

to substitute for IC in elderly patients or in patients who are younger but are unsuitable for IC because of severe comorbidities, as was the case for our patient, who presented with relatively indolent AML, displaying a normal karyotype and a low peripheral WBC count, the latter being an identified favorable prognostic factor to achieve a therapeutic response in AML patients treated with azacitidine [8]. In the context of a relatively non-aggressive disease which had shown a previous response to azacitidine, re-treatment with the same agent resulted in long-lasting disease control with a reduced BM blast count and significant hematological improvement, such that our patient presented the clinical features of a relatively indolent MDS rather than an aggressive myeloproliferative disorder, such as AML.

In conclusion, our case is indicative of the possibility of re-treatment with azacitidine in AML if the evolution to AML from high-risk MDS was related to a treatment interruption for reasons other than hematologic progression in patients who initially responded very well to hypomethylating therapy.

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Prevalent factor XII deficiency in cancer patients with isolated aPTT prolongation

TO THE EDITOR: Prolongation of activated partial thromboplastin time (aPTT) is one of the common problems in the field of consultative hematology. When considering a patient with aPTT prolongation, other combined coagulation abnormalities should be identified first. If prolongation of prothrombin time (PT) or thrombocytopenia is also observed, possible causes such as liver disease or disseminated intravascular coagulation may be considered as one of the differential diagnoses. If a patient has no other coagulation abnormalities, including PT prolongation, thrombocytopenia, or decreased fibrinogen level, the patient can be considered to exhibit isolated aPTT prolongation. Isolated aPTT prolongation should be carefully examined, because hemophilia may also be present in this population [1]. In addition, confirmation through repeated tests is also needed, because various laboratory errors, including inadequate venous puncture, delayed analysis, incorrect preparation of plasma, and use of heparin, may cause isolated and transient aPTT prolongation.

The plasma mixing test is the cornerstone test for the initial differential diagnosis of persistent and isolated aPTT prolongation; corrected cases suggest factor deficiency, while uncorrected cases suggest the presence of an inhibitor, such as lupus anticoagulant [2]. We examined the cause of isolated aPTT prolongation in cancer patients before cancer surgery.

We found that most patients with isolated aPTT prolongation who were scheduled for cancer surgery had factor deficiency (88.8%), primarily factor XII (75.0%). Intrinsic factors of the coagulation pathway were measured in 44 patients (Fig. 1). Clinical data, including the history of bleeding tendency, type of surgery, and post-operative bleeding or thromboembolic outcomes, as well as laboratory results, including aPTT, change in hemoglobin level, activities of factors VIII, IX, XI, XII, von Willebrand factor antigen (vWF:Ag), and vWF ristocetin cofactor (vWF:RCo), were

