Case report

Acquired hemophilia as a rare cause of excessive bleeding during dentistry: report of two cases and short review

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Abstract

Acquired hemophilia is a rare coagulation disorder that is not diagnosed by routine clinical laboratory tests. Thus, many perioperative or acute emergent bleeding complications remain unclear until the underlying cause is specified. We report two cases of postoperative bleeding in the context of dental surgery in which subsequent acquired hemophilia could be confirmed and present a short review from the literature.

Keywords: *bleeding complications; acquired hemophilia; dental surgery*

Introduction

Acquired hemophilia is a rare clinical entity and has no indication for screening before minor surgery such as tooth extraction. All the more, it can be of high clinical relevance once a complication has occurred. Little is known in the context of silent acquired hemophilia in cases of minor or emergent surgery. We report two cases of dental surgery reflecting such clinical circumstances and classify these throughout the current literature.

Case reports

Case 1

A 39-year-old female patient was admitted to our department following an unexplainable strong bleeding after extraction of a wisdom tooth which could not be controlled locally and by the topical administration of tranexamic acid.

A previous wisdom tooth extraction a few years ago had been uncomplicated, in particular without increased or prolonged bleeding. She had a successful delivery 14 months ago and reported increased postpartum bleeding. In addition, she had noted increased hematoma tendency after delivery. A few days before the consultation, she had also experienced a spontaneous hematoma at the palm without trauma. Fifteen years ago, she had been diagnosed for immune thrombocytopenia with platelet counts between 90.000-100.000/µl, but had not suffered from severe bleeding in this context. She did not have concomitant disease and did not take any regular medication. The family history was unremarkable regarding bleeding events or bleeding disorders.

Physical examination showed an excessive swelling of the left half of the face, a hematoma descending from the facial and mandibular area to the throat and the thorax, and spontaneous hematoma of the forearm (Figure 1). Further physical examination was unremarkable.

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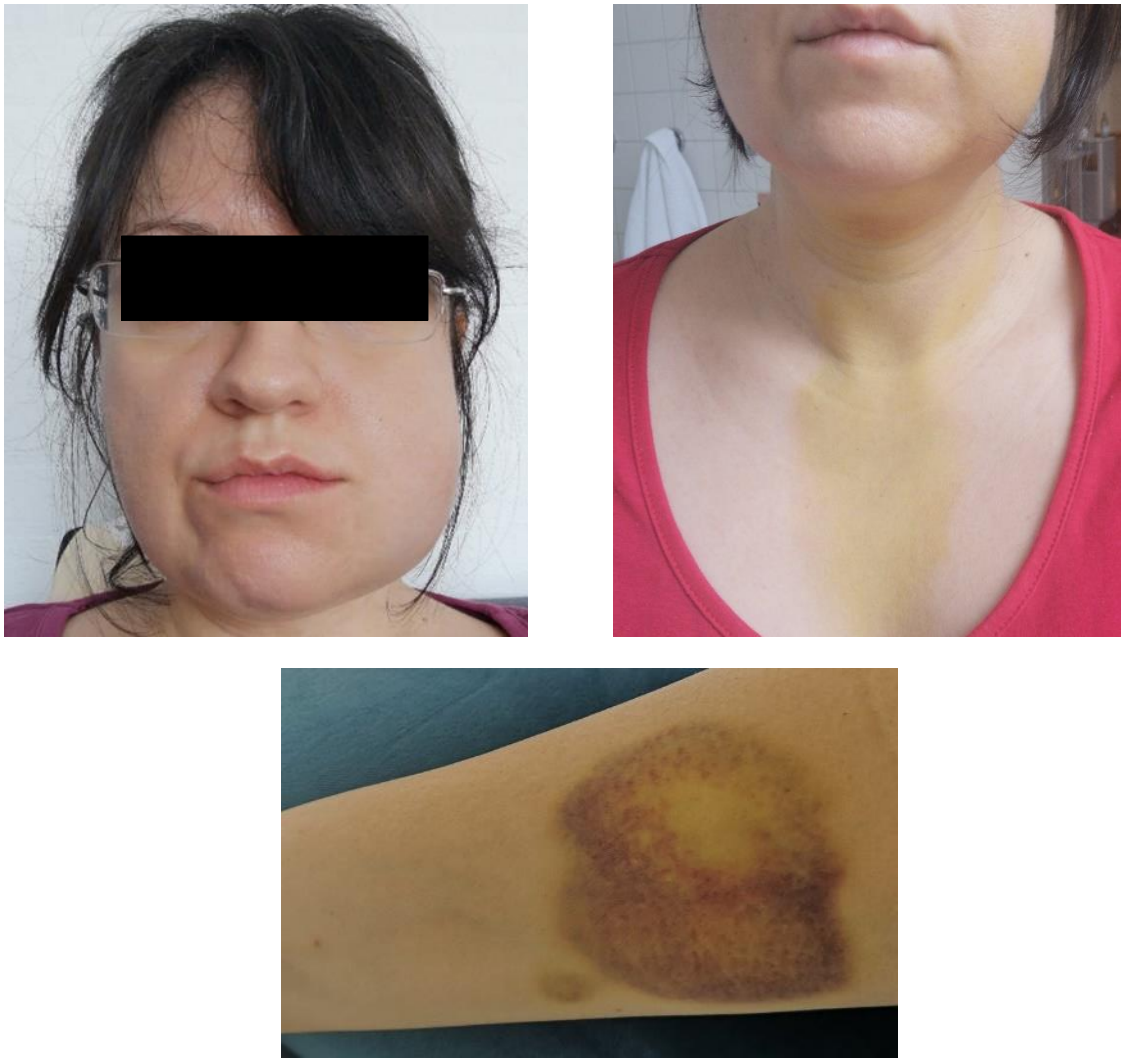

