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PLATELET–NEUTROPHIL CROSSTALK IN LEUKEMIA: MECHANISMS, IMMUNOTHROMBOSIS AND THERAPEUTIC IMPLICATIONS – A REVIEW

Komail Hasnain[1], **Talha Saleem**[*2]

[1]*Department of Medical Laboratory Technology, Superior University, Lahore*
[*2]*Faculty of Allied Health Sciences, Superior University, Lahore*

[1]komailhasnain418@gmail.com, [*2]talha.saleem@superior.edu.pk

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Corresponding Author: *
Talha Saleem

Abstract

Background: *Leukemia is a complicated blood cancer that is characterized by immune dysfunction and thrombo-inflammation. The cross-linkage of platelet neutrophils, especially with the help of NETs and adhesion cues, promotes disease development, thrombosis, immune surveillance, and treatment resistance.*

Objective: *To establish the platelet neutrophil interaction in the pathophysiology and progression of leukemia.*

Methodology: *A structured-literature review was performed, which is a systematic-search procedure in the form of narrative. Peer-reviewed articles published between January 2020 and December 2025. Original research papers, systematic reviews, and high-quality narrative reviews were captured and conference abstracts without the full text and irrelevant editorials were not.*

Results: *The activation of platelets facilitates neutrophil recruitment and neutrophil NET through PSGL-1 and P-selectin. High NETs cause immunothrombosis, endothelial injury and leukemic progression. Platelet-derived factors also increase the survival, chemoresistance of leukemic cells, and are associated with poor clinical outcomes.*

Conclusion: *Platelet-neutrophil cross talk leads to inflammation, coagulation and leukemia development. Overproduction of platelet activation and NET release produces an immunosuppressive, prothrombotic environment that is disease sustaining. This pathway should be targeted to enhance the results in leukemia.*

INTRODUCTION

Neutrophil extracellular traps (NETS) have become the connecting pivots of inflammation, coagulation and progression of leukemia because they interact closely with platelets and leukemic cells. Such a review identifies that neutrophils have an enhanced tendency to form NET in leukemias, especially in CML and CLL, because of the soluble mediators (IL-8, G-CSF, and TNF), and platelet-activating factors, which generate a pro-thrombotic and pro-inflammatory environment. Extracellular DNA, histones, and neutrophil elastase are examples of NET components that increase adhesion of leukemic cells to the endothelium, inhibit apoptosis and chemotherapy and stimulate release of tissue factor-carrying micro vesicles, which facilitate disseminated intravascular coagulation (DIC) and vascular issues. Interestingly, platelet activation also enhances NETosis and thus immunothrombosis is a vicious circle. The adult

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disease in AML is highly exuberant in NETs, and they are associated with NPM1 mutations and stromal loops of inflammation, and in pediatric acute leukemia is antagonized by granulocyte immaturity resulting in infection but not thrombosis. In this way, platelet to neutrophil NET crosstalk is a key process in leukemia pathophysiology where excessive or defective NET dysregulation is at the center of disease progression, thrombosis, immune evasion, and response to treatment.[1]

Neutrophils and platelets are common cells of blood circulation that are traditionally known to serve different purposes in haemostasias and innate immunity respectively. Nevertheless, accumulating data points to the fact that their interplay has much more interactions well beyond these classical functions and has a key role in the pathogenesis of thrombo-inflammatory diseases. The idea of immunothrombosis explains the synergistic effect of platelet activity and neutrophil recruitment to trigger coagulation, prevent the spread of pathogens, and result in inflammation. This platelet neutrophil interaction is specifically important in the disease, leukemia, where platelet activity and neutrophil behaviour are severely dysregulated and the progression of the disease, thrombotic complications, and the microenvironment inflammatory response depend on it. The study of the mechanisms of platelet neutrophil crosstalk in leukemia could thus provide new information on the thrombo-inflammatory nature of leukemia and be able to identify possible therapeutic options to regulate thrombosis without affecting haemostasis.[2]

Traditionally mediators of haemostasis and innate immunity, platelets and neutrophils have been identified as active contributors to the microenvironment in leukemic immunology, and it is their interaction that causes immune dysfunction and disease development. Strong and functional phenotypic and functional defects of neutrophil in leukemia and specifically chronic lymphocytic leukemia (CLL), that encompass defects in phagocytosis, chemotaxis, long-term survival, and excessive neutrophil extracellular trap (NETs) development. Meanwhile, platelets are inflammatory and immunomodulatory cells that have the ability to recruit, activate and reprogram neutrophils by the means of soluble mediators and contacting receptors. This platelet neutrophil cross-linkage facilitates a thrombo-inflammatory condition and supports a tumor-supportive microenvironment by enhancing net formation, maintaining leukemic B-cell survival due to BAFF, APRIL and other factors, and plays a role in T-cell suppression. In addition, leukemic niche cytokines (including IL-8, IL-10, G-CSF, and GM-CSF) also contribute to this conversation, and extend neutrophil lifespan and prejudice them towards an immunosuppressive phenotype (CD16, CD62L). The insights into platelet neutrophil interactions as the cause of immune dysregulation, neutrophil polarization, and inflammatory support to leukemic cells give important understanding of the thrombo-inflammatory characteristic of leukemia and new therapeutic possibilities to inhibit NET formation, neutrophil polarization, and microenvironmental signaling pathways.[3]

