Systemic lupus erythematosus associated with sickle-cell disease: a case report and literature review

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Abstract

Introduction: The occurrence of systemic lupus erythematosus has been only rarely reported in patients with sickle-cell disease.

Case presentation: We describe the case of a 23-year-old North-African woman with sickle-cell disease and systemic lupus erythematosus, and discuss the pointers to the diagnosis of this combination of conditions and also present a review of literature. The diagnosis of systemic lupus erythematosus was delayed because our patient’s symptoms were initially attributed to sickle-cell disease.

Conclusions: Physicians should be alerted to the possible association of sickle-cell disease and systemic lupus erythematosus so as not to delay correct diagnosis and initiation of appropriate treatment.

Keywords: Sickle-cell disease, systemic lupus erythematosus

Introduction

Sickle-cell disease (SCD) is a prevalent genetic disorder that includes sickle-cell anemia (the homozygous and most common form of SCD (SS)), sickle-cell hemoglobin C (SC) and sickle-cell β thalassemia (S/β thal) [1]. The protean clinical features of SCD result from chronic variable intravascular hemolysis and microvascular ischemia, leading to damage in multiple organs [2]. The occurrence of connective tissue diseases, in particular systemic lupus erythematosus (SLE), has only been rarely reported in patients with SCD [2]. The incidence of SLE in patients with SCD is not known because most of the published studies are case reports. Due to similar clinical manifestations, diagnosis of SLE in patients with SCD may be difficult and is often delayed. We report the case of a patient who developed symptoms initially attributed to SCD, but on further investigation underlying SLE was revealed.

Case presentation

A 23-year-old North-African woman with no family history of SCD was admitted to our department of internal medicine with symptoms of anemia, bone pain, arthralgia and fever. Her symptoms had been developing for six weeks with alteration of her general condition and abdominal pain. On physical examination our patient was pale; she had a temperature of 39.5°C, her blood pressure was 130/75mmHg and heart rate was 100 beats/minute. The patient had slight splenomegaly, pain on pressure in the long bones and arthritis in her knees.

Blood test results showed normocytic anemia at 6.6g/dL with a high reticulocyte count (230,000 cells/mm3), hyperleukocytosis with granulocytosis (leukocyte count 16,500 cells/mm3, polymorphonuclear cells 9500 cells/mm3) and moderate thrombopenia (100,000 cells/mm3). Further investigations showed diminished haptoglobin (0.08mg/L), elevated lactate dehydrogenase (4670UI/L) indirect hyperbilirubinemia (21mg/L) with moderate cytolysis and cholestasis (aspartate aminotransferase 43U/L, alanine aminotransferase 65U/L, phenylalanine ammonia lyase 217U/L and γ-glutamyl transpeptidase 188U/L). Hemoglobin (Hb) electrophoresis test results showed Hb S at 50.3 percent, Hb C at 44 percent and
Hb A1 at 0 percent, confirming a diagnosis of SCD (hemoglobin S/C).

Our patient's erythrocyte sediment rate was 110mm/first hour, her C-reactive protein level was 38mg/L (range <6mg/L), fibrinogen was 6.4g/L (24g/L) and serum protein electrophoresis showed a polyclonal IgG 24g/L (range 9 to 13g/L) with normal immunofixation. Results of a chest X-ray were normal. Abdominal ultrasonography, transthoracic and transesophageal echocardiography results were also normal. A thoraco-abdominal scan revealed numerous splenic infarctions. The results of a bone scan showed diffuse bone infarcts. Her symptoms were attributed to SCD and hence our patient received blood transfusions, antibiotics and analgesics, but with no improvement. Her fever and arthritis failed to respond to this treatment. Instead, the evolution of her condition was marked by the development of arthritis in her hands and relapse of anemia.

Blood culture test results were negative, and the result of a tuberculin skin test was an 8mm induration. There was no BK virus found in repeated sputum and urine examinations, and procalcitonin test results were negative.

