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Vitamin K Deficiency Bleeding Leading to a Diagnosis of Crohn's Disease

Luisa Agnello[1], Chiara Bellia[1], Lucio Lo Coco[2], Silvana Vitale[2], Felicia Coraci[2], Filippa Bonura[2], Rossella Gnoffo[2], Mariasanta Napolitano[3], Antonietta Caruso[1], Giulia Bivona[1], Bruna Lo Sasso[1], and Marcello Ciaccio[1,2]

[1]Sezione di Biochimica Clinica e Medicina Molecolare Clinica, Dipartimento di Biopatologia e Biotecnologie Mediche e Forensi, Università degli Studi di Palermo, [2]U.O.C. CoreLab, Azienda Ospedaliera Universitaria Policlinico, Palermo, and [3]U.O.C. Ematologia, Azienda Ospedaliera Universitaria Policlinico, Palermo, Italy

Abstract. We report the case of a 45-years-old man who came to Emergency Room of Polyclinic for a sudden onset of localized ecchymosis and widespread hematomas. He was subjected to blood count and first level investigations to assess the coagulation. Based on the results, second level investigations were performed. The endoscopy of the gastrointestinal tract with the histological examination has allowed the diagnosis of Crohn's disease. Vitamin K deficiency causes the formation of forms of vitamin K-dependent clotting factors that can not perform their pro-coagulant action. Consequently, patients present hemorrhagic manifestations. Clinical and laboratory features observed in this patient show that the deficiency of vitamin K-dependent coagulation factors may reveal a complex clinical condition such as a inflammatory bowel disease.

Key Words: Crohn's disease, Vitamin K, thromboelastogram

Introduction

Vitamin K is an important coenzyme of hepatic γ-carboxylation of blood coagulation factors (FII, FVII, FIX, FX) and physiological inhibitors of coagulation (anticoagulant protein C and S) [1]. While an inherited enzyme deficiency involving vitamin K metabolism is an extremely rare condition in adults, acquired vitamin K deficiency can occur in diseases that prevent the absorption of fats such as cystic fibrosis, celiac disease, and inflammatory bowel disease. It can also occur in patients undergoing major surgery or in those treated with long-term parenteral nutrition and broad-spectrum antibiotic therapy [2]. The classical clinical signs of vitamin K deficiency are skin and mucosal bleedings. Characteristic laboratory data are a prolonged prothrombin time (PT) or activated partial thromboplastin time (aPTT), which are corrected by treatment with vitamin K. Crohn's Disease (CD) is classified as an inflammatory bowel disease (IBD). IBDs are a heterogeneous group of idiopathic, chronic, relapsing, inflammatory conditions primarily affecting the gastrointestinal tract. CD is diagnosed based on clinical, radiological, endoscopic, and histological parameters. Patients usually suffer from symptoms such as abdominal pain and diarrhea, which may be complicated by intestinal fistulas, intramural abscesses, and bowel obstruction [3]. These patients have been reported to be at high risk of developing a deficiency of fat-soluble vitamins, including vitamin K [4,5].

Address correspondence to Marcello Ciaccio, MD; Dipartimento di Biopatologia e Biotecnologie Mediche e Forensi, Sezione di Biochimica Clinica e Medicina Molecolare Clinica, Università degli Studi di Palermo, Policlinico Universitario – Via del Vespro, 129-90127, Palerno, Italy; phone: 39 091 6553296; fax: 39 091 6553275 e mail: Marcello.ciaccio@unipa.it

Case report

We report the case of a 45-year-old Caucasian man presented to the Emergency Room (ER) of the University General Hospital Policlinico "P. Giaccone" in Palermo, Italy, because of a sudden onset of upper and lower limbs localized ecchymosis and widespread hematomas. No history of spontaneous or induced bleeding episode, neither antibiotics and non-steroidal anti-inflammatory drugs intake was reported. The patient presented arterial hypertension, which was treated with ACE inhibitors, and, in 2011, he underwent an inguinal hernia surgery without any complications. On admission, he underwent to the following tests: complete blood cell count with morphological examination of peripheral blood smear, a kidney and hepatic function test, and first level coagulation assays (PT, aPTT and fibrinogen). No

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Table 1. *Results of first level coagulation assays performed in basal condition and after mixing test at room temperature (RT) and at 37°C.*

Test	Basal	MixTest at R.T.	MixTest at 37°C	Clinical reference value
PT	No coagulation	12.7 sec. Ratio 1.10 INR 1.09	13.0 sec. Ratio 1.12 INR 1.11	11.0-13.0 sec. Ratio 0.8-1.2 INR 0.9-1.3
aPTT	57.7 sec Ratio 1.92	27.7 sec. Ratio 0.92	28.2 sec. Ratio 1.04	24-36 sec. Ratio 0.8-1.2
FBN	331 mg/dL	-	-	150-450 mg/dL

Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin time; FBN, fibrinogen; INR, international normalized ratio.

