Case Report

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Recurrent Stevens–Johnson syndrome in a patient with systemic lupus erythematosus: a case report

Noha Ibrahim Ahmed Eltahir[1], Shaima N Elgenaid[2], Mohammed Elmujtba Adam Essa[3,4,5], Abdelkareem A. Ahmed[3,6,7,8], Ayman Sati Sati Mohamed[3,4], Mustafa Mohammed Ali Hussein[3,4], Azza Abubaker[9], Elnazir Mohamed Elsayed[10], Sulafa Eisa Mohammed Ibrahim[11], Osman Mohamed Ibrahim[12] and Elnour Mohammed Elagib[1]

Abstract

Systemic lupus erythematosus (SLE) is a systemic disease that affects many organs. A few patients with SLE develop Stevens–Johnson syndrome (SJS), a life-threatening disease characterized by the appearance of a partial-thickness burn in the skin and mucous membranes. This report aims to

[1]Department of Medicine and Rheumatology, Omdurman Military Hospital, Khartoum, Sudan
[2]Faculty of Medicine, University of Khartoum, Khartoum, Sudan
[3]Departments of Clinical Medicine, Medical and Cancer Research Institute (MCRI), Nyala, Sudan
[4]Faculty of Medicine, Al Fashir University, Al Fashir, Sudan
[5]Surgery Research Department, Sudanese Medical Research Association, Khartoum, Sudan
[6]Department of Physiology and Biochemistry, Faculty of Veterinary Science, University of Nyala, Nyala, Sudan
[7]Biomedical Research Institute, Darfur University College, Nyala, Sudan
[8]Institute of Molecular Biology, University of Nyala, Nyala, Sudan
[9]Faculty of Medicine, Omdurman Islamic University, Khartoum, Sudan
[10]Faculty of Medicine, Department of Histopathology, Russian Military Medical Academy, Saint Petersburg, Russia
[11]Department of Histopathology, Sudan Medical Specialization Board, Khartoum, Sudan
[12]Department of Dermatology and Venereal Diseases, Omdurman Military Hospital, Khartoum, Sudan

Corresponding author:
Mohammed Elmujtba Adam Essa, Department of Clinical Medicine, Medical and Cancer Research Institute (MCRI), Alcinema Street, PO Box 155, Nyala, South Darfur State, Sudan.
Email: Awadali818@yahoo.com

increase awareness among clinicians about the relationship between SLE and SJS. An 18-year-old man was admitted to the rheumatology department of Omdurman Military Hospital with a skin rash that was preceded by symptoms of a short febrile illness. He had a maculopapular rash on his palms, soles, trunk, and mucous membranes. The patient had been diagnosed with SLE at 10 years of age and had had SJS three times since the diagnosis of SLE. Investigations to exclude other diagnoses were conducted, and a skin biopsy showed features consistent with early SJS. The patient received intravenous hydrocortisone, oral prednisolone, and oral acyclovir. The lesions resolved 3 weeks after treatment with acyclovir and he was discharged in good condition. A young patient with SLE and recurrent SJS with no immunodeficiency responded very well to the conventional SJS therapy after 3 weeks of treatment.

Keywords
Maculopapular rash, recurrent, systemic lupus erythematosus, Stevens-Johnson syndrome, fever, autoimmune disorder