Serology test results for human immunodeficiency virus, hepatitis B, hepatitis C, brucellosis and typhoid fever were all negative. Cytobacteriological urine analysis revealed no bacteria but microscopic hematuria (670 cells/mm³). Proteinuria results were negative.

The results of a Coombs test performed on admission were strongly positive for IgG. Immunological investigations revealed a positive anti-nuclear antibody (1/2600) result, and a positive anti-Sm result. Anti-DNA antibody tests were negative. A test for anti-extractable nuclear antigen antibodies (anti-ENA) was negative. C3 levels and C4 levels were normal (respectively, 0.95g/L and 0.3g/L). Tests for anti-phospholipid antibodies were negative. A diagnosis of SLE associated to SCD was established, with five of the diagnostic criteria of the American College of Rheumatology being met. Steroids were administered as a pulse of methylprednisolone 1g/day for three days followed by oral prednisone at 1mg/kg/day with hydroxychloroquine. Her symptoms quickly improved. At her 18-month follow up, she was in clinical remission on prednisone 5mg per day and hydroxychloroquine; she had not experienced a sickle-cell crisis and her lupus is still quiescent.

Discussion

In the present report we described the case of a Moroccan woman with SCD and coexistent SLE. The overlap of SLE and SCD is of interest, but the limited number of patients that have been reported previously implies that the association is uncommon [3]. Only 40 similar cases have been reported in the literature over the last 50 years [2-16] (Table 1). The African/Afro-Caribbean/African-American population is predisposed to contracting both SCD and SLE, explaining the fact that most patients with this association are African women (70 percent in Table 1 and 73 percent in the series by Michel et al.). All reported cases were relatively young at the time of lupus diagnosis (mean age 23 years, range eight to 57 years). All of them had SCD several years before SLE. Articular involvement is the most frequent lupus-related symptom, present in 84 percent of cases, followed by serositis (36 percent), and glomerulonephritis class III or IV (11 percent). Cutaneous manifestations are not frequently mentioned. Positive anti-nuclear antibody (ANA) results were found in 34 cases. Prognosis was favorable in 80 percent of cases (Table 1). Patients with SCD present with a defective activation of the alternate pathway of the complement system; this is the reason why these patients are at increased risk of capsulate bacteria infection, such as from pneumococci [15]. Some authors have suggested the hypothesis that this defect may lead to immune complex disorders secondary to failure to eliminate antigens, predisposing these patients to autoimmune diseases, but this has not been confirmed in other studies [3,11,13]. The clinical features of SLE and SCD have certain elements in common. Diverse manifestations such as polyarthritis, anemia, fever, visceral pain, renal, cardiovascular and pulmonary involvement are common in both conditions. Owing to the overlap of clinical features in the two diseases it may easy to confuse them, as occurred with our patient.

Further, the frequency and titers of antibodies in SCD have been reported as relatively higher than in population controls, making the diagnosis more challenging in clinical practice [17].

Toly-Ndour et al. reported that 50 percent of 88 patients with SCD had positive anti-nuclear antibody results and 20 percent had titers greater than one in 200, but only one patient developed rheumatoid arthritis five years later and no patients developed SLE [18]. In this series, patients treated with hydroxyurea had ANA-positive results less frequently than non-treated patients (P=0.053) [18].

Large prospective epidemiological studies are necessary to determine whether the prevalence of immune complex diseases is increased in patients with SCD.

