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Case report

Rowell syndrome: Case report and review of the literature

Síndrome de Rowell: reporte de un caso y revisión de la literatura

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ABSTRACT

Rowell syndrome is a rare disease which consists of lesions of lupus erythematosus and erythema multiforme in patients with a characteristic immunological pattern, given by the presence of positive antinuclear antibodies in a mottled pattern and the absence of infectious and/or pharmacologic triggers. We present a case of a 23-year-old woman with a 4-year history of recurrent episodes of vesicles and blisters, of soft consistency and erythematous base on upper and lower limbs, affecting the oral and nasal mucosa; associated with chilblains, Raynaud's phenomenon, ulcers in oral and nasal mucosa and polyarthralgia; skin biopsy reported erythema multiforme, with negative direct immunofluorescence and positive speckled pattern antinuclear antibodies, findings that fulfil the diagnostic criteria of Zeitouni et al. (2000) and Torchia et al. (2012) for the diagnosis of Rowell's syndrome.

Palabras clave:
Síndrome de Rowell
Eritema multiforme
Lupus eritematoso sistémico
Anticuerpos antinucleares

RESUMEN

El síndrome de Rowell es una enfermedad infrecuente que se presenta como lesiones de lupus eritematoso y eritema multiforme en pacientes con un patrón inmunológico característico, determinado por la presencia de anticuerpos antinucleares positivos patrón moteado y la ausencia de factores desencadenantes infecciosos o farmacológicos. Se presenta el caso de una mujer de 23 años, con cuatro años de evolución de episodios recurrentes de vesículas y ampollas de consistencia blanda y base eritematosa, en miembros superiores e inferiores, con afectación de la mucosa oral y nasal, asociado con lesiones tipo perniosis (chilblain), fenómeno de Raynaud, úlceras en mucosa oral y nasal y poliartralgias. La biopsia de piel reportaba eritema multiforme, con inmunofluorescencia directa negativa y anticuerpos antinucleares patrón moteado positivos, hallazgos que cumplían con los criterios diagnósticos de Zeitouni et al. del año 2000 y de Torchia et al. del 2012 para el diagnóstico de síndrome de Rowell.

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Introduction

Rowell syndrome (RS) is a non-frequent entity, characterized by the presence of lupus erythematosus (LE), associated lesions of erythema multiforme (EM) type and characteristic immunological findings. This association was first described in 1922, but was not recognized as a disease until it was named RS in 1963.[1–3] To date, around 95 cases of EM-like lesions associated with LE have been described in the literature, so there is not enough information to determine the worldwide prevalence.[3] The majority of cases reported have been female patients, with a 3:1 ratio before puberty and 9:1 after puberty, and a mean age of 32 years.[3,4] Since it first description, it has been questioned in the literature whether RS is actually a distinct clinical entity or simply a coincidence of the coexistence between LE and EM, hence there is no consensual classification to avoid a misdiagnosis of this syndrome, which makes it difficult to recognize it.[1,3] We present the case of a 23-year-old female patient who presented LE lesions associated with EM lesions, along with positive antinuclear antibodies (ANA), speckled pattern and perniosis-type lesions (*chilblain*), associated with Raynaud's phenomenon, ulcers in the oral and nasal mucosa and polyarthralgia.

Clinical case

A 23-year-old female patient with a history of 4 years of evolution of appearance of vesicles and blisters of soft consistency and erythematosus base, initially in the palms of the hands with subsequent expansion to upper limbs, lower limbs, feet and soles, and involvement of the oral and nasal mucosa, associated with burning pain in the feet and hands. This picture recurred every 6 months and had an approximated duration of 15 days. The patient had a history of migraine in the adolescence, and regarding the review by systems she reported the presence of inflammatory polyarthralgia in the wrists, proximal interphalangeal joints, knees and ankles, and Raynaud's phenomenon since the age of 15 years, in addition to perniosis-type lesions *(chilblain)* in the hands and feet, malar erythema and ulcers in oral and nasal mucosa for 4 years, subsequent to the first episode of the disease.

