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Review Article

Pathology Section

Pseudothrombocytopenia: A Narrative Review of Mechanisms, Laboratory Recognition, and Clinical Implications

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ABSTRACT

Pseudothrombocytopenia (PTCP) is a laboratory artefact characterised by spuriously low platelet counts resulting from in-vitro platelet clumping, most commonly due to Ethylenediaminetetraacetic Acid (EDTA)-dependent agglutination. Although clinically benign, failure to recognise PTCP can lead to significant consequences, including unnecessary platelet transfusions, inappropriate corticosteroid therapy, avoidable bone marrow biopsies, and delays in surgical procedures. The prevalence of PTCP ranges from approximately 0.1% in the general population to 0.1-2% among hospitalised patients, with higher detection rates in critically-ill, oncology, and autoimmune disease populations. PTCP may be transient or persistent and can recur in predisposed individuals. The present review summarises the mechanisms, laboratory recognition, confirmatory approaches, and clinical implications of PTCP, emphasising the role of peripheral smear examination, analyser flag interpretation, and alternative anticoagulants. Emerging technologies, including artificial intelligence-assisted detection, have further enhanced diagnostic accuracy. Increased awareness among clinicians and laboratory professionals is essential to ensure appropriate interpretation of platelet counts and to prevent unnecessary interventions.

Keywords: Automated platelet count, Platelet clumping, Haematology analyser, Platelet satellitism, Pseudothrombocytopenia

INTRODUCTION

Accurate platelet estimation is fundamental to clinical decision-making, and laboratory artefacts such as Pseudothrombocytopenia (PTCP) can significantly impact diagnostic interpretation. PTCP is a benign laboratory phenomenon characterised by spuriously low platelet counts on automated haematology analysers due to in-vitro platelet clumping. Despite its benign nature, misinterpretation may lead to unnecessary investigations and inappropriate therapeutic interventions [1].

Patients with PTCP are typically asymptomatic and show no evidence of bleeding, petechiae, or purpura. The condition is most frequently associated with EDTA-dependent platelet clumping, a pre-analytical event occurring after sample collection. Recognition of PTCP is crucial to avoid diagnostic confusion with true thrombocytopenic disorders such as immune thrombocytopenia and to prevent unwarranted treatments, including corticosteroids, intravenous immunoglobulin, or platelet transfusions [1,2].

The epidemiology of PTCP varies across clinical settings. Its prevalence in the general population is approximately 0.1% of all blood counts, increasing to 0.1-2% in hospitalised patients. Among outpatients evaluated for thrombocytopenia, PTCP may account for up to 15-17% of cases. Higher detection rates are observed in critically-ill patients, oncology populations, and individuals with autoimmune disorders, likely reflecting increased testing frequency and immune dysregulation. PTCP may be transient or persistent, with recurrence documented in certain individuals due to circulating antiplatelet antibodies [2].

Mechanistically, EDTA-induced calcium chelation alters the platelet membrane glycoprotein IIb/IIIa complex, exposing cryptic epitopes that bind antiplatelet antibodies and result in platelet agglutination [3]. With the widespread use of automated analysers, PTCP has become an increasingly recognised analytical challenge [4]. Hence, the present review aimed to summarise current insights into its mechanisms, laboratory recognition approaches, and clinical implications of PTCP, with emphasis on practical approaches for accurate diagnosis.

Etiopathogenesis

The EDTA-dependent PTCP is the most common form and results from in-vitro platelet agglutination following calcium chelation. Removal of calcium disrupts the platelet membrane glycoprotein IIb/IIIa complex, exposing neoantigens that bind circulating antiplatelet autoantibodies, most commonly of the IgG class, although IgM and IgA types have also been reported [5-8]. This antigen-antibody interaction leads to platelet agglutination, forming aggregates that are miscounted as larger particles or leukocytes by automated analysers, resulting in spuriously low platelet counts. This phenomenon occurs exclusively in-vitro, typically within minutes of venipuncture [9,10].

The antibodies implicated are often cold-reactive and function optimally at room temperature, explaining the temperature-dependent nature of platelet clumping [11,12]. Delayed sample processing or storage at ambient temperature enhances aggregation, whereas rapid analysis or cooling samples to 4°C may reduce, but not eliminate, this effect [13]. Importantly, these changes do not occur in-vivo, as physiological calcium levels maintain the structural integrity of the platelet membrane.

