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Ethylenediaminetetraacetic Acid-dependent Platelet Aggregation, Satellitism, and Phagocytosis in a Case in Which Aggregation was Resolved using Kanamycin Blood Collection Tubes

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Abstract

BACKGROUND: This study aimed to investigate ethylenediaminetetraacetic acid (EDTA)-dependent pseudothrombocytopenia (EDTA-PTCP) a rare but significant phenomenon in clinical laboratories that cause diagnostic errors and unnecessary treatments.

CASE PRESENTATION: Here, we present an 83-year-old male patient with dyspnea and blood sputum and illustrate how EDTA, commonly used in complete blood count testing, causes falsely low platelet counts due to platelet aggregation and phagocytosis. Initially, the patient's blood tested by the impedance method with a Sysmex XN-3000 analyzer demonstrated abnormally low platelet counts. However, further tests using different assays (fluorescent platelet count) and anticoagulants indicated the presence of EDTA-PTCP. Blood smear revealed platelet aggregation, satellitism, and phagocytosis that predominantly involve neutrophils. Remeasurements demonstrated significant improvement in platelet count and histogram waveform after incorporating K2-EDTA-added blood to K2-EDTA + kanamycin (KM)-containing vacutainer. These results indicate that remeasuring platelet counts after dissociation of platelet aggregation in EDTA-added blood with an additive such as KM is an effective method of handling EDTA-PTCP when platelet aggregation is observed. In addition, in vitro mixing studies were conducted with healthy control using platelet-poor plasma (PPP), prepared from EDTA and EDTA + KM blood collection tubes. It demonstrated that adding PPP from EDTA + KM tubes to whole blood did not decrease platelet count over time, unlike PPP from EDTA tubes. This revealed that KM, an aminoglycoside antibacterial agent, inhibited platelet aggregating factors in the patient's plasma. The patient's positive results for anti-ds-DNAIgG antibodies indicated active systemic lupus erythematosus, emphasizing a potential immunological mechanism of EDTA-PTCP in autoimmune diseases.

CONCLUSION: The study reveals that EDTA causes platelet satellitism and phagocytosis by leukocytes, although the exact mechanism of EDTA-induced platelet phagocytosis remains unclear. In conclusion, this case demonstrates that using blood collection tubes other than those containing EDTA salt is a viable option in various laboratories, emphasizing the need for awareness and appropriate management of EDTA-PTCP in clinical practice.

Introduction

Complete blood count (CBC) testing is one of the most prevalent and routine clinical tests performed today and plays a crucial role not only in diagnosis but also in patient monitoring and prognostication [1]. Many automated hematology analyzers combine measurement principles, such as impedance methods, to ensure the accuracy and reproducibility of clinical specimen results, and these analyzers detect red blood cell, white blood cell, and platelet abnormalities with good sensitivity. However, measurement variations due to various hematological artifacts remain a challenge for some automated analyzers [2], [3].

Pseudothrombocytopenia (PTCP) is an *in vitro* phenomenon that is characterized by various etiologies that cause falsely low platelet counts based on the hematology analyzer used. These include anticoagulant-induced platelet agglutination, platelet satellitism, cold-induced agglutinins, oversized platelet occurrence, minuscule thrombi formation, and flawed techniques in blood sample collection [4].

Ethylenediamine tetraacetic acid (EDTA) is prominently used as an anticoagulant for CBC testing, and EDTA-dependent pseudothrombocytopenia (EDTA-PTCP) has been reported to occur at a frequency of approximately 0.09–0.21% using EDTA [5], [6]. Based on the frequency of EDTA-PTCP, it is a rare phenomenon, occurring more frequently in a variety of

patients, including those with autoimmune diseases, neoplastic diseases, cardiovascular diseases, and liver diseases, but can also occur in healthy individuals [7]. Platelet aggregation by EDTA salts is categorized into two main types: Platelet aggregation and platelet satellitism, which is observed adherence of platelets to polymorphonuclear leukocytes. It has been reported that platelet aggregation is caused by a change in the epitope on platelet membrane protein glycoprotein (GP) IIb/IIIa due to the chelation of divalent cations by EDTA salt and the reaction of immunoglobulins and other substances in the blood [8], [9], [10], [11].

