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Fatal Vascular Involvement in Systemic Lupus Erythematosus Following Epidermolysis Bullosa Acquisita

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Epidermolysis bullosa acquisita may be associated with various systemic diseases, including systemic lupus erythematosus. We describe the clinical and immunological findings in a 38-year-old woman with epidermolysis bullosa acquisita and systemic lupus erythematosus. The epidermolysis bullosa acquisita preceded a dramatic flare of systemic lupus erythematosus and fatal cerebral vasculitis. If serologic evidence of lupus erythematosus develops during the course of epidermolysis bullosa acquisita, a thorough investigation is warranted to rule out potentially life-threatening systemic lupus erythematosus. ***Key words: bullous SLE; autoantibodies against type VII collagen.***

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Epidermolysis bullosa acquisita (EBA) is a chronic, subepidermal blistering disease, characterized by the presence of autoantibodies against type VII collagen within anchoring fibrils that are located at the dermo-epidermal junction (1, 2). A number of published reports suggest that EBA may be associated with various systemic diseases such as inflammatory bowel disease, systemic lupus erythematosus (SLE), amyloidosis, thyroiditis, multiple endocrinopathy syndrome, rheumatoid arthritis, pulmonary fibrosis and diabetes (3–7). It seems that some of these associations may be chance occurrences only. However, some of the diseases may have the same autoimmune etiology. The coexistence of EBA and SLE has been reported on several occasions (7–10), but this dual diagnosis has been challenged by others (11–13). We describe a patient with EBA who developed SLE subsequently, resulting in death due to fatal cerebral vasculitis in spite of vigorous treatment. Death due to fatal vascular involvement in a syndrome consisting of SLE after EBA has not been reported as of yet.

CASE REPORT

A 38-year-old woman was admitted with a 2-month history of a mildly pruritic blistering eruption. The lesions had developed initially on her face and later spread to involve the neck, axillae, groin, mucous membranes, and, to a lesser extent, the extremities. She had previously been in relatively good health except for an episode of dog biting. There was no family history of bullous or connective tissue diseases.

Physical examination revealed widespread, non-grouped, tense bullae on both erythematous and non-erythematous bases scattered over her trunk and extremities (Fig. 1). Scarring and milia were present and Nikolsky's sign was absent. Several erosions were present on the oral buccal mucosa, lips, tongue, and labia majora and minora. There were severe conjuctival injections on both her eyes. The remainder of the physical examination was within normal limits. Laboratory values on admission disclosed the following results or values: hemoglobin, 10.5 mg/dl; hematocrit, 31.6%; WBC count, 17.3×10^9/l with lymphopenia (4.4%); erythrocyte sedimentation rate, 36 mm/h; urinalysis, normal; VDRL, non-reactive; automated serum chemistry test, normal; ANA titer, 1:640, with a speckled pattern; negative anti-Ro, La, Sm, RNP, and native DNA antibodies; serum complement (C3, C4), normal; CH_{50} assay, normal. HLA class II typing revealed phenotypes DR4 and DR11. A biopsy specimen of an early lesion showed a subepidermal bulla containing neutrophils, eosinophils and lymphocytes (Fig. 2). Direct immunofluorescence showed a strong linear-granular deposition of IgG at the dermo-epidermal junction and weaker deposition of IgM and IgA (Fig. 3). Indirect immunofluorescence using a salt-split normal human skin substrate revealed a linear IgG, which stained the dermal side of the lamina lucida cleavage plane (Fig. 4). Western immunoblot studies using human dermal extracts revealed that the patient's serum antibodies bound to the 290-kD dermal proteins, which represent the EBA antigens (Fig. 5). On the basis of these observations, a diagnosis of EBA was made. Because the patient responded only partially to prednisone therapy, dapsone therapy was started (50 mg twice daily) and the skin lesions began to subside. She was discharged from the hospital and continued to show improvement as an outpatient, except for her oral