Although EDTA is most frequently implicated, platelet clumping has also been reported with other anticoagulants such as sodium citrate, heparin, and Citrate-theophylline-adenosine-dipyridamole (CTAD) [9]. In some cases, broadly reactive antibodies result in multi-anticoagulant PTCP, which may mimic true thrombocytopenia if not correctly recognised. Non antibody mechanisms, including paraproteinemia, cold agglutinins, and elevated fibrin degradation products, may also contribute to artifactual thrombocytopenia [10]. A related but distinct phenomenon, platelet satellitism, occurs when platelets adhere to neutrophils via Fc receptor-mediated binding, producing a characteristic rosette-like appearance on peripheral smear [11].

Several risk factors and associated clinical conditions have been linked to PTCP. The condition has been reported in association with autoimmune diseases, malignancies, infections, and inflammatory states, although these associations are often incidental and attributed to increased laboratory testing rather than direct causation. Critically-ill patients and those undergoing frequent blood sampling are more likely to exhibit PTCP. Certain medications, including chemotherapeutic agents and monoclonal antibodies such as abciximab, have also been implicated. Rare familial cases have been described [2,10]. Despite these associations, PTCP may occur in otherwise healthy individuals, highlighting its unpredictable nature.

PTCP assumes particular clinical importance in specific settings. In surgical patients, spuriously low platelet counts may lead to unnecessary postponement of procedures or unwarranted transfusions. In obstetric practice, PTCP may mimic gestational thrombocytopenia or hypertensive disorders such as pre-eclampsia, resulting in inappropriate interventions. In oncology patients, where thrombocytopenia is frequently encountered due to chemotherapy or marrow involvement, PTCP may confound treatment decisions and lead to dose modifications or delays. Similarly, in intensive care settings, frequent laboratory monitoring may increase the likelihood of detection and contribute to diagnostic uncertainty [1,2,4,12]. Awareness of PTCP in these contexts is essential to avoid misinterpretation.

Laboratory Features and Recognition

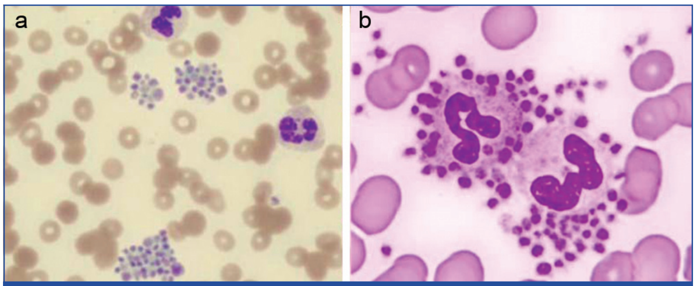
Modern haematology analysers determine platelet counts based on particle size and electrical impedance. In PTCP-affected samples, platelet aggregates exceed the analyser's platelet size threshold or are misclassified as leukocytes, leading to spuriously low platelet counts and occasionally falsely elevated white blood cell counts. When platelet counts are disproportionately low and inconsistent with the patient's clinical presentation, immediate laboratory reassessment is warranted. Automated parameters alone cannot reliably differentiate true thrombocytopenia from EDTA-induced aggregation; confirmation requires peripheral smear examination and repeat analysis using alternative anticoagulants [6,12].

Most modern analysers are equipped with programmed alert systems or flags that signal abnormal particle distributions. Common analyser messages indicating PTCP include "PLT clumps," "abnormal platelet distribution," or "verify smear." These warnings appear when the analyser detects optical or impedance signals consistent with platelet aggregates. The platelet histogram serves as an effective supplementary tool for identifying PTCP. In normal samples, the histogram displays a smooth, unimodal curve representing homogeneous platelet distribution, whereas EDTA-induced PTCP produces a flattened or truncated curve, sometimes with secondary peaks corresponding to larger platelet aggregates [13]. Platelet event scatter plots can further assist recognition by differentiating single platelet populations from high-volume aggregates. Accurate interpretation of these histogram abnormalities and analyser flags enables early recognition of PTCP even before microscopic confirmation, minimising unnecessary sample recollection and improving laboratory turnaround time [14].

Peripheral blood smear examination remains the gold standard for confirming PTCP. Examination of Wright- or Leishman-stained smears typically reveals discrete platelet aggregates with normal morphology and no red cell fragmentation. This microscopic correlation not only confirms the artifactual nature of thrombocytopenia but also rules out other causes, such as true thrombocytopenia or analyser malfunction. Representative smear findings are shown in [Table/Fig-1] [3,13].