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of auto-antibodies that lead to various systemic manifestations.[1] The most common cutaneous manifestations in SLE are malar rash, photosensitive dermatitis, discoid rash, and vasculitic lesions.[2] Some patients present with Stevens–Johnson syndrome (SJS) as part of the condition.[3] SJS is a life-threatening condition that affects the skin and mucous membranes and involves less than 10% of the body surface area.[4] It is an unusual condition affecting 1.1 to 7.1 cases per million people per year, with a mortality rate of 1% to 5%.[5,6] SJS can present as a febrile illness associated with detachment of the epidermis (the Nikolsky sign), affecting the skin and mucosa in more than 90% of cases.[5,7,8] Other manifestations such as nephritis, hepatitis, respiratory tract involvement, and hematological changes have also been documented.[5] The diagnosis is based on clinical presentation and on histological features of a skin biopsy. The typical Nikolsky sign can be present but is not specific for SJS.[8] Supportive care and medications including intravenous steroids, immunoglobulin, and cyclosporin are the main management approaches.[8–12] Presentation with SJS as a part of SLE is rare, although a few studies have reported SJS in patients suffering from SLE without previous notable cause; in some of these cases, SJS was the initial presentation.[3,13] Rare cases are documented among patients with childhood-onset SLE; it has been reported that 0.4% to 0.6% of juvenile SLE cases have SJS.[14,15] The disease is not known to be an inherited condition, although there are some unknown genetic relations in most patients, and genetic changes increase the risk of having SJS. For example, individuals with the B1502 allele of the human leukocyte antigen (*HLA*) gene have experienced SJS after taking carbamazepine, and those with the *HLA* B1508 allele have experienced SJS after taking allopurinol. We believe that this case report will rekindle knowledge and awareness in Sudanese clinicians of SJS in patients with SLE.

Case presentation

Our patient was an 18-year-old male university student who was diagnosed with SLE at the age of 10 by a pediatric rheumatologist based on clinical and laboratory findings; however, the patient had no records of the initial diagnosis at the time of presentation. He had continuously active disease due to poor compliance with his regular medication and poor follow-up. During the 8 years since diagnosis of SLE, he had had SJS three times with similar presentations each time. Each attack of SJS was preceded by febrile illness, for which the patient had visited local health centers and was given antibiotics or antimalarial drugs, which are considered a triggering factor for SJS. He presented to Omdurman Military Hospital (Khartoum, Sudan) on 25 April 2018 with a skin rash that was preceded by symptoms of a short febrile illness. The rash was minimally painful. He had no other symptoms related to SLE. His mother reported that he had developed convulsions with the last attack and underwent magnetic resonance imaging of the brain, which showed viral encephalitis. On examination, the patient had a maculopapular rash involving the trunk, palms, soles, and mucous membranes, affecting less than 10% of his body surface area. Examination of the lesions on his back and chest showed purpuric macules and papules, as well as well-defined violaceous annular plaques on the back and upper chest. He had erythematous macules and patches with some overlying erosions and hemorrhagic crusts on his hands. Chilblain-like lesions on the tips of some digits and skin peeling were noted. Mouth lesions showed mucosal erosions and hemorrhagic mucositis involving all of the mouth and lips (Figures 1–3). There was no ocular involvement, no target lesions, and no other SLE-related manifestations. All vital signs were normal. On the basis of this presentation, the differential diagnoses included skin infection, SLE-related mucocutaneous manifestation, SJS, acute cutaneous lupus erythematous (ACLE),

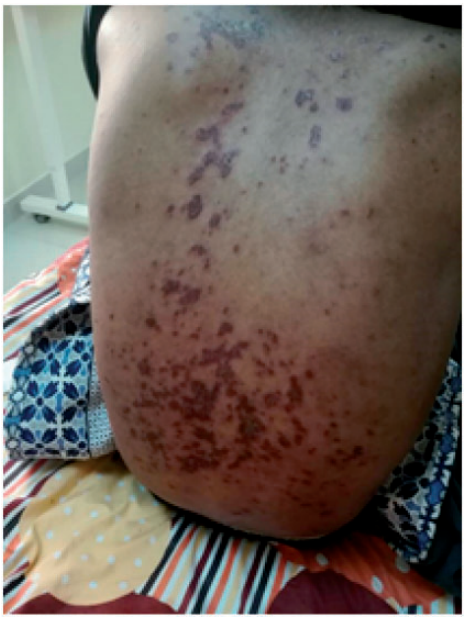

Figure 1. Purpuric macules and papules and well-defined violaceous annular plaques on the back.