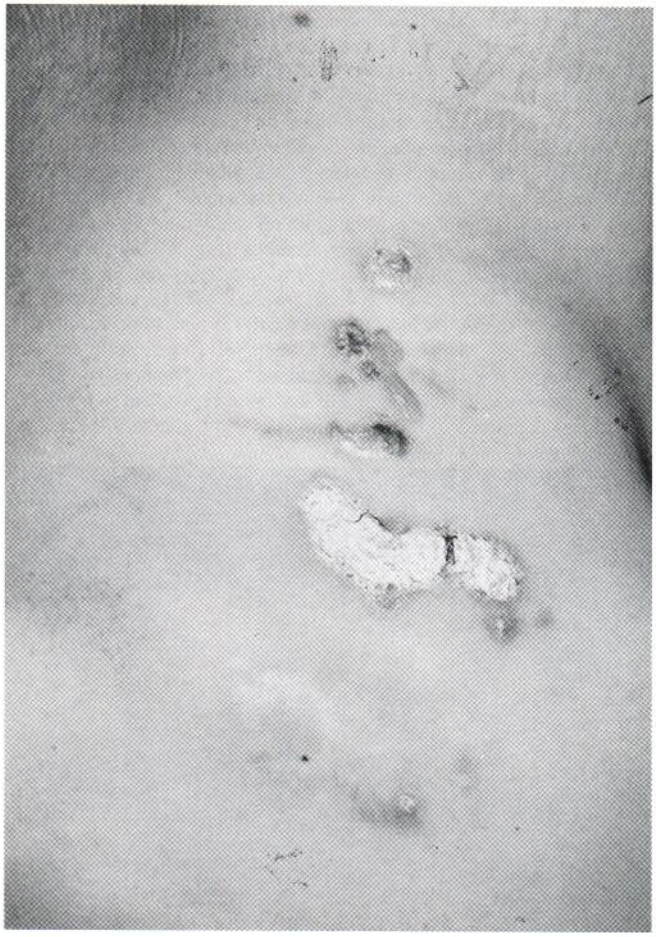

Fig. 1. Bullae, erosions and atrophic scarring are present on the trunk of the patient.

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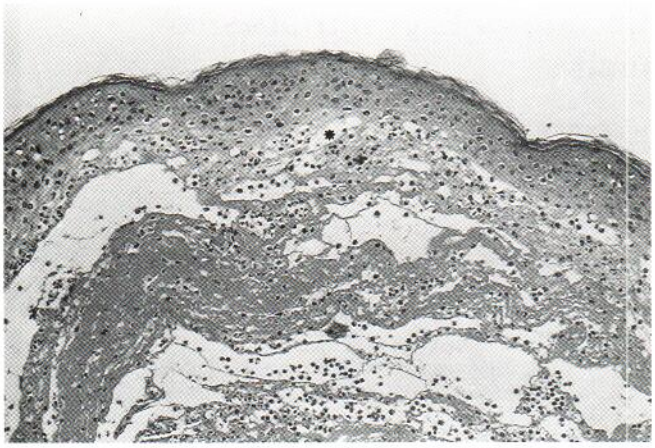

Fig. 2. Biopsy taken from a blister showing a subepidermal blister (*asterisk*) containing many neutrophils and a dense upper dermal infiltrate of neutrophils and eosinophils (hematoxylin-eosin stain, ×40).

ulcerations. Dapsone therapy was discontinued because of gastrointestinal intolerance, and prednisone therapy (40 mg/day) was recommended.

