



Ethylenediaminetetraacetic Acid (EDTA)-Induced Thrombocytopenia: A Case Report

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Abstract

Ethylenediaminetetraacetic Acid (EDTA)-Induced Thrombocytopenia is a fairly rare *in vitro* immunological mediated phenomenon characterized by a spuriously low platelet count on automated analyzers secondary to antiplatelet autoantibodies which cause platelets to aggregate in specimens ant coagulated with EDTA. The aggregations of platelets result in a false increase in leukocytes as giant platelets are counted as lymphocytes. Failure to detect this EDTA-Induced Thrombocytopenia could result in unnecessary laboratory investigations and superfluous interventions. EDTA-induced thrombocytopenia is sometimes prevented by other anticoagulants such as sodium citrate or heparin. In this article we reported a case of a 23-year-old female with EDTA-induced thrombocytopenia and a falsely increased leukocyte count confirmed by the use of a citrated tube and a peripheral smear without platelet aggregation.

Keywords: EDTA induced-thrombocytopenia; Pseudothrombocytopenia; Citrate; Heparin; Thrombocytopenia; Platelet aggregation; Platelet clumping; Peripheral blood smear

Introduction

Ethylenediaminetetraacetic Acid (EDTA)-induced thrombocytopenia is a common laboratory phenomenon which requires distinction and differentiation from a disease condition. It is defined as an *in vitro* phenomenon of platelet aggregation resulting in spurious reporting of a low platelet count by automatic analyzers, which are typically EDTA-dependent [1]. Even though EDTA-induced thrombocytopenia can be seen in patients with known malignancies, it has also been observed in normal individuals. The main hallmark of EDTA-induced thrombocytopenia is platelet aggregation. Platelet aggregates are not counted as platelets by analyzers, but as leukocytes. This phenomenon can be suspected on the platelet histogram, and a manual review of the blood smear can confirm the presence of these aggregates [2].

EDTA is a well-known anticoagulant in the haematology laboratory as a calcium chelator. The most important advantage of using EDTA is that blood cells are not distorted, making it ideal for use in haematology. In order to distinguish between true thrombocytopenia from EDTA-induced thrombocytopenia, other anticoagulants such as sodium citrate, oxalate and heparin are employed, which usually normalizes the platelet counts [3]. Even though thrombocytopenia can be detected in these alternative anticoagulants, the incidence is much lower than EDTA samples.

EDTA-induced thrombocytopenia can be diagnosed easily; but results are not properly analyzed (warning flags, histograms and blood films) leading to misdiagnoses of patients and placing a financial constraint with unnecessary transfusions and unwanted diagnostic testing.

Case Report

A 23-year-old female of Afro-Caribbean origin was referred to her primary care physician because thrombocytopenia was detected upon doing a Complete Blood Count (CBC) and differential as a component of a routine medical. She was asymptomatic, with no history of drug usage, or recent infection. There was no history of weight loss, melena, epistaxis, petechiae, ecchymosis or purpura. The initial CBC reveals normal parameters apart from an alarmingly low platelet count; $18 \times 10^9/L$ and a leukocytes count of $11.2 \times 10^9/L$. A

peripheral smear was subsequently prepared and it revealed platelet aggregations with moderate giant platelets. Family history, physical and systemic examination was unremarkable. We postulated that the low platelet count was due to EDTA-induced platelet aggregation. This was confirmed by a normal platelet and leukocyte count, $259 \times 10^9/L$ and $8.6 \times 10^9/L$ respectively, with specimen collected in a citrated tube and the absence of aggregated platelets on the peripheral smear.

Discussion

EDTA induced thrombocytopenia (also referred to as EDTA-induced Pseudothrombocytopenia (EDTA-PTCP) is a phenomenon caused by EDTA-dependent anti-platelet auto-antibodies that recognize platelet antigens modified by EDTA [4-9]. These antiplatelet antibodies, usually IgG or IgM, and rarely IgA, recognize platelet antigens on the platelet membrane modified by EDTA [10-13]. In contrast to serious and potential life-threatening causes of thrombocytopenia [14-16]. EDTA-PTCP is solely an *in vitro* effect without any clinical relevance [11]. Cation chelation by EDTA leads to a conformational change of the platelet membrane GPIIb-IIIa complex unmasking a cryptic epitope that becomes accessible for autoantibodies [17]. This leads to platelet clumping/aggregation *in vitro* resulting in spuriously low platelet counts using automated analysers in patients with normal platelet levels. The analyzers count the resulting platelet clumps as single giant platelets or as small lymphocytes in the white blood cell aperture [18,19], which may result in a slightly elevated white blood cell count. The phenomenon is present in both healthy subjects and patients with various diseases and its incidence has been reported to be 0.09-0.21% [4].

It is necessary for clinicians to consider the possible presence of pseudothrombocytopenia in cases of patients having low platelet counts without any hemorrhagic tendency [5] as observed in this case.

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Received January 23, 2017; Accepted February 09, 2017; Published February 15, 2017

Citation: Pitkin F, Mitchell T, Randall S (2017) Ethylenediaminetetraacetic Acid (EDTA)-Induced Thrombocytopenia: A Case Report. J Tradit Med Clin Natur 6: 209.

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“Unrecognized Pseudothrombocytopenia may result in unnecessary diagnostic testing and clinical concern. A microscopic examination can identify platelet clumping and repeat CBC tests using a different anticoagulant can affirm the diagnosis” [18]. In this case, we were able to confirm EDTA induced thrombocytopenia with the use of a citrated tube and a peripheral smear. Additionally, we also observed a significant reduction in the leukocytes count. While most reports indicate successful confirmation with the use of citrated tubes others have cited inconsistencies [10-13] which seem to eliminate citrated tubes and by extension heparin tubes, as reliable alternatives. According to one source, the best technique for obtaining accurate platelet counts in pseudothrombocytopenia subjects is to collect and examine blood sample at 37°C [6]. This approach has not proven to be most effect as there have been reports that platelet clumping will still be present in about 20% of patients [20].

In the quest for a gold standard the use of aminoglycosides has been suggested. Studies have shown that the prior addition of aminoglycosides to anticoagulants completely prevented the aggregation of platelets in EDTA-dependent PTCP subjects although the mode of action is not known [10]. In addition, the supplementation of aminoglycosides to EDTA-anticoagulated samples after blood withdrawal induced dissociation of aggregated platelets in blood samples from patients with EDTA-dependent PTCP [10,14,15]. Confirmation of EDTA induced thrombocytopenia is best helped by a method that is easy and perpetually effective as is said of the addition of aminoglycosides either before or after collecting the specimen.

In cases where aminoglycosides are not readily available the utilization of the citrated tube and testing at 37°C could prove beneficial in detecting EDTA induced thrombocytopenia even with minimal aggregation.

In conclusion, the case demonstrates the importance of not excluding EDTA-induced thrombocytopenia in instances where patients present with low platelet counts, platelet aggregation on peripheral smear and no physical findings or history suggestive of thrombocytopenia. Detection of EDTA-induced thrombocytopenia is very important for physicians as well as laboratory personnel as it averts unnecessary laboratory investigations and superfluous interventions. While sophisticated approaches to preventing EDTA-induced platelet aggregation, such as addition of aminoglycosides, exist, for developing countries the utilization of the citrated tube with correction for dilution remains a quick and easy means of detecting EDTA-induced thrombocytopenia.

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