Unusual presentation of more common disease/injury

Rowell syndrome – case report with discussion of significance of diagnostic accuracy

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Correspondence to Dr Cornelia S L Müller, c_mueller1977@yahoo.de**Summary**

Rowell syndrome is a very controversial condition and though defining diagnosing criteria exist, many previously published cases lack one or more of these criteria. It represents the combination of cutaneous lupus erythematosus and erythema multiforme in one single individual. In order to discuss relevance of diagnostic and defining criteria the authors use a case seen in our outpatient service that was primarily diagnosed as Rowell syndrome. But due to lacking criteria, the authors rediagnosed this patient as an unusual variation of lupus erythematosus.

BACKGROUND

To date, Rowell syndrome (RS) is an infrequently diagnosed disease. Initially described in 1963, RS represents the combination of cutaneous lupus erythematosus (LE) and erythema multiforme (EM) in an individual.^{1 2} Rowell *et al* published that 4 of 120 patients suffer from EM like lesions in association with discoid LE.² RS must be differentiated clinically from photosensitive eruptions of subacute cutaneous LE and classical bullous LE.³ The histopathologic findings include an alteration of the interface zone with single apoptotic keratinocytes resembling EM, as well as a superficial and deep perivascular lymphocytic infiltrate and interstitial mucinosis to a variable extent, characteristic for lupus dermatitis.

Rowell *et al* specified in their pioneer work the association of LE, EM like lesions and serum immunological abnormalities not further specified.² But, cases which were described subsequently lacked most of these imprecise criteria.⁴ Therefore, Zeitouni *et al* published a redefinition of the RS in 2000, based on the observation that some criteria may be important for diagnosis but are not constantly observed in previous cases.⁵ Lupus dermatitis and EM like skin lesions as well as a speckled pattern of antinuclear antibodies were defined as major criteria that have to be fulfilled completely. As minor criteria they defined chilblains, anti-Ro/La-antibodies and a positive rheumatoid factor. In their opinion, cases diagnosed as RS should fulfil at least all three major criteria and one minor criterion.⁵

CASE PRESENTATION

We report an adult male that consulted our outpatient service in the last year. The patient presented with a several months lasting history of recurrent pruritic multiform like skin lesions mainly on the trunk (figure 1). No seasonal correlation or photosensitivity was observed. He did not show any associated diseases, no facial butterfly erythema, no Raynaud's phenomena. No oral, genital or ocular lesions were noted. No preceding herpes-virus-infection was noted. No drugs were taken prior to first occurrence of the skin lesions. A comprehensive metabolic panel, antinuclear

antibodies, rheumatoid factor, erythrocyte sedimentation rate, C reactive protein, coagulation panel, urine analysis and chest radiography were normal. The blood cell count with differential analysis was normal.

In conclusion, due to EM like clinical changes in addition to lupus-like changes in histology, we primarily diagnosed LE related erythema exsudativum multiforme (Rowell's syndrome). But, after concise re-evaluation of the patient's symptoms and correlation with the published defining criteria of Zeitouni *et al* from 2000, we had to change diagnosis to an unusual form of LE with multiform like skin lesions due to missing antinuclear or rheumatoid factor, chilblains or other features of RS.⁵

INVESTIGATIONS

Two skin biopsies were performed, revealing a similar picture. H&E staining showed an orthokeratotic epidermis with a slight superficial and deep dermal perivascular and perifollicular lymphocytic infiltrate and follicular plugging, as well as slender dermal mucinosis and single intraepidermal apoptotic keratinocytes. Focal interface dermatitis could be observed (figure 2). Additional immunohistochemistry revealed clusters of CD123 positive plasmacytoid dendritic cells within the inflammatory infiltrate (figure 2).

TREATMENT

The patient could be successfully treated topically with potent steroids, but showed severe postinflammatory hyperpigmentation in the previously affected areas. Due to good response to ointment with glucocorticoids we resigned applying different systemic therapies (eg, cyclosporine A).

DISCUSSION

Over the years more than 40 cases of 'RS' have been published, most of which lacked the criteria original described by Rowell *et al* or precised by Zeitouni *et al*.^{2 5} In most of the cases, the coexistence of LE and EM is seen as a kind of overlap syndrome.^{4 6} Thus, the genuine character of the

Figure 1 Multiforme like skin lesions located at the trunk.

disease and existence of the RS as an entity must be critically discussed.

Up to now, a therapeutic standard for Rowell's patients does not exist. Nevertheless, therapeutic options are not well documented. Several therapeutic regimes are known, including corticosteroids, methotrexate, dapsone, hydroxychloroquine and azathioprin as single case reports. In the majority of cases, these drugs have been used due to the underlying LE.^{3 4 6 7} Most reports show a successful treatment of RS using systemic steroids and additional immunosuppressive drugs. Recently, in a distinct case of Rowell's syndrome in another male patient we observed fast resolution of lesions after administration of oral cyclosporine, while treatment with oral steroids alone always lead to relapse.⁸ To the best of our knowledge this was the first case published with successful treatment of RS with cyclosporine, as in the case described by Lee *et al* cyclosporine had to be discontinued due to its side effects.⁷ However, Lee *et al* could report of a successful treatment of RS with mycophenolat-mofetil.⁷ In 2008, Duarte *et al* used oral prednisolone over 1 month to resolve the RS lesions in a patient.¹ Further immunosuppression was not needed. In 2005, Aygödan *et al* reported two cases of RS successfully treated with hydroxychloroquine.⁹ Azathioprine as combinational therapy has also been used in the treatment of RS.¹⁰ Zeitouni *et al* presented the case of a 59-year-old woman with no improvement under the treatment with steroids and methotrexate. Therefore they started a therapy with dapsone and the lesions resolved within a few days.⁵

In subsequent publications, existence of RS as distinct entity has been very critically discussed.⁴ In 1989, Parodi *et al* concluded that most of the cases are coincidental appearances of EM in patients with a LE.¹¹ Roustan *et al* reported a case of a patient with known LE who developed an acute generalised eruption of EM in addition to a speckled pattern of antinuclear antibodies.¹⁰ This case was diagnosed as RS even though no minor criterion was fulfilled.

