Explosive bullous pemphigoid with high serum total IgE: Serum IgE as a biomarker that reflects disease activity

Hyun Jung Kwon, MD,[a] Ga Ram Ahn, MD,[a] Sun Young Choi, MD, PhD,[b] Kapsok Li, MD, PhD,[a] and Seong Jun Seo, MD, PhD[a]
Seoul, South Korea

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INTRODUCTION

Bullous pemphigoid (BP) is a chronic autoimmune blistering disease characterized by pruritic, tense bullae and urticarial plaques. BP is associated with significant mortality, with 1-, 2-, and 5-year mortality rates of 19.46%, 29.13%, and 58.03%, respectively, in South Korea.[1] The main pathogenesis involves IgG autoantibodies against hemidesmosomal proteins: BP 180 and BP 230. IgE autoantibodies are increasingly reported in BP.[2] Herein we report a case of refractory BP with a fatal outcome and discuss the possible relationship between total serum IgE and disease activity.

Abbreviations used:

BMZ: basement membrane zone
BP: bullous pemphigoid

CASE REPORT

A 52-year-old female patient was admitted to our department with an extensive bullous dermatosis evolving over the course of 4 days (Fig 1, *A*). On physical examination, multiple erythematous targetoid patches with vesicles and bullae were observed on the trunk, extremities, and face. The skin lesions progressed despite treatment with methylprednisolone 1 mg/kg/day. The patient had been taking green vegetable juice for 3 weeks, but denied a history of any drug intake. Repeated skin biopsies were obtained from lesional and perilesional skin. Histologic examination revealed subepidermal blisters and perivascular inflammatory infiltrates composed of numerous eosinophils in the superficial dermis and inside the bullae (Fig 2). An immunofluorescence staining demonstrated linear complement C3 and IgG deposits along the basement membrane zone (BMZ) (Fig 3). Initial laboratory evaluation was otherwise normal except for peripheral blood eosinophilia (7.6%, reference range 0%-7.0%) and increased aminotransferase enzymes (aspartate transaminase 47 IU/L, reference range 0-34 IU/L; alanine transaminase 55 IU/L, reference range 0-40 IU/L). To evaluate for a possible paraneoplastic disorder, bone marrow biopsy was performed but did not reveal any abnormalities. Under a diagnosis of BP, treatment was started with methylprednisolone 1.5 mg/kg/day. One week later, dapsone 50 mg/day and cyclosporine 5 mg/kg/day were administered instead of corticosteroids because of the persistent appearance of new lesions. However, Nikolsky sign was still present and generalized erythroderma occurred (Fig 1, *B*). Thereafter, she was treated with mycophenolate mofetil 2 g/day and monthly cycles of intravenous immunoglobulin 2 g/kg for over 2 month. Rituximab (375 mg/m^2 weekly for 4 weeks) was introduced because the lesions were refractory. Despite 2 cycles of rituximab therapy and adjuvant treatment with prednisolone (0.4 mg/kg/

From the Department of Dermatology, Chung-Ang University College of Medicine, Seoul[a]; and Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul.[b]

Dr Choi is currently affiliated with the Department of Dermatology, Seoul Paik Hospital, Inje University College of Medicine, Seoul, Korea.

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Correspondence to: Seong Jun Seo, MD, PhD, Department of Dermatology, Chung-Ang University Hospital, 224-1 Heukseok-dong, Dongjak-ku, Seoul 156-755, South Korea. E-mail: drseo@hanafos.com.

