A PATIENT WITH FXII DEFICIENCY, JAK2-MUTATION POSITIVE CHRONIC MYELOPROLIFERATIVE NEOPLASM AND RECURRENT THROMBOEMBOLIC EVENTS

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Introduction and Aim: Factor XII (FXII) deficiency is a rare disorder associated with a prolonged coagulation test (aPTT) indicating bleeding diathesis but without clinically major bleeding tendencies. In opposite to this laboratory finding, it is clinically associated with an increased risk of developing thromboembolic events. The aim of this case report is to present a female patient with severe FXII deficiency, very prolonged aPTT, recurrent thromboembolic events and diagnosis of JAK2-mutation positive chronic myeloproliferative neoplasm (MPN), without hemorrhagic diathesis despite dual anticoagulation and antiaggregation therapy. We also performed review of the literature regarding FXII deficiency, its clinical significance and open questions regarding that rare coagulation disorder. ***Case Report:*** We present a female patient born in 1959, with a history of severe obesity and arterial hypertension, which in 2010 developed deep vein thrombosis (DVT) of the right arm during hormone replacement therapy. Laboratory findings showed prolonged aPTT. Warfarin was introduced into therapy for two years, followed by treatment with acetylsalicylic acid, without hemorrhagic complications. In January 2014, after cholecystectomy she developed pulmonary embolism, DVT of the right leg, with very prolonged aPTT verified again (>150 s), clinically without signs of hemorrhagic diathesis. She was treated with low molecular weight heparin with bridging to warfarin and was referred to a hematologist due to prolonged aPTT. Extended diagnostic workup revealed low activity of FXII (<0.02 KIU/L), elevated activity of FVIII (2.52-3.5 KIU/L) and VWF (VWF:RCo 251%, VWF:Ag 317%). Also JAK2V617F mutation was found indicating chronic MPN, and acetylsalicylic acid therapy was started along with warfarin, and later cytoreductive therapy with hydroxyurea was initiated because of JAK2-mutation positive chronic MPN. During subsequent 4-year follow-up, the patient was without thromboembolic incidents, adequately anticoagulated, without hemorrhagic diathesis despite dual anticoagulation and antiaggregation therapy and permanently prolonged aPTT. ***Conclusion:*** Repeating prolonged aPTT in a person with no signs of bleeding diathesis requires diagnostic workup for the possible lack of contact factors including FXII. The presented patient with acquired and hereditary thrombophilia and recurrent thrombotic incidents has an indication for long term dual anticoagulant and antiaggregation therapy that is well tolerated without bleeding complications.

Key words: FXII deficiency, thromboembolic events, prolonged aPTT, bleeding, myeloproliferative neoplasm

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INTRODUCTION

Factor XII (FXII) is a plasma glycoprotein and clotting factor that participates in coagulation and fibrinolysis, and has a role in inflammatory processes. FXII starts the coagulation cascade and inflammatory processes *via* the intrinsic coagulation pathway and the bradykinin-producing kallikrein-kinin system (1).

Activation of FXII leads to thrombin generation due to a series of proteolytic reactions and plays a role in thrombus formation (2).

FXII deficiency is a rare blood disorder that causes prolonged coagulation test-activated partial thromboplastin time (aPTT) mimicking bleeding diathesis but without the presence of clinically significant bleeding

tendencies. It was first described in 1955. Factor XII is also known as Hageman factor, named after the patient in whom this condition was first diagnosed and who later died due to massive pulmonary embolism after immobility (2-4).

Inherited FXII deficiency is in general an autosomal recessive disorder but FXII deficiency may also be an acquired disorder (4). The incidence of FXII deficiency is approximately 1/1 000 000 individuals (4,5), and the prevalence of moderate and severe FXII deficiency is 1.5%-3% in the general population (6). Factor XII levels are lower in patients of Asian descent (7).

On the other hand, acquired FXII deficiency has been occasionally described in patients with leukemia, nephrotic or antiphospholipid syndrome (8,9).