But, these authors discuss also the possibility of a coexistence of LE and EM that cannot be completely discarded, although no causative or classically associated factor for the erythema was found.¹⁰ In conclusion, Roustan *et al* interpreted this case as an example that the RS is a subcategory of subacute cutaneous LE.¹⁰ This thesis is supported by Aygödan *et al*.⁹ They reported two cases and a review of the published literature from 1963 to 2003. In this review, the authors ascertained that most patients diagnosed as RS were women. Furthermore, they found that the speckled pattern of antinuclear antibodies was the most constant factor in the reported patients.⁹ Aygödan *et al* also declared that anti-Ro/La-antibodies contribute to the formation of a speckled pattern of antinuclear antibodies, so it can be expected that there is a coexistence of these antibodies. Furthermore patients with chilblains often show a speckled pattern of antinuclear antibodies in blood sample, so it can be presumed that the formation of speckled pattern of antinuclear antibodies could be part of the immunological disturbance in these patients.⁹ Additionally, they stated that patients with chilblains have a positive rheumatoid factors in more than 50% of the cases. Aygödan *et al* came to the conclusion that a speckled pattern of antinuclear antibodies and a positive rheumatoid factor are both associated with perniones. Concerning the histological finding of necrotic keratinocytes the authors noticed that they are found in LE and in EM equally, so they cannot serve as discriminating feature on morphology.⁹ Due to these overlapping characteristics in clinical, laboratory and histological findings Aygödan *et al* propose that the RS is a subentity of subacute LE with EM.⁹

Shteyngarts *et al* stated that the RS is mostly not reproducible and that immunological disturbances may be coincidental.⁶ Thus, Modi *et al* supported this thesis by assuming that RS may be a sort of lupus masquerading as EM.⁴ Recently, this thesis was strengthened by the research of Vermi *et al*, who could show a pathogenetic role of plasmacytoid dendritic cells in LE via production

Figure 2 (Top) H&E stain revealing orthokeratotic epidermis with a slight superficial and deep dermal perivascular and perifollicular lymphocytic infiltrate. Focal alteration of the interface zone (left). Magnification x100. (Bottom) Clusters of CD123 positive plasmacytoid dendritic cells within the inflammatory infiltrate (right). Magnification x100.

of type I interferon.¹² Currently, Zelger *et al* reviewed all known common, rare or atypical manifestations of cutaneous LE and included RS as a very rare manifestation within the spectrum of LE with characteristic defining criteria proposed by Zeitouni *et al*.^{5 13}

These findings support the argumentation that RS indeed is rather a subtype of LE than a separate entity. Still of controversial discussion is the usefulness of lupus band test (LBT) in the diagnosis and in particular, in differential diagnoses of cutaneous LE and its clinical and histological mimickers. In the case presented herein, LBT failed to be positive. Hence, it is completely unclear, if this excludes an underlying LE or not. George R, *et al* determined in 1995 sensitivity, specificity and predictive value of the LBT in discoid and systemic LE (SLE) and found a high negative predictive value of LBT in SLE suggesting that it is valuable in excluding diseases clinically similar to SLE.^{14 15} Regrettably, interpretation of LBT requires detailed knowledge of the site of the biopsy, deposit components, morphology and brightness of the immunofluorescent band.¹⁵

As LBT is still a controversial diagnostic procedure that should be interpreted in conjunction with clinical findings and other serological and immunopathological parameters, the negative result in our case does not obviate that we are

dealing with a special type of LE with clinical appearance of EM. Creation of special entities must not depend on single diagnostic and laboratory procedures. Confirming diagnoses have to include all available clinical, histological and laboratory information of the patient.

But, why disapproving the existence of Rowells syndrome as a LE related erythema exsudativum multiforme? Instead of declining the whole syndrome we should start being correct and precise in clinical diagnosis. It would be of great benefit if all practising dermatologists use the existing clinical and laboratory criteria Zeitouni *et al* tried to accumulate with more homogeneous scientific information.⁵ Therefore, precise medical history and clinical examination of the patients is mandatory in order to rule out a herpes simplex virus or *Mycoplasma pneumonia* infection, lupus dermatitis or drug-related dermatoses.

In conclusion, comprehensive summary of all the earlier published cases as well as re-evaluation of our own case in this report and in the previous report from 2011, RS seems to be part of spectrum within the wide range of distinct manifestations of cutaneous LE. Consequently, these cases should be named RS only if all the defining criteria are fulfilled in order to collect information on the course and the prognosis as well as therapeutic options on a more rational basis in the future. In conclusion, we propose using the published criteria and name diseases accurately.

Learning points

- ▶ RS describes the combination of cutaneous LE and EM in one single individual.
- ▶ Major defining diagnostic criteria are: lupus dermatitis and EM like skin lesions as well as a speckled pattern of antinuclear antibodies.
- ▶ As minor criteria serve: chilblains, anti-Ro/La-antibodies and a positive rheumatoid factor.
- ▶ RS sensu strictu should fulfil at least all three major criteria and one minor criterion.
- ▶ Differential diagnoses are photosensitive eruptions of subacute cutaneous LE and classical bullous LE.
- ▶ Precise exploration of medical history and clinical examination of the patients is mandatory in order to make the diagnosis of Rowells syndrome and published criteria and name diseases accurately should be used accurately.

Competing interests None.

Patient consent Obtained.

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