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Intersecting Pathologies: Understanding the Clinical Impact of HIV on Sickle Cell Disease

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Abstract

Sickle Cell Disease (SCD) and Human Immunodeficiency Virus (HIV) are two distinct but prevalent conditions that often coexist, particularly in populations at high risk for both diseases. The intersection of these two pathologies presents unique challenges in clinical management, as each condition can exacerbate the complications of the other. This review explores the clinical impact of HIV on SCD, highlighting the overlapping pathophysiological mechanisms, including immune dysregulation, chronic inflammation, and increased susceptibility to infections. The review further examines the increased risk of co-morbidities such as kidney disease, stroke, and cardiovascular complications in patients with both HIV and SCD. The pathophysiology of both HIV and SCD is multifaceted and complex. HIV-induced immunosuppression worsens the already compromised immune system in individuals with SCD, leading to a heightened risk of infections and organ dysfunction. Additionally, the chronic inflammation associated with both conditions accelerates vascular damage, contributing to complications such as pulmonary hypertension, stroke, and acute chest syndrome. The review also addresses the diagnostic challenges clinicians face in differentiating between symptoms of SCD and HIV, emphasizing the need for accurate and timely diagnosis to prevent mismanagement.

Keywords: HIV, Sickle Cell Disease, Pathophysiology, Co-morbidities, Management Strategies

Introduction

(SCD) Sickle Cell Disease and Human Immunodeficiency Virus (HIV) are two significant health conditions that disproportionately affect populations in sub-Saharan Africa, the Caribbean, and African-American communities in the United States. SCD is a hereditary hematologic disorder characterized by the presence of abnormal hemoglobin (HbS), which causes red blood cells to take on a sickle shape, leading to vascular occlusion, hemolysis, and tissue damage. HIV, on the other hand, is a viral infection that primarily targets CD4+ T cells. weakening the immune system and leaving individuals vulnerable to opportunistic infections and other complications. While each disease presents its own set of challenges, their coexistence in a single patient complicates diagnosis, treatment, and overall disease management.¹⁻² Patients with both HIV and SCD face a myriad of challenges. The immune system dysfunction caused by HIV exacerbates the alreadv compromised immune status of individuals with SCD, making them more susceptible to infections, particularly bacterial and fungal pathogens. Additionally, both conditions involve chronic inflammation, which contributes to the development of vascular complications. The combination of immune suppression and vascular dysfunction increases the risk of organ damage, including renal failure, stroke, and pulmonary hypertension. These intersecting pathologies pose a complex clinical picture that requires an integrated and multidisciplinary approach to patient care.³⁻⁴ SCD itself has a range of debilitating symptoms, including acute pain episodes, organ damage, and increased risk of stroke. The presence of HIV adds another layer of complexity, as HIV treatment regimens (primarily antiretroviral therapy, or ART) can interact with medications used to manage SCD, such as hydroxyurea, blood transfusions, and pain management therapies. The side effects of ART, including hepatotoxicity and kidney damage, can exacerbate the renal complications associated with SCD, particularly HIV-associated nephropathy (HIVAN). In contrast. HIV medications may need to be adjusted or changed based on potential interactions with other treatments, adding to the difficulty of creating a cohesive treatment plan for these patients.⁵⁻⁶

The burden of managing HIV and SCD coinfection is particularly high in resource-limited settings, where both diseases are prevalent and healthcare infrastructure may be insufficient to provide optimal care. The intersection of these diseases calls for a comprehensive understanding of both their independent and combined impacts on health. Early diagnosis and appropriate management strategies are essential in preventing severe outcomes, yet the overlapping symptoms these conditions can make diagnosis of challenging. For instance, chest pain, shortness of breath, and fever are common in both HIV-related opportunistic infections and SCD-related complications like acute chest syndrome, making differentiation between the two difficult without careful diagnostic workup.⁷⁻⁹ Research into the clinical impact of HIV on SCD is still emerging, with much of the available literature focusing on either one condition or the other, but rarely on their intersection. However, it is clear that HIV infection can significantly affect the clinical course of SCD, particularly through increased susceptibility to infections, renal complications, and cardiovascular events. Moreover, the immunosuppressive effects of HIV and the inflammatory response in SCD patients further heighten the severity of complications. This interplay requires more focused research to unravel the mechanisms behind these interactions identify and more effective management strategies.¹⁰⁻¹¹