EDTA-PTCP is a relatively uncommon clinical laboratory result, but it causes diagnostic errors, overtreatment, such as unnecessary platelet transfusions, and invasive and unnecessary testing such as bone marrow testing [12]. Therefore, the true platelet count should be reported to the clinical side when EDTA-PTCP is observed, considering the blood collection technique, anticancer therapy, and etiology.

Herein, we report a rare case in which the use of EDTA as an anticoagulant in a blood collection tube caused simultaneous platelet aggregation, satellitism, and phagocytosis by neutrophils. Platelet satellitism is an even rarer phenomenon in EDTA-PTCP, with an estimated frequency of 0.008%. It is characterized by platelet rosetting around neutrophils and in rare cases around other blood cells, causing pseudothrombocytopenia in the impedance method [13].

Moreover, we discuss the results of an *in vitro* mixing study with a healthy control, conducted to confirm whether the platelet aggregation in this case was EDTA dependent. In recent years, the addition of kanamycin (KM), used as an antimicrobial agent, has become a popular method for EDTA-dependent platelet aggregation [14], [15]. However, responding to a case, such as the one presented here, in which platelet aggregation, satellitism, and phagocytosis by neutrophils occurred simultaneously, remains unclear. Here, we describe our experience using KM to improve platelet counts in patients with EDTA-PTCP with multiple findings.

Case Report

An 83-year-old male patient who had dyspnea and occasional blood sputum was referred to our hospital because of the lack of treatment efficacy at the previous hospital. The blood specimen was collected directly from the veins using a drawing needle, tube holder, and a K2-EDTA-containing vacutainer (NIPRO CORPORATION, Osaka, Japan). It was processed within 1 h after collection and analyzed at our laboratory.

Table 1 shows laboratory data. The white blood cell count was 8,300/μL, which was within the normal range, whereas hemoglobin (Hb) was 10.7 g/dL and platelet was 4.9 × 10^4/μL, which was low. The aspartate aminotransferase (AST) was 40 U/L, alanine aminotransferase (ALT) was 34 U/L, and γ-glutamyl transpeptidase (γ-GT) was 78 U/L, which were slightly high, indicating abnormal liver function, and C-reactive protein was 12.26 mg/dL, which was high and confirmed an inflammatory response (reference range: ≤0.14 mg/dL). The XN-3000 automated hematology analyzer (Sysmex Corporation, Hyogo, Japan) is used for CBC testing in our laboratory, but the initial measurement of 4.9 × 10^4/μL was made by the impedance mode (PLT-I). Further, the counting result improved to 10.8 × 10^4/μL when we suspected some kind of artifact and reperformed the measurement using the fluorescent platelet mode (PLT-F). However, a blood smear was prepared for microscopic observation since the histogram at the time of platelet measurement was abnormal, which revealed platelet aggregation, satellitism, and phagocytosis mainly due to neutrophils (Figure 1). Therefore, the patient specimens remaining after the CBC measurement were transferred to blood collection tubes with different compositions, in which EDTA and the antibacterial drug KM were used as anticoagulants, and the measurements were reperformed. The procedure in detail is described below. The patient's whole blood at 1 ml was added to the K2-EDTA + KM-containing vacutainer (NIPRO CORPORATION, Osaka, Japan) blood collection tube, agitated for 30 s using a vortex, mixed for 5 min, and remeasured in impedance mode (PLT-I).

The result revealed further improved platelet to 17.0 × 10^4/μL and a similar waveform of the histogram to that of the normal measurement. Blood smears were prepared from the EDTA + KM collection tubes and observed under a microscope in terms of the EDTA collection tubes. Platelet satellitism and phagocytosis were determined by visual judgment of 100 neutrophils by a medical technologist, and the percentages of neutrophils with at least five platelets adhering to the cell periphery and neutrophils phagocytosing platelets were calculated. The results revealed that dissociation of platelet aggregation occurred when blood was added from the EDTA to the EDTA + KM collection tube, and platelet adhesion was dissociated from neutrophils, despite the slight presence of platelet adhesion around neutrophils. However, there was no obvious improvement in platelet phagocytosis by neutrophils (Figure 2).

