**Case Report/Case Series**

**Detection of Type VII Collagen Autoantibodies Before the Onset of Bullous Systemic Lupus Erythematosus**

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_Bullous systemic lupus erythematosus (BSLE) is a rare vesiculobullous eruption favoring photoexposed areas and mucous membranes. Vesicles and bullae of varying sizes can appear with crusting and resolve as hyperpigmented patches. The absence of milia and scarring, as well as the prominence in trauma-prone areas, distinguishes this entity from epidermolysis bullosa acquisita (EBA). The histology of BSLE primarily shows subepidermal blisters and neutrophilic upper dermal infiltrates; direct immunofluorescence and immunoblot studies confirmed the diagnosis of BSLE. Immunoblotting and enzyme-linked immunosorbent assay studies of the patient’s serum obtained 3 months before the onset of BSLE showed the presence of anti–type VII collagen autoantibodies. Levels of anti–type VII collagen IgG increased after bullous lesions appeared. Within 1 month after initiating dapsone therapy and increasing the dosage of prednisone, skin lesions promptly resolved. One year after the onset of BSLE, the anti–type VII collagen IgG decreased below levels observed before the inception of the bullous lesions._

**Report of a Case**

_A 50-year-old African American woman with type II diabetes mellitus and a 6-month history of SLE was seen at the University of Texas Southwestern dermatology outpatient clinic. She manifested positive American College of Rheumatology SLE criteria, including arthritis, oral ulcers, photosensitivity, discoid lupus erythematosus, positive antinuclear antibody test results, and immunologic disorder (positive anti-Smith antibodies). She had a 3-week history of a pruritic, vesiculobullous eruption covering her perioral area, trunk, axillae, arms, and inner thighs._

At the onset of the eruption, the patient was taking prednisone (7.5 mg daily), which had been tapered from 15 mg daily 1 month previously. She had also been taking chloroquine phosphate (250 mg daily on weekdays and 125 mg daily on weekends) and mycophenolate mofetil (500 mg twice daily) for the past 3 months. In response to the rash and presumed lupus flare due to her arthritis, the elevated double-stranded DNA titers, and her low complement levels, her rheumatologist had increased the prednisone dosage below those documented before the onset of the immunobullous disease._
age to 30 mg daily. The patient also had discontinued the mycophenolate mofetil and chloroquine herself because she was concerned about drug reactions.

On physical examination, multiple tense vesicles and bullae with hemorrhagic crusting and annular erythematous plaques were observed on her back, chest, abdomen, eyebrows, forearms, upper arms, inner thighs, axillae (Figure 1A), and perioral area (Figure 1B). The patient had diffuse scarring alopecia on her scalp, with hypopigmented patches and underlying erythema on the crown, consistent with discoid lupus erythematosus.

A biopsy specimen from the edge of a bulla on the right upper arm showed a subepidermal vesiculobullous dermatosis with neutrophils, occasional lymphocytes, and red blood cells within the blister cavity and a sparse perivascular infiltrate with lymphocytes and neutrophils (Figure 2A). Direct immunofluorescence showed a linear pattern (Figure 2B) of C3, IgA, and IgG along the basement membrane zone. Indirect immunofluorescence studies of the patient's serum on salt-split skin (which is normal skin treated with 1 M sodium chloride that splits the epidermis and dermis at the basement membrane level) showed positive IgG binding to the dermal side at a titer of 1:10 (Figure 2C).

Immunoblot studies of a recombinant of the noncollagenous (NC1) domain of type VII collagen confirmed that the patient had IgG autoantibodies directed against this signature antigen (Figure 3A). After the diagnosis of BSLE was made, the patient was treated with dapsone (50 mg twice daily) and commenced a tapering dose of prednisone, starting at 40 mg daily. One month later, the patient had experienced a significant decrease in vesicles. After 3 months of skin inactivity, the patient’s prednisone was discontinued, and dapsone was discontinued 4 months later. Twelve months after the eruption, the patient had hyperpigmented macules and patches in her perioral area, axillae, trunk, and arms, with no bullae or vesicles.