On dermatological examination there was a patient with a chronic dermatosis located in the upper and lower limbs, characterized by multiple erosions, papules and erythematous-violaceous plaques of different sizes (Fig. 1), in addition to multiple erythematous-violaceous blisters and vesicles, with a target pattern, some with erosion of different sizes on the surface, located on the palms (Fig. 2). Joint pain or swelling was not found at the time of physical examination. In the year 2019, studies were conducted, in which positive ANA 1:80 speckled pattern and positive IgG beta 2 glycoprotein were evidenced (Table 1). In addition, in the biopsy of the hand skin, there were findings of EM with thin orthokeratotic epidermis, vacuolar damage of the basal layer with abundant necrotic keratinocytes; dermis with discrete perivascular lymphocytic infiltrates, pigment leakage and melanophages. One year later, in a new immunofluorescence biopsy of the left leg, skin with hyperkeratosis, focal epidermal necrosis of the upper portion of the epidermis resting on the epithelium, with reactive and re-epithelialization changes was observed; in the dermis, there was slight perivascular lymphocytic inflammatory infiltrate with discrete edema and fibrosis, in relation to the epithelium with reparative changes. The immunofluorescence: IgA, IgG, IgM, C3, C4, C1q and fibrinogen were non-reactive, histological findings consistent with repair of EM. The patient had been treated with methylprednisolone 4 mg/day and methotrexate 15 mg/week for 4 months, which

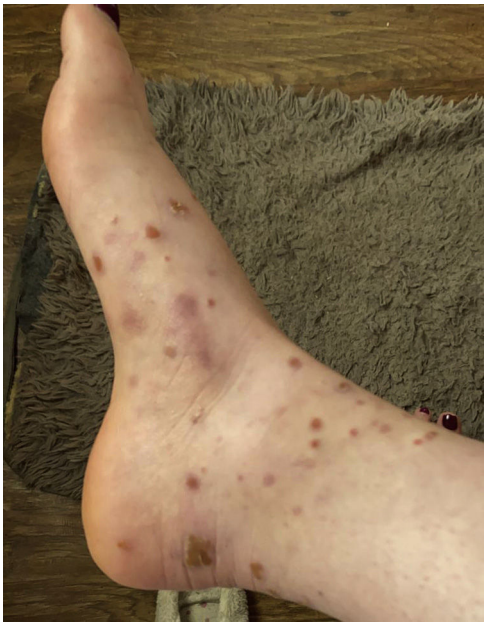

Figure 1 – Multiple erosions, erythematous-violaceous papules and plaques with well-defined regular borders, of 3 to 15 mm. Figure provided by the patient.

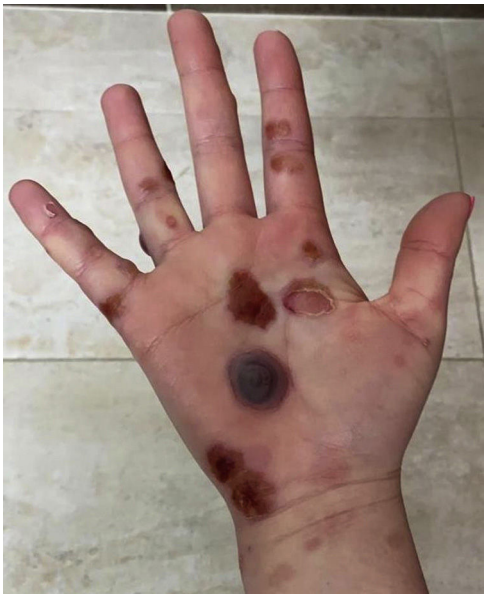

Figure 2 – Multiple erythematous-violaceous blisters with target pattern, some with erosion on the surface and erythematous-violaceous plaques with well-defined regular borders of 6 to 20 mm. Figure provided by the patient.

Table 1 – Paraclinical tests of the patient.

Paraclinical tests	Results	Reference values
Semiautomated CRP	2.58 mg/l	0.30–5.00 mg/l
ESR	4 mm/h	20 mm/h
Semiautomated or automated RF	<10 IU/ml	10.0–14.0 mg/dl
Automated C3	101.3 mg/dl	90.0–180.0 mg/dl
Automated C4	17.6 mg/dl	10.0–40.0 mg/dl
p-ANCA	Negative	
c-ANCA	Negative	
ANA	Positive dilution 1/80 speckled pattern	Dilution less than 1/40
Anti-DNA antibodies Semiautomated or automated	Negative	
ENA	Negative	
Semiautomated or automated anti-SSA Ro antibodies	2.4 U	0.0–20.0 U
Semiautomated or automated anti-SSB antibodies	4.1 U	0.0–20.0 U
Semiautomated or automated anti-SM antibodies	3.1 U	0.0–20.0 U
Anti-RNP antibodies	3.2 U	0.0–20.0 U
Beta 2 glycoprotein 1 IgG	84.21 U	0–20 U
Beta 2 glycoprotein 1 IgM	2.38 U	0–20 U
Lupus anticoagulant	44.0 s	31–44 s
Anticardiolipin IgG antibodies	4.2 IU/ml	<7.0 IU/ml
Anticardiolipin IgM antibodies	0.8 IU/ml	<7.0 IU/ml

