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CASE REPORT

Hemorrhage of Upper Digestive and Respiratory Tracts in a Child with Glanzmann Thrombasthenia

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ABSTRACT

Glanzmann thrombasthenia (GT) is an autosomal recessive platelet disorder that could cause mild to severe bleeding episodes. The incidence is approximately 1 per 1,000,000 births. Patients with GT frequently have mucocutaneous bleeding with absent platelet aggregation in response to all physiologic stimuli, but a normal platelet count and morphology. Specifically, the glycoprotein IIb/IIIa (GP IIb/IIIa) complex is either inadequate or dysfunctional. This case reports a 3.5-year-old boy with Glanzmann thrombasthenia who had two episodes with uncontrolled hemorrhage from upper digestive and respiratory tracts, the first with the bleeding point found in the left tonsil and the second in the adenoids.

Keywords: Glanzmann thrombasthenia, platelet disorders, childhood bleeding, platelet, aggregation.

INTRODUCTION

Glanzmann thrombasthenia (GT) is an extremely rare (1/1,000,000) genetic disorder that is characterized by a deficiency or functional impairment of glycoprotein IIb/IIIa (GP IIb/IIIa), which acts as a receptor for fibrinogen on the platelets and plays the main role in platelet aggregation and adhesion (1). However, it is more frequent in ethnic groups that display higher incidences of consanguinity such as selective Arab populations. Many studies have shown predominance in women as compared to men (58% *versus* 42%) (2).

The platelets of GT patients are unable to bind fibrinogen, and the formation of clots is impossible in cases of bleeding. Patients with GT are always at risk of serious bleeding, especially during a potential surgery. Invariably these patients have a normal count of platelets and occasionally a low count of red blood cells due to iron deficiency (because of previous bleeding events). Coagulation laboratory tests, including PT (Prothrombin

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Time), aPTT (activated Partial Thromboplastin Time) and fibrinogen, are normal in GT and they help to rule out other coagulation factor deficiencies and fibrinogen disorders. The diagnosis is confirmed by platelet light transmission aggregometry and platelet glycoprotein expression study by flow cytometry (1, 3).

The diagnosis of the disease is commonly made during childhood, before the age of five, or more rarely during adolescence (4). Glanzmann thrombasthenia can be a severe hemorrhagic condition but the prognosis is very good with the appropriate supportive care. There is a clinical variability of this syndrome. Some patients have only minimal bruising, while others have severe, frequent and potentially fatal hemorrhages. Episodes of mucocutaneous bleeding and spontaneous bruising, gingival bleeding (for women during adolescence or later) or epistaxis, have been reported as clinical features of the disorder. Moreover, there is a difficulty in controlling postoperative bleeding, skin injuries and dental procedures (4, 5).

There is no specific treatment for GT. Patients usually require specific, supportive treatment during a bleeding episode. Special concern should be given prior to an operation or a dental therapy. Antifibrinolytics and recombinant activated factor VII (rFVIIa) in combination with platelet transfusions are provided to patients, which represent the main treatment method for severe bleeding episodes. However, frequent platelet transfusions may lead to the development of antibodies against platelets (alloimmunization). In addition, antifibrinolytics (aminocaproic acid, tranexamic acid) could be used locally on the bleeding site or/and systemically in severe bleeding episodes. In rare critical cases, allogeneic hematopoietic stem cell transplantation (HSCT) could be a potential therapy (6-9). However, the severity of the bleeding episodes along with the risks of transplantation should be taken into consideration before proceeding to HSCT. This therapy is still under investigation and only sporadic cases have been reported in literature (10).

The purpose of our study was to report a rare case of a child with GT who had two episodes with uncontrolled hemorrhage from the upper digestive and respiratory tracts. The successful management of this rare condition is highlighted. ❑

CASE PRESENTATION

A 3.5-year-old male child arrived at the Emergency Department (ED) in September 2022 due to persistent bleeding from the left tonsil for the last 24 hours. Hematologic examinations showed a normal platelet count, normal PT, normal aPTT and a hemoglobin (Hb) level of 9 g/dL. The child was immediately transfused with concentrated red blood cells, according to the pediatrician's instructions, and he was taken to the operating room (OR) by the otorhinolaryngologists for hemorrhage control. Under general anesthesia, the bleeding source was found on the left tonsil. The hemorrhage was successfully controlled with bipolar thermocoagulation and local use of neurosurgical patties impregnated with tranexamic acid (antifibrinolytic factor). The child was discharged from the hospital in a stable clinical condition, five days postoperatively, with a Hb level of 10.4 g/dL and a platelet count of 460,000/μL.

After this bleeding episode from the tonsil, the diagnosis of GT was established by the pediatric hematologists in October 2022. According to the child's medical history, the parents mentioned incidents of easy bruising and prolonged bleeding following minor cutaneous injuries. The laboratory tests had displayed normal platelet count, aPTT and PT. The diagnosis of GT was established by platelet light transmission aggregometry, which showed decreased aggregation with all agonists except ristocetin. Furthermore, the platelet glycoprotein expression study, using flow cytometry, showed decreased CD41 (GPIIb) and CD61 (GPIIIa).

