Systemic Lupus Erythematosus Associated with Erythema Multiforme : A Rare Case Report of Rowell's Syndrome

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Abstract

Introduction

Rowell's syndrome (RS) is an uncommon presentation of systemic lupus erythematosus (SLE) with erythema multiforme (EM)-like lesions associated with specific serological changes, including positive rheumatoid factor (RF), speckled anti-nuclear antibody (ANA), positive rheumatoid factor, or anti-La antibodies in the serum.

Case Presentation

Our case, a 41-year-old male, presented with features of EM. Upon investigation, we identified underlying systemic lupus erythematosus, marking a rare instance of SLE presenting for the first time as EM.

Case Discussion

Classical or true EM is precipitated by trigger factors such as infective agents like the herpes simplex virus, Mycoplasma pneumoniae, drugs like anticonvulsants, antibiotics, and non-steroid anti-inflammatory drugs, any underlying malignancy, or connective tissue disorders, and is not associated with any specific serological abnormalities. EM cases associated with LE lesions where an EM trigger factor is missing are considered an RS diagnostic criterion.

Conclusion

In this case report, the importance of considering RS as a differential diagnosis in all patients with LE exhibiting EM-like lesions is emphasized, especially when there is no evidence of triggering factors. Early diagnosis and prompt treatment are crucial to preventing complications.

Keywords: Rowell Syndrome, Systemic Lupus Erythematosus, Erythema Multiforme, Anti-nuclear Antibodies, Rheumatoid Factor

Key Clinical Message:

RS should be considered as a differential diagnosis in all patients with LE presenting EM-like lesions when there is no evidence of triggering factors. Failing to do so may result in underdiagnosis and underestimation of the disease. Early diagnosis and prompt treatment of RS are required to prevent irreversible complications.

Introduction

Rowell's syndrome (RS) is an uncommon entity in which patients with systemic lupus erythematosus (SLE) rarely develop characteristic lesions similar to those of erythema multiforme (EM)-like skin lesions, in the presence of specific serological abnormalities (1–4). Firstly, the association between lupus and EM was described by Scholtz in 1922. In 1963, Professor Neville Rowell and his colleagues reported four female patients with discoid lupus erythematosus (DLE) and EM-like skin lesions (among 120 patients with DLE) (2,3). SLE is a chronic autoimmune-mediated inflammatory disorder with multisystem and multiorgan manifestations, while EM is an acute, immune-mediated condition linked to infection, medications, and autoimmune disorders without special autoantibodies, as seen in autoimmune disorders. EM is distinguished by evident target lesions on the skin, accompanied by erosion, blisters, or bullae of mucosal areas (such as the mouth, genitals, and eyes) (3,5).

To reach a diagnosis, meeting all major criteria along with one minor criterion is necessary. Major criteria include the presence of systemic or cutaneous lupus erythematosus (CLE), erythema multiform-like lesions, and antinuclear antibodies (ANA). Minor criteria include the presence of chilblains, anti-Ro, or anti-La antibodies or rheumatoid factor (RF) (4). While the precise etiopathogenesis of RS remains unclear, it is believed to be triggered by factors such as drugs, infections, ultraviolet exposure, cigarette smoking, and psychological stress (1,3). Eventually, RS is considered a rare but distinct entity in rheumatology, and systemic lupus erythematosus (SLE) presenting initially as EM-like lesions is quite uncommon (2).

Case Presentation

A 41-year-old male presents to the clinic with a chief complaint of fever and rashes for the past two days. The fever had a gradual onset and was relieved upon taking medication. The patient reports a maximum temperature of 100°F and denies experiencing chills or rigor. The rashes initially appeared on the neck and gradually spread throughout the entire body, including the hands, legs, and feet. The rashes started as small erythematous papules and enlarged with central necrosis. The patient also reports a history of taking diclofenac tablets for two days, which was approximately four days before the onset of the rash. No other significant medical history is reported, including the absence of respiratory symptoms, chest pain, gastrointestinal symptoms, jaundice, photosensitivity, urinary symptoms, a history of rash in the past, or any history of red or frothy urine. The patient denies any recent travel, intravenous drug use, or promiscuous sexual habits. The patient provides a history of using steroids after the onset of symptoms.

On physical examination, multiple violaceous plaques with central necrosis and a peripheral erythematous to hypopigmented halo are observed over the anterior neck, abdomen, posterior back, bilateral dorsum of the hands, soles, bilateral lower limbs, and feet. The patient's nails demonstrate splinter hemorrhages, nail fold erythema, and red lunula. The patient's vital signs are as follows: pulse rate of 100 beats per minute, temperature of 100°F, blood pressure of 180/80 mmHg, and oxygen saturation level of 96%.