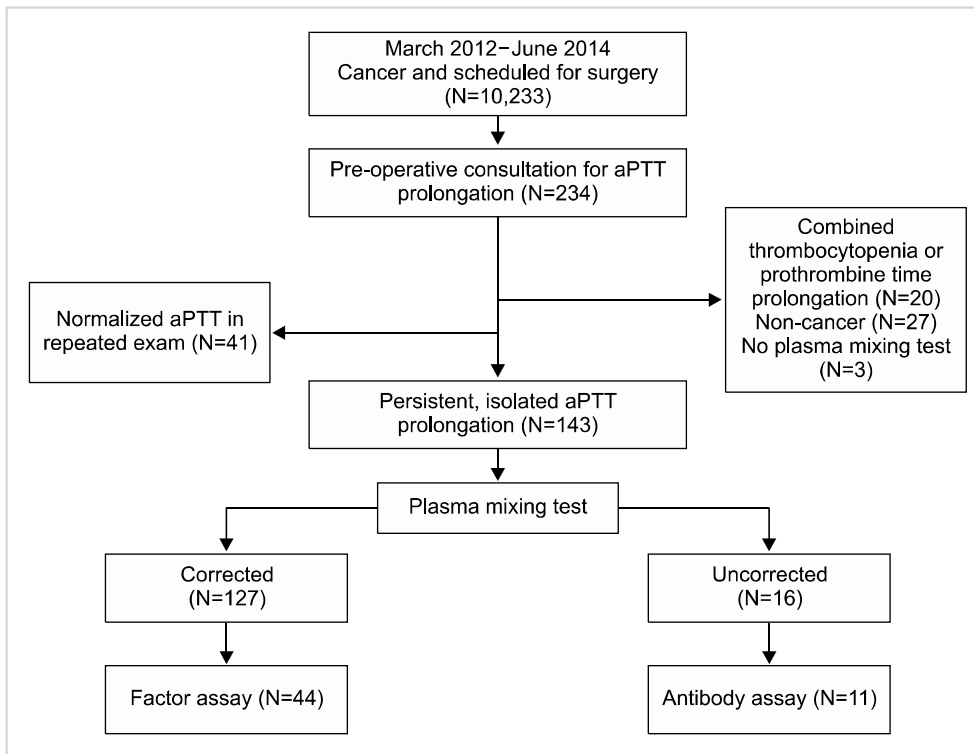


Fig. 1. Flowchart of patient selection. Abbreviation: aPTT, activated partial thromboplastin time.

retrospectively reviewed. Bleeding risk associated with surgery was stratified as previously reported [3]. Surgeries associated with a high bleeding risk were as follows: coronary artery bypass, heart valve replacement surgery, intracranial or spinal surgery, aortic aneurysmal repair, peripheral artery bypass, other major vascular surgery, major orthopedic surgery (e.g., hip or knee replacement), reconstructive plastic surgery, major cancer surgery, prostate surgery, and bladder surgery. The median age was 53 years (range, 24–81 years), and 29 patients (65.9%) were female. Twenty-two patients (50.0%) were scheduled for surgery due to thyroid cancer, and 13 patients (29.5%) were scheduled to undergo an operation with a high risk of bleeding (Table 1).

Among 44 patients, 75.0% had factor XII deficiency. Factor VIII and XI deficiency was detected in 25.0% and 20.5% of patients, respectively. In contrast, there was no patient with factor IX deficiency. Only a small percentage of patients showed vWF:Ag and vWF:RCo deficiency (7.5% and 2.5%, respectively; Table 2). The decrease in peripheral blood hemoglobin and hematocrit after surgery was -1.1 ± 0.9 g/dL and $-3.8 \pm 3.4\%$ (mean \pm standard deviation), respectively. Post-operative events, including emergency operation and red blood cell (RBC) transfusion due to bleeding during or after surgery, occurred in only three patients. There was no thromboembolic event in 44 patients.

The first patient was a 53-year-old woman who had mild coagulation factor VIII deficiency (FVIII:C 41%) and who underwent left lobectomy of the thyroid and neck dissection due to thyroid cancer. She had experienced hematoma at the surgical site and underwent an emergency operation

Table 1. Baseline characteristics.

Variables	Subgroup	N (%)
Total No.		44 (100%)
Gender	Male	15 (34.1%)
	Female	29 (65.9%)
Cancer type	Thyroid cancer	22 (50.0%)
	Head and neck cancer	4 (9.1%)
	Lung cancer	3 (6.8%)
	Gastrointestinal cancer	3 (6.8%)
	Gynecologic cancer	5 (11.4%)
	Genitourinary cancer	3 (6.8%)
	Others	4 (9.1%)
Surgery	High risk	13 (29.5%)
	Others	31 (70.5%)
Age, median (range)		53 yr (24–81)
aPTT, median (range)		47.1 sec (43.7–54.4)

Abbreviation: aPTT, activated partial thromboplastin time.

for hematoma evacuation on post-operative day 26. Unfortunately, we could not confirm the causal relationship between factor deficiency and the post-operative bleeding event in this case. The second patient was a 66-year-old woman with gynecological cancer. She had undergone major operations, including total colectomy, omentectomy, and peritonectomy and experienced post-operative disseminated intravascular coagulation. Accordingly, transfusion was needed in this patient. She had mild factor XII deficiency (FXII:C 39%) before surgery. The last patient was a

Table 2. Results of coagulation factors of the intrinsic pathway.

