

Childhood Bullous Pemphigoid in Association with Hyperimmunoglobulin E Syndrome

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Abstract: Bullous pemphigoid is an acquired immunobullous disorder affecting predominantly the elderly. It is very rare in children and exceptional in infants. Hyperimmunoglobulin E syndrome is a rare primary immunodeficiency characterized by a triad of high serum levels of polyclonal immunoglobulin E with peripheral eosinophilia, recurrent staphylococcal infections of the skin and lungs, and pruritic dermatitis. Variable associated features include coarse facies, cold cutaneous abscesses, and osteopenia. This report describes, to the best of my knowledge, the first instance of childhood bullous pemphigoid associated with hyperimmunoglobulin E syndrome in a 6-month-old boy.

Bullous pemphigoid (BP) is an acquired immunobullous disorder that mostly affects the elderly. Its incidence in childhood and infancy is unknown; however, it is thought to occur very rarely (1). About 70 patients with childhood BP have been reported, 20 of which are at 1 year of age or younger (1–5). The main clinicopathologic and immunologic properties of childhood BP are usually indistinguishable from those of adult BP. However, the childhood version differs from its adult counterpart by having more frequent mucosal involvement as well as marked involvement of the palms and soles. In addition, no association with malignancy in childhood BP has been reported (1,3–6).

Hyperimmunoglobulin E (hyper-IgE) syndrome, previously termed Job or Buckley syndrome, is a rare and complex primary immune deficiency characterized by high levels of polyclonal IgE in serum (> 2000 IU/mL), chronic eczematous dermatitis, recurrent staphylococcal infections of the skin and lungs, and bone abnormalities (7). The frequent skin infections usually start in infancy and include furuncles, most commonly around the face,

cold abscesses (tumorlike large fluctuant masses or cysts filled with pus), and cellulites. Although *Staphylococcus aureus* is the most frequently infecting organism, there is a wide spectrum of other bacterial infections with mainly encapsulated organisms such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. Fungal infections including thrush and candidal onychomycosis are also common. The upper respiratory tract is frequently infected, chronically causing sinusitis, discharging otitis media, otitis externa, and mastoiditis (8). To date, about 250 occurrences of hyper-IgE syndrome have been reported in the English language literature (7,8). Rare instances of autoimmune disorders such as systemic lupus erythematosus (SLE) (9–12), juvenile dermatomyositis (13), and membranoproliferative glomerulonephritis (14) in association with this syndrome have been described previously. Herein, an infant with BP and a history of recurrent skin and respiratory system infections, and chronic eczematous dermatitis since the age of 2 months in whom the medical evaluation demonstrated typical features of hyper-IgE syndrome is described.

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CASE REPORT

A 6-month-old boy born to nonconsanguineous, healthy parents was admitted with widespread bullous lesions of 2 weeks duration. The history revealed that he had experienced recurrent upper respiratory system infections, bronchopneumonia, discharging otitis media as well as severe eczematous dermatitis with frequent secondary infections and multiple episodes of oral thrush since the age of 2 months. Family history was insignificant. He was the first and single child of the family. Examination revealed numerous tense and eroded bullae, mostly on erythematous bases, involving also the anterior part of the oral cavity (hard palate and buccal mucosae), palms, and soles. The lower extremities were most severely affected. In addition, eczematous dermatitis was present on the scalp and ear lobes (Fig. 1). He also had an upper respiratory infection and bilateral suppurative otitis media with a low grade fever of 37.5°C.

Laboratory analyses revealed a high sedimentation rate of 35 mm/hour, leukocytosis ($11.5 \times 10^6/\text{mL}$), and eosinophilia ($1.95 \times 10^6/\text{mL}$). The serum IgE level was 8100 IU/mL (normal value 0–100 IU/mL); other immunoglobulin levels were normal. Antinuclear antibody was negative. A skin biopsy specimen taken from the edge of an intact bulla showed a subepidermal blister containing eosinophils. Direct immunofluorescence (DIF) demonstrated linear IgG and C3 deposition along the dermoepidermal junction (Fig. 2). Type IV collagen was demonstrated along the floor of the blister cavity by a direct immunoperoxidase technique, confirming that the level of epidermal separation was above the lamina densa. On the basis of these findings, a diagnosis of BP associated with hyper-IgE syndrome was established.