Chronic myeloproliferative neoplasms (MPNs) include chronic myeloid leukemia, chronic neutrophilic leukemia, polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia not otherwise specified and MPN unclassifiable (MPN-U) (10). They are associated with an acquired thrombophilic state due to abnormalities of MPN-clone derived blood cells and normal vascular cells, which acquire a prothrombotic phenotype and release circulating procoagulant microparticles, as well as acquired activated protein C resistance (11).

JAK2 mutation has been identified in most patients with PV and in about half of patients with PMF and ET, and has been associated with a higher incidence of thrombosis (12-14).

MPNs accompanied with coagulation factor deficiency have rarely been described in the literature. Acquired hemophilia and acquired von Willebrand syndrome with bleeding diathesis in patients with MPN, especially ET, has been reported a few times (15-17), while ET with FXII deficiency has been described in just one case report where the patient presented with severe hemorrhage (9).

In this work, we present the first case report, according to our knowledge, of a patient with JAK2-mutation positive MPN accompanied with severe factor XII deficiency and recurrent thromboembolic events, without any hemorrhagic diathesis. In addition, we performed a review of the literature using PubMED database regarding FXII deficiency, its clinical significance and open questions associated with that rare coagulation disorder.

CASE REPORT

A Caucasian female born in 1959 was referred in December 2014 to a hematologist at the Center for Inherited and Acquired Disorders of Hemostasis, Zagreb University Hospital Center in Zagreb, Croatia, due to prolonged aPTT (>150 s). She had a history of extreme obesity, arterial hypertension and an abortion in the first trimester. Her family history was positive for vascular ischemic stroke (CVI) and malignant diseases (lung cancer), without evidence for bleeding disorders.

In 2010, the patient presented with deep venous thrombosis (DVT) of the right axillary and brachial vein during hormone replacement therapy (HRT). Laboratory testing showed prolonged aPTT. Warfarin therapy was initiated achieving therapeutic INR, followed by treatment with acetylsalicylic acid 100 mg *per* day after two years of warfarin, without hemorrhagic complications.

In January 2014, she underwent cholecystectomy due to acute cholecystitis and received thromboprophylaxis with low molecular weight heparin (LMWH) postoperatively while being in the hospital. Three weeks after discharge from the hospital, she was urgently hospitalized to the intensive care unit due to massive pulmonary embolism, DVT of the right leg, paroxysmal atrial fibrillation and non-sustained ventricular tachycardia. Again, very prolonged aPTT (>150 s) was noted, without hemorrhagic diathesis. She was treated with therapeutic doses of LMWH with bridging to warfarin.

Afterwards, in December 2014, the patient was referred to a hematologist at the Center for Inherited and Acquired Disorders of Hemostasis, Zagreb University Hospital Center and extended diagnostic workup repeatedly revealed a very low activity of FXII (<0.02 KIU/L), elevated activity of FVIII (2.52-3.5 KIU/L) and VWF (VWF:RCo 251%, VWF:Ag 317%). JAK2V617F mutation was found (with low erythropoietin level and periodically with very discrete increase in hemoglobin concentration) indicating JAK2-mutation positive chronic MPN, most likely PV. She did not have splenomegaly on abdominal ultrasound (US) and she refused bone marrow analysis that was suggested to confirm and distinguish the subtype of JAK2-mutation positive chronic MPN. Furthermore, heterozygous polymorphism for the MTHFR gene was confirmed, while polymerase chain reaction (PCR) analysis of Factor V Leiden and FII 20210A showed no alterations. Homocysteine levels were normal, while protein S and C activities were slightly decreased (protein C 52%, protein S 38.6%; the patient was on warfarin at the time of sampling). Chest x-ray and abdominal US were within the normal range. Serum tumor markers were within

the normal range and laboratory tests for antiphospholipid syndrome and other most common autoimmune disorders were completely negative. Acetylsalicylic acid therapy was started along with warfarin after conformation of positive JAK2V617F mutation.

At 5-month follow-up, a slight increase in the red blood cell/hemoglobin/hematocrit, platelet and leukocyte count in peripheral blood was noted, still without splenomegaly, and cytoreductive therapy with hydroxyurea at a daily dose of 500 mg was initiated because of JAK2-mutation positive chronic MPN, most likely PV.

