# The Diagnostic and Therapeutic Labyrinth: A Case Study and Review of Coexistent Sickle Cell Disease and Rheumatoid Arthritis

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**Abstract- The coexistence of sickle cell disease (SCD) and rheumatoid arthritis (RA) presents a significant diagnostic and therapeutic challenge due to overlapping clinical features, primarily musculoskeletal pain. SCD, a hereditary hemoglobinopathy, is characterized by vaso-occlusive crises (VOCs) causing severe ischemic pain, while RA is a systemic autoimmune disease defined by chronic, erosive polyarthritis. Misattributing RA symptoms to SCD can delay diagnosis and treatment, leading to irreversible joint damage. This manuscript presents a composite case study of a patient with both conditions to illustrate the complex diagnostic pathway. We review the key clinical, serological, and radiological features that differentiate RA-related arthropathy from SCD-related bone pain. Specifically, we highlight the critical role of autoantibodies, such as anti-cyclic citrullinated peptide (anti-CCP), which maintain high specificity for RA even in the context of SCD's chronic inflammatory state. We discuss the therapeutic intricacies, including the risks of triggering VOCs with certain immunosuppressants and the need for a multidisciplinary management approach. Furthermore, we explore the Ayurvedic perspective, viewing SCD as Sahaj Pandu and RA as Aamavata, and discuss potential integrative treatments like the herbo-mineral formulation AYU-HM Premium and the use of Acupen to manage inflammation and pain from a holistic standpoint. This manuscript underscores the necessity of maintaining a high index of suspicion for concomitant autoimmune diseases in SCD patients with atypical or persistent arthralgia to ensure timely diagnosis and optimize patient outcomes.**

**Keywords: Sickle Cell Disease (SCD), Rheumatoid arthritis (RA), Vaso-occlusive crises (VOC), Anti-cyclic citrullinated peptide (anti-CCP, Autoimmunity; Integrative therapy, AYU-HM Premium, Acupen, Aamavata, Sahaj Pandu, Multidisciplinary management.**

## INTRODUCTION

Sickle cell disease (SCD) is one of the most common and severe monogenic disorders worldwide, caused by a point mutation in the beta-globin gene that leads to the production of abnormal hemoglobin S (HbS). Under hypoxic conditions, HbS polymerizes, causing red blood cells to deform into a rigid, sickle shape. These sickled cells can block small blood vessels, leading to vaso-occlusive crises (VOCs), which manifest as excruciating pain, chronic organ damage, and a state of chronic inflammation and hemolysis [2,6]. The musculoskeletal system is a primary target, with patients frequently experiencing debilitating bone and joint pain, avascular necrosis (AVN), and osteomyelitis.

Rheumatoid arthritis (RA) [4,5] is a chronic systemic autoimmune disease of unknown etiology, characterized by persistent synovial inflammation that leads to progressive joint destruction, disability, and systemic complications. The hallmark of RA is a symmetric polyarthritis, preferentially affecting the small joints of the hands and feet, accompanied by

morning stiffness and the presence of specific autoantibodies, namely rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP [5,6,8]) antibodies.

The confluence of SCD and RA in a single patient is considered a rare phenomenon [6-8], but its true prevalence may be underestimated due to the significant overlap in symptomatology. Joint pain is the common denominator, often leading clinicians to attribute all musculoskeletal complaints in an SCD patient to the underlying hemoglobinopathy. This diagnostic overshadowing can result in a significant delay in identifying and treating RA, allowing for the progression of irreversible erosive joint damage. The chronic inflammatory milieu of SCD, characterized by endothelial activation and elevated inflammatory cytokines, could theoretically predispose individuals to autoimmunity, making this coexistence a subject of growing clinical interest.

Differentiating the acute, episodic pain of a VOC from the chronic, insidious inflammation of RA is paramount for appropriate management. The therapeutic path is equally complex, as standard RA treatments like glucocorticoids and certain disease-modifying antirheumatic drugs (DMARDs) carry risks of exacerbating SCD-related complications. This manuscript aims to elucidate this complex clinical scenario through a composite case study, review the key distinguishing features, discuss management strategies, and introduce an integrative Ayurvedic perspective on treatment.

## Case Presentation

A 33-year-old woman with a known history of homozygous sickle cell disease (HbSS), diagnosed in childhood, presented with a six-month history of persistent joint pain. Her SCD was moderately severe, requiring hospitalization for VOCs two to three times per year, typically managed with hydration and analgesic. She reported a new pattern of pain, distinct from her usual crises. The pain was symmetric, affecting the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of both hands, as well as her wrists and the metatarsophalangeal (MTP) joints of her feet. She described significant morning stiffness lasting over an hour, which moderately improved with activity.

