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Rheumatoid Arthritis in Patients with Sickle Cell Disease: Clinical Challenges and Management Insights from a Case Series in Basrah

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Abstract

The hallmarks of sickle cell disease (SCD), a genetic hemoglobinopathy, include chronic hemolysis, vaso-occlusive crises, and systemic consequences, such as musculoskeletal symptoms that can sometimes resemble those of rheumatoid arthritis (RA). This case series examines the clinical challenges and RA management strategies in five SCD patients, comprising three women and two men, aged 21–52 years. Important observations are the complexity of treatment due to comorbidities such as severe anemia and vaso-occlusive crises, as well as the delayed identification of RA because of symptoms that cross with SCD, like joint pain and inflammation. Patients responded differently to methotrexate (MTX), the major disease-modifying therapy. Two had modest disease activity; others required glucocorticoids or biological agents like rituximab, which sometimes resulted in SCD complications. While it benefited some individuals, the exact function of hydroxyurea was still unknown. Especially, alleviating the anemia caused by Methotrexate (MTX) requires folate supplements. The series stresses the need for a multidisciplinary approach, tailored treatments, and higher suspicion for RA when SCD patients suffer from persistent joint discomfort. These discoveries underline the part that chronic inflammation plays in the pathogenesis of both SCD and RA, therefore stressing the importance of close surveillance and customized treatment to enhance effects.

More Information

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Introduction

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy associated with chronic hemolysis, episodic vaso-occlusive crises (the principal manifestation of SCD), and various life-threatening complications leading to significant end-organ damage. The clinical disease results from the inheritance of single-base mutations in the globin gene (homozygous or compound heterozygote), triggering, generation of haemoglobin S, responsible for the aforementioned sickle cell anemia manifestations. These manifestations frequently occur when red blood cells (RBCs) are distorted (become sickle-shaped) due to the polymerization of hemoglobin S upon deoxygenation [1].

Sickle cell anemia is a life-threatening disease affecting about three million individuals globally. Thirty-four million people carry the trait, a main source of new cases, especially in Africa and certain zones in Asia.

Annually, a hundred thousand individuals lose their lives because of sickle cell disease complications [2].

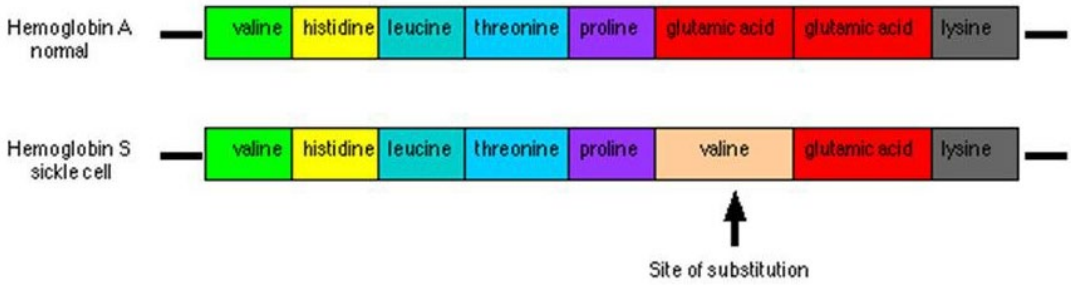

Figure 1: Comparison of Normal and Sickle Cell Hemoglobin Amino Acid Sequences

In addition to the usual precipitating factors of different types of sickle cell crises, several additional factors may result in provoking an inflammatory response in patients with sickle cell anaemia, like RBC alteration with subsequent release of substantial amounts of

- Microparticles
- Free haemoglobin
- Damage-associated molecular patterns (DAMP)

among others, which may represent an appealing target for novel therapies in the future [3].

Until recently, Hydroxycarbamide was the only disease-modified medication utilized in sickle cell anaemia, and as the curative modalities (Hematopoietic stem cell transplantation, Autologous gene-based therapy, Gene addition or transfer, and Gene editing) They are not an option for most patients.

In the next few years, a new therapeutic era will start with the introduction of crizanlizumab, voxelotor, and L-glutamine [4,5].

It is well known that sickle cell anemia carries many musculoskeletal and rheumatological complications that may possess significant morbidity and lifelong disabilities like avascular necrosis, especially of femoral heads, septic arthritis, osteomyelitis, osteoporosis, and dactylitis, among others. These complications may pose a diagnostic problem when they occur in sickle cell anemia patients who suffer from recurrent severe Vaso-occlusive crises, which in turn may precipitate these complications [6].

