Prolonged Partial Thromboplastin Time Without Bleeding History; Fletcher Factor Deficiency

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ABSTRACT

A 67-year-old patient was admitted to the hospital to perform an esophagogastrectomy because a lesion at the lower esophagus was strongly suspicious for cancer. Her medical history and her family history were negative for bleeding tendency or thrombosis. Her activated partial thromboplastin time (aPTT) was prolonged (44 s) whereas her prothrombin time (PT) was normal (11 s) presurgery. Mixing of her plasma with normal plasma corrected her prolonged aPTT (27.9 s). Prolonged incubation shortened the patient's aPTT (36.3 s). Fletcher factor activity was found to be 50%. The patient underwent an esophagogastrectomy without bleeding complications under spinal anesthesia. Fletcher factor deficiency, a rare disorder, should be considered in patients who have no history of bleeding tendency with a prolonged aPTT. Surgical interventions are safe in these patients.

Key Words: aPTT, Surgery, Fletcher factor, Prekallikrein.

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INTRODUCTION

Preoperative evaluation of hemostasis is crucial to assess the risk of per-and peri-operative bleeding. The most effective screening method is to obtain a thorough history of bleeding[1]. Preoperative screening tests mostly include activated partial thromboplastin time (aPTT), prothrombin time (PT), bleeding time, and platelet count[2]. Hematologists are frequently consulted for preoperative coagulation abnormalities.

Prolonged aPTT is not an uncommon abnormality encountered during preoperative evaluation. It may indicate the presence of antiphospholipid antibodies or a factor deficiency in the intrinsic and/or common pathways of blood coagulation. These routine evaluations may result in diagno-

sing rare genetic disorders such as Fletcher factor (FF) deficiency.

Here we present a 67-year-old white female who had negative history for a bleeding tendency. FF deficiency was diagnosed in this patient during the evaluation for a prolonged aPTT detected at routine preoperative evaluation.

CASE REPORT

A 67-year-old patient was admitted to the hospital because of a history of gastroesophageal reflux, dysphagia, and weight loss. Her dysphagia was initially to liquids and subsequently to solid foods. A barium swallow study revealed a mass in the lower esophagus causing obstruction. She underwent an upper gastrointestinal endoscopy. A biopsy of the mass was consistent with Barrett's esophagus and strongly suspicious for esophageal cancer. An esophagogastrectomy was planned. Her medical history was positive for schizophrenia, depression, and transient ischemic attacks. Her surgical history was positive for a hysterectomy, a cholecystectomy, and a repair of the right humeral fracture, none of which was complicated by bleeding or thrombosis. Her medications included chlorpromazine, clonidine, and haloperidol. There was no history of bleeding tendency in her parents and children. Preoperative studies were as follows; WBC 9.1 x 10^9/L, Hb 9.5 g/dL, platelet count 407 x 10^9/L, activated partial thromboplastin time (aPTT) 44 s (control 27.3 s), PT 11 s (INR 1.0), ALT 26 U/L, AST U/L, creatinine 0.7 mg/dL. A repeated aPTT was prolonged as well. Mixing of her plasma with an equal volume of normal plasma completely corrected the patient's prolonged aPTT (from 44.5 seconds to 27.9 seconds). Factor levels were as follows: F VIII 225%, F IX 107%, F XI 80%, F XII 105%, and ristocetin cofactor 185%. Bleeding time was 4 minutes. Prolonged incubation at 37°C shortened her aPTT from 44.5 s to 36.3 s. FF activity was found to be 50%. She underwent an esophagogastrectomy without major bleeding complications, and pathologic examination revealed Barret's esophagus but no evidence of cancer.

DISCUSSION

Hathaway et al first identified FF deficiency in a family in 1965[3]. Four siblings in this family had a markedly prolonged activated partial thromboplastin time aPTT without abnormal bleeding. Subsequently, Wuepper et al identified this factor as plasma prekallikrein[4].

FF, a gamma globulin with two forms having molecular weights of 85.000 and 88.000, is synthesized mostly in the liver[5]. The genes of FF and F XI are localized on chromosome 4, and their cDNAs share a 58% homology[5].

FF, Hageman factor (F XII) and high molecular weight kininogen (HMWK) participate contact activation reactions. When plasma is exposed to negatively charged surfaces, F XII is first activated (F XIIa). F XIIa and F XII fragments activate FF and generate the enzyme kallikrein (Figure 1)[6]. HMWK plays a role in this activation. Kallikrein, as a protease, liberates kinins from kininogens, activates F XII by generating F XII fragments, activates plasminogen, converts prorenin to renin, interacts with human leukocytes, and destroys C1 components[5].

FF deficiency is inherited in an autosomal-recessive pattern. Heterozygous individuals characteristically have no history of bleeding or thrombosis with intermediate to normal levels of prekallikrein. These patients are detected incidentally with normal hemostasis tests except a markedly prolonged aPTT as was the case in our patient. Shortening of prolonged aPTT with extended incubati-

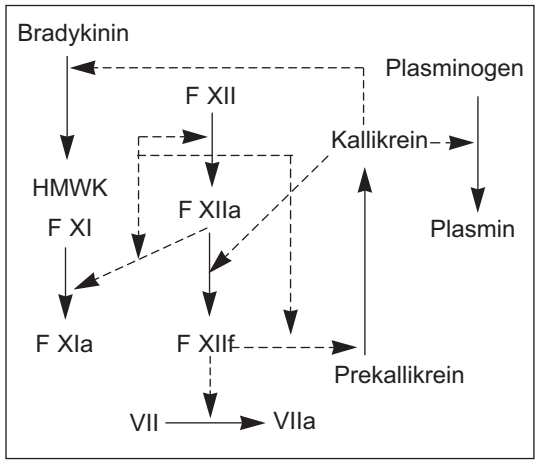

Figure 1. Role of kallikrein in coagulation and fibrinolysis.

on of the sample in the presence of a contact factor such as glass, kaolin, and silica is a clue for the investigation of a contact factor deficiency[7]. Homozygous individuals have low prekallikrein levels by functional assays. However, Saito et al have shown the presence of prekallikrein antigen in 5 of 18 patients whose functional assays indicated that they were homozygous FF deficient[8]. Most of homozygous are also symptoms free despite in vitro impaired intrinsic fibrinolysis, decreased chemotactic activity and decreased kinin generation have been shown[5,9]. Some cases with severe FF deficiency who developed recurrent hemarthrosis and hematoma, myocardial infarction, multiple cerebral thromboses have been reported[10-12].

FF deficiency should be considered in patients with no history of bleeding or thrombosis and with a markedly prolonged aPTT, particularly when the prolonged aPTT is corrected by mixing with normal plasma, or extended incubation.

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