The classical functions of platelets and neutrophils are supplemented by the modern functions of regulating the leukemic tumor microenvironment by intricate platelet-leukocyte interactions that favor inflammation, immunomodulation, and thrombosis. Activated by tumor- or leukemia-generated signals, platelets P-selectin (CD62P) is expressed and binds PSGL-1 on neutrophils triggering integrin activation (Mac-1), two-way cellular interactions, and release of chemokines, cytokines and damage associated mediators such as HMGB1. This cross-linkage increases neutrophil recruitment, neutrophil rearrangement and neutrophil extracellular traps (NETs) and consequently provokes platelets through TLR4 and platelets procoagulant scaffold which increases immunothrombosis. The neutrophils, and to a greater extent in CLL, play a dysfunctional role in leukemia, including over-production of NET and ineffective immunity, also playing a role in a protumoral and prothrombotic niche. In this way, platelet neutrophil interactions are not only in the pathophysiology of cancer-related thrombosis but also in immune evasion, inflammatory signaling,

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and disease development, which makes this interaction an important and potentially targetable mediator in the pathophysiology of leukemia.[4]

Platelets take part in the initial tethering and rolling of leukocytes, particularly neutrophils, through the expression of P-selectin on their surface that binds to PSGL- 1. This contact facilitates a strong adhesion through the use of 2 - integrins and activates the leukocytes to release inflammatory mediators and increases recruitment to the location of vascular injury or inflammation. Platelet leukocyte aggregates are thus a vital bridge between thrombosis and inflammation.[5]

Platelets are currently being considered as powerful regulators of tumor development. Platelets activated in addition to their hemostatic role play a role in interaction with tumor cells and leukocytes that promotes immune evasion, inflammatory communication and metastatic growth. By its surface adhesion molecules and soluble mediator release, platelets have the potential to kill tumor cells by immune response and regulate the activity of leukocytes within a tumor microenvironment. In my current study, The review found that platelet–neutrophil crosstalk drives inflammation, thrombosis, immune evasion, and leukemic progression. Neutrophils in CML and CLL show increased NET formation triggered by inflammatory cytokines (IL-8, G-CSF, TNF-α). Platelets induce NETosis via P-selectin/PSGL-1 binding and release of mediators like PF4 and TGF-β, creating a positive feedback loop that sustains thrombo-inflammation. Platelet–neutrophil complexes (PNCs) rise from ~6% to up to 30% in leukemia, promoting immunothrombosis. NET components enhance leukemic cell adhesion, protect against apoptosis, and contribute to DIC. Platelets physically shield leukemic blasts, while neutrophils release BAFF/APRIL to support B-cell survival and suppress T-cells. These interactions remodel the microenvironment to support survival, angiogenesis, and chemoresistance. Finally, adult AML exhibits excessive NETs with thrombosis, whereas pediatric leukemia shows fewer NETs, increasing infection risk but lowering thrombosis risk.

LITERATURE REVIEW

Thomopoulos *et al.,* (2022) reviewed that demonstrates that Chronic Neutrophilic Leukemia (CNL) is an infrequent BCR/ABL-negative myeloproliferative neoplasm with persistent mature neutrophilic leukocytosis, hepatosplenomegaly and bad prognosis. The authors refer to CSF3R mutations, especially the T618I mutation, as the mutation central to the disease and a major diagnostic criterion and accentuate the complicated genetic picture that includes the ASXL1, SETBP1, TET2 and spliceosome genes, which play a role in the disease progression and prognosis. CNL is heterogeneous and at risk of developing acute myeloid leukemia, and has poor prognosis (median life expectancy is approximately 2 years). Conventionally, hydroxyurea of the therapeutic agents only provides temporary control, ruxolitinib presents encouraging but inconsistent responses, and allogeneic stem cell transplantation has the only potentially curative treatment but still carries significant risks to the treatment. The authors also find that more in-depth molecular insights are necessary to come up with more effective, specific treatments to this aggressive and poorly-characterized malignancy. [6]

