CASE REPORT

Concomitant hypofibrinogenemia and factor XI deficiency as rare cause of bleeding during urgent dentistry: case report and short review of the literature

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ABSTRACT

Hypofibrinogenemia and Factor XI deficiency are rare defects of hemostasis, potentially leading to spontaneous bleeding manifestations and increased bleeding risk during surgery, dentistry, and interventions. Due to the different mode of inheritance, the concomitance of both defects is extremely rare and the clinical management of combined hypofibrinogenemia and factor XI deficiency is not standardized.

Here, we report a rare case of concomitant genetically determined hypofibrinogenemia and factor XI deficiency as a cause of increased spontaneous bleeding and bleeding complications during dentistry. The diagnostic procedure including screening assays, single clotting factor determinations, genetic analyses, and also use of thrombin generation assays (TGA) are described. Also, we present our considerations regarding the development of an adequate prophylaxis of bleeding with fibrinogen concentrate in this case. The literature regarding the issue is briefly discussed.

KEYWORDS: hypofibrinogenemia; factor XI deficiency; bleeding; dentistry

INTRODUCTION

Inherited and acquired defects of hemostasis are associated with increased spontaneous bleeding and bleeding complications during surgery, dentistry und interventions [1]. In general, disorders of primary hemostasis, leading to disturbed platelet adhesion and/or platelet aggregation, and disorders of secondary hemostasis, associated with reduced fibrin formation and fibrin stabilization must be distinguished. Combined genetically determined defects of hemostasis are very rarely found. The have been also termed "familial multiple coagulation factor deficiencies" (FMCFDs) and belong to the group of orphan diseases due to their very low prevalence [2].

Here, we present the rare case of concomitant genetically determined hypofibrinogenemia and factor XI deficiency associated with bleeding abnormalities and its management during urgent dentistry.

CASE REPORT

A 29-year-old male patient presented to our department for hemostasis evaluation prior to urgent root resection of teeth. After extraction of painful wisdom teeth, he had developed abnormal bleeding which persisted over one week after the dentistry. Other bleeding manifestations were not reported. The family history was remarkable, since two cousins were diagnosed for genetically determined factor XI deficiency and other family members exhibited an abnormal bleeding tendency of unknown cause. The patient was otherwise healthy. There was no regular medication.

Laboratory work-up revealed a prolonged partial thromboplastin time (PTZ) resulting in a quick value of 68 %, whereas activated partial thromboplastin time (aPTT) was unremarkable. As cause of prolonged PTZ a significantly reduced concentration (fibrinogen antigen 0.7 g/l, normal range 1.9–4.3 g/l) and activity of fibrinogen (quick-derived fibrinogen 77 mg/dl, normal range 180-350 mg/dl), fibrinogen Clauss-method 59 mg/dl, normal range 200-400 mg/dl)) were detected. Due to reduced fibrinogen, thrombin time (25.4 seconds, normal range < 17 seconds) and reptilase time (28.4 seconds, normal range < 20 seconds) were prolonged. These findings were compatible with the diagnosis of hypofibrinogenemia. Further standard laboratory, in particular blood count, liver values, renal function parameters and inflammation markers were within normal range.

In addition, we performed further diagnostic work-up and detected a reduced factor XI activity of 55 % (normal range

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65-150 %), compatible with genetically determined factor XI deficiency which had also been diagnosed in other family members of the patient. A factor XI inhibitor as another potential cause of reduced factor XI activity was ruled out by mixing studies. Remarkably, reduction of factor XI activity did not lead to aPTT prolongation (32 seconds, normal range 25-37 seconds) and the defect would have been missed if we would not have determined single clotting factor activities.

Other defects of plasmatic hemostasis and von Willebrand disease were ruled out. Whereas platelet function analyzer (PFA) closure times were unremarkable, aggregometry was significantly abnormal with reduced aggregation after activation with ADP (5 µM), collagen and arachidonic acid, but normal aggregation after Ristocetin (1.5 mg/dl) stimulation. This finding was explained by abnormal platelet aggregation in vitro, not caused by a platelet disorder, but by reduced fibrinogen binding to platelet fibrinogen receptors due to hypofibrinogenemia.

