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Funding sources: S.P. Tan is sponsored by the University of Edinburgh College of Medicine and Veterinary Medicine PhD Studentship and the Scottish Overseas Research Students Awards Scheme.

Conflicts of interest: none declared.

Successful management of severe infant bullous pemphigoid with omalizumab

DOI: 10.1111/j.1365-2133.2011.10748.x

MADAM, Bullous pemphigoid (BP) is exceptional during childhood.[1] Autoantibodies directed against the hemidesmosomal proteins BP180 and BP230 are found in most adult patients with BP (review in reference[2]). In infants with BP (IBP), as in adult patients, topical corticosteroids are usually effective for disease control,[3] but sometimes may require additional treatments[4,5] in the most severe form.

A 5-month-old male infant was referred to our hospital (considered as day 0) for the management of IBP that failed to respond to oral prednisolone 2·5 mg kg^{-1} daily. At 4 months, IBP had been diagnosed (Fig. 1) and confirmed by histopathological examination showing a subepidermal blister with a dermal infiltrate of eosinophils and a few lymphocytes. Direct immunofluorescence (IF) showed linear IgG, C3 deposits on the basement membrane zone (BMZ), and a few linear IgA deposits. No IgE deposits were observed on the BMZ. The blood cell count showed major eosinophilia ($11{\cdot}5 \times 10^9$ L^{-1}). The total IgE serum level was elevated (636 KU L^{-1}), as were the anti-BP180 and anti-BP230 serum antibody enzyme-linked immunosorbent assay (ELISA) values (Fig. 2). IgG2 and IgG3 circulating anti-BMZ antibodies were detected by indirect IF on normal human salt-split skin. No circulating anti-BP180 or anti-BP230 IgE antibodies were detected by immunoblot on human epidermal extract, or by indirect IF on normal or 1 mol L^{-1} NaCl-split human skin. Despite increasing the prednisolone dose to 3 mg kg^{-1} daily, and administering three intravenous (IV) pulses of methylprednisolone 120 mg, topical betamethasone 0·05%, dapsone 2 mg kg^{-1} daily and azithromycin 10 mg kg^{-1} daily, the disease remained uncontrolled. The patient was then treated with a 100-mg subcutaneous injection of omalizumab (calculated from the asthma chart) on day 17. During the following days, the number of new blisters and urticarial lesions decreased dramatically. Disease control was achieved by day 25. Omalizumab injections were continued every 2 weeks for a 3-month period and were then administered monthly for 4 months. After a 7-month follow-up period, no clinical relapse had occurred (Fig. 1). Anti-BP180 (but not anti-BP230) antibody ELISA values decreased after treatment (Fig. 2).

Some experimental and clinical data suggest that eosinophils and IgE may play an important role in BP physiopathology. Up to 86% of adult patients with BP have anti-BP180 IgE autoantibodies.[6] In an animal model using nude mice grafted with human skin, it was shown that injection of purified IgE isolated from patients with BP induced similar clinical and histological lesions.[7] Omalizumab is approved by the U.S. Food and Drug Administration in severe atopic asthma management. It is a recombinant humanized monoclonal antibody that binds to the Cε3 domain of IgE and prevents free IgE from binding to the basophils and the mast cell high-affinity IgE receptor.[8]

Given the successful use of omalizumab in a previous case of adult BP[9] and our patient's high total IgE level, elevated eosinophil blood count and dermal eosinophilic infiltrate, we hypothesized that blocking IgE–eosinophil pathways could be a potential alternative to immunosuppressive agents. We made this assumption before knowing that the patient did not have anti-BP180 or anti-BP230 IgE autoantibodies.

