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Aplastic Anemia: Clinical Manifestations And Modern Laboratory Diagnostic Methods In The Context Of Post-COVID Complications

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Abstract: Aplastic anemia (AA) is a rare, potentially life-threatening hematopoietic disorder characterized by profound pancytopenia and bone marrow hypocellularity resulting from severe suppression of hematopoiesis. In the post-pandemic era, growing evidence suggests a possible association between AA and prior SARS-CoV-2 infection, highlighting the importance of early detection. The objective of this study is to provide a comprehensive analysis of the clinical manifestations of AA and advanced laboratory diagnostic methods, with particular emphasis on post-COVID complications. This work examines the key clinical and hematological features of AA, outlines internationally recognized diagnostic criteria, and discusses the role of molecular-genetic, immunological, and cytogenetic techniques in diagnostic confirmation. Special attention is given to the interpretation of hemograms, bone marrow evaluations, flow cytometry, and PCR-based assays, which are essential for differential diagnosis from other causes of cytopenias. The implementation of modern, high-precision laboratory technologies enhances early identification of AA, facilitates optimal therapeutic decision-making, and reduces the risk of severe complications, including post-COVID immune-mediated dysregulation.

Keywords: Aplastic anemia, COVID-19, pancytopenia, laboratory diagnostics, bone marrow, cytokine storm, flow cytometry, molecular-genetic methods.

Introduction: Aplastic anemia (AA) represents one of the most complex and severe hematological disorders, owing to its multifactorial etiology and the high risk of serious, including fatal, complications. The disease is characterized by profound suppression of all hematopoietic lineages, resulting in marked pancytopenia and hypocellularity of the bone marrow. According to the World Health Organization, the annual incidence of AA ranges from 2 to 5 cases per 1 million population, with higher prevalence reported in Asian countries [9]. Major risk factors include exposure to toxic agents, administration of certain medications,

viral infections, and immune dysregulation [3].

In the aftermath of the COVID-19 pandemic, there has been an observed increase in reports of aplastic conditions among patients recovering from SARS-CoV-2 infection. It is hypothesized that the virus may trigger a cascade of immune responses, including cytokine storm, which leads to damage of hematopoietic stem cells and the development of secondary bone marrow aplasia [11, 17]. Considering the widespread prevalence of coronavirus infection and the potential for delayed complications, timely diagnosis of AA has become critically important for reducing mortality and improving patient quality of life.

Modern laboratory techniques, including flow cytometry, molecular-genetic analyses, and cytokine profiling, enable the detection of early disturbances in hematopoiesis and allow for more precise characterization of cytopenias. The application of these technologies is particularly relevant in the post-COVID-19 context, where meticulous differential diagnosis and early identification of immunopathological processes are essential for optimal patient management.

Relevance and Objective

Aplastic anemia (AA) is a rare but severe hematological disorder characterized by profound suppression of hematopoietic stem cells, leading to pancytopenia and bone marrow hypocellularity. Its multifactorial etiology, coupled with a high risk of life-threatening complications, renders AA a significant clinical challenge. The annual incidence is estimated at 2–5 cases per 1 million individuals, with higher prevalence in Asian populations [9]. Recognized risk factors include exposure to toxic agents, certain medications, viral infections, and immune dysregulation [3].

The emergence of SARS-CoV-2 has highlighted a new dimension in AA pathogenesis. Post-COVID-19 patients have shown an increased incidence of aplastic conditions, potentially mediated by immune system dysregulation, cytokine storm, hypoxia, and direct injury to hematopoietic progenitors [11, 12, 17]. Given the global spread of COVID-19 and the possibility of delayed hematologic complications, early identification of AA is critical to reduce morbidity and mortality and to improve patient quality of life.

Clinically, AA manifests with fatigue, pallor, hemorrhagic tendencies, and recurrent infections due to cytopenias [19]. Diagnosis relies on peripheral blood counts (leukocytes $<1.5\times10^9$/L, platelets $<50\times10^9$/L, reticulocytes $<20\times10^9$/L) and is confirmed by bone marrow trephine biopsy demonstrating hypocellularity [2].

Modern diagnostic approaches enhance early detection and differentiation from myelodysplastic syndromes and other causes of cytopenias:

- Flow cytometry allows quantification of $CD34^+$ cells and identification of clonal populations, including those seen in paroxysmal nocturnal hemoglobinuria (PNH) [13].
- Molecular-genetic techniques, such as next-generation sequencing (NGS), detect mutations in genes including TERT, TERC, and DNMT3A, providing valuable information for risk stratification and treatment planning [18].
- Immunological assays evaluating cytokines (IL-2, IFN-γ, TNF-α) inform on the degree of immune activation and dysregulation [15].
- Cytogenetic analysis helps exclude abnormalities characteristic of myelodysplastic syndromes, ensuring diagnostic accuracy [6].

