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RELATIONSHIP BETWEEN HEMORRHAGIC SYNDROMES AND ONCOHEMATOLOGICAL DISEASES IN CHILDREN

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Abstract: This article provides a comprehensive analysis of the pathogenetic mechanisms, clinical manifestations, and diagnostic significance of hemorrhagic syndromes in the pediatric population, with particular emphasis on their association with oncohematological diseases. In childhood, hemorrhagic manifestations are commonly attributed to primary hemostatic disorders such as thrombocytopenia, coagulation factor deficiencies, or vascular wall abnormalities. However, in a considerable number of cases, hemorrhagic syndrome may represent an early clinical sign of underlying malignant hematological conditions. The study explores the molecular and cellular mechanisms linking bone marrow dysfunction to the development of hemorrhagic complications. Special attention is given to impaired hematopoiesis, quantitative and qualitative platelet abnormalities, reduced synthesis of coagulation factors, and endothelial dysfunction as central components of the pathophysiological process. Acute lymphoblastic leukemia, acute myeloid leukemia, aplastic anemia, and myelodysplastic syndromes are discussed as major pediatric oncohematological disorders frequently accompanied by bleeding manifestations.

Keywords: hemorrhagic syndrome, pediatric hematology, oncohematological diseases, acute lymphoblastic leukemia, acute myeloid leukemia, thrombocytopenia, coagulation disorders, bleeding complications

Introduction: Hemorrhagic syndrome represents a complex clinical condition characterized by spontaneous or excessive bleeding resulting from disturbances in one or more components of the hemostatic system. In pediatric practice, bleeding manifestations are frequently encountered and may range from mild mucocutaneous hemorrhages to severe, life-threatening internal bleeding. Although many cases are associated with benign or transient causes such as immune thrombocytopenia or inherited coagulation factor deficiencies, hemorrhagic syndrome in children may also serve as an early indicator of serious underlying systemic disorders, particularly oncohematological diseases. The pediatric hematopoietic system is highly dynamic

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and sensitive to pathological alterations. Malignant transformation of hematopoietic stem and progenitor cells disrupts normal bone marrow architecture and function, leading to impaired production of erythrocytes, leukocytes, and platelets. As a result, thrombocytopenia and qualitative platelet dysfunction frequently develop, creating a predisposition to bleeding complications. In this context, hemorrhagic manifestations may be among the first clinical signs of acute leukemias, myelodysplastic syndromes, aplastic anemia, and other bone marrow failure states.

Acute lymphoblastic leukemia and acute myeloid leukemia are the most common pediatric malignancies worldwide and are often accompanied by significant hemostatic disturbances. The pathophysiology of bleeding in these conditions is multifactorial, involving bone marrow infiltration by malignant blasts, suppression of normal megakaryopoiesis, disseminated intravascular coagulation in certain subtypes, endothelial injury, and treatment-related cytopenias. Furthermore, intensive chemotherapy protocols, while essential for disease control, may exacerbate hemorrhagic risk by inducing profound thrombocytopenia and mucosal damage. Early recognition of the association between hemorrhagic syndrome and oncohematological disorders is crucial for improving diagnostic accuracy and clinical outcomes. Delayed identification of malignant hematologic diseases may result in severe complications, including massive bleeding, intracranial hemorrhage, and multi-organ dysfunction. Therefore, comprehensive evaluation of pediatric patients presenting with unexplained bleeding should include detailed clinical assessment, complete blood count analysis, peripheral smear examination, and, when indicated, bone marrow investigation and advanced molecular diagnostics.

Despite advances in pediatric oncology and hematology, challenges remain in differentiating primary hemostatic disorders from bleeding manifestations secondary to malignant bone marrow pathology. A systematic and evidence-based approach is required to establish clear diagnostic algorithms and risk stratification models. Understanding the pathogenetic link between hemorrhagic syndrome and oncohematological diseases not only facilitates timely intervention but also contributes to the development of individualized therapeutic strategies aimed at reducing morbidity and mortality. The aim of this study is to analyze the clinical and pathogenetic relationship between hemorrhagic syndromes and pediatric oncohematological diseases, to evaluate their diagnostic and prognostic significance, and to highlight the importance of early multidisciplinary management in affected children.