The mechanisms by which omalizumab was effective in this case remain unclear. It does not seem to involve the specific IgG2 and IgG3 humoral response, as BP180 autoantibodies were still detectable 4 months after the first injection.[2] The efficacy of omalizumab is paradoxical as no anti-BMZ IgE or IgG4 antibodies were detected. Although two techniques failed to detect anti-BMZ IgE antibodies, we cannot rule out that anti-BMZ IgE antibodies were present but not detected for technical reasons. We therefore hypothesize that omalizumab might interfere with cells involved in the BP-specific immune response, such as T lymphocytes or eosinophils. Indeed, *in vitro* experiments have shown that omalizumab is able to induce eosinophil apoptosis and downregulation of proinflammatory cytokines

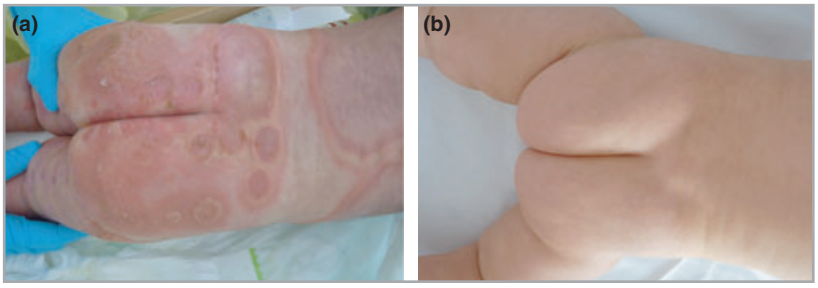
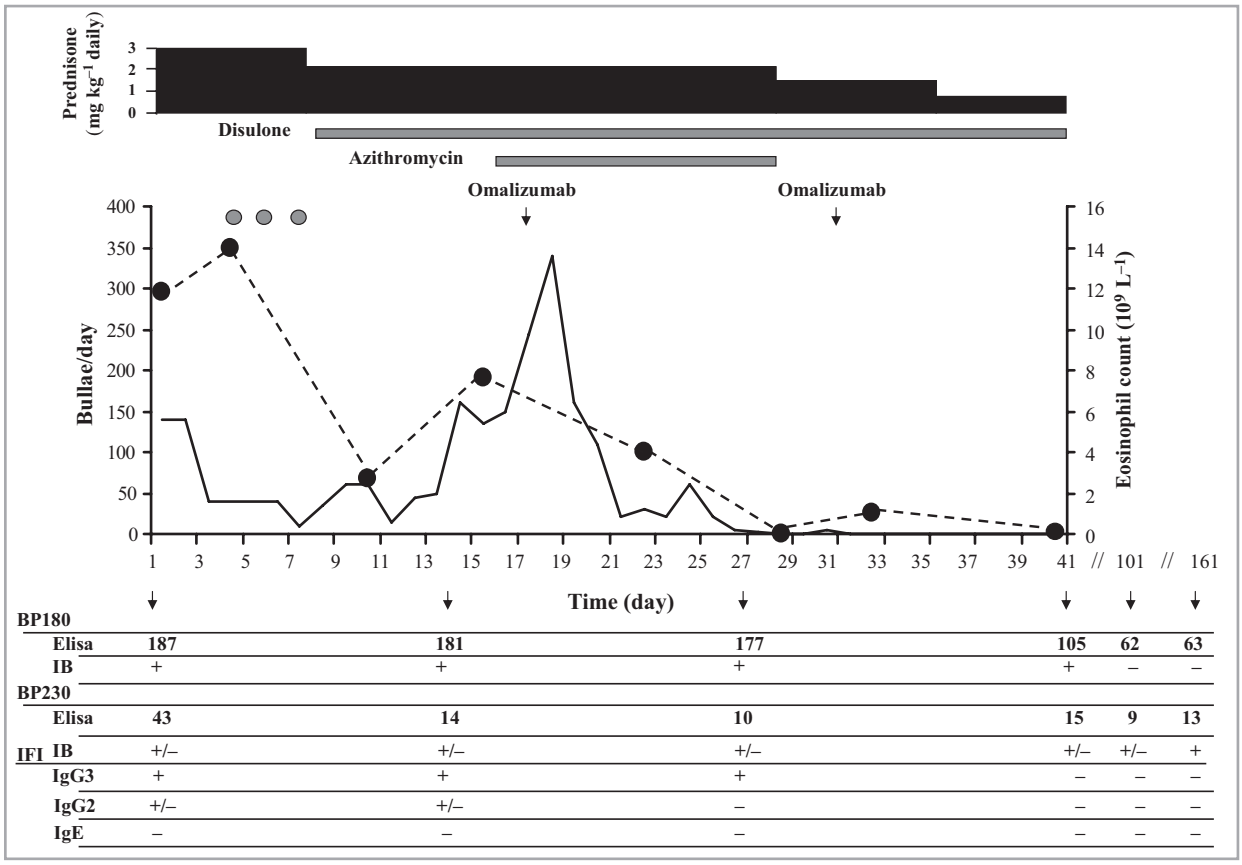