Fig. 1. Clinical signs of bleeding in the presented case. **A**: excessive swelling of the left half of the face; **B**: hematoma; **C**: spontaneous hematoma at the forearm.

In the laboratory examination, a prolonged aPTT of 57 seconds (normal range 25-37 seconds) indicating a defect of plasma hemostasis was detected. Prothrombin time and thrombin time were unremarkable. Further diagnostic work-up showed an underlying reduction of factor VIII activity to 8 % in a clotting assay and 16% in chromogenous assay (normal range 50-150%). Other coagulation factor activities (factors II, V, VII, IX, X, XI, XII, and XIII) were within normal range. In addition, von Willebrand disease could be ruled out (normal activity and concentration of von Willebrand factor). Furthermore, the platelet count was slightly reduced to 113,000/µl (normal range 150,000-400,000/µl) and there was no indication for a platelet function disorder (normal closure times in the platelet function analyzer (PFA), normal platelet aggregation). In the further work-up, plasma mixing studies were highly pathological, indicating the presence of an inhibitor directed against factor VIII. In the Bethesda Assay, an inhibitor titer of 2.1 Bethesda Units was determined. Thus, the diagnosis of acquired hemophilia due to an inhibitor directed against coagulation factor VIII was established.

A steroid treatment with prednisolone 1 mg/kg body weight (absolutely 75 mg daily) was initiated. The patient was advised to cancel a flight planned for holidays and she did so. She was further advised not to take any medication affecting the platelet function and possibly increasing the bleeding risk. Under steroid treatment, the factor VIII activity slowly increased up to normal levels and no other bleeding manifestations occurred. The

prednisolone dosage was slowly tapered (Figure 2). The patient is still under our regular control and now undergoes treatment with cyclophosphamide 100 mg/d and prednisolone 10 mg/d, because the acquired hemophilia turned out to be steroid dependent and did not resolve completely when prednisolone was reduced. In the future, we will try to achieve a steroid-free treatment of the patient.