We conducted periodic acid–Schiff (PAS) staining of blood smears to confirm that the pericellular cells observed on the smears during EDTA addition were platelets. The PAS stain is prominently used as an adjunctive test for inflammatory and infectious skin diseases, but it is also used to stain platelets. Figure 3 shows the staining results. Many platelets were observed around neutrophils, with platelet phagocytosis in some.

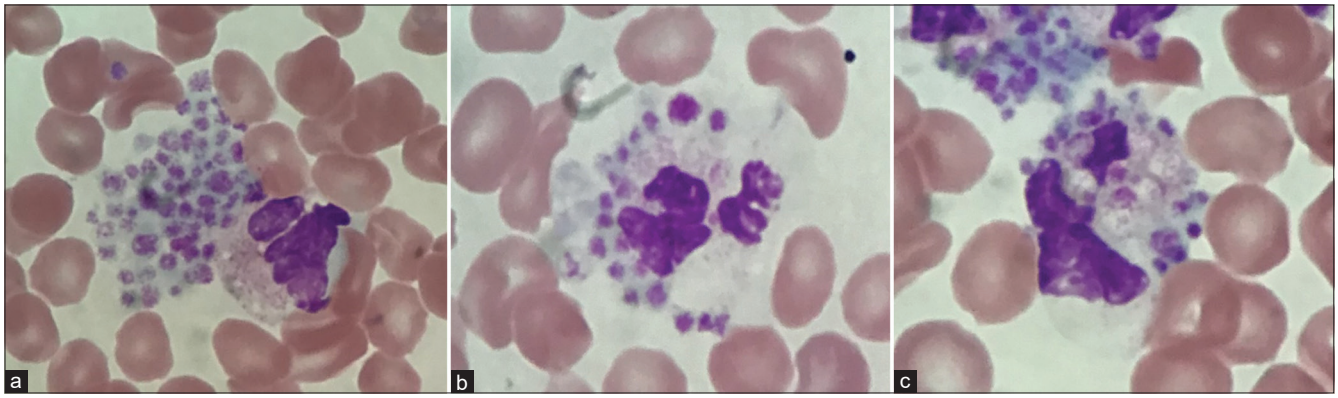


Figure 1: Blood smears when ethylenediaminetetraacetic acid salts were used as an anticoagulant (×100 oil immersion). (a) Platelet aggregation, (b) Platelet satellitism, (c) Platelet phagocytosis

Platelet phagocytosis was reported to be induced in healthy control by adding plasma from patients with EDTA-dependent platelet phagocytosis to the whole blood of healthy control *in vitro* [16]. Therefore, a mixing test with plasma addition was performed as an additional study to confirm that platelet aggregation in the present case is EDTA-dependent and that platelet phagocytosis can be induced in healthy control *in vitro*. Healthy control whose ABO matched that of the cases were selected as the subject for the additional study.

Table 1: Laboratory data

Complete blood count		Biochemistry			
WBC	8,300/μL	TP	6.1g/dL	LDL-C	49mg/dL
Stab	0.5%	Alb	3.1g/dL	HDL-C	32mg/dL
Seg	84.5%	T-Bil	0.7mg/dL	Fe	28μg/dL
Eo	0.5%	D-Bil	0.4mg/dL	Ferri	194ng/mL
Lym	6.0%	AST	40U/L	Na	122mmol/L
Mono	7.5%	ALT	35U/L	K	3.6mmol/L
A-Lym	1.0%	γ-GT	77U/L	Cl	87mmol/L
RBC	324×10⁴/μL	ALP	86U/L	Ca	8.1mg/dL
Hb	10.7g/dL	AMY	30U/L	IgG	1,230mg/dL
Hct	30.8%	LD	357U/L	IgA	235mg/dL
Plt	4.9×10⁴/μL	CRP	12.11mg/dL	IgM	56mg/dL
MCV	95fL	BUN	20.7mg/dL	Other	
MCH	33.0pg	Cre	0.93mg/dL	Anti-dsDNAIgG Antibody	18.50U/mL
MCHC	34.7%	TG	49mg/dL		(Positive)