Fig 1. (a) Skin lesions in a 5-month-old boy suffering from pemphigoid bullous; large urticarial areas and bullae are spread over the back and buttocks. (b) The same infant at 10 months of age after seven injections of omalizumab.



BP180						
Elisa	**187**	**181**	**177**	**105**	**62**	**63**
IB	+	+	+	+	–	–
BP230						
Elisa	**43**	**14**	**10**	**15**	**9**	**13**
IFI IB	+/–	+/–	+/–	+/–	+/–	+
IgG3	+	+	+	–	–	–
IgG2	+/–	+/–	–	–	–	–
IgE	–	–	–	–	–	–

Fig 2. Progression over the first 40 days of the number of new bullae per day (black line) and eosinophil count (dashed line/black circles). Note that after day 33, the bullae had disappeared. Three high-dose methylprednisolone pulses were administered on days 4, 5 and 6 (1 g per 1.73 m^2 body surface/pulse) (grey circles). Disulone® (Sanofi, Paris, France) was prescribed from day 8 to day 54 at 2 mg kg^{-1} daily and azithromycin from day 16–28 at 10 mg kg^{-1} daily. Omalizumab (100 mg) was started on day 17 and then injected every 2 weeks for the first 3 months before being gradually spaced. Evolution of anti-BP180 and BP230 antibodies is shown during the first 100 days. IB, immunoblotting; IFI, indirect immunofluorescence; ELISA, enzyme-linked immunosorbent assay; +, positive; +/–, weakly positive.

synthesized by T lymphocytes.[10] In conclusion, this observation reports the efficacy of omalizumab in a case of severe IBP, and suggests that this drug can be effective even in the absence of circulating or *in vivo* bound anti-BMZ IgE antibodies.

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Funding sources: none.

Conflicts of interest: none declared.

Clozapine-induced symmetrical drug-related intertriginous and flexural exanthema: first reported cases

DOI: 10.1111/j.1365-2133.2011.10758.x

MADAM, Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) refers to an uncommon, yet distinctive clinical pattern of drug eruption that occurs after systemic exposure to the offending agent. We report two cases of clozapine-induced SDRIFE. Two patients (patient 1, a 42-year-old male; patient 2, a 56-year-old male) with a history of schizophrenia presented to the dermatology department with a symmetrical, erythematous rash affecting the axillae and groins. Patient 1 had a florid presentation with erythema and scaling extending to the trunk and lower extremities (Figs 1, 2). He was prescribed an antifungal medication without any improvement. Patient 2 had a less dramatic presentation with a confluent, erythematous macular rash affecting his axillae and antecubital fossae. Both patients were on treatment with clozapine as medication for schizophrenia for 6 and 4 months, respectively.

Histology from lesional skin biopsies showed epidermal hyperkeratosis, parakeratosis and foci of subcorneal pustules filled with neutrophils. There was a mixed inflammatory infiltrate in the dermis of lymphocytes, neutrophils and eosinophils (Fig. 3). No micro organisms were noted on periodic acid–Schiff (PAS) and Gram staining.