Under suspicion of concomitant genetically determined hypofibrinogenemia and factor XI deficiency, genetic analyses were initiated: Genetic analyses of the factor XI gene including exons and flanking sites showed the heterozygous missense mutation c.802C>T, p.(Arg268Cys) in exon 8. This mutation has previously been described and is associated with factor XI deficiency. In addition, genetic analyses of the fibrinogen FGA, FGB and FGG genes were performed showing the heterozygous missense mutation c.380A>G, p.(Tyr127Cys) in exon 4 of the FGA gene. Although this mutation has not been previously described, further evaluation with the "Polyphen-2 Software" (Polymorphism Phenotyping, http://genetics.bwh.harvard.edu/pph/) indicated causality of this mutation for fibrinogen deficiency. Thus, genetic analyses confirmed the presumptive diagnosis of concomitant genetically determined hypofibrinogenemia and factor XI deficiency.

To develop the best strategy for prophylaxis for dentistry, both defects were individually evaluated regarding their relevance for bleeding:

Factor XI deficiency was only mild according to the residual activity of 55%. However, the lack of association of severity of factor XI deficiency and abnormal bleeding is well known. For further evaluation, we performed a thrombin generation assay (TGA) in platelet-poor plasma and yielded normal results for peak thrombin (227 nM, reference range 43-367 nM) and total thrombin (3.043 nM, reference range 1236-2945 nM), indicating that thrombin generation was not impaired by the clotting factor deficiency. On the contrary, fibrinogen parameters were reduced significantly below the normal range with a fibrinogen concentration of 0.7 g/l and fibrinogen activity of 77 mg/dl and 59 mg/dl determined as quick-derived fibrinogen and fibrinogen determined by the Clauss method. As a consequence of these examinations, we did not assume a relevance of factor XI deficiency for bleeding in this case and decided only to treat hypofibrinogenemia prior to surgery.

At the morning of tooth extraction, we applied a total of 4g fibrinogen concentrate (Haemocomplettan, CSL Behring) which led to a normalization of immunologically determined fibrinogen levels (0.8 g/l and 2.2 g/l before and after substitution, normal range 1.9–4.3 g/l) and fibrinogen activity determined with the Clauss method (61 mg/dl and 171 mg/dl before and after substitution, normal range 200-400 mg/dl) (Figure 1), thrombin time (25 sec and 14.9 sec before and after substitution, respectively, normal range 10.3-16.6 seconds) and reptilase time (26.4 sec and 18.4 sec before and after substitution, respectively, normal range < 20 sec). With this preparation, dentistry was uneventful, particularly without abnormal bleeding. We applied a second dose of totally 2g fibrinogen concentrate on the 4th day after extraction which again led to an adequate raise of immunologically determined fibrinogen concentration (1.6 and 4.3 g/dl before and after substitution, respectively), and function fibrinogen determined with the Clauss method (98 mg/dl and 152 mg/dl before and after substitution), and again to a normalization of the reptilase time (25.1 sec and 19.8 sec before and after substitution, respectively). Relevant laboratory parameter before and after substitutions are summarized in Table 1 and fibrinogen activity before and after substitution are also depicted in Figure 1. The further course was unremarkable without bleeding complications. The procedure was well tolerated without any side-effects.

We recommended consultations in our department in yearly intervals, in case of abnormal bleeding or prior to surgery and dentistry, especially in predictable, i. e. non-urgent cases. The patient was advised not to take medication with inhibiting effect on platelet function to prevent spontaneous bleeding. In addition, we recommended a diagnostic work-up in family members of the patient to exclude the present defects or the combination of both.

DISCUSSION

Coagulation defects are well known as risk factors for spontaneous and provoked abnormal bleeding, particularly in the perioperative setting. Among these defects associated with abnormal bleeding, rare inherited defects and acquired defects, most commonly associated with antithrombotic medication, liver disease or uremia must be distinguished.

Table 1. Relevant laboratory parameters before and after substitution of fibrinogen on the day of dentistry (day 0) and on the 3rd postoperative day (day 3) [TGA thrombin generation assay; n.d. not determined].

Parameter	Reference range	Laboratory before and after fibrinogen substitution (day 0)		Laboratory before and after fibrinogen substitution (day 3)	
fibrinogen (Clauss method)	200-400 mg/dl	61	171	98	152
fibrinogen antigen	1.9-4.3 g/l	0.8	2.2	1.6	4.3
thrombin time	10.3-16.6 sec	25	14.9	23.6	18.5
reptilase time	< 20 sec	26.4	18.4	25.1	19.8
coagulation factor XI	65-150 %	46	n.d.	44	n.d.
peak thrombin (TGA)	43-368 nM	227	135	128	136
total thrombin (TGA)	1236-2945 nM	3043	2659	2538	2617

