CASE REPORT

Ref: Ro J Rheumatol. 2015;24(4)
DOI: 10.37897/RJR.2015.4.8

Rowell Syndrome – a controversial clinical entity

Iulia-Tania Andronache[1,2], Cristina Suta[1,2], Claudiu Ionescu[1], Anca Calistrat[1], Maria Suta[1,2]

[1]Rheumatology Department, IInd Internal Medicine Clinic,
Sf. Apostol Andrei Emergency Clinical County Hospital, Constanta
[2]3rd Department, Ist Clinical Disciplines, Faculty of Medicine, Ovidius University, Constanta

ABSTRACT

Rowell syndrome is considered to be an unusual association between systemic lupus erythematous (SLE), ery-thema multiforme-like lesions and an immunological pattern consisting of speckled ANA, positive rheumatoid factor and positive anti-La (SSB) antibodies.
We present the case of an 81 year old woman with late-onset SLE who developed an erythema multiforme-like rash, with a speckled antinuclear antibodies (ANA) immunofluorescence pattern and a positive rheumatoid factor. The key in establishing the diagnosis was the biopsy of the lesion, which set the diagnosis of Rowell syndrome.

Keywords: Rowell syndrome, systemic lupus erythematous, erythema multiforme

BACKGROUND

Rowell syndrome is defined by the association between systemic lupus erythematous (SLE), erythema multiforme (EM) and characteristic immunological findings. Ever since 1963, when the condition was described by Rowell (1), there have been discussions in the literature whether this syndrome is a stand-alone clinical entity or a mere coincidence.

The diagnosis criteria established by Zeitouni et al. in 2000 may be divided in major criteria (SLE, discoid lupus erythematosus or subacute lupus erythematosus, erythema multiforme like lesions, with or without mucous involvement and positive antinuclear antibodies – ANA – with a speckled immunofluorescence pattern) and minor criteria (chilblains or pernio, positive antiRo or antiLa antibodies and a positive rheumatoid factor). In order to establish positive diagnosis all the major criteria and at least one minor criteria need to be fulfilled (2).

We present the case of a patient with late-onset systemic lupus erythematosus, with speckled ANA immunofluorescence pattern and a positive rheumatoid factor (RF), who developed an EM-like rash.

CASE PRESENTATION

An 81-year old woman with one year history of late-onset systemic lupus erythematosus with systemic (fever, anorexia, weight loss), musculoskeletal (myalgia, polyarthritis), cutaneous (photosensitivity), hematological (leukopenia and lymphopenia) and immunological manifestations (ANA intensely positive with a speckled pattern, positive anti dsDNA antibodies and a positive rheumatoid factor) presents for painful and pruritic erythematous plaques over her thighs, chest and back. The patient has interrupted her treatment regimen with Hydroxycloroquine (complains of malaise) and continued her 5 milligrams a day corticosteroid treatment. She also has a history of osteoporosis with vertebral fractures (biphosphonate treatment for the past three years).

Physical examination at the moment of the admission showed multiple annular erythematous squamous plaques with vesicular borders and central erosions over her thighs, chest (Figures 1 and 2), arms and back. She also complained of polyarthralgia in her interphalangeal and metacarpophalangeal joints, but without peripheral arthritis.

