von Willebrand Disease Revealed after Dental Post-extractional Bleeding: A Case Report
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Abstract:
A persistent post-extractional bleeding in an apparently healthy patient must warn dentists about a possible bleeding diathesis such as misdiagnosed von Willebrand disease (vWD), hemophilia A, and hemophilia C. Mild type of vWD and mild hemophilia A can be diagnosed in women with menorrhagia, in persons with excessive mucocutaneous bleeding such as bruising without recognized trauma, in persons with recurrent nose bleeds and prolonged oral cavity bleeding including gingivorragia after brushing or flossing teeth or dental cleaning or extractions, and in persons with persistent post-extractional bleeding. Dentists have indeed a primordial role in the management of post-extractional bleeding complications related to these diseases and in the orientation of patient to a specialized medical center for further investigations and management. In this study, a case of mild vWD was diagnosed after persistent post-extractional bleeding of the right second maxillary molar, on a 43-year-old patient without medical or bleeding history. Extraction of 17 was performed and 24 h later persistent bleeding was noted. Ruling out local causes by clinical examination and periapical radiograph, a complete blood screening including complete blood count, platelets count, bleeding time, prothrombin time (PT), and cephalin kaolin clotting time (CKCT) was performed to evaluate the primary hemostasis and coagulation. Prolonged CKCT (46.30 s) and normal PT (14 s) illustrated a disorder function of intrinsic coagulation pathway including Factors VIII, IX, and XI. Factors VIII and IX had normal values. Further laboratory investigations of Ag von Willebrand factor and its ristocetin cofactor activity permitted the diagnosis of vWD.

Key Words: Bleeding, hemophilia A, hemophilia C, post-extractional, von Willebrand

Introduction
The post-extractional hemorrhagic risk in a healthy patient with no documented medical history is rare. When local etiology of post-extractional persistent bleeding and consumption of anticoagulant or antiplatelet medicine are ruled out, a screening of the coagulation is recommended. Further investigations and appropriate laboratory tests must be done to screen hemostasis factors and function. Hemostasis disorders were described in von Willebrand disease (vWD), hemophilia A, B, and C.

vWD may cause excessive or extended bleeding. This condition is often inherited as an autosomal dominant trait, but may develop in adult life, in rare cases. It is the most common of inherited bleeding disorders affecting an estimated prevalence of 0.1 to 1% in the population worldwide. vWD is associated with mutations on chromosome 12 in the region p13.2, encoding the von Willebrand factor (vWF), which is synthesized in endothelial cells and megakaryocytes. vWF aids in the adhesion of platelets at a site of bleeding, and it also binds to Factor VIII acting as a transport molecule.

The current International Society on Thrombosis and Hemostasis Scientific and Standardization Committee classified vWD into three subtypes:
- Type 1 - vWD is a partial quantitative deficiency of essentially normal vWF: It affects 85% of patients
- Type 2 - vWD is a qualitative deficiency and defective vWF (further subdivided into Types 2A, 2B, 2M, and 2N)
- Type 3 - vWD is a virtually complete quantitative deficiency of vWF and mostly diagnosed in childhood.

Clinical expression of vWD is usually mild in Type 1, increasing in severity in Types 2 and 3. However, mild vWD may be clinically insignificant and misdiagnosed.

Mild type of vWD can be diagnosed in women with menorrhagia, in persons with excessive mucocutaneous bleeding such as bruising without recognized trauma, and in persons with recurrent nose bleeds and prolonged oral cavity bleeding including gingivorragia after brushing or flossing teeth or dental cleaning or extractions.

Hemophilia represents a variety of bleeding disorders associated with a genetic deficiency of any one of the following clotting factors: Factor VIII (hemophilia A), Factor IX (hemophilia B), and Factor XI (hemophilia C).

Hemophilia A is the most significant and widely recognized form of hemophilia. It accounts for 80% to 85% of bleeding diatheses associated with a specific clotting factor deficiency.
being transmitted in an X-linked pattern. Females typically carry the trait, but it is expressed primarily in males. Approximately 1 in 8,000 to 10,000 males is born with this genetic disease. It is a heterogeneous disorder that is caused by any one of a variety of mutations associated with the gene for Factor VIII. It can be severe, moderate, and mild. The moderate and mild types can be diagnosed in adults either after persistent post-extractional bleeding or in women after menorrhagia.

Hemophilia B or Christmas disease is similar to hemophilia A in its presentation, being transmitted in an X-linked fashion. It is much less common than hemophilia A, occurring with a prevalence of 1 in 50,000.

