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Mini Review

Thrombocytopenia in Epstein-Barr Virus Infection as A Hidden Clinical Clue

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Abstract: Thrombocytopenia is a frequently overlooked yet clinically relevant manifestation of Epstein-Barr virus (EBV) infection, particularly in children. Although it is commonly associated with EBV-related conditions, thrombocytopenia is often misdiagnosed as primary immune thrombocytopenia or dismissed as an incidental finding. This review summarizes current evidence linking EBV infection and thrombocytopenia, highlighting its potential as an early clinical clue. We emphasize the importance of timely EBV testing in pediatric patients with unexplained thrombocytopenia and advocate for greater clinical awareness and multidisciplinary research. Recognizing thrombocytopenia as more than a minor laboratory abnormality may improve diagnostic accuracy, guide appropriate treatment, and inform future research directions.

Keywords: EBV; thrombocytopenia; infectious mononucleosis; CAEBV

1. Thrombocytopenia in EBV Infection: An Underrecognized Clinical Feature

Epstein-Barr virus (EBV) is a ubiquitous human γ-herpesvirus that infects more than 90% of the global population and establishes lifelong latency. Its clinical spectrum includes infectious mononucleosis (IM), chronic active EBV infection (CAEBV), EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH), and various EBV-related malignancies. Among these, IM, CAEBV, and EBV-HLH are the major non-malignant EBV-associated disorders, most of which occur in children and adolescents.

The typical clinical features of EBV infection include fever, lymphadenopathy, and atypical lymphocytosis. In contrast, thrombocytopenia is a less recognized yet clinically relevant manifestation. It is often overlooked, misdiagnosed as primary immune thrombocytopenia (ITP) [1], or considered a minor and nonspecific laboratory abnormality. EBV infection is increasingly recognized as an infectious trigger of secondary ITP [2]. While various viral pathogens, including influenza virus and SARS-CoV-2, have been associated with virus-induced thrombocytopenia [3,4], EBV is one of the more frequently implicated viruses in pediatric cases.

In the context of HLH, pancytopenia including thrombocytopenia is common and has not been shown to have distinguishing value in clinical practice to date. It is also not unique to EBV-HLH. In contrast, the occurrence of thrombocytopenia in IM or CAEBV, particularly when it deviates from the typical disease course or expected

clinical presentation, may indicate atypical disease progression or warrant further clinical evaluation, although its predictive value has not been clearly established. However, comprehensive understanding and mechanistic studies are still lacking. Clinical awareness remains limited, treatment strategies are not yet well developed, and the underlying biological mechanisms are unclear.

This article aims to emphasize the clinical relevance, underlying mechanisms, and management implications of thrombocytopenia in EBV infection, particularly in pediatric populations. By raising awareness of this often-overlooked manifestation, we hope to improve diagnostic accuracy, guide appropriate treatment strategies, and stimulate further research into its pathophysiology.

2. Clinical Correlation between EBV Infection and Thrombocytopenia

Thrombocytopenia in EBV infection may increase bleeding risk, which can impair short-term recovery or long-term quality of life, and therefore warrants clinical attention. Thrombocytopenia is a common hematologic abnormality in patients with EBV infection, though its frequency and severity vary by disease type. In T/NK cell-type CAEBV, thrombocytopenia is observed in approximately 58.8% of patients at diagnosis, often reflecting underlying immune dysregulation and disease activity [5]. In contrast, about 25% to 50% of patients with infectious mononucleosis (IM) may develop mild to moderate thrombocytopenia [6,7]. These cases are typically asymptomatic or associated with minor bleeding manifestations. However, severe thrombocytopenia, although rare (1.5% of EBV-induced IM cases) [8], can lead to serious complications. Among affected individuals, 78.4% had platelet counts below 10×10^9/L, 75.7% were 21 years of age or younger, 64.9% presented with petechiae, purpura, or other signs of bleeding, and 5.4% died from hemorrhagic complications related to thrombocytopenia [7].

In pediatric patients who initially present with bleeding manifestations and are found to have significant thrombocytopenia, EBV infection should be considered in the differential diagnosis. EBV-associated thrombocytopenia can be confirmed through serological testing and EBV DNA quantification. A favorable clinical response to antiviral therapy or intravenous immunoglobulin suggests a possible association, although the underlying mechanisms remain unclear. Interestingly, in some cases, thrombocytopenia may be the earliest or even the sole clinical manifestation, sometimes preceding classical IM symptoms [2,9]. Delayed-onset thrombocytopenia during convalescence has also been reported, underscoring the need for extended clinical monitoring.

From a diagnostic standpoint, it is important to distinguish between primary and secondary ITP. Primary ITP refers to isolated thrombocytopenia without an identifiable cause, while secondary ITP occurs in association with underlying conditions such as infections, autoimmune disorders, or malignancies. Differentiation is clinically relevant because management strategies and prognosis may vary; for example, treatment of secondary ITP often includes addressing the underlying cause, which can improve outcomes. EBV is one of the most frequently implicated viral pathogens in secondary ITP in children. However, the clinical features of infection-related secondary ITP often mimic those of primary ITP at initial presentation, making accurate diagnosis dependent on virologic evaluation.