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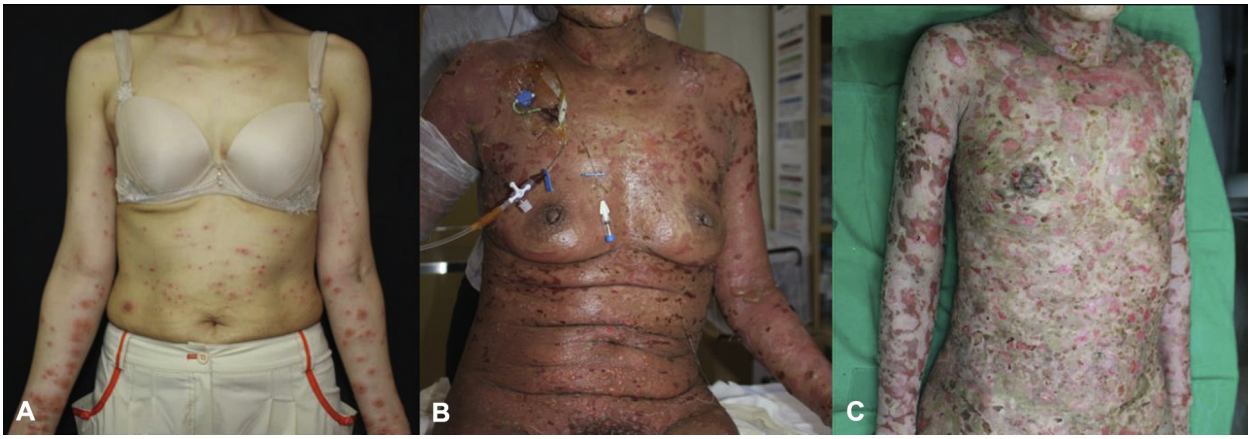

Fig 1. **A**, Multiple tiny bullous lesions around targetoid patches on both arms and trunk at admission. **B**, Rapid progression of disease included Nikolsky sign and severe erythroderma. **C**, Old crusted patches and newly formed bullae were admixed.

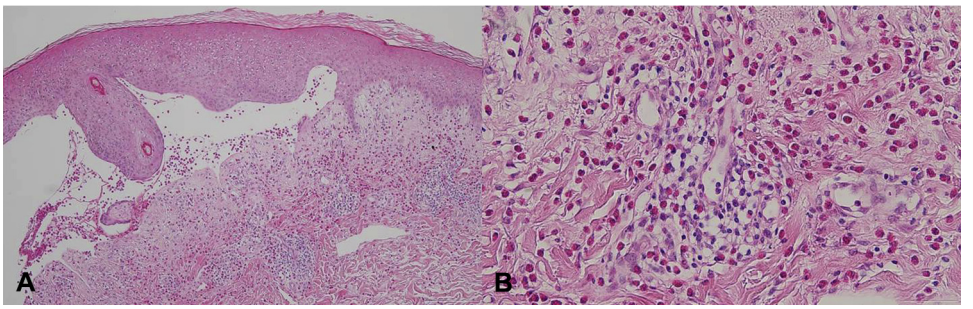

Fig 2. Subepidermal blisters and perivascular eosinophilic infiltrates in the superficial dermis and inside blisters. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×100; **B**, ×400.)

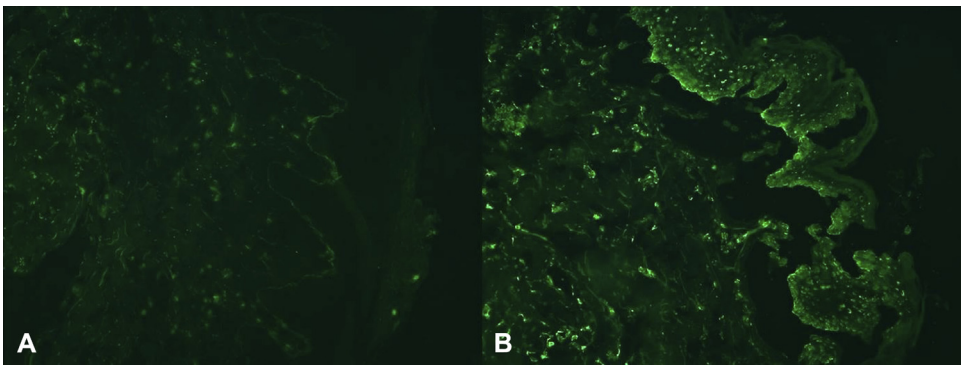

Fig 3. Linear, continuous, and intense deposition of complement C3 in the basal membrane zone (**A**) and IgG deposition (**B**) on the epidermal side of the cleavage using an indirect salt split-skin study. (**A**, Direct immunofluorescence staining; original magnification: ×200.) (**B**, Indirect immunofluorescence staining; original magnification: ×200.)

day), the patient constantly had flare-ups with only brief improvement (Fig 1, *C*). In the end, the patient died of sepsis originating from pneumonia.