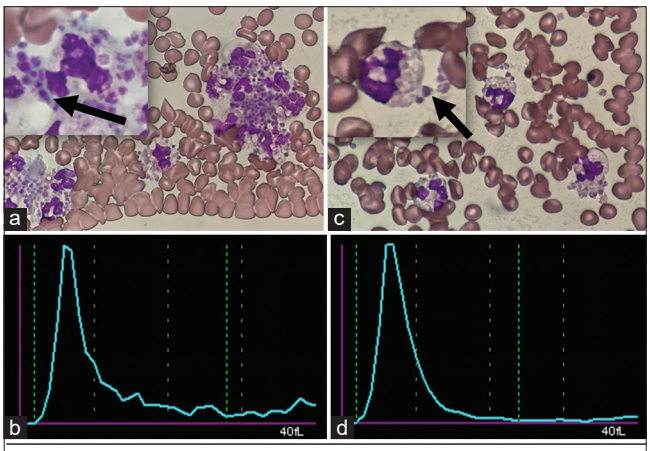
Platelet-poor plasma (PPP) was obtained by centrifuging anticoagulated whole blood from patients' EDTA and EDTA + KM collection tubes at 3,000 g for 15 min in the mixing study. The resulting EDTA- and EDTA + KM-derived PPP were mixed in equal volumes with healthy control that did not demonstrate EDTA aggregation. The two conditions performed in this study are described below.

1. PPP from EDTA blood collection tube of patient + whole blood of healthy control
2. PPP from EDTA + KM blood collection tube of patient + whole blood of healthy control.

Figure 4 shows the change over time in platelet counts when the platelet count is set at 100% immediately after mixing, and blood smears at each time point after the addition of EDTA-derived PPP. The results revealed that adding PPP obtained from EDTA + KM blood collection tubes to whole blood without causing EDTA agglutination did not decrease the platelet count over time. However, a decrease in platelet count was observed over time when EDTA-derived PPP was added, and platelet aggregation, satellitism, and phagocytosis by neutrophils were observed in the specimens over time.

Discussion

Here, we report a case of EDTA-dependent platelet aggregation, satellitism, and phagocytosis in a patient in which aggregation was resolved using KM blood collection tubes.



	Anticoagulant used	
	EDTA (PLT-I)	EDTA-KM
Automated platelet count (/μL)	4.9×10^4	17.0×10^4
Platelet aggregation	Present	Slightly present
Platelet satellitism	Present (84%)	Slightly present (8%)
Platelet phagocytosis	Present (15%)	Present (13%)

EDTA : ethylenediamine tetra acetic acid

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Figure 2: Comparison of platelet counts, histograms, and blood smear results in ethylenediaminetetraacetic acid (EDTA) and EDTA + KM. Blood smear when using an EDTA collection tube. (a) PLT histogram when using EDTA blood collection tubes. (b) Blood smear when using an EDTA + KM collection tube, (c) PLT histogram when using EDTA + KM blood collection tubes, (d) Comparison of platelet counts and blood smear results using EDTA and EDTA + KM

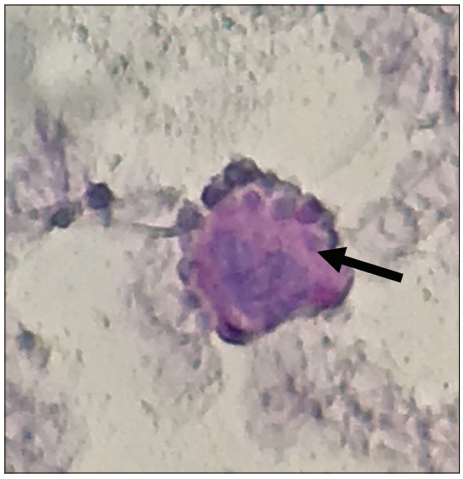

Figure 3: PAS staining

On admission, the blood smear demonstrated platelet satellitism and phagocytosis by neutrophils, with pseudothrombocytopenia. Those platelet aggregation and phagocytosis may have caused the platelet count to be very low at 4.9 × 10^4/μL. The platelet measurement method used for the initial measurement was the impedance method, which did not count the aggregated platelets, causing a false low value. Therefore, we reperformed measurement using the XN-3000's fluorescent platelet mode (PLT-F), which selectively stains platelets with oxazine dye.

