Glanzmann's Thrombasthenia: A Rare Cause of Recurrent Profuse Epistaxis

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Abstract Though epistaxis is a commonplace emergency encountered in the Otorhinolaryngology clinic, recurrent, severe and intractable cases are relatively less common. In those cases where no local causes are found that could explain such episodes, systemic causes, including hematological disorders should be considered, and thoroughly explored. However, routine hematological investigations often fail to identify a definite cause. Here we report about a 23 year-old woman presenting with severe recurrent epistaxis due to Glanzmann's thrombasthenia—a rare, autosomal recessive disease. Never before Glanzmann's thrombasthenia has been reported to present with severe epistaxis as its sole feature.

Keywords Epistaxis · Glanzmann's thrombasthenia · Platelet aggregation defect

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Introduction

Epistaxis is a commonplace entity encountered in the Otorhinolaryngology clinics. However, recurrent epistaxis in an otherwise asymptomatic adult is not seen frequently, necessitating detailed investigations for finding out the probable etiology. In this report, a rare hematological disorder causing recurrent epistaxis in a young adult female is presented.

Case Report

A 23 year-old housewife, a mother of two, visited the Otorhinolaryngology emergency of a tertiary referral hospital with profuse, sudden onset nose-bleed, with no history of antecedent trauma. Her vitals were stable, though she looked pale. She was urgently admitted and an attempt was made to control the bleeding with framecycin-soaked Merocel sponges. Though the severity of the bleeding decreased, steady oozing continued around the edges of the sponges along with trickling from the nasopharynx. We replaced them after 24 h of observation with antibiotic-soaked gauze packs. Apart from a low hemoglobin (6 gm %), her routine investigations were inconspicuous. Two units of packed cells were transfused, and she was put on parenteral hemostatic drugs and antibiotics.

However, following removal of pack after 48 h, she started to re-bleed, this time more profusely, and required a posterior nasal space pack for its control in addition to a more securely inserted fresh anterior nasal pack. Similar episodes of removal of nasal pack were followed by bleeding, and thereby required further packing. This occurred four times during her stay in the hospital, with few bleeding-free days intervening in between these

episodes. Detailed history revealed several events of similar spontaneous, non-traumatic recurrent epistaxis, necessitating hospital admission, four times during the last 3 years.

The severe, unrelenting epistaxis continually hampered our efforts to ascertain its cause as every episode of nasal pack removal was followed by a fresh bleed necessitating repacking. Once she had a bleeding-free period of about 5 days, a battery of diagnostic tests was scheduled. On anterior rhinoscopy and nasal endoscopy, neither any focal bleeder nor any mass lesion (with or without ulceration or proliferation) could be seen. However, there was widespread raw nasal mucosa. X-ray (occipitomeatal view) and CT scan of nose and paranasal sinuses also failed to reveal any mass lesion. With no definite bleeder, attempts to cauterize the more active oozing points were done with bipolar hemostatic forceps but without success, as the patient started to re-bleed a day later.

The results of the proceedings till now prompted us to focus our search for systemic secondary causes, especially the hematological factors. Prior to the first episode of epistaxis 3 years back, she did not have any instance of unnatural bleed in terms of duration or severity. However, successive investigations (Tables 1 and 2) pointed the diagnosis more in favor of thrombasthenia. There were mucocutaneous bleed (recurrent epistaxis, menorrhagia) with pallor, normal platelet count and morphology and positive platelet aggregation test. Putting these together, along with the fact that the clotting time (CT) and bleeding time (BT) were within normal limits with no features of coagulation defects and vascular and platelet abnormalities, the diagnosis of Glanzmann's thrombasthenia was certain.

Further management of the patient was now directed in addressing this rare hematological disorder. 5 Units of platelet were transfused, along with other supportive

Table 1 Search for systemic secondary causes of the bleeding episodes

Investigations	Findings
Routine investigations (including bleeding time, clotting time)	Within normal limits
Liver & renal function tests	Within normal limits
History of associated comorbidities (diabetes mellitus, hypertension)	Nil
Family history of similar bleed	Similar episodes of epistaxis in her brother, but details unavailable
Menstrual history	Irregular menorrhagic episodes for the last 4–5 years
Addiction (smoking, alcohol)	Nil
Intake of implicating drugs (NSAIDs, nasal steroid spray, antiplatelet agents etc.)	Nil

NSAID non-steroidal anti-inflammatory drug

Table 2 Search for hematological factors

Investigations	Findings	Inference
Family history of similar bleed	Similar episodes of epistaxis in her brother, but details unavailable	Inconclusive
Previous history of similar bleed	Epistaxis four times in the last 3 years, irregular menorrhagic episodes for the last 4–5 years	Suggestive
Physical examination	Severe pallor, no petechial spots, no 3rd space collection, no signs/history of easy bruisability	Vascular defects and/or coagulation factor abnormalities seem unlikely
Routine hematological investigations	Bleeding time & clotting time, platelet count and morphology within normal limits	
aPTT, PT, TT, Factor XIII assay (clot stability test in urea)	Values within normal limits	Coagulopathy ruled out
Platelet aggregation tests	No aggregation with natural platelet agonists (ADP, collagen, amino acids), 39% aggregation with ristocetin	Positive platelet aggregation test (thrombasthenia very likely)

aPTT activated partial thromboplastin time

PT prothrombin time

TT thrombin time

ADP adenosine diphosphate

measures. The patient and her relatives were counseled, and special emphasis was given over the fact that there is no definite curative treatment for this disease.