One month after her discharge, there was widespread recurrence of her cutaneous bullous eruption. At this time the patient noted malaise, arthralgia, generalized swelling and fever. She was readmitted and pertinent laboratory findings at this time included the presence of ANA (titer 1:160 on HEp-2 cell substrate, and speckled pattern); hemoglobin, 8.8 mg/dl; hematocrit, 29.2%; WBC count 7.7×10^9/l with lymphopenia (6.4%); erythrocyte sedimentation rate, 62 mm/h; urinalysis, normal; serum iron and total iron binding capacity, normal; anti-platelet antibody, negative; direct and indirect Coombs' tests, negative. Despite treatment with prednisone, 40 mg twice daily, and azathioprine, 50 mg twice daily, the patient's clinical status continued to deteriorate, and evidence of neurological abnormalities, including seizure, dizziness, difficulty in thinking, loss of memory, paraesthesiae and jerkiness of the left side of the body, rapidly developed. A computed tomography scan of the brain revealed mild brain swelling and right cortical infarction. Magnetic resonance imaging of the brain revealed multiple small cortical infarcts secondary to systemic vasculitis (Fig. 6). She was considered at that time to fulfill at least four of the American Rheumatism Association (ARA) (Atlanta) criteria for SLE. These were the following: (1) positive ANA titer, (2) oral ulcer, (3) lymphopenia, and (4) CNS abnormalities. With evidence of CNS involvement, treatment was instituted with 1.0 g of methyl prednisolone by infusion daily. Despite the pulse therapy of prednisone, there was no improvement in her SLE, and blisters continued to develop at sites of mild trauma. Progressive

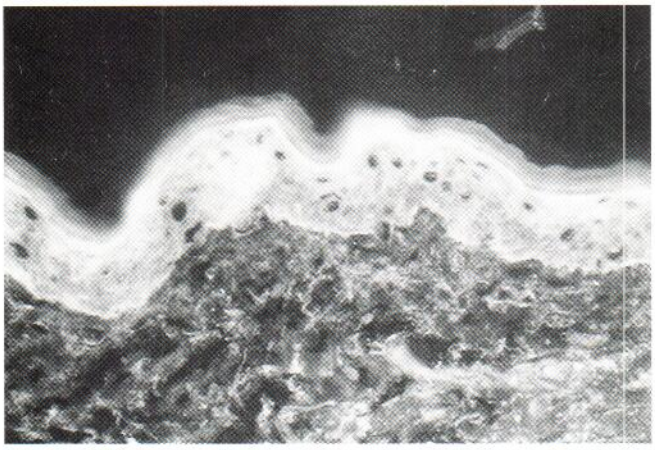

Fig. 3. Direct immunofluorescence showing linear-granular patterns of IgG deposits at the BMZ. Staining for IgM and IgA showed similar patterns; magnification ×240.

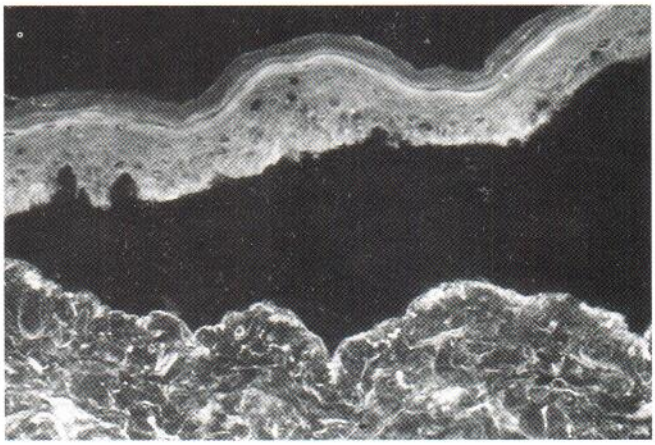

Fig. 4. Indirect IgG immunofluorescent microscopy on 1.0 M NaCl-split human skin using a 1:10 dilution of serum. The photomicrograph shows a linear band of IgG on the dermal side of the split (lower portion of the photograph). There are also deposits on the nuclei of keratinocytes (upper portion of the photograph), consistent with antinuclear antibodies; magnification ×240.