Li *et al.,* (2023) reviewed extensive description of the essentiality of interactions between plates and other cellular elements in the development and evolution of tumors. The authors emphasize that platelets do not merely play a role in hemostasis but also play an active role in tumorigenesis as they interact with tumor cells, immune cells, erythrocytes, monocytes, macrophages, dendritic cells, and lymphocytes in the tumor microenvironment. These interactions facilitate cancer development in various ways and mechanisms, including stimulation of tumor cell proliferation, angiogenesis, immune evasion, inflammation, thrombosis and tumor metastasis. The paper highlights how platelets that are activated by tumors attract immune and blood cells, regulate inflammatory processes, induce epithelial-mesenchymal transition, and shield

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circulating tumor cells against immune death. In addition, platelet-mediated signaling was demonstrated to control immune suppression and vascular remodeling, which form a conducive microenvironment in the presence of tumors to survive and extend. Altogether, the authors find that platelet-cellular crosstalk is the key regulatory factor in cancer pathogenesis and could be an objective in immunotherapy of cancer and anti-metastatic therapy.[7]

Mulas *et al.,* (2022) analyzed the prognostic worth of CBC based inflammatory markers in myeloid malignancies and their applicability in the HSCT scenario. High neutrophil-to- lymphocyte ratio (NLR) and leucocyte counts are always linked to poor survival, increased thrombotic risk, and disease progression, whereas low lymphocyte counts are associated with poor immune surveillance and poor outcomes. Early transplantation Lymphocyte and monocyte recovery is associated with better patient survival and fewer complications. In sum, the authors conclude that CBC-based parameters are inexpensive and easy to calculate prognostic measures, which can be used in addition to molecular markers, but large-scale validation is required.[8]

Su *et al.,* (2021) reviewed the SDF-1/CXCR4 signaling axis plays an important role in the progression and treatment of acute leukemia. The authors indicate that CXCR4 controls the migration, homing, and survival of leukemia cells in the bone marrow microenvironment, which makes the diseases progress, develop resistance to chemotherapy, and have a poor prognosis. There were worse clinical outcome and risk of relapse with increasing CXCR4 expression in AML patients and in ALL patients. Moreover, the researchers prove that the CXCR4-target therapy with the help of certain antagonists has the capability to drive the leukemia cells out of the protective niches and enhance the efficiency of chemotherapy and stem cell transplantation. All in all, the authors conclude that CXCR4 is a possible prognostic and therapeutic target biomarker in the management of acute leukemia.[9]

Kaiser *et al.,* (2023) reviewed the principle of inflammatory hemostasis, indicating that platelets maintain the integrity of the vascular structures in the situation of inflammation, infection, and malignancy without the development of conventional clots. The platelets behave primarily as individual cells and migrate to the location of leukocyte extravasation and inhibit micro bleeding by receptor-specific signaling, secretion and procoagulant activities, unlike the trauma-induced hemostasis that is operated by platelets as multi-cellular formations. The authors conclude that thrombocytopenia is a significant aggravator of inflammatory bleeding, and platelets have an indispensable and context-specific contribution to maintaining endothelial barrier functioning beyond thrombus formation.[10]

Taghiloo *et al.*, (2024) reviewed the two-way cross-communication between leukemic cells and immune cells in the tumor microenvironment focusing on the remodeling of the bone marrow niche by leukemic cells supporting the immune evasion and disease progression. They explain the role of the changes in cytokine signaling, immune checkpoint pathways and metabolic interactions in the inhibition of efficient T- and NK-cell responses and in the promotion of leukemic cell survival and resistance to drug therapy. The authors are of the opinion that the focus on these microenvironmental interactions is a promising way to enhance the efficacy of immunotherapy in leukemia.[11]

Ten *et al.,* (2021) reviewed disseminated intravascular coagulation (DIC) is defined as a frequent and life-threatening complication in the acute leukemia due to the abnormal activation of the coagulation system. According to the authors, acute promyelocytic leukemia is more prone to bleeding whereas thrombosis is more prevalent in other types of leukemia. They highlight that the primary management of leukemia is based on the early treatment with the aid of transfusion therapy to prevent the risk of bleeding. In general, the paper has identified DIC as one of the primary causes of negative clinical outcomes in patients with acute leukemia.[12]

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Patnaik *et al.*, (2022) reviewed critically analyzed chronic myelomonocytic leukemia (CMML) as a clonal hematologic disease with unremitting monocytosis and the development of acute myeloid leukemia. The authors insist that genetic alterations and clinical features are extremely important in the risk stratification and diagnosis. They indicate that Allogeneic stem cell transplantation is the only curative and hypomethylating agents are normally used to manage the disease. On the whole, the paper highlights the importance of molecular and clinical variables to enhance prognosis and interventions in CMML.[13]

Xie *et al.*, (2025) reviewed points to the emerging position of platelet-based and platelet membrane-coated nanodrug delivery system in cancer therapy. The authors expound that platelets are more likely to increase targeted delivery of chemotherapeutic, immunotherapeutic, gene, and photothermal agents and limit systemic toxicity because of their natural tumor-homing capacity, immune evasion (CD47), and extended circulation duration. They conclude that platelet-mediated drug delivery has a good preclinical potential, but additional research is needed to have safe clinical translation.[14]