Conclusions

This report illustrates the importance of considering associated diseases when clinical findings are unexplained by SCD alone, or are unresponsive to the conventional treatment. Early diagnosis and the initiation of appropriate treatment may decrease morbidity and mortality in these patients.
| Lead author/year/reference | Sex/origin | Age of SCD onset | Age of SLE onset | SLE features | Immunologic features | Hemoglobin type | Treatment | Outcome |
|----------------------------|------------|------------------|------------------|--------------|----------------------|-----------------|-----------|---------|
| Cherner 2010 [3]           | F/Afro-Caribbean | 13               | 21               | Arthritis, fever | ANA+                 | SS              | Prednisone | Clinical improvement |
|                           |            |                  |                  | Malar rash     | Anti-CCP+            |                 |           |         |
|                           |            |                  |                  | Gut vasculitis  | Anti-RNP+            |                 |           |         |
|                           |            |                  |                  |               | ACL+                 |                 |           |         |
|                           |            |                  |                  |               | Renal disease (biopsy not performed) | Anti-DNA+ |           |         |
| Cherner 2010 [3]           | F/Afro-Caribbean | 7                | 41               | Skin rash      | ANA+                 | SS              | Prednisone | Clinical improvement |
|                           |            |                  |                  |               | Anti-RP+            |                 |           |         |
| Appenzeller 2008 [4]       | F/African-American | NA               | 16               | Fever, arthritis | ANA+                 | SS              | Prednisone | Clinical improvement |
|                           |            |                  |                  | Photosensitivity | Anti-DNA+            |                 |           |         |
|                           |            |                  |                  | Cardiomyopathy  | Anti-SM+             |                 |           |         |
|                           |            |                  |                  | Pericarditis    |                      |                 |           |         |
| Appenzeller 2008 [4]       | F/African-American | 15               | 21               | Arthritis      | ANA+                 | SS              | Prednisone | Clinical improvement |
|                           |            |                  |                  | Pleuritis       | Anti-DNA+            | SS              | Hydroxychloroquine |         |
|                           |            |                  |                  | Lymphadenopathy | Anti-Sm+             |                 |           |         |
| Appenzeller 2008 [4]       | F/African-American | NA               | 57               | Arthritis      | ANA+                 | SS              | Prednisone | Clinical improvement |
|                           |            |                  |                  | Photosensitivity | Anti-Sm+             | SS              | Hydroxychloroquine |         |
|                           |            |                  |                  | Discoid lesions |                      |                 |           |         |
|                           |            |                  |                  | Raynaud’s phenomenon |                    |                 |           |         |
| Michel 2008 [2]            | F/NA       | NA               | 30               | Arthritis      | ANA+                 | SS              | Prednisone | Deceased |
|                           |            |                  |                  | Pericarditis    | Anti-DNA+            |                 |           |         |
|                           |            |                  |                  | Pleuritis       | Anti-Sm+             |                 |           |         |
|                           |            |                  |                  | GN class II     |                      |                 |           |         |
| Michel 2008 [2]            | M/NA       | NA               | 40               | Arthritis      | ANA+                 | SS              | Prednisone | Remission |
|                           |            |                  |                  | Discoid lesions |                      |                 | Hydroxychloroquine |         |
| Study          | Gender | Age | Diagnosis | Antinuclear Antibodies | Patient Outcomes | Therapies                                      |