Recently, and with increased awareness about the concomitant existence of autoimmune disorders and sickle cell anaemia, researchers have tried to study the different aspects of this relation, aiming to understand aetiology, clinical differential points, and the proper therapeutic strategies for these overlapped diseases [7].

Rheumatoid arthritis (RA) is a prototypical inflammatory joint disease that may initially target symmetrically small hands and feet synovial joints, resulting in morning stiffness and arthritis. Some patients may experience a wide variety of extra-articular manifestations, such as secondary sicca syndrome, Atlanto-axial instability, interstitial lung disease, among many others.

Unrelenting rheumatoid arthritis (RA) activity will eventually end in joint deformities, which are superadded by various other co-morbidities, resulting in premature death, especially from cardiac causes [8,9,10].

The prevalence of rheumatoid arthritis (RA) around the world is estimated to be approximately 0.46-1%, with an annual incidence of 0.02–0.05%, which is variable according to the global regions and ethnic groups [11,12].

The diagnosis of rheumatoid arthritis is usually based on clinical background, depending on the pattern, duration, and distribution of the involved joints in conjunction with the antibodies like rheumatoid factor or anticitrullinated peptide autoantibodies and inflammatory markers, specifically erythrocyte sedimentation rate and/or C-reactive protein [13].

Rheumatoid-specific antibodies may possess prognostic values and sometimes can predict the severity of the illness and response to treatment [14].

Rheumatoid arthritis (RA) is treated essentially with methotrexate, which is still the cornerstone of DMARDs in addition to short steroid courses.

The introduction of biologics and targeted synthetic DMARDs has mitigated the natural history of the disease in a high percentage of patients, reducing the aggressive course of the disease and preventing a lot of articular and extra-articular complications [13,15].

Roughly, studies observe that autoimmune diseases (especially those individuals with positive serology) develop more in sickle cell disease patients, and these coexistences are so far more prevalent in women than men. Rheumatoid arthritis is the most common autoimmune disease in this combination [16].

Although the previous observations about this correlation are extremely rare, it is proposed that rheumatoid arthritis in combination with sickle cell

disease is more aggressive, with early widespread joint damage (more erosion and juxta-articular osteopenia) and a high percentage of rheumatoid arthritis specific antibody positivity. In general, arthritis tends to occur at younger ages than its counterparts, so poor consequence is expected [17].

The Musculoskeletal manifestations of sickle cell anemia may obscure the diagnosis of rheumatoid arthritis (RA), and many patients will have established joint deformities and irreparable complications at the time of diagnosis [18].

Case 1

A 39-year-old female who is a known case of sickle-cell anemia presents to the Hematology outpatient clinic with small hand joints, metatarsalgia, and bilateral knee arthritis associated with prolonged morning stiffness.

Previously, she suffered from pulmonary embolism and was kept on Apixaban 5 mg twice daily. Also, she was kept on Hydroxyurea 500 mg daily. The echo study showed moderate tricuspid regurgitation, and an abdominal ultrasound scan revealed elements of recurrent splenic infarctions.

Instantly, she was sent for RF and ACPA, which were elevated in high titres. Again, the inflammatory markers were elevated. She fulfills the required criteria, and a presumptive diagnosis of Rheumatoid Arthritis was made.

Methotrexate (MTX) 10 mg weekly was initiated and increased gradually, reaching 20 mg weekly alongside daily folic acid. During the initial phase of her treatment, low-dose glucocorticoid was prescribed (Prednisolone 10 mg daily), which resulted in severe bone and joint pain that required hospital admission and eventually led to stopping this medication.

She is now doing well on this regimen with slow but steady improvement in her general condition, with improvement in her blood indexes and normal liver enzymes and renal function. The disease activity remains high with new joint involvement and intractable symptoms.

The decision was then to start biologics, but she had previously been diagnosed with inactive hepatitis C, so two doses of Rituximab were given in addition to another trial of daily 10 mg prednisolone and high-dose COX-2 inhibitor (120 mg Etoricoxib). She is still under strict outpatient supervision with nearly daily follow-up by hematologists and rheumatologists, with encouraging initial lessening in disease activity.

Case 2

A 21-year-old Sickler female with sickle cell disease was transferred to the rheumatology clinic with inflammatory small hand joint arthritis. This was associated with Morning stiffness > 60 minutes.

On Examination, there were more than 10 tender hand joints and bilateral knee swelling. RF was positive, but ACPA was negative with elevated ESR.

