Rowell Syndrome with Palmoplantar Involvement and Suspected Epitope Spreading

Alessandra Marini[1], Heike Draeger[1], Matthias Schneider[2], Andrea Niedermeier[3], Michael Hertl[3], Thomas Ruzicka[1] and Ulrich R. Hengge[1*]

Departments of [1]Dermatology and [2]Endocrinology, Diabetology and Rheumatology, Heinrich-Heine-University, Düsseldorf, and [3]Department of Dermatology, Philipps University, Marburg, Germany. [*]E-mail: ulrich.hengge@uni-duesseldorf.de

Accepted November 7, 2006.

Sir,

We describe here a 20-year-old woman with erythema multiforme-like lesions that were diagnosed as Rowell syndrome. We also discuss the overlap between bullous lupus erythematosus (BLE) and other auto-immune blistering diseases.

CASE REPORT

During her summer holidays a 20-year-old female patient developed severe erythema, itching and small blisters in the face, on the chest, palms and soles. The peri-oral region was spared (Fig. 1A). On examination, target-like lesions were noted on the neck, chest and, strikingly, the palms and soles (Fig. 1B). The Nikolski sign was negative. Some lesions also showed scaling. She had aphthous lesions in the mouth, up to 10 mm in size. Her medical history was remarkable for recurrent Herpes simplex virus (HSV) infections (genital and mouth), retinal vasculopathies and acral Raynaud's disease. At age 18 years, systemic lupus erythematosus (SLE) with lupus nephritis was diagnosed that was henceforth well controlled with azathioprine (100 mg/day). No other medication was taken.

Several histology specimens showed an interface dermatitis with lymphocytes and neutrophils, necrotic keratinocytes, small subepidermal blisters and cytoid bodies (Fig. 2). IgG and C3 were deposited in a lupus band-like pattern in perilesional skin, as evidenced by direct immunofluorescence (DIF) (data not shown). She had axillary lymphadenopathy. A chest X-ray, abdominal ultrasound and gynaecological examination were unremarkable. Haemoglobin 9.9 mg/dl, white blood cells (WBC) 3.75×10^6/µl, differential complete blood count revealed 93% neutrophils and 4% lymphocytes. Serum chemistry and C-reactive protein were unremarkable. Viral swabs were negative for HSV-, varicella zoster virus (VZV)-, human herpes virus (HHV)-6- and HHV-7-DNA. *Candida albicans* was detected on the cervix, throat and stool.