Laboratory investigations reveal a hemoglobin level of 10.21 g/dL, a total leukocyte count of 4830 cells/mm^3, and a random blood sugar level of 158 mg/dL. The erythrocyte sedimentation rate was 35 mm/hr (reference range: 0-20). The liver function test and renal function test were normal. Serological tests revealed positive antinuclear antibodies (ANA) with a speckled pattern, positive anti-double-stranded DNA (anti-dsDNA) antibodies, and positive rheumatoid factor (RF). However, the tests for scrub typhus, brucella antibodies, leptospirosis, and typhoid were negative. HIV, HBsAG, and HCV were non-reactive.

A wound swab was sent for culture, which came sterile. A skin biopsy was performed on the right forearm, and the histopathological examination revealed a skin fragment lined by keratinized stratified squamous epithelium. The biopsy showed areas of ulceration, follicular plugging, and mixed inflammatory cell exocytosis. As shown in the figure 4, the dermis exhibited edema and hemorrhage, with thrombi formation and degene-

rated endothelial cells in a few vessels. Dense mixed inflammatory infiltrates were observed throughout the dermis, primarily in the peripilar unit, including the perivascular region. The erector pili muscle appeared unremarkable, while the subcutis was scant and unremarkable. Focal areas showed subepidermal bulla and lymphocytic infiltration at the dermo-epidermal junction.

Based on the patient's clinical presentation, including the fever, a characteristic rash with central necrosis and peripheral halo, oral ulcers, nail hemorrhages, positive anti-dsDNA antibodies, and a positive ANA with a speckled pattern, the initial differential diagnoses to consider include systemic lupus erythematosus (SLE) and bullous erythema multiforme.

Our patient was subsequently managed with hydroxychloroquine, prednisolone, steroid ointment, a proton pump inhibitor, and sunscreen cream after the diagnosis. Following the treatment, the skin lesions gradually resolved. The skin lesions during presentation, over a period of 3 weeks and 6 weeks, are shown in figures 1, 2, and 3.

Case Discussion

SLE is a chronic, recurrent, potentially fatal multisystem autoimmune and inflammatory connective tissue disorder whose diagnosis can be difficult due to the broad range of clinical manifestations and the lack of pathognomic features or specific laboratory tests (6–8). Before puberty, the female-to-male ratio of SLE occurance is 3:1; after puberty, the ratio increases to 9:1. SLE is generally classified into chronic cutaneous LE (CCLE), subacute cutaneous LE (SCLE), and acute cutaneous LE (ACLE) (6,7).

The kidneys, brain, lungs, heart, skin, and joints are the major organs affected by SLE, with commonly presenting symptoms including fatigue, fever, arthralgias, myalgias, weight loss, rash, oral ulcers, thrombocytopenia, and leucopenia. The mainstay of laboratory testing for the diagnosis of SLE is the assessment of ANA. While a positive ANA test result is useful in diagnosis, it is not specific for SLE. In contrast, anti-ds DNA is relatively specific for SLE (8). Up to 30% of patients will present with cutaneous symptoms, including butterfly-shaped facial rash, red macules, papules, and plaques, alopecia, and mucosal ulcers. (5)

In the case of the patient, the likely diagnosis of SLE was made based on the clinical presentations, including fever, oral ulcers, and a positive anti-ds DNA.

EM, on the other hand, is an acute, immune-mediated mucocutaneous condition characterized by the presence of multiple symmetric, typical, or atypical target lesions with or without crusting at the center of the lesion and concentric color variation mainly on extremities (hands, feet, and the extensor aspects of limbs), with or without itching and prodromal symptoms (7).

Classical or true EM is precipitated by trigger factors such as infective agents like herpes simplex virus, mycoplasma pneumoniae, drugs like anticonvulsants, antibiotics, and non-steroid anti-inflammatory drugs, any underlying malignancy, or connective tissue disorders, and is not associated with any specific serological abnormalities commonly seen in autoimmune disease or with chilblain (6,7,9). In the case of the patient, there was no identifiable precipitating cause of erythema multiforme.

True EM is never associated with any specific autoimmune or serological abnormalities. In our patient, the skin manifestations and histopathologic findings are suggestive of EM, but the absence of any triggering factors does not favor the diagnosis of true EM.

Cases of EM associated with LE lesions where an EM trigger factor is missing, are considered a diagnostic criterion for RS (10). Rowell syndrome was originally described in 1963 by Rowell et al., who identified four females with discoid LE, EM-like lesions, and the presence of one of the following serology: speckled ANA, anti-Ro/La antibody, or rheumatoid factor (RF) (1). RS is characterized by the combination of EM, LE, and typical serological abnormalities (11).