She was advised to start Methotrexate (MTX) 10 mg weekly and daily folic acid 5 mg with an initial trial of prednisolone 30 mg in a tapering manner, which produced dramatic improvement in her symptoms. A period of non-adherence to her medications, especially folic acid, resulted in a megaloblastic blood picture with high MCV. She was admitted to the hospital because of excruciating left thigh pain without any localizing signs on examination, and even with an MRI scan. Calcium and vitamin D were added to her after the discovery of osteopenia on the DEXA scan. She is now clinically stable on the aforementioned medications. She stopped hydroxyurea without any adverse events.

Case 3

A 28-year-old male teacher who is a known case of Sickle Cell anemia presented to the rheumatology outpatient clinic in November 2022 with bilateral hand, wrist, elbow, and shoulder pain. At that time, the inflammatory markers were elevated.

Alongside elevated RF and ACPA. He was diagnosed with Rheumatoid Arthritis and Methotrexate (MTX), daily Folic Acid 5 mg with Prednisolone 20mg.

After an initial improvement of joint pain, he suffered from a severe painful crisis that obligated his caring physician to admit him to the hematology ward.

Immediately, the prednisolone 20 mg was halved with rapid tapering. He is now on Methotrexate (MTX) and daily Folic Acid 5mg, with good disease control and stable laboratory indices. He was kept on Hydroxyurea 500 mg twice daily. During this period, his wife became pregnant and gave birth to his 3rd child, who is now in perfect health.

Case 4

A 52-year-old female, a general practitioner, consulted a private rheumatological clinic in May 2022, complaining of moderate left knee effusion. She is a known case of sickle cell anemia on Folic Acid 5 mg daily only. Years ago, she underwent a right hip replacement for severe osteoarthritis. She was previously diagnosed with Rheumatoid Arthritis based on small joint arthritis, high inflammatory markers, and elevated RF and ACPA. Despite high Rheumatoid disease activity at that time (DAS-28-5.52), she refused to take Methotrexate (MTX) because of concerns about the side effects. She used only NSAIDs to relieve her symptoms at that time.

After many attempts to convince her, she started Methotrexate (MTX) in addition to her previous medication with bridge prednisolone 15mg in a tapering manner. Soon after, she had resolution of all her symptoms, but with borderline and sometimes very low hemoglobin values on follow-up. One month later, the hematologist prescribed her Hydroxyurea and some tonics (B12 Shots), and her hemoglobin levels

started to rise to acceptable levels (from 4.8 g/dL in May /2022 to 7.9 g/dl in December 2023 and then on) with a great reduction in the inflammatory markers.
In August 2022, she suffered from severe vertigo; an Atlanto-Axial subluxation was suspected. X-ray cervical spine (in Flexion & Extension) was performed, which revealed severe spondylotic changes, especially between the 5th and 6th cervical vertebrae, for which symptomatic treatment and home exercise were enough to resolve the symptoms. She returns to being fully active and keeping a good quality of life, except for recurrent incidences of bronchopneumonia.

Case 5

A 47-year-old government employee, who is a known case of sickle-beta thalassemia, presented to the rheumatology outpatient clinic with about 3 years' history of hand and foot pain, small hand joints and wrist swelling with prolonged morning stiffness. On hand examination, there were Mild bilateral 2nd and 3rd MCP synovial hypertrophy and mild ulnar deviation.
At that time, the inflammatory markers were elevated (C-reactive protein), and ACPA antibodies were marginally raised, but RF was negative.
He was initiated on Methotrexate (MTX) 7.5 mg weekly, which was escalated to 10 mg weekly, then to 12.5 mg weekly in addition to folic acid 5 mg daily. This was parallel to prednisolone 5 mg daily. There was slow but sustainable improvement in his condition.
During the period of follow-up, He developed a feature of secondary Fibromyalgia Syndrome with depressive symptoms, which responds partially to Duloxetine 30 mg daily. One year before this presentation, he was admitted to the ICU because of severe shortness of breathing and elevated D-dimer, and was diagnosed with Pulmonary embolism.
Since that, he was kept on Rivaroxaban 10 mg for 6 months, and the haematologists advised him to stop smoking, and he was kept on Hydroxyurea 500 mg daily.
Now he is under outpatient clinic care with fortnightly supervision by a rheumatologist and hematologist, with noticeable improvement in his rheumatological symptoms and laboratory indices.

