPIIIa (CD61) (2,5). Although posttraumatic mucocutaneous bleedings are common, ocular manifestations such as hyphema are very rare (6).

Traditional treatment for bleeding events in GT includes supportive care, antifibrinolytic agents and platelet transfusion (5). Platelet transfusions are usually effective to stop bleeding in GT, but have disadvantages such as alloimmunization. Platelet antigens causing alloimmunization are human leukocyte antigen (HLA) and the human platelet antigen (HPA) system. Patients with GT may need repeated episodes of transfusion, so that they are candidates for the risk of developing alloantibodies either to HLA antigens or glycoprotein IIb/IIIa. Transfusions of both platelets and packed red blood cells should be given with leukocyte depletion filters to decrease the risk of alloimmunization (3,7,8). Also, the use of single donor platelets restricts the exposure to HLA antigens (3). For exact diagnosis of alloimmunization in GT is detection of anti platelet GPIIb/IIIa or anti HLA antibodies. Clinically persistent bleeding or rebleeding despite an adequate amount of platelet suspension also suggests platelet refractoriness due to alloimmunization (9). Although we could not perform the assays for detection of antibodies and could not monitor the bleeding inside the eye, bleeding time (IVY and PFA-100) was used for the assessment of effectiveness of plaletet transfusion and platelet refractoriness due to alloimmunization was considered (10). The management of platelet refractoriness because of alloimmunization includes platelet transfusion with HLA-matched and donor-recipient cross-matched platelets. It is reasonable to try plasmapheresis to remove the offending antibodies in GT, but the efficacy of such treatment is not defined and it provides only short-term benefit (11).

In 2004, rFVIIa was approved by the European Medicines Agency (EMA) for GT patients who are refractory to platelet transfusions (4). In GT, a tissue factor (TF) dependent mechanism operates to generate thrombin for initial platelet activation with exposure of coagulant surface. This thrombin generation is not sufficient for fibrin formation. The high dose rFVIIa can directly activate factor X on activated platelets independent of tissue factor, increasing the rate of thrombin generation (4,12). In 2014, the US Food and Drug Administration (FDA) additionally approved rFVIIa for the treatment of bleeding episodes and perioperative management of patients with GT who are refractory to platelet transfusions, with or without the presence of anti-platelet alloantibodies (13,14). HLA-matched or cross-matched platelet suspensions could not be obtained for our patient and we treated him with aFVIIa.

Patients with GT are susceptible to hyphema even after minor trauma so they should be conscious of this danger. Although traumatic hyphema treated with platelet transfusions has previously been reported in a GT patient, to our knowledge our case is the first report of a GT patient with hyphema successfully treated with rFVIIa (6).

In conclusion, rFVIIa should be considered as an alternative therapy for the treatment of GT patients with platelet refractoriness including ocular bleeding.

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