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Glanzmann Thrombasthenia: A Rare Hematological Disorder with Oral Manifestations: A Case Report

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Abstract

Aim: The aim of this report is to present a case of Glanzmann thrombasthenia (GT) with oral manifestations requiring periodontal management along with a discussion of the clinical, hematologic, and molecular level features of the disease.

Background: GT is a rare hematological disorder with oral manifestations affecting platelets and clotting. It is characterized by spontaneous bleeding from mucosal tissues and excessive bleeding following skin damage. It belongs to the group of hereditary platelet disorders and is due to a defect in one of two genes, platelet membrane glycoprotein (GP) IIb/IIIa.

Report: A 22-year-old female patient with a history of Type I GT and long-term care using platelet transfusion was referred for management of her gingival bleeding. Dental treatment included scaling, polishing, oral hygiene instructions, along with a prescription for anti-plaque agents. There was pronounced improvement in her periodontal condition after treatment. Reduced gingival bleeding resulted in an increase in her hemoglobin level from a pre-treatment level of 2 gm% to 8 gm% during her last visit. The patient was followed for eight months with no further periodontal complications.

Summary: A pronounced improvement in the periodontal condition of a GT patient occurred following routine scaling and polishing procedures along with proper oral hygiene maintenance instructions. The result was a reduction of the patient's gingivitis and associated spontaneous bleeding and an improvement in her hemoglobin

status. GT patients should be managed for their periodontal problems following a hematological consultation. The importance of proper maintenance of oral hygiene as well as regular recall visits should be emphasized.

Keywords: Glanzmann thrombasthenia, blood platelet disorders, periodontal disease

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Introduction

Glanzmann thrombasthenia (GT) is a rare autosomal recessive bleeding disorder characterized by a quantitative or qualitative abnormality of platelet membrane glycoprotein (GP) IIb/IIIa receptors.[1] Based on the degree of GP IIa/IIIb deficiency, fibrinogen binding, and clot retraction, patients with GT are classified as having Type 1, Type 2, or a variant type.[2,3] The features of this disorder include a normal platelet count, normal prothrombin time, normal partial prothrombin time, a prolonged bleeding time, and an absence of platelet aggregation. This life-long bleeding diathesis results from defective aggregation of platelets and the lack of subsequent clot formation.[4] The clinical signs exhibited by patients with GT include mucocutaneous hemorrhage with vulnerability to bruising, mennorahagia, epistaxis, gingival hemorrhage, and intermittent episodes of gastrointestinal bleeding.[4] As in most individuals with hereditary hematologic disorders, thrombasthenia is typically diagnosed at an early age. GT should be considered in the differential diagnosis of patients exhibiting symptoms of complicating coagulopathies because it could be life threatening.

GT is important from a periodontal point of view because of the frequent gingival hemorrhage observed in these patients. Trauma and pressure are reported to be the most frequent causes of bleeding in these patients.[2] Dental management of these patients is considered to be complicated because the severity of bleeding is unpredictable and special precautions are warranted before any surgical procedure is initiated. Although extensive studies have been done on various aspects of the disorder, very few reports have appeared regarding the gingival and periodontal manifestations of GT and their management. This paper reports a case of GT along with a discussion on its clinical, hematologic, and molecular level features and periodontal management.

Case Report

Diagnosis

A 22-year-old female patient was referred for periodontal therapy from the Hematology department of a medical care facility for the management of severe spontaneous gingival bleeding. Her history revealed she was born to parents with second-degree consanguinity. She had a normal birth weight and growth pattern until two years of age when she experienced the first episode of spontaneous bleeding from her nasal cavity. No medical consultation was sought at that time. Later a bluish discoloration associated with minor injuries was noticed on her skin. Severe gingival bleeding was noted at the age of five making routine oral hygiene procedures such as toothbrushing and flossing almost impossible. Oral hygiene was less than ideal because she could only use a powdered dentifrice and her fingers to clean her teeth.

The severity of bleeding increased with time. Her menstrual cycle started at the age of ten; her periods were regular and usually lasted five days. Increased bleeding was noted during menarche and a blood transfusion was initiated at that time. Initially a transfusion was required only yearly. The frequency of transfusion has been increased to twice a week for the past year.

A general examination revealed the patient to be moderately built for her age with severe pallor. Her vital statistics appeared to be within normal range. Detailed hematologic examination was performed for the patient and is given in Table 1.

