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Coexisting rheumatoid arthritis and sickle cell disease: case series and literature review

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Summary

Rheumatoid arthritis (RA) is rarely reported among patients with sickle cell disease (SCD). RA treatment in these patients is believed to be more challenging due to fear of increasing the risk of infection and complications of SCD. We are reporting 7 patients with concurrent SCD and RA. The average age at the time of the diagnosis of RA was 33.3 ± 12.6 years (ranging from 16 to 53 years), and most were women (5/7). Most of the patients were positive for rheumatoid factor (6/7) or anticyclic citrullinated peptide (6/7). Four patients were treated with hydroxyurea. The most used antirheumatic drugs were methotrexate (7/7), biologic agents (5/7), and prednisone (4/7). Two patients were in remission, four had low and one had high disease activity. Four patients (4/7) had avascular necrosis, two in the shoulders and two in the hip joints. Four patients had emergency visits or hospitalizations within one year of the diagnosis of RA, but none had blood transfusions, infections, or death. The start of antirheumatic medication was not associated with an increased risk of infection, blood transfusions, emergency visits, or hospitalizations, nor with a worsening of laboratory measures. The findings suggest that the treatment of RA in patients with SCD should follow the same strategy as in patients without SCD. However, treatment should be individualized according to the individual patient's risk of infection and SCD complications.

Introduction

Sickle cell disease (SCD) is an inherited hemoglobin disorder characterized by chronic hemolysis, vaso-occlusion, multiorgan damage, and increased mortality (1, 2). Repeated episodes of SCD can present with severe acute pain, acute chest syndrome, avascular necrosis, nephropathy, retinopathy, and leg ulcers (1, 2). The prevalence of SCD in Saudi Arabia and nearby countries is much higher than the global average, ranging from 0.24% to 5.8% for the disease (homozygous form) and from 1.02% to 45.8% for the trait (heterozygous form) (3, 4).

Rheumatoid arthritis (RA) is rarely reported among patients with SCD. The prevalence has been estimated to range from 0.2% to 0.94% among two large populations of SCD (5, 6). The similarity of the musculoskeletal manifestations of SCD and RA frequently causes delays in the diagnosis of RA and the initiation of appropriate management (7-9). Therefore, destructive arthropathy and limitation of joint function can be the first presentation in these cases (8, 9). Furthermore, the treatment of RA in patients with SCD can be challenging, as some antirheumatic drugs can interact with hydroxyurea (the main SCD drug), precipitate an SCD crisis, or increase the risk of infection (10, 11). Finally, there is limited data on the impact of the use of relatively recent biological therapy in patients with co-existing SCD and RA (11).

In this report, we describe a series of seven patients with coexisting SCD and RA treated with different disease-modifying antirheumatic drugs (DMARDs). The report focused on the impact of RA treatment on relevant laboratory measures, the need for blood transfusions, the risk of infections, and the number of emergency visits or hospitalizations. In addition, up-to-date literature review of similar cases was conducted to facilitate comparisons.

Our research received ethics board approval from King Abdulaziz City of Science and Technology, Saudi Arabia. IRB registration number: H-02-J-002.

Since our investigation involved reviewing patient electronic records and no biological samples from participants were taken, the participants' written approval consent was not taken.

Case Series

We are reporting seven patients with concurrent SCD and RA. All patients were regularly followed in the rheumatology and hematology clinics of a large referral hospital (King Fahd Hospital) in Jeddah, Saudi Arabia. SCD was diagnosed by hemoglobin electrophoresis before the appearance of RA in all patients. RA was diagnosed according to the 2010 Rheumatoid Arthritis Criteria of the American College of Rheumatology/European League against Rheumatism (12). The demographic and clinical characteristics of the patients are shown in Table 1. The mean age at the time of RA diagnosis was 33.3 ± 12.6 years (ranging from 16 to 53), and the mean duration of follow-up after RA diagnosis was 4.5 ± 3.9 years. Five patients were women and two were men. Hemoglobin electrophoresis showed a high percentage (82.8%) of type S hemoglobin. Most of the patients were positive for rheumatoid factor (RF, 6/7), anti-cyclic citrullinated peptide (anti-CCP, 6/7), or both (5/7). The mean hemoglobin level was 7.6 ± 1.8 g/dL, white blood cells (WBC) were $12.9 \pm 5.3 \times 10^9/L$ and platelet count was $415.8 \pm 218.1 \times 10^3 /\mu L$. Only one patient had a family history of RA. RA involved the wrist joints (7/7), metacarpophalangeal joints MCPJ (6/7), knees (6/7), elbows (1/7), or ankles (1/7).