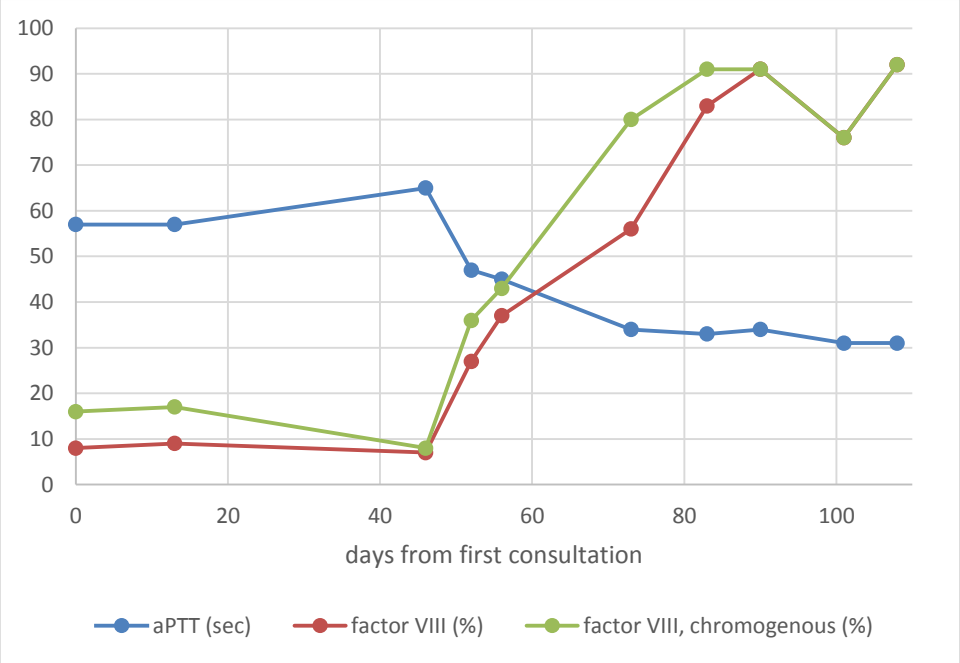

Fig. 2. Factor aPTT and factor VIII activity in two different assays at the patient's first presentation and follow-up.

Case 2

The 31-year-old female patient presented to our department because of a continuous rebleeding over a period of 10-14 days after wisdom tooth extraction. At first presentation two weeks after extraction, the patient was free from bleeding signs after careful sewing and topical administration of tranexamic acid. Other bleeding symptoms were not reported. Previous tooth extractions had been unremarkable regarding bleeding, in addition uncomplicated appendectomy was performed in the previous year. Apart from autoimmune Hashimoto thyroiditis, she had no other known diseases. At first admission, the patient was on regular medication with L-thyroxin for the thyroid disease and also received antibiotic treatment with amoxicillin due to the complication of extraction.

At first presentation in our department, there was no evidence for active bleeding. Rebleeding after tooth extraction had also stopped after local dentistry and careful sewing. Other bleeding symptoms were not present.

Laboratory examination revealed a prolongation of aPTT to 61 seconds (normal range 25-37 seconds), prothrombin time and also thrombin time were within normal range. Further examination showed a reduction of factor VIII activity to 3 % in a clotting assay and to 26% in a chromogenous assay (normal range 50-150%). In plasma mixing studies, an inhibitor against coagulation factor VIII could be detected. Other coagulation tests, in particular activity of other coagulation factors (II, V, VII, IX, X, XI, XII, XIII), von Willebrand parameters and also platelet count and platelet function assays showed normal results, ruling out the presence of other coagulation defects. Based on the laboratory findings, the diagnosis of acquired hemophilia caused by an inhibitor directed against factor VIII was established.

Due to the diagnosis, a planned long-term travel was cancelled. The patient was advised not to take any medication potentially impairing platelet function and, thus, promoting bleeding or increasing the bleeding risk. Corticosteroid treatment with prednisolone 150 mg/d (2 mg/kg bodyweight) was initiated and well tolerated. In addition, tranexamic acid was prescribed in a daily dosage of 1 g three times daily. Two days later, the patient reported mild bleeding symptoms at the site of tooth extraction that stopped spontaneously. Eight days after first presentation, the suture material was removed by the dentist; at this time, the factor VIII activity had been increased to 31 % in the clotting assay. To prevent another rebleeding, we administered 5 mg of recombinant activated factor VIIa (NovoSeven®) once shortly before the intervention. The procedure was uneventful, without rebleeding.