Systemic corticosteroid therapy (1 mg/kg/day) for 3 weeks combined with oral amoxicillin/clavulanate and skin care yielded rapid improvement. Corticosteroid therapy was then tapered and discontinued over a

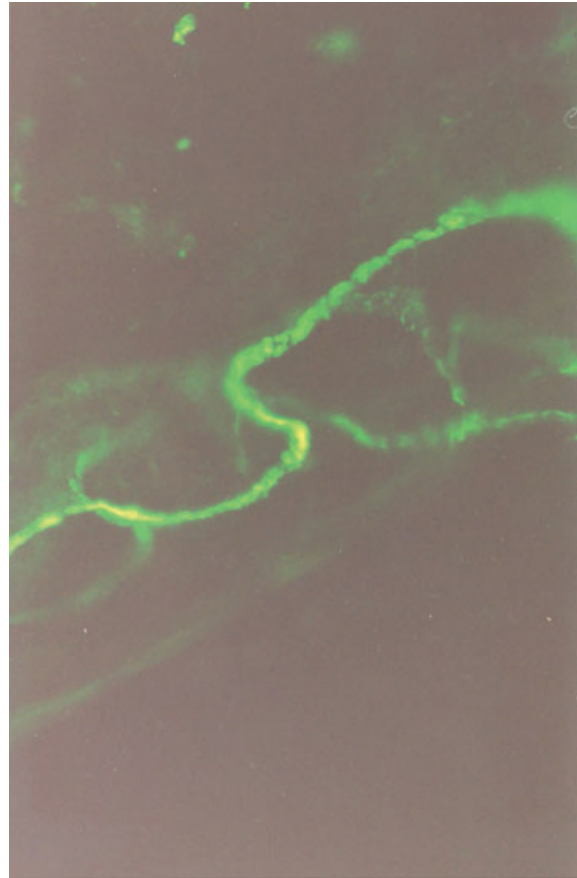


Figure 2. Direct immunofluorescence showing linear deposition of IgG at the dermoepidermal junction.

2-month period. However, a recurrence of BP with less severe lesions was observed 4 weeks after the cessation of corticosteroid therapy. At that time, the infant had no mucosal involvement, but did have several crusted and impetiginous lesions on the face and scalp, eczematous dermatitis involving the ears, and widespread pruritic papulopustules with occasional vesicles on the legs,

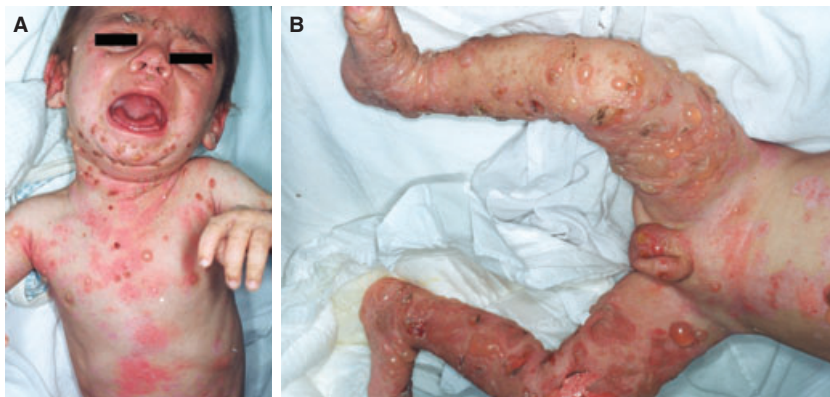


Figure 1. (A) Widespread tense bullae and erosions involving the hard palate, buccal mucosae, palms, and soles. (B) Note more severe involvement of the lower extremities.

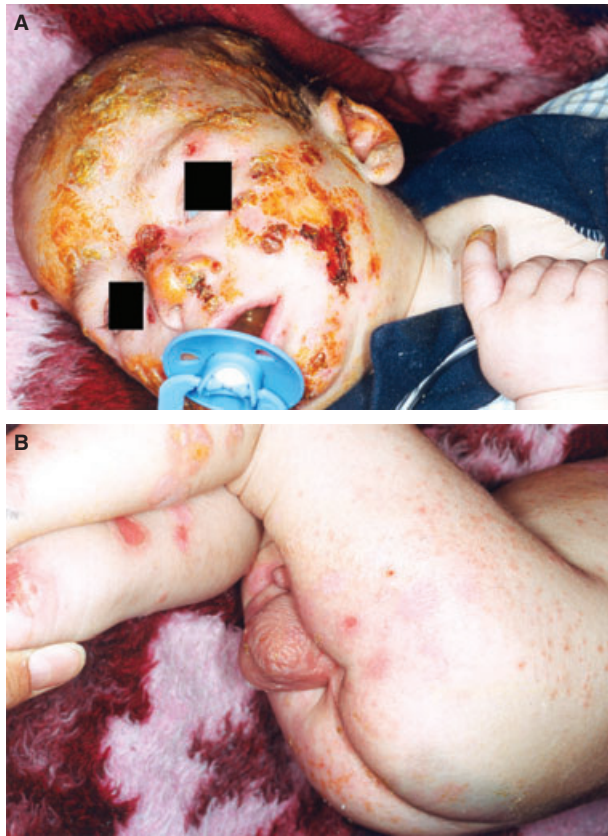


Figure 3. (A) Recurrence of bullous pemphigoid with impetiginization and crusting on the face. (B) Papulopustular lesions along with bullous and erosive lesions on the lower extremities.

