

mortality rate of patients with BP is still high, ranging from 13% to 38%.^{1,2} Recently, we reported the effectiveness of rituximab, a monoclonal anti-CD20 antibody, as first-line therapy for pemphigus.³ Therefore, we have attempted to measure the utility of rituximab as first-line therapy for BP.

From 2010 to 2012 we performed a retrospective case-control study in a referral centre in Taiwan, including patients with the generalized form of BP requiring systemic treatment. Diagnosis of BP was based on typical clinical presentations, characteristic histopathological findings, and the presence of autoantibodies on direct and/or indirect immunofluorescence studies. In the first-line combination therapy group (group R), the regimen included four weekly infusions of 500 mg rituximab (MabThera™; Roche, Basel, Switzerland), and corticosteroids, with a starting dose of prednisolone of 0.5 mg kg⁻¹ daily (Table 1). The dose of corticosteroids was tapered rapidly after disease was controlled. Each dose lasted for 3–4 weeks, with a total duration of < 6 months. As a comparison (group C), to ensure the similarity of severity, we included patients from the same period receiving a similar starting dose of prednisolone for at least 6 months (Table 1). We excluded those with localized or mild disease, which could be controlled by topical treatment or a short course of systemic treatment. All patients were followed for 1 year or until death. In both groups, the average age, BP Disease Area Index values,⁴ blood eosinophil counts and the presence of comorbidities were similar (Table 2). More than 90% of patients in group R achieved complete remission (CR), a status of no established or new lesions for at least 2 months,⁴ which was significantly higher than in group C ($P = 0.02$). Notably, eight of the patients achieving CR in group R achieved CR off therapy (CROff). Of these eight patients, four maintained CROff during the follow-up period of > 2 years. The other four experienced disease recurrence. Nevertheless, relapses in these cases were mild and easily controlled. The mean duration of CROff in these four patients was 27 weeks (range 22–35 weeks). The risk of infection was slightly lower in group R than in group C (31% vs. 53%), but it was not statistically significant ($P = 0.22$). Urinary tract infection and pneumonia were the leading infections in groups R and C, respectively. The 1-year mortality rate of group R was much lower than that of group C (15% vs. 37%), but it was not significantly different ($P = 0.18$).

To date, only anecdotal reports have mentioned the use of rituximab in BP.^{5,6} Our study is the first to use rituximab as a first-line treatment in BP, and demonstrates a significantly better rate of CR than conventional treatment. A recent review article reports infection and mortality rates of around 20%, and suggests that careful and close monitoring may be necessary.⁷ These results are consistent with ours. Indeed, infections are the most important cause of mortality in our study, as also reported in another study.⁸ Nevertheless, our study provides a comparison and shows that first-line combination therapy has similar or even lower rates of infection and mortality than conventional treatment. This might result from rapid tapering and withdrawing

systemic corticosteroids in group R (Table 2), as a lower dose of systemic corticosteroids may reduce the rate of mortality.⁹

In conclusion, we demonstrate that first-line combination therapy with rituximab and corticosteroids is effective and relatively safe for moderate-to-severe BP. A large prospective study is needed to confirm our observations.

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References

- Joly P, Baricault S, Sparsa A et al. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol* 2012; **132**:1998–2004.
- Li J, Zuo YG, Zheng HY. Mortality of bullous pemphigoid in China. *JAMA Dermatol* 2013; **149**:106–8.
- Cho YT, Lee FY, Chu CY et al. First-line combination therapy with rituximab and corticosteroids is effective and safe for pemphigus. *Acta Derm Venereol* 2014; **94**:472–3.
- Murrell DF, Daniel BS, Joly P et al. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol* 2012; **66**:479–85.
- Kasperkiewicz M, Shimanovich I, Ludwig RJ et al. Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. *J Am Acad Dermatol* 2011; **65**:552–8.
- Lourari S, Herve C, Doffoel-Hantz V et al. Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. *J Eur Acad Dermatol Venereol* 2011; **25**:1238–40.
- Shetty S, Ahmed AR. Treatment of bullous pemphigoid with rituximab: critical analysis of the current literature. *J Drugs Dermatol* 2013; **12**:672–7.
- Barrick BJ, Lohse CM, Lehman JS. Specific causes of death in patients with bullous pemphigoid as measured by death certificate data: a retrospective cohort study. *Int J Dermatol* 2015; **54**:56–61.
- Cai SC, Allen JC, Lim YL et al. Mortality of bullous pemphigoid in Singapore: risk factors and causes of death in 359 patients seen at the National Skin Centre. *Br J Dermatol* 2014; **170**:1319–26.