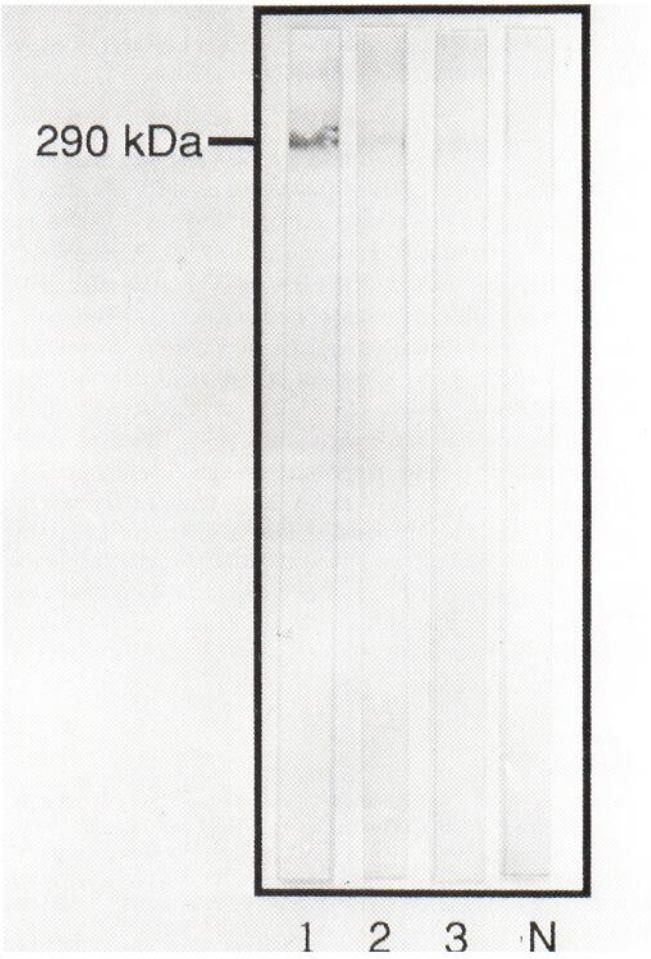

Fig. 5. Western immunoblot illustrating that the patient's circulating autoantibodies, which stain the dermal side of 1 M NaCl-split skin, react to a 290-kD antigen in a dermal extract of normal human skin. *Lane 1*: monoclonal antibodies to NC-1 domain of type VII collagen (Telios, San Diego, CA); *lane 2*: EBA serum containing high titer of antibodies to type VII collagen as a positive control; *lane 3*: patient's serum reacting with a 290-kD dermal polypeptide; *lane N*: normal human serum as a negative control.