During the next 4-year follow-up, the patient was without thromboembolic incidents, adequately anticoagulated with INR within the therapeutic range, without hemorrhagic diathesis despite dual anticoagulation and antiaggregation therapy and with permanently prolonged aPTT and very low FXII, with normal complete blood count on hydroxyurea therapy and without splenomegaly.

Reversible and irreversible risk factors for thrombosis in this patient are shown in Figure 1.

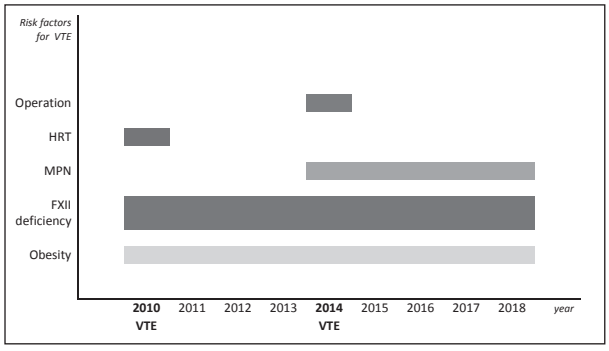

Fig. 1. *Risk factors for VTE*

This figure shows risk factors for our patient with recurring VTE. She had 2 transient risk factors (HRT and operation) while also having FXII deficiency and obesity. Also in 2014 she was diagnosed with MPN which by itself is higly associated with thromboembolic incidents.

DISCUSSION

The association between FXII deficiency and thrombotic disease has always been the subject of interest and discussion. Several studies have shown that FXII deficiency may increase the risk of thrombosis. A study by Lämmle *et al*. suggested that homozygous FXII deficiency may be associated with an increased risk of venous thrombosis, while partial FXII deficiency by itself is not a strong risk factor for thrombosis (18). Another study revealed that half of normal plasma concentration of FXII seemed to be sufficient for vessel-occlusive clot formation (19). A study that investigated the prevalence of venous thrombosis in patients with factor FXII deficiency showed that at the time of thrombosis, other concomitant acquired or congenital prothrombotic conditions were present (20).

Venous thromboembolism is a complex disease related to interactions between both modifiable and non-modifiable risk factors. In our patient, there were several factors of permanent hypercoagulability of the blood, including severe FXII deficiency, repeatedly elevated activity of FVIII and VWF, JAK2-mutation positive MPN accompanied by acquired prothrombotic conditions such as extreme obesity, HRT and surgery (Fig. 1). The cumulative effect of these acquired prothrombotic conditions probably contributed more to the development of venous thromboembolism than the FXII deficiency alone.

Due to acquired and hereditary thrombophilia, recurrent thrombotic events and no bleeding problems, long-term dual anticoagulation and antiaggregation therapy is indicated in our patient.

Coagulation factor XII also has other important roles. It has been associated with hereditary angioedema, where C1-inhibitor deficiency causes uncontrolled proteolytic activity of FXII with excessive bradykinin formation and angioedema (21). The activation of the kallikrein-kinin system *via* FXIIa has also been proven to be involved in various acute and chronic inflammatory conditions such as sepsis or rheumatoid arthritis (22,23). Susceptibility to infections may also be due to reduced neutrophil activation in FXII deficient patients (24). FXII deficiency has also been strongly associated with primary and secondary recurrent abortions, due to microthrombi of the placenta vessel and placenta infarction, leading to adverse outcomes (25). Our patient also had a history of one abortion. Currently, studies are focused on the role of coagulation FXII in the pathophysiology of cardiovascular and cerebrovascular diseases. Recent studies have shown that FXII contributes to atherothrombosis and stroke, while its deficiency provides thromboprotection from mechanical and chemical induced arterial thrombosis in mice (26,27). Additional cohorts of FXII deficient patients are needed to study the association with thrombosis.

