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A Case Report of Glanzman Thrombasthenia with Anterior Mediastinal Hematoma and Factor V Leiden Mutation

Ön Mediastende Hematomu Olan ve Faktör V Leiden Mutasyonu Bulunan Glanzman Trombastenili Bir Olgu Sunumu

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ABSTRACT
Glanzmann thrombasthenia (GT) is an autosomal recessive disease associated with platelet aggregation dysfunction with normal platelet count, causing bleeding diathesis. GT is characterized by decreased levels or decreased function of the glycoprotein IIb-IIIa (GPIIb-IIIa) complex and therefore results in an increased tendency to bleeding as the aggregation phase of primary hemostasis cannot be sufficiently formed. Factor V Leiden mutation is a genetic mutation predisposing to thrombophilia. We present this case in which Factor V Leiden mutation and Glanzmann thrombasthenia with hematoma in the anterior mediastinum are rarely seen together.

Keywords: Glanzmann thrombasthenia, factor V leiden, hematoma, thrombophilia

ÖZET
Glanzmann trombasteni (GT), normal trombosit sayısı ile trombosit agregasyon disfonksiyonu ile ilişkili, kanama diyatezi oluşturan otozomal resesif geçişli bir hastalıktır. GT, glikoprotein IIb-IIIa (GPIIb-IIIa) kompleksinin azalmış seviyeleri veya azalmış işlevi ile karakterize edilir ve bu nedenle, birincil hemostazın kümelenme fazı yeterince oluşturulamadığından artan kanama eğilimi ile sonuçlanır. Faktör V Leiden mutasyonu, trombofili için yatkınlık oluşturan genetik bir mutasyondur. Faktör V Leiden mutasyonu ve Glanzmann trombastenisi ön mediastende hematom ile birlikte nadiren birlikte görüldüğü bu olguyu sunuyoruz.

Anahtar Kelimeler: Glanzmann trombasteni, faktör V leiden, hematom, trombofili

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INTRODUCTION

Glanzmann thrombasthenia is an inherited bleeding disorder caused by the absence, deficiency or dysfunction of glycoprotein IIb IIIa in the platelet membrane. These integrins, which form platelet glycoprotein (GP) IIb/IIIa, which act as the main platelet receptor for fibrinogen, are encoded by the ITGA2B and ITGB3 genes. (Nair et al., 2002). Platelets have a crucial role in thrombus formation with their procoagulant activities. Most patients present with mucocutaneous bleeding at an early age, despite variability in clinical phenotype. Management of bleeding is generally possible with measures to provide local hemostasis, platelet transfusions or hemostatic agents including recombinant Factor VIIa in cases that develop alloimmunization against IIb-IIIa (Botero et al., 2020).

One of the key components in the anticoagulant pathway is protein C; when activated (APC) degrades coagulation factor V and factor VIII (Dahlbäck et al., 1993). Congenital APC resistance is usually caused by a single point mutation (G → A) at nucleotide position 1691 in the factor V gene, resulting in factor V Leiden mutation (Factor V: Q506) (Bertina et al., 1994). Resistance to APC due to factor V Leiden mutation is the most common hereditary thrombophilic defect (Lane et al., 1996). Mutated factor V is resistant to inactivation by APC, resulting in increased thrombin formation with a tendency to hypercoagulation (Rai et al., 2001). There are rare cases and studies in the literature in which Factor V and Glanzmann thrombasthia are seen together. In this article, we believe that the review of a patient with Glanzman Thrombasthenia with anterior mediastinal hematoma and Factor V Leiden mutation can contribute to the literature, since bleeding diathesis can limit bleeding to the vital area.

CASE REPORT

A 14-year-old male patient applied to our outpatient clinic because of frequent nose and gum bleeding. The patient, who stated that he did not use any medication including acetyl salicylic acid, revealed pale skin on physical examination and in the complete blood count, WBC:6500/mm3, Hb: 9.7 g/dL, PLT:365000/mm3, MPV:9 fL, INR:1.11, APTT:26'', TT:18'', Fibrinogen:400 and values were normal. The patient's system findings were normal and hepatosplenomegaly was absent. In the peripheral smear, 52% neutrophils, 32% lymphocytes, 14% monocytes, 2% eosinophils were seen, and platelets were abundant but unclustered. Platelets were of normal size, although abundant and scattered, there were no atypical cells. Upon the appearance of melena and occult blood in the stool, the patient was admitted to the service for gastrointestinal bleeding, 1 unit of erythrocyte and thrombocyte suspension and oral transaminic acid (25 mg/kg) therapy were given. The bleeding time of the patient was over 20 minutes, there was no response to collagen, ADP, epinephrine in the platelet aggregation test, and the response to ristocetin was normal. In the patient whose mother and father were consanguineous marriage, the expression level of CD41 (GPIIb) and CD61 (GPIIIa) on the platelet surface was found to be very low at the level of 3% as a result of flow cytometry, which was examined considering autosomal recessive inheritance glanzmann thrombasthenia. Followed up with iron treatment due to the presence of iron deficiency anemia, patient was admitted to our clinic again with severe chest pain complaints after 2 months. Physical examination was normal, had no problem except Hb: 8.9 in the complete blood count. There

were no atypical cells in the peripheral smear, and thrombocytes were again abundant and scattered. A mass localized in the anterior mediastinum was detected in the chest radiography of the patient. Cardiac examination and tests (ECG, ECHO) were normal. The presence of a localized hematoma in the anterior mediastinum was observed in the CT scan of the patient. Although the patient had Glanzmann thrombasthenia, it was noteworthy that he was able to limit a bleeding localized to the anterior mediastinum. Thereupon, the presence of possible protorombotic risk factors in the patient was investigated and Factor V Leiden mutation was found to be homozygous positive. The other prothrombotic mutations were not absent. It was thought that this situation might contribute to bleeding control. In the follow-up of the patient, the mass due to the hematoma regressed. The patient was treated with classical Glanzmann's treatment and transfusion of thrombosis suspension was performed.The patient is still followed up in a stable condition.

