A rare case of not-so-benign factor XII deficiency

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ABSTRACT

Background: Factor XII is an important part of the coagulation cascade. Its deficiency is benign but has been rarely associated with myocardial infarction and venous thrombosis.

Case Presentation: We present a case of a young lady who presented with a pulmonary embolism after supraventricular arrhythmia ablation. She was later found out to have factor XII deficiency. Her treatment course with rivaroxaban was uncomplicated and she stayed well afterward.

Conclusion: This report adds to the growing evidence of possible not-so-benign nature of factor XII deficiency.

Keywords: Factor XII deficiency, pulmonary embolism, cardiac ablation, coagulation, thrombosis.

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Background:

Factor XII deficiency is a rare, autosomal recessive disorder with an estimated incidence of one in a million [1]. Described mostly in the Asian population, this condition is usually benign and asymptomatic. Interestingly, it causes prolongation of clotting *in vitro* without increasing the risk of significant clinical bleeding [1]. In fact, paradoxically, there have been some reports of factor XII deficiency being associated with thrombotic complications, including venous thromboembolism and myocardial infarction (MI) [2]. We hereby present an unusual case of a young lady who was found to have factor XII deficiency after suffering a pulmonary embolism (PE) immediately following a cardiac ablation.

Case Presentation

Patient information

A 21-year-old woman, without any significant past medical history, who swims competitively at her university, underwent cardiac ablation for paroxysmal supraventricular tachycardia which she was having for the past 3 years. A week after the procedure, she presented with symptoms of acute onset chest pain that radiated to her back and also shortness of breath.

Physical exam

Her vital signs at presentation were as follows: BP 114/63, pulse 98/minute, temperature 36.6°C, respiratory rate 20/minute. Her breath and heart sounds were normal. There was no murmur or loud P2 sound. Abdomen was soft and non–tender. There was no calf swelling or tenderness. She was awake, alert, and oriented without any neurological deficit.

Diagnostics

She was found to have a segmental PE on Computerized tomography pulmonary angiography (CTPA, Figure 1). At the time, she was taking estrogen–based oral contraceptives which were stopped after the diagnosis of the PE. Ultrasound Doppler of the veins of the lower limbs did not reveal any thrombus. She did not have any risk factor for a hypercoagulable state, except for the use of oral contraceptive pills. She has no family history of repeated miscarriages nor venous thromboembolism. The catheter ablation was otherwise uncomplicated and she was neither immobilized nor bed–ridden afterward. A subsequent hypercoagulability workup, including protein C, protein S, anti–thrombin III, lupus anticoagulant, and anticardiolipin [(Immunoglobulin M (IgM) and Immunoglobulin G (IgG)], was all negative. However, her activated partial thromboplastin time (aPTT) was very high (184.2 seconds), while the prothrombin time and international normalized ratio (INR) were normal. Mixing study normalized the aPTT suggesting a factor deficiency. The clotting factor assay revealed a severe deficiency of factor XII (<1%), while factor VIII, IX, and XI activities were normal. High molecular weight kininogen (HMWK) and prekallikrein factor activity were tested and were 125% and 127%, respectively (Table 1).

Table 1. Pertinent labs.

LAB	PATIENT'S VALUE	NORMAL VALUE
Prothrombin time	12.0	1.02–12.9 seconds
INR	1.0	0.9–1.1
aPTT	184.2	25.1–36.5 seconds
Factor VIII assay	132	68%–156% activity
Factor IX assay	92	92%–161% activity
Factor XI	148	70%–150% activity
Factor XII assay	<1	57%–165% activity
Mixing study	aPTT corrected	N/A
HMWK	125%	65%–135%
Prekallikrein	127%	55%–207%
Protein C	98	77%–147%
Protein S	140	51%–140%
Antithrombin III	127	81%–125%
Lupus anticoagulant	NEG	Negative
Anticardiolipin IgG	7	0–14 GPL/ml
Anticardiolipin IgM	4	0–12 MPL/ml
Beta–2 glycoprotein IgG	0	0–20 SGU
Beta–2 glycoprotein IgM	1	0–20 SMU
Factor V Leiden	Normal	Normal
Prothrombin gene	Normal	Normal
LDH	188	120–246 U/l
WBC	5.4	4–10 × 10 3/ul
Hemoglobin	13.5	11.5–16.0 g/dl
Hematocrit	40	40%–52%
Platelets	270	140–400 × 10 3/ul
Sodium	740	136–145 mEq/l
Potassium	4.0	3.5–5.1 mEq/l
Chloride	103	99–109 mEq/l
Bicarbonate	27	20–31 mEq/l
BUN	11	9–23 mg/dl
Creatinine	0.73	0.5–1.10 mg/dl
Calcium	9.1	8.6–10.2 mg/dl
Total protein	7.5	6.4–8.3 g/dl
Albumin	5.0	3.5–5.2 g/dl
ALT	18	1–33 U/l
AST	22	14–34 U/l
Bilirubin (Total)	0.7	0.3–1.2 mg/dl
Alkaline phosphatase	59	53–141 U/l

HMWK, High molecular weight kallikrein; IgG, Immunoglobulin G; IgM, Immunoglobulin M; LDH, Lactate dehydrogenase; TSH, Thyroid stimulating hormone; WBC, White cell count; BUN, Blood urea nitrogen; ALT, Alanine transaminase; AST, Aspartate transaminase; GPL, IgG phospholipid units; MPL, IgM phospholipid units; SGU, Standard IgG units; SMU, Standard IgM units.

