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Bullous pemphigoid of infancy – report and review of infantile and pediatric bullous pemphigoid

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Abstract

A 4-month-old infant was observed with an acute itchy bullous dermatosis, predominantly involving the extremities, which revealed a dermal infiltrate rich in eosinophils, C3 deposits at the dermal-epidermal junction, and circulating antibodies to BP180 antigen, confirming the diagnosis of bullous pemphigoid. He was initially treated with deflazacort 1 mg/kg/day, further increased to 2 mg/kg/day, followed by reduction over seven weeks with complete clinical resolution within this period. We discuss epidemiology, etiology, relationship with vaccination, clinical features, and treatment of this relatively rare bullous dermatosis in the pediatric age.

Keywords: bullous pemphigoid, vesiculobullous skin diseases, infant, vaccination

Introduction

Blisters in children mainly result from acute eczema, viral or bacterial infections, and, less commonly, mechanobullous or immunobullous diseases. Bullous pemphigoid (BP) is an acquired subepidermal immunobullous disease typical for advanced age. However, it can also affect children [1]. In 2008, Waisbourd-Zinman et al. reported different clinical presentations of pediatric BP depending on the age of the child, with a predominat acral involvement with large and tense bullae in infants (< 12 months, [2]). The incidence of BP in infants is unknown. Although reported to be rare, it is considered the second most common acquired immunobullous disease in infants, after linear IgA dermatosis [3]. Escreva texto ou o endereço de um Web site ou traduza um documentoTraduzir do: Português

Case Synopsis

A 4-month-old male infant developed pruritic erythematous palmar and plantar lesions that within 4 weeks progressed to the abdomen and limbs, sparing the face and mucous membranes despite topical glucocorticoid treatment. When observed at the department of Dermatology, the infant had highly pruritic generalized urticarial plaques with tense bullae and vesicles filled with clear fluid. The lesions were significantly more intense on the palms and soles, where they exhibited a dyshidrosiform pattern (**Figure 1**). Nikolsky sign was negative and there were no systemic signs.

This infant, born after a full-term pregnancy and normal delivery with excellent Apgar scores, was being exclusively breastfed and there was no previous

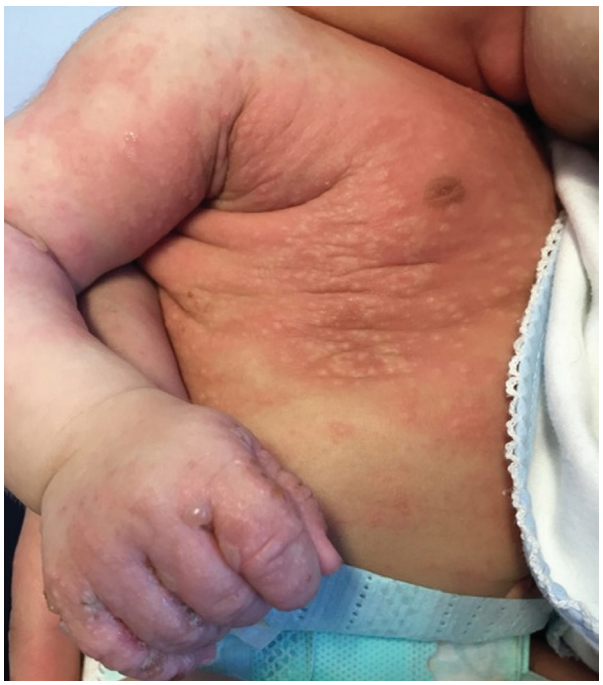

Figure 1. *Generalized urticarial lesions with tense bullae and vesicles and important acral involvement.*

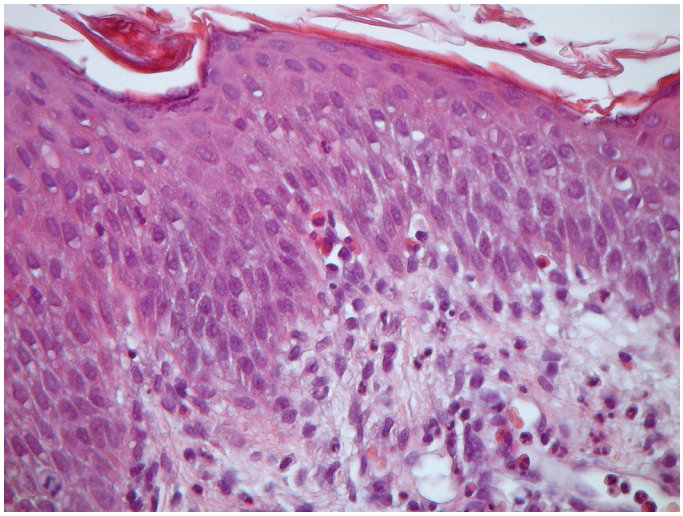

Figure 2. *Histopathology (hematoxylin and eosin, original magnification x400) showing a dermal leukocyte infiltrate rich in eosinophils.*