Clinical Implications and Differential Diagnosis

The PTCP is a laboratory artefact without bleeding risk or underlying haematologic disease. Its recognition prevents unnecessary diagnostic procedures and inappropriate interventions such as platelet transfusion or corticosteroid therapy [2-4]. Although most cases are EDTA-dependent, some involve multi-anticoagulant PTCP, in which platelet aggregation persists across citrate, heparin, or CTAD tubes due to broadly reactive antibodies targeting platelet surface epitopes under different ionic conditions [8,9]. Differentiation from ITP is crucial, as the latter reflects genuine peripheral platelet destruction with increased marrow megakaryocytes, whereas PTCP shows normal marrow morphology and platelet aggregates only in-vitro. The diagnostic features of different PTCP types are summarised in [Table/Fig-2] [2,9,14].



[Table/Fig-1]: Photomicrographs showing (a) High-power view of platelet clumps due to EDTA effect (400×), and (b) Platelet satellitism around neutrophils (1000×). (Source: Author-generated images from the Department of Pathology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, India); Images are anonymised and used with patient consent for academic purposes.

Type of PTCP	Anticoagulant	Mechanism	Confirmatory findings
EDTA-dependent	EDTA (K2 or K3)	Calcium chelation exposes GP IIb/IIIa epitopes → antibody binding → in-vitro clumping	Normal count in citrate or $MgSO_4$; aggregates on smear
Citrate-dependent	Sodium citrate	Similar mechanism at lower calcium levels	Clumping in citrate; absent in $MgSO_4$
Heparin-associated	Heparin or CTAD	HIT-like antibody-mediated aggregation	Aggregation in the heparin sample; absent in $MgSO_4$
Multi-anticoagulant	EDTA, citrate, heparin±CTAD	Broad-reactivity antibodies	Clumping in multiple anticoagulants; normal in $MgSO_4$
Platelet satellitism	Usually EDTA	Fc receptor-mediated platelet-neutrophil adhesion	Satellite formation around neutrophils on smear

[Table/Fig-2]: Types of PTCP, implicated anticoagulants, mechanisms, and confirmatory findings.

Failure to recognise PTCP can result in significant clinical and economic consequences. Patients may undergo unnecessary platelet transfusions, invasive diagnostic procedures such as bone marrow biopsy, and inappropriate corticosteroid therapy under the assumption of immune thrombocytopenia. These interventions expose patients to avoidable risks, including transfusion reactions and treatment-related adverse effects. Additionally, misdiagnosis may lead to prolonged hospital stays, delays in surgical or oncological treatment, and repeated laboratory investigations. The cumulative effect contributes to increased healthcare costs and resource utilisation. Early recognition through peripheral smear examination and confirmatory testing can prevent these adverse outcomes and improve patient management [15].

Management

Management of PTCP focuses on recognition rather than treatment. In patients with recurrent PTCP, a permanent laboratory alert should be added to prevent repeated diagnostic confusion. When platelet aggregation is suspected in EDTA samples, repeat testing with sodium citrate, heparin, or Magnesium Sulfate ($MgSO_4$) is indicated, along with peripheral smear review. Normalisation of platelet counts in these samples, together with visible aggregates on smear, confirms the artifactual nature of thrombocytopenia [9,16]. $MgSO_4$ offers superior platelet preservation through stabilisation of membrane integrity and inhibition of calcium-dependent aggregation [16].

Importantly, the effective communication between the haematology laboratory and clinicians ensures diagnostic accuracy and avoids unnecessary therapies.

Technological Developments and AI Integration

Recent advances in haematology automation have markedly improved PTCP detection. Modern analysers employ multi-angle light scattering, fluorescence platelet channels, and sophisticated algorithm-based flagging systems to distinguish platelets from aggregates [17]. Artificial Intelligence (AI)-integrated systems can analyse scattergram patterns to detect signal deviations caused by platelet clumping, even when counts appear within reference ranges. These AI-based analysers outperform conventional impedance systems in identifying platelet aggregation and reduce the need for manual smear verification [2]. Comparative performance characteristics of conventional and AI-enhanced analysers are presented in [Table/Fig-3] [17,18].

Features	Conventional analyser	AI-enhanced analyser
Detection principle	Impedance/optical scatter	Multi-angle scatter with deep learning
Accuracy for clump detection	Moderate	High
Smear verification requirement	Frequent	Reduced
Pattern interpretation	Manual	Automated correlation
Turnaround time	Longer	Shorter

[Table/Fig-3]: Comparison of conventional and AI-enhanced analysers for the detection of pseudothrombocytopenia.