Hemophilia C or Rosenthal syndrome is a hemostatic plasma glycoprotein which circulates as a serine protease zymogen of activated Factor XI. It is essential for the generation of thrombin during coagulation. Factor XI deficiency is one of the most frequent genetic disorders in Ashkenazi Jews (it affects 8% of them). Unlike hemophilia, Factor XI deficiency is rarely manifested as spontaneous bleeding; the associated bleeding usually occurs after trauma, surgery, or other challenges to hemostasis.

In this study, a case of prolonged bleeding after a dental extraction (maxillary second right molar) in an apparently healthy patient conducting after appropriate laboratory tests, to the diagnosis of vWD is reported.

**Case Report**

A 43-year-old male patient consulted us for full mouth rehabilitation. His medical observation revealed a scar resulting from trauma in 2003, on the right frontal region, and in 2006, on the forearm following an occupational accident by the grinder. He did not report any abnormal bleeding complication during and after these two accidents.

Orofacial history revealed multiple extractions. In 2009, mild bleeding for 24 h after extraction of 24 and 36 was noticed, these bleeding episodes resolved without any treatment.

Our treatment plan involved extraction of 17, 45, and 48. The periapical radiograph showed a radiolucency image at furcation of 17 (Figure 1).

Second maxillary right molar was extracted under periapical analgesia (scandicain special 2% with epinephrine 1:100,000) and the patient left our dental surgery with a controlled bleeding.

On the 3rd day, the patient presented with the same clinical situation with an overlapped clot covering adjacent teeth and impression of the antagonist was noticed (Figure 3).

Elimination of the clot was done, and results of blood tests showed the followings:
- PC 266 000 G/mm$^3$ and BT (with Duke Method) 1’ 45” which are normal values.
- PT was 14 s and witness time 11 s. CKCT was 46.30 s. He had a prolonged CKCT and normal PT which illustrated a disorder function of intrinsic coagulation pathway including Factors VIII, IX, and Factor XI.

The patient was referred to a hematologist to explore coagulation factors and to diagnose a possible blood diathesis responsible of this coagulation disorder. The hematologist
asked for liver screening factors, creatinine, and Factor VIII. Furthermore, Etamsylate (Dicynone® 500 mg tablets, 1 tablet each 8 h for 1 week), an antihemorrhage drug capable of reducing BT, was prescribed.

On 7th post-operative day, bleeding persisted and the hematologist, after the normal result of liver factors and creatinine, suspected a local factor and referred the patient to an oral maxillofacial surgeon who performed bone compression on the alveolar socket and filled the socket with gauzes, then sutured wound edges.

At 9th post-operative day, a cone beam computed tomography of the extracted site was performed, and it showed a fracture of the buccal cortex (Figure 4), which was surgically removed.

Then, the hematologist prescribed a desmopressin spray (Minirin® inhaler), which induced liberation of stock form of vWF. Moreover, for the first time, bleeding was controlled for 48 h.

On 11th post-operative day, the patient presented again the extra-alveolar clot and at that time, a platelet transfusion of 7 units was administrated with per-os iron.

Meanwhile, the dosage of Factor VIII showed normal value (83%). Hemophilia A was ruled out due to lack of deficiency of Factor VIII. Further investigations were done on Ag vWF and ristocetin cofactor (RCO).

On 15th post-operative day, the extra-alveolar clot of firm consistency was eliminated. The therapeutic protocol was established including hospitalization for 5-7 days with a transfusion of platelet factors on a daily basis till achievement of a complete coagulation, and a minor surgery at the 1st day to eliminate the clot and suture wound edges were provided. Bleeding was controlled at day 17, and we did not need to install this protocol.

Ag of vWF and RCO activity permitted the diagnosis of vWD. Follow-up of the site after 3 months (Figure 5).

**Discussion**

In the dental office, some systemic diseases cannot be identified by medical questionnaire and observation due to the lack of clinical symptoms and signs. Some of these diseases can be associated with bleeding or immunity disorders. 

Persistent bleeding after tooth extraction can be due to a local complication like non-respect of the post-extraction recommendations (mouth rinses abstention, elimination of clot by aspiration,...), bone fracture, persistence of residual root,... In most cases, history of hemorrhage, clinical examination, and periapical radiograph are sufficient to rule out these etiologies. 

When these local etiologies were ruled out, the use of local hemostasis agents such as collagen, oxidized regenerated cellulose, and hemostatic sponge with sutures and/or associated with local compression using gauze moistened with tranexamic acid or etamsylate or a splint, which ensure sustained compression.