Main part: Hemorrhagic syndrome in pediatric patients represents a clinically significant and pathogenetically heterogeneous condition that often reflects complex disturbances within the hemostatic system. In childhood, bleeding manifestations may arise due to quantitative platelet deficiency, qualitative platelet dysfunction, coagulation factor abnormalities, vascular wall defects, or combined mechanisms. However, when hemorrhagic syndrome presents with systemic symptoms such as persistent fever, fatigue, pallor, lymphadenopathy, or hepatosplenomegaly, the probability of an underlying malignant hematologic disorder substantially increases. In such cases, bleeding is not merely a peripheral hemostatic abnormality but rather a manifestation of profound bone marrow pathology and systemic dysregulation. The pathophysiological link between hemorrhagic syndrome and oncohematological diseases is primarily mediated through disruption of normal hematopoiesis. Malignant transformation of hematopoietic stem cells leads to uncontrolled proliferation of immature blast cells, which

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progressively infiltrate the bone marrow and suppress physiological cell line differentiation. As megakaryopoiesis becomes impaired, thrombocytopenia develops, often reaching critical levels. In addition to quantitative platelet reduction, qualitative platelet dysfunction frequently occurs due to altered maturation and defective granule formation, further aggravating bleeding risk. Consequently, even minor trauma or spontaneous microvascular injury may result in clinically significant hemorrhage.

In acute leukemias, particularly acute lymphoblastic leukemia and acute myeloid leukemia, hemorrhagic manifestations are observed in a considerable proportion of pediatric patients at initial presentation. The severity of bleeding correlates not only with platelet count but also with bone marrow blast infiltration and systemic inflammatory activation. Certain subtypes of acute myeloid leukemia are associated with disseminated intravascular coagulation, characterized by simultaneous activation and consumption of coagulation factors, leading to paradoxical thrombotic and hemorrhagic complications. This consumption coagulopathy further compromises hemostatic balance and increases the risk of life-threatening bleeding, including intracranial hemorrhage. Aplastic anemia and myelodysplastic syndromes similarly predispose children to hemorrhagic complications through bone marrow failure mechanisms. In aplastic anemia, hypocellularity of the marrow results in pancytopenia, with thrombocytopenia being a central determinant of mucocutaneous bleeding. In myelodysplastic syndromes, ineffective hematopoiesis and dysplastic megakaryocyte development contribute to both decreased platelet production and functional impairment. These conditions illustrate that hemorrhagic syndrome in pediatric practice should always prompt evaluation of bone marrow integrity and proliferative activity.

Endothelial dysfunction represents another critical component in the pathogenesis of bleeding in oncohematological diseases. Malignant cells, inflammatory cytokines, and chemotherapeutic agents may damage vascular endothelium, increasing capillary fragility and permeability. This vascular component explains the frequent presence of petechiae and ecchymoses even when platelet counts are moderately reduced. Furthermore, systemic inflammatory mediators alter the delicate equilibrium between procoagulant and anticoagulant pathways, thereby contributing to hemostatic instability. Therapeutic interventions themselves significantly influence hemorrhagic risk. Intensive chemotherapy protocols, while essential for achieving remission in leukemia, induce profound cytopenias, including severe thrombocytopenia. Mucositis resulting from cytotoxic therapy predisposes to gastrointestinal bleeding, whereas invasive procedures such as central venous catheter placement may provoke additional hemorrhagic events. Thus, hemorrhagic syndrome in children with oncohematological diseases often reflects a combination of disease-related and treatment-related factors.

Laboratory evaluation plays a decisive role in clarifying the etiology of bleeding. Persistent thrombocytopenia unresponsive to conventional therapy, the presence of circulating blasts in peripheral blood smear, abnormal white blood cell counts, and unexplained anemia should immediately raise suspicion for malignant hematologic pathology. Bone marrow examination remains the gold standard for diagnosis, allowing assessment of cellularity, blast percentage, and lineage distribution. Modern immunophenotypic and molecular techniques further refine diagnostic precision and enable risk stratification. Clinical observations demonstrate that early identification of malignant causes of hemorrhagic syndrome significantly improves prognosis. Children diagnosed at an early stage, before the development of severe hemorrhagic

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complications, have higher remission rates and lower mortality. Conversely, delayed diagnosis may result in catastrophic outcomes, particularly in cases of intracranial bleeding or massive gastrointestinal hemorrhage. Therefore, unexplained or atypical hemorrhagic manifestations should never be regarded as benign without comprehensive hematologic investigation.