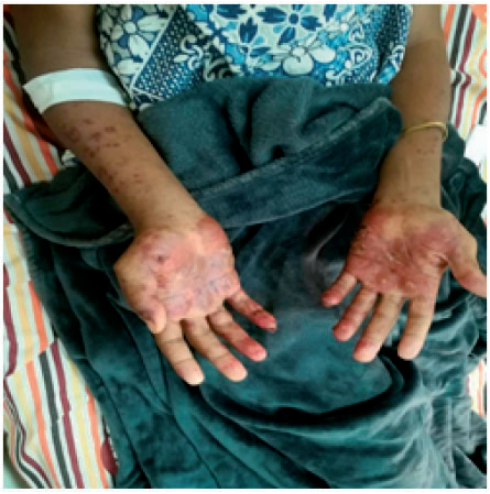

Figure 2. Hand involvement with erythematous macules and patches with some overlying erosions and hemorrhagic crusts.

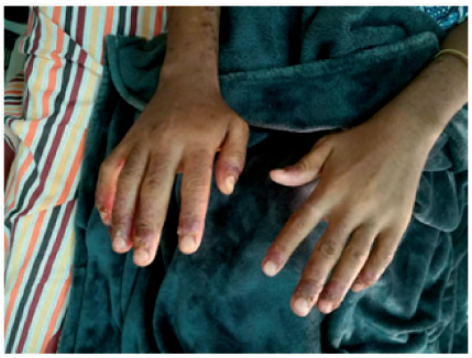

Figure 3. Erythematous macules and patches with chilblain-like lesions on the tips of some digits and skin peeling.

toxic epidermal necrolysis (TEN), and drug-induced lesions. The patient had no family history of similar conditions. Laboratory evaluations revealed hemoglobin of 85%, a white blood cell (WBC) count of 4.8×10^9/L (normal range: 4–11×10^9/L), erythrocyte sedimentation rate of 40 mm/hour (normal range: <20 mm/hour), blood urea nitrogen of 36 mg/dL (normal range: 7–20 mg/dL), serum creatinine of 1.1 mg/dL (normal range: 0.5–1.1 mg/dL), total immunoglobulin (Ig) E level of 101.8 IU/mL (normal range: 150–1000 IU/mL), IgM of 0.90 g/L (normal range: 0.4–2.5 g/L), IgG of 15.0 g/L (normal range: 6.0–16.0 g/L), anti-double strand DNA antibodies of 31 (positive: ≥25 U/mL), and anti-nuclear antibody (ANA) titer by ELISA of 2.3 (positive: >1.2 index value). The patient had negative or normal results for anti-histone antibodies and viral screening, a complement C3 level of 30 mg/dL (normal range: 80–178 mg/dL), and C4 level of 6 mg/dL (normal range: 12–42 mg/dL). Skin biopsies were taken from the affected areas and sent for histological study. Sections showed a small skin biopsy exhibiting alterations in the vacuolar epidermal interface with lymphocytic infiltration and pigment incontinence (Figure 4). The skin lesions were consistent with early changes of SJS. There were no facilities for immune fluorescence; therefore, it was not performed.

The patient was admitted, and supportive care, intravenous (IV) fluids, and IV proton pump inhibitor were initiated. The patient first received IV hydrocortisone, followed by oral prednisolone. Because he had a possible history of herpes encephalitis, he was also treated with IV acyclovir (750 mg/8 hours) for 3 weeks, followed by a prophylaxis dose of oral acyclovir 250 mg/day. Intravenous immunoglobulin was considered but was not needed. The patient's condition improved markedly, and the rash had completely resolved after 3 weeks (Figure 5). For continuous management of his condition, he was started the immunosuppressant medication CellCept 500 mg twice a day (Genentech, San Francisco, CA, USA).