Table 1: Demographic and Clinical Characteristics of the Cases

	Sex	Patient age	Duration of RA	Dose of MTX	Usage of Hydroxyurea	RA Disease Control	Sickle cell crisis over the last 3 years
Case 1	Female	39	1 Year	15-20 mg per week I.M	Yes, 500 mg daily	High disease activity	4
Case 2	Female	21	3 years	7.5 mg per week oral	No, stop it 1 year ago	Low disease activity	3
Case 3	Male	28	3 years	10 mg per week oral	Yes, 500 mg twice daily	Low disease activity	2
Case 4	Female	52	5 Years	10 mg per week oral	Yes, 500 mg twice daily	Low disease activity	0
Case 5	Male	47	1 year	12.5mg per week oral	Yes, 500 mg daily	Moderate disease activity	0

Discussion

This case series demonstrates the importance of a multidisciplinary approach in managing rheumatoid arthritis (RA) in patients with sickle cell anemia (SCA). Differentiating RA from SCD-related musculoskeletal symptoms, such as painful crises or avascular necrosis, requires a high index of suspicion. This deleterious combination (the development of rheumatoid arthritis in patients with sickle cell disease) is not an uncommon problem in the daily practice in regions with a high prevalence of this haemoglobinopathy, especially with the advances of rheumatoid arthritis diagnosis by incorporating the specific antibodies with the rheumatological clinical signs and prolong survival of sickle cell anaemia patients [19].
In sickle cell disease, incessant immune system activation is prompted by exposure to intracellular contents, especially hemoglobin, which is considered a powerful proinflammatory agent.
The release of hemoglobin activates different types of cells that are crucial in the inflammatory process initiation and continuation, like dendritic cells, in addition to monocytes and macrophages, and encourages these cells to produce pro-inflammatory cytokines such as interleukins and tissue necrosis

factors that may have a causal relationship in triggering the initiation of Rheumatoid Arthritis [20].

It is well known that Methotrexate (MTX) has been the cornerstone remedy in the treatment of rheumatoid arthritis since 1951, and it exerts its therapeutic effect through the suppression of dihydrofolate reductase, reducing the body storage of folate, which is essential for DNA synthesis and cellular renewal [21].

The data regarding folate deficiency and the severity of sickle cell crisis attacks are contradictory, though the concomitant Hyperhomocysteinaemia that results from low folate levels tends towards increasing the severity of vaso-occlusive crisis [22, 23].

Despite the aforementioned, the existing literatures recommend using the customary approaches in dealing with rheumatoid arthritis (RA) patients who also suffer from sickle cell disease, enforcing tailored therapies according to the patients' comorbidities and their general health status and pointing to the increased risk of adverse events as the increase risk of infection while using these approaches [24].

A challenging problem facing regular practice is the delay in presentation to suitable clinical care because of the struggle in early reaching the diagnosis for this inflammatory disorder in the presence of background sickle cell anaemia [25].

When considering the different aspects of managing this simultaneous coexistence, some facets could be thought-provoking. In concordance with Diakité, and although our patients suffered initially from anemia that was severe in one case (Case 4), low-dose Methotrexate was utilized with satisfactory results on both rheumatological and hematological aspects [26].

As sickle cell anemia is considered as unrelenting pro-inflammatory condition, so, a study tried to observe the effects of low-dose Methotrexate in sickle cell anemia patients and found it to be of benefit in reducing the chronic musculoskeletal pain and improving quality of life, which could be partially due to reduce levels of TNF-α and several other inflammatory mediators and increased sensory sensitivity via reduction of central nociceptive signaling in the spinal cord through activation of the A1 receptor [20, 27].

Although not proven, the administration of glucocorticoids, which is usually used as bridge therapy to bring inflammatory symptoms of rheumatoid arthritis under control, may precipitate severe vaso-occlusive crisis or other life-threatening sickle cell disease complications in addition to increasing the risk of re-hospitalization [28, 29].

Most of the literature about the usefulness and safety of anti-TNF-α inhibitors in dealing with rheumatoid arthritis in sickle cell anemia reveals that they are well tolerated and as effective as if they are used in their counterparts without sickle cell disease, but the increased risk of infection remains a major concern [24, 30].

The role of Hydroxyurea, which essentially reduces the frequency and severity of vaso-occlusive crisis via increased Hemoglobin F levels in the treatment of this dreadful co-existence, is still Doubtful [31].

Conclusion

In conclusion, rheumatoid arthritis in sickle cell disease (SCD) patients is difficult to diagnose and treat due to overlapping musculoskeletal symptoms. This case series highlights these problems. While methotrexate is effective, it requires folate supplements to treat anemia. Initiation of glucocorticoids might trigger vaso-occlusive crises, but with time, they become tolerable at the prescribed dosage. Rituximab has a potential beneficial role but carries significant risks of infection. As the function of hydroxyurea is unknown, a multidisciplinary approach is needed to balance RA management with SCD consequences. The results emphasize the need for increased clinical suspicion for RA in SCD patients, customized therapies, and more research to optimize therapy in this complex comorbidity.

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