A case of thrombophagocytosis in a neonate: a rare observation highlighting the importance of timely platelet analysis

Joris Godelaine^{1*}, Christine Van Laer¹, Nancy Boeckx^{1,2}, Mercedeh Tajdar^{1,3}

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ABSTRACT

Background: Thrombophagocytosis refers to the phagocytosis of platelets by neutrophils or monocytes and is an uncommon finding, most often reported in bacterial infections. It may be linked to ethylenediaminetetraacetic acid (EDTA)-induced conformational changes in platelet membrane glycoproteins, which expose cryptantigens and promote immune-mediated interactions, resulting in platelet clumping, satellitism, and phagocytosis. If unrecognized, these *in vitro* artifacts can cause falsely low platelet counts, leading to pseudothrombocytopenia.

Case presentation: A 1-day-old neonate, born to a mother with a history of liver transplant on long-term immunosuppression, presented with normal initial blood values. However, the automated hematology analyzer flagged the sample, prompting microscopic review, which revealed thrombophagocytosis by neutrophils and, to a lesser extent, monocytes along with platelet satellitism. Repeat analysis of the same sample after 4 hours showed a marked decrease in platelet levels (160×10^9 /I to 88×10^9 /I), consistent with ongoing *in vitro* thrombophagocytosis. Maternal blood showed no abnormalities, and neither mother nor neonate had signs of infection.

Conclusion: This case illustrates neonatal thrombophagocytosis in the absence of infection, suggesting the phenomenon is not exclusively infection-related. Our findings illustrate that delayed sample analysis can significantly lower platelet counts, risking misdiagnosis of thrombocytopenia. Awareness of EDTA-related artifacts is therefore essential for accurate laboratory interpretation and clinical decision-making.

Keywords: Thrombophagocytosis, pseudothrombocytopenia, platelet phagocytosis, case report.

Type of Article: CASE REPORT Specialty: Hematology

Correspondence to: Joris Godelaine

*Department of Laboratory Medicine, University Hospitals Leuven, Belgium.

 $\textbf{Email:} \ Joris.godelaine@uzleuven.be$

Full list of author information is available at the end of the article.

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Background

Thrombophagocytosis refers to the phagocytosis of platelets by neutrophils or monocytes. It is a rarely observed phenomenon, mostly in patients displaying bacterial infection, and is possibly related to the exposure of cryptantigens on platelets due to ethylenediaminetetraacetic acid (EDTA) exposure [1-7]. EDTA can induce conformational changes in platelet membrane glycoproteins, exposing cryptantigens that trigger immune-mediated interactions, leading to platelet clumping, satellitism, and possibly phagocytosis [1,2,7]. In this report, we present a case of thrombophagocytosis observed in a term neonate who displayed no signs of infection. Moreover, we illustrate that delayed analysis of samples displaying this phenomenon may falsely decrease platelet levels, thereby highlighting the implications for platelet count accuracy and laboratory practice.

Case Presentation

A 1-day-old male neonate was born to a mother with a history of liver transplant in light of Wilson's disease, for which she was on long-term immunosuppressive medication, including tacrolimus (6.5 mg twice daily) and azathioprine (75 mg daily). The pregnancy and induced delivery proceeded largely uneventfully, without reported complications. The neonate was stable at birth with normal vital signs. Initial laboratory testing, performed immediately upon receipt of the sample in the laboratory, revealed normal hemoglobin (19.4 g/l; reference 14.5-22.5 g/l), platelets $(160 \times 10^9/l)$; reference $150-450 \times 10^9/l)$, and white blood cells $(25 \times 10^9/l)$; reference $9.4-34 \times 10^9/l)$, with mild absolute neutrophilia $(21.4 \times 10^9/l)$; reference $5-21 \times 10^9/l$). However, the automated hematology cell counter (Sysmex XN-20; Sysmex Corporation, Kobe, Japan) flagged the sample as suspicious due to abnormal white blood cell and reticulocyte scattergrams (scatterplots available in Figure

S1), prompting review of a peripheral smear using digital microscopy (Cellavision DI-60; Sysmex Corporation, Kobe, Japan).

Subsequent microscopic examination of the white blood cells revealed the presence of thrombophagocytosis by the patient's neutrophils and, to a lesser extent, monocytes (Figure 1). Simultaneous platelet satellitism was observed. Similar findings were also observed in blood samples obtained 24 and 48 hours later. As blood values remained within reference ranges, no further follow-up samples were collected. Maternal blood was also analyzed to assess a potential familial factor in the observed thrombophagocytosis, but no platelet phagocytosis could be observed in the mother's blood smear examination.