Factor	N	Median (%)	IQR (%)	Reference range (%)	Subnormal value (%; patients)	
VIII	44	84	60–113	60–150	25.0% (11/44)	
IX	44	96.5	82.5–116.5	60–150	None	
XI	44	80.5	63–103.5	60–140	20.5% (9/44)	
XII	44	49.5	41.5–71.5	60–140	70.5% (31/44)	
vWF:Ag	40	99.8	63.2–123.2	47–197	7.5% (3/40)	
vWF:RCo	O blood group	22	85.6%	69.6–160.4	52–154	None
	Non-O blood group	18	116.45%	103.9–145.9	60–200	5.6% (1/18)

Abbreviations: IQR, Interquartile range; vWF:Ag, von Willebrand factor antigen; vWF:RCo, von Willebrand factor ristocetin cofactor.

52-year-old man. He received bilateral T8–L3 posterior fixation due to spinal cord compression. He needed RBC transfusion due to intra-operative bleeding, although coagulation factor deficiency was not found. We could not detect a significant association between coagulation factor deficiency and post-operative bleeding in patients with cancer and isolated aPTT prolongation.

Our findings demonstrated that the main cause of isolated aPTT prolongation in patients with cancer might be a factor deficiency rather than the presence of an inhibitor such as lupus anticoagulant. In addition, the most commonly deficient factor was coagulation factor XII. In contrast, a previous study investigating the cause of isolated aPTT prolongation in general patients in an acute care setting demonstrated that the prevalent cause of aPTT prolongation was the presence of lupus anticoagulant [4]. When considered with our results, this suggests that the etiology of isolated aPTT prolongation might differ according to the disease subgroup. To our knowledge, the current study is the first to examine and report the cause of isolated aPTT prolongation and the frequency of factor deficiency of the intrinsic coagulation pathway in patients with cancer.

Factor XII deficiency, a rare congenital disorder, has sporadically been reported in case reports worldwide. Moreover, until the current report, there was only one report of three cases with genetically confirmed severe congenital factor XII deficiency in Korean patients [5]. Except for sporadic case reports, there have been only a few studies investigating factor XII deficiency in the clinical context. Factor XII deficiency is also known to be associated with thromboembolism as well as bleeding risk [6].

One Greek report showed that factor XII activity was significantly lower in women who experienced recurrent spontaneous abortion, while all normal controls had normal factor XII activity [7]. However, there was no peri-operative thromboembolic event in our study population. Furthermore, factor XII deficiency was not associated with post-operative bleeding events, though one female patient with mild factor XII deficiency received RBC transfusion after a major operation.

Although the degree of factor XII deficiency in our patients with cancer was mild and the definition of the lower

limit of normal for factor XII is somewhat variable (54% to 70%) [8, 9], we consider it valuable to report an unexpected high incidence of factor XII deficiency in patients with cancer and isolated aPTT prolongation.

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Pseudo gray platelet syndrome: the first case report in Korea

TO THE EDITOR: Currently, the most common blood test in hospitals, complete blood count (CBC), is typically performed by automated hematology analyzers. However, pseudothrombocytopenia caused by pseudo gray platelet syndrome (PGPS) might cause errors in CBC test results. Here we report what we believe to be the first reported case of PGPS in Korea.

CASE

The patient was a 46 year-old woman who came to our hospital for a general health checkup. She had no history of bleeding tendency, and neither did any of her three sisters. She had one son and one daughter who were fraternal twins; also without history of bleeding tendency. Her blood was collected into ethylenediaminetetraacetic acid dipotas-

sium salt dehydrate (EDTA-2K, 3.3 mmol/L) and the CBC was measured using a Sysmex XE-2100 (Sysmex, Kobe, Japan). During the general health checkup, CBC had been studied with the blood collected in the EDTA tube. The CBC results included a platelet count of $63 \times 10^9/L$, white blood cell (WBC) count of $3.31 \times 10^9/L$, and hemoglobin level of 13.0 g/dL. The mean platelet volume (MPV) and platelet distribution width (PDW) were 'unmeasurable'. Based on these findings, we made a peripheral blood film. The blood film showed gray agranular platelets with aggregation (Fig. 1A).