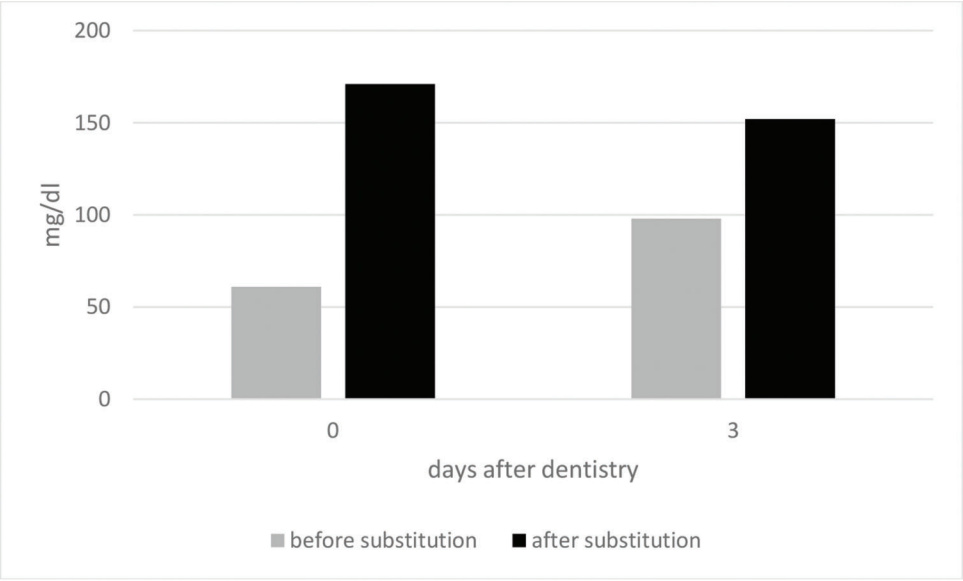

Fig. 1. Fibrinogen activity determined with the Clauss method on the day of dentistry and on the third postoperative day before and after fibrinogen substitution (mg/dl).

Among coagulation disorders, hypofibrinogenemia and factor XI deficiency are very rare bleeding disorders.

Genetically determined hypofibrinogenemia is a rare bleeding disorder characterized by a reduction of functionally active fibrinogen [3,4]. A prevalence of approximately 1:100.000 can be assumed although exact data regarding the frequency of this bleeding disorder are currently not available. The phenotype of congenital fibrinogen disorders is highly heterogeneous. Affected patients may be asymptomatic, show signs of increased or abnormal bleeding, and may even develop thrombotic events in some cases. Whereas bleeding is pathophysiologically caused by inadequate formation of a hemostatic thrombus, thrombosis may be induced by modification of the fibrinogen structure, consequently leading to increased resistance to lysis and altered clot stiffness. Affected individuals may also be asymptomatic and also be detected accidentally by abnormal laboratory findings or exhibit spontaneous or provoked bleeding symptoms. The genes encoding for the three different chains of the fibrinogen molecule are localized on the long arm of chromosome 4 at positions q31.3 (FGA), 4q31.3 (FGB), and 4q32.1(FGG). A variety of mutations leading to hypofibrinogenemia have been identified so far [5]. The diagnosis of hypofibrinogenemia can be established by determination of functional fibrinogen as quick-derived fibrinogen (QD) or, more exactly, fibrinogen determined with the Clauss method, and also immunological determination of fibrinogen concentration. A ratio of functional fibrinogen to fibrinogen antigen levels <0.7 may indicate the presence of dysfibrinogenemia, i.e., disturbed fibrinogen function. Significant reduction of fibrinogen levels is also reflected by a prolongation of the thrombin time (TT), the reptilase time, and, in severe cases also prothrombin time and aPTT. Genetic diagnostic work-up can be performed to identify the underlying defect [5].

Patients with mild hypofibrinogenemia with fibrinogen levels of >1 g/l do normally not exhibit bleeding symptoms. Patients with fibrinogen levels below 1 g/l may have an increased bleeding risk and should receive fibrinogen substitution prior to surgery or major dentistry to raise fibrinogen levels to more than 1 g/dl and, thus, to prevent bleeding. In addition, antifibrinolytic agents may also be used for patients with minor bleeding or minor surgery [3,4].