In order to further explore the phenomenon of throm-bophagocytosis in the neonate, we re-analyzed the initial sample in which platelet phagocytosis was first observed via the Sysmex XN-20 analyzer approximately 4 hours after initial measurements [to obtain additional scatter-grams (Figure S1)]. Interestingly, despite no clotting or platelet aggregates present in the sample, this repeat measurement illustrated a significant decrease in platelets compared to the initial value (88 vs. 160 x 10°/l), which was not expected based on the stability of platelets in EDTA-anticoagulated blood [8].

Discussion

Several EDTA-related artifacts in hematology, such as platelet clumping and satellitism, are well documented and may falsely lower platelet counts [1,2,7]. These phenomena are related to the chelation of Ca²⁺ ions by EDTA, which in turn induces conformational platelet membrane changes with exposure of cryptantigens on glycoprotein IIb/IIIa, which can subsequently be targeted by autoantibodies [1,2,7]. Thrombophagocytosis by neutrophils may potentially likewise be an in vitro EDTA artefact [1,2,7]. The in vitro nature of this phenomenon may be confirmed by repeating the analysis in a specimen collected in, for example, sodium citrate or with a capillary blood sample (collected without anticoagulant). Regrettably, such samples were not available for our patient. Likewise, as samples were only obtained up to 48 hours after birth (as there was no clinical indication for further sampling), we could not determine whether the observed thrombophagocytosis was a transient process or rather an enduring phenomenon in our patient.

Thrombophagocytosis has thus far only been described sporadically, most commonly in the setting of a bacterial infection [1-7]. In the current case, no indication of bacterial or other infection was present that warranted laboratory investigation, and the mother's drug regimen (tacrolimus, azathioprine) was the only noteworthy finding. Although it is possible that the mother's immunosuppressive therapies may have played a role in the manifestation of this

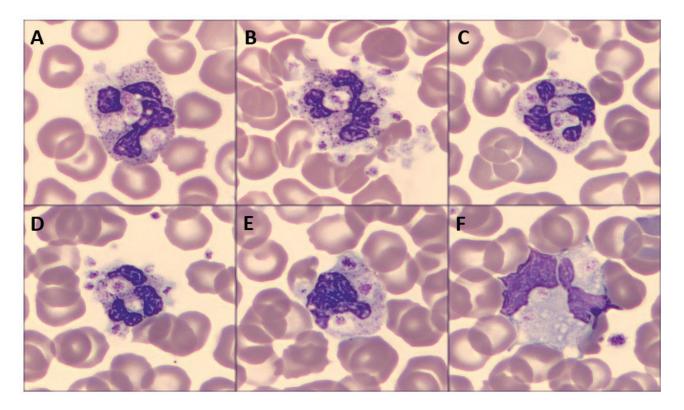


Figure 1. Thrombophagocytosis. Digital micrograph (100x) obtained via DI-60 after May-Grünswald Giemsa staining showing thrombophagocytosis by neutrophils (panels A-E) and monocytes (panel F). Platelet satellitism can also be observed (panels B, D).

phenomenon in the neonate, as tacrolimus and azathioprine have demonstrated (limited) transplacental passage, further study would be required to confirm this hypothesis [9,10]. However, given that platelet phagocytosis could not be observed in maternal blood and that tacrolimus and azathioprine are widely used drugs while platelet phagocytosis is only observed rarely, the role of the immunosuppressive drugs in inducing thrombophagocytosis in the neonate is likely limited.

Interestingly, we were able to demonstrate that a delayed re-analysis of the neonate's initial EDTA-anticoagulated sample resulted in a marked decrease in platelet count despite the absence of visible clotting or platelet aggregates. As such, this finding suggests that ongoing in vitro thrombophagocytosis may progressively consume platelets over time, which may have important implications for clinical laboratories and patient care. For example, a delayed processing of samples displaying thrombophagocytosis can yield artificially low platelet values, resulting in pseudothrombocytopenia. If not recognized as an artifact, these falsely decreased counts could subsequently lead to unnecessary diagnostic workup for thrombocytopenia, inappropriate transfusion decisions, or unwarranted therapeutic interventions. Laboratories should therefore implement protocols to ensure the timely analysis of samples. Moreover, when thrombophagocytosis is encountered in a sample, the laboratory should consider alternative anticoagulants (e.g., sodium citrate) or fresh capillary samples to confirm true platelet levels. Clinicians should also be aware of EDTA-dependent changes and interpret low platelet counts with caution when phagocytosis or satellitism is observed, particularly in the absence of clinical signs of bleeding or thrombocytopenia.