ANA: automated antinuclear antibodies; C3: serum complement C3; C4: serum complement C4; c-ANCA: anti-neutrophil cytoplasmic antibodies, cytoplasmic pattern; ENA: extractable nuclear antigens; RF: rheumatoid factor; p-ANCA: anti-neutrophil cytoplasmic antibodies, peripheral pattern; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

had to be discontinued due to adverse effects expressed as adynamia, hair loss and persistence of EM lesions. At the time of consultation, she had been under treatment with acyclovir 800 mg/day for 4 months, with partial response. In the last 2 months she is being managed with hydroxychloroquine 200 mg/day, with adequate clinical response that manifests itself by disappearance of the skin lesions and reduction of the burning pain in hands and feet (Fig. 3).

Discussion

RS was described for the first time in 1922 by Scholtz, who considered that EM was not part of systemic lupus erythematosus (SLE), but it was related to the intake of drugs.[5] Later, in 1963 Rowell et al. described it as SLE, EM not associated with medicines, positive rheumatoid factor (RF), ANA speckled pattern and positive anti-Ro/SSA.[6] In 1995, Bhat et al. suggested the inclusion of perniosis-type lesions (*chilblain*) as inclusion criterion.[2] Later on, Zeitouni et al. divided the diagnostic criteria into major and minor.[7] In the major criteria they included LE (acute, subacute or systemic), EM-like lesions and positivity of ANA; and the minor criteria included the presence of

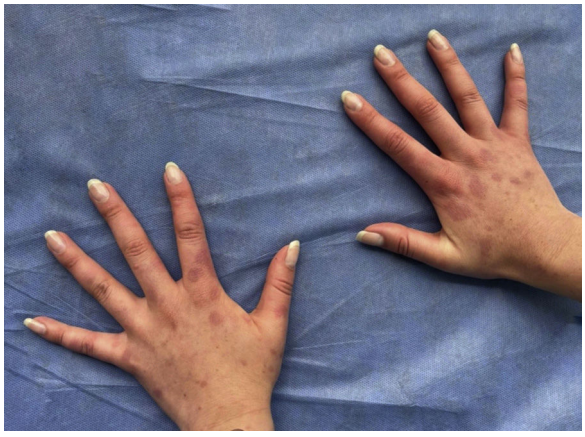

Figure 3 – Evolution of the lesions one month after having started treatment with hydroxychloroquine 200 mg/day.

perniosis-type lesions (*chilblain*), anti-Ro/SSA or anti-La/SSB antibodies and positive RF (Table 2).[7]

Despite several case reports that inform the simultaneous appearance of SLE and EM, as well as the diagnostic criteria described, the criteria for the diagnosis of RS are still subject of debate. Torchia et al. proposed new diagnostic criteria and defined the RS as an autonomous type of chronic cutaneous lupus erythematosus (CCLE) within the spectrum of the cutaneous diseases specific of LE (Table 2).[8] On the other hand, Antiga et al. have a different opinion on the patients with EM-like lesions, according to which, in the context of SLE and CCLE they represent morphological variants of LE-specific skin lesions, rather than a distinct entity.[9]

According to the criteria of Zeitouni et al.,[7] the patient meets the 3 major criteria (LE lesions, positive ANA speckled pattern and EM lesions) and a minor criterion (presence of perniosis-type lesions [*chilblain*]), sufficient to establish the diagnosis of RS; in addition, she meets the 4 major criteria defined by Torchia et al.[8] (perniosis-type lesions (*chilblain*), LE lesions, positive ANA speckled pattern, lesions of EM and negative DIF of the EM lesions) and 2 minor criteria (absence of infectious or pharmacological triggers, or of arthralgias in the wrists, proximal interphalangeal joints, knees and ankles).