In summary, the reviewed literature consistently demonstrates that platelet–neutrophil crosstalk is a fundamental driver of leukemia pathophysiology. Across multiple studies, activated platelets have been shown to induce neutrophil extracellular trap (NET) formation primarily through P-selectin/PSGL-1 interactions, creating a pro-thrombotic and pro-inflammatory microenvironment that supports leukemic cell survival, immune evasion, and chemoresistance. This bidirectional interaction amplifies immunothrombosis, contributing to both disease progression and life-threatening complications such as disseminated intravascular coagulation and venous thromboembolism. Furthermore, the leukemic microenvironment actively reprograms both platelets and neutrophils toward tumor-supportive phenotypes, establishing a self-sustaining cycle of inflammation, coagulation, and malignancy. Despite these advances, significant gaps remain regarding subtype-specific mechanisms and clinical translation. Nevertheless, targeting the platelet–neutrophil axis—whether through NET inhibition, P-selectin blockade, or anti-platelet therapies—emerges as a promising therapeutic strategy to improve outcomes in leukemia patients.

METHADOLOGY

This study was conducted as a structured literature review with a narrative synthesis approach, aiming to systematically identify, evaluate, and synthesize published evidence on platelet–neutrophil crosstalk in leukemia, focusing on mechanisms, immunothrombosis, and therapeutic implications. A comprehensive search was performed across five electronic databases—PubMed/MEDLINE, Scopus, Google Scholar, Web of Science, and Embase—using key terms such as "platelets," "neutrophil extracellular traps (NETs)," "leukemia," "immunothrombosis," and "tumor microenvironment," limited to peer-reviewed articles published in English between January 2020 and December 2025. Original research articles, systematic reviews, and high-quality narrative reviews were included, while conference abstracts without full text, editorials, commentaries, and studies exclusively on solid tumors without relevance to leukemia were excluded. Two independent reviewers screened titles and abstracts, retrieved full texts of eligible articles, and extracted data using a standardized form covering study characteristics, key findings on platelet–neutrophil interactions, NETosis, immunothrombosis mechanisms, and therapeutic implications. Quality assessment was performed using AMSTAR-2 for systematic reviews and the Newcastle-Ottawa Scale for observational studies; narrative reviews were assessed for clarity and consistency. Due to heterogeneity in study designs and outcomes, a narrative synthesis was performed, grouping findings into thematic categories: NETs in leukemia, platelet activation and NET induction, platelet–neutrophil aggregates, immune evasion, leukemic microenvironment remodeling, and therapeutic targets. As this was a review of publicly available published literature, no ethical approval was required.

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MAIN BODY

1. Leukemia and Tumor Microenvironment

Leukemia is a heterogeneous group of hematological malignancies characterized by uncontrolled proliferation of abnormal hematopoietic cells in the bone marrow and peripheral blood. Unlike solid tumors, leukemia does not form a solid mass but develops within the bone marrow microenvironment, where leukemic cells interact with stromal cells, endothelial cells, immune cells, platelets, and neutrophils. These cellular interactions play a critical role in leukemic cell survival, proliferation, immune evasion, and resistance to chemotherapy. The concept of the leukemic microenvironment suggests that leukemia progression is not only dependent on genetic mutations but also on interactions between leukemic cells and surrounding cells. Platelets and neutrophils are now recognized as important regulators of this microenvironment, where they contribute to inflammation, coagulation, angiogenesis, and immune suppression. Therefore, platelet–neutrophil interaction plays a significant role in leukemia pathophysiology.[15]