Conclusion

This case highlights the phenomenon of thrombophagocytosis, which may not only be limited to infectious settings. Although we could not conclusively determine EDTA anticoagulant as the causative factor for this phenomenon, we illustrated that delayed analysis of samples displaying thrombophagocytosis can result in falsely decreased platelet levels and, hence, pseudothrombocytopenia. Awareness of this artifact and timely processing of blood samples are crucial to ensure accurate platelet counts and avoid misdiagnosis.

What is new

Thrombophagocytosis, the phagocytosis of platelets by neutrophils and monocytes, has previously only been described rarely (e.g., 11 reports since 1994) and mostly in the setting of bacterial infections. In the current case, the authors illustrate that the phenomenon may also present in non-infectious settings, as no infection was apparent in the neonate. Moreover, this case report is also the first to illustrate that delayed analysis of samples displaying thrombophagocytosis may result in falsely decreased platelet

levels (pseudothrombocytopenia), thereby highlighting the importance of timely analysis. As such, this report aims to inform medical professionals about the potential impact of this rarely observed phenomenon.

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List of abbreviations

EDTA ethylenediaminetetraacetic acid

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Funding

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Informed consent

No written informed consent was required per institution's policy, as all patients (and/or their guardians) visiting our hospital (University Hospitals of Leuven, Belgium) agree with the use of anonymized data and leftover materials for research purposes via opting-out agreement.

Consent for publication

Due permission was obtained from the parents of the patient to publish the case and the accompanying images.

Ethical approval

Ethical approval is not required at our institution for anonymous case reports.

Author details

Joris Godelaine¹, Christine Van Laer¹, Nancy Boeckx^{1,2}, Mercedeh Tajdar^{1,3}

- 1. Department of Laboratory Medicine, University Hospitals Leuven, Belgium
- 2. Department of Oncology, Laboratory of Experimental Hematology, University of Leuven, Leuven, Belgium
- 3. Department of Microbiology, Immunology and Transplantation, University of Leuven, Leuven, Belgium

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Summary of the case

1	Patient (gender, age)	Male, 1 day
2	Final Diagnosis	Healthy, displaying thrombophagocytosis by neutrophils and monocytes
3	Symptoms	None
4	Medications	None, maternal medications: azathioprine, tacrolimus
5	Clinical Procedure	Laboratory analysis via automated hematology analyzer and microscopy
6	Specialty	Laboratory medicine

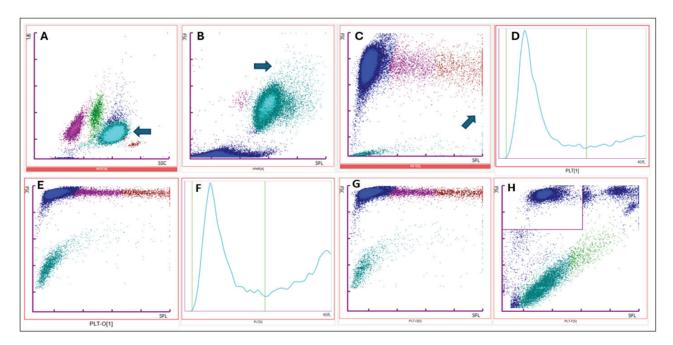


Figure S1. Sysmex XN-20 scatterplots of the neonatal blood sample. The automatic hematology analyzer flagged the sample as suspicious due to an abnormal WBC scattergram [due to i) the clustering location of the light blue neutrophil population in the WDF scattergram (A) which displayed an increased side fluorescence and ii) due to the presence of an increased number of particles on the BASO:WBC border in the WNR scattergram (B)] and an abnormal reticulocyte scattergram (scattergram C; due to the presence of particles with high levels of side fluorescence). Scattergrams: A) WDF channel, B) WNR channel, C) RET-channel, D) PLT (impedance) scattergram of initial measurement (platelets 160×10^{9} /l), E) PLT-O scattergram of initial measurement (platelets 159×10^{9} /l), F) platelet (impedance) scattergram of second measurement (platelets 88×10^{9} /l), G) PLT-O scattergram of second measurement (platelets 103×10^{9} /l), and H) PLT-F scattergram of second measurement (platelets 103×10^{9} /l). The second measurement of platelets (F-H) occurred approximately 4 hours after the initial measurements (panels A-E).