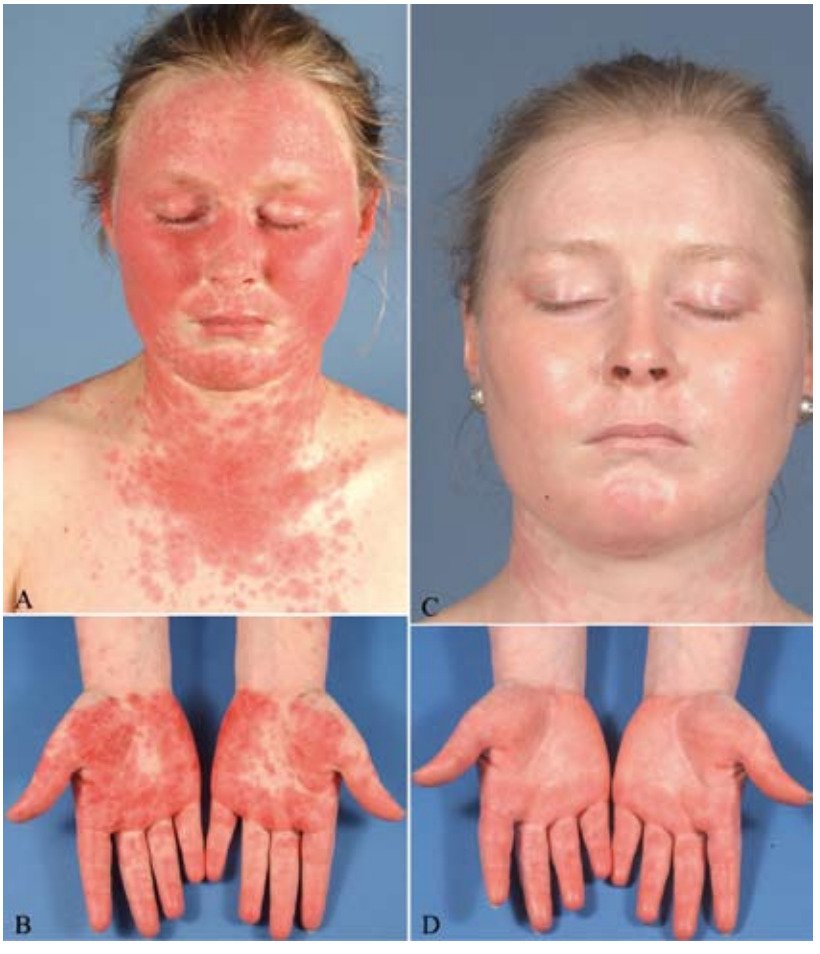

Fig. 1. Confluent facial erythema (A) with sparing of the perioral region showing small confluent vesicles on ultraviolet light exposed skin. (B) On the palms small vesicles, erosions and confluent erythema with target-lesion-like appearance on higher magnification. (C and D) Almost complete resolution after 3 weeks.

Given the patient's history, erythema multiforme in association with recurrent HSV infection was suspected with regard to the distribution pattern. Furthermore, phototoxic dermatitis, drug reaction (the patient took aspirin for menstrual pain) viral rash and BLE were also considered.

Antinuclear antibodies were positive (1:10.240) with a speckled pattern. Anti-DNA antibodies: 34 U/ml (positive). The serum contained antibodies against the extractable nuclear antigens RNP70, RNPc, SmB, SmD and Ro60. Serum was also tested for auto-antibodies against the dermo-epidermal junction by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). IIF with salt-split human skin showed IgG reactivity with the nuclei of epidermal cells and weak reactivity with the epidermal portion of split skin. By ELISA there was reactivity against several BP180 epitopes: the NH_2-terminal domain (aa490–812) and the COOH-terminal domain (aa1048–1465), and extracellular portion of the BP180 antigen (BPAG2, collagen XVII). Antibodies to collagen type VII were negative.

As the patient had no immediate history of HSV infection and HSV-DNA analysis was negative, treatment was performed with systemic corticosteroids (prednisolone 80 mg/day) and with oral amphotericin B as well as fluconazole (200 mg/day). Local treatment consisted of topical mometasone furoate cream and wet dressings (NaCl). The oral ulcers were treated with topical 0.1% triamcinolone ointment. Mometasone furoate under occlusion was applied

 ISSN 0001-5555
DOI: 10.2340/00015555-0242

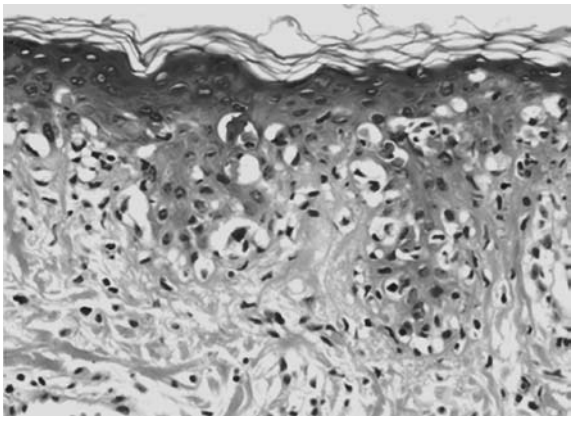

Fig. 2. Atrophic epidermis with confluent vacuolar degeneration of basal keratinocytes and dilated blood vessels. Numerous cytoid bodies and apoptotic keratinocytes are present in the epidermis.

to the palmar and plantar lesions. Within 3 weeks of treatment the lesions had almost cleared (Fig. 1C, D).

DISCUSSION

Bullous lesions are associated with lupus erythematosus (LE) in less than 5% of cases (1). The disease has been termed bullous lupus erythematosus by Sontheimer (2). Two types can be distinguished: (*i*) bullous lesions developing in LE-specific skin lesions, e.g. in subacute cutaneous LE (SCLE) as an extension of the vacuolar degeneration of basal keratinocytes; (*ii*) Vesiculobullous eruptions may also develop in areas not associated with LE skin lesions in patients with SLE (3, 4). IIF studies using salt-split skin demonstrated dermal binding and Western blot analysis revealed that these auto-antibodies bind to the non-collagenous portion of type-VII collagen (5, 6). In another study, it was concluded that patients with BLE may have auto-antibodies to multiple basement membrane components, such as the BP230 (BPAG1), laminin-5 and laminin-6 (7). Moreover, coexisting bullous pemphigoid and SLE have also been described (8).