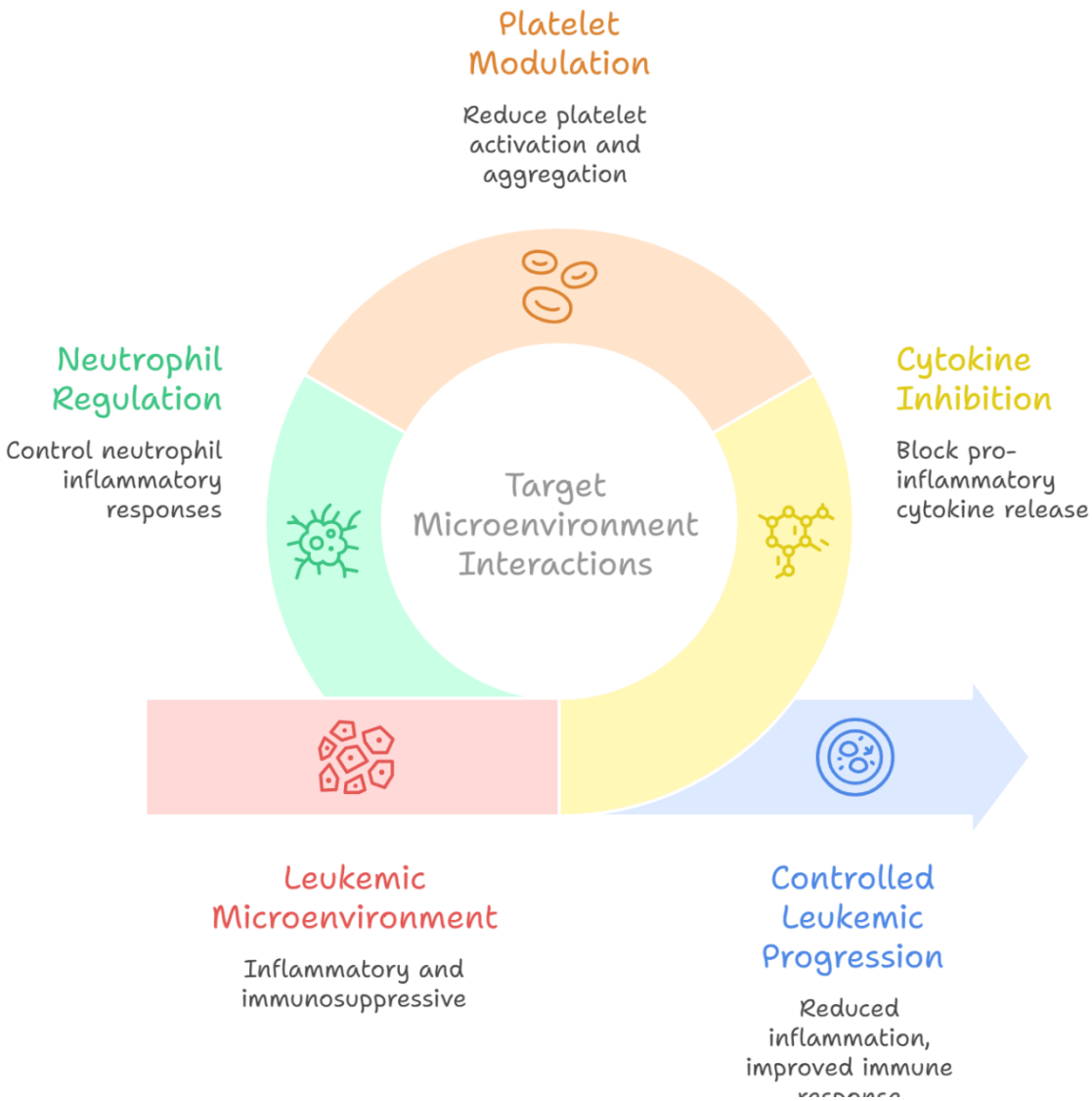

Figure 1: Targeting Leukemia Microenvironment

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2. Platelets in Leukemia

Platelets are small anucleate blood components derived from megakaryocytes in the bone marrow and are traditionally known for their role in hemostasis and thrombosis. However, recent studies have shown that platelets are also involved in inflammation, immune regulation, tumor growth, and metastasis. Platelets contain alpha granules and dense granules that store cytokines, chemokines, growth factors, and coagulation factors, which are released upon platelet activation. Platelets also play a major role in cancer-associated thrombosis, which is a common complication in leukemia patients. Activated platelets interact with neutrophils and monocytes to form platelet–leukocyte aggregates that contribute to inflammation and thrombosis. Therefore, platelets are not only hemostatic cells but also inflammatory and immune-modulating cells that contribute significantly to leukemia progression.[16]