Three months before her BSLE onset, a serum sample had been collected from the patient, who had been receiving a stable dosage of prednisone (15 mg daily) for 2 months because she had enrolled in the University of Texas Southwestern Cutaneous Lupus Registry, which is a longitudinal observational study of the disease course of patients with cutaneous lupus. Twelve months after her BSLE appeared, another serum sample was drawn from the patient, who had been taking chloroquine phosphate (250 mg daily) for 4 months. Immunofluorescence studies of the serum sample drawn before BSLE onset on salt-split skin showed IgG bound to the dermal side at a titer of 1:5 (Figure 3B). Immunoblot studies of the NC1 type VII collagen recombinant again demonstrated IgG autoantibodies against this particular antigen in the serum samples drawn 3 months before and 3 weeks after the eruption had started (Figure 3A). During the course of the patient's immunobullous lesions, quantitation of IgG anti–type VII collagen autoantibodies by enzyme-linked immunosorbent assay (MBL International) revealed sequential values of 9.23 U/mL (3 months before disease onset), 71.74 U/mL (3 weeks after disease onset), and 2.30 U/mL (12 months after disease onset).

Discussion

This case report describes novel findings in a patient with BSLE with anti–type VII collagen autoantibodies in her serum 3 months before the onset of the disease. In these autoantibodies, we found a specific antigen in the lamina densa and the sublamina densa fibrillar area of the dermal-epidermal junction, type VII collagen is composed of 3 α chains containing a central collagenous triple helix and domains in the amino-terminal (NC1) and carboxy-
terminal (NC2) ends. The immunodominant domains of type VII collagen recognized by IgG autoantibodies from patients with BSLE (and EBA) reside in the NC1 domain. Passive transfer of purified rabbit anti-type VII collagen IgG in adult nude, Balb/c,
dromewithpositiveRoautoantibodieshavebeenobservedto
Moreover, 58% of patients with SLE showed escalating double-
stranded DNA antibodies, were present in their bloody ears be-
Bodies, such as antinuclear antibodies and anti–double-
chambers may be responsible for the appearance of patho-
getic autoantibodies, resulting in epidermal-dermal separa-
A case for the pathogenic potential of autoantibodies in lupus
levels may be an important event in the evolution of BSLE.
The disease wanes as these autoantibodies level off or decline.13 Moreover, patients with Sjögren's syndrome with positive Ro autoantibodies have been observed to later develop subacute cutaneous lupus.14

Using the serum sample repository from the University of Texas Southwestern Cutaneous Lupus Registry, we also measured anti-type VII collagen IgG by enzyme-linked immunosorbent assay in age and sex-matched patients with SLE (n = 13), patients with discoid lupus erythematosus (n = 13), and healthy control subjects (n = 14). All these serum samples had levels of anti-type VII collagen IgG below the established positive threshold. The same samples were lower than those observed in our patient’s serum before and during the BSLE eruption and in the serum samples from 2 patients with EBA serving as positive controls (Table). We were able to confirm findings from a previous study10 that the serum of patients with SLE without BSLE does not contain significant levels of anti-type VII collagen autoantibodies.

Twelve months after the initial eruption, our patient’s serum showed markedly decreased levels of anti-type VII collagen IgG. At that time, the patient’s BSLE was quiescent. A similar finding was previously reported in a patient with Sjögren's syndrome and SLE overlap with BSLE, whose anti-type VII collagen IgG was undetectable at the time of BSLE remission.16 The rise and fall in levels of anti-type VII collagen autoantibodies during the course of a patient’s BSLE disease imply that they have possible usefulness as biomarkers, which can be used to assess disease activity and guide treatment.

Limitations of this study include the small sample size (with the findings observed in 1 patient) and the limited follow-up period of 1 year. In addition, the use of concurrent immunosuppressant medications may alter autoantibody levels. However, the patient herein was receiving stable dosages of her immunosuppressants before and after her BSLE eruption.

Conclusions
In summary, anti-type VII collagen autoantibodies were detected 3 months before the inception of BSLE in a patient with SLE. Their levels subsequently increased after disease onset and decreased with disease resolution. We hypothesize that surpassing a critical level of anti-type VII collagen autoantibodies may be an important event in the evolution of BSLE. An alternative explanation would be that the patient had nonpathogenic autoantibodies before her BSLE. Epitope spreading may be responsible for the appearance of pathogenic autoantibodies, resulting in epidermal-dermal separation and eventual onset of her BSLE.2,17 Larger prospective studies in patients with BSLE measuring levels of anti-type VII collagen autoantibodies throughout their disease course for an extended time frame would be helpful in determining whether these autoantibodies could be reliable disease markers.

