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Case Report

Essential thrombocytosis accompanied by coagulation factor XII deficiency: a case report

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Abstract: Essential thrombocytosis (ET) is a type of myeloproliferative neoplasm with clinical manifestations of thrombosis and hemorrhage, the mechanisms of which remains unclear. Some researches indicated that ET is mainly related to the defect of platelet function and the abnormality of coagulation mechanism. A few reports showed that ET accompanied by acquired hemophilia. However, no evidence of ET with coagulation factor XII deficiency has been published. we here report a case of ET accompanied with coagulation factor XII deficiency, which had clinically significant bleeding tendency.

Keywords: Essential thrombocytosis, coagulation factor XII deficiency, myeloproliferative disease, von Willebrand disease

Introduction

Essential thrombocytosis (ET) is a type of myeloproliferative neoplasm (MPN) with unknown causes. Recently, the pathogenesis of ET is thought to be related to V617F mutation in JAK2 gene [1]. The clinical manifestation of ET is mainly the significant increase in platelet number, accompanied by thrombosis and hemorrhage. Some reports suggested that hemorrhage in ET was mainly related to the relative deficiency of von Willebrand factor (vWF) or the reduction of macromolecular vWF polymers. Coagulation factor XII, a serine protease, is mainly synthesized by the liver, acting as a promoter of the intrinsic coagulation pathway. Coagulation factor XII deficiency is either congenital or acquired. Congenital coagulation factor XII deficiency is a kind of rare autosomal recessive hereditary disease, and its clinical manifestation is low factor concentration without significant bleeding. Therefore, coagulation factor XII deficiency is often diagnosed before surgeries or during routing coagulation tests. Because no severe bleeding is related to this disease, no special treatment is required. Acquired coagulation factor XII deficiency is extremely rare and is related to coagulation factor XII inhibitors produced in patients with leukemia or nephrotic syndrome. ET accompanied by acquired hemophilia was reported for a few times [2-4]. However, ET with coagulation factor XII deficiency has never been reported before. Here, we report a rare case of ET accompanied with coagulation factor XII deficiency. The patient had unusual clinical manifestations including severe hemorrhage.

Case report

A 69-year-old man was admitted to Qianfoshan Hospital of Shandong University on 24 April 2014 due to a large area of skin ecchymosis accompanied by swelling and pain on the right knee. The patient admitted to hospital 6 days after the event occurred because of no obvious reason. Local county hospital found the patient had significantly elevated platelet concentration (2138×10^9/L) and prescribed aspirin (to prevent platelet aggregation) and painkiller. During the treatment, the patient's condition became worse: a large area of ecchymosis appeared on the left waist, hip and thigh; swelling in the right knee was aggravated; hematoma on his right leg. Then, the patient was transferred to our hospital.

Admission examination showed that: large areas of ecchymosis were observed on the left