PLT-F selectively stains platelets with oxazine dye after specimens are diluted with the diluent in the XN-3000. Specimens are measured by flow cytometry after reagent treatment, and platelet in PLT-F is measured by detecting information from lateral fluorescence and forward scattered light. The advantage of PLT-F is that it is less susceptible to crushed erythrocytes and small erythrocytes and measures approximately 5 times more specimens than the impedance method PLT-I, allowing accurate measurement of even specimens with low platelet counts [17], [18], [19]. PLT-F remeasurement demonstrated some improvement to 10.8 × 10^4/μL but remains below the reference range (reference range: 15–35 × 10^4/μL). Platelet aggregation was observed after PLT-F measurement, thus 1 mL of the patient specimens remaining was added to an EDTA + KM blood collection tube and remeasured after processing, revealing a platelet count of 17.0 × 10^4/μL.

The blood smears prepared from EDTA + KM showed a slight amount of platelet adherence around neutrophils, but there was a significant improvement, and the platelet was within the reference range. However, the use of anticoagulants other than EDTA and the incorporation of different additives, such as aminoglycoside antibiotics, into blood samples as a proactive step before conducting a blood cell count, have been recommended.

From previous reports, no significant changes in platelet count or blood cell morphology were observed after incubation at room temperature for 150 min when KM was preadded to EDTA to anticoagulated blood from patients with EDTA-PTCP. Furthermore, rapid dissociation of platelets without obvious changes in blood cell morphology was observed when KM was added to EDTA-anticoagulated blood samples from patients with EDTA-PTCP within 30 min of blood collection, and complete blood cell count and histogram patterns were similar to those examined immediately after blood collection. These results reveal that the addition of aminoglycoside antibiotics is an effective method for diagnosing EDTA-PTCP and assessing platelet counts in affected patients, either before or after blood sampling [15], [20].

Based on these previous reports, our laboratory has been reassessing EDTA-PTCP by adding EDTA blood to the EDTA + KM blood collection tube when EDTA-PTCP is detected. An additional mixed study revealed that the platelet counts decreased over time in healthy control when PPP obtained from the patient's EDTA collection tube was added, but not when EDTA + KM was added, indicating that this was an EDTA-dependent thrombocytopenia and that the addition of KM, which is an aminoglycoside antibacterial agent, inhibited platelet aggregating factors in the patient's plasma.

Moreover, the biochemical tests listed in Table 1 showed ferritin of 194 ng/mL (male reference range: 39.4–40 ng/mL), which is within the reference range. We initially suspected hemophagocytic lymphohistiocytosis (HLH) because platelet phagocytosis was observed in the blood smear. However, ferritin of ≥500 μg/L meets the criteria for hyperferritinemia according to the HLH-2004 guidelines [21], but adult patients with HLH were found to have markedly higher ferritin levels, so HLH was not actively suspected.

EDTA-PTCP has also been reported in patients with systemic lupus erythematosus (SLE), and the patient presented here was positive for anti-ds-DNAIgG antibodies, indicating active SLE [22].

Although the mechanism of EDTA-PTCP remains unclear, it may be due to an immunological mechanism of aggregation against GPIIb/IIIa, a glycoprotein on the platelet surface. The mechanism of platelet satellitism remains unknown, but it is thought of as a bridge formation between platelets and FcγRIII on neutrophils, which is mediated by IgG autoantibodies directed against the EDTA-induced epitope of platelet GP IIb/IIIa [23]. The patient in this case had an autoimmune disease, such as SLE, which was thought to predispose to EDTA-PTCP due to autoantibodies. However, the mechanism of platelet phagocytosis induced by EDTA salt remains unclear, although studies reported severe infection and malignant lymphoma [24], [25].

Other laboratory reports included platelet counts when EDTA-PTCP is observed, with blood collected again with an anticoagulant different from EDTA, such as heparin or sodium citrate.