Pathophysiology of Sickle Cell Disease and HIV

Sickle Cell Disease (SCD) and Human Immunodeficiency Virus (HIV) are distinct pathologies, but when they coexist, their combined effects on the body can lead to a complex set of challenges for both diagnosis and treatment. Understanding the pathophysiology of each condition individually and the interactions between them is essential for managing patients with both SCD and HIV.¹² Sickle Cell Disease is

primarily a genetic disorder of hemoglobin, the oxygen-carrying protein in red blood cells. The mutation that causes SCD results in the production of hemoglobin S (HbS), which tends to polymerize and form rigid, sickle-shaped red blood cells under low oxygen conditions. These sickle-shaped cells cause blockages in small blood vessels, resulting in vaso-occlusion, ischemia, and tissue damage. The impaired blood flow also leads to hemolysis, where red blood cells are prematurely destroyed, releasing free hemoglobin into the bloodstream and contributing to anemia. This ongoing vascular obstruction and hemolysis lead to a wide range of complications, including acute pain crises, stroke, organ damage, increased risk of infection. Chronic and inflammation and endothelial dysfunction are also prominent features of SCD, further exacerbating the risk of cardiovascular and renal complications.¹³⁻¹⁵

HIV, caused by the HIV-1 virus, attacks and progressively weakens the immune system, primarily targeting CD4+ T lymphocytes, which are crucial for orchestrating the immune response. The virus causes the gradual destruction of these cells, impairing the body's ability to fight off infections and leading to immunodeficiency. HIV infection can also result in chronic immune activation and inflammation, even in patients with well-controlled HIV on antiretroviral therapy (ART). This persistent immune activation contributes to a range of non-AIDS-related complications, including cardiovascular disease, renal dysfunction, and accelerated aging. HIV also induces a state of immune dysregulation, which can make it harder for the body to manage the inflammation and hypercoagulability associated with conditions like SCD. Additionally, as HIV progresses, it can lead to infections, opportunistic malignancies, and complications such HIV-associated as nephropathy (HIVAN), which can exacerbate preexisting renal damage in SCD patients.¹⁶⁻¹⁸ When HIV and SCD co-exist, the pathophysiological interplay between the two diseases can complicate the clinical picture. The immune suppression caused by HIV, along with the chronic inflammation seen in both diseases, leads to a

heightened vulnerability to infections. Moreover, the endothelial dysfunction and vascular damage induced by both SCD and HIV increase the risk of thrombotic events, stroke, and pulmonary hypertension. In particular, the combination of chronic immune activation and vascular injury accelerates the development of cardiovascular and renal complications. This dual burden can exacerbate organ dysfunction, especially in the kidneys, where both HIVAN and sickle cellrelated renal issues, such as glomerulopathy and nephropathy, contribute to progressive renal failure. The immune dysregulation in HIV patients also makes it difficult to control the chronic inflammation present in SCD, leading to a vicious cycle of vascular injury and worsening disease.¹⁹⁻²¹

Co-morbidities in HIV and Sickle Cell Disease

The coexistence of Human Immunodeficiency Virus (HIV) and Sickle Cell Disease (SCD) in a single patient significantly increases the risk and complexity of several co-morbidities, which compound the burden of disease management. Both HIV and SCD independently contribute to immune dysregulation, organ dysfunction, and chronic inflammation, but together they create a synergistic effect, increasing the incidence and severity of complications. Co-morbidities in patients with both conditions affect multiple organ systems, including the cardiovascular, renal, pulmonary, and hematological systems, and require a multifaceted approach to treatment.²²

1. Renal Complications: One of the most significant co-morbidities in patients with both HIV and SCD is renal dysfunction. In SCD, kidney damage is primarily caused by hematuria, glomerulopathy, and nephropathy associated with long-term sickle cell-related damage. Additionally, sickle cells obstruct blood flow to the kidneys, leading to ischemia and progressive renal impairment. In HIVinfected patients. HIV-associated nephropathy (HIVAN) is a well-established complication that leads to kidney failure. HIVAN is characterized focal segmental by glomerulosclerosis, which further exacerbates