An intraoral examination revealed a moderate amount of dental calculus on the buccal aspect of maxillary first molars and the lingual aspect of mandibular posterior teeth. The gingiva appeared to be very pale with spontaneous bleeding from the maxillary left and the mandibular right

Table 1. Results of hematological examination.

	Values from Patient Samples	Normal Values
Hemoglobin	2 gm/dL	12-16 gm/dL
Total White Blood Cell Count	6200 cells/µL/cu mm	4,300-10,800 cells/µL/cu mm
Differential Count Neutrophils Lymphocytes Eosinophils	 67% 29% 4%	 50-70% 25-35% 1-3%
Platelet Count	260,000/mL	150,000-350,000/mL
Packed Cell Volume	30.4%	36-48%
Bleeding Time (Ivy Method: Normal 2 –6 minutes)	More than 15 minutes	Up to 10 minutes
Clotting Time (Lee and White: Normal 10 – 20 minutes)	13 minutes	5-10 minutes
Prothrombin Time	15.9 minutes	Up to ± 3 seconds
Activated Partial Thromboplastin Time	29.9 minutes	45-60 seconds
Clot Retraction	Nil	
Platelet Aggregation with Adrenalin Collagen ADP Ricocetin	 Absent Absent Absent Normal	
Blood Picture	Mildly microcytic hypochromic with normal platelet morphology	

posterior regions, even with slight provocation of the tissue (Figures 1a and b).

The consistency, contour, and position of gingiva were satisfactory except for slight gingival recession on labial aspect of tooth #41. The detailed results of the periodontal evaluation of the patient consisting of plaque and gingival index scores, periodontal probing depths, calculus index, and clinical attachment levels are shown in Table 2.

Treatment

Treatment included supra as well as subgingival scaling and polishing along with platelet transfusion. Oral hygiene instructions were also

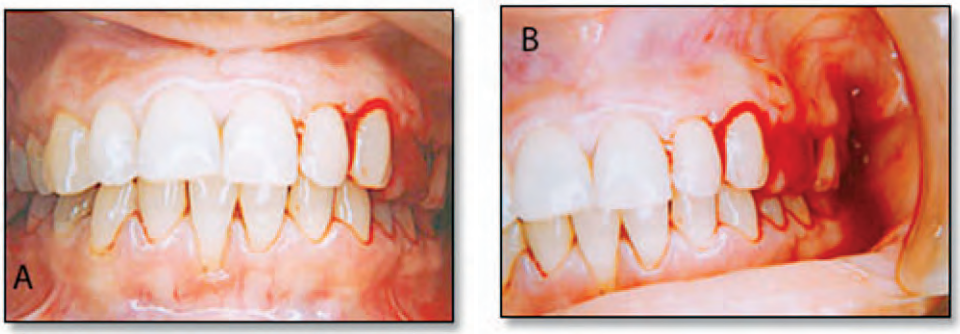

Figure 1. A. Clinical appearance of the patient at initial visit. Note pale appearance as well as spontaneous bleeding from maxillary left posterior region. **B.** Closer view of bleeding site in the maxillary left posterior region.

Table 2. Detailed periodontal examination data.

Data Element	Value
Plaque Index	1.3 ± 0.25
Gingival Index	1.9 ± 0.12
Calculus Index	2.2 ± 0.38
Probing Depth	1.46 ± 0.08
Clinical Attachment Level	0.98 ± 0.24

given. Antiplaque agents like toothpaste and 0.12% chlorhexidine mouth rinse were prescribed. The patient had weekly follow-up recall visits for the first month and then monthly visits for the next eight months. The supragingival stains due to use of chlorhexidine were removed using ultrasonic scaling and polishing during these recall visits.

The gingival condition improved in terms of color, consistency, and a reduction in bleeding tendency (Figure 2).

There was a marked increase in hemoglobin concentration from 2 gm% to 8 gm% during the patient's final recall visit. This can be attributed to the reduced gingival bleeding observed with periodontal management of the problem. No additional complaints were reported during the recall visits.

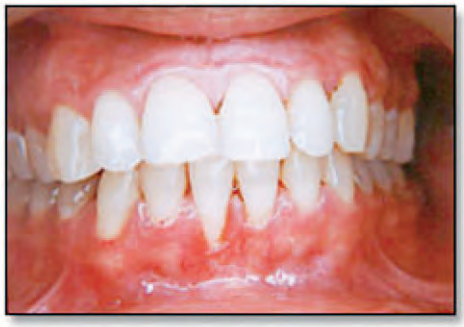

Figure 2. Gingiva after eight months of periodontal therapy. Note the improvement in color and the reduction in bleeding.

