A case of Quebec platelet disorder with interstitial pneumonia

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To the Editor: The activity of fibrinolytic enzymes is complex. Abnormal bleeding can be caused by over-expression of plasminogen activators or a lack of fibrinolysis inhibitor. Quebec platelet disorder (QPD), an autosomal dominant disorder, with increased gene expression of PLAU encoding urokinase plasminogen activator (u-PA), causes a gain-of-function abnormality in fibrinolysis. Tissue plasminogen activator (t-PA) exists in various tissues and cells. When pulmonary interstitial cells are damaged, t-PA can be released and promote the activation of plasminogen. The interstitial pulmonary fibrosis (IPF) can cause vascular injury and leakage of t-PA, resulting in their elevation in alveoli.¹ Patients can present with fibrinolytic system abnormalities, and anti-fibrinolytic therapy combined with glucocorticoids can effectively prolong the survival time.

A 62-year-old man presented with a history of dermal ecchymosis and thrombocytopenia for 20 years, and interstitial pneumonia that was treated with glucocorticoids for 3 years. We carried out the following examinations: hematologic examinations, blood coagulation test, tumor assessment, and rheumatism series. The results of hematologic examinations showed: white blood cell 6.74 × 10⁹/L, hemoglobin 145 g/L, platelet 34 × 10⁹/L, red blood cell 1012/L, hemoglobin 145 g/L, platelet 34 × 10⁹/L, red blood cell 1012/L, and the D-dimer concentration increased significantly to 20,516 ng/mL. We tried to treat hypofibrinogenemia by fibrinogen infusion. However, the concentration of Fbg did not increase after fibrinogen infusion, and the skin ecchymosis of this elderly man did not improve. We realized that the pathogenesis of hypofibrinogenemia was hyperfibrinolysis, not the consumption of platelets and clotting factors. We changed the strategy by using fibrinolysis inhibitors (tranexamic acid) and anti-coagulants. Fortunately, the concentration of Fbg increased gradually, and the patient’s ecchymosis improved. Simultaneously, the concentration of D-dimer decreased gradually with fibrinolysis inhibitor therapy.

The patient said his father died many years ago and had a medical history of thrombocytopenia, but his parents and his daughter were not available for pedigree tracing. Fifteen years ago, the patient underwent surgery for great saphenous vein exfoliation with a decreased platelet count. His platelet count was lower than normal, the coagulation profile showed normal prothrombin time and activated partial thrombin time, but the fibrinogen (Fbg) concentration was 1.05 g/L, significantly lower than normal level; however, the D-dimer concentration was 17,452 ng/mL, significantly higher than normal. Furthermore, the activity of factor XIII (FXIII) was detected by a urea dissolution test. The positive results indicated that the activity of FXIII was decreased and the percentage of FXIII activity was 37.7%, slightly lower than normal. We did not find evidence of tumors or rheumatic diseases, and other “secondary causes” for decreased FXIII. The platelet function assay showed decreased aggregation of platelets after exposure to various stimulants, such as adenosine diphosphate, arachidonic acid, collagen, and epinephrine.

We performed bone marrow aspiration in 2017 and 2019. Bone marrow hemocytology indicated megakaryocyte maturation disorder. To increase the platelet count, we used 15,000 IU/day recombinant human thrombopoietin combined with 40 mg/day dexamethasone (days 1–4).² However, the platelet count remained below normal. In addition, the Fbg concentration progressively declined to 0.85 g/L, and the D-dimer concentration increased significantly to 20,516 ng/mL. We tried to treat hypofibrinogenemia by fibrinogen infusion. However, the concentration of Fbg did not increase after fibrinogen infusion, and the skin ecchymosis of this elderly man did not improve. We realized that the pathogenesis of hypofibrinogenemia was hyperfibrinolysis, not the consumption of platelets and clotting factors. We changed the strategy by using fibrinolysis inhibitors (tranexamic acid) and anti-coagulants. Fortunately, the concentration of Fbg increased gradually, and the patient’s ecchymosis improved. Simultaneously, the concentration of D-dimer decreased gradually with fibrinolysis inhibitor therapy.

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semi-quantitative polymerase chain reaction on his peripheral blood specimen. The results showed a normal PLAU copy number in plasma, and higher gene copy number of PLAU in platelets. This elderly male was diagnosed with QPD. After fibrinolysis inhibitor (tranexamic acid) therapy, his skin ecchymosis stopped.

We considered that the reduced platelet count and function were associated with megakaryocyte abnormalities in QPD. In QPD, the platelet aggregation function is reduced with plasma thrombopoietin levels decreasing dramatically. Therefore, the platelet counts are typically approximately 50% lower than normal.[3] Ectopic over-expression of u-PA in platelet alpha granules results in severe deficiency of factor V and activated plasminogen, leading to the degradation of fibrinogen. Delayed-onset bleeding (12–24 h after injury) occurs in QPD because u-PA can be released into the formed blood clots and accelerate clot lysis. In cases of hemostatic challenge (eg, elective surgery, extensive trauma, and tooth extraction), these patients experience excessive bleeding only when fibrinolytic inhibitors (eg, tranexamic acid and aminohexanoic acid) are not used. Therefore, oral fibrinolysis inhibitors can be used to treat patients with QPD.

Two years ago, this patient was diagnosed with interstitial pneumonia and prednisone (30 mg/day, with a gradual reduction in the daily oral dose) relieved his symptoms. We compared his CT images from 2 years ago [Figure 1A] and found that the interstitial exudative lesion was significantly improved [Figure 1B]. Inversely, the D-dimer concentration increased significantly to 20,516 ng/mL, and the Fbg concentration progressively declined to 0.85 g/L in 2019. We hypothesized that abnormal t-PA secretion by lung interstitial cells played an important role, and prednisone might have a limited effect on the prevention of disease progression and t-PA secretion.[4] There have been investigations about the use of anti-fibrotics in treating IPF.[5] The secondary hyperfibrinolysis of this patient is attributed to both the QPD and interstitial pneumonia.

This patient benefited from fibrinolytic inhibitors. Similar to the situation in other bleeding patients with QPD, platelet transfusions generally had no effect in this patient; however, fibrinolytic inhibitors disrupt interactions between plasminogen (plasmin) and lysine residues in fibrin, thus improving the symptoms of the patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and that due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

References