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renal dysfunction. The combination of these two conditions accelerates kidney injury and significantly increases the risk of end-stage renal disease (ESRD), requiring dialysis or kidney transplantation.²³⁻²⁴

- 2. Cardiovascular **Complications**: The cardiovascular system is another organ system heavily impacted by both HIV and SCD. Sickle cell patients are at an increased risk of stroke, pulmonary hypertension, and heart failure due to vaso-occlusion, chronic hemolysis, and endothelial dysfunction. HIV infection, especially if untreated or inadequately treated, leads to chronic inflammation and immune activation, which increases the risk of atherosclerosis. myocardial infarction, and cardiovascular events. The combined effects of HIV-related inflammation and SCD-induced vascular damage further amplify the likelihood of cardiovascular complications, particularly pulmonary hypertension, a common finding in both conditions. These dual insults contribute to a higher risk of mortality and morbidity due to cardiovascular diseases in co-infected patients.25-26
- 3. Pulmonary **Complications**: Pulmonary issues are also a frequent co-morbidity in individuals with both HIV and SCD. In SCD, the frequent occurrence of acute chest syndrome, characterized by the rapid onset of chest pain, hypoxia, and respiratory distress, is a major cause of morbidity and mortality. HIV-positive patients are more susceptible to pulmonary infections, including tuberculosis, pneumonia, and opportunistic infections such as Pneumocystis jirovecii pneumonia. The combination of SCD and HIV compromises pulmonary function, increases the risk of respiratory failure, and may lead to the development chronic of obstructive pulmonary disease (COPD). Moreover, both conditions contribute to pulmonary vascular remodeling, which can result in pulmonary hypertension. Managing these pulmonary complications requires a careful balance of antiviral therapy, antibiotics, and SCDspecific treatments.²⁷⁻²⁸
- 4. Hematological Issues: Hematological complications are another area of concern in patients with both HIV and SCD. HIV infection induces immune dysregulation, which can interfere with the bone marrow's ability to produce blood cells, leading to an increased risk of anemia, thrombocytopenia, and neutropenia. This is compounded in SCD, where anemia is already a hallmark of the disease due to the premature destruction of sickle-shaped red blood cells. Additionally, patients with both conditions may face difficulties in managing pain crises, as immune suppression from HIV treatment may interfere with the body's ability to respond to Furthermore, the use of these crises. antiretroviral therapy (ART) in HIV patients, especially protease inhibitors, can exacerbate hemolysis, further worsening anemia in SCD The patients. management of these hematological issues requires careful monitoring and adjustments to treatment regimens to prevent exacerbations and ensure optimal red blood cell production.²⁹⁻³⁰
- 5. Infections: Infections represent one of the most common and serious co-morbidities in patients with both HIV and SCD. HIVinfected individuals have a weakened immune system, making them more susceptible to opportunistic infections, which are common in SCD due to functional asplenia and impaired immune responses. Common infections in coinfected patients include bacterial, fungal, and viral infections, as well as the reactivation of latent infections such as tuberculosis and cytomegalovirus (CMV). The risk of severe infections is exacerbated by the chronic inflammation associated with both conditions. For example, the use of immunosuppressive regimens can further increase ART susceptibility to infections, making preventive measures such as vaccination, prophylactic antibiotics, and regular screening critical in managing co-infected individuals.³¹⁻³²
- 6. **Bone and Joint Complications**: Both HIV and SCD have notable effects on bone health, leading to an increased risk of bone and joint complications. In SCD, avascular necrosis (AVN) is common due to sickle cell-induced

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vaso-occlusion and compromised blood supply to the bones. HIV infection, especially in untreated or poorly controlled cases, also leads to bone loss and osteopenia due to immune system dysregulation, low vitamin D levels, and ART-related side effects. The combination of conditions these two accelerates bone deterioration, leading to higher rates of fractures, joint deformities, and increased pain, significantly affecting the quality of life of affected individuals.³³⁻³⁴