During the course of disease, total serum IgE levels continuously increased from 89 to >3748 kU/L, and eosinophilia persisted despite multiple therapies (Fig 4). The total serum IgE level was consistent with disease severity, which was assessed by autoimmune bullous skin disorder intensity score.[3]

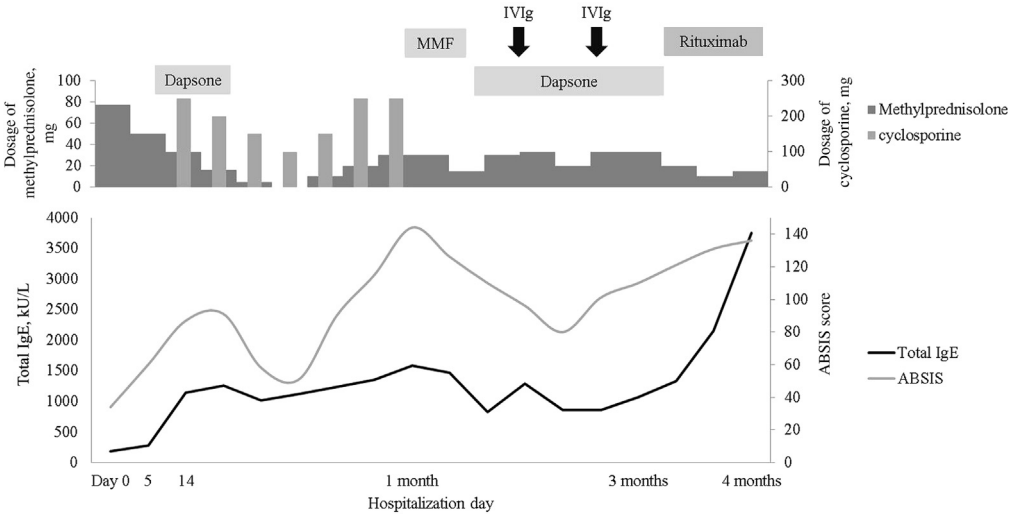

Fig 4. Serologic levels of total serum IgE consistently increased over a period of 4 months. The clinical severity score assessed by ABSIS was generally consistent with serum total IgE level. *ABSIS*, Autoimmune Bullous Skin Disorder Intensity Score; *IVIg*, intravenous IgG; *MMF*, mycophenolate mofetil.

DISCUSSION

BP involves IgG BMZ autoantibodies that mainly react with BP 230 and BP 180. In addition to IgG autoantibodies, several studies have emphasized the importance of IgE autoantibodies in the pathogenesis of BP.[3,4] The severity of BP is correlated with the levels of autoantibodies targeting the hemidesmosomal protein, which is primarily comprised of IgG and IgE classes.[5] IgG is the predominant antibody against BMZ components, but studies have shown that most (70%) patients with BP also have elevated levels of serum IgE, and 25% of patients with BP also have IgE deposits at the BMZ.[6] Recent studies also reported a possible correlation between IgE BP antibodies and BP disease activity.[7] The presence or level of IgE BP 180 autoantibodies was associated with broader skin lesions, higher prednisolone dosage, and longer duration required for remission.[8] There were several successful cases that responded to treatment with omalizumab, a humanized IgE monoclonal antibody in these reports.[7,8] Those reports suggest IgE-dependent mechanisms might play some pathophysiologic role in BP.[9] Although enzyme-linked immunosorbent assay for IgG or IgE to BP 180 and BP 230 was not performed, the persistent high serum total IgE level might have been associated with lesion refractoriness and the fatal outcome. A positive correlation between serum total IgE levels and BMZ antibody levels in BP has been reported.[10]

In our experience, BP unresponsiveness to both conventional and many off-label treatment regimens is unusual. In cases of severe and fulminant BP that do not respond to the conventional treatment regimen, the presence of IgE autoantibody targeting BMZ should be assessed. Serial assessment of serum IgE levels might be a useful strategy for following the activity of the BP and improving treatment of refractory BP.

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