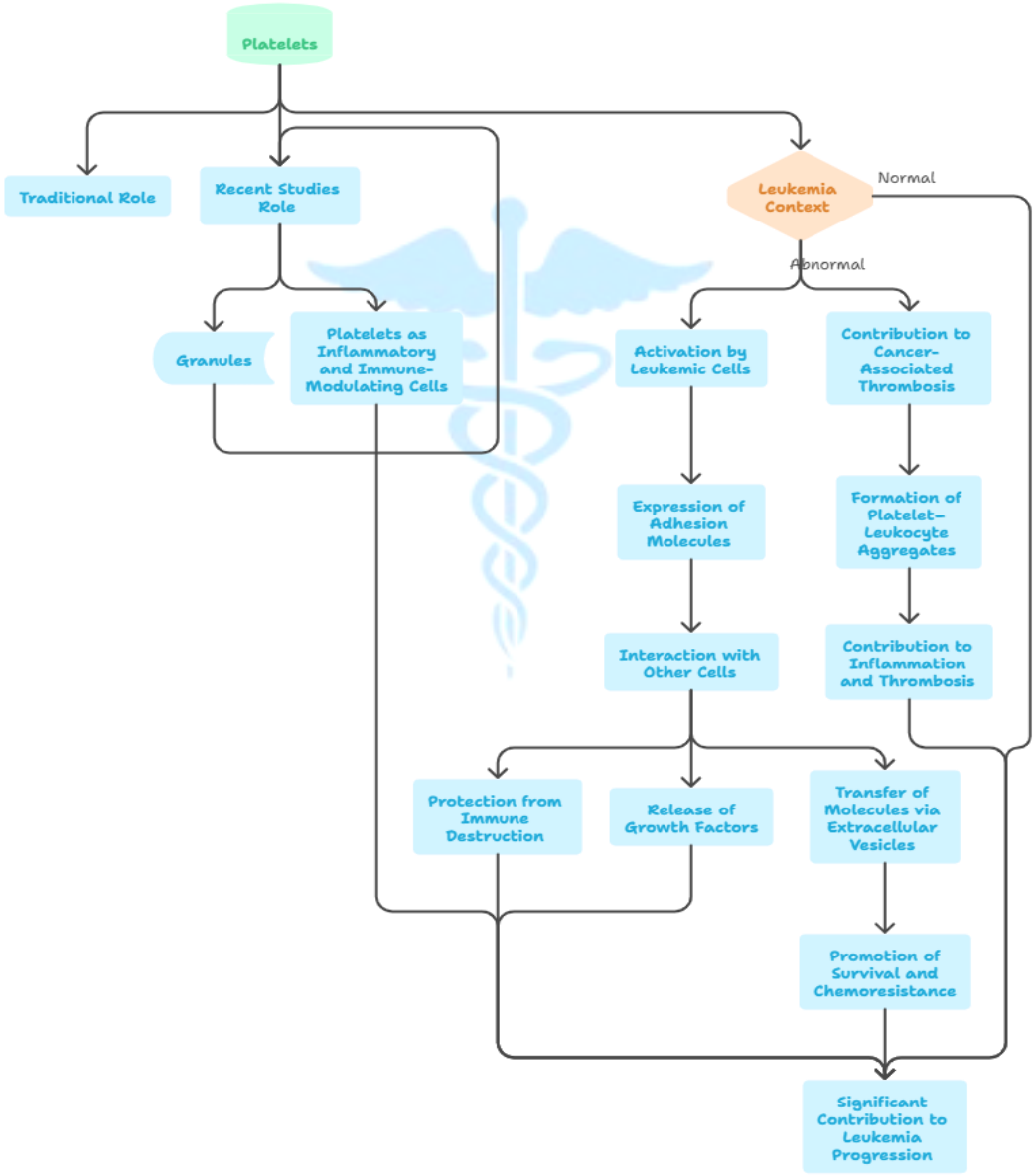

Figure 2: Platelet involvement in Leukemia Progression

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3. Neutrophils in Leukemia

Neutrophils are the most abundant leukocytes in peripheral blood and are essential components of the innate immune system. They play a major role in host defense through phagocytosis, degranulation, reactive oxygen species production, and neutrophil extracellular trap formation. Neutrophils are produced in the bone marrow and released into circulation, where they respond to infection and inflammation. One of the most important functions of neutrophils in leukemia is the formation of neutrophil extracellular traps (NETs). NETs are web-like structures composed of extracellular DNA, histones, and antimicrobial proteins released by activated neutrophils. NETs play an important role in trapping pathogens but also contribute to thrombosis, inflammation, and cancer progression when dysregulated.[17]