Differential diagnosis between primary immune thrombocytopenia and leukemia-associated thrombocytopenia represents a particularly important clinical challenge. While immune thrombocytopenia is typically characterized by isolated thrombocytopenia with otherwise normal hematologic parameters, malignant conditions often present with additional abnormalities such as anemia, leukocytosis or leukopenia, and constitutional symptoms. Careful clinical reasoning combined with laboratory assessment is essential to avoid misdiagnosis and inappropriate management. From a prognostic perspective, the degree and pattern of bleeding may reflect underlying disease severity. Severe thrombocytopenia below critical thresholds is strongly associated with major hemorrhagic events. Moreover, certain cytogenetic and molecular abnormalities in leukemia correlate with increased risk of coagulopathy and poor clinical outcome. Recognition of these risk factors allows implementation of preventive strategies, including timely platelet transfusion, administration of coagulation factor concentrates, and individualized chemotherapy dose adjustments.

Multidisciplinary management constitutes a cornerstone of care for pediatric patients with hemorrhagic syndrome secondary to oncohematological disease. Close collaboration between pediatricians, hematologists, oncologists, transfusion specialists, and intensive care teams ensures rapid stabilization and etiological treatment. Supportive therapy, including transfusion of platelet concentrates and fresh frozen plasma, should be carefully balanced against potential complications such as alloimmunization and transfusion-related reactions. In summary, hemorrhagic syndrome in children frequently represents a clinically visible manifestation of deeper hematologic pathology. The interrelationship between bone marrow failure, malignant cellular proliferation, endothelial injury, inflammatory activation, and therapeutic cytotoxicity forms a complex pathogenetic network leading to bleeding complications. Comprehensive diagnostic algorithms and early etiological treatment are essential for improving survival and reducing morbidity in pediatric patients. Recognition of hemorrhagic syndrome as a potential marker of oncohematological disease significantly enhances clinical vigilance and supports timely intervention.

Conclusion and recommendations: The performed analysis confirms that hemorrhagic syndrome in pediatric patients represents not merely a symptomatic disturbance of the hemostatic system, but in many cases a clinically significant indicator of underlying oncohematological pathology. The pathogenetic relationship between malignant transformation within the bone marrow and the development of bleeding manifestations is multifactorial and involves suppression of normal hematopoiesis, impaired megakaryocyte maturation, quantitative and qualitative platelet defects, endothelial dysfunction, and imbalance of coagulation mechanisms. In acute leukemias and bone marrow failure syndromes, thrombocytopenia is often combined with anemia and leukocyte abnormalities, reflecting global disruption of hematopoietic function. This systemic involvement distinguishes secondary hemorrhagic syndrome from primary immune thrombocytopenia and other isolated coagulation disorders. Therefore, persistent or atypical bleeding in children—especially when accompanied by constitutional symptoms—must always prompt comprehensive hematologic evaluation. Early diagnostic verification using complete blood count analysis, peripheral smear examination, bone

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marrow assessment, and modern immunophenotypic and molecular techniques significantly improves clinical outcomes. Timely identification of malignant hematologic diseases allows initiation of etiologically targeted therapy and reduces the risk of severe complications such as intracranial hemorrhage and disseminated intravascular coagulation. Overall, recognition of hemorrhagic syndrome as a potential early manifestation of oncohematological disease enhances clinical vigilance, reduces diagnostic delay, and contributes to improved survival and quality of life in pediatric patients.

Recommendations:

1. All children presenting with unexplained or recurrent hemorrhagic manifestations should undergo complete hematologic evaluation, including peripheral smear analysis.
2. Persistent thrombocytopenia combined with anemia or leukocyte abnormalities requires mandatory bone marrow examination to exclude malignant pathology.
3. Early use of immunophenotyping and molecular diagnostics is recommended in suspected oncohematological cases for accurate classification and risk stratification.
4. Platelet transfusion thresholds and supportive therapy should be individualized according to bleeding severity and underlying disease activity.
5. Multidisciplinary clinical protocols should be implemented to minimize diagnostic delay and optimize outcomes in pediatric patients with hemorrhagic syndrome.

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