

# Sustained clinical response to rituximab in a case of life-threatening overlap subepidermal autoimmune blistering disease

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The conventional treatment for the autoimmune bullous skin diseases is broad-spectrum immunosuppressive regimen typically combining systemic corticosteroids with adjuvant immunosuppressive therapeutic agents. Orphan diseases in the pemphigus, pemphigoid, and epidermolysis bullosa acquisita groups of clinical disorders are often clinically severe, requiring long-term treatment with such drugs or drug combinations. Rituximab, a chimeric recombinant monoclonal antibody targeting CD20(+) B cells, has recently been suggested to be effective in the treatment of pemphigus with relatively few adverse effects. The clinical value of rituximab in other immune-mediated blistering diseases has been less thoroughly examined. We report a case of a woman who presented initially with the Brunsting-Perry phenotype of cicatricial pemphigoid who subsequently developed severe generalized subepidermal blisters healing with scarring and milia formation thought to be clinically compatible with epidermolysis bullosa acquisita, although type VII collagen autoantibodies were never identified. Treatment with a number of conventional systemic agents was unsuccessful and complicated by methicillin-resistant *Staphylococcus aureus*-induced cutaneous ulcers and near-fatal gram-negative sepsis. This woman has enjoyed an 18-month complete clinical remission after a single inductive 4-week cycle of intravenous rituximab. This outcome supports the idea that systemic memory B-cell depletion with drugs such as rituximab should be considered for therapeutically refractory subepidermal autoimmune blistering diseases in addition to intraepidermal autoimmune blistering diseases. A potential role for the immunologic phenomenon of epitope spreading in the generation of overlapping features of autoimmune blistering diseases, and its contribution to therapeutic refractoriness ("hardening"), is discussed. (J Am Acad Dermatol 2011;64:773-8.)

**Key words:** autoimmune blistering disease; bullous pemphigoid; epidermolysis bullosa acquisita; rituximab.

**R**ituximab is a chimeric recombinant monoclonal antibody that can temporarily deplete circulating CD20(+) B cells in human beings. Originally approved for the treatment of B-cell

#### Abbreviations used:

BP: bullous pemphigoid  
CP: cicatricial pemphigoid  
EBA: epidermolysis bullosa acquisita  
IVIG: intravenous immunoglobulin  
PV: pemphigus vulgaris

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Dr Sontheimer's contributions to the preparation of this work were supported by The Richard and Adeline Fleischaker Chair in Dermatology Research at the University of Oklahoma Health Sciences Center.

Conflicts of interest: None declared.

Presented at the Oklahoma State Dermatologic Society Annual Meeting, Oklahoma City, OK, April 18, 2008.

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Published online May 24, 2010.

0190-9622/\$36.00

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doi:10.1016/j.jaad.2009.09.045

lymphomas, it was serendipitously observed that the skin lesions of paraneoplastic pemphigus resolved in several patients undergoing rituximab therapy for B-cell lymphoma.<sup>1</sup> This led to small open studies of rituximab in autoantibody-mediated blistering skin disorders such as pemphigus vulgaris (PV). Rituximab therapy, initially given with high doses of human intravenous immunoglobulin (IVIG) and more recently as a stand-alone agent, has now been anecdotally reported to be successful in controlling disease activity in a number of patients with PV, often within 6 weeks of treatment initiation.<sup>2-4</sup> We now report a complete sustained clinical

response to a single inductive cycle of intravenous rituximab in a woman with a near-fatal chronic subepidermal autoimmune bullous disease of mixed phenotype that had been resistant to multiple conventional immunosuppressive regimens. The hypothesis has been raised by others that early intervention with B-cell targeting drug such as rituximab could reduce morbidity and mortality from both intraepidermal and subepidermal autoimmune blistering skin.<sup>3</sup>

### CASE REPORT

A 56-year-old woman was referred to our department initially in February 2007 for a 2-year history of severe, therapeutically refractory cicatricial pemphigoid (CP). Before the onset of scalp blistering she had been healthy with the exception of long-standing insulin-dependent diabetes mellitus and a vision disturbance thought possibly related to Vogt-Koyanagi-Harada disease.