Discussion

There are a few cases of SJS reported among SLE patients. Our patient had been diagnosed with SLE in childhood and since then had developed SJS three times before the current presentation. SJS can present as a febrile illness associated with target lesions, followed by widespread erythematous or purpuric macules, which involve the buccal, genital, and ocular mucosa in more than 90%; flaccid bullae may be present.[5,7,8,11] In this case, the patient presented with skin lesions having an appearance and distribution consistent with SJS. In addition, he had a history of febrile illness before appearance of the rash. SJS is a T cell-mediated immune response that occurs due to binding of antigen to major histocompatibility complex 1. Activation of $CD8^+$ cells induces apoptosis of keratinocytes and detachment of the epidermis from the dermal papillae. Tumor necrosis factor (TNF)-α, nitric oxide, interleukin (IL)-8, and cell adhesion antibodies also play a role in the disease process.[11,17]

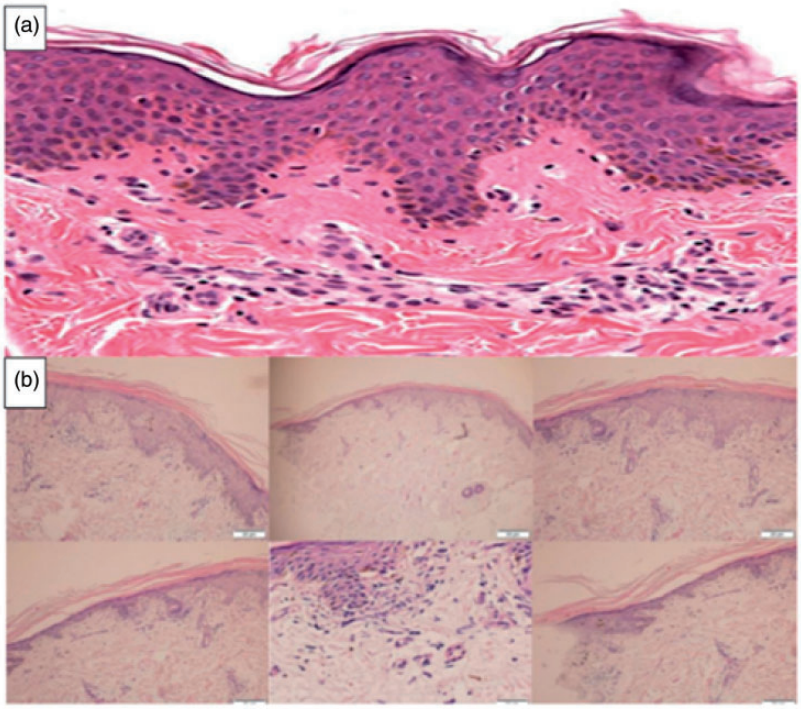

Figure 4. (a) Normal skin histology showing epidermis and superficial dermis;[16] (b) sections from the skin biopsy exhibiting vacuolar epidermal interface alteration with lymphocytic infiltration and pigment incontinence.

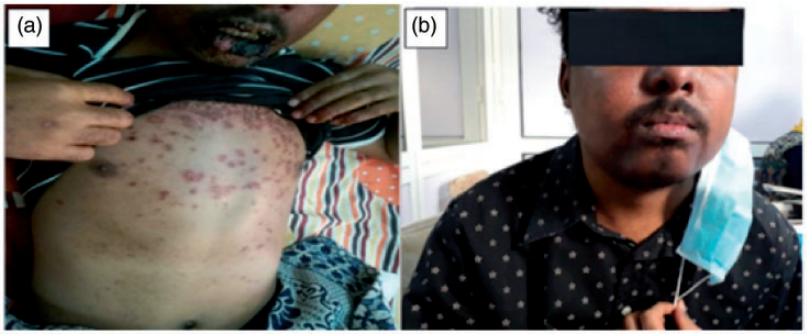

Figure 5. (a) Mucosal erosions and hemorrhagic mucositis involving the mouth and lips, and purpuric macules, papules, and well-defined violaceous annular plaques on the upper chest; (b) appearance after 3 weeks of treatment.