As shown in Table 1, four patients were treated with hydroxyurea. The most frequently used drug for RA was methotrexate (7/7), followed by biologics (5/7) and prednisone (4/7). The most widely used biological therapy was adalimumab (4/7), followed by etanercept (2/7), abatacept (2/7), rituximab (1/7), and tocilizumab (1/7). Cases 2, 6, and 7 have been switched to multiple biological agents to control RA activity. After treatment and according to the Clinical Disease Activity Index Measure, two patients were in remission, four patients had low disease activity, and one patient had high disease activity. Four

patients had avascular necrosis in the shoulders (2/4) or hips (2/4). Four patients had emergency visits/hospitalizations within one year of diagnosis of RA, but none had blood transfusions, infections, or death.

As shown in Table 2, there were no significant differences between hemoglobin levels and WBC counts between a year before and after the diagnosis of RA ($p=0.917$ and $p=0.310$, respectively). There was a slight decrease in platelet count after the diagnosis of RA (from 501.2 ± 262.0 to 415.8 ± 218.1), which did not reach statistical significance ($p=0.063$). No infections were detected, nor were blood transfusions performed a year before and after the diagnosis of RA. There was a decrease in the number of emergency visits or hospitalizations (from 4.9 ± 9.4 to 1.2 ± 1.0 visits). However, the difference was not statistically significant ($p=0.317$) and was primarily driven by incomplete data for a patient.

Literature Review

We reviewed the case reports and case series of patients with concurrent SCD and RA published over the past four decades. Data from 13 studies that describe 54 patients are summarized in Tables 3 and 4 (5-10, 13-19). They were published in developed countries (63%) and developing countries (37%), but none in Saudi Arabia or the Middle East. The mean age at the time of the diagnosis of RA was 33.3 years (range 6.5-64 years), and the mean duration of follow-up was 4.6 years (range 0-17 years). Most (85%) of the patients were women. The predominant genotype of SCD was Hb-SS (85%), followed by Hb-SC (12%) and Hb- β plus thalassemia (3%). Most of the patients were positive for RF (96%) and/or anti-CCP (91%). The mean hemoglobin level was 7.2 g/dL (ranging from 3.6 to 8.6), the WBC count was $10.9 \times 10^9/L$ (ranging from 7.8 to $11.50 \times 10^9/L$), and the platelet count was $401 \times 10^3/\mu L$ (ranging from 211 to $657 \times 10^3/\mu L$). The frequency of relevant presentations or complications was 59% for hemolytic crisis, 54% for erosive arthritis, 41% for avascular necrosis, 40% for vaso-occlusive crisis, and 35% for acute chest syndrome.

As shown in Table 4, 51% of the patients were treated with hydroxyurea and 47% had at least one blood transfusion. The most used drugs were prednisone (75%), methotrexate (62%), hydroxychloroquine (37%), biologics (27%), leflunomide (21%), sulfasalazine (15%), and azathioprine (2%). The biological DMARDs used the most were etanercept (20%), adalimumab (11%), and rituximab (5%). There were no reports of use of abatacept or tocilizumab. Approximately 39% of the patients obtained RA remission with the treatments used. Approximately 40% of the patients had serious infections and 13% died after RA treatment.

Discussion

The current case series shares several demographic and clinical characteristics with previously reported patients with co-existing SCD and RA (5-10, 13-19). For example, current and previous data had a female predominance and a relatively young age at the time of RA diagnosis (33 years). Most of the patients had seropositive RA for approximately 4.5 years in addition to the SCD diagnosed earlier. SCD was treated with hydroxyurea in more than half of the patients. However, the treatment of RA was relatively different. For example, methotrexate and prednisone were the only traditional drugs used in current patients, while also hydroxychloroquine and leflunomide were used in other patients. Additionally, biologic DMARDs were used more frequently in our patients (71%) compared to those from the literature (27%). The low prevalence of biologic DMARDs in previous reports may be related to its relatively recent introduction in the treatment of RA. Another major difference in this series of cases is the outcome. For example, blood transfusions, infections, and mortality were not reported in our patients, while they occurred in 47%, 40% and 13%, respectively, of the patients in previous studies. One possible explanation could be the short period of observation in the current cohort. Furthermore, current patients had a slightly lower

remission rate compared to previous patients (29% *versus* 39%). However, it is difficult to compare this rate due to the lack of data on disease activity in most previous reports.