The patient returned after six days for a follow-up CBC. This time, the blood was collected into both EDTA and sodium citrate tubes. The platelet count of blood in sodium citrate was $261 \times 10^9/L$, with a WBC count of $4.72 \times 10^9/L$ and hemoglobin level of 12.0 g/dL. The MPV was 11.4 fL (normal range, 7.9–11.8) and PDW was 13.5 fL (normal range, 9.1–19.4). Blood films were prepared immediately after venipuncture from both EDTA and citrate tubes. The EDTA blood showed poorly stained agranular gray platelets (Fig. 1B) while the blood in sodium citrate showed normal platelets with purple-stained granules (Fig. 1C). We also used electron microscopy (EM) to examine the platelets, using a transmission electron microscope (Jeol, JEM-1010, Tokyo, Japan) to examine cellular structure. Platelet-rich plasma (PRP) was separated by centrifugation at $100 \times g$ for 10 minutes at room temperature. Before EM, PRP samples were fixed, dehydrated in 35% ethanol for 15 minutes, and then embedded, sectioned into ultra-thin slices (70 nm), and stained in uranyl acetate for 2 hours. Platelet activation was apparent and only a few storage granules were found in EDTA blood (Fig. 2A). However, no platelet activation was present in sodium citrate and many α -granules were visible in the cytoplasm (Fig. 2B).

DISCUSSION

We report a case of PGPS. The patient had pseudothrombocytopenia and agranular platelet morphology similar to gray platelet syndrome (GPS). Unlike GPS, however, this finding was noted only when the blood was collected into the EDTA-containing tube, and not when the blood was

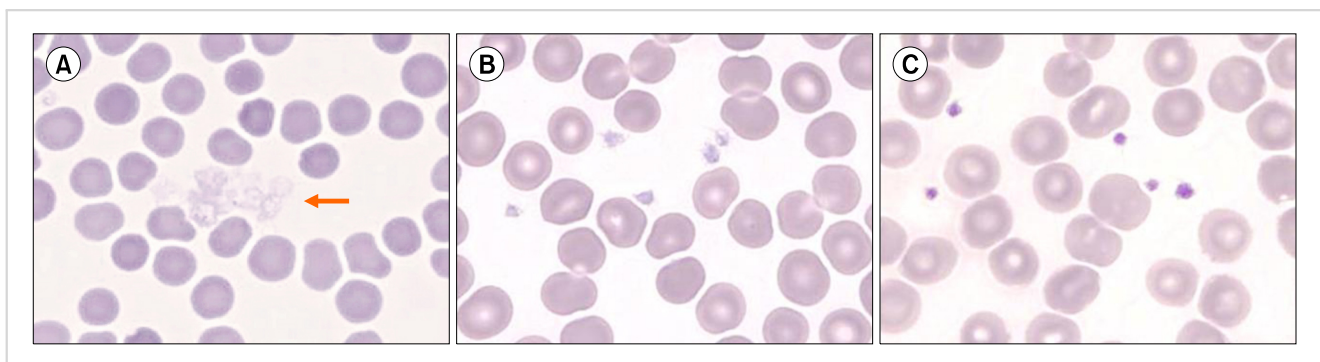


Fig. 1. Pseudo gray platelets. (A) Blood collected in EDTA 4 hours prior showing aggregated agranular gray platelets (arrow). (B) Blood collected into EDTA showing large and pale agranular platelets. (C) Blood collected into sodium citrate showing normally stained platelets with tiny purple granules. Blood films were prepared immediately after venipuncture ($\times 1,000$, Wright-Giemsa stain).