In November 2022, the child arrived at the ED again due to severe continuing nasal bleeding for the last five hours. There was no other symptom such as runny nose, fever or cough. Prior to his arrival at the hospital, the parents had given him tranexamic acid (antifibrinolytic factor) orally. The physical examination revealed blood coming from the right nostril. During this second episode, the child was admitted to the Otorhinolaryngology Department. rFVIIa, tranexamic acid (at a dose of 25 mg/kg), pooled platelet concentrates and packed red blood cells were administered intravenously to the patient according to the specialists' (pediatric hematologists) instructions. Three hours later, due to the inability to

control the bleeding, it was decided to proceed surgically.

Under general anesthesia, the bleeding point was found on the adenoids over the right eustachian tube orifice (Figure 1). The control of bleeding was unsuccessfully attempted by using bipolar thermocoagulation (Figure 2). Thus, gauzes infused with tranexamic acid were placed on the adenoids and temporary control of bleeding was achieved. Unfortunately, bleeding was recurred after packing removal. Three more attempts to control bleeding were performed with both posterior and anterior packing (Bellocq), using gauzes infused with tranexamic acid. The first two attempts failed. After the third one, due to a hemoglobin level of 7 g/dL, rFVIIa was administered in a dose of 60 μg/kg. In parallel, one unit of packed red blood cells and one unit of pooled packed platelet concentrates were transfused to achieve hemodynamic stability. Subsequently, posterior nasopharyngeal packing was reinforced with neurosurgical patties infused with an adrenaline solution (1:10,000). Two neurosurgical patties were placed in each nasal cavity and four on the adenoids (bleeding point). Consequently, the hemorrhage was controlled.

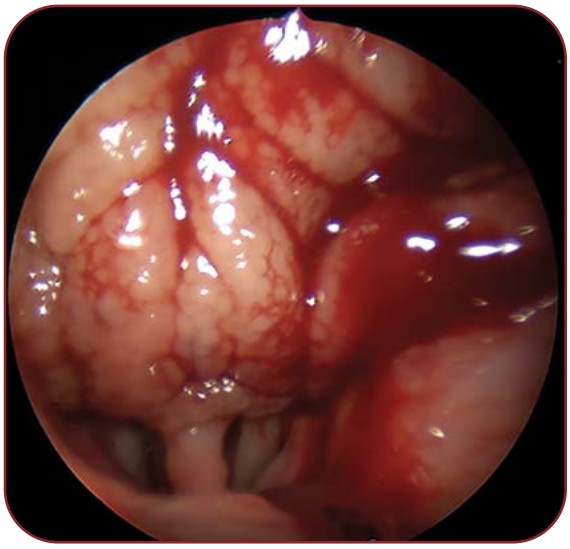

FIGURE 1. The hemorrhagic point on the adenoids, over the right eustachian tube orifice

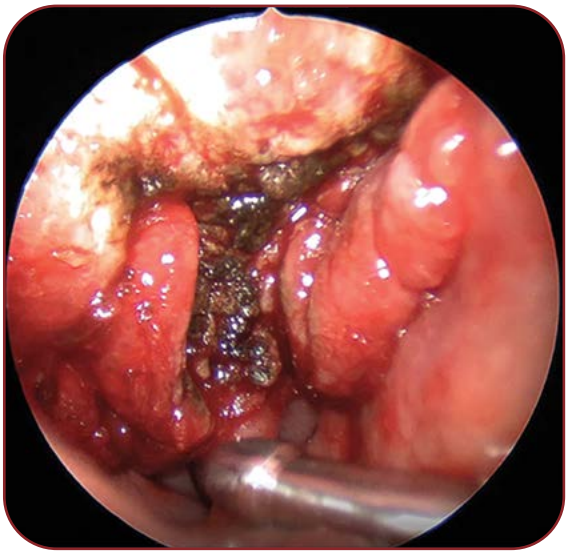

FIGURE 2. Persistent hemorrhage after using bipolar thermocoagulation

Due to the high risk of a recurrent bleeding after his extubating and the hemodynamic instability, the patient was airlifted intubated to a Children's Hospital with an intensive care unit and a Pediatric Bleeding Diathesis Department. The following day, the child was extubated after removing the anterior and posterior nasal packing, without any recurrence of bleeding and remained hospitalized, under close supervision of both otorhinolaryngologists and pediatric hematologists for four days. Then, he was discharged from the hospital in a stable clinical condition. No other bleeding episode was observed within the next six months. ❑

DISCUSSION

Glanzmann thrombasthenia is a rare bleeding disorder that is inherited in an autosomal recessive pattern. It has an estimated incidence of 1 *per* 1,000,000 on a global scale (11). However, a higher incidence has been noted in some populations such as those found in South, where the phenomenon of consanguineous marriage is common, allowing expression of autosomal recessive traits (2). Similar results have been observed in Jordanian Arabs, French Gypsies and Iraqi Jews. The highest prevalence, about 1 *per* 200,000, has been noticed in Iran (12-14).