Treatment of RA in patients with SCD is believed to be more challenging than in those without SCD (13). Regular use of corticosteroids in patients with coexisting SCD and RA is generally not recommended due to the risk of developing a vaso-occlusive crisis, acute chest syndrome, and rehospitalization (20, 21). However, a short course of high-dose corticosteroids can improve symptoms without significant adverse reactions (22). Corticosteroids are used because of their immediate effect on controlling inflammation associated with RA. They can be used as an initial therapy until other DMARDs achieve their therapeutic effect. However, the use of immunosuppressive drugs in the treatment of RA, including methotrexate, corticosteroids, and biologic DMARDs, can increase the risk of developing severe infections in patients with SCD who are already vulnerable to infections (11).

The use of methotrexate with or without biologic DMARDs and corticosteroids in our patients was not associated with an increased risk of infection, blood transfusions, emergency visits, or hospitalizations, nor with a worsening of laboratory measures. Similarly, a recent case series of eight patients with SCD and RA in Turkey showed that the start of antirheumatic drugs (mainly traditional DMARDs) was not associated with an increase in the frequency of SCD-related crises or serious infections (13). Furthermore, another relatively recent case series of eight patients with SCD and RA in the United States showed that the introduction of antirheumatic drugs (mainly traditional DMARDs) was not associated with a significant change in the number of hospital admissions due to painful events in the 5-year period before and after the diagnosis of RA (16).

Conclusions

We are reporting a case series of seven patients with concurrent SCD and RA in Saudi Arabia. The use of methotrexate with or without biologic DMARDs and corticosteroids in our patients was not associated with an increased risk of infection, blood transfusions, emergency visits, hospitalizations, or worsening of laboratory measures. The findings suggest that the treatment of RA in SCD should follow the same strategy as in patients without SCD. The treatment plan should be individualized according to the individual patient's risk of infection and SCD complications. The current finding still needs further confirmation from larger perspective studies that focus on drug interactions and adverse events of different DMARDs, including biological agents.

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Table 1. Demographic and clinical characteristics, and outcomes among patients with concomitant sickle cell disease and rheumatoid arthritis.

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Total average*
Age at RA diagnosis	53	25	16	42	39	34	24	33.3±12.6
Female gender	Y	Y	N	Y	Y	Y	N	5 (71.4%)
Sickle hemoglobin (HbS, %)	80.0	97.7	81.5	86.6	89.7	80.1	64.0	82.8±10.4
Positive rheumatoid factor (RF)	Y	Y	Y	Y	Y	N	Y	6 (85.7%)
Positive ACPA	Y	Y	Y	Y	Y	Y	N	6 (85.7%)
Smoking	N	Y	N	N	N	N	N	1 (14.3%)
Family history of RA	N	N	N	N	N	N	Y	1 (14.3%)
Treatments								
Hydroxyurea	N	Y	Y	N	N	Y	Y	4 (57.1%)
Methotrexate	Y	Y	Y	Y	Y	Y	Y	7 (100.0%)
Prednisone	N	Y	N	Y	N	Y	Y	4 (57.1%)
Biologics	Y	Y	Y	N	N	Y	Y	5 (71.4%)
Adalimumab	Y	Y	N	N	N	Y	Y	4 (80.0%)
Abatacept	N	N	N	N	N	Y	Y	2 (40.0%)
Tocilizumab	N	N	N	N	N	N	Y	1 (20.0%)
Etanercept	N	Y	Y	N	N	N	N	2 (40.0%)
Rituximab	N	Y	N	N	N	N	N	1 (20.0%)
Duration of RA follow up (years)	1.3	11.0	7.6	1.9	0.4	6.4	3.2	4.5±3.9
RA CDAI	3.6	2.8	2.2	3.2	6.0	6.0	23.0	6.7±7.3
Outcomes								
RA activity								
Remission (≤ 2.8)	N	Y	Y	N	N	N	N	2 (28.6%)
Low activity (2.9 -10)	Y	N	N	Y	Y	Y	N	4 (57.1%)
Moderate activity (10.1-22)	N	N	N	N	N	N	N	0 (0.0%)
High activity (>22)	N	N	N	N	N	N	Y	1 (14.3%)
Blood transfusion	N	N	N	N	N	N	N	0 (0.0%)
Infections	N	N	N	N	N	N	N	0 (0.0%)
Avascular necrosis (AVN)	Y	N	N	Y	N	Y	Y	4 (57.1%)
AVN of hips	Y	N	N	N	N	Y	N	2 (50.0%)
AVN of shoulders	N	N	N	Y	N	N	Y	2 (50.0%)
Emergency visit/hospitalization	N		Y	Y	N	Y	Y	4 (66.7%)
Death	N	N	N	N	N	N	N	0 (0.0%)

RA, rheumatoid arthritis; ACPA, anti cyclic-citrullinated peptide antibodies.

