Case Report

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EDTA-Dependent Pseudothrombocytopenia Associated with Hashimoto's Thyroiditis: A Case Report and Current Literature Review

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Abstract

Pseudothrombocytopenia (PTCP) can be an analytical error in the automatic blood cell count. Blood samples containing autoantibodies against platelets collected in ethylenediaminetetraacetic acid (EDTA) tubes can lead to platelet accumulation at room temperature. Agglutinated platelets are detected as larger cells using automated counters, which incorrectly leads to falsely low results. Hence, when a low platelet count is noted, PTCP must also be considered. In this study, we report a case of EDTA-dependent PTCP in a patient who has Hashimoto's thyroiditis with the current literature review.

Keywords: Pseudothrombocytopenia, Hashimoto's thyroiditis, EDTA

Introduction

Gowland first discovered this phenomenon in 1969 (1). The prevalence of this phenomenon in ethylenediaminetetraacetic acid (EDTA) is estimated to be 0.03-0.27% of the general population (2-4); however, multiple anticoagulant pseudothrombocytopenias (PTCPs) with citrate, heparin, or sodium fluoride have also been described. Cation chelation by EDTA leads to a conformational change of the platelet membrane GPIIb-IIIa complex, unmasking a cryptic epitope, which becomes accessible for autoantibodies. Antibodies are predominantly of the IgG type but act as cold agglutinins that react with platelets *in vitro* (5). Although harmless, failure to make this important distinction leads to unnecessary diagnostic tests, delays in surgery and treatment, and unnecessary platelet transfusions. Therefore, it is crucial to take into account PTCP when a low platelet count occurs. In this study, we report a case of EDTA-dependent PTCP.

Case Report

A 53-year-old woman was admitted to the hospital for long-term weakness. The patient complained of progressive fatigue in the last year. A physical examination revealed that the patient was overweight and had a BMI of 28.7. Laboratory analysis including complete blood count, biochemistry, free T4, thyroid peroxidase antibody (anti-TPO), and thyroid stimulating hormone (TSH) were analyzed. TSH: 4.38 mU/L (normal range: 0.27 to 4.2 uIU/mL), free T4: 11.7 ng/L (8.9 to 17.4 ng/L), anti-TPO: 795.2 IU/mL (normal range: 0-9 IU/mL), and platelet count: 14.000/UL (normal range: 142.000 to 424.000 /mm^3).

Thrombocytopenia was detected in previous laboratory tests. Hypothyroidism was diagnosed, and treatment with levothyroxine was initiated. The patient was referred to the hematology department for an evaluation of thrombocytopenia. A peripheral blood smear was compatible with PTCP. The first suggestion was that a complete blood count should be performed in a citrate tube. The thrombocyte count performed in the EDTA tube was 14.000/UL, whereas that in the citrate tube was 175.000/UL. The patient was diagnosed with pseudotrombocytopenia on the basis of laboratory findings. The patient progressed well with levothyroxine treatment. All subjects provided informed consent, and patient anonymity was preserved.

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Discussion

Thrombocytopenia is defined as a platelet count of $<150\times10^9$/L, although patients with a platelet count $>50\times10^9$/L are usually asymptomatic. Patients with thrombocytopenia rarely experience severe spontaneous bleeding. It is more common when the platelet count is $<20\times10^9$/L, and particularly when $<10\times10^9$/L. The clinical history establishes the cause of thrombocytopenia. This includes asking about recent infections, drug/vaccination history, travel history, diet (B12/folate deficiencies), past medical history, pregnancy status, and alcohol intake, along with establishing any features associated with malignancy (6).

In a patient with new thrombocytopenia, a repeat full blood count along with a citrated or heparinized blood sample should be taken both to confirm thrombocytopenia and to exclude PTCP caused by artefactual clumping (7). An accurate assessment is essential to ensure the sustainable management of the patient. The initial approach should include a clinical history, examination, complete blood count, and blood film analysis.

Pseudothrombocytopenia, a relatively common finding in clinical laboratories, can lead to diagnostic errors, overtreatment, and further (even invasive) unnecessary testing. The condition is most often seen in blood samples anticoagulated with EDTA, although citrate, oxalate, or heparin have also been implicated (8-10). EDTA-induced PTCP, the most frequently seen form in clinical practice, occurs mainly due to the reaction of antiplatelet antibodies (11). This mechanism is based on the binding of an antiplatelet autoantibody to the glycoprotein (GP) IIb/IIIa receptor on the cell membrane of platelets. The combined effect of EDTA's chelating effect on calcium ions and low temperature affects platelet membrane GP complex IIb/IIIa and exposes the GP IIb epitope. When the autoantibody binds to the GP IIb epitope, platelet aggregation occurs, which is observed in peripheral blood smears (12).

To avoid anticoagulant-induced PTCP, mainly associated with EDTA, either citrate or magnesium sulfate should be used as an anticoagulant (13). What is striking, however, is that the patients did not have a history of bleeding or recurrent hematoma despite extremely low platelet counts. Another helpful possibility is to perform the platelet count as early as possible after blood sampling, but this is not suitable for routine use.

However, it is the laboratory's responsibility to detect, confirm, or exclude PTCP in daily routine analyses. The reliability of automated hematologic analyzers is unsatisfactory. New technologies, such as fluorescence or optical platelet counting, should be implemented in clinical laboratories because they will provide valuable and suitable support for correcting spuriously low platelet counts. In patients with known PTCP, a venipuncture system with an alternative anticoagulant should be used before measuring platelet counts. Based on the available information, *in vitro* platelet aggregates have been reported for all alternative anticoagulants except magnesium sulfate, although this is rare. Supplementation of anticoagulant samples with aminoglycosides before blood sampling is controversial and ultimately unsuitable for routine use (14).

No particular disease was strongly associated with the presence of PTCP or showed significant differences from a control population of healthy individuals. However, the incidence of EDTA-PTCP appears to increase with hospitalization or in patients with specific disorders, such as autoimmune diseases (13,15). In a study that included 49 patients with diagnosed PTCP and 69 healthy volunteers, 23.8% of the patients had diabetes mellitus, 32.5% were hypertensive, 26.3% had an atherosclerotic heart disease, 5% had a history of cerebrovascular accidents, and 10% had hypothyroidism. Hospitalization was required for thirty-eight of them (76.25%), and 8% of the patients had coexisting diseases (14).

As our study has shown, the combination of hypothyroidism and PTCP is unmistakable. According to this information, both clinicians and laboratory specialists must be careful when evaluating thrombocytopenia.

Ethics

Informed Consent: All subjects provided informed consent, and patient anonymity was preserved.

Authorship Contributions

Surgical and Medical Practices: E.O.A., Y.E.D., Concept: E.O.A., Y.E.D., M.K., Design: E.O.A., Y.E.D., M.K., I.Y., Data Collection or Processing: E.O.A., Y.E.D., Analysis or Interpretation: E.O.A., Y.E.D., M.K., Literature Search: E.O.A., Y.E.D., M.K., Writing: E.O.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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