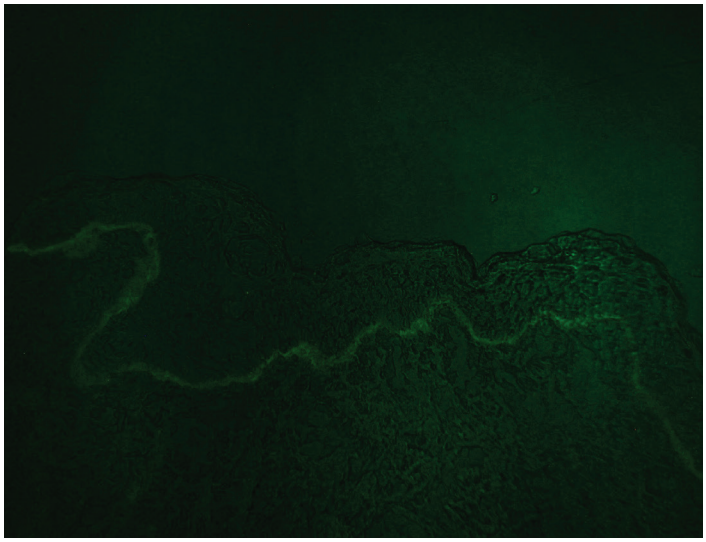

Figure 3. *Direct immunofluorescence - a linear pattern of C3 immunodeposits at the dermal-epidermal junction.*

history of infection or other disease. One week before the onset of the dermatosis, he was vaccinated against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type b (Pentavac®), rotavirus (RotaTeq®), and hepatitis B (Engerix B®), according to the vaccination protocol.

Laboratory studies revealed leukocytosis (16.2 x109/L) with eosinophilia (18.9%; 3.06x109/L) and negative serological markers for herpes simplex virus (HSV)-1, HSV-2, enterovirus, coxsackievirus, and syphilis. Histopathology showed a dermal infiltrate rich in eosinophils but no subepidermal blister (**Figure 2**). Direct immunofluorescence (DIF) showed a linear pattern of C3 immunodeposits at the dermal-epidermal junction (DEJ) and indirect imunofluorescence (IFI) revealed an intense staining at the DEJ (**Figure 3**). Enzyme-linked immunosorbent assay (ELISA) showed a high titer of autoantibodies against BP180-NC16A antigen (> 200 U/mL; normal < 20 U/mL) and was negative for BP230, confirming the diagnosis of BP.

Treatment was started with oral deflazacort (1 mg/kg/day), dimetindene (0.1 mg/kg/day) and topical methylprednisolone aceponate 0.1% cream. After one week, as there was no significant improvement, deflazacort dose was increased to 2 mg/kg/day. We could then document, during weekly consultations, a gradual clinical improvement. Therefore, the oral corticosteroid dose was progressively reduced.

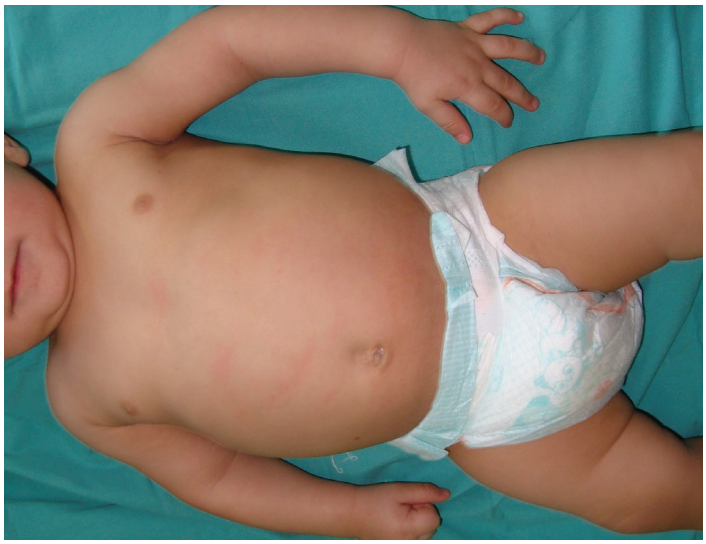

Figure 4. *Complete clinical resolution after systemic corticosteroid treatment.*

Within seven weeks, the infant was completely clear and oral corticosteroids were then stopped (**Figure 4**). He was free of lesions at one-year follow-up, with no need for further therapy and no recurrence after further vaccination with the same immunogens, following the regular protocol.