Discussion

GT, initially described by Glanzmann in 1918, is an autosomal recessive disorder with no sex difference affecting one of two genes, either platelet membrane glycoprotein IIb or IIIa.[2] This GP, an integrin, also known as $\alpha_{II}b\ \beta 3$, is a receptor for fibrinogen as well as for several other adhesive glycoproteins like Von Willebrand's factor, fibronectin, vitronectin, and thrombospondin.[5] In GT, one or both of these proteins are mutated in some manner resulting in failure of platelet aggregation following stimulation and, thus, blood clot formation.

GP IIb and IIIa exist together as a dimer and are referred to as GP IIb/IIIa. This, once activated, will bind to one end of fibrinogen. Another platelet with its own GP IIb/IIIa can then bind to the other end of fibrinogen allowing formation of a large collection or aggregation of blood platelets commonly called a blood clot.[2] In GT, the GP IIb/IIIa is defective; the platelet can no longer bind with one another and a blood clot fails to form.[6]

The dysfunctional GP IIb/IIIa receptor can either be absent or present on the platelet surface. The platelets of all patients with GT are functionally indistinguishable in that they do not aggregate in response to physiologic agents promoting clot formation like adenosine diphosphate (ADP), thrombin, or epinephrine.[3] The diagnosis of GT is made based upon important clinical characteristics such as bleeding from mucous membrane, prolonged bleeding time, and tendency to bruise easily with minor trauma. The diagnosis is confirmed using laboratory tests[4] (Table 3) as well as recently developed cDNA probes for studying restriction fragment length polymorphisms in GP IIb/IIIa gene.[5]

The disease is very rare, and approximately only 300 cases have been reported worldwide in the medical literature.[3] The genetics underpinning the disease is very diverse; to date, only a total of 26 and 23 mutations of GP IIb and IIIa, respectively, have been identified.[2] The gene has been localized to chromosome 17 and it is believed by some researchers that GT is the consequence of point mutations resulting in missense or nonsense codons; deletions and insertions; or RNA splice mutations.[3] The disorder is recessive and heterozygous individuals are asymptomatic. Typically at least one GP is not properly formed leaving the other unpaired in the endoplasmic reticulum where it is degraded. Platelet aggregation, which requires the entire complex, is deficient or completely absent.[7]

Patients with GT are classified as having Type 1, Type 2, or a variant type based on the degree of GP IIa/IIIb deficiency, fibrinogen binding, and clot retraction.[3] Patients with Type 1, the most severe form of disease, have less than 5% of the normal amount of GP IIb/IIIa present in their platelets and an absence of fibrinogen binding and clot retraction. The patient in this report had parents with second-degree relatives (cousins) who also suffered from Type 1 GT. At the time of this writing, platelet transfusion was completely withdrawn, which is a sign of obvious improvement in the

Table 3. Data for laboratory diagnosis of Glanzmann thrombasthenia.

Test	In cases with Glanzmann Thrombasthenia
Bleeding Time	Prolonged
Aggregation of platelets in response to physiologic agents (Adrenalin, Thrombin)	Failure
Platelet Count	Within reference range
Platelet Morphology	Normal
Prothrombin Time and Activated Partial Thromboplastin Time	Within reference range
Urinanalysis	Proteineuria and microscopic hematuria
Sodium Dodecyl Sulfate – polyacrylamide gel electrophoresis of radiolabeled platelet proteins	Absence of GP IIb/IIIa

patient's condition. Individuals with Type 2 GT have only 10 to 20% of the normal amount of GP IIb/IIIa that can bind to fibrinogen resulting in a moderately deficient clot retraction capability. One other form of GT is a variant type having greater than 50% of the normal amount of GP IIb/IIIa resulting in extremely variable fibrinogen binding and clot retraction. The probability of death among GT patients of all types is estimated at the range of 5 to 12.8%.