In October 2005, a private dermatologist first saw the patient and started treatment with clobetasol foam and tacrolimus 0.1% ointment with minimal benefit. Because of worsening scalp involvement and the spread of blisters to her upper extremities he obtained a skin biopsy specimen for hematoxylin-eosin and direct immunofluorescence examination.

The hematoxylin-eosin examination as read by an outside dermatopathologist showed a fibrosing dermatitis with eosinophils. The direct immunofluorescence examination was reported as demonstrating a linear band of IgG along the basement membrane zone focally extending along adnexal structures. The report noted that in areas of epidermal-dermal separation the IgG band appeared to be adhering mostly to the dermal side of the blister. IgM and C3 bands of similar morphology but weaker intensity at the dermoepidermal junction were also observed. IgA was not present. These findings were interpreted as being characteristic of the pemphigoid group of immunobullous disease and consistent with CP. A comment was made that these findings were suggestive of autoantibodies directed against epiligrin. Further subtyping of the antigenic specificity of this subepidermal blistering disorder was not performed at that time.

After the diagnosis of possible anti-epiligrin CP the patient received a negative evaluation for internal malignancy. A trial of cyclosporine and mycophenolate failed to help the disease and prednisone at 60 mg/d was then started with the advent of mucosal ulcerations; these cleared but the patient experienced generalized flares with taper. When the addition of mycophenolate mofetil up to a dose of 2000 mg/d failed to give the patient relief, a trial of

etanercept was started. Etanercept was stopped soon after when the patient was hospitalized for rhabdomyolysis, a complication from her cholesterol medications. The patient was again placed on high-dose prednisone on which she remained until presentation to our clinic. The etanercept was never restarted.

Approximately 2.5 years after onset of her scalp blistering skin disease the patient was referred to our academic center. At that time she was grossly cushingoid, having gained 40 lb since starting corticosteroid therapy. She displayed marked scarring alopecia most prominent on the parietal area of her scalp (Fig 1, A). In addition, she exhibited a generalized distribution (trunk and all 4 extremities) of large tense blisters intermixed with crusted erosions (Fig 1, B and C).

Initially, attempts were made to maximize the mycophenolate mofetil by increasing her dose to 3000 mg/d. Upon seeing no improvement with this approach, a request was made to the patient's insurance carrier for approval of a trial of intravenous rituximab, which was denied. The patient was then placed on high-dose IVIG for 3 months without clinical improvement. Her course was complicated by cutaneous methicillin-resistant *Staphylococcus aureus* infection causing abdominal skin ulceration (Fig 1, D) that slowly responded to oral sulfamethoxazole-trimethoprim therapy.

Because of the recalcitrant nature of her bullous skin disease, an attempt was made to further subtype her blistering disorder as anti-epiligrin CP or the inflammatory subtype of epidermolysis bullosa acquisita (EBA). Patient serum was sent to Dr Kim Yancey's reference laboratory at the University of Texas Southwestern Medical Center in Dallas, TX, for characterization of her epidermal-basement membrane autoantibody binding specificity. However, a screen of her serum by indirect immunofluorescence examination on saline-split normal-appearing skin was negative for basement membrane zone antibodies. Therefore, further immunologic analysis was not performed. Even though this patient continued to have active bullous skin disease, it was presumed that her recent immunosuppressive therapy had depressed levels of circulating autoantibody below the level that could be detected by indirect immunofluorescence microscopy.

During the course of her disease, it was noted that blistering lesions over her upper extremities healed with scarring and milia formation (Fig 1, E). This observation in addition to the generalization and therapeutic refractoriness of her blistering disease further challenged the notion that this patient's underlying diagnosis was Brunsting-Perry CP. At that juncture the possibility of EBA presenting as

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