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Case presentation

Mycophenolate mofetil therapy for pediatric bullous pemphigoid

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Abstract

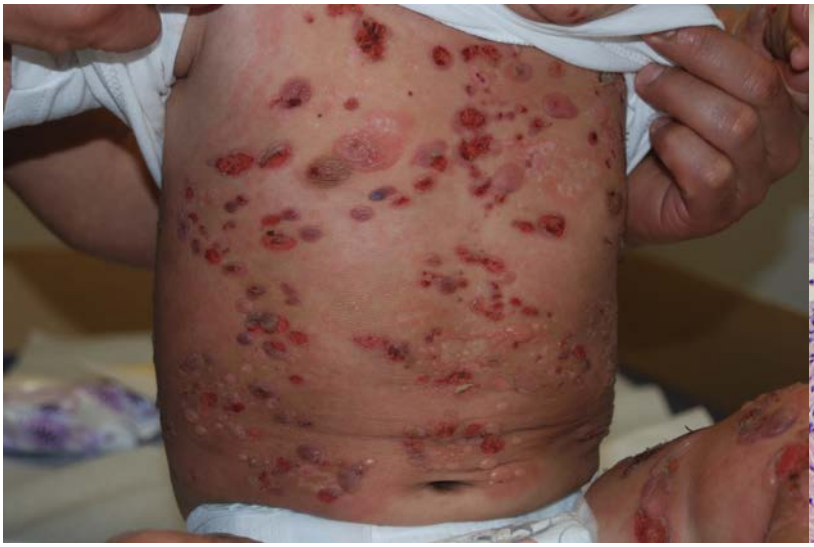
Bullous pemphigoid (BP) is a common autoimmune blistering disease in the adult population, but extremely rare in the pediatric population. Childhood BP usually has a favorable prognosis and responds well to topical and oral steroids. However, for patients that do not respond to corticosteroids, therapeutic alternatives are scarce. We report a case of a toddler with recalcitrant BP who was successfully treated with mycophenolate mofetil (MMF).

Keywords: vesiculobullous diseases, bullous pemphigoid, mycophenolate mofetil, immunosuppressive therapy

Case synopsis

A 16-month-old boy presented with worsening pruritic urticarial plaques and tense bullae (Figure 1) that began approximately one week after receiving his scheduled immunizations. Biopsies revealed a subepidermal bullous dermatosis with eosinophils (Figure 2), and direct immunofluorescence (DIF) was positive for strong linear IgG and C3 at the dermal epidermal junction. There was no significant positivity for IgM, IgA, or fibrin with appropriate reactive controls. Immunostaining for type IV collagen highlighted the basement membrane at the floor of the blister. Indirect immunofluorescence (IIF) was positive for linear deposits of IgG anti-basement membrane zone autoantibodies at the blister roof on salt-split skin. Staining on rodent bladder epithelium was negative. IIF did not reveal circulating IgA antibodies, excluding the possibility of linear IgA bullous dermatosis (LABD). Enzyme-linked immunosorbent assay (ELISA) for anti-BP180 autoantibody titers were elevated at 230 IU/ml. Other pertinent laboratory tests included a white blood cell count of 14.52 cells/mL (normal 5.98-13.51 cells/ml) and prominent eosinophilia of 3.13 cells/ml (normal 0.02-0.82 cells/ml). These clinical and laboratory findings were consistent with a diagnosis of BP. Thus, the patient was started on oral prednisone 1 mg/kg/day and topical steroids. Despite this treatment, his cutaneous disease worsened and he developed oral involvement, which led to an increase of the prednisone dose to 2 mg/kg/day and the addition of dapsone

with partial improvement. The patient was hospitalized for superinfection with *Staphylococcus aureus*. The infection was treated successfully with clindamycin and dapsone was discontinued. Following recovery of the acute infection, mycophenolate mofetil (MMF) was initiated at 30mg/kg/day. Because MMF needs several weeks to induce therapeutically relevant immunosuppression, prednisone was slowly tapered at a rate of 1mg/week over three months. Within two months of initiating this therapy his skin lesions cleared and the anti-BP180 antibodies decreased to 59 IU/ml. He received MMF for six months and, subsequently, it was slowly tapered down over 3 months; his skin remained clear (Figure 3). He did not experience any flares during MMF therapy or in the subsequent 4 months.