Assessment

Marked elevation of aPTT, correction of aPTT with mixing studies, normal HMWK, and prekallikrein activity and finally severely depressed activity of factor XII confirmed the diagnosis of factor XII deficiency.

Interventions

She was started on Rivaroxaban for 3 months for treatment of presumably provoked venous thromboembolism (VTE).

Follow–up and outcomes

Her symptoms rapidly resolved. She had a regular follow–up with the hematologist. Repeat imaging confirmed resolution of the PE (on CTPA, Figure 1). She experienced neither recurrence of thrombosis nor abnormal bleeding despite using anticoagulants.

Discussion

Factor XII is essential for clotting *in–vivo* but patients who are deficient in this glycoprotein are usually asymptomatic.

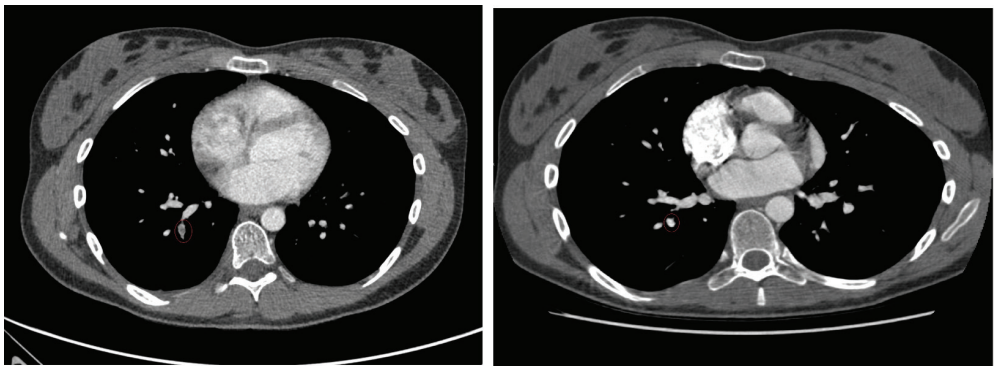

Figure 1. *CTPA showing PE of the right lower lobe vessel (left side) with resolution in subsequent CT after treatment (right side).*

Its deficiency arises from a mutation in the TaqI polymorphic site within the gene on chromosome 5. Factor XII deficiency does not appear to cause a bleeding diathesis nor does it protect against VTE [3]. In fact, there have been reports linking factor XII deficiency with recurrent miscarriages and hypercoagulability [4]. John Hageman, the first patient ever in whom this trait was discovered died of PE after 12 days of sustaining a pelvic fracture [5]. Halbmayer et al. [6] found a significant association of factor XII deficiency with the development of recurrent arterial thromboembolism ($p < 0.003$) as compared with healthy subjects. A recent observational study (2016) found the same association [7]. In contrast, a Swiss study in 1999 that followed patients for 6 years concluded that partial (Factor XII 1%–59%) and probably severe (Factor XII <1%) factor XII deficiency does not confer hypercoagulability [8]. Another study following 79 patients (21 homozygotes, 58 heterozygotes) for the development of arterial thrombosis and MI did not find any increased risk of thrombosis in such patients [9]. Whether or not factor XII deficiency was the sole etiology for this particular patient's venous thromboembolic complication is debatable but is concerning enough to warrant future prophylactic postoperative anticoagulation, especially if the bleeding risk is minimal with the use of anticoagulation.

Conclusion

We conclude that in the presence of another risk factor for VTE, such as surgery or immobilization, factor XII deficient patients can possess a higher risk of VTE than the normal population. Given the extreme rarity of this condition, we do not advocate for routinely screening for factor XII deficiency from a cost–effectiveness standpoint. However, in patients who are found to have a markedly prolonged PTT in the setting of a clotting complication, assessing for factor XII deficiency may be warranted, as these patients may benefit from prophylactic anticoagulation for future exposure to an increased hypercoagulable state.

Acknowledgment

None

List of Abbreviations

CTPA	CT pulmonary angiogram
HMWK	High molecular weight kininogen
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
MI	Myocardial infarction
PE	Pulmonary embolism
PTT	Partial thromboplastin time

Consent for publication

Verbal consent was taken.

Ethical approval

Not required.

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Summary of the case

Patient (gender, age)	1	21, F
Final diagnosis	2	Pulmonary embolism, factor XII deficiency
Symptoms	3	Chest pain and dyspnea
Medications	4	Rivaroxaban
Clinical Procedure	5	N/A
Specialty	6	Hematology