Corresponding author:
Iulia-Tania Andronache
E-mail: andronacheiulia@gmail.com

Article History:
Received: 24 November 2015
Accepted: 5 December 2015

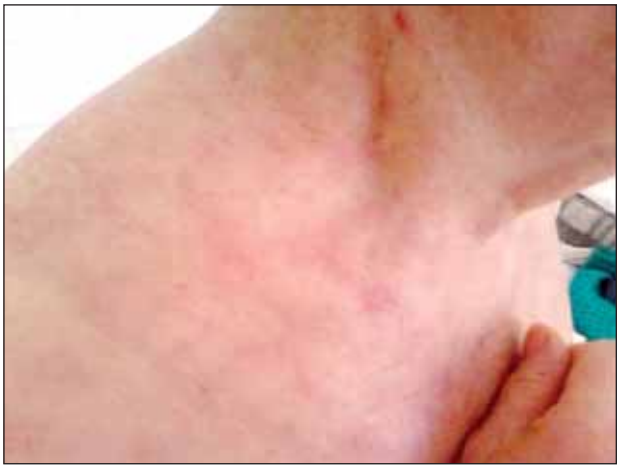

FIGURE 1. *Latero-cervical erythema multiforme lesions*

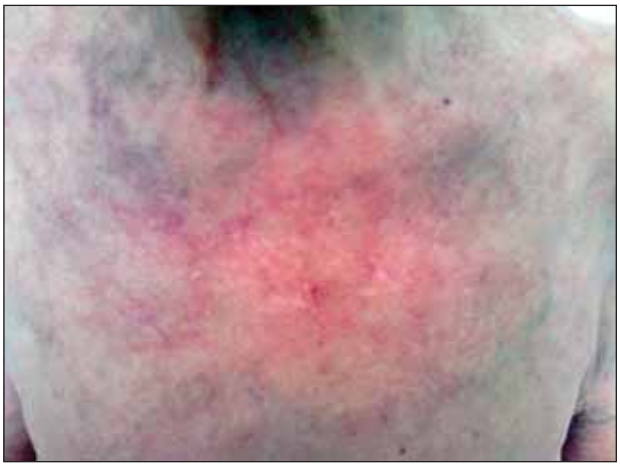

FIGURE 2. *EM lesions on chest (multiple annular erythematous squamous plaques)*

Laboratory tests revealed an erythrocyte sedimentation rate of 56 mm/h, C reactive protein of 2.74 mg/dl, leukopenia (3.410/µl) with lymphopenia (400/µl) and a mild anemia (11.2 g/dl). The antinuclear antibodies were intensely positive (1/3,200) with a speckled immunofluorescence pattern and the tests for anti-Ro, anti-La antibodies were negative. The liver function tests, kidney function tests and serum complement were within normal values.

Skin biopsy taken from a lesion on the back showed slight atrophy, with marked keratinocyte necrosis, hyperkeratosis, parakeratosis and vacuolar basal changes. In the superficial dermis there was edema with inflammatory perivascular, perianexial and interstitial lymphocytic and plasmocytic infiltrate, extending towards the epidermis interpreted by the pathologists as compatible with erythema multiforme (Figure 3).

Based on the patient's pathological history (SLE), clinical manifestations at admission (erythema multiforme-like rash), laboratory tests performed (antinuclear antibodies intensely positive (1/3,200) with a speckled immunofluorescence pattern, a history of positive RF (3) and the histopathological examination, the diagnosis of Rowell's syndrome has been established. Therapy was started with Hydroxycloroquine 400 mg/day and Prednisone 30 mg/day (with subsequent decrease of corticosteroid doses due to osteoporosis) with partial resolution of the symptoms.

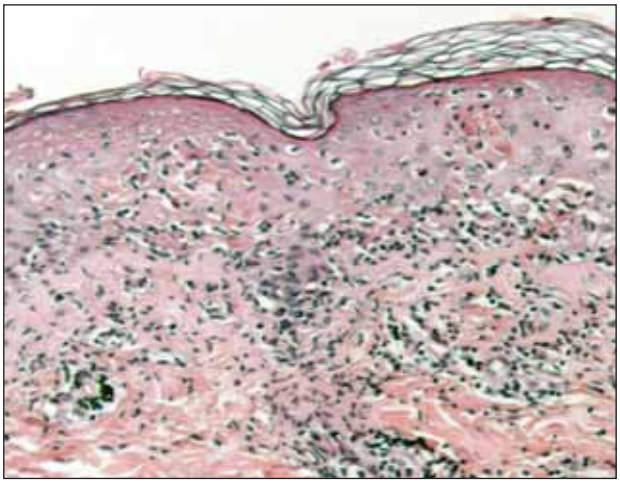

FIGURE 3. *Skin biopsy, H-E coloration 40x, lymfocytic perivascular infiltrate, vacuolar basal degeneration and keratinocyte necrosis*

DISCUSSIONS

The first reports regarding the association between discoid lupus erythematosus (SLE) and erythema multiforme (EM) were made in 1922 by Scholtz. Later on, in 1963, Rowell et al. defined a syndrome consisting in discoid lupus erythematosus, erythema multiforme-like rash and immunological abnormalities such as positive RF, an ANA immunofluorescence speckled pattern and anti SjT antibodies (later identified as anti Ro/SSA and anti La/SSB). All four patients identified by Rowell et al. as having this condition were women, with discoid lupus, speckled immunofluorescence pattern, positive Rheumatoid Factor, anti SjT antibodies and pernio. Since Rowell established these criteria, there were multiple reports) of this so called Rowell's syndrome (71 patients) (3) and many of them did not fulfill all the clinical an serological features.

TABLE 1. *Rowell syndrome diagnosis criteria according to various authors (Rowell et al, Lee at al, Zeitouni et al)*

Rowell criteria (1)	Lee et al criteria (5)	Zeitouni et al criteria (2)	
Lupus erythematosus	Lupus erythematosus	Major	Lupus erythematosus (LE): systemic LE, discoid LE or subacute cutaneous LE
			Erythema multiforme-like lesions (with/ without involvement of the mucous membranes)
			(Speckled pattern of antinuclear antibody
Erythema multiforme-like lesions (with absence of any known precipitating factors)	Erythema multiforme-like lesions (with absence of any known precipitating factors) Chillblains	Minor	Chilblains
			Anti-Ro antibody or anti-La antibody
			Positive rheumatoid factor
Immunological abnormalities in the serum: – Speckled pattern of antinuclear antibody – Anti-La (SS-B) antibody – Positive rheumatoid factor	Immunological abnormalities in the serum: – Speckled pattern of antinuclear antibody – Anti-La (SS-B) antibody – Positive Arheumatoid factor		
		Proposed diagnostic criteria for Rowell's syndrome. All three major and at least one minor criteria are required.	