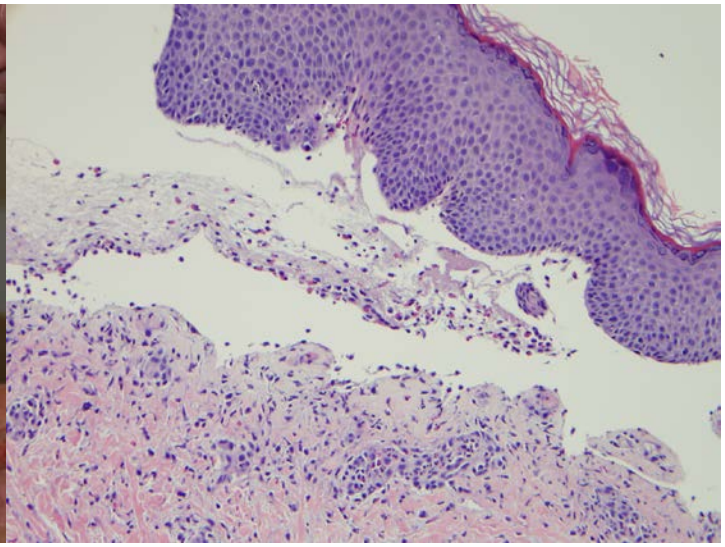


Figure 1. Tense bullae involving trunk and extremities. **Figure 2.** Subepidermal blister with eosinophils. (hematoxylin-eosin, original magnification x200)

Discussion

Bullous pemphigoid (BP), initially described by Lever in 1953, is the most common autoimmune blistering disorder [1]. It is characterized immunologically by the presence of autoantibodies directed against 2 antigens found in the hemidesmosomes of the dermal-epidermal junction, i.e., BP antigen 1 (BPAG1 or AgBP230), and BPAG2 (or AgBP180 or collagen XVII) [2, 3]. BP primarily affects the elderly, but it may rarely occur in children as young as 2 months of age [4].

BP often starts as pruritus with urticarial or erythematous plaques that evolve over weeks to months into large, tense, or sometimes hemorrhagic bullae. Acral involvement is frequently seen in affected infants, whereas genital and oral involvement is more common in older children [5]. Ocular involvement may not occur until years after the onset of the condition and presents as dryness of the eyes with a feeling of chronic, intractable conjunctival irritation [5].

As with most autoimmune blistering diseases, the precise reason for autoantibody formation is unknown, although several HLA subclasses have been associated with an increased susceptibility to this disorder [6]. Drug intake and viral infections have been reported as possible triggering events [7]. Furthermore, it has been noted that BP in infancy may present shortly after vaccination [8, 9, 10]. However, this relationship is controversial and may be purely coincidental because the frequency of vaccination during childhood is high.

The differential diagnosis varies according to the stage of the disease. The initial pruritic, urticarial plaques need to be differentiated from atopic dermatitis, urticarial, or erythema multiforme. Bullous lesions can also be seen in impetigo, LABD, dermatitis herpetiformis, bullous