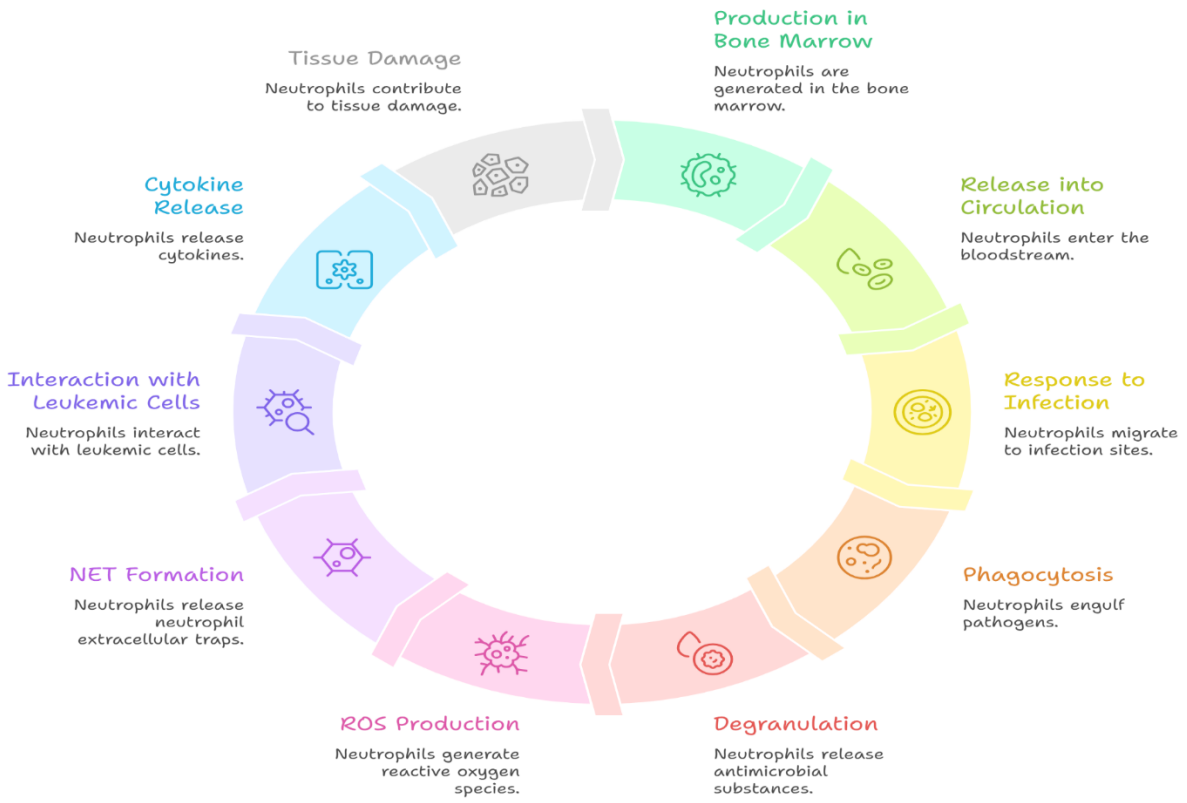

Figure 3: Neutrophil Cycle in Leukemia

4. Neutrophil Extracellular Traps (NETs) in Leukemia

Neutrophil extracellular traps are networks of chromatin fibers released by neutrophils during a process called NETosis. NET formation involves chromatin decondensation, nuclear membrane breakdown, and release of DNA and antimicrobial proteins into the extracellular space. NETs contain DNA, histones, neutrophil elastase, myeloperoxidase, and other proteins. Excessive NET formation has been observed particularly in chronic lymphocytic leukemia and chronic myeloid leukemia, where neutrophils show increased survival and inflammatory activity. In acute myeloid leukemia, NETs are associated with inflammation, thrombosis, and disease progression. However, in pediatric leukemia, immature neutrophils produce fewer NETs, resulting in increased susceptibility to infections rather than thrombosis.[18]

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5. Platelet–Neutrophil Interaction

Platelet–neutrophil interaction is a key mechanism linking inflammation, coagulation, and immune responses. Activated platelets interact with neutrophils through adhesion molecules and soluble mediators. The most important interaction occurs through P-selectin expressed on activated platelets, which binds to PSGL-1 receptors on neutrophils. This interaction leads to neutrophil activation, integrin activation, and formation of platelet–neutrophil aggregates. Platelets also release chemokines and cytokines that recruit neutrophils to sites of inflammation and vascular injury. Neutrophils, in turn, release reactive oxygen species and proteases that activate platelets. This bidirectional interaction creates a feedback loop that enhances inflammation and thrombosis.[19]

6. Platelet–Neutrophil Interaction in Leukemia Progression

In leukemia, platelet–neutrophil interaction plays a major role in disease progression and complications. Leukemic cells release cytokines that activate platelets and neutrophils, leading to the formation of platelet–neutrophil aggregates and NETs. These processes contribute to thrombosis, inflammation, and leukemic cell survival. Additionally, platelet–neutrophil interaction plays a major role in leukemia-associated thrombosis and disseminated intravascular coagulation, which are common complications in leukemia patients.[20]

