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Case Report

Absolute immature platelet count helps differentiate thrombotic thrombocytopenic purpura from hypertension-induced thrombotic microangiopathy

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ABSTRACT

ADAMTS13 activity measurement is used in the diagnostic algorithm of thrombotic thrombocytopenic purpura (TTP), but results may not be available before initiation of therapeutic plasma exchange (TPE). The immature platelet fraction (%-IPF) and the calculated absolute immature platelet count (A-IPC) represent a test of real-time thrombopoiesis, and can be performed in most laboratories using automated analyzers. Here we report on using A-IPC kinetics to exclude idiopathic TTP in a patient with severe hypertension, thrombocytopenia, and acute renal failure, which was confirmed by a normal ADAMTS13. The complete resolution of thrombocytopenia occurred once blood pressure was controlled favoring a diagnosis of hypertension-induced thrombotic microangiopathy.

1. Introduction

Thrombotic microangiopathy (TMA) is defined clinically by the presence of thrombocytopenia and microangiopathic hemolysis. Multiple conditions can lead to a TMA presentation including idiopathic thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), severe hypertension, disseminated intravascular coagulation (DIC), systemic vasculitis, malignancy and medications [1].

Out of all TMA diagnoses, TTP has the highest potential for mortality. Clinical trials by the Canadian Apheresis Group decisively showed that therapeutic plasma exchange (TPE) improved the clinical outcomes of patients with TTP [2] from the high mortality that characterized the diagnosis in the pre-TPE era [3]. It is well documented that deficiency in ADAMTS13, a zinc-containing metalloproteinase of von Willebrand factor (vWF), plays a critical role in the pathogenesis of idiopathic TTP [4,5]. ADAMTS13 functions by preventing the formation of ultra-large vWF multimers that can mediate spontaneous platelet activation leading to microvascular thrombosis. ADAMTS13 deficiency, caused by genetic mutations or autoantibodies, can be diagnostic of TTP [5]. Nevertheless, at most institutions ADAMTS13 testing is a sent-out test with a long turnaround time. Often, TPE is initiated solely on clinical presentation before testing results are available, which may lead to unnecessary procedures and a delay in appropriate treatment of non-TTP patients [6].

Immature platelets are newly released from the bone marrow into the circulation with a larger size and greater RNA content than mature platelets [7]. The immature platelet fraction (%-IPF) and its derived absolute immature platelet count (A-IPC) represent a non-invasive test of real-time thrombopoiesis. A high %-IPF has been suggested as an indicator of thrombocytopenia due to rapid platelet consumption [8], while a low %-IPF is characteristic of bone marrow suppression states [9]. We have previously reported that %-IPF is helpful to adjust therapy in the setting of TPE-refractory TMA [10], and that A-IPC increments can

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be used to predict the clinical course of idiopathic TTP in response to therapy [11]. Here we report a case where %-IPF/A-IPC was used to exclude idiopathic TTP and diagnose hypertension-induced TMA.

2. Case description

A 25-year-old African-American female with a history of poorly controlled hypertension presented to our institution with a 3-day history of nausea, vomiting and abdominal pain. Her blood pressure (BP) was 236/133 mmHg, hemoglobin (Hb) 6.8 g/dL with extensive schistocytes on peripheral smear, lactate dehydrogenase 1102 U/L, haptoglobin <8 mg/dL, D-dimer 790 ng/mL, platelet count of 63×10^9/L, and creatinine 13.7 mg/dL. She had a similar episode 4 months earlier when she presented to an outside hospital with hypertension (223/126 mmHg), hemolytic anemia (Hb 7.4 g/dL), schistocytes on peripheral smear, platelet count of 66×10^9/L, and acute renal failure (creatinine 8 mg/dL). At that time, idiopathic TTP was suspected although never confirmed by ADAMTS13 testing. The patient was treated with three TPE and anti-hypertensive medications that led to platelet count normalization. On this admission to our institution she was treated with anti-hypertensive medications (Nicardipine, 40 mg i.v.; Labetalol 400 mg and Hydralazine 50 mg, p.o. three times/day; Amlodipine 10 mg, p.o., daily), and daily TPE was started on the second day of hospitalization. A sample for ADAMTS13 testing was obtained prior to TPE initiation and A-IPC was followed daily. As we previously described, the A-IPC of idiopathic TTP patients with ADAMTS13 deficiency is approximately 4×10^9/L at initial presentation with an increment to $>10 \times 10^9$/L in response to TPE [11]. The patient's A-IPC was 4.6×10^9/L on admission and remained unchanged at $5 \pm 1 \times 10^9$/L after three TPE procedures (Fig. 1A). In contrast, her platelet count almost doubled, reaching 110×10^9/L at the end of the third TPE. The fast rising platelet count and lack of A-IPC increases were inconsistent with the A-IPC kinetics of idiopathic TTP. In addition, her ADAMTS13 testing showed normal activity (80%; normal: > 66.7% activity), further excluding the diagnosis of idiopathic TTP. Based on these laboratory results, TPE was discontinued and treatment was focused on tight blood pressure control. Of notice, the patient was started on anti-hypertension regimens on the first day of hospitalization, and by the end of the 3-day-TPE treatment, her BP had decreased to 163/99 mmHg. Nine days post-TPE cessation, the patient's platelet count reached 150×10^9/L when BP stabilized at 154/89 mmHg which was sustained even 16 days post-admission (Fig. 1B).