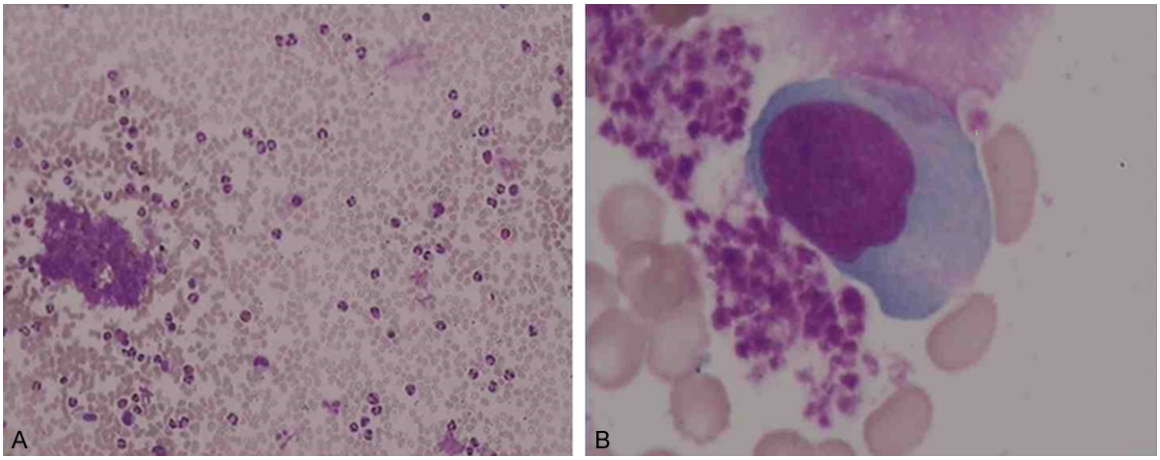

Figure 1. Wright-Giemsa staining of bone marrow smears. Wright-Giemsa A (0.5 ml) was added onto the smear for 1 min, then adding Wright-Giemsa B on top of Wright-Giemsa A. The solution was mixed thoroughly by aspiration and dispensing with a pipette. After 10 minutes, the solution was washed off by running water, followed by drying and visual examination under a bright light microscope. A. × 200 magnifications; B. × 400 magnifications.

waist, hip and the right thigh and groin; significant swelling occurred on the right knee, which exhibited violaceous color and limited movement, with no depression seen when pressed; the dorsal artery of both feet had normal pulsation. The patient had no history of special medical or familial genetic diseases.Blood routine examination results: white blood cell count, 36.75 × 10^9/L; neutrophils, 32.18 × 10^9/L; hemoglobin, 106.0 g/L; platelet count, 2863 × 10^9/L. Coagulation routine examination results: prothrombin time, 13.3 s (reference values 9.8-12.1 s); plasma fibrinogen, 6.03 g/L (reference values 1.8-3.5 g/L); activated partial thromboplastin time, 68.90 s (reference values 22.7-31.8 s); plasma D-dimer, 4.86 mg/L (reference values 0-0.55 mg/L); coagulation factor VIII, IX and X functions were normal; vWF, normal Ag determination result. Factor XII activity was 12%. Coagulation factor antibodies were not found in coagulation factor inhibitor screening or titer tests. The value of glutamic-pyruvic transaminase was 29.7 U/L; the value of glutamic-oxaloacetic transaminase was 35.3 U/L; the concentration of urea was 8.7 mmol/L; the concentration of creatinine was 91.6 μmol/L; the value of lactate dehydrogenase was 570.4 U/L. Autoantibodies were negative, while anticardiolipin antibodies were negative. Abdominal sonography showed liver cysts and splenomegaly with the thickness of the spleen being 48 mm. Sonography of blood vessels in lower extremity showed: arteriosclerosis occurred in the right lower limb; the thickness of superficial femoral veins on the right was unevenly narrowed (due to the oppression from the surrounding tissue); blood flow in popliteal veins on the right and inter-muscular veins was slowed down, showing hypercoagulable state of the blood. Two times of bone marrow punctures were performed by dry tap aspirations, showing platelets being distributed in the shapes of sheets (**Figure 1**). Bone marrow biopsy showed extremely active proliferation, including myeloid hyperplasia, proliferation of megakaryocytes, and mild hyperplasia of cells at immature stage. The patient also showed a little positive CD34 and CD117, locally proliferated fibrous tissue, and reticular fibers with "++" (**Figure 2**). Monitoring of JAK V617 mutation showed that 80% cells had mutated JAK V617 gene (**Figure 3**). BCR/ABL fusion gene was negative. Chromosome examination showed 46 chromosomes including sex chromosomes XY (male). The patient was then diagnosed to have both ET and coagulation factor XII deficiency.

The patient was administered orally with hydroxyurea (1 g, tid), and treated with *Salvia miltiorrhiza Bunge* or *Aescuven forte* to reactivate blood circulation, supplemented with coagulation factors by infusion of fresh plasma. The condition of the patient was improved. More than 10 days later, subcutaneous ecchymosis diminished and lower extremity swelling regressed. Blood routine re-examination showed: white blood cell count, 4.50 × 10^9/L; red blood cell count, 3.27 × 10^{12}/L; hemoglo-