DISCUSSION

GT is the most common inherited platelet dysfunction characterized by platelet aggregation deficiency (Laguerre et al., 2013). Typically, patients may have episodes of spontaneous mucocutaneous bleeding, as well as any kind of bleeding inside and outside the body (Nurden et al., 2012). This usually results in a lifelong hemorrhagic predisposition in patients.

Although GT is a rare autosomal recessive disease, it has a higher incidence rate in some populations where consanguineous marriage is common (Ali et al., 2008). GT is seen all over the world, especially in French novels where consanguineous marriage is common, Iraqi Jews, South Indian Hindus, Jordanian nomadic tribes (Botero et al., 2020) and Iran (Farsinejad et al., 2011) as well as Turkey. Therefore, in Turkey, especially in Southern Anatolia where consanguineous marriage is high (44.8%) (Southern Anatolian Region of Turkey) and rural areas (28.2%) (Kaplan et al., 2016), the possibility of the disease is high.

Early diagnosis is very important in GT disease. Recognition of GT in childhood can prevent unconscious use of aspirin and non-steroidal anti-inflammatory drugs, but may allow early treatment. In addition, uncontrolled and unstoppable bleeding may lead to various complications in patients with undiagnosed GT. Especially in patients with symptoms such as easy bruising (petechiae, purpura, ecchymosis), gingival bleeding, and menorrhagia, the bleeding severity of the disease should also be taken into consideration. Responses to agonists such as ADP, epinephrine, collagen and ristocetin should be controlled. In addition to these analyzes, it should be tested whether or not the expression of surface markers of GPIIb (CD41) and GPIIIa (CD61) is reduced or not using flow cytometry (Kannan & Saxena, 2009; Iqbal et al., 2016). Genetic analysis should be performed for further studies following flow cytometry.

All subtypes of GT are associated with homozygous or heterozygous mutations in ITGA2B and ITGB3 encoding GPIIb and GPIIIa. (French, 1998). Subtypes of GT, Type I and Type II, are caused by mutations that cause deficiency (i.e., less than 5% of normal) or decrease (i.e., 5-20% of normal) of the GP IIb / IIIa complex on the platelet surface (Siddiq et al., 2011). In addition, rare mutations can also cause a dysfunctional complex that is expressed under normal or normal, termed Type III (20-100%) or variant (Sebastiano et al., 2010). These

classifications allow molecular abnormalities to be compared better with clinical diseases, but unfortunately there is no major correlation between the two.

Basically, heterozygotes with normal platelet function tests appear asymptomatic.. Symptomatic conditions can be seen more frequently in patients with homozygous mutant. Findings seen in this case are consistent with GT findings in the literature. GT patients generally tend to bleed for life. It was noteworthy that our patient with a rare anterior mediastinal hematoma controlled localized bleeding. Because it may be difficult to control bleeding in the anterior mediastinum. The presence of a restricted hematoma in the anterior mediastinum in our patient diagnosed with Type I GT suggested that prothrombotic factors might exist in the patient. The fact that our patient had only homozygous Factor V Leiden mutation may have allowed symptomatic localized bleeding to be controlled. It has been observed that such mutations are seen in GT cases with less bleeding (Gultekin et al., 2019). However, there is no conclusive evidence yet to support this hypothesis.

CONCLUSION

In conclusion, Factor V Leiden mutation and other prothrombotic genetic risk factors can be screened in GT patients and in GT patients with limited hematoma as in this case. In a study conducted in Turkish children diagnosed with GT, four new missense mutations in the ITG2AB gene (horse exon 4; c.570 T> G alteration, horse exon 13 c.1277 T> A, c. T> G alterations, at exon 19 c.1921 A> G) and a new missense mutation (horse exon 5; c.680 A> C) in the IGTB3 gene (Tokgoz et al., 2015). The presence of various mutations seen in GT patients can bring different results in phenotype. In particular, Factor V Leiden mutation may be an important prothrombotic genetic factor that can control bleeding in patients with GT who have a lifelong bleeding profile. Therefore, the presence of protombotic risk factors should be considered in some cases with GT in the clinic. In the future, research on this subject can be done.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Author contributions

Contribute to the emergence and maintenance of the article: HT, ÜÇ, TD, KZÇS
Plan, design: HT, ÜÇ
Data collection / processing of collected data to prepare for analysis: HT, ÜÇ, TD, KZÇS
Data analysis: HT, ÜÇ, TD, KZÇS
Literature review: TD, KZÇS
Writing and corrections: TD, KZÇS
Checking and reviewing: HT, ÜÇ
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