Afterwards, corticosteroid treatment with prednisolone was tapered weekly without reoccurrence of bleeding when the factor VIII activity rapidly normalized (Figure 3). The patient still presents to our department at close intervals to further reduce or adapt the medication.

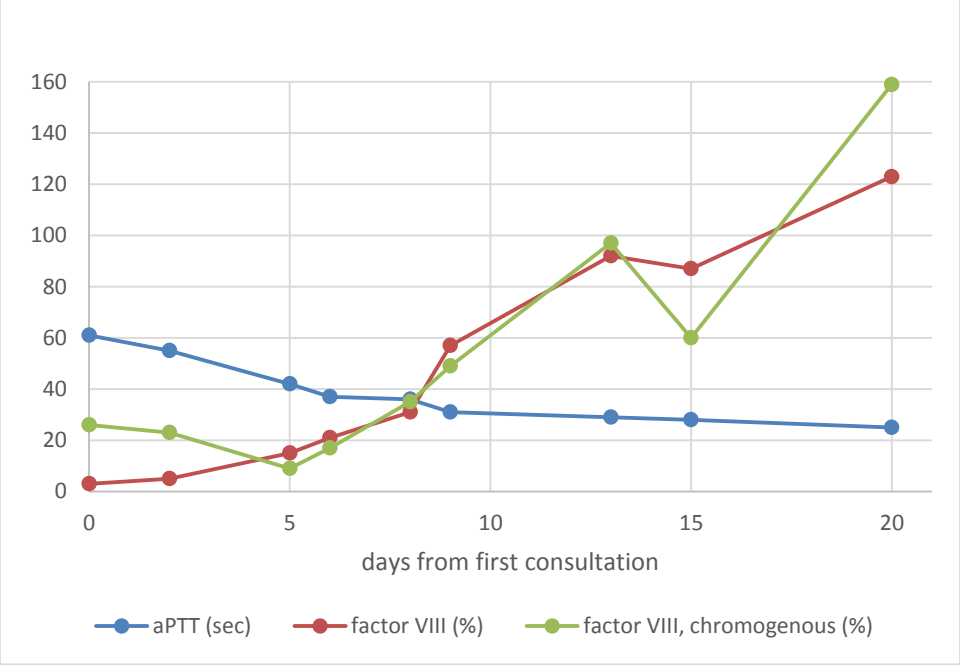

Fig. 3. Factor aPTT and factor VIII activity in two different assays at the patient's first presentation and follow-up.

Discussion

Congenital and acquired bleeding disorders may promote bleeding in patients undergoing dentistry. In this setting, perioperative bleeding has been reported in a large variety of congenital bleeding disorders such as von Willebrand disease, platelet dysfunction and inherited defects of plasma hemostasis such as hemophilia A and B, factor VII deficiency and others. Among acquired defects of hemostasis associated with bleeding in association with dentistry, thrombocytopenia and acquired platelet function disorders are the most commonly reported defects [1, 2].

Here, we present the management of two cases in which a severe and potentially life-threatening acquired bleeding disorder was diagnosed after abnormal bleeding during dentistry. Acquired hemophilia is a very rare clinical disorder associated with spontaneous or provoked bleeding symptoms and increased bleeding risk in surgical procedures. The annual incidence is estimated to be 1:1000.000, but the diagnosis is often missed due to unawareness and, thus, the number of undetected cases is considerably high [3-6].

The disorder is caused by autoantibodies directed against coagulation factor VIII in previously healthy individuals. The disorder can be idiopathic and in more than half of the affected persons, no underlying disorder can be found. In the other affected persons, acquired hemophilia is secondary to an underlying disorder or condition, most commonly solid or hematological malignancy or an autoimmune disease such as systemic lupus erythematosus (SLE) [5]. In the first case we present here, an association with the patient's pregnancy one year prior to diagnosis should be assumed, since bleeding signs were present as peripartum bleeding and thereafter spontaneous hematoma occurred. In the second case, the cause of acquired hemophilia remained so far unclear and idiopathic origin must be assumed.