7. Neurocognitive and Psychiatric Disorders: The neurocognitive and psychiatric impact of living with both HIV and SCD is another critical area of concern. SCD is associated with neurocognitive impairments, such as learning disabilities, memory deficits, and stroke-related neurological damage, while HIV can lead to neurocognitive disorders such as HIV-associated dementia or HAND (HIVassociated neurocognitive disorder). The stress and burden of managing two chronic diseases can also increase the risk of mental health issues, including depression and anxiety. Furthermore, both HIV and SCD have been associated with social stigma. which exacerbate mental health can challenges and hinder treatment adherence, making it imperative to integrate mental health support into the comprehensive care plan.³⁵

Diagnostic Challenges and Clinical Implications

Diagnostic Challenges and Clinical Implications in HIV and Sickle Cell Disease

The co-existence of Human Immunodeficiency Virus (HIV) and Sickle Cell Disease (SCD) presents significant diagnostic challenges due to the overlapping clinical features and the intricate interplay between both conditions. Accurate diagnosis and timely management are crucial, but the complex nature of these diseases, combined with their co-morbidity, can often lead to delays in diagnosis or misdiagnosis.

- 1. Overlap of Symptoms and Presentation: Both HIV and SCD present with overlapping symptoms, such as anemia, fatigue, fever, and pain. In SCD, pain crises resulting from vasoocclusion, acute chest syndrome, and stroke are common, while HIV-positive individuals may also experience systemic symptoms, such as fever and malaise, due to opportunistic infections or HIV-related complications. These overlapping symptoms can complicate the process of distinguishing between the two conditions and can delay the initiation of appropriate treatment. Additionally, chronic pain is a hallmark of both diseases, but its origins may be multifactorial, requiring careful clinical evaluation to differentiate between pain due to sickle cell crises, HIVrelated neuropathies, or musculoskeletal complications associated with antiretroviral therapy (ART). As a result, healthcare providers need to consider both conditions when evaluating a patient with these symptoms, requiring a detailed medical history and a comprehensive diagnostic approach.³⁶⁻³⁷
- 2. Challenges in Laboratory Diagnosis: The laboratory diagnosis of HIV and SCD is challenging in co-infected patients. Sickle Cell Disease is diagnosed by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) to identify the presence of abnormal hemoglobin S (HbS). However, these tests can be confounded by HIV-related anemia hematologic or abnormalities. such lymphopenia, as neutropenia, or thrombocytopenia, which can result from either HIV infection itself or the use of antiretroviral therapy (ART). HIV testing, typically confirmed by enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR), is necessary for HIV diagnosis, but it is essential to rule out potential hematological abnormalities caused by ART or opportunistic infections. Furthermore, ART-associated complications, such as anemia, neutropenia, and thrombocytopenia, exacerbate can the hematologic abnormalities seen in SCD,

further complicating the diagnosis. Renal function tests, including serum creatinine and urine albumin, are crucial to detect HIVassociated nephropathy (HIVAN) in these patients, but they may be influenced by sickle cell-related kidney complications, making it difficult to distinguish between the two causes of renal dysfunction. Accurate laboratory diagnosis requires a comprehensive understanding of both conditions and a multidisciplinary approach to avoid diagnostic pitfalls.³⁸⁻³⁹

- 3. Imaging and Clinical Evaluation: Imaging studies, such as chest X-rays, CT scans, and MRIs, are essential for evaluating the presence of complications like acute chest syndrome, stroke, or pulmonary hypertension, which are common in both HIV and SCD. However, the interpretation of these images can be complex in co-infected individuals. For example, pulmonary infiltrates seen on a chest X-ray could be indicative of acute chest syndrome in SCD, or they could represent an opportunistic infection in an HIV-positive patient, such as pneumonia or tuberculosis. The evaluation of strokes or central nervous system (CNS) involvement in these patients requires careful consideration of both sickle cell-related ischemic events and potential HIV-associated neurocognitive disorders or infections. This complexity underscores the need for clinicians to have a thorough understanding of the clinical manifestations of both diseases to avoid missing critical diagnoses. Furthermore, the co-occurrence of HIV-related immunosuppression and SCDassociated vascular abnormalities means that patients may be at heightened risk for infections, complicating the interpretation of clinical and laboratory findings.⁴⁰⁻⁴¹
- 4. Complications in Antiretroviral Therapy Management: One of the diagnostic challenges in managing co-infected patients is determining the optimal antiretroviral therapy (ART) regimen while managing the sickle cell disease. ART drugs, particularly protease inhibitors and certain nucleoside reverse

