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Infantile bullous pemphigoid refractory to corticosteroids: Response to cyclosporine

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ABSTRACT

Bullous pemphigoid is a common autoimmune bullous skin disease in elderly patients, but it is rare in children. We present the case of a 4-month-old boy diagnosed with bullous pemphigoid that was refractory to conventional treatment, who achieved remission after 2 weeks of treatment with cyclosporine without experiencing any adverse effects.

Keywords: *bullous pemphigoid; pediatrics; cyclosporine; monoclonal antibodies.*

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INTRODUCTION

Among autoimmune blistering diseases, bullous pemphigoid (BP) is the most common in adults, although it rarely occurs in childhood. In children, the median age of onset is 4-5 months; 50% of cases occur during the first year of life, and there is a second peak in incidence at age 8.[1]

In this disease, IgG autoantibodies are produced against the hemidesmosomal proteins BP180 (collagen XVII) and BP230, which are in the basement membrane region. Type 2 proinflammatory cytokines, including interleukin (IL) 4 and IL-13, play an important role in its pathogenesis.

Various factors have been identified that may act as triggers for this disease, including medications (spironolactone, furosemide, amoxicillin, ciprofloxacin, among others), viral infections, radiation therapy, and, in pediatric cases, vaccinations.[2]

The location of skin lesions and the course of the disease differ between adult and pediatric patients. In children, although it typically begins with severe symptoms, the prognosis is generally favorable, with relapses being rare. In adults, however, the prognosis varies, and the condition usually follows a chronic and recurrent course.

Clinically, BP may begin with a prodromal phase characterized by intense pruritus and eczematous or urticarial lesions, followed by tense blisters containing serous fluid. In children under 12 months of age, lesions are most commonly found on the extremities, with rare mucosal involvement and a negative Nikolsky sign.[3] Laboratory tests may reveal eosinophilia and elevated IgE levels.

Given the low incidence of PA in childhood and the limited evidence available on the management of refractory forms, we present the following clinical case.

CLINICAL CASE

A 4-month-old male patient, born at term, with no significant personal or family history, presented with vesicular lesions on his hands and feet that had appeared a few days earlier. With a presumptive diagnosis of hand, foot, and mouth disease, symptomatic treatment was provided, and age-appropriate vaccinations were postponed.

Ten days later, the patient developed widespread eczematous lesions with secondary infection, sparing the face and skin folds, accompanied by intense itching. Emollients,

Figure 1. Skin lesions

Erythematous and edematous plaques with tense blisters on the face, trunk, and limbs.

cephalexin, corticosteroids, and systemic antihistamines were prescribed due to suspected impetigo.

Five days later, erythematous and edematous plaques were observed on the face, trunk, and limbs, over which taut, itchy blisters had formed (*Figure 1*). Given the suspicion of an autoimmune bullous dermatosis, further tests were ordered:

- General laboratory tests: normal complete blood count and blood chemistry, except for eosinophilia (3100/mm³).
- Viral serology tests: HIV, cytomegalovirus, Epstein-Barr virus, hepatitis B and C (all negative).
- Antinuclear antibodies (ANA) and complement factors C3 and C4, normal values.
- Immunological tests: lymphocyte counts, protein profile, and immunoglobulins within normal ranges.
- Skin histopathology: subepidermal blister with a dense inflammatory infiltrate predominantly composed of eosinophils and accompanying lymphocytes, located in the interstitial and perivascular spaces of the dermis (*Figure 2*).
- Direct immunofluorescence (DIF): linear deposition of IgG and C3 at the dermo-epidermal junction; IgA and IgM negative (*Figure 3*).

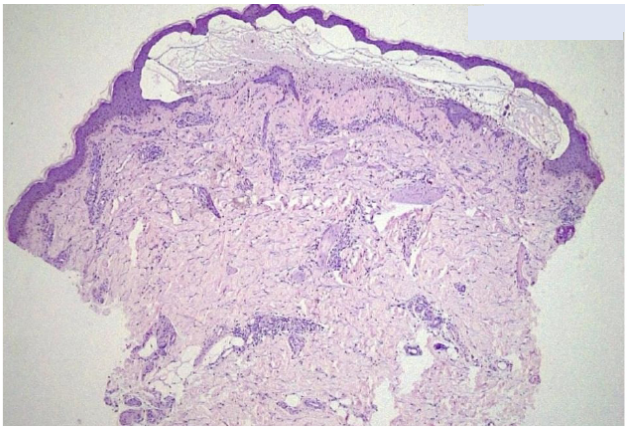
The patient was diagnosed with severe bullous pemphigoid (involving >30% of the body surface area), admitted to the hospital, and started on oral methylprednisolone at 1 mg/kg/day, with a partial response. Following disease progression at two weeks, intravenous immunoglobulin (2 g/kg) was administered, antihistamine therapy was intensified, and gabapentin (15 mg/kg/day every 8 hours) was added due to uncontrollable pruritus. With normal glucose-6-phosphate dehydrogenase (G6PDH) levels, treatment with dapsone (2 mg/kg/day) was initiated, but no clinical response was observed.

Due to the refractory nature of the condition, dupilumab was considered; however, because it was unavailable, cyclosporine 3 mg/kg/day was prescribed orally. With this approach, the dermatosis and pruritus were controlled within two weeks. After two months without new lesions, the treatment was gradually tapered and discontinued, with no relapses at 19 months of follow-up (*Figure 4*).