With time, our patient recuperated, and, before discharge, was advised to visit the Hematology clinic for further course of action. Till date, for the last 5 months, she has been reported to do well without any recurrence of epistaxis.

Discussion

Management of epistaxis, the commonest nasal emergency requiring admission [1], constitutes a great deal of workload in the Otorhinolaryngology department. Most, however, being self-limiting, do not warrant detailed examination for finding out the etiology. Also, ~70–80% are idiopathic, with no discernable cause even after an extensive search [2].

However, recurrent epistaxis requiring aggressive management everytime due to its severity, certainly mandates a detailed investigation. Most studies regarding recurrent epistaxis have been centered on elderly patients, where atherosclerosis and other age-related causes, associated with hypertension, are mostly implicated. But similar events in a young female without any associated comorbidities, and the gravity of the nosebleed being such that she had been rendered anemic, demand special attention.

Hematological diseases are rare causes of recurrent epistaxis. Among the vascular causes, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) deserves special mention. Inherited blood dyscrasias causing epistaxis is mostly caused by von Willebrand disease (vWD), though others, like Hemophilia and coagulopathies are also responsible [3, 4]. These are usually reflected in the hematological assessments including BT, CT, activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), platelet count and morphology, and, if required, individual coagulation factor assay. All these were essentially within acceptable limits in our patient, and are distinctively so in a picture that resembles thrombasthenia. The diagnosis is confirmed by the typical characteristics of bleeding that our patient had, along with the platelet aggregation reports, and can be further verified by platelet receptor assay through flowcytometry.

Glanzmann's thrombasthenia (GT), an extremely rare hematological disorder of platelet aggregation with an incidence of one in a million <http://www.frca.co.ukdocumentsGlanzmannThrombasthenia.pdf.pdf>, is an autosomal recessive disorder (chromosome 17). Defective platelet receptors GpIIb/IIIa cause impaired platelet aggregation, thereby increasing bleeding tendencies. This disorder

affects the megakaryocyte lineage, where platelet glycoprotein receptors IIb/IIIa, remaining as α IIb β 3 integrin family in the cell surface, and being responsible for platelet incorporation into the developing thrombus at the site of vessel injury, are quantitatively/qualitatively defective [5, 6, <http://www.frca.co.ukdocumentsGlanzmannThrombasthenia.pdf.pdf>]. This causes poor thrombogenesis and clot retraction. These platelets fail to aggregate with natural agonists e.g., adenosine diphosphate (ADP), collagen, thrombin, epinephrine and amino acids, but show aggregation with ristocetin [7], reflecting normal levels of plasma von Willebrand factor and surface glycoprotein Ib/IX. Depending upon the IIb/IIIa receptor levels, GT can be either type 1 (severe; <5%), type 2 (less severe; 10–20%), or type 3 (normal levels, but functionally inactive) <http://www.frca.co.ukdocumentsGlanzmannThrombasthenia.pdf.pdf>. However, this does not correlate with disease severity.

Though symptomatology of GT mostly initiate in childhood with equal sex predilection, one pioneering study in Paris [8] has recently shown almost a 3:2 female preponderance, with the average age of diagnosis at 20. Our patient was a 23 year-old female and her first episode of epistaxis was indeed at age 20.

Bleeding manifestations are generally mucosal - epistaxis, purpura, gingival bleed and menorrhagia [9, 10], with epistaxis often being severe [11]. However, bleeding episodes, unless complicated by trauma or malignancy, are rarely fatal; rather, with age it decreases. Our patient presented with recurrent severe epistaxis that was controlled with great difficulty. She also had menorrhagia. A normal coagulation profile ruled out bleeding diatheses involving coagulation factor deficiency, including vWD. The normal BT and platelet picture excluded vascular disorders and thrombocytopenia, respectively. The platelet adhesion defect comparable to GT, i.e., the Bernard-Soulier syndrome, can also be easily overlooked in a setting of ristocetin-induced aggregation and normal platelet count and morphology. In fact, GT is the only disorder where platelet aggregation is absent to all natural agonists [11].

Mucocutaneous bleeding and the characteristic platelet aggregation behavior are pathognomonic of GT [9], and these, along with the normal platelet count and morphology, provide a clear-cut diagnostic picture [11]. Our patient fulfilled all essential criteria required for diagnosis. However, assay for platelet α IIb β 3 integrin can be carried out, especially in a newly diagnosed patient, with monoclonal antibodies and flowcytometry [12, 13].