transcriptase inhibitors. can cause or exacerbate hematologic abnormalities, including anemia and neutropenia, which are also common in SCD. This complicates the monitoring of these patients, as ART side effects can mimic or worsen symptoms related to SCD. For instance, ART-induced bone marrow suppression may exacerbate the anemia already present in sickle cell disease, making it challenging to determine the appropriate course of action. Additionally, HIV-related immunosuppression may increase the risk of opportunistic infections, which can complicate the clinical picture in SCD patients. Therefore. monitoring ART adherence. side effects. and possible interactions with SCD treatments, such as hydroxyurea, becomes critical. The clinical implications of such complications often require frequent adjustments to therapy and close monitoring, which may lead to the need for more specialized care in managing these patients.42

5. Multidisciplinary Approach and Early **Referral**: Given the complexity of managing HIV and SCD co-infection, а multidisciplinary approach involving hematologists, infectious disease specialists, nephrologists, cardiologists, pulmonologists, and pain specialists is crucial for optimizing care. This approach helps ensure that both diseases are adequately managed and that their interactions are carefully monitored. For example, nephrologists can address renal complications like HIVAN. while cardiologists can manage the cardiovascular effects of both HIV and SCD. Furthermore, the need for early referral to specialized care providers is essential to avoid delays in diagnosis and treatment. The involvement of a well-coordinated care team can also aid in addressing the social and psychological challenges that these patients face, including stigma, access to care, and medication adherence. A proactive and collaborative approach is paramount to reducing morbidity and mortality in individuals with both HIV and SCD.43

Management Strategies and Treatment Considerations in HIV and Sickle Cell Disease Co-Infection

Managing patients with both HIV and sickle cell disease (SCD) requires a comprehensive, individualized treatment approach to address the complex interplay between these two conditions. Treatment strategies must not only target the management of the individual diseases but also account for the potential interactions and compounding effects of each. This approach should be multidisciplinary, incorporating input from hematologists, infectious disease specialists, nephrologists, pain management experts, and other healthcare providers to optimize patient outcomes.

- 1. Antiretroviral Therapy (ART) and Sickle **Considerations**: Cell Disease The cornerstone of HIV management in coinfected patients is the initiation and adherence to effective antiretroviral therapy (ART). ART helps reduce HIV viral load, preserve immune function, and prevent progression to acquired immunodeficiency syndrome (AIDS). However, the choice of ART regimen in patients with SCD must take into consideration the potential side effects of these drugs, particularly those that may exacerbate hematologic abnormalities. Some ART drugs, such as protease inhibitors and certain nucleoside reverse transcriptase inhibitors (NRTIs), can cause or worsen anemia and neutropenia. These adverse effects must be closely monitored to avoid further complications related to SCD, such as vasoocclusive crises organ damage. or Additionally, drug interactions between ART sickle cell treatments, and such as hydroxyurea, must be carefully managed to prevent detrimental effects. ART regimens should be personalized based on the patient's genotypic resistance patterns, viral load, and underlying health conditions, while taking special care to minimize hematologic toxicity.44
- 2. Management of Sickle Cell Disease Complications: For patients with both HIV and SCD. managing SCD-related equally complications is important in improving quality of life and preventing longterm morbidity. Common complications of SCD include pain crises, stroke, acute chest syndrome, organ damage, and infections. The management of pain crises, often triggered by vaso-occlusion, involves a combination of hydration, pain control (typically opioids and adjunct therapies), and blood transfusions in severe cases. Preventive therapies, such as hydroxyurea, are often utilized to reduce the frequency of pain crises by promoting the production of fetal hemoglobin, which helps prevent sickling of red blood cells. However, the use of hydroxyurea must be closely monitored, as ART and hydroxyurea may have overlapping toxicities, particularly in relation to hematologic effects. Blood transfusions may be necessary in cases of severe anemia or acute chest syndrome, but careful management is required to avoid iron overload, a complication that can be exacerbated by certain ART regimens. The implementation of comprehensive, individualized care plans that include early recognition and treatment of sickle cell complications improving is critical to outcomes in these patients.⁴⁵
- 3. Management **HIV-Related** of Complications and Co-Morbidities: HIVrelated complications, such as opportunistic infections, immune suppression, and HIVassociated nephropathy (HIVAN), must also be carefully managed in co-infected patients. Prophylactic treatments for infections, including pneumocystis jirovecii pneumonia (PCP), mycobacterium tuberculosis, and cytomegalovirus (CMV), should be initiated as per standard HIV care guidelines. HIVAN, which can lead to kidney failure, requires early identification through regular renal function monitoring and urine tests for albumin. In some cases, antiretroviral therapy may itself exacerbate renal dysfunction, particularly in patients who are also affected