Table 2. *Results of second level coagulation assays performed in basal condition, and after mixing test at room temperature (RT) and at 37°C.*

Coagulation Factors	Basal	MixTest at R.T.	MixTest at 37°C	Clinical reference value
Factor II	17.8%	64.2%	65.8%	80-130%
Factor V	85.2%	-	-	60-140%
Factor VII	2.9%	75.8%	74.2%	50-130%
Factor VIII	124%	-	-	50-150%
Factor IX	11.4%	162.8%	158.4%	65-150%
Factor X	8.5%	93.3%	95.6%	77-130%
Factor XI	105%	-	-	65-150%
Factor XII	90.8%	-	-	50-150%
Physiological coagulation inhibitors	**Basal**	**MixTest at R.T.**	**MixTest at 37°C**	**Clinical reference value**
Antithrombin	94.6%	-	-	80-120%
Protein C	58%	80.4%	79.5%	70-140%
Protein S	64%	75.6%	76.6%	74-146%

Table 3. *Fibrinolytic parameters*

Fibrinolytic parameters		Clinical reference value
D -dimer	125 ng/mL	10-250 ng/mL
FDP	< 10 µg/mL	< 10 µg/mL
Plasminogen	116 %	80-130%
α2-Antiplasmin	108 %	98-122%

Abbreviations: FDP, fibrin degradation products.

alterations were reported except prolonged PT and aPTT as shown in **Table 1**. Based on these data, an ultrasonography examination of the upper abdomen and second level coagulation assays including platelet function tests, dosages of coagulation factors [protein C and S, antithrombin, fibrinolytic parameters (d-dimer, FDP, plasminogen and α2-antiplasmin)], a mixing test, and a thromboelastogram (TEG) were performed. The abdominal echography revealed no significant abnormalities involving liver parenchyma, biliary tree, and the spleen. Platelets function testing (PFA100) showed no alteration of the haemostatic capacity of platelets both for collagen/ADP and collagen/epinephrine. Second level coagulation assays revealed decreased level of FII, FVII, FIX and FX, but normal level of FV, a decreased level of Protein C and S, normal Antithrombin levels, and fibrinolytic parameters in normal ranges **(Tables 2&3)**. All abnormal parameters were corrected after the mixing test, performed both at room temperature and at 37°C. The TEG performed on citrated whole blood did not show any alteration, but it revealed an elongation of the "reaction time" not allowing clot formation when performed on platelet-poor plasma. A possible explanation of the different behavior of the two TEG assays is that the "reaction time" is prolonged in the case of severe coagulation factors deficiency, low platelet count (<50000/mm^3), and low fibrinogen levels (<100mg/dL). In cases like the one described, in order to detect a defect of plasmatic coagulation factors, it is appropriate to remove platelets from the sample so the "reaction time" will be elongated only in relation to the concentration of plasma coagulation factors. TEG assays performed after mixing the substance with normal plasma showed the complete normalization of the "reaction time". Finally, a TEG performed after treatment with intramuscular administration of vitamin K showed normal clot formations.

Based on the results of laboratory investigations, a diagnosis of combined deficiency of vitamin K-dependent coagulation factors was made. Accordingly, the patient was hospitalized, and he received treatment with vitamin K. Initially, oral vitamin K administration (10 mg) did not produce any correction of PT and aPTT values that were reached with parenteral administration.

In order to understand the etiology of vitamin K deficiency, the following laboratory assays were performed: sieroprotein electrophoresis, albumina plasma levels, cholesterol, triglyceride, erythrocyte sedimentation rate (ESR), C Reactive Protein (CRP), faecal calprotectin, screening for autoimmunity, and a urine and stool examination. The results of these investigations showed an increase of ESR ,CRP, faecal calprotectin, and gammaglobulin levels.

Endoscopic examinations of the gastro enteric tract (gastroscopy and colonoscopy with biopsy and histologic examination) led to the diagnosis of Crohn's Diseases. Areas of chronic inflammation, comprising increased lamina propria plasma cells and lymphocytes, were associated with architectural distortion consisting of patchy, mild to severe, neutrophilic inflammation, including neutrophilic cryptitis, crypt abscesses, and erosions. The patient was assigned to the Gastroenterology Unit.

Discussion

Vitamin K is a fat-soluble vitamin with an essential role in the haemostatic process. Once vitamin K is absorbed from the gastrointestinal tract, it is transported to the liver *via* the hepatic portal vein where it acts as an essential cofactor for the conversion of peptide-bound glutamate to gamma-carboxy glutamic acid (Gla) residues in a number of specialized Gla-containing proteins, including coagulation factors [6]. Patients suffering from vitamin K deficiency present bleeding symptoms associated with prolonged PT and/or aPTT values.

Crohn's Disease is an idiopathic, chronic regional enteritis that can affect the gastrointestinal tract from mouth to anus, but it commonly involves the terminal ileum. Although the exact etiologies are uncertain, the pathogenesis of the disease is the result of three interacting elements: genetic susceptibility factors, enteric micro flora abnormalities, and immune-mediated tissue injury [7]. Clinically, the disease has a chronic, indolent course, and it tends to relapse. Patients commonly present with symptoms related to ileocecal inflammation such as cramping, prolonged diarrhea, and low-grade fever [8].

We report the case of a patient who did not show any clinical common manifestations of the disease at presentation, but he suddenly experienced skin hemorrhagic manifestations due to an acquired

vitamin K deficiency. In an attempt to evaluate this deficit, we performed a laboratory test consistently with the clinical suspicion of a malabsorption related to vitamin K deficiency. Accordingly to *The second European evidence-based Consensus on the diagnosis and management of Crohn's disease*, the diagnosis of CD was made on the basis of endoscopic, histological and serological examinations [9]. The case described represents an atypical condition because vitamin K deficiency frequently occurs late in clinical history of CD and in association with alterations in bone metabolism [5,10]. In this patient, bone metabolism related markers and 25-hydroxyvitamin D resulted in the normal range, and no bone mineral density alterations were ever detected by the dual-energy x-ray absorptiometry (DEXA) scan. Also the patient's nutritional status, evaluated by serum pre-albumin and albumin, revealed no alterations.

In conclusion, Crohn's disease is a heterogeneous entity comprising a variety of complex phenotypes in terms of age of onset, disease location and disease behavior. In this case report, vitamin K deficiency occurs early and it is associated with bleeding events. No cases of bleeding as onset symptom of CD are described and the potential selective malabsorption of vitamin K has been never reported in literature. The underlying mechanisms of vitamin K malabsorption is still under investigation.

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