abdomen and in the diaper area (Fig. 3). Bacterial cultures from crusted lesions and pustules grew *S. aureus*. Re-evaluation of the patient revealed very high levels of total IgE (18,700 IU/mL), anti-staphylococcal IgE (11,400 IU/mL), and leukocytosis ($18.5 \times 10^6/\text{mL}$) with eosinophilia ($6.5 \times 10^6/\text{mL}$). He had no fever and the remaining examination findings were normal. Skin biopsy could not be performed at that time because of the lack of his parents' permission. He was again successfully treated with a short course of systemic prednisolone (0.5 mg/kg/day) combined with oral and topical anti-staphylococcal therapy, and with topical corticosteroid application on the eczematous and pruritic lesions. He was then started on daily trimethoprim-sulfamethoxazole (10 mg/kg/day) for prophylaxis.

DISCUSSION

Hyperimmunoglobulin E syndrome, first described by Davis et al in 1966, and subsequently by Buckley et al in 1972 (7,8), has variable features and no single laboratory or clinical investigation is adequate to confirm the diag-

nosis. Skin, sinopulmonary, and bone infections are the most common features. Skin rash is typically pruritic, often lichenified, and in a distribution atypical for atopic dermatitis. The pruritus is most probably secondary to intradermal mast cell histamine release triggered by the elevation of IgE (15). Chamlin et al (7) described eight patients with the hyper-IgE syndrome whose skin biopsy specimens showed the findings of eosinophilic spongiotic dermatitis similar to eosinophilic pustular folliculitis. In our patient a skin specimen could not be obtained from papulopustular lesions; however, bacteriologic cultures from those grew *S. aureus*.

Nonimmunologic features such as failure or delay in shedding of the primary teeth owing to lack of root resorption, recurrent fractures, and hyperextensible joints usually occur in patients older than 8 years (16). Due to a cytokine-mediated bone resorption process, involving monocytes and prostaglandin E_2 , fractures may also occur. The characteristic coarse-featured facies consisting of a prominent forehead, wide alar base to the nose, regardless of race, and a wide outer canthal distance as well as scoliosis are seen mostly after 16 years of age (17).

Most instances of hyper-IgE syndrome are sporadic. Autosomal dominant transmission has also been reported, including male to male transmission. Grimbacher et al (16) showed a disease locus in the proximal 4q region. Renner et al (18) described an autosomal recessive form, which is distinguished from the dominant form by the lack of skeletal and dental abnormalities and more frequent association with autoimmune diseases. Several mechanisms may be responsible for immune deficiency in this syndrome, including decreased acute inflammatory response, defective neutrophil chemotaxis, poor antibody responses to immunization, and selective insufficiency in the secretion of γ -interferon (IFN- γ) resulting from the imbalance in the Th1/Th2 cytokine production and other abnormalities in cellular immunity (15). Borges et al (17) reported that lymphocytes from patients with hyper-IgE syndrome had an impaired response to interleukin (IL)-12, resulting in decreased IFN- γ production, which could be of key importance in the pathogenesis of the immune abnormalities of this syndrome. Increased expression of IL-13 in CD4+ cells may account for raised IgE levels (19).

Prophylactic antibiotics, skin care, and the prompt treatment of infection are the mainstays of the treatment of hyper-IgE syndrome. Unlike atopic dermatitis, the dermatitis often improves with prophylactic antibiotics alone. Other treatment alternatives available for patients with more severe involvement include H_1 antagonists, cromoglycate, levamisole, isotretinoin, cyclosporin A, IFN- γ , high-dose intravenous γ -globulin, plasmapheresis, and bone marrow transplant (7,8).

Neoplasia, recurrent traumas, systemic diseases, vaccination, drugs, and psoriasis have been reported as possible triggering factors of BP in some cases. Childhood BP presenting within the first year of life is very rare. It is normally self-limited and usually responds well to either topical or systemic steroids when treatment is initiated before the disease becomes widespread (1,2,4). Its definitive diagnosis requires DIF studies and sometimes characterization of the target antigen as a clinical and histologic overlap with other acquired or congenital blistering disorders is usual (20). In addition to IgG autoantibodies, IgA-specific antibodies against BP180 have been shown in three out of four infants with BP, suggesting a possible relationship between BP and linear IgA bullous dermatosis in children (21). Bullous pemphigoid may also be related to the production of anti-BP180 antibodies of IgE class. Subepidermal vesiculation in BP is often preceded by the development of urticarial plaques. Immunoglobulin E class basement membrane zone antibodies have been observed to induce eosinophil infiltration and histologic basement membrane blisters, suggesting that IgE autoantibodies might play a role in the early phase of the disease (22). Fairley et al (23) demonstrated anti-BP180 IgE antibodies in addition to IgG autoantibodies in eight out of the ten sera from BP patients, and very similar reactivity patterns for IgE and IgG with subregion-2 of NC16A, a noncollagenous stretch of the BP180 ectodomain and the primary target of pathogenic autoantibodies. Furthermore, they observed antigen-specific histamine release only in three patients with detectable circulating IgE antibodies against NC16A. On the basis of these data, it would be logical to check the existence of anti-BP180 IgE autoantibodies in our patient, who had very high serum IgE levels. But, unfortunately, this investigation could not be performed because of technical problems.

