Coagulation Conundrum: A Case of an Elevated INR Secondary to Combined Factor V and VII Deficiency

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Abstract
Congenital factor V (FV) and factor VII (FVII) deficiency is a rare coagulopathy, caused by two distinct independently segregating genetic defects. A 54-year-old female presented to hospital with non-ST elevation myocardial infarction. Workup revealed an elevated international normalized ratio (INR) of 2.0 (normal range 0.8–1.2). Thrombin time (TT), partial thromboplastin time (PTT), and Clauss fibrinogen were normal. Her only prior bleeding event was a lower gastrointestinal (GI) bleed occurring during antiplatelet therapy. She was not on chronic anticoagulant therapy. Her INR did not correct to normal despite 30 mg of oral/intravenous vitamin K. Hepatic synthetic function was normal arguing against an acquired coagulopathy of liver disease. Coagulation factor levels revealed reduced levels of FV and FVII. A combined congenital FV and FVII deficiency was felt to be the most likely diagnosis. During her hospital stay, she underwent coronary artery bypass grafting with perioperative recombinant FVIIa and is expected to have confirmatory genetic testing. Our case demonstrates the value of a thorough bleeding history and the importance of following up patients with such a history.

Résumé
Le déficit congénital en facteur V et en facteur VII est une coagulopathie rare, causée par deux défauts génétiques hétérozygotes indépendamment distincts. Une femme de 54 ans se présente à l’hôpital en raison d’un infarctus du myocarde sans sus-décalage du segment ST. Le bilan diagnostique révèle un rapport international normalisé (RIN) élevé de 2,0 (intervalle normal de 0,8 à 1,2). Le temps de thrombine (TT), le temps de thromboplastine partielle (TTP) et le dosage du fibrinogène de Clauss sont normaux. Le seul antécédent d’hémorragie est une hémorragie digestive basse survenue pendant un traitement antiplaquettaire. Elle ne suit pas une anticoagulothérapie à long terme. Le RIN ne s’est pas normalisé malgré l’administration par voie orale/intraveineuse de 30 mg de vitamine K. Le fonctionnement de la synthèse hépatique est normal, ce qui exclut la coagulopathie découlant d’une hépatopathie. Les taux des facteurs de coagulation révèlent un faible taux de facteur V et de facteur VII. Le diagnostic le plus probable semble être un déficit congénital combiné en facteur V et en facteur VII. Au cours de son séjour à l’hôpital, la patiente a subi un pontage aortocoronarien accompagné de l’administration périopératoire de facteur VII activé recombinant et attend la confirmation du
Initially, coagulopathy of liver disease was suspected given a finding of hepatic steatosis on abdominal imaging (Figure 1); however there was no biochemical or imaging evidence of cirrhosis or impaired hepatic synthetic function. Specifically, bilirubin, albumin, platelets, and liver transaminases were in the normal range. Vitamin K deficiency was felt to be unlikely given the lack of response to high doses of oral and intravenous vitamin K. Given her long-standing coagulopathy without a clear explanation, additional factor assays were ordered (Table 1). A diagnosis of congenital FV and FVII deficiency was suspected. Confirmatory genetic testing is pending.

During her hospital stay, she underwent coronary artery bypass grafting. Two doses (4 mg) of recombinant activated FVII were administered perioperatively. She also received two units of fresh frozen plasma (FFP) and two units of adult pooled platelets, two grams of fibrinogen concentrate, and four units of packed red blood cells perioperatively. Her coagulation parameters during surgery revealed an INR of 1.1 (normal range 0.8–1.2), PTT of 54 seconds (normal range 22–35 seconds), Clauss fibrinogen of 1.6 g/L (normal range 1.6–4.2 g/L), and TT of 35 seconds (normal range 20–30 seconds).

Case Presentation

A 54-year-old female presented to hospital with non-ST elevation myocardial infarction (NSTEMI). Her past medical history included coronary artery disease, colon cancer treated with hemicolecetomy, prior lower gastrointestinal (GI) bleed with an unremarkable colonoscopy, type 2 diabetes mellitus, hypertension, and dyslipidemia. There was no family history of bleeding or thrombotic disorders. Her medications included metformin, hydrochlorothiazide, and olmesartan. She was not taking any anticoagulant drugs. Previously, she reported taking clopidogrel, which was stopped a few years prior due to rectal bleeding. Her physical exam was benign and did not reveal any bruises or petechiae.

In hospital, she was started on clopidogrel and fondaparinux for the treatment of a NSTEMI. Cardiac nuclear Persantine stress test revealed ST segment changes with Persantine and with exercise. Myocardial perfusion imaging showed transient ischemic dilatation and reduced flow reserve, suggestive of a proximal left anterior descending artery lesion. While awaiting definitive management, she developed rectal bleeding and fondaparinux was stopped. Esophagogastroduodenoscopy and colonoscopy did not reveal any obvious source of bleeding.

Workup revealed an elevated international normalized ratio (INR) of 2.0 (normal range 0.8–1.2). Thrombin time (TT) (29 seconds; normal range 29–30 seconds), partial thromboplastin time (PTT) (23 seconds; normal range 22–35 seconds), and Clauss fibrinogen (2.2 g/L; normal range 1.6–4.2 g/L) were normal. The INR did not correct to normal despite her receiving a cumulative dose of 30 mg intravenous and oral phytonadione (vitamin K) over 5 days.

On review of previous laboratory results, it was noted that she had an elevated INR of 1.7 on at least two prior occasions separated by several years. Her APTT and platelet counts in the proceeding several years were normal. She had received frozen plasma empirically prior to surgeries done outside of the country in the remote past, including a prior hemicolecetomy, but did not report specific bleeding complications.

Figure 1. Abdominal ultrasound showing mild hepatomegaly and diffuse hepatic steatosis with no hepatic lesions.

Keywords: elevated INR; factor V deficiency; factor VII deficiency; combined factor deficiency
INR, prior use of FFP in the perioperative period, and history of rectal bleeding on antiplatelet therapy all hinted at a congenital coagulopathy. Specialized factor assays can assist with the diagnosis and management of patients with undifferentiated coagulopathy.

**Disclosures**

In the last 36 months, Dr. Crowther has participated in a DSMB for Bayer, has received personal funding and/or set on advisory boards for Servier Canada, Asahi Kasei, Precision Biologicals, and Hemostasis Reference Laboratories, and has prepared educational materials and/or provided presentations and/or moderated educational sessions for Pfizer, CSL Behring, and Diagnostica Stago. Dr. Crowther has past and current relationships with a number of not-for-profit and for profit entities that are not pharmaceutical manufacturers. He holds the Leo Pharma Chair in Thromboembolism Research at McMaster University and he has participated in a variety of medical legal proceedings examining hematologic and thromboembolic concerns. Dr. Mithoowani received personal fees from Leo Pharma. None of the other authors have conflicts of interest to disclose.

Informed consent was obtained from the patient. All authors contributed to at least one of the following categories: (i) conception and design; (ii) drafting of the original manuscript; and (iii) critical review of the original manuscript. No funding source was used for this project.

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