Glanzmann thrombasthenia is characterized by an early onset of hemorrhagic episodes. The diagnostic algorithm includes a series of laboratory tests, in addition to a detailed medical history of bleeding symptoms. When examining the patient, it is crucial to inspect the skin for signs of bruising as the mucocutaneous regions, including the nostrils, for evidence of bleeding. The number and morphology of platelets and the duration of hemorrhagic episodes, along with light

transmission aggregometry and flow cytometric analysis are the basic diagnostic methods of GT.

Many studies have reported that although most patients were diagnosed at the age of seven to eight years, the average age of the first hemorrhagic episode was before the age of five, even at birth or infancy (15, 16). Also, regarding gender incidence, the ratio of men to women ranges between 1:1.2 to 1:1.9 (16, 17).

Bleeding in patients with GT mainly affects both the skin and mucosa (epistaxis, skin bleeding after injury, gingival bleeding, menorrhagia in women) (11, 17, 18). Symptoms such as bleeding from the earlobe, spleen, musculoskeletal system, joints and central nervous system that are common in secondary hemostasis disorders are infrequent in patients with GT, which is a primary hemostasis disorder. Generally, in patients who had their first hemorrhagic episode during adolescence, bleeding occurred as either postoperative hemorrhage or menorrhagia (15, 17). However, there are studies that report complications such as hematoma, ecchymosis, and hemarthrosis (mainly in the knee joint) in approximately 19%, 19%, and 6% of cases, respectively (18).

Patients with GT benefit from being managed in a specialized center for inherited bleeding disorders providing the appropriate treatment and recommendations. The proper selection and use of treatment methods in patients with GT is vital, not only for bleeding control but also for preventing complications such as alloimmunization against blood factors and transmission of infectious diseases due to transfusions (19). Primarily, GT patients should receive adequate knowledge about their platelet disorder, including education on preventing bleeding such as avoiding certain medications (NSAIDs or aspirin) and high-impact physical activities.

Furthermore, local treatment measures can be used to control mild to moderate bleeding episodes. These measures may include applying pressure (in cases of skin injuries or gingival hemorrhage), nasal packing in cases of epistaxis, fibrin sealants or local use of antifibrinolytic factors (tranexamic acid, aminocaproic acid). Additionally, systemic antifibrinolytics can be administered orally or/and intravenously, such as tranexamic acid and aminocaproic acid. In severe bleeding episodes, patients require some combination of three main treatment options to achieve haemostasis: antifibrinolytics (tranexamic acid, aminocaproic acid), rFVIIa and platelet transfusion (19). rFVIIa carries the risk of an immune response against it, at a rate of approximately 4%, and should only be used for very severe bleeding circumstances that is not possible to be controlled with other measures (19, 20). However, reported findings showed that 60% to 84% of patients with GT required blood clotting inductions to control bleeding, depending on the number and severity of bleeding episodes (14, 15, 18).

Platelet transfusion has been a mainstay of therapy for years, but the benefit must be weighed against the risk of causing alloimmunization. As a result, it could render GT patients refractory to subsequent platelet transfusions. If a decrease in Hb concentration coexists, a red blood cell transfusion becomes essential (15). In parallel, regarding transfusions (of platelets or red blood cells) in patients with GT, there are few studies where transmission of infectious diseases, such as hepatitis B or C, has been reported at a rate of about 14% (15, 21).

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only substantial cure for GT, but it involves serious risks, including organ graft-*versus*-host disease, dysfunction, infections and death. As a result, the increased risk of critical complications after HSCT and the fact that there is still insufficient data to support the supremacy of this therapeutic option restricts its wide use as a treatment. Therefore, the decision to transplant a patient with GT should take into account the severity of bleeding episodes against the high risks of HSCT. Eventually, though still in experimental stage, gene therapy is a highly promising prospect for GT patients. However, further research that would ensure safety in human models is required. Until gene therapy is available, allogeneic HSCT should be considered for patients with GT in addition to a medical history of severe hemorrhagic episodes (6, 22, 23). ❑

CONCLUSIONS

The diagnosis and efficient management of patients with GT have many associated challenges. Bleeding from the skin and mucosal membranes is common in children with GT. Spontaneous bleeding episodes are detected mainly in the upper digestive and respiratory tracts, especially during viral diseases. Due to the

difficulty of controlling these bleedings, coordinated treatment must be attempted with the cooperation of otolaryngologists, pediatricians and specialized hematologists. Occasionally, as in the current case, the patient should be taken to the operating room for the management of the bleeding in combination with measures such as antifibrinolytics, rFVIIa and transfusion of platelets and red cells. Our incident indicates the need for a Children's Intensive Care Unit and a High Care Unit for the safe treatment and management of children with GT. Hematopoietic stem cell transplantation will need to become more standardized for GT patients and recognized as a treatment option early in life. In addition, the further progress of gene therapy technology will offer an alternative option to cure this disease. Conclusively, GT is considered a severe hemorrhagic disorder but the prognosis is outstanding with the appropriate supportive care. ❑

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