Factor XI deficiency, also known as hemophilia C or Rosenthal syndrome, was discovered in 1953 in patients with abnormal bleeding following dentistry. It is also a rare coagulation disorder with an autosomal pattern of inheritance and an estimated incidence of 1: 100.000 in the general population, but a high incidence among Ashkenazi Jews of 8-10% has been reported. As an explanation, the prevalence of such rare disorders is increased in populations with high rate of intermarriage. Factor XI deficiency is caused by mutations of the F11 gene which is localized on chromosome 4. In general, factor XI deficiency can lead to reduced thrombin generation, resulting in an abnormal bleeding tendency. However, it has been demonstrated that the residual factor XI activity in affected patients does not well correlate with the presence and severity of bleeding symptoms. In symptomatic patients, soft-tissue bleeding such as epistaxis are the most common spontaneous bleeding symptoms and provoked bleeding due to trauma, surgery or dentistry can also occur. The prolongation of the partial activated thromboplastin time (aPTT) in combination with normal prothrombine time (PT) in the initial diagnostic work-up can in rare cases be caused by factor XI deficiency, but other causes for isolated aPTT prolongation such as factor XII deficiency, hemophilia, or lupus anticoagulant are much more frequently found. Although factor XI concentrates are available, the substitution of factor XI with specific concentrates is limited in Germany due to the low availability of the products. In most cases, affected patients receive only unspecific prophylaxis with antifibrinolytic agents, in severe cases factor XI can be substituted by fresh-frozen plasma, but high volume is needed which may lead to infusion overload [6,7].

The combination of both rare inherited bleeding disorders, hypofibrinogenemia and factor XI deficiency, is very rare. In a series of 82 patients with familiar multiple coagulation

factor deficiencies (FMCFDs), there was only one patient with the combination of these both rare defects [1]. It must be stressed that concomitance of these both defects is not caused by a single genetic defect but by a combination of different genetic defects, one of them leading to factor XI deficiency and one to hypofibrinogenemia.

In the case of concomitant coagulation defects predisposing to bleeding, the management remains a challenge: it has to be decided, whether to apply treatment for one of the defects, for the other, or for both. To allow this, the relevance of both defects and, in particular, their contribution to abnormal bleeding or increased bleeding risk, must be defined. If only one defect is clearly related to bleeding and the impact of the second defect on bleeding is assumed to be low or even neglectable, only the major defect should be addressed therapeutically. If both concomitant defects are of relevance, both have to be considered to prevent bleeding or to minimize the bleeding risk.

In our case, hypofibrinogenemia was regarded as the major risk factor for bleeding and, thus, fibrinogen was substituted prior to major dentistry. In the current guidelines, fibrinogen substitution in hypofibrinogenemia is recommended with a functional fibrinogen below 100 mg/dl and/or an immunologically determined fibrinogen antigen below 1 g/l. The functional relevance of reduced fibrinogen for fibrin formation is also reflected by a prolongation of the thrombin time and the reptilase time in the presented case [3,4].

On the contrary, factor XI deficiency was only mild with a residual activity of 40-50 %. Since factor XI activity of more than 40% is regarded as sufficient for adequate hemostasis, this defect was regarded to be of minor, if any, relevance for bleeding [6,8]. This was also reflected by further analyses showing normal peak thrombin and normal total thrombin in a thrombin generation assay (TGA) in platelet-poor plasma (PPP); TGA can help to clarify if mild coagulation defects have an impact of thrombin generation and, if so, to what extent. Notably, performing TGA in platelet-poor plasma (PPP) of the patient only allows an assessment of coagulation factor deficiencies on thrombin generation, but is not influenced by potential concomitant defects of the platelets, particularly thrombocytopenia or platelet dysfunction. In patients with hemophilia, an association of thrombin generation measured with a TGA, bleeding risk and bleeding severity has been reported and the test has been proposed as additional procedure to allow best care for these patients [9,10]. TGA in platelet-poor plasma was also evaluated as a tool to predict bleeding in patients with factor XI deficiency, but the results were inconsistent: whereas some did not find an association of reduced TGA with bleeding in factor XI deficient patients [11], the assay has been proposed for treatment monitoring in factor XI deficient patients [12,13]. In our opinion, the assay could be useful for additional evaluation in factor XI deficiency since there is a known lack of association between residual clotting factor activity and bleeding phenotype in this rare bleeding disorder.

CONCLUSION

We present a rare case of concomitant genetically determined hypofibrinogenemia and factor XI deficiency. The diagnostic work-up and the clinical management of the patient in elective major dentistry are depicted. We propose TGA as an additional diagnostic tool for the evaluation of the bleeding risk in mild or concomitant coagulation disorders to allow optimized risk assessment and management of respective patients.

Informed consent

Written informed consent for publication was obtained from the patient for publication of the case.

Conflict of interest

The authors declare no conflict of interest in context with this manuscript.

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None.

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