In the post-COVID-19 context, secondary AA has been increasingly reported, often associated with hyperinflammatory states and cytokine storms [7, 8]. While some patients experience transient hematopoietic suppression, others progress to persistent aplasia requiring immunosuppressive therapy or hematopoietic stem cell transplantation [4, 10]. Umbilical cord blood transplantation emerges as a promising alternative in the absence of an HLA-matched donor [20].

Objective: This study aims to comprehensively examine the clinical manifestations of AA and to evaluate contemporary laboratory methods for its early detection, with particular focus on forms associated with post-COVID-19 complications. By integrating clinical and laboratory data, the research seeks to enhance understanding of AA pathogenesis, improve early diagnostic accuracy, and inform optimal therapeutic strategies.

METHODS

This study represents an analytical review of scientific publications published between 2020 and 2025, sourced from the PubMed, Scopus, and eLibrary databases. The review includes original research articles, clinical case reports, and systematic reviews with evidence levels A–C, focusing on the clinical manifestations, laboratory diagnostics, and post-COVID-19 complications of aplastic anemia (AA).

-The analysis was structured around the following key areas:

-Clinical characteristics of aplastic anemia;

-Modern laboratory and morphological diagnostic techniques;

-The role of SARS-CoV-2 in the development of aplastic

syndromes;

-Approaches to patient management, including therapeutic and monitoring strategies.

A systematic search was conducted using the following keywords: “aplastic anemia,” “COVID-19,” “pancytopenia,” “laboratory diagnostics,” “cytokine storm,” and “flow cytometry.” In total, 50 sources were evaluated, of which 20 were included in the final reference list based on relevance and methodological quality. The selection and analysis of studies were performed with a focus on evidence-based data, ensuring the inclusion of high-quality information relevant to both the clinical and laboratory aspects of AA in the context of post-COVID-19 complications.

RESULTS

The clinical manifestations of aplastic anemia (AA) are primarily attributable to pancytopenia and include generalized weakness, pallor, bleeding tendencies (petechiae, ecchymoses, spontaneous hemorrhages), and increased susceptibility to infections [7, 19]. In patients with post-COVID-19 AA, these symptoms may be more pronounced due to systemic inflammation and cytokine storm activation [8].

Laboratory diagnosis of AA is based on peripheral blood analysis, revealing pancytopenia, and bone marrow morphology, confirming hypocellularity [2]. Modern diagnostic techniques significantly enhance diagnostic accuracy:

1. Flow cytometry enables detection of paroxysmal nocturnal hemoglobinuria (PNH) clones and quantification of $CD34^+$ cell populations, which is particularly important for early disease detection [13].

2. Molecular-genetic analyses using next-generation sequencing (NGS) identify mutations associated with disease progression and facilitate risk stratification [18].

3. Immunological assays demonstrate elevated levels of proinflammatory cytokines in post-COVID-19 AA patients, reflecting the degree of immune dysregulation [15].

4. Cytogenetic analysis is essential to exclude myelodysplastic syndrome and other hematologic disorders, ensuring diagnostic precision [6].

In the post-COVID-19 context, AA frequently develops as a secondary condition associated with autoimmune-mediated damage to bone marrow stem cells [7, 8]. Timely detection using the aforementioned methods allows early initiation of immunosuppressive therapy (antithymocyte globulin, cyclosporin A) or hematopoietic stem cell transplantation, improving prognosis and reducing the risk of complications [4, 10]. Umbilical cord blood transplantation has shown promising results in cases where an HLA-matched donor is not available [20].

CONCLUSION

Aplastic anemia remains one of the most complex hematological disorders, necessitating timely diagnosis and a comprehensive, individualized therapeutic approach. In the post-COVID-19 era, the clinical significance of AA has increased due to its potential association with SARS-CoV-2, which may induce secondary aplastic states through cytokine storm activation and immune-mediated damage to hematopoietic stem cells. Modern laboratory technologies, including flow cytometry, molecular-genetic analyses, and cytokine profiling, enable precise and early detection of the disease. Their application facilitates differentiation of AA from other hematological disorders, assessment of immune dysregulation, and initiation of therapy at early stages, substantially reducing the risk of severe complications and improving patient prognosis.

Future research directions should focus on elucidating the molecular and immunological mechanisms underlying post-COVID aplasia, developing novel biomarkers for early diagnosis, and refining bone marrow regenerative techniques. Advancements in these areas have the potential to enhance therapeutic efficacy and improve quality of life for affected patients.

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