More recent attempts to classify this condition were made by Lee et al in 1995, suggesting the inclusion of chilblains (pernio) to the diagnostic criteria, and in 2000 Zeitouni et al defined major and minor criteria in order to offer a more consistent approach to the diagnosis (2) (Table 1). However, this expansion of criteria made the syndrome less specific.

The concept of Rowell syndrome has become lately rather controversial, some considering that the association of SLE and EM is a mere coincidence or that the cases reported were rather misdiagnosed cases of subacute SLE (3-6). Indeed, it may be challenging to clinically differentiate between annular and polycyclic lesions of subacute cutaneous LE and EM (5). Other authors have suggested that Rowell syndrome might be either a variant of cutaneous lupus erythematosus, a subtype of chronic lupus erythematosus or an independent LE subtype (3,7-12).

A modified version of Gilliam's classification of LE-non-specific skin disease includes erythema multiforme. (13,14). However, a 2012 multicenter database analysis from the European Society of CLE (EUSCLE) found that the nonspecific lesions including erythema multiforme (EM) lesions were represented by less than 2% (15).

The absence of an obvious precipitating factor for EM, be it infections, drugs, neoplasia or inflammatory bowel disease (2,4,6,10), which could have complicated the picture and the presence of immunological abnormalities made us classify our patient's condition as Rowell syndrome. So far, multiple case reports describing Rowell's syndrome fulfill current diagnostic criteria proposed by Zeitouni (3,7-9). Our patient presented here does not fit all the current criteria for a diagnosis of Rowell's syndrome, respectively the presence of anti-Ro antibodies and chilblains. However, the histopathological examination of the skin biopsy was consistent with EM, excluding the possibility that these were merely a cutaneous manifestation of lupus. The differential diagnosis is based on clinical appearances, histopathology and serologic findings (16) (Table 2).

The case's particularity consists in the late onset of the SLE and the absence of other cutaneous manifestations. According to the literature, cutaneous manifestations are very common in SLE patients (over 80% display skin symptoms sometime during the course of the disease and in 20-25% of patients cutaneous manifestations are the first symptom of SLE disease) (17). An important problem in a case of late onset SLE is corticoid therapy in association with osteoporosis and osteoporotic fractures.

The treatment regimens reported in the literature consisted in corticosteroids and immunosuppression with azathioprine or antimalarial drugs (mainly hydroxycloroquine) either standalone or in combination (7-9). Other authors also mention cyclosporine as a therapeutic option (18). The response to treatment is variable and frequent recurrences were reported. In spite of the rather large doses of oral steroids, our patient's lesions were relatively resistant

TABLE 2. *Clinical and histologic findings of bullous SLE, EM, Rowell syndrome and SCLE*

	Bullous SLE	EM	Rowell syndrome	SCLE
Epidemiology	12-14 years of age; F>M	Young adults; 20-40 years of age; M > F	Females; 31-72 years of age	Young middle-aged women
Distribution	Face, neck, upper trunk, shoulders, hands (primarily in sun-exposed areas)	Dorsal hands, palms, soles, extensor surfaces, neck, perineum	Primarily affects arms, legs; less often seen on trunk, face	Annular or papulosquamous eruption of shoulders, extensor surfaces of arms, dorsal hands, upper back, common on chest. Telangiectasias
Oral lesions	Rare	25%-60% of cases	Rare	Rare
Laboratory values	As per ARA criteria	Mild elevation of ESR, WBC	Positive serum rheumatoid factor, speckled ANA, precipitating antibodies	Positive ANA (75%). Positive SS-A/RO antibodies via immunoassay (60%). Positive RF (30%-40%)
Histology	Subepidermal vesicles with neutrophils, nuclear fragments, and fibrin at tips of dermal papillae	Early: Swelling of endothelial cells, superficial perivascular mononuclear infiltrate. Late: Hydropic degeneration, necrosis of individual keratinocytes, subepidermal bullae	Similar to EM; prominent necrosis of keratinocytes	Liquefaction of basal cell layer perivascular, periappendageal, mononuclear cell infiltrate in upper third of dermis
Immunology	Linear IgA, IgG, IgM and less frequently C3 at basement sublamina densa	Early: Granular IgM, C3 in capillary dermal blood vessels. Late: Granular C3 along dermal-epidermal zone.	Similar to EM	Lesional; linear IgA, lgG, IgM, C3 at d-e junction in 60% of patients; nonlesional – 35% of patients
Course/prognosis	Often flares with systemic disease activity; responsive to dapsone	Erupts over 3-5 years days; heals in 2 weeks. 22%-37% recurrence rate	Long Standing:Recurs frequently over many years	50% may be classified as SLE although systemic disease is mild; is photoexacerbated; antimalarials, systemic corticosteroids useful