Some explanations for the etiology of childhood BP include nonspecific maternal antibodies that can induce an autoimmune reaction with secondary expression of hidden antigens or other maternally transmitted factors such as autoreactive lymphocytes (2). Although primary autoimmune diseases are exceptional in infants, the possibility of a primary autoimmune disease in infancy cannot be excluded. The most current theory for the pathogenesis of autoimmunity is antigenic mimicking, in which a foreign antigen (e.g., infectious agents, drugs, vaccines) structurally resembling a self-antigen provokes a cross-reactive antibody response (4,6). Some instances of BP with a close relation of vaccination (hepatitis B, influenza, and tetracoq vaccines as well as tetanus toxoid booster), have been reported in children, most often in infants (1,3–6,20,24). A few occurrences have been reported in association with various autoimmune disorders (25–28). The associated diseases and possible triggering factors of childhood BP are summarized in Table 1.

In the present patient, the diagnosis of hyper-IgE syndrome was established on the basis of the presence of high polyclonal and anti-staphylococcal IgE levels, recurrent skin and respiratory tract infections, past oral candidiasis attacks, as well as a recurrent eczematous dermatitis with a pruritic papulopustular/vesicular eruption. The diagnosis of BP was verified with DIF and type IV collagen staining. Development of BP in this child appears to be independent of vaccination as he had previously received three doses of tetracoq vaccines without complication. The prevalence of autoimmune diseases is known to increase with the failure of certain host defense mechanisms, especially with a deficiency in complement or IgA, as seen in hyper-IgE syndrome (9). A few instances of this syndrome have been previously reported in association with some autoimmune diseases, mainly connective tissue disorders such as SLE (five

TABLE 1. Associated Disorders and Possible Triggering Factors in Children with Bullous Pemphigoid

Reference	Patients (age, sex)	Associated disorders and possible triggering factors
1	3.5 mos, M	Tetracoq (diphtheria-tetanus-pertussis-poliomyelitis) vaccine
3	4 mos, M	
4	4 mos, M	
5	2 mos, F	
20	5 mos, M	DT vaccine without pertussis
24	2 mos, F	Tetracoq + hepatitis B + <i>Haemophilus influenzae</i> B vaccines
25	10 mos, F	Autoimmune hemolytic anemia, thymic hypoplasia, and T lymphocyte deficiency
26	20 mos, F	Coomb's positive autoimmune hemolytic anemia and giant cell hepatitis with liver kidney microsomal antibody positivity (13 mos after liver transplantation)
27	12 yrs, F	Membranous glomerulonephropathy
28	11 yrs, F	Ulcerative colitis
6	12 yrs, F	Hepatitis B vaccine
29	9 mos, F	Homeopathy treatment comprising sulfur, mercury, cantharides, and Rhus (Toxicodendron) for atopic dermatitis
Present case	6 mos, M	Hyperimmunoglobulin E syndrome

patients) and juvenile dermatomyositis (one patient) (9–13). Tanji et al (14) suggested that continuous antigen stimulation may have caused immune complex glomerulonephritis in their patient with the hyper-IgE syndrome. North et al (11) proposed that the increased number of infections may augment the probability of cross-reactions occurring between foreign and self-antigens, or the impaired antibody responses seen in this syndrome may generate insoluble immune complexes in their patients with associated SLE. Likewise, it may be hypothesized that repeated skin and respiratory infections may have served as a triggering factor for autoantibody production resulting in the development of BP in the current patient, as already proposed for postvaccination BP occurrences.

To the best of my knowledge, this is the first report of childhood BP in a patient who also had several features of the hyper-IgE syndrome. The emergence of immunologic and clinical features of BP in this child with defective host defense mechanisms appears to be unlikely to be fortuitous and may help clarify the pathogenesis of childhood BP. On the basis of this and previous reports, it could be also concluded that the hyper-IgE syndrome might be a risk factor for the development of autoimmune disease of any kind. Dermatologists should pay close attention in order to promptly identify children with the hyper-IgE syndrome, for whom significant morbidity and even mortality are possible, as they may be the first physicians to see such patients.

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