Table. Anti-Type VII Collagen IgG Levels in the Serum Samples of the Case Patient 3 Months Before, 3 Weeks After, and 12 Months After Disease Onset and in Other Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Sample</th>
<th>Anti-Type VII Collagen IgG Level, U/mL</th>
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<tbody>
<tr>
<td>Case patient with bullous systemic lupus erythematosus</td>
<td></td>
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<tr>
<td>3 mo Before disease onset</td>
<td>9.23</td>
</tr>
<tr>
<td>3 wk After disease onset</td>
<td>71.74</td>
</tr>
<tr>
<td>12 mo After disease onset</td>
<td>2.30</td>
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<tr>
<td>Other patients, mean (SD)</td>
<td></td>
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<tr>
<td>Patients with epidermolysis bullosa acquisita (n = 2)</td>
<td>141.46 (67.01)</td>
</tr>
<tr>
<td>Healthy control subjects (n = 14)*</td>
<td>0.11 (0.40)</td>
</tr>
<tr>
<td>Patients with discoid lupus erythematosus (n = 13)*</td>
<td>0.36 (0.93)</td>
</tr>
<tr>
<td>Patients with systemic lupus erythematosus (n = 13)*</td>
<td>0.23 (0.37)</td>
</tr>
</tbody>
</table>

* Serum samples were obtained from the University of Texas Southwestern Cutaneous Lupus Registry and showed significantly lower anti-type VII collagen IgG levels compared with patients with epidermolysis bullosa acquisita (P < .01). None of the samples were positive for anti-type VII collagen IgG.

and C57BL/6 mice resulted in the formation of skin blisters and erosions.9 Similarly, purified anti-type VII collagen antibodies from the serum of patients with EBA injected in hairless mice showed that these antibodies can induce EBA-like skin lesions.10 Based on our observations that anti-type VII collagen autoantibodies had been present in our patient before and had increased after her bullous lesions appeared, we hypothesize that there is a critical threshold of these antibodies in circulation that is surpassed before the skin eruption occurs in BSLE.

The presence and accumulation of circulating autoantibodies have been previously observed in patients with lupus. A large prospective study5 of 130 military recruits who were followed up before their SLE diagnosis showed that multiple autoantibodies, such as antinuclear antibodies and anti-double-stranded DNA antibodies, were present in their blood years before their diagnosis and the onset of systemic symptoms. Moreover, 58% of patients with SLE showed escalating double-stranded DNA antibody levels leading up to their SLE diagnosis.11 A case for the pathogenic potential of autoantibodies in lupus can be made with neonatal lupus, in which transplacental transfer of Ro, La, and ribonucleoprotein autoantibodies occurs from mother to fetus.12 The disease wanes as these autoantibodies level off or decline.13 Moreover, patients with Sjögren's syndrome with positive Ro autoantibodies have been observed to later develop subacute cutaneous lupus.14
When devising morphological descriptions, it would seem that dermatologists in years gone by had their heads in the clouds, with several descriptions alluding to phenomena related to the weather.

During the Buergger test, the reactive hyperemia observed in patients with peripheral vascular disease is often described as a “sunset red.” The vesicles of cutaneous anthrax are often described as “cloudy,” as is the saliva of patients with Sjögren disease. Miliaria crystallina have been likened to dew drops, and the classical description of varicella zoster is that of “dew drops on rose petals.” The distribution and morphologic characteristics of guttate psoriasis have been likened to raindrops, and the dyschromia of chronic arsenic toxicity has been more vividly compared to “rain drops on a dusty road.” Dermoscopic examination of Kaposi sarcoma may sometimes reveal a multicolored rainbow, livido racemosa has been compared to bolts of lightning, and perhaps one of the most fascinating clinical signs in dermatology is the Lichtenberg figures that appear on patients who have been struck by lightning.

Winter brings with it a range of descriptions such as the “footprints in the snow” of pseudopelade. Snowflake opacities are seen in the cornea of patients with onychocchoria, and frosting is a clinical end point often sought in chemical peels.

In dermatology, an erosion refers to a loss of epidermis, although erosion also refers to weathering of soil, rocks, and other geologic structure by the action of nature.

The night sky has further inspired a range of descriptions. The lunula derives its name from its crescent shape, which resembles that of a half-moon. Several lesions are described as having stellate morphologic characteristics, including keratosis lichenoides chronica, atrophie blanche, calciphylaxis, and the central white patches of dermatofibromas. The starburst pattern is observed in Spitz nevi, and the red comet sign is observed in the nail beds of patients with tuberous sclerosis. Histopathologically, precursor B lymphoblastic lymphoma is said to resemble a starry sky, and patients with argyria are reported to have silver deposits forming a “stars in heaven” pattern under dark-field examination.

The celestial realm has informed countless descriptions in dermatology. While the connections at times may seem tenuous, the silver lining is that they aid recall and brighten one’s day.

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