by SCD, as both conditions increase the risk of nephropathy. Nephrologists play a crucial role in managing kidney disease, with potential treatments ranging from optimizing ART to considering dialysis in severe cases. In terms of managing immunosuppression, the careful use of immunomodulatory therapies, such as corticosteroids or other agents, may be required to address inflammation without compromising the patient's immune function. Furthermore, managing the potential overlap of infections and inflammatory responses between HIV and SCD requires vigilance in monitoring for signs of sepsis, pneumonia, and other bacterial infections.⁴⁶

- 4. Pain Management and Palliative Care: Chronic pain management is a critical aspect of treating HIV-positive SCD patients. Both HIV and SCD can cause persistent pain, through vaso-occlusive whether crises. neuropathic pain, or musculoskeletal discomfort exacerbated by ART-related side effects. Opioid pain management is frequently used, but long-term opioid therapy raises concerns about tolerance, dependency, and constipation side effects such as or gastrointestinal distress. Therefore. а multimodal approach to pain management, including non-opioid analgesics, adjunct therapies (e.g., gabapentin for neuropathic pain), and psychological support, should be considered. Non-pharmacologic interventions, such as physical therapy, acupuncture, and cognitive-behavioral therapy, can also play an essential role in improving pain management outcomes and reducing the need for narcotic medications. In the context of HIV-related neuropathy, early referral to pain specialists and the use of antiretroviral medications with neuroprotective properties may also improve pain control. Palliative care, focusing on improving the quality of life and managing both the physical and psychological aspects of the disease, should be part of the care plan. particularly for those with advanced disease or complex symptomatology.⁴⁷
- **Support** 5. Psychosocial and Patient **Education**: Given the chronic nature of both HIV and SCD, patients with these comorbidities face significant psychosocial challenges, including the stigma of living with both a genetic disorder and a communicable disease. Providing adequate psychosocial support, including counseling, support groups, and education on the importance of adherence to therapy, is vital in improving patient outcomes. These patients may face difficulties in managing their treatment regimens, accessing care, and maintaining social support networks. Healthcare providers should address the emotional and social impacts of HIV and SCD, providing resources and referrals to community organizations that offer additional support. Educating patients and their families about the potential interactions between HIV medications and SCD treatments, as well as the need for regular follow-up visits and lab monitoring, can also enhance adherence to both ART and SCD-related therapies. Building a supportive relationship with patients can empower them to manage their health more effectively, reducing anxiety and improving overall well-being.⁴⁸

Conclusion

Managing HIV-positive patients with sickle cell disease (SCD) presents a complex challenge that requires a multifaceted and individualized approach. The interactions between antiretroviral therapy (ART) and SCD treatments, the potential for overlapping complications such as infections, organ damage, and pain crises, and the presence of co-morbidities necessitate comprehensive care. Early and regular monitoring, particularly of hematologic, renal, and immune functions, is essential in preventing complications and optimizing treatment outcomes. A personalized treatment strategy that takes into account the unique needs of each patient, while being mindful of the interactions between HIV and SCD therapies, is critical for improving both the shortand long-term health of these patients. In addition medical management, a collaborative, to multidisciplinary approach is paramount. The

involvement of hematologists, infectious disease specialists, nephrologists, pain management teams, and mental health professionals ensures that patients receive holistic care that addresses not only their physical health but also their emotional and psychosocial well-being. This approach fosters better patient adherence to treatment regimens and empowers them to take an active role in their healthcare, ultimately leading to improved quality of life.

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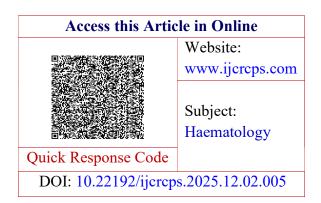
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