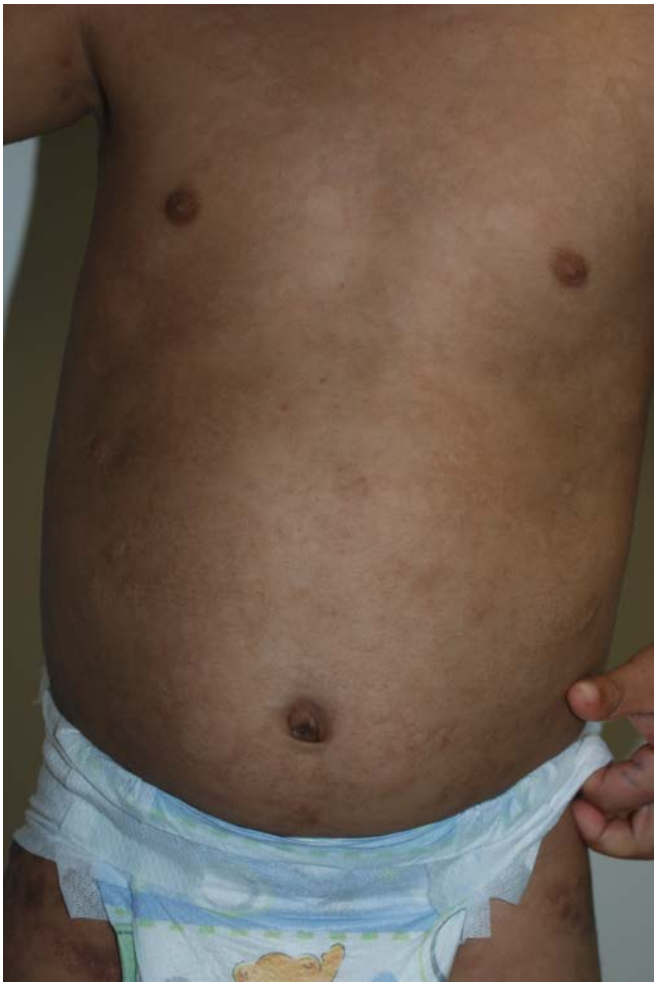


Figure 3. Residual hypopigmentation on areas of previous bullae.

systemic lupus erythematosus, and epidermolysis bullosa acquisita. Diagnosis is established by clinical, histological, and immunofluorescence analysis. Biopsies show subepidermal blisters with an eosinophilic infiltrate. DIF of perilesional skin samples shows linear deposition of mainly IgG or C3 along the basement membrane. Additional studies include IIF and ELISA. IIF reveals circulating IgG autoantibodies directed against BP180⁄230 glycoproteins binding linearly at the dermal-epidermal junction of monkey esophagus, and/or binding to the roof of an artificial blister cavity of salt-split human skin. ELISA detects IgG autoantibodies directed against the NC16A domain of BP180 [11].

BP treatment is based more on clinical experience than on controlled studies. Systemic corticosteroids are the mainstay of treatment. Sulfapyridine, dapsone, azathioprine, cyclosporine, and rituximab have been used as steroid-sparing agents and/or in corticosteroid-refractory BP [7, 12, 13]. Erythromycin with or without nicotinamide has been beneficial in some children, presumably owing to its anti-inflammatory effects [14]. In our patient, combined therapy of systemic corticosteroids and dapsone was unsuccessful.

Taking into account our patient's hospitalization for super-infection, his poor response to conventional treatment, and the need for therapy with minimal side effects, we decided to start mycophenolate mofetil (MMF). MMF is a prodrug of mycophenolic acid, which inhibits the rate-limiting enzyme in de novo synthesis of guanosine nucleotides, i.e., inosine monophosphate dehydrogenase. T and B lymphocytes are more dependent on this pathway than other cell types. Thus, MMF is effective at inhibiting T and B cell proliferation, inducing T cell apoptosis, and blocking antibody production by B cells [15]. This drug has previously been utilized in the treatment of adults with BP. It was found that MMF was equally effective to azathioprine in inducing disease remission (100%) when combined with corticosteroids. However, the MMF group had less liver toxicity [16]. In children, MMF therapy has also demonstrated to be safer when compared with other immunosuppressive agents for the treatment of atopic dermatitis, lupus nephritis, and nephritic syndrome [17-19]. This case illustrates that MMF could be a therapeutic alternative to traditional systemic immunosuppressive agents, with less favorable side-effect profiles, in treating refractory BP in children.

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