The diagnosis of an underlying bleeding disorder, including acquired hemophilia, should be considered when relevant spontaneous bleeding symptoms occur for unknown reason. In the reported cases, the involved dentists fortunately initiated further diagnostic work-up, which allowed the diagnosis and adequate treatment of the acquired bleeding disorder. If they would not have reacted adequately, the diagnosis could have been missed and severe bleeding complications up to fatal bleeding could have been developed. This illustrates that awareness of the dentist in this case can be decisive for the further course and the prognosis of the patients.

The diagnosis of acquired hemophilia is established by laboratory coagulation examinations [5]. In general, the occurrence of abnormal spontaneous or induced bleeding may suggest the presence of an underlying inherited or acquired bleeding disorder. In acquired hemophilia, bruising, hematoma, muscle and soft tissue bleeding are the most common bleeding symptoms and are present in approximately 90% of the patients at the time of diagnosis. Bleeding can also occur in the context of surgery or invasive procedures. In our first case, bruising was also present as a bleeding sign. Both cases were, however, diagnosed after unexplainable enhanced or prolonged bleeding following dental procedures.

When the presence of a coagulation defect is suspected, further diagnostic work-up is required. To allow adequate diagnosis and treatment, the patient should be presented to a physician specialized on disorders of hemostasis.

The first step of laboratory diagnosis is the determination of standard coagulation parameters. The typical laboratory finding in acquired hemophilia is an isolated (newly diagnosed) prolongation of the activated partial thromboplastin time (aPTT) with normal prothrombin time (PT) and normal platelet count. In further work-up, factor VIII activity has to be determined and is significantly reduced to less than 40 %, with residual activity below 1 % in 50 % of the cases. It must be stressed that the bleeding tendency or bleeding risk in acquired hemophilia might be underestimated, particularly when factor VIII activity is not strongly reduced; patients with acquired hemophilia may exhibit spontaneous threatening bleeding symptoms when factor VIII activity is only mildly reduced, whereas patients with inherited genetically determined hemophilia nearly only show spontaneous bleeding when the factor VIII activity is lower than 1%. Although reduced factor VIII activity is the key finding in patients with acquired hemophilia, other causes of reduced factor VIII activity such as congenital or genetically determined hemophilia and inherited or acquired von Willebrand disease have to be ruled out. To detect autoantibodies against factor VIII as the characteristic and defining criterion of acquired hemophilia, plasma mixing studies are performed. These assays are based on the inhibition of factor VIII activity in normal plasma by factor VIII inhibitors present in the patient's plasma. The Bethesda assay and also enzyme-linked immunosorbent assays (ELISA) are used to quantify the anti-factor VIII autoantibody by titer determination. Per definition, 1 Bethesda unit (BU) is defined as the antibody titer that neutralizes 50 % of factor VIII in normal plasma after incubation for two hours at a temperature of 37°C [5].

It must be stressed that acquired hemophilia is an important, although rare diagnosis in patients with prolongation of the aPTT. If not only the aPTT, but also the PT is

prolonged, a large variety of defects has to be excluded. If only the aPTT is prolonged, this may be caused not only by the reduction of factor VIII, but also by a deficiency of coagulation factors XII, XI, and IX; moreover, lupus anticoagulants may lead to prolongation of the aPTT, strongly dependent on the lupus-sensitivity of the agent. Other rare cases of isolated aPTT prolongation include a high-molecular-weight kininogen (HMWK) or precallicrein deficiency. Moreover, anticoagulant agents such as direct oral anticoagulants (NOAK) and Vitamin K antagonists (VKA) may lead to aPTT prolongation. In case of isolated aPTT prolongation, laboratory studies should be performed to rule out alternative or additional causes of aPTT prolongation. Since acquired hemophilia occurs as a secondary disorder in concomitance with an underlying disease, diagnostic work-up in affected patients is recommended to exclude underlying disorders such as malignancy and autoimmune disease. The diagnosis of such an underlying disease can significantly influence the therapeutic approach and have an impact on the patient´s prognosis.