Case Discussion

BP is an immune-mediated disease associated with circulating autoantibodies against two well-characterized antigens, which are components of hemidesmosomes: BP antigen (BPA)1/BP230 and BPA2/BP180 (collagen XVII – more precisely, its NC16A extracellular domain, [4]). In most BP patients, IgG recognizes the BP180-NC16A ectodomain

and this seems to be an early and central step in the etiopathogenesis. Thereafter, variable epitope spreading can occur with IgG recognition of intracellular epitopes (BPA1/BP230), leading to tissue damage [4]. Indeed, a correlation was described between a greater disease severity and reactivity to both the extracellular and intracellular epitopes, BP180 and BP230 [4]. Our patient was positive for BP180 and negative for BP230 and this seems to be the usual finding in infantile BP [5], including previous cases from our department [6]. Perhaps this may explain why infantile BP usually has a better clinical course than in the elderly. However, Matsuda et al. reported an infantile case with circulating antibodies both to BP180 and BP230 with a good prognosis, although with a short follow-up (three months, [7]).

The etiologic factors behind the onset of the disease in the pediatric age are not defined. In infants, an outbreak of BP was attributed to vaccination but a causal relationship has been difficult to establish owing to the large number of immunizations during this period of life [6]. Besides, the continuation of the vaccination program did not lead to recurrence of BP [8,9], as in this patient.

BP has been stated to be rare in infancy [10]. However, more than 60 cases of infantile BP have been reported and the number of the reported cases has increased especially during the last 15 years. Taking into account all published cases of pediatric BP, some authors report that this diagnosis is much more uncommon in infants than it is after 12 months of age [1]. However, according to other authors, the majority of cases occur under the age of 12 months, as in the present and other cases from our department [6]. Therefore, it should be highlighted that infantile BP is not as rare as often mentioned [1,2], but further studies are needed to clarify the epidemiology of BP in the pediatric age.

Pediatric BP and BP in the elderly have similar histological and immunopathological features, but pediatric BP usually has a benign course and an excellent prognosis. Response to treatment is better with complete resolution within one year under treatment [1,6,8] and relapses are rare [1,8,11]. Lesional localization in pediatric BP is frequently different from adult BP: acral involvement with a dishydrotic pattern is the main presentation in the first year of life (infants), as in our patient, whereas genital lesions are considered more frequent after the first year [2].

The diagnosis of BP should be considered in the case of a bullous dermatosis in an infant, especially when the palms and soles are affected. A skin biopsy with DIF showing a linear deposition of C3 and IgG at the basement membrane zone has been considered the gold standard for diagnosis [10,11]. The importance of autoantibody titers has been discussed with some studies reporting a more recalcitrant disease with higher antibody titers, therefore suggesting the relevance of this value for treatment decisions [10]. Nevertheless, despite the high antibody titers, our patient responded promptly to oral cortisteroids, with no need for steroid sparing agents; we were able to stop the corticosteroids very early. In some cases, systemic corticosteroids have to be prolonged up to a few months, but total duration is highly variable. In most patients, remission occurs within a few weeks to a few months of topical or oral corticosteroid treatment, depending on individual response [5].

For a long time there were no treatment algorithms for pediatric BP. Some authors suggested topical clobetasol propionate as the first-line treatment, but systemic corticosteroids, such as prednisolone (1 to 2 mg/kg/day), were more often pointed out as the treatment of choice, with good tolerance [3]. In 2014, a treatment algorithm for infantile BP was proposed, considering disease severity, response to initial treatment, and specific characteristic of corticosteroid sparing agents. According to this algorithm, all infants should be treated with mid- to high potency topical corticosteroid as a first line, but in generalized disease (>10% body surface area) – as in the case of the infant described – systemic corticosteroids should be added to topical treatment. When a high dose of corticosteroid is needed for disease control, steroid sparing agents are often added. Dapsone was considered the first choice owing to its effectiveness and tolerance, but exclusion in glucose-6-phosphate dehydrogenase deficiency is recommended [9]. However, other steroid sparing agents, especially intravenous immunoglobulins and mycophenolate mofetil, have also been used [9, 12].

Conclusion

Infantile BP is an uncommon immune-mediated disease, although not as rare as previously stated. It is usually related to anti-BP180 antibodies and shows particular clinical features (involvement of palms and soles) and a good response to corticosteroid treatment. Further studies are needed to ascertain the etiology and improve treatment protocols.

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