Table 2. Laboratory measures and outcomes among patients with sickle cell disease from a year before to a year after diagnosis of rheumatoid arthritis.

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Total (Mean±SD)	P-value*
Hemoglobin (g/dL)									
Before	6.3	8.5	7.4	8.2	6.3	9.5	7.2	7.6±1.2	0.917
After	6.3	8.4	9.4	8.2	5.4	9.7	5.5	7.6±1.8	
White blood cells count (10 ⁹ /L)									
Before	13.0	11.5	11.8	20.0	9.0	14.9	14.4	13.5±3.5	0.310
After	12.8	8.4	10.4	23.0	7.0	13.5	15.0	12.9±5.3	
Platelets (10 ⁹ /L)									
Before	221	421	533	290	395	650	999	501.2±262.0	0.063
After	262	374	444	230	190	652	759	415.8±218.1	
Number of infections									
Before	0	0	0	0	0	0	0	0.0±0.0	NA
After	0	0	0	0	0	0	0	0.0±0.0	
Number of blood transfusions									
Before	0	0	0	0	0	0	0	0.0±0.0	NA
After	0	0	0	0	0	0	0	0.0±0.0	
Number of emergency visits or hospitalizations									
Before	0	26	2	3	0	2	1	4.9±9.4	0.317
After	0	.	2	2	0	2	1	1.2±1.0	

Table 3. Summary of demographics and clinical characteristics of patients with Sickle cell disease (SCD), and Rheumatoid arthritis (RA) in previous studies.

Study	Country	N	Current age	Female gender	Age at RA diagnosis	Duration of RA	RF +ve	ACPA +ve	Sero (+ve) RA	Hb (SS)	Hb (SC)	Hb (SBT)	Hb (g/dl)	WBC (10 ⁹ /L)	Platelets (10 ⁹ /L)	HC	AVN	ACS	VOC	EA
Kimyon-2022 (13)	Turkey	8	43 (18-70)	7/8	39 (16-64)	3.8 (1-11)	6/8	4/8	6/8	--	--	--	--	--	--	8/8	4/8	3/8	4/8	1/8
Sharma-2021(14)	India	1	29	1/1	29	0	1/1	1/1	1/1	0/1	0/1	1/1	9.6	10.4	455	1/1	0/1	0/1	0/1	0/1
Roizenblatt-2020(15)	Brazil	6	35 (21-58)	6/6	30 (19-52)	4.8 (1-10)	6/6	6/6	6/6	4/6	2/6	0/6	--	11.4	364	3/6	4/6	2/6	5/6	5/6
Helvacı-2018(5)	Turkey	1	44	1/1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MecFarlane-2017(6)	USA	7	41.7	--	36.9±3.9	--	6/7	5/7	--	--	--	--	7.4	--	--	--	--	5/7	--	3/6
Muthu-2016(16)	USA	8	44.5 (25-60)	7/8	37.9 (22-55)	6.6 (0-16)	8/8	8/8	8/8	8/8	0/8	0/8	7.1	--	--	4/8	1/8	1/8	1/8	3/8
ManaPPallil-2016(17)	India	1	28	1/1	27	1	1/1	1/1	1/1	--	--	--	7.8	10.2	211	0/1	0/1	0/1	1/1	0/1
Leung-2015(18)	UK	1	20	1/1	--	--	1/1	--	--	1/1	0/1	0/1	3.6	--	--	0/1	1/1	--	1/1	1/1
Adelowo-2011(7)	Nigeria	2	7 & 17	1/2	6.5 & 16.5	0.5	2/2	1/2	2/2	2/2	0/2	0/2	--	--	--	2/2	1/2	1/2	2/2	1/2
Michel-2008(10)	France	15	40.4 (24-53)	11/15	35.0±5.6	5.5 (1-17)	14/15	--	--	13/15	2/15	0/15	--	--	--	5/15	5/15	4/15	2/15	12/15
Arana-2006(19)	Colombia	1	36	1/1	35	1	1/1	--	--	1/1	0/1	0/1	8.5	7.8	246	1/1	1/1	--	--	1/1
Eberhard-2002(8)	USA	1	18	1/1	16	2	--	--	--	--	--	--	--	--	--	1/1	1/1	1/1	0/1	0/1
Nistala-2001(9)	UK	1	15.5 (15-16)	2/2	12 (10-14)	3.5 (1-6)	2/2	--	--	--	--	--	6.7	11.5	657	2/2	1/2	1/2	2/2	1/2
Total	-	54	37.7 (7-70)	40/47 (85%)	33.3 (6.5-64)	4.6 (0-17)	47/49 (96%)	32/35 (91%)	24/26 (92%)	29/34 (85%)	4/34 (12%)	1/34 (3%)	7.2 (3.6-8.6)	10.9 (7.8-11.5)	401 (211-657)	27/46 (59%)	19/46 (41%)	18/51 (35%)	18/45 (40%)	28/52 (54%)