Apart from the symptomatic management (nasal packing for epistaxis, oral contraceptive pills for menorrhagia, and local application of fibrin sealants and thrombin), the mainstay of management is repeated platelet transfusions [7]. However, repeated packing may initiate a vicious cycle by irritating the nasal mucosa and causing rebleeding

<http://www.frca.co.ukdocumentsGlanzmannThrombasthenia.pdf.pdf> (as seen in our patient). Also, repeated platelet transfusions ultimately result in alloimmunisation by the production of anti-GpIIb/IIIa antibodies [8, 9].

Recently, successful use of recombinant factor VIIa (NovoSeven®; Novo Nordisk A/S, Malov, Denmark) offers an alternative approach to early hemostasis, especially for patients with antibodies and/or a history of refractoriness to transfusion [14]. Other treatment modalities include desmopressin (DDAVP) <http://www.frca.co.ukdocumentsGlanzmannThrombasthenia.pdf.pdf>. In extreme conditions, allogeneic bone marrow transplants have also been performed on 2 patients till date <http://www.frca.co.ukdocumentsGlanzmannThrombasthenia.pdf.pdf>. However, with appropriate supportive care, patients of GT have an excellent prognosis¹² [11], and most have been reported to have minimal impact on the quality of their daily lives.

Summary

- Incidents of recurrent intractable bleeding are relatively rare, and search for a cause in such cases should always be carried out.
- Absence of a local etiology should prompt a more cautious but extensive look into the systemic causes, keeping a low threshold of suspicion.
- Hematological disorders form one of the chief causes of recurrent, intractable epistaxis. However, routine hematological investigations often fail to identify such a cause, necessitating specialized investigations.
- Glanzmann's thrombasthenia, an autosomal recessive inherited hematological disorder, is an exceptionally rare cause of recurrent epistaxis.
- Glanzmann's thrombasthenia presenting solely as recurrent severe epistaxis has also not been reported earlier.

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Conflict of interest None

References

1. Juselius H (1974) Epistaxis, a clinical study of 1,724 patients. *J Laryngol Otol* 88:317–327
2. Stell PM (1977) Epistaxis. *Clin Otolaryngol* 2:263–273
3. Katsanis E, Luke K, Hsu E (1988) Prevalance and significance of mild bleeding disorders in children with recurrent epistaxis. *J Pediatr* 113:73–76
4. Tami TA, Merrell JA (2009) Epistaxis. In: Snow JB Jr, Wackym PA (eds) *Ballenger's otorhinolaryngology head and neck surgery*, 17th edn. BC Decker Inc., People's Medical Publishing House. Ch 44. p 551
5. Kunicki TJ, Pidard D, Rosa JP, Nurden AT (1981) The formation of Ca^{2+} -dependent complexes of platelet membrane glycoproteins IIb and IIIa in solution as determined by crossed immunoelectrophoresis. *Blood* 58:268
6. Hynes RO (1992) Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 69:11
7. Handin RI. Disorders of the platelet and vessel wall. In: Kasper LD et al (eds) *Harrison's principles of internal medicine*, 16th edn. McGraw-Hill. Ch 101 p 678
8. George JN, Caen JP, Nurden AT (1990) Glanzmann's thrombasthenia: the spectrum of clinical disease. *Blood* 75:1383
9. Nurden AT, George JN (2005) Inherited abnormalities of the platelet membrane: Glanzmann's thrombasthenia, Bernard-Soulier syndrome, and other disorders. In: Colman et al. (eds) *Hemostasis and thrombosis, basic principles and clinical practice*, 4th edn. Lippincott Williams & Wilkins, Philadelphia (in press)
10. Bellucci S, Caen J (2002) Molecular basis of Glanzmann's thrombasthenia and current strategies in treatment. *Blood Rev* 16:193
11. Nurden AT (2006) Glanzmann thrombasthenia. *Orphanet J Rare Dis* 1:10. doi:10.1186/1750-1172-1-10
12. Wilcox DA, Wauthier JL, Pidard D, Newman PJ (1994) A single amino acid substitution flanking the fourth calcium binding domain of α IIb prevents maturation of the α IIb β 3 complex. *J Biol Chem* 269:4450
13. Ruiz C, Liu CY, Sun WH et al (2001) A point mutation in the cysteine-rich domain of glycoprotein (GP) IIIa results in the expression of a GPIIb-IIIa (α IIb β 3) integrin receptor locked in a high affinity state and a Glanzmann thrombasthenia-like phenotype. *Blood* 98:2432
14. Poon MC, D'Oiron R, Von Depka M et al (2004) Prophylactic and therapeutic factor VIIa administration to patients with Glanzmann thrombasthenia: results of an international survey. *J Thromb Haemost* 2:1096