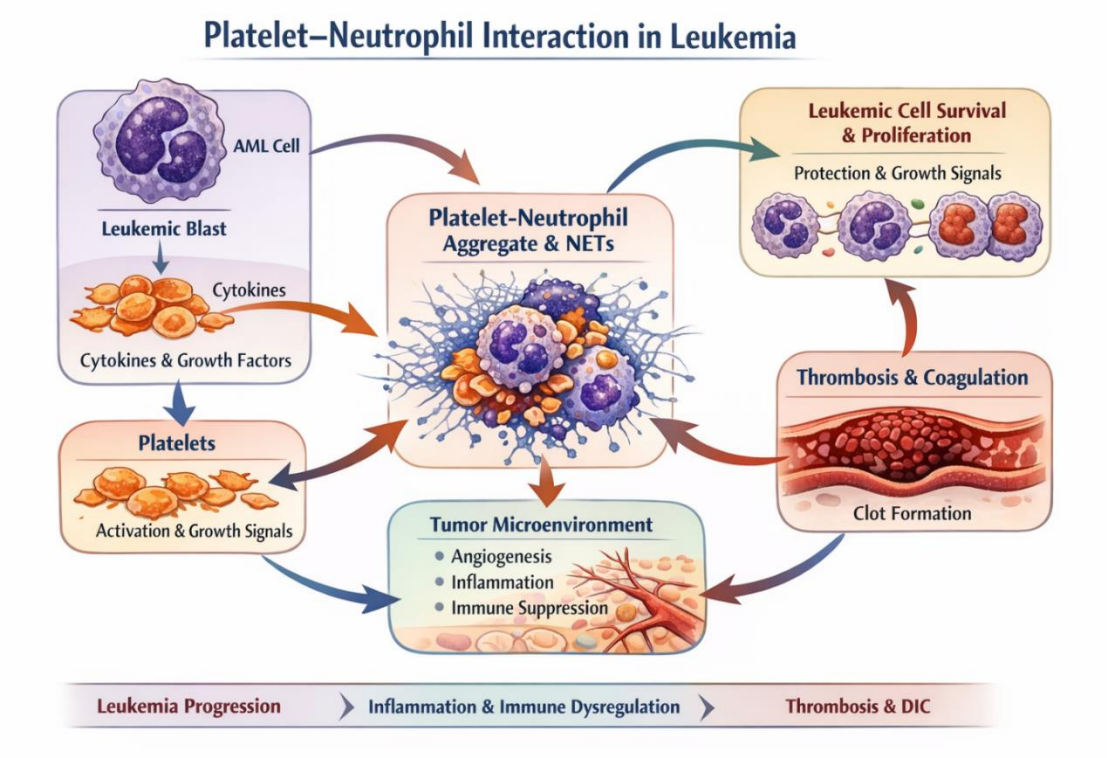

Figure 4: Platelet-Neutrophil Interaction in Leukemia

The review found that platelet–neutrophil crosstalk drives inflammation, thrombosis, immune evasion, and leukemic progression. Neutrophils in CML and CLL show increased NET formation triggered by inflammatory cytokines (IL-8, G-CSF, TNF-α). Platelets induce NETosis via P-selectin/PSGL-1 binding and release of mediators like PF4 and TGF-β, creating a positive feedback loop that sustains thrombo-inflammation. Platelet–neutrophil complexes (PNCs) rise from ~6% to up to 30% in leukemia, promoting immunothrombosis. NET

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components enhance leukemic cell adhesion, protect against apoptosis, and contribute to DIC. Platelets physically shield leukemic blasts, while neutrophils release BAFF/APRIL to support B-cell survival and suppress T-cells. These interactions remodel the microenvironment to support survival, angiogenesis, and chemoresistance. Finally, adult AML exhibits excessive NETs with thrombosis, whereas pediatric leukemia shows fewer NETs, increasing infection risk but lowering thrombosis risk.

Table 1: Role of Platelet–Neutrophil Interactions in Leukemia

Aspect	Key Findings	Mechanisms Involved	Clinical Implications
Neutrophil Extracellular Traps (NETs)	Increased NET formation in leukemia, especially in CML and CLL	Cytokines (IL-8, G-CSF, TNF-α) stimulate neutrophil activation and NETosis	Promotes inflammation, thrombosis, and leukemic progression
Platelet-Induced NET Formation	Platelets enhance NET formation via direct interaction with neutrophils	P-selectin–PSGL-1 binding, release of PF4, TGF-β, interleukins	Sustains thrombo-inflammatory feedback loop
Platelet–Neutrophil Complexes (PNCs)	Increased from ~5.7–7.2% (normal) to ~30% in leukemia	Platelet adhesion to neutrophils under inflammatory conditions	Drives immunothrombosis and disease severity
NETs in Leukemic Cell Survival	NET components support leukemic cell adhesion and survival	Extracellular DNA, histones, and microvesicles activate coagulation pathways	Contributes to DIC and disease progression
Immune Evasion	Platelets and neutrophils protect leukemic cells from immune attack		

CONCLUSION

Platelet–neutrophil interaction plays a central role in the pathophysiology of leukemia by linking inflammation, thrombosis, immune evasion, and tumor microenvironment regulation. Through mechanisms such as neutrophil extracellular trap (NET) formation, platelet activation, and cytokine release, these interactions promote leukemic cell survival, proliferation, adhesion, and resistance to therapy. They also contribute to serious complications like thrombosis and disseminated intravascular coagulation. Overall, platelet–neutrophil crosstalk creates a supportive microenvironment for leukemia progression and represents a promising target for future therapeutic strategies aimed at improving disease outcomes.

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