3. Proposed Mechanisms Underlying EBV-Associated Thrombocytopenia

The pathogenesis of EBV-associated thrombocytopenia remains largely unknown and may involve multiple contributing factors [10–14]: (1) Direct suppression of megakaryopoiesis by EBV: EBV can directly infect and impair hematopoietic progenitor cells and megakaryocytes in the bone marrow, leading to decreased platelet production and myelosuppression. In vitro studies have shown that EBV may inhibit megakaryocyte differentiation and maturation, contributing to thrombocytopenia; (2) Autoantibody-mediated platelet destruction: EBV infection may trigger autoimmune responses, leading to the production of antiplatelet antibodies or immune complexes. Molecular mimicry may result in immune-mediated misrecognition and attack on platelets. IgG, IgA, and IgM autoantibodies can target platelet surface antigens, resulting in phagocytosis by splenic macrophages and complement-mediated lysis; (3) Chronic activation of the reticuloendothelial system (RES): EBV or EBV-antibody immune complexes may chronically activate the RES, particularly in the spleen and liver, contributing to sustained platelet clearance; (4) Non-specific binding by heterophile and polyclonal antibodies: During primary EBV infection, naïve B cells may generate heterophile antibodies, some of which are autoreactive and capable of binding to platelets, leading to their destruction. In the latent phase, polyclonal antibodies produced by infected B cells may also include antiplatelet reactivity.

Progress in elucidating these mechanisms has been limited by the lack of suitable animal models, the difficulty in obtaining relevant tissue specimens, and the inherent complexity of the underlying pathophysiology.

4. Strategies for Managing EBV-Associated Thrombocytopenia

Clinicians should maintain a high index of suspicion for EBV infection as an underlying cause of unexplained thrombocytopenia, particularly in the following populations: children and adolescents; individuals presenting with clinical features suggestive of EBV infection such as fever, abnormal liver function, or atypical lymphocytes in peripheral blood; and patients with thrombocytopenia accompanied by skin or mucosal bleeding or hepatosplenomegaly. A diagnosis of ITP should be made with caution, especially in the absence of thorough exclusion of viral etiologies. It is recommended that EBV serology and EBV DNA quantification be incorporated into the diagnostic evaluation of thrombocytopenia.

In cases of EBV-associated mild thrombocytopenia, the condition is often self-limiting and does not require specific treatment. Observation and regular follow-up, including complete blood count and EBV DNA monitoring, are generally sufficient. For moderate to severe thrombocytopenia or when bleeding symptoms are present, antiviral therapy (effective in selected cases but requiring further clinical validation) and immunomodulatory treatments may be considered. In patients with significant bleeding, intravenous immunoglobulin or corticosteroids may be indicated, although steroids should be used with caution and are generally reserved for individuals with prominent immune dysregulation or high-risk features. For patients with severe thrombocytopenia or life-threatening bleeding, platelet transfusion may be used as a temporary measure. In cases of CAEBV or refractory disease, early hematopoietic stem cell transplantation should be considered, especially in those with recurrent cytopenias, organ damage, or a high risk of malignant transformation. When EBV-associated thrombocytopenia occurs as part of a defined disease entity, such as EBV-HLH or EBV-positive lymphoproliferative disorders, treatment should be directed toward the underlying condition. For example, patients with EBV-HLH may require cytokine-targeted therapy, etoposide-based chemotherapy, or even hematopoietic stem cell transplantation, following HLH-2004-based protocols.

5. Call for Research and Awareness

There is a growing need to carry out multicenter and systematic studies to better understand the epidemiological characteristics, underlying mechanisms, and clinical course of EBV-associated thrombocytopenia. Large-scale population-based research is recommended to clarify its incidence, progression, and clinical outcomes, providing valuable data to support early identification and effective clinical management. At the same time, advanced multi-omics approaches, such as single-cell RNA sequencing and DNA methylation profiling, should be applied to explore the complex interactions between EBV and the hematopoietic system. Establishing and refining in vitro hematopoietic models or humanized mouse models may help validate key pathological pathways and support the development of targeted therapies.

From a clinical perspective, it is important to develop early recognition scoring systems that incorporate clinical features, virological markers, and immune indicators to improve the detection and timely management of EBV-related hematologic abnormalities. In adolescents and young adults presenting with acute thrombocytopenia, EBV infection should be considered as a potential cause even in the absence of typical symptoms of infectious mononucleosis. Routine testing for EBV IgM antibodies in such cases may help reduce misdiagnosis and inappropriate treatment.

EBV-associated hematologic disorders deserve greater attention as a focus of interdisciplinary research spanning pediatrics, infectious diseases, and hematology. Strengthening awareness, advancing mechanistic investigations, and improving clinical readiness are essential to enhancing patient care and fostering collaboration across medical disciplines.

6. Conclusions

Thrombocytopenia is a potentially serious but often overlooked manifestation of EBV infection and may, in some cases, represent a form of secondary ITP. Rather than being dismissed as an incidental laboratory finding, it should be recognized as a potential early clinical clue, especially when typical symptoms of infectious mononucleosis are absent. Early identification of EBV-associated thrombocytopenia can facilitate timely diagnosis, guide appropriate management, and help distinguish it from primary ITP, thereby reducing the risk of misdiagnosis and ensuring proper treatment.

Author Contributions

R.W.: conceived and designed the article; Y.S. and L.G.: prepared the initial draft; Y.S. and J.G.: also contributed to referencing and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest. Given the role as Editorial Board Member, Ran Wang had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

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