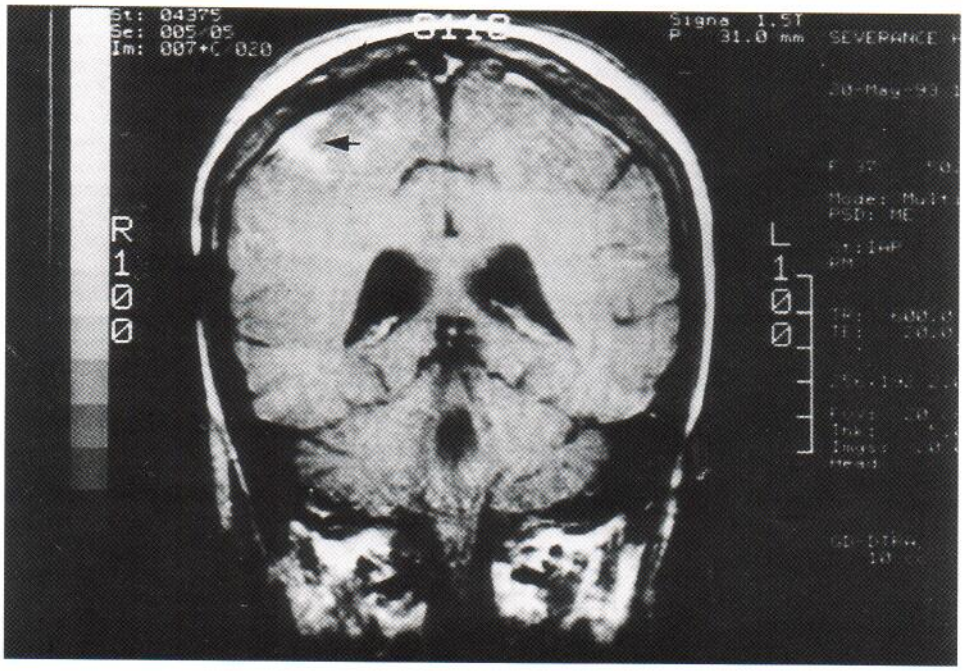

Fig. 6. Magnetic resonance imaging of the brain showing a large right-sided parieto-central infarction (*arrow*).

disseminated intravascular coagulation developed and she died 1 month later.

DISCUSSION

The relationship between bullous SLE and EBA is an interesting question that has not been satisfactorily resolved. The question as to whether the coexistence of SLE and EBA is really an expression of bullous SLE is subject to debate. Clearly, they are closely related disorders, since both are characterized histologically by inflammatory subepidermal blisters and immunologically by circulating and tissue-bound autoantibodies to type VII collagen (1, 2, 12, 13). They also appear to have similar genetic features (14). In contrast to EBA, however, bullous SLE occurs in young women, does not usually cause scarring, and is likely to have a response to treatment with dapsone (12, 13, 15, 16). Furthermore, the histology of blisters in bullous SLE more closely resembles dermatitis herpetiformis than EBA, although EBA patients with clinical and histologic features more closely resembling bullous eruption of SLE have recently been described (17–19). Initially, the diagnosis of EBA rather than bullous SLE would have best fitted our patient, because, at that time, she did not fulfill the ARA criteria for SLE, and atrophic scarring and milia were present on her healed lesions. However, the presence of antinuclear antibodies and partial response to dapsone therapy in our patient suggested the diagnosis of bullous SLE; it might be that our patient had a bullous SLE from the onset.

Because of the lack of specific autoantibodies such as anti-native DNA or anti-Sm antibodies for LE, the diagnosis of SLE was difficult in this patient. However, the neurological symptoms and positive ANA favored a diagnosis of SLE (20). Apart from SLE, vasculitis of large arteries due to giant cell and Takayasu's arteritis are other diagnostic possibilities. However, the patient's age and the positive ANA argue against the diagnosis of large-vessel vasculitis. Furthermore, CNS disorders are uncommon in rheumatic diseases except for SLE (21). The clinical manifestations of arthralgias and oral ulcers also supported this diagnosis.

A review of the literature disclosed a number of cases of reported coexistent SLE and EBA, prior to the case presented here (16, 22). In most of these cases, the diagnosis of SLE is made before the development of blistering. Therefore, these lesions have been variously reported as bullous SLE, vesiculobullous SLE, or SLE with herpetiform blisters. Only five case reports in which the blistering eruption clearly preceded the diagnosis of SLE have been previously published (8–10). In the case presented here, EBA lesions occurred 4 months before the diagnosis of SLE.

The course of the bullous eruption in patients with SLE is generally favorable and usually lasts from several weeks to several months, although it may persist for a year or more. On the other hand, the prognosis of SLE tends not to be so favorable (8, 15, 23), and this phenomenon was demonstrated in our patient, whose ultimate outcome was fatal. If serologic evidence of lupus-associated autoantibodies such as ANA develops during the course of EBA, a thorough investigation is warranted to rule out potentially life-threatening SLE.

With the establishment of a diagnosis of EBA with SLE in this patient, a fundamental question must be answered: does EBA merely represent an early expression of various cutaneous findings of SLE, in other words, is bullous LE the coexistence of EBA and SLE, or does it indicate a common trigger mechanism for two different autoimmune diseases with similar pathogenesis? Further investigations will be needed to clarify these interesting conceptual and nosological issues.

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