RA; Rheumatoid Arthritis, SCD; Sickle Cell Disease, RF; Rheumatoid Factor, ACPA; Anti-Cyclic Citrullinated Peptide Antibody, Genotypes: Sickle Cell Anemia (SS), Sickle Hemoglobin- C disease (SC), Sickle Beta- plus Thalassemia (SBT), Hb;hemoglobine, WBC; white blood cell, HC; hemolytic crisis, AVN; avascular necrosis. ACS; acute chest syndrome, VOC; Vaso-occlusive crisis, EA; erosive arthritis.

Table 4. Summary of management and outcomes of patients with sickle cell disease and rheumatoid arthritis in previous case reports and case series.

	Study	HU	Bl trans	MTX	PRED	HCQ	LEF	SLZ	LEF	AZA	Biologics	ETN	ADA	RTX	ABA	TOC	RA remission	Serious infection	Death
1	Kimyon-2022 [13]	7/8	--	4/8	7/8	7/8	2/8	4/8	2/8	0/8	1/8	1/8	0/8	0/8	0/8	0/8	2/8	4/8	--
2	Sharma-2021 [14]	1/1	1/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	--	0/1	0/1
3	Roizenblatt-2020 [15]	4/6	4/6	6/6	4/6	0/6	2/6	0/6	2/6	0/6	4/6	1/6	3/6	1/6	0/6	0/6	2/6	--	--
4	Helvaci-2018 [5]	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5	McFarlane-2017 [6]	--	--	3/7	5/7	1/7	3/7	--	3/7	0/7	1/7	--	--	--	--	--	--	--	--
6	Muthu-2016 [16]	--	--	3/8	3/8	3/8	3/8	1/8	3/8	1/8	1/8	0/8	1/8	0/8	0/8	0/8	2/8	--	--
7	Manappallil-2016 [17]	1/1	1/1	1/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1
8	Leung-2015 [18]	--	1/1	1/1	1/1	--	--	--	--	--	--	--	--	--	--	--	0/1	--	--
9	Adelowo-2011 [7]	0/2	2/2	2/2	2/2	0/2	0/2	0/2	0/2	2/2	2/2	0/2	0/2	0/2	0/2	0/2	2/2	0/2	0/2
10	Michel-2008 [10]	5/15	4/15	12/15	14/15	5/15	1/15	2/15	1/15	0/15	4/15	4/15	1/15	1/15	0/15	0/15	6/15	7/15	3/15
11	Arana 2006 [19]	0/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	1/1	0/1
12	Eberhard-2002 [8]	1/1	0/1	0/1	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	--	0/1
13	Nistala 2001 [9]	0/2	1/2	1/2	2/2	0/2	0/2	1/2	0/2	1/2	1/2	0/1	0/1	0/1	0/1	0/1	0/2	0/2	0/2
	Total	19/37 (51%)	14/30 (47%)	33/53 (62%)	40/53 (75%)	19/52 (37%)	11/52 (21%)	8/52 (15%)	11/52 (21%)	1/52 (2%)	14/52 (27%)	9/44 (20%)	5/44 (11%)	2/44 (5%)	0/44 (0%)	0/44 (0%)	17/44 (39%)	12/30 (40%)	3/23 (13%)

HU, hydroxyurea; Bl trans, Blood transfusions; MTX, methotrexate; PRED, Prednisone; HCQ, hydroxychloroquine; LEF, leflunomide; SLZ, sulfasalazine; AZA, azathioprine; ETN, Etanercept; ADA, Adalimumab (Humira); RTX, Rituximab; ABA, Abatacept (Orencia); TOC, Tocilizumab (Actemra).