Classic EM remits spontaneously and is associated with trigger factors such as infections (herpes virus, pneumonia caused by mycoplasma) or drugs (antibiotics, nonsteroidal anti-inflammatory drugs and anticonvulsants), malignancy and connective tissue disorders; furthermore, EM is never associated with any specific autoimmune serological abnormality.[10,11] The patient presented cutaneous manifestations an histopathological findings suggestive of EM, however, the chronicity of the disease and the absence of specific triggering factors, associated with positive autoimmune markers, did not favor the diagnosis of classical EM.

Cutaneous manifestations of RS are diverse and may include erythema, papules, target lesions, vesicles, blisters and urticarial lesions, most commonly distributed in the arms and legs; the trunk and the face are less frequent distributions.[12]

On the other hand, the ANA speckled pattern, which is the characteristic most commonly present in RS, is described in

Table 2 – Diagnostic criteria for Rowell Syndrome.

Rowell et al.[6]	Bhat et al.[2]	Zeitouni et al.[7]	Torchia et al.[8]
LE EM-like lesions (with absence of precipitating factors) ANA speckled pattern Anti-SJT antibodies (anti-La/SS-B) Positive RF	LE EM-like lesions (with absence of precipitating factors) Perniosis-type lesions (*chilblain*) ANA speckled pattern Anti-La/SSB antibodies Positive RF	*Major criteria:* SLE, DLE or SCLE EM-like lesions (with/without mucosal involvement) ANA speckled pattern *Minor criteria* Perniosis-type lesions (*chilblain*) Anti-Ro/SSA or anti-La/SSB Positive RF	*Major criteria:* CCLE (DLE and/or perniosis-type lesions [*chilblain*]) EM-like lesions (typical or atypical target lesions) At least one: speckled ANA, positive anti-Ro/SSA and anti-La/SSB Negative DIF in EM-like lesions *Minor criteria:* Absence of infectious or pharmacological triggers Absence of localization typical of EM (acral and mucosal) Presence of at least an additional ARA criterion for the diagnosis of SLE in addition to discoid eruption and ANA, excluding photosensitivity, malar rash and oral ulcers
Diagnosis of RS: all criteria	*Diagnosis of RS: all criteria*	*Diagnosis of RS:* 3 major criteria + one minor criterion	*Diagnosis of RS:* 4 major criteria + one minor criterion

ANA: antinuclear automated antibodies; ARA: American Rheumatism Association; EM: erythema multiforme; RF: rheumatoid factor; DIF: direct immunofluorescence; LE: lupus erythematosus; CCLE: chronic cutaneous lupus erythematosus; SCLE: subacute cutaneous lupus erythematosus; DLE: discoid lupus erythematosus; SLE: systemic lupus erythematosus; RS: Rowell syndrome.

approximately 88% of cases, while RF is the least preserved characteristic, present only in 41%.[2] Rowell et al. described that ANA were usually positive in patients who presented lupus with low systemic involvement, such as perniosis-type lesions (*chilblain*) and, in addition, that these antibodies were more frequent in the patients who had a positive RF.[6] The patient presented positive ANA 1:80 speckled pattern, with presence of perniosis-type lesions (*chilblain*), but with negative RF.

The diagnosis of LE usually precedes the onset of EM lesions, sometimes for many years and with very few exceptions.[3,8] The patient might be considered one of these exceptions, since she first presented EM-like lesions, with subsequent advent of the other clinical manifestations.

The prognosis and treatment of RS are similar to those of SLE or of discoid lupus erythematosus, that occur alone; therapeutic regimens include oral prednisone at high or medium doses, in combination with azathioprine or antimalarials such as chloroquine or hydroxychloroquine, dapsone or cyclosporine.[13] Currently, the patient is under management with hydroxychloroquine 200 mg/day, with important improvement of symptomatology.

Conclusion

Despite RS is an infrequent entity, the diagnosis should be considered in patients with LE and EM-like lesions, when there is no evidence of a triggering factor. The present case highlights the need to suspect RS, even in young patients, as well as the importance of joint management between rheumatology and dermatology. In addition, it continues to be an entity with disputed diagnostic criteria, so it is necessary to perform additional studies to develop a consensual classification and thus avoid erroneous diagnoses.

Ethical considerations

I declare and confirm that I have obtained all consents required by current legislation for the publication of any personal data or images of patients, research subjects or other persons who appear in the article.

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Conflict of interest

The authors declare that they have no conflict of interest.

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