From Fitzgerald et al – Journal of the American Academy of Dermatology, Nov. 1996
Note: SLE – systemic lupus erythematosus; SCLE – subacute cutaneous lupus erythematosus; EM – erythema multiforme

but, the treatment improved the patient's quality of life, esthetic impact, diminished local pain and pruritus.

In our opinion, in spite of the controversial aspects regarding the existence of Rowell's syndrome (3,6,8), this diagnosis should be consider in any patient with these specific clinical features and immunological abnormalities. A good collaboration between rheumatologist, dermatologist and pathologist is necessary in order to establish proper diagnosis and treatment, thus improving the outcome and quality of life.

REFERENCES

1. **Rowell NR, Beck S, Anderson JR.** – Lupus erythematosus and erythema multiforme-like lesions. *Arch Dermatol* 1963; 88: 176±80.
2. **N.C. Zeitouni, D. Funaro, R.A. Cloutier, et al.** – Redefining Rowell's syndrome; *British Journal of Dermatology* 2000; 142: 343±346.
3. **Antiga E., Caproni M., Bonciani D. et al.** – The last word on the so-called 'Rowell's syndrome'? *Lupus* 2012; 21: 577-85.
4. **Aydogan K., Karadogan S., Balaban Adim S. et al.** – Lupus erythematosus associated with erythema multiforme: report of two cases and review of the literature. *J Eur Acad Dermatol Venereol* 2005; 19: 621-627.
5. **Lee S., Schloss E., Kowichi J.** – Rowell's syndrome: a case report with subacute cutaneous lupus erythematosus and erythema multiforme. *Can J Dermatol* 1995; 7:807±10.
6. **Modi G.M., Shen A., Mazloom A., et al.** – Lupus erythematosus masquerading as erythema multiforme: does Rowell syndrome really exist? *Dermatol Online J* 2009; 15: 5.
7. **Roustan G., Salas C., Barbadillo C.** – Lupus erythematosus with an erythema multiforme-like eruption. *Eur J Dermatol* 2000; 10: 459-462.
8. **Khandapur S., Suchibrata S., Singh M.** – Rowell's syndrome revisited: reported of two cases from India. *Int J Dermatol* 2005; 44: 545-549
9. **Marzano A.V., Lazzari R., Polloni I. et al.** – Drug-induced subacute cutaneous lupus erythematosus: evidence for differences from its idiopathic counterpart. *Br J Dermatol* 2011; 165: 335-41.

10. **Hautmann G., Lotti T.** – Psychoactive drugs and skin. *J Eur Acad Dermatol Venereol* 2003; 17: 383-293
11. **Shteyngarts A.R., Warner M.R., Camisa C.** – Lupus erythematosus associated with erythema multiforme: does Rowell's syndrome exist? *J Am Acad Dermatol* 1999; 40: 773-777.
12. **Torchia D.** – Rowell syndrome categorized as cutaneous lupus erythematosus subtype. *J Am Acad Dermatol* 2012; 67:417-21.
13. **Gilliam J.N., Sontheimer R.D.** – Distinctive cutaneous subsets in the spectrum of lupus erythematosus. *J Am Acad Dermatol.* 1981; 4:471-5;
14. **Sontheimer R.D.** – Skin manifestations of systemic autoimmune connective tissue disease: Diagnostics and therapeutics. *Best Pract Res Clin Rheumatol.* 2004;18:429-62.
15. **Biazar C., Sigges J., Patsinakidis N. et al.** – (2013) EUSCLE coauthors. Cutaneous lupus erythematosus: first multicenter database analysis of 1002 patients from the European Society of Cutaneous Lupus Erythematosus (EUSCLE). *Autoimmun Rev* 12: 444-454
16. **Fitzgerald E.A., Purcell S.M., Kantoret G.R. et al** – Rowell's syndrome: report of a case – Journal of the American Academy of Dermatology, Nov. 1996
17. **Rothfield N., Sontheimer R.D., Bernstein M.** – Lupus erythematosus: Systemic and cutaneous manifestations. *Clin Dermatol.* 2006;24:348-62
18. **Müller C.S., Hinterberger L.R., Vogt T.** – Successful treatment of Rowell syndrome using oral cyclosporine A. *Int J Dermatol* 2011; 50:1020-2.