RS is an uncommon presentation of lupus erythematosus with erythema multiforme-like lesions associated with specific serological changes, including positive rheumatoid factor (RF), speckled ANA, positive rheumatoid factor, or anti-La antibodies in the serum (7,11,12). The speckled pattern of ANA is the most consistent

diagnostic feature of Rowell's syndrome. Anti-La antibodies and rheumatoid factor seem to be less consistent features (9). In our case, the patient had a positive RF and a positive ANA with a speckled pattern.

There is a question as to whether the EM-like lesions of RS represent a subset of SCLE since vesicobullous lesions that resemble EM may occur rarely in SCLE. However, the vesicobullous lesions of SCLE do not result in clinical necrosis or scarring, and the histopathological features do not include necrosis of keratinocytes (11). Skin biopsy of the patient reveals areas of ulceration, follicular plugging, mixed inflammatory cells exocytosis, edematous, and hemorrhagic dermis with thrombi formation suggestive of inflammatory dermatoses as depicted in figure 4.

In patients with SCLE, a positive ANA is seen in 75%; the pattern is usually homogenous. Positive anti-Ro is found in 60% and a positive rheumatoid factor in 30–40%. Immunofluorescence of lesional skin reveals linear IgA, IgM, and C3 at the dermo-epidermal junction in 60% of patients. The immunofluorescence from an EM-like lesion in our patient was negative (11).

Before considering a diagnosis of RS, it is important to rule out common triggering agents and other differentials of EM. In this case, no precipitating factor for EM was identified. Also, a diagnosis of RS is based on the presence of major and minor criteria, as seen in Table 1 (1). All three major and at least one minor criteria are required to confirm RS (9).

In our patient, as all the major criteria, along with one minor criterion i.e., positive RF, were present, we consider our case to be a classic RS.

Table 1: Criteria for RS Diagnosis by Zeitouni et al. (1).

Major Criteria: Must meet all	Lupus Erythematosus (LE): systemic LE, discoid LE or subacute cutaneous LE Erythema multiforme-like lesions with or without mucosal involvement Speckled pattern of anti-nuclear antibody
Minor Criteria: Need at least 1	Positive rheumatoid factor Anti-Ro antibody or Anti-La antibody Chilblains

RS is a rare but distinct entity in rheumatology, and SLE presenting initially as EM-like lesions is quite uncommon (2). Our case was an example of a similar situation where SLE initially presented as an EM-like lesion.

Controversy has developed in recent years about whether to consider RS as an independent disease. Several investigators believe RS is a subtype of subacute lupus erythematosus, and clinical and histological distinctions between them are challenging due to variations in the histopathological changes. The pathological evaluation of the skin lesion might reveal EM and/or lupus erythematosus-like manifestations (3). Similarly, the major pathological feature of our case includes both an EM and a LE lesion. Overall, in addition to being diagnosed with SLE and EM, our case fully meets the diagnostic criteria for RS.

The therapeutic regimen used for RS and the prognosis are similar to those of SLE or DLE that occurs alone. The majority of the reported cases showed a satisfactory response to corticosteroids with azathioprine, antimalarial drugs such as chloroquine or hydroxychloroquine, dapsone, or cyclosporine (10,12). Our patient was subsequently managed with hydroxychloroquine (200 mg once daily), prednisolone (1 mg/kg/day), steroid ointment, a proton pump inhibitor, and sunscreen cream after the diagnosis. Following the treatment, the skin lesions gradually resolve, as shown in figures 1, 2, and 3.

Our case is unique as the patient presented to us with features of EM, and on investigation, we found underlying systemic lupus erythematosus, thus SLE presenting for the first time as EM. Very rarely, SLE may initially present with recurrent episodes of EM-like lesions. A high index of suspicion is needed for

diagnosing RS, and it should be considered in all patients with LE with EM-like lesions where there is no evidence of a precipitating factor. Early diagnosis and prompt treatment of RS are required to prevent irreversible complications.

Conclusion

Our case emphasizes the importance of considering RS as a differential diagnosis in all patients with LE presenting EM-like lesions in the absence of triggering factors. Not being able to do so results in underdiagnosis and underestimation of the disease, which will result into irreversible complications. Certainly, clinicians need to be aware of the cutaneous signs associated with systemic diseases to facilitate early diagnosis and timely treatment before potentially life-threatening complications develop. Hence, thorough and comprehensive research needs to be undertaken to establish the existence of RS as a separate entity.

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None

Conflict of Interest:

Authors' have no conflict of interest to declare

Consent statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Authors' Contribution

MB, NKS, SP and SB wrote the original manuscript, reviewed and edited the manuscript. AB, KD, SK, SKJ, EA and DS reviewed and edited the manuscript.

Data availability statement

All the required information is available in the manuscript itself.

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