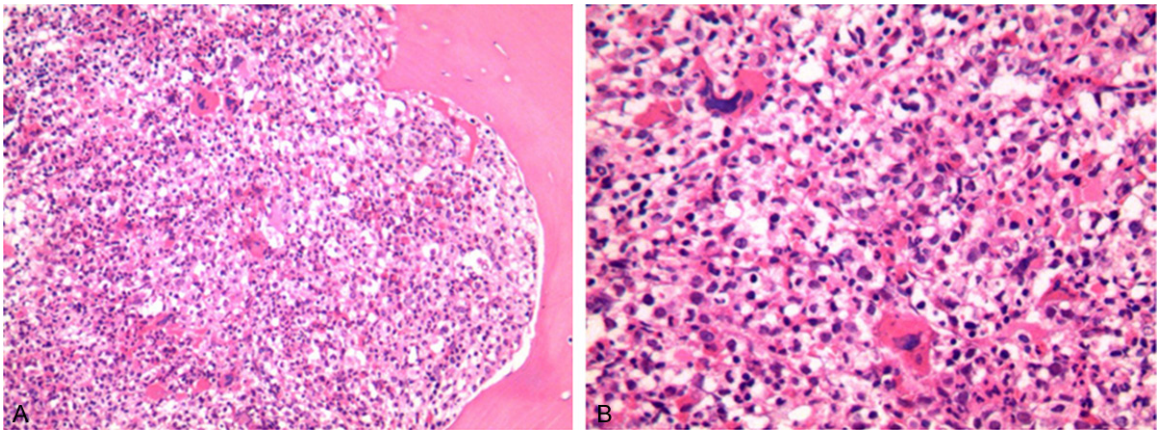

Figure 2. Pathological investigation of bone marrow. The tissues were fixed with 10% formalin, decalcified by 2% nitric acid for 2-4 hours, and dehydrated using 70%, 80% and anhydrous alcohol for 1 hour, respectively; transparented by xylene twice (half an hour for each), and paraffin-embedded for 1 hour before section, followed by heating at 65°C for 1 hour. Sections were stained with hematoxylin and eosin and examined under a bright light microscope. A. × 100 magnifications; B. × 200 magnifications.

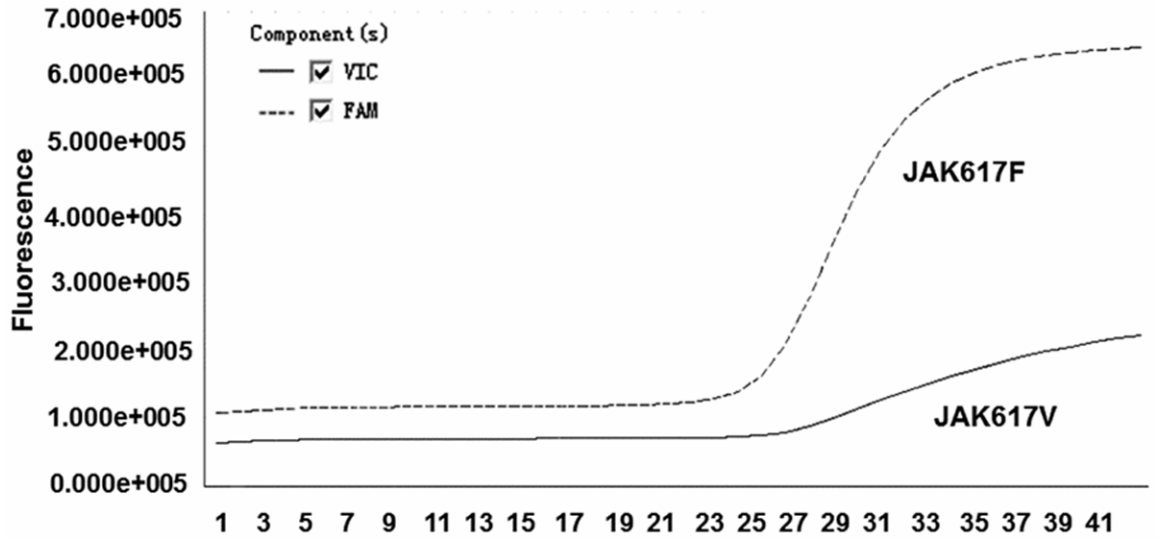

Figure 3. JAK2 V617F amplification curve for the detection of JAK2 V617 gene mutation. Fluorescence probe FAM represents JAK2 V617F mutants. VIC represents wild-type JAK2 V617F. The X axis indicates CT values, while the Y axis is fluorescence intensity. RNA was extracted from bone marrow cells for cDNA synthesis. The probes and primers were from Dalian Bio-Technology (China). Fluorescence quantitative PCR was performed with an initial 10 minutes of incubation at 95°C, followed by 40 cycles of 15 s at 95°C and 1 minute at 60°C.

bin, 82.0 g/L; platelet count, 355 × 10^9/L. The patient health condition improved and was discharged from the hospital. One month follow-up blood routine examination showed normal platelet, activated partial thromboplastin time of 31.90 s, and coagulation factor XII activity of 63%. Until August 2014, the patient is still in follow-ups.