The patient's clinical presentation was suggestive of idiopathic TTP; however, her history of poorly controlled hypertension, normal ADAMTS13 activity, lack of A-IPC increment in response to TPE, and the association of platelet count normalization with BP control favored a diagnosis of hypertension-induced TMA.

3. Methods

3.1. %-IPF measurement

The optical platelet count and %-IPF in the peripheral blood were obtained using Sysmex XE-5000 automated hematology analyzer, software 00–10, according to manufacturer's protocols (Sysmex America Inc., Mundelein, IL, USA) and as previously described [12]. Specifically, immature platelets were identified based on volume and fluorescence staining of the platelet's RNA, reported as a fraction of the optical platelet count (%-IPF). The A-IPC was derived by multiplying the %-IPF by the optical platelet count.

3.2. TPE protocol

TPE was performed using the COBE® Spectra Apheresis System (Terumo BCT, Lakewood, CO, USA) according to the manufacturer's recommendations, our institutional standard protocols, and as previously described [10]. In each procedure, a 1–1.5 plasma volume was exchanged with ABO/Rh-type specific fresh frozen plasma. Citrate dextrose-A was used as anticoagulant solution. One gram of calcium chloride in 250 mL normal saline at 60–70 mL/h was used as

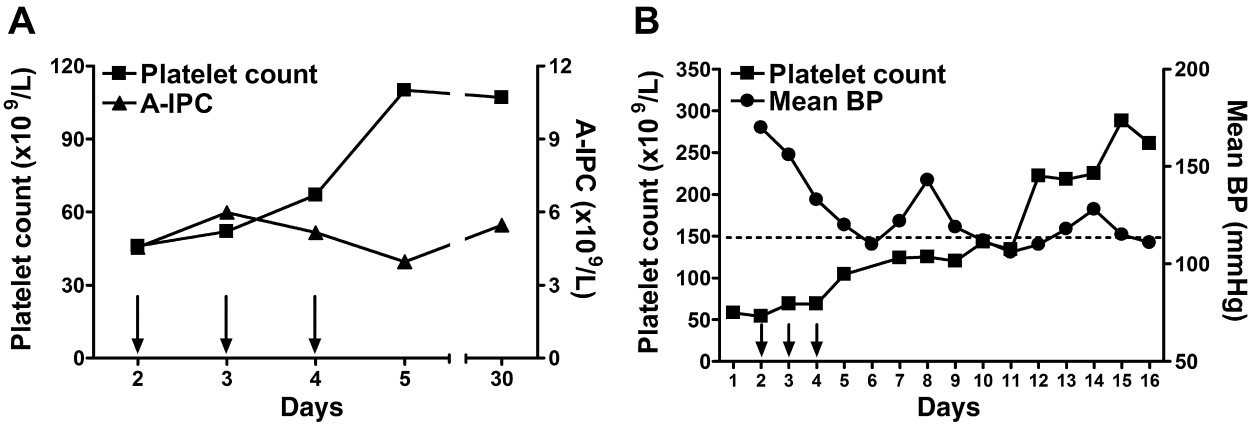

Fig. 1. (A) Platelet count and A-IPC kinetics during and after TPE treatment. Arrows indicate days of TPE procedures. (B) Platelet count comparison to mean systolic blood pressure. Normalization of platelet count was associated with successful blood pressure control. Dotted line represents the lower limit of normal range of platelet count.