The lack of information regarding this rare condition might be due to the limited number of national registries, which leads to inappropriate diagnosis and management, but creation of patient registries could help resolve this problem. A retrospective analysis of 36 patients with FXII deficiency referred to our Center for Inherited and Acquired Disorders of Hemostasis during the 2005-2017 period was conducted. Out of 36 patients, nearly half were men, while the median age was 45.5 (range, 17-89) years. In 20 patients, the reason for consulting a hematologist was preoperative

workup, while 16 patients were referred due to prolonged aPTT. Only nine (25%) patients had very reduced FXII levels (<0.02 KIU/L), which was clinically manifested with mild bleeding in five patients and recurrent infections in six patients, whereas 13 (36.1%) patients had thrombotic events, mainly venous thromboembolism (eight patients had VTE and five patients presented with arterial thrombosis) (28).

To conclude, a repeatedly prolonged aPTT in a patient without hemorrhagic diathesis requires additional workup for a possible FXII deficiency with still several open questions regarding its clinical significance and treatment modalities.

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SAŽETAK

BOLESNICA S MANJKOM FXII, JAK2-MUTACIJA POZITIVNOM KRONIČNOM MIJELOPROLIFERATIVNOM NEOPLAZMOM I PONAVLJANIM TROMBOEMBOLIJSKIM INCIDENTIMA

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Uvod i cilj: Manjak faktora XII (FXII) je rijedak poremećaj povezan s produženim testom koagulacije (APTV) laboratorijski ukazujući na moguću sklonost krvarenju, no bez klinički značajnih krvarenja. Suprotno laboratorijskom nalazu, klinički je povezan s povećanim rizikom razvoja tromboembolijskih incidenata. Cilj ovoga rada je prikazati bolesnicu s teškim manjkom FXII, izrazito produženim APTV-om, ponavljajućim tromboembolijskim incidentima i dijagnozom JAK2-mutacija pozitivne kronične mijeloproliferativne neoplazme (MPN) bez hemoraške dijateze unatoč dvojnoj antikoagulacijskoj i antiagregacijskoj terapiji. Također je učinjen pregled literature o manjku FXII i njegovom kliničkom značenju, s otvorenim pitanjima o ovom rijetkom koagulacijskom poremećaju. ***Prikaz bolesnice:*** Prikazujemo bolesnicu rođenu 1959. godine s anamnezom izrazite pretilosti i arterijske hipertenzije. Bolesnica je 2010. godine imala duboku vensku trombozu (DVT) desne ruke tijekom uzimanja hormonske nadomjesne terapije. Tada se u laboratorijskim nalazima verificirao produženi APTV. Primala je varfarin tijekom dvije godine nakon čega je uvedena terapija acetilsalicilnom kiselinom, bez hemoraških komplikacija. U siječnju 2014. nakon kolecistektomije dolazi do razvoja masivne plućne embolije, DVT desne noge uz ponovno verificiran vrlo produženi APTV (>150 s), klinički bez znakova hemoraške dijateze. Liječena je niskomolekularnim heparinom s premoštavanjem na varfarin. Upućena je hematologu zbog produženog APTV-a, a učinjenom se ekstenzivnom obradom utvrde vrlo niska aktivnost FXII (<0,02 KIU/L), povišena aktivnost FVIII (2,52 KIU/L) i VWF (VWF:RCo 251 %, VWF:Ag 317 %) te točkasta mutacija V617F u genu za JAK2, nakon čega je uvedena i acetilsalicilna kiselina uz varfarin, a kasnije i citoreduktivna terapija hidroksiurejom zbog JAK2-mutacija pozitivne kronične MPN. Tijekom iduće 4 godine praćenja bolesnica je bez novih tromboembolijskih incidenata, dostatno antikoagulirana, bez hemoraških incidenata unatoč dvojnoj antikoagulacijskoj i antiagregacijskoj terapiji i trajno izrazito produženom APTV-u. ***Zaključak:*** Ponavljajući produženi APTV u osobe koja nema znakove krvarenja zahtijeva obradu na mogući manjak kontaktnih faktora uključujući FXII. U prikazane bolesnice sa stečenom i nasljednom trombofilijom i ponavljajućim trombotskim incidentima indicirana je dugotrajna dvojna antikoagulantna i antiagregacijska terapija koju dobro podnosi bez krvarećih komplikacija.

Ključne riječi: manjak FXII, tromboembolijski incidenti, produženo APTV, krvarenje, mijeloproliferativna neoplazma