The etiology of SJS varies, including infections, drugs, and vaccines, with medications considered the most common cause.[5,18] In this case, the patient had no history of medication use. Investigations revealed that his IgE level was not increased, making a drug reaction less likely as a cause. Tapering of steroid has been

documented as a cause of SJS,[5] but the patient was not compliant with his drug therapy. Furthermore, IgM and IgG were normal, making primary immunodeficiency unlikely as an underlying cause of his recurrent condition. Such a presentation could be seen secondary to skin infection but the patient's WBC count was normal and no neutrophil infiltration was found in the skin biopsy, making this cause also less likely. The patient had a previous continuous flare of SLE as he was not taking his medication regularly and not attending regular follow-up visits; clinical evaluations revealed active SLE with a positive ANA titer and low complement levels. In this case, the possibility of having a cutaneous manifestation of SLE was high. SLE is a disease with a wide spectrum, having different cutaneous manifestations such as malar rash, photosensitive dermatitis, discoid rash, vasculitic lesions, and others.[2] At the same time, the likelihood of SJS was significant based on the clinical picture.[8] Diagnosis of lupus-associated vesiculobullous lesions may be difficult and these conditions can be life-threatening. ACLE lesions can present similarly to SJS or TEN lesions, with painful flaccid bullae and vesicles and a positive Nikolsky sign. It can start in photo-distributed areas and then become generalized. But the onset of SJS/TEN is like that of ACLE, being subacute and significantly longer (weeks or months) than that of drug-induced SJS/TEN (hours or days). Another difference is mucosal involvement, which is more extensive in drug-induced SJS/TEN than in ACLE.[19] Our patient had mucosal involvement and the onset of his condition was acute. ACLE can also present as target lesions and erythema multiforme-like lesions;[19] however, the patient had no such lesions on examination. In accordance with the Systemic Lupus International Collaborating Clinics (SLICC) diagnostic criteria for SLE, ACLE is associated with the presence of extra-cutaneous involvement.[19] Our patient presented, at the time, with only mucocutaneous manifestations.

The final diagnosis was made by skin biopsy and histological analysis of the specimen, which revealed basal keratinocyte vacuolation and keratinolysis with dermal lymphocytic infiltration. Typical histopathology features of SJS are keratinocytes and epidermal necrosis with mild dermal lymphocytic infiltration.[17] The same findings in our patient confirmed the diagnosis of SJS. He responded well to treatment with supportive care, intravenous steroids, and immunosuppressive drugs, which is an effective management regimen for SJS.[8–10] The patient's history of herpes virus infection could represent a trigger for SJS. In a study done in children, about 26% of SJS and TEN cases were associated with herpes infection.[20] Recent studies have indicated the role of hydroxychloroquine in activating the host defense machinery against viral infection, as it can enhance the expression of antiviral factors such as interferon-β and cytokines IL-6 and TNF-α.[21] In our patient, the rash had mostly resolved with minimal residual scarring after 3 weeks. Mild lesions in SJS usually heal within weeks, with no functional loss if the eyes are not affected, but minimal scarring may occur.[17]

Conclusion

This is the first reported case of recurrent SJS in a patient with SLE in Sudan. An 18-year-old man presented with maculopapular rash; further investigation revealed active SLE and a skin biopsy showed basal keratinocyte vacuolation, keratinolysis, and pigment incontinence consistent with SJS. This was the fourth time the patient had developed SJS; therefore, immunodeficiency was considered a cause of the recurrent disease but immunoglobulin levels and viral screening were normal.

The patient responded very well to conventional SJS therapy and the lesions disappeared after 3 weeks of treatment.

Ethics statement

Ethical approval for this study was obtained from the Federal Ministry of Health in Sudan. Written consent was obtained from patient for the publication of this case report and accompanying images.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Mohammed Elmujtba Adam Essa https://orcid.org/0000-0002-1050-2771

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