|---------------|--------|-----|-----------|------------------------|------------------|-----------------------------------------------|
| Michel 2008 [2] | F/NA   | 32  | Thrombocytopenia | ANA+ Anti-DNA+         | SC               | Hydroxychloroquine Remission                  |
| Michel 2008 [2] | F/NA   | 35  | Arthritis, Cutaneous vasculitis, Raynaud’s phenomenon, GN class II | ANA+ Anti-DNA+ Anti-Sm+ Anti-SSA+ Anti-RNP | SS               | Prednisone Hydroxychloroquine Methotrexate     |
| Michel 2008 [2] | F/NA   | 27  | Arthritis | ANA+ Anti-DNA+         | SS               | Prednisone Hydroxychloroquine Remission       |
| Michel 2008 [2] | F/NA   | 25  | Arthritis, GN class III, Jaccoud arthropathy, Major depression | ANA+ Anti-DNA+ Anti-RNP+ ACL+ | SS               | Prednisone Hydroxychloroquine Remission       |
| Michel 2008 [2] | M/NA   | 26  | Arthritis | ANA+ Anti-DNA+ Anti-RNP+ ACL+ | SC               | Hydroxychloroquine Clinical improvement       |
| Michel 2008 [2] | F/NA   | 28  | Arthritis, GN class IV, Bullous lupus | ANA+ Anti-DNA+ Anti-Sm+ Anti-RNP+ | SS               | Prednisone Hydroxychloroquine Dapsone         |
| Michel 2008 [2] | F/NA   | 32  | Arthritis, Kikuchi’s disease, Autoimmune hepatitis | ANA+ RF+ | SS               | Prednisone Remission                          |
| Michel 2008 [2] | F/NA   | 40  | Arthritis, Discoid lupus, Venous thrombosis | ANA+ Anti-Ro+ ACL | SS               | Hydroxychloroquine Clinical improvement       |
| Name                  | Gender | Race | Age | Symptoms                          | Antibodies | Treatment | Outcome         |
|----------------------|--------|------|-----|-----------------------------------|-------------|-----------|-----------------|
| Michel 2008 [2]      | F/NA   | NA   | 38  | Arthritis                         | ANA+, SS   | Prednisone | Clinical improvement |
|                      |        |      |     |                                   |             | Hydroxychloroquine |               |
| Michel 2008 [2]      | F/NA   | NA   | 17  | Arthritis, Thrombocytopenia       | ANA+, SS   | Prednisone | Clinical improvement |
|                      |        |      |     |                                   |             | Hydroxychloroquine |               |
| Michel 2008 [2]      | F/NA   | NA   | 35  | Pedal and peri-orbital edema, Ascites and renal failure | ANA+, SC | Prednisone | Dialysis |
|                      |        |      |     |                                   |             | Anti-DNA+ | Cyclophosphamide |            |
| Oqunbiyi 2007 [6]    | M/African | NA  | 8   | Malar rash                        | ANA+, SS   | Prednisone | Clinical improvement |
|                      |        |      |     |                                   |             | Hydroxychloroquine |               |
| Khalide 2005 [7]     | F/NA   | NA   | 16  | Heart failure Renal failure Pericarditis Pulmonary emboli Polyneuropathy Generalized seizures | Anti-DNA+, Anti-Sm+, Lupus anticoagulant+ | Prednisone | Clinical improvement |
|                      |        |      |     |                                   |             | Hydroxychloroquine, azathioprine |               |
| Khalide 2005 [7]     | M/NA   | NA   | 16  | Discoid rash Polyarthritis Partial seizures | ANA+, SS   | Prednisone | Clinical improvement |
|                      |        |      |     |                                   |             | Hydroxychloroquine |               |
| Khalide 2005 [7]     | M/NA   | NA   | 23  | Skin rash Pleuritis Arthritis    | ANA+, SS   | Prednisone | Hydroxychloroquine | Lost to follow up |
|                      |        |      |     |                                   |             | ACL+       |                 |
| Name                  | Gender, Race     | Age | Presenting Symptoms                  | Laboratory Findings | Treatment          | Outcome                  |
|-----------------------|------------------|-----|--------------------------------------|---------------------|--------------------|--------------------------|
| Khalide 2005 [7]      | F/NA             | 28  | Raynaud’s phenomenon, Arthritis      | ANA+                | Prednisone         | Clinical improvement     |
| Saxena 2003 [8]       | M/African-American | 9   | Arthritis                            | ANA+                | Prednisone         | Clinical improvement     |
| Saxena 2003 [8]       | F/African-American | 7   | Fever, Acute chest syndrome, Pericarditis, Seizures | ANA+               | Prednisone         | Clinical improvement     |
| Saxena 2003 [8]       | F/African-American | 11  | Fever, Arthritis, Skin rash, Seizures, Cardiomegaly | ANA+               | Prednisone         | Clinical improvement     |