Treatment of acquired hemophilia must always address two different aspects: Symptomatic treatment includes the prevention and treatment of the bleeding manifestations. Causal treatment yields towards the elimination of the underlying cause, mainly the treatment of an underlying disorder or condition, and the reduction or, optimally, elimination of the factor VIII inhibitor. Basic measures include symptomatic treatment of bleeding and general care, avoiding procedures that may induce bleeding such as surgery or other invasive procedures, and stopping medication that may aggravate the bleeding manifestations if possible. However, since severe vascular disease requiring antithrombotic treatment or anticoagulation can also be present, careful consideration of the thrombotic or vascular risk of affected patients is also required [5].

The prevention and treatment of potentially life-threatening bleeding manifestations is crucial in the management of patients with acquired hemophilia. It must be stressed that in contrast to inherited hemophilia, factor VIII concentrates are not useful to establish adequate hemostasis since the high titer inhibitors inactivate not only the endogenous factor VIII, leading to acquired hemophilia, but also the substituted factor VIII. To prevent or treat bleeding manifestations in this setting, agents allowing to establish an adequate hemostasis by bypassing the factor VIII dependent coagulation processes are used. These agents include mainly recombinant activated factor VIII (rFVIIa), activated prothrombin complex preparations (APCC), also known as “factor VIII bypassing activity” (FEIBA), and recombinant porcine factor VIII. These agents allow to establish adequate hemostasis even in the absence of factor VIII and are effective in acquired hemophilia in the majority of affected patients [5]. In rare cases, combined treatment and additional therapeutic measures such as immunoadsorption have been used [7].

In the presented cases, bleeding symptoms were only mild and not life-threatening and we decided not to apply these agents on a regular daily basis. However, since potential rebleeding could have occurred, we decided to apply rFVIIa once during removal of the suture material. Antifibrinolytic agents, mainly tranexamic acid, can also be used in acquired hemophilia. Since these agents have a generally good effect on mucosal bleeding as the presenting symptom of both of our patients, we decided to use this antifibrinolytic agent until normalization of the factor VIII activity. A future option for treatment of acquired hemophilia could also be the bispecific antibody emicizumab that allows to achieve adequate hemostasis in the absence of factor VIII. The agent has been approved for the treatment of inherited hemophilia A, and studies regarding its use in patients with acquired hemophilia have been initiated [8, 9].

The second main part of treatment in acquired hemophilia is causal and yields at significant reduction or elimination of the factor VIII inhibitor. Immunosuppressive agents, in particular corticosteroids alone or in combination with cyclophosphamide are most frequently used for the initial treatment. The monoclonal anti-CD20-antibody rituximab is used as second line treatment when the first

line treatment with corticosteroids with or without cyclophosphamide is not effective after six weeks of treatment [5].

In the first case presented, acquired hemophilia was steroid-dependent and factor VIII activity began to drop when corticosteroid dosage was reduced. For this reason and due to side effects of the corticosteroids (weight gain, prediabetic metabolism), we added cyclophosphamide to allow reduction of prednisolone. The second case, however, responded very quickly on corticosteroid treatment and the patient tolerated the treatment very well.

Conclusions

To summarize, we report two rare cases of acquired hemophilia diagnosed after abnormal bleeding following dental procedures. Awareness of the abnormality led the dentists to initiate further diagnostic work-up regarding hemostasis, which allowed adequate treatment in both patients and potentially prevented severe and fatal bleeding complications. Dentists should be aware of bleeding disorders as a cause of abnormal, enhanced or prolonged bleeding during dentistry and, in these cases, refer the patients to a coagulation specialist for further diagnostic work-up and treatment.

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Written informed consent was obtained from the patients for publication of this case report.

Conflicts of interest

The authors declare that they have no competing interests.

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