Patient 1 was weaned off clozapine and antipsychotic therapy was substituted with olanzapine. This resulted in a dramatic clearance of the rash. Patient 2 was weaned off clozapine as well and this led to a gradual clearing of the rash. Moderate-potency topical steroids were used in both patients.

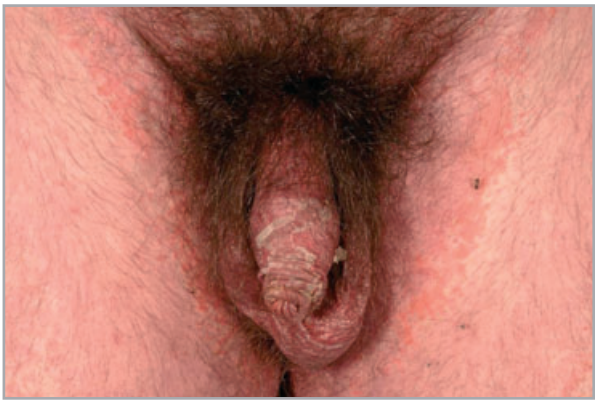

Fig 1. Symmetrical rash affecting groin.

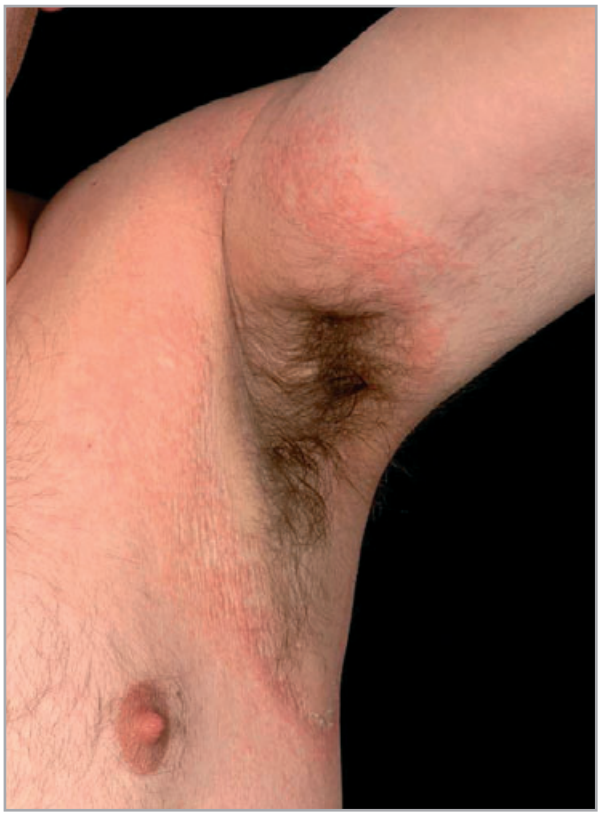

Fig 2. Rash affecting the axilla.

SDRIFE now replaces the term 'baboon syndrome', which was introduced over two decades ago to describe a cutaneous drug eruption resembling the red gluteal area of baboons.[1] This occurs after systemic exposure to type-4 allergens and has been historically associated with a mercury-induced exanthem in patients with previous contact sensitization. This condition is characterized by the following diagnostic criteria,[2,3] which were fulfilled by both our patients:

1 Occurrence after exposure to systemic drugs either at the first or after a repeated dose.

2 Sharply demarcated erythema of the buttocks and/or V-shaped erythema of the inguinal area.

3 Involvement of at least one other intertriginous or flexural localization.

4 Symmetry.

5 Absence of systemic symptoms.

Typical of a delayed hypersensitivity reaction, the rash can appear a few weeks to several months after ingestion of the causative drug. The appearance is often confused with a contact dermatitis.[2] Although the clinical picture of SDRIFE is characteristic, the histology can be variable and range from dermal lymphohistiocytic inflammation with eosinophils to bullous manifestations with neutrophils. The case we illustrate is slightly unusual in having subcorneal pustule formation.[4]