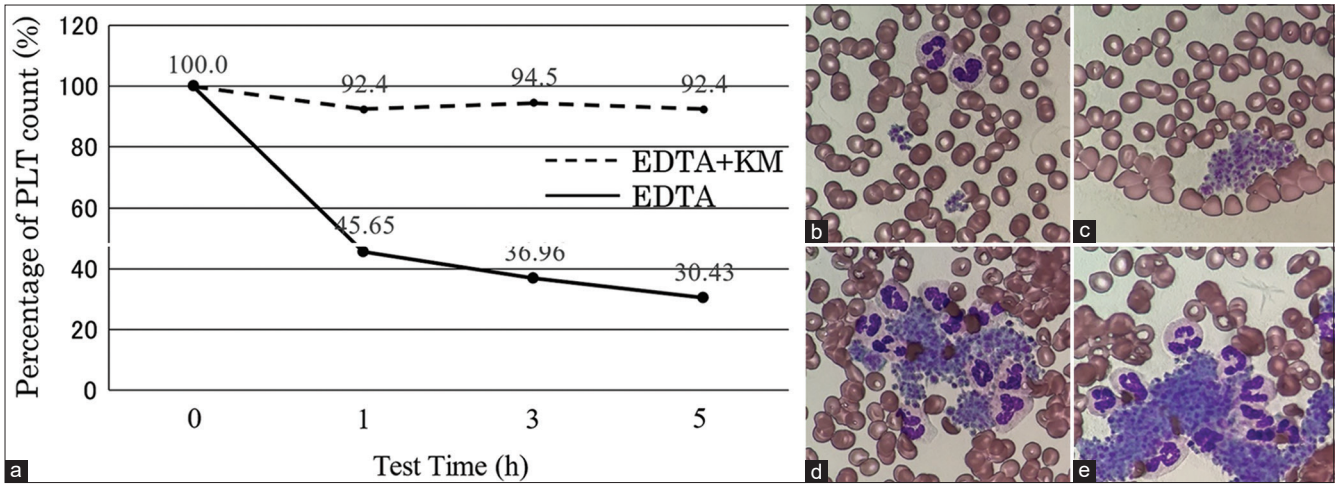

Figure 4: Eventual and morphological changes when platelet values immediately after mixing are set at 100%. (a) Changes over time in platelet counts after adding patient plasma, (b) Blood smear in ethylenediaminetetraacetic acid (EDTA) collection tube immediately after adding patient plasma, (c) Blood smear in EDTA collection tube 1 h after adding patient plasma, (d) Blood smear in EDTA collection tube 3 h after adding patient plasma, (e) Blood smear in EDTA collection tube 5 h after adding patient plasma

The present study revealed that platelet aggregation dissociation and neutrophil adhesion were greatly improved by adding blood to EDTA + KM blood collection tubes after EDTA collection, not only in patients with simple EDTA-dependent platelet aggregation but also in those with platelet satellitism. However, platelets phagocytosed by neutrophils do not change in the phagocytosis rate of neutrophils when blood is transferred to the EDTA + KM blood collection tubes and are reported as less than the original platelet values. However, the advantage of the method using the EDTA + KM blood collection tube introduced here is that it requires blood drawing once and the burden on the patient is small.

In the future, we plan to examine whether similar results can be obtained when cases such as the one presented here are observed, and further additional studies will contribute to the elucidation of these mechanisms.

Conclusion

Herein, we described a rare case in which platelet aggregation, satellitism, and phagocytosis were observed when EDTA salt was used as an anticoagulant. We reported that the use of blood collection tubes with EDTA + KM added as an anticoagulant is useful not only for EDTA-dependent platelet aggregation, which is rare but is encountered in routine testing but also for very rare phenomena, such as platelet satellitism, described here. However, it was possible to report the patient's original platelet count to some extent, although it should be noted that platelets adhere slightly around leukocytes even after EDTA blood is added to the EDTA + KM collection tube and that once platelets are phagocytosed by neutrophils, they remain phagocytosed after transfer to the EDTA+KM collection tube. The use of EDTA + KM for reporting results is considered applicable to EDTA-PTCP regardless of the size of the laboratory.

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