| Saxena 2003 [8]       | F/African-American | 14  | Seizures                             | ANA+                | Prednisone         | Septic shock due to pneumococcal bacteremia |
| Saxena 2003 [8]       | M/African-American | 17  | Malar rash, Splenomegaly, Arthritis, Pericarditis | ANA+               | Prednisone         | Hemodialysis dependent   |
| Name           | Ethnicity       | Age | Symptoms                                      | Treatments                  | Outcome                      |
|---------------|----------------|-----|----------------------------------------------|-----------------------------|------------------------------|
| Shetty 1998   | F/Afro-Caribbean | 9 months | Cardiomegaly, GN class V, Arthritis, Pulmonary infiltrate, Pericarditis, Myocarditis | Prednisone                  | Clinical improvement         |
| Pham 1997     | F/Afro-Caribbean | NA 18 | Arthritis, Nephrotic syndrome, ANA+ | Prednisone                  | Clinical improvement         |
| Katsanis 1987 | F/Afro-Caribbean | NA 16 | Arthritis, ANA+, Malar rash, Photosensitivity, Pleuritis, Pericarditis, Renal class II | Hydroxychloroquine           |                              |
| Katsanis 1987 | F/Afro-Caribbean | NA 15 | Arthritis, ANA+, Pleuritis, Anti-DNA+ | Prednisone                  | Clinical improvement         |
| Warrier 1984  | F/Afro-Caribbean | NA 11 | Malar rash, Alopecia, Arthralgia, Seizures, Hepatosplenomegaly | Prednisone                  |                              |
| Luban 1980    | F/African-American | NA 8  | Discoid lesions, Pericarditis, Myocarditis | Prednisone                  |                              |
| Luban 1980    | F/African-American | NA 14 | Fever, Renal disease | Prednisone                  |                              |
| Author          | Gender | Race              | Age | Duration | Diagnosis                          | ANA | SS   | Treatment          | Outcome          |
|-----------------|--------|-------------------|-----|----------|------------------------------------|-----|------|--------------------|------------------|
| Karthikeyan 1978 [14] | F      | African           | 4   | 15       | Arthritis                          | ANA+|       | Prednisone         | Clinical improvement |
|                  |        |                   |     |          | Raynaud’s phenomenon               |     |      |                    |                  |
|                  |        |                   |     |          | Photosensitivity                    |     |      |                    |                  |
| Wilson 1976 [15] | F      | African-American  | 30  | 40       | Arthritis                          | ANA+| SS   | Prednisone         | Deceased          |
|                  |        |                   |     |          | Positive LE cells                   |     |      |                    |                  |
|                  |        |                   |     |          | Pleuritis                          |     |      |                    |                  |
|                  |        |                   |     |          | Libman-Sacks endocarditis          |     |      |                    |                  |
| Wilson 1976 [15] | F      | African-American  | Four months | 16 | Arthritis                          | ANA+|       | Prednisone         | Clinical improvement |
|                  |        |                   |     |          | Hepatitis                          |     |      |                    |                  |
|                  |        |                   |     |          | Pneumonitis                        |     |      |                    |                  |
| Wilson 1976 [16] | F      | African-American  | NA  | 27       | Arthritis                          | ANA+| SS   | No treatment for SLE | Deceased          |
|                  |        |                   |     |          | Histopathologic evidence for SLE on post-mortem examination |     |      |                    |                  |

ACL=anti-cardiolipin antibodies; ANA=anti-nuclear antibodies; anti-ENA=anti-extractable nuclear antigen antibodies; GN=glomerulonephritis; NA=not available; RF=rheumatoid factor; anti-RNP=anti-ribonucleoprotein antibodies; SCD=sickle-cell disease; SLE=systemic lupus erythematosus; anti-SSA=anti-Sjögren syndrome antigen A antibodies.
Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MM was the major contributor to the writing of the manuscript. ZTM and performed the literature research in PubMed. MAad and MAo gave final approval for the version to be published. All authors read and approved the final manuscript.

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