Fluorescence-based platelet channels, such as the PLT-F mode on Sysmex XN analysers, further improve count accuracy by quantifying nucleic acid content instead of relying solely on particle size [18]. Integration of fluorescence and AI-driven modalities enhances standardisation and minimises operator-dependent variability in platelet counting worldwide.

Preanalytical Variables and Laboratory Policy

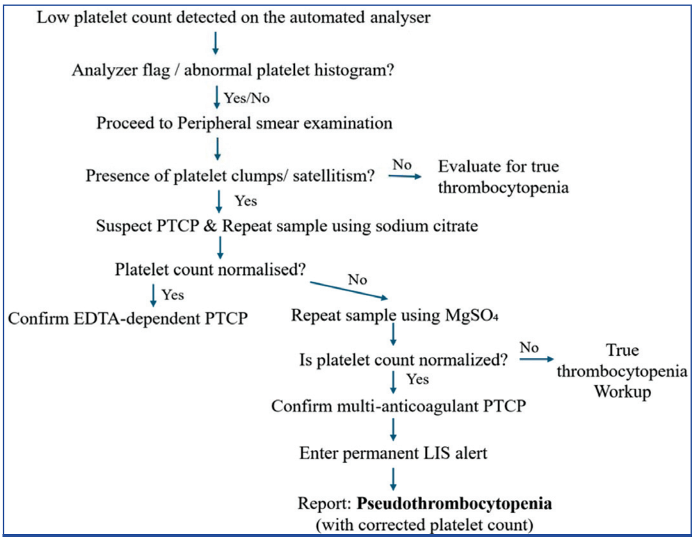
Preanalytical factors such as delayed sample handling, temperature variation, or excessive agitation may influence platelet counts even with automated systems [19]. Although pneumatic tube transport has minimal effect on complete blood count parameters [20], maintaining optimal preanalytical conditions, immediate gentle mixing, prompt smear preparation, and timely analysis is essential for reliability [21]. When analyser flags or abnormal histograms are encountered, repeat testing using alternative anticoagulants, particularly $MgSO_4$, is recommended due to its superior platelet stabilisation [9,15,22]. Moreover, effective clinician-laboratory communication remains key to preventing misdiagnosis and ensuring patient safety.

Clinical Correlation and Diagnostic Algorithm

Accurate differentiation of PTCP from true thrombocytopenia requires a structured diagnostic workflow. The recommended approach involves sequential evaluation of analyser data and histograms for abnormal platelet distributions, microscopic confirmation of platelet clumps or satellitism, repeat testing using alternate anticoagulants (sodium citrate or $MgSO_4$), and correlation with clinical history [2,13,15]. Restoration of platelet counts in alternate anticoagulant samples and visualisation of aggregates confirm PTCP, whereas persistent thrombocytopenia warrants evaluation for true haematologic disorders. A standardised Institutional laboratory workflow for suspected PTCP is illustrated in [Table/Fig-4] to facilitate systematic evaluation and reduce diagnostic errors [23].

After workflow

The algorithm outlines a stepwise approach beginning with the identification of low platelet counts and analyser flags, followed by



[Table/Fig-4]: Institutional laboratory workflow for suspected pseudothrombocytopenia (PTCP).

peripheral smear confirmation of platelet clumping. Repeat testing with alternative anticoagulants such as sodium citrate and $MgSO_4$ helps confirm EDTA-dependent or multi-anticoagulant PTCP. Persistent abnormalities warrant evaluation for true thrombocytopenia. Documentation through a permanent Laboratory Information System (LIS) alert is recommended to prevent recurrent misdiagnosis.

Limitation(s)

The present review has certain limitations. As a narrative review, study selection was not based on systematic review methodology, and heterogeneity among included reports may limit generalisability of conclusions.

CONCLUSION(S)

Pseudothrombocytopenia (PTCP) is a benign analytical artefact that poses significant diagnostic challenges in modern haematology practice. Prompt recognition through peripheral smear examination, appropriate use of alternative anticoagulants, and effective clinician-laboratory communication are essential to avoid misdiagnosis. Integration of standardised laboratory protocols, enhanced analyser technologies, and increasing awareness among clinicians will further improve diagnostic accuracy and patient safety. Future incorporation of AI-assisted diagnostic systems may enhance early detection and reduce diagnostic ambiguity in routine practice.

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