When local agents and means fail to control post-extractional hemorrhage, a systemic disease with bleeding diathesis must be considered. The most frequently diagnosed diseases after persistent post-extractional bleeding are mild vWD, mild hemophilia A, and hemophilia C.

vWD is the most common hereditary clotting disorder that features defects of the three components of hemostasis (capillaries, coagulation mechanism, and platelets). The main defect is the qualitative and quantitative deficiency in the
larger molecule portion of Factor VIII. vWF controls platelet adhesion to subendothelium and regulation of plasma level of Factor VIII coagulation activity; consequently, it is responsible for normal hemostasis.11,17,18,23

Mild von Willebrand type can be diagnosed usually in persons with recurrent nose bleeds and prolonged oral cavity bleeding including gingival bleeding9,14,16,18 after brushing or flossing teeth or dental cleaning or extractions.9,15,18 Whereas mild hemophilia A and hemophilia C are rarely manifested as spontaneous bleeding, the associated bleeding usually occurs after trauma, surgery as a tooth extraction, or other challenges to hemostasis.21 In the present case, the patient had multiple extractions and traumatic accident in the last 10 years without bleeding complication like reported in his medical observation. After extraction of maxillary second molar and uncontrolled post-operative bleeding with local agents and compression, a systemic disease must be suspected, and further investigations are required to rule out mild hemophilia A, mild vWD, and hemophilia C.

The initial investigation done by oral surgeon consisted in a PC, BT, PT, and CKCT.19,20,22,24

PC 266,000 G/mm³ ruled out a quantitative problem like thrombocytopenia or thrombocytosis. The platelet’s functions are evoked by the association with other coagulation tests.

BT is a test of primary hemostasis, and mainly of platelet function in vivo, rather than a laboratory test. It is the best screening for acquired or congenital functional or structural platelet disorder.27,28 In our patient, BT (with Duke Method) was 1’45” which is a normal value.

PT screens extrinsic and common coagulation pathway and is useful for detecting coagulation deficiencies, liver disease, and disseminated intravascular coagulation. Normal range is 10-14 s. This test measures prothrombin but also Factors V, VII, and X. However, CKCT screens intrinsic and common coagulation pathway and depends on contact factors plus Factors VIII, IX, and reactions with Factors X, V, II, and I. Normal range is from 26.0 to 33.5 s (Table 1).27-30

In the present case, PT was 14 s and it was considered abnormal when the gap is more than 50%, compared to witness time (11 s), and CKCT was 46.30 s and it was considered abnormal when the gap is more than 10 s in comparison to witness time. This prolonged CKCT and normal PT and PC which illustrated a disorder function of intrinsic coagulation pathway including Factors IX, VIII, and XI.

Meanwhile, the dosage of Factor VIII was a normal value (83%), and hemophilia A was ruled out due to lack of deficiency of Factor VIII. Further investigations of Ag vWF and RCO activity were needed to confirm vWD.

Before hemostasis disorder was not diagnosed, apparently healthy patient, an extraction can be done. However, after a diagnosed vWD, extraction must be done in a hospital setting. In this case, extraction of 17 was performed, but extraction of 45 and 48 was delayed to be done in hospital after blood test and

Figure 4: Cone beam computed tomography showing fracture of buccal cortical bone.

Figure 5: Healing site 3 months after extraction.
von Willebrand disease revealed after extraction ... Aoun N et al

Table 1: Frequent etiologies of prolonged BT, PT, and CKCT.27

<table>
<thead>
<tr>
<th>Test</th>
<th>Prolonged BT</th>
<th>Prolonged PT (TQ)</th>
<th>Prolonged CKCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent vascular defect</td>
<td>Platelet function defect</td>
<td>Oral anticoagulation therapy</td>
<td>Heparin treatment</td>
</tr>
<tr>
<td>Vascular abnormality</td>
<td>Fibrinogen deficiency</td>
<td>Liver disease</td>
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<tr>
<td>vWD</td>
<td>Vitamin K deficiency</td>
<td>vWD</td>
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<tr>
<td></td>
<td>Prothrombin deficiency</td>
<td>Circulating anticoagulant</td>
<td>Hemophilia</td>
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<td>Massive blood transfusion</td>
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</tbody>
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BT: Bleeding time; PT: Prothrombin time; CKCT: Cephalin kaolin clotting time; vWD: von Willebrand disease

permission of his hematologist. The other dental treatments (crown and restorative dentistry) were executed later on.

Conclusion

Some systemic diseases can be escaped at the medical questionnaire and medical observation in the dental office because of lack of signs and symptoms. Some diseases can be diagnosed after a complication of a simple non-surgical extraction. A persistent bleeding after a tooth extraction always warrants further investigations for systemic coagulation disorders. Mild vWD is mostly diagnosed after this kind of complication. The general dentist must be familiar with these kinds of complications and should manage to refer preferably to specialized centers.

References