Initially, her symptoms were attributed to an atypical presentation of SCD arthropathy. However, the persistence of symptoms and the presence of soft, boggy swelling over the affected joints prompted a rheumatology consultation. On examination, she had tenderness and palpable synovitis in multiple small joints, consistent with inflammatory arthritis. There was no evidence of dactylitis or pain localized over long bones, which were characteristic of her previous VOCs. Her hematological parameters were at her baseline for SCD, with no acute drop in hemoglobin or significant rise in markers of hemolysis [2,6].

This clinical picture raised suspicion for a superimposed inflammatory arthritis, leading to a comprehensive diagnostic workup to differentiate between SCD-related pain and a new autoimmune process like RA.

## Diagnostic Workup and Differential Diagnosis

The diagnostic process in a patient with SCD and suspected RA hinges on a careful evaluation of clinical signs, specific serological markers, and characteristic imaging findings. While both conditions cause joint pain and can present with elevated inflammatory markers like C-reactive protein (CRP), several key features allow for their differentiation.

## Serological Markers: The Decisive Clues

The most crucial step was the serological evaluation for autoimmunity. While general inflammatory markers can be elevated in both conditions, autoantibodies provide high specificity for RA.

- Autoantibodies: The patient's bloodwork revealed a positive rheumatoid factor (RF) and, most significantly, a high-titer of anti-CCP [5,6,8] antibodies. The presence of anti-CCP [5,6,8] is highly specific for RA, with a specificity reported to be between 95-98%. Importantly, the chronic inflammation associated with SCD is not known to cause false-positive anti-CCP [5,6,8] results. Therefore, a positive anti-CCP [5,6,8] in an SCD patient with inflammatory arthritis is a strong indicator of coexistent RA.

- Hemolysis Markers: To rule out an ongoing VOC, markers of hemolysis [2,6] were checked. Her lactate dehydrogenase (LDH), reticulocyte count, and indirect bilirubin were at her baseline levels and not acutely elevated, which would have been expected during a sickle cell crisis. This divergence—positive autoimmunity markers without signs of acute hemolysis [2,6] was pivotal in pointing towards RA.
- The serologic markers that best separate rheumatoid arthritis (RA) flares from sickle cell disease (SCD) [1-3] crises are autoantibodies for RA and hemolysis [2,6]-associated markers for SCD, alongside specific differences in acute-phase reactants

Table: 1 The serologic markers

| Marker | RA Flare | SCD Crisis |
|---|---|---|
| RF, anti-CCP | Positive/ raised | Absent |
| CRP | Raised | Raised |
| LDH | Baseline | Raised |
| Reticulocyte count | Baseline | Raised |
| Bilirubin | Baseline | Raised |
| ESR | Raised | Variable/ unreliable |

Autoantibodies (RF, anti-CCP [5,6,8]) are highly specific for RA flares, while LDH, reticulocyte count, and bilirubin elevations best signal SCD crises when acute-phase reactants rise.

Table: 2 Clinical and Radiological Differentiation

| Feature | Rheumatoid Arthritis (RA) | Sickle Cell Disease (SCD) Arthropathy |
|---|---|---|
| Joint Pattern | Symmetrical polyarthritis, affecting small joints (MCP, PIP, MTP, wrists) | Asymmetrical, often affecting large joints (hips, knees, shoulders) and long bones |
| Morning Stiffness | Prominent, typically lasting >1 hour | Usually absent or brief |
| Nature of Pain | Chronic, persistent, and inflammatory in nature | Acute, severe, and episodic (during crises) |
| Serology | Positive anti-CCP and/or RF | Negative anti-CCP/RF; elevated LDH, reticulocytes, bilirubin during crisis |
| Radiology | Marginal bone erosions, joint space narrowing, periarticular osteopenia | Bone infarcts, avascular necrosis (especially of the femoral head), H-shaped vertebrae |

Radiographs of the patient's hands and feet confirmed the diagnosis, revealing classic RA findings of marginal erosions and joint space narrowing in the affected MCP and MTP joints. These were distinct from the signs of AVN and bone infarcts visible on previous imaging of her hips and long bones.

Management and Therapeutic Challenges

The management of coexistent RA and SCD is a delicate balancing act, requiring close collaboration between specialists. The goal is to control the autoimmune inflammation of RA without exacerbating the underlying SCD.

The patient was started on hydroxychloroquine and a low dose of methotrexate [5,6] (MTX). MTX, a cornerstone of RA therapy, required careful monitoring due to its potential for myelosuppression, which could worsen her baseline anemia. Folic acid supplementation was essential. Initially, a short course of low-dose corticosteroids [6] was considered for symptomatic relief but was used with extreme caution, as high doses are known to be a potential trigger for vaso-occlusive crises.

Ayurvedic and Integrative Perspective

From an Ayurvedic viewpoint, the dual diagnosis can be understood through the lens of dosha imbalances and tissue (*dhatu*) dysfunction.