Previous reports and clinical management of this disorder presented only palliative measures of treatment without using hemostatic agents. These agents are not considered because of the complex nature of the disease involving both quantitative and qualitative defects.[4] However, desmopressin (DDAVP) was successfully used following a dental procedure in one person but its use is not routinely recommended.[8,9] Refractory bleeding in individuals with GT requires the transfusion of normal platelets, and the use of human leucocyte antigen-matched platelets to prevent alloimmunization complications is recommended.[10] The last resort in these patients and those who have developed alloimmunization with autoantibodies include bone marrow transplants and administration of the recombinant factor VIIa.9 Patients who had undergone these treatment modalities effectively recovered and more research into these treatment strategies is underway.

Pretreatment consultation with a hematologist and platelet transfusion is often necessary in GT patients prior to surgical or dental procedures and childbirth.[12] In the present case a complete-mouth dental prophylaxis and oral hygiene instructions along with a platelet transfusion were provided and after eight months the gingival bleeding was minimized. The patient was able to use an atraumatic soft bristle brush as an adjunct to the treatment performed. Anti-plaque agents like 0.12% chlorhexidine and toothpaste were prescribed and were found to be helpful in controlling plaque accumulation. The problem of tooth staining from chlorhexidine was managed with regular use of ultrasonic scalers and polishing with rubber cups.

It is recommended all medications that might increase the risk of bleeding should be avoided. The most important part of patient management is making them and their relatives aware of the nature of disease, the importance of preventive measures, and the need for medical as well as dental consultations at appropriate intervals.

Summary

Periodontal management of a patient with a rare hematological disorder, GT, is presented. A pronounced improvement in the periodontal condition of a GT patient occurred following routine scaling and polishing procedures along with proper oral hygiene maintenance instructions. The result was a reduction of the patient's gingivitis and associated spontaneous bleeding and an improvement in her hemoglobin status.

Clinical Significance

GT should be considered in the differential diagnosis of conditions with severe bleeding from mucous membranes. Studies[1,4,12] report the most difficult bleeds to correct are those from mucosa of the oral cavity and nose. Rarely are deeper gastrointestinal hemorrhages reported. Any dental procedure performed in these patients should be preceded by hematological consultation. Proper follow up is considered to be an essential part in these cases. Patients as well as relatives should be made aware of the importance of oral hygiene measures as well as simple tips in preventing the occurrence of bleeding episodes.

References

1. French DL, Coller BS. Hematologically important mutations; Glanzmann Thrombasthenia: Blood cells, molecules and diseases. 1997; 23:39-51.
2. Toygar HU, Guzeldemir E. Excessive gingival bleeding in two patients with glanzmann thrombasthenia. J Periodontol. 2007; 78:1154-1158.
3. Green M E: Thrombasthenia: Article on e – medicine: Internet resource: www.emedicine.com
4. Bisch FC, Bowen KJ, Hanson BS, Kudryk VL, Billman MA. Dental considerations for a Glanzmann thrombasthenia patient – Case report: J Periodontol. 1996; 67:536-540.
5. Kantarci A, Cebeci J, Firatli E, Atamer T, Tuncer O. Periodontal management of Glanzmann's thrombasthenia – Report of 3 cases. J Periodontol. 1996; 67:816-820.
6. Newman PJ, Ponez M. Inherited disorders of platelets: In Scriver C R, Beandet, William S S editors: Molecular and metabolic basis of disease: McGram & Hill Inc: 1995; 3335-3358.
7. GR Lee, J Foerster, J Lukens, F Paraskevas, JP. Wintrobe's clinical hematology: 10th ed: Philadelphia: Williams & Wilkins: 1999.
8. Lombardo VT, Sottilota G. Recombinant activated factor VII combined with desmopressin in preventing bleeding from dental extraction in a patient with Glanzmann's thrombasthenia. Clin Appl Thromb Hemost. 2006; 12:115-6.
9. Kobrinsky NL, Israels ED, Bickis MG. Synergestic shortening of the bleeding time by desmopressin and ethamsylate in patients with various constitutional bleeding disorders: Am J Pediatric Hemato Oncol. 1991; 13:437-441.
10. Sniecinski, MR O'Donnell, B Nowicki, LR Hill. Prevention of refractoriness and HLA – alloimmunization using filtered blood products: Blood. 1998; 71:1402-1407.
11. MC Poon, C Demers, F Jobin, JW Wu. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia: Blood. 1999; 94:3951-3953.
12. Glanzmann Thrombasthenia: Internet resource from Glanzmann foundation: www.glanzmann.org.

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