According to Gammon & Briggaman (1) the criteria for BLE are: (*i*) satisfaction of the American College of Rheumatology criteria for SLE, (*ii*) an acquired, non-scarring bullous eruption arising on, but not limited to, sun-exposed skin, (*iii*) a subepidermal blister with a predominantly neutrophilic infiltrate in the basement membrane zone, (*iv*) IgG and C3 deposits in peri-lesional skin, (*v*) circulating antibodies to type-VII collagen, and (*vi*) immunoglobulin deposits co-distributed with anchoring fibrils and type-VII collagen (1). However, the definition of BLE was later broadened to include auto-antibody reactivity against various epidermal antigens described above (7, 9).

The phenomenon of SLE in association with auto-immune subepidermal blistering skin diseases can be explained by 2 possible mechanisms: (*i*) organ-specific auto-immune disease against the basement membrane zone that is provoked by systemic auto-immunity, a hallmark of SLE; (*ii*) "epitope-spreading" describing an immunological event, in which a primary auto-immune or inflammatory process causes tissue injury, releasing previously "sequestered" antigenic epitopes (10). The deposition of immunoglobulins may cause injury to adjacent components such as BP180 (11). Auto-antibody-mediated loss of hemidesmosomal adhesion may facilitate a secondary auto-immune reaction against the second auto-antigen, BP230. In the patient described here, bullous lesions were associated with IgG auto-antibodies against the 2 major antigenic epitopes of BP180. A recent study suggested that this pattern is associated with involvement of the mucous membranes (11). To our knowledge, this is one of the first cases of bullous SCLE with IgG reactivity against BP180. We consider this immunological finding as a secondary auto-immune response (epitope spreading).

Rowell syndrome has to be differentiated from photosensitive eruptions of SCLE and classical BLE. In the original publication by Rowell, 4 of 120 patients with discoid LE also had erythema multiforme-like lesions. All patients suffered from Raynaud's syndrome and presented with positive rheumatoid factors (12). They also presented a similar pattern of immunological abnormalities with antinuclear antibodies of the speckled type. However, none of the patients had involvement of the palms and soles. We would therefore like to add our case with target-like lesions and prominent involvement of the palms and soles to the features of Rowell syndrome (erythema multiforme-like LE).

REFERENCES

1. Gammon WR, Briggaman RA. Epidermolysis bullosa acquisita and bullous systemic lupus erythematosus. Diseases of autoimmunity to type VII collagen. Dermatol Clin 1993; 11: 535–547.
2. Sontheimer RD. The lexicon of cutaneous lupus erythematosus – a review and personal perspective on the nomenclature and classification of the cutaneous manifestations of lupus erythematosus. Lupus 1997; 6: 84–95.
3. Hall RP, Lawley TJ, Smith HR, Katz SI. Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. Ann Intern Med 1982; 97: 165–170.
4. Gammon WR, Woodley DT, Dole KC, Briggaman RA. Evidence that anti-basement membrane zone antibodies in bullous eruption of systemic lupus erythematosus recognize epidermolysis bullosa acquisita autoantigen. J Invest Dermatol 1985; 84: 472–476.
5. Shirahama S, Furukawa F, Yagi H, Tanaka T, Hashimoto T, Takigawa M. Bullous systemic lupus erythematosus: detection of antibodies against noncollagenous domain of type VII collagen. J Am Acad Dermatol 1998; 38: 844–848.
6. Barton DD, Fine JD, Gammon WR, Sams WM Jr. Bullous systemic lupus erythematosus: an unusual clinical course and detectable circulating autoantibodies to the epidermolysis bullosa acquisita antigen. J Am Acad Dermatol 1986; 15: 369–373.
7. Chan LS, Lapiere JC, Chen M, Traczyk T, Mancini AJ,

Paller AS, et al. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. Arch Dermatol 1999; 135: 569–573.
8. Miller JF, Downham TF 2nd, Chapel TA. Coexistent bullous pemphigoid and systemic lupus erythematosus. Cutis 1978; 21: 368–373.
9. Yell JA, Allen J, Wojnarowska F, Kirtschig G, Burge SM. Bullous systemic lupus erythematosus: revised criteria for diagnosis. Br J Dermatol 1995; 132: 921–928.
10. Vanderlugt CJ, Miller SD. Epitope spreading. Curr Opin Immunol 1996; 8: 831–836.
11. Giudice GJ, Emery DJ, Diaz LA. Cloning and primary structural analysis of the bullous pemphigoid autoantigen BP180. J Invest Dermatol 1992; 99: 243–250.
12. Rowell NR, Beck JS, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. A syndrome with characteristic immunological abnormalities. Arch Dermatol 1963; 88: 176–180.