- SCD as Sahaj Pandu [9]: SCD is seen as a congenital form of anemia (Sahaj Pandu [9]), rooted in a genetic defect (Beeja Dushti). It involves a vitiation of Rakta Dhatu (blood tissue) and an aggravation of the Vata and Pitta doshas, leading to circulatory obstruction, pain, and systemic weakness.
- RA as Aamavata [10]: RA is classically described as Aamavata [10]. This condition arises from impaired digestive fire (Agni), leading to the formation of Ama (toxic metabolic byproducts). This Ama circulates in the body, combines with Vata dosha, and settles in the joints (Shleshma Sthana), causing the characteristic pain, swelling, and stiffness.
- An integrative approach could complement conventional therapy by addressing these underlying imbalances.
- AYU-HM Premium: This herbo-mineral formulation has been studied for its role in managing SCD. It contains ingredients like Haritaki and Guduchi, which are known for their antioxidant and immunomodulatory properties, along with mineral preparations (bhasmas) believed to support blood health. Clinical evidence suggests AYU-HM Premium [11,12] may help reduce the sickling process and decrease the frequency of pain crises, thereby improving the overall quality of life in SCD patients.
- Acupen has demonstrated dual urate-lowering and anti-inflammatory actions, along with analgesic and tissue-protective effects [13,14]. This multi-targeted approach positions Acupen [13] as a promising candidate for the management of gouty arthritis, rheumatoid arthritis, and osteoarthritis. For both Aamavata [10] and the pain from SCD, such therapy aims to pacify aggravated Vata and reduce inflammation.
- Integrated Approach: Combining conventional treatment with Ayurvedic dietary recommendations, Panchakarma detoxification, and stress management techniques

An integrative treatment plan would involve using AYU-HM Premium [11,12] to support blood health and reduce SCD-related stress, while Acupen [13] could target the inflammatory pain pathways relevant to both conditions. This would be combined with Ayurvedic dietary and lifestyle modifications aimed at strengthening Agni, reducing Ama, and balancing the doshas.

## DISCUSSION

The coexistence of SCD and RA, while uncommon, represents a critical diagnostic intersection that demands clinical vigilance. The chronic inflammatory nature of SCD can mask the onset of a systemic autoimmune disease, as musculoskeletal pain is an expected and frequent complaint. Our case illustrates that a change in the pattern, location, or character of joint pain in an SCD patient particularly the development of symmetric small-joint synovitis with

prolonged morning stiffness—should immediately raise suspicion for a superimposed inflammatory arthritis like RA.

The diagnostic cornerstone in this scenario is serological testing for RA-specific autoantibodies. The high specificity of anti-CCP [5,6,8] antibodies is maintained in the SCD population, making it an invaluable tool to confirm an RA diagnosis and distinguish it from non-autoimmune SCD arthropathy. A positive anti-CCP [5,6,8] test in this context should not be dismissed as a false positive caused by chronic inflammation but should be seen as a clear signal of underlying RA.

Managing these coexistent conditions requires a nuanced, patient-centered approach. The therapeutic arsenal for RA must be deployed with a full understanding of its potential impact on SCD. For example, while corticosteroids [6] are effective for RA flares, they must be used cautiously due to the risk of inducing AVN or VOCs. Similarly, the myelosuppressive potential of drugs like methotrexate [5,6] necessitates diligent monitoring of blood counts in patients with pre-existing anemia. Biologic agents may offer a safer and more effective alternative for refractory RA in this population, though long-term data remain limited. The successful management of our patient highlights the indispensable role of a collaborative, multidisciplinary [6,7,8] team comprising a hematologist and a rheumatologist.

## CONCLUSION

The diagnosis of rheumatoid arthritis in a patient with sickle cell disease is a clinical challenge that can be overcome with a high index of suspicion and a systematic diagnostic approach. Clinicians must be attuned to atypical joint symptoms that deviate from a patient's usual pattern of vaso-occlusive pain. The use of specific serological markers, especially anti-CCP [5,6,8] antibodies, is critical for an accurate and timely diagnosis. Management must be carefully tailored, balancing the need for effective immunosuppression for RA against the risk of exacerbating SCD related complications. A collaborative, multidisciplinary [6,7,8] approach is essential to navigate these therapeutic complexities and improve the long-term outcomes for patients living with this rare and challenging dual diagnosis.

A holistic approach [9] combining conventional DMARDs, careful monitoring, and evidence-based Ayurvedic support such as AYU-HM Premium [11,12], Acupen [13] may offer a safer, synergistic path for long-term management.

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## Conflict of Interest

Dr. Atul M. Desai is the principal investigator and inventor associated with T-AYU-HM Premium and Acupen, proprietary herbo-mineral formulations developed by ATBU Harita Pharmaceuticals Pvt. Ltd., India. However, this potential conflict has been transparently managed, and all analyses, interpretations, and conclusions are presented with academic objectivity.

The remaining authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

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