DISCUSSION

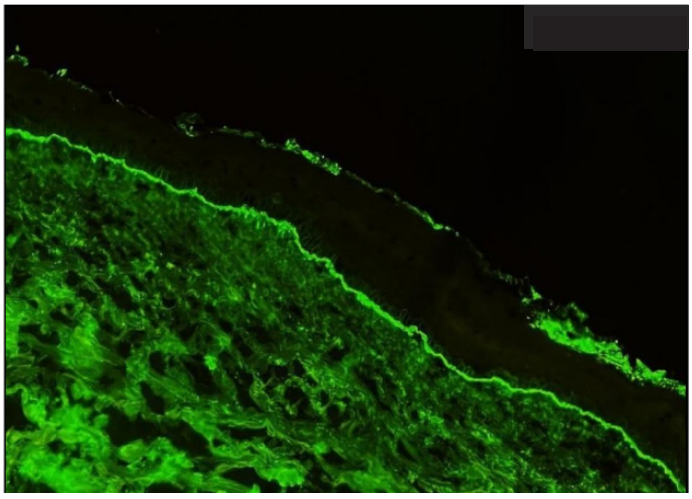
The diagnosis of BP is confirmed by histopathological examination, which reveals a subepidermal blister associated with an inflammatory infiltrate predominantly composed of eosinophils in the dermis, and by immunofluorescence (of healthy perilesional skin), which shows linear deposits of IgG and complement factor C3 in the dermoepidermal junction. Our patient presented clinical features consistent with infantile BP, which was confirmed by both of these diagnostic tests.

Figure 2. Histopathology: subepidermal blister



Inflammatory infiltrate with a predominance of eosinophils in the interstitial and perivascular spaces of the dermis (hematoxylin-eosin).

Figure 3. Direct immunofluorescence



Linear deposition of IgG and C3 at the dermo-epidermal junction.

Glucocorticoids are the first-line treatment and are effective in most cases; high-potency topical corticosteroids such as clobetasol can be used for mild cases, and prednisone at a dose of 0.5 to 1 mg/kg/day for moderate to severe disease.[4]

In some cases, it is necessary to combine conventional treatment with immunomodulatory therapies that have a sparing effect on corticosteroids, such as tetracyclines (doxycycline 200 mg/day, contraindicated in

Figure 4. Follow-up at 2 months of treatment

Generalized residual hypopigmented macules.

children under 8 years of age) or dapsone at a dose of 1.5 mg/kg/day. In patients with contraindications or comorbidities, lack of response to conventional treatment, or extensive disease, the use of immunosuppressive agents is recommended, such as azathioprine (1-3 mg/kg/day), mycophenolate mofetil (600 mg/m² twice daily), methotrexate (5-12.5 mg once weekly, subcutaneously or intramuscularly), or cyclosporine (3-5 mg/kg/day).[4]

Dapsone is often considered the next treatment option in cases of partial response or steroid resistance due to its efficacy, good tolerability, and low cost. Furthermore, it has a long history of safe use as a first-line treatment for linear IgA dermatosis, the most common autoimmune bullous dermatosis in childhood.[5] In the case presented, no clinical response was observed, so it was decided to escalate the treatment.

Cyclosporine, a calcineurin inhibitor that reduces IL-2 synthesis and T-cell proliferation, is effective in adults with steroid-resistant bullous pemphigoid. However, evidence supporting its use as monotherapy is limited. Although the 2022 European guidelines mention it as an option in refractory cases, they do not recommend it as routine treatment due to its adverse effect profile.[4-6] There are isolated reports in the pediatric population describing a good clinical response.[7]

In our patient, cyclosporine was prescribed due to its availability; he showed a good clinical response at a dose of 3 mg/kg/day, and the disease was controlled after two weeks. The usual therapeutic serum range for cyclosporine is 100-350 ng/mL. The most common adverse effects include nausea, vomiting, and hypertrichosis, while the most serious include impaired renal function and hypertension.[6,7] During treatment, clinical and laboratory monitoring (complete blood count, liver function tests, renal function, electrolytes, lipid profile, and blood pressure) was performed, with no abnormalities noted. Serum cyclosporine levels were not measured because the test was not available at our facility.

In cases of refractory bullous pemphigoid or when conventional treatments are contraindicated, biologic therapies offer a treatment alternative. Our patient received intravenous immunoglobulin at a dose of 2 g/kg but showed no clinical response.[4-8] Other treatment options include omalizumab and rituximab (an anti-CD20 monoclonal antibody); however, the safety profile of the latter remains under debate. Omalizumab, a humanized anti-IgE monoclonal antibody, may be particularly suitable for patients with elevated IgE levels.[4]

Recently, dupilumab, a human IgG4 monoclonal antibody that targets the IL-4Rα receptor and inhibits IL-4 and IL-13 signaling, has been used off-label in pediatric patients.[9,10] In June 2025, it was approved by the Food and Drug Administration (FDA) for the treatment of bullous pemphigoid in adults, currently constituting the first and only approved targeted therapy for this condition. However, its use in pediatric patients has not yet been approved.[11] In our case, it was not possible to access this therapy promptly.

In conclusion, cyclosporine could be considered an effective, accessible, low-cost treatment option with a favorable safety profile that should be considered in cases of pediatric PA that are refractory to other treatments. ■

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