Discussion

Coagulation factor XII deficiency is a kind of rare disease. Coagulation factor XII is also known as Hageman factor, which participates in the contact phase of the intrinsic coagulation system and initiates intrinsic coagulation pathway by activating coagulation factor XI. Coagulation factor XII can also change prekallikrein into kallikrein. In recent years, the fibrinolysis effect of coagulation factor XII attracts more and more concerns and is thought to be greater than the effect of coagulation factor XII in intrinsic coagulation pathway. Currently, researches on coagulation factor XII are mainly focused on cardiovascular and cerebrovascular diseases [5]. Patients with coagulation factor

XII deficiency had no tendency of hemorrhage, but potential risks of thrombosis. Some researchers suggest using coagulation factor XII activity and antigen levels as screening tests for prothrombotic state [6]. Most patients with coagulation factor XII deficiency have reduced antigen levels and activity of coagulation factor XII simultaneously, as well as negative cross reactive material. By now, only a few reports showed inconsistent coagulation factor XII antigen levels and activity [7], mainly due to abnormal structure of coagulation factor XII that led to positive cross reactive material.

The clinical manifestation of ET is significantly increased platelet number, accompanied with thrombosis and hemorrhage. The incidence of hemorrhage is 3.6-37%, with less severity. By contrast, thrombosis is often severe and becomes the major cause of death. The mechanism of hemorrhage in ET is not clear yet, but thought to be the following points. First, platelet dysfunction, reduced adhesion and aggregation functions, and abnormal release function [8, 9]. Second, abnormal coagulation mechanism. When platelet count is > 1500 × 10^9/L, hemorrhage was more frequently observed, probably due to the acquired defects of vWF [10]. In patients with myeloproliferative disease, deficiency of vWF polymers leads to protein dysfunction and elevated platelet count. Third, thrombosis, infarction, and infarct rupture. Fourth, drugs used in anti-thrombotic, anti-coagulant and anti-platelet treatments might cause severe hemorrhage.

The patient had obvious bleeding tendency. Coagulation tests showed significantly prolonged activated partial thromboplastin time (> 10 s). Coagulation factor activity tests showed normal VIII, IX and XI factor activity and reduced XII factor activity (by 12%). In contrast to reports by literatures, the patient with coagulation factor XII deficiency had severe bleeding, which indicated the combination with ET. Because the patient had no familial history of hemorrhage and coagulation factor XII levels returned to normal in follow-ups, it was highly possible that the patient had acquired coagulation factor XII deficiency. Studies indicated that coagulation factor XIIa inhibits thrombin-induced platelet aggregation by binding to glucoprotein Ib-IX-V complex on platelet surface [11]. Because of the excessive number of platelet in ET patients, the number of coagulation factor XIIa was reduced. The reduced activity of coagulation factor XII might indicate the prothrombotic state of the patient.

MPN accompanied with coagulation factor deficiency was rare. ET patients with significantly increased platelet number (≥ 1500 × 10^9/L) might have von Willebrand disease. Mori N et al. [2] reported a case of ET accompanied with acquired coagulation factor VIII deficiency. Kremyanskaya M et al. [3] also discovered a case of MPN accompanied with acquired hemophilia. However, there is no report on MPN accompanied with coagulation factor XII deficiency by now. From this case, more understandings about ET were raised. First, routine coagulation test and coagulation factor tests are necessary for the correct diagnosis of coagulation factor deficiency. Second, changes in the coagulation mechanism of the patient should be monitored during anti-coagulant and thrombolysis treatments of ET, in order to prevent severe hemorrhage. Third, patients with platelet number > 1500 × 10^9/L might have relatively high risks for the combination of acquired hemophilia or coagulation factor deficiency. For these patients, administration of aspirin should be restrained, and fresh plasma or coagulation factors should be supplemented when using hydroxyurea or interferon to inhibit the proliferation of megakaryocytes.

In conclusion, the relationship between coagulation factor XII deficiency and myeloproliferative disease is not clear yet. More clinical cases and experiences are still needed to understand the mechanism of coagulation factor XII deficiency as a complication or an accompanied disease.

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Disclosure of conflict of interest

None.

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