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Congenital hemidysplasia with ichthyosiform naevus and limb defects (CHILD) syndrome without hemidysplasia

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DEAR EDITOR, Congenital hemidysplasia with ichthyosiform naevus and limb defects (CHILD) syndrome is a rare X-linked dominant disorder caused by mutations in NSDHL.^{1,2} This gene encodes the enzyme 3 β -hydroxysterol dehydrogenase, which

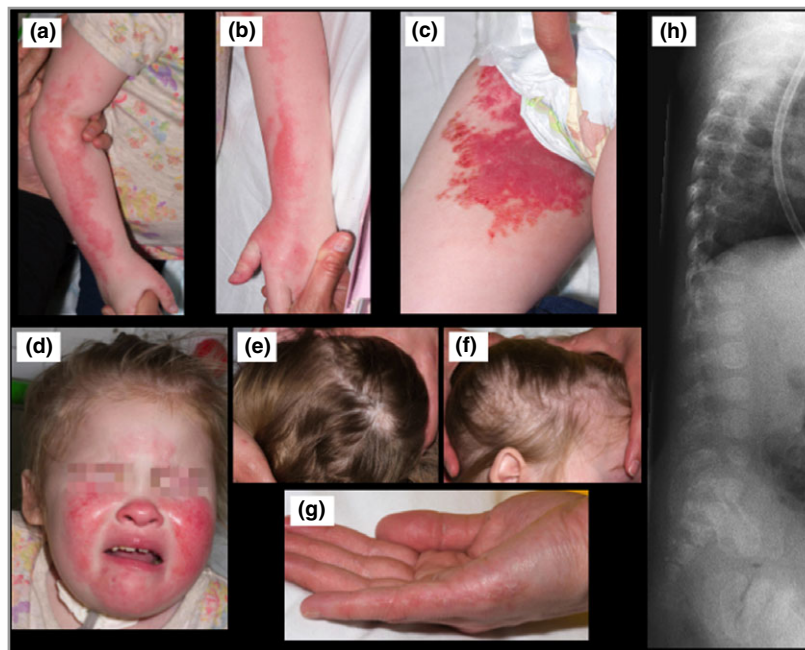


Fig 1. (a–d) Clinical and radiological images. Large erythematous xerotic plaques in a linear distribution on both upper limbs, affecting the right groin and thigh, and diffusely bilaterally on the cheeks. (e, f) Small areas of nonscarring alopecia bilaterally on the scalp. (g) Linear area of erythema and hyperkeratosis on the mother's right hand. (h) A lateral view of the spine showing punctate calcifications in the vertebrae, typical of chondrodysplasia punctata.

catalyses a step in the cholesterol biosynthetic pathway.¹ Characteristic signs present at birth or in the first weeks of life, namely strikingly unilateral ichthyosiform skin lesions with a sharp midline demarcation, and ipsilateral limb defects (ranging from hypoplasia of the phalanges to absence of the entire extremity).^{1,3} The face is usually spared. The central nervous system, lungs, heart and kidneys can also be involved.² We report a case of CHILD syndrome without the characteristic hemidysplasia.

A 7-year-old girl was referred to our department for evaluation of areas of persistently inflamed and hyperkeratotic skin. She was born at 35 weeks of gestation by caesarean section for breech presentation, without gross limb defects. Her medical history revealed a radiological diagnosis of spinal chondrodysplasia punctata with atlantoaxial subluxation and intermittent spinal compression, bilateral hip subluxation, severe neurodevelopmental delay, chronic lung disease requiring tracheostomy and night-time ventilation, gastro-oesophageal reflux and gastrostomy feeding. Brain magnetic resonance imaging had revealed general loss of white matter bulk but with no asymmetry. The skin lesions had been present from birth, and persistent symptoms were recurrent painful fissuring and pruritus. Cutaneous examination revealed inflammatory ichthyotic lesions along the lines of Blaschko on both upper limbs (right more than left), in the right groin, and diffusely on both cheeks. In addition, there were areas of persistent nonscarring alopecia bilaterally on the scalp, one circular and well circumscribed, and the other more diffuse, with no evidence of trichotillomania. Dysmorphic facial features included deep-set eyes and epicanthic folds. Importantly, and compatible with previous reports,⁴ the patient's mother had similar but much milder linear hyperkeratotic skin lesions affecting the right arm and hand, but was otherwise unaffected (Fig. 1).

Skin biopsy of affected skin from the patient showed features compatible with ichthyosiform dermatosis: acanthosis and extension of rete pegs of the epidermis, marked parakeratotic scaling with loss of the granular layer, occasional clusters of neutrophils, and perivascular and dermal lymphohistiocytic infiltrates (Fig. 2), but without the characteristic verruciform xanthoma of CHILD syndrome. Array comparative genomic hybridization analysis of peripheral blood leucocyte DNA was normal, excluding large copy number changes (resolution 150 kb). Sanger sequencing

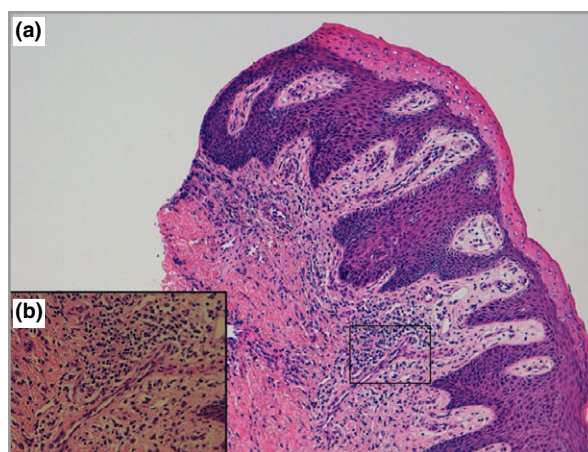


Fig 2. (a, b) Skin biopsy showing features compatible with ichthyosiform dermatosis: acanthosis and extension of rete pegs of the epidermis, marked parakeratotic scaling with loss of the granular layer, occasional clusters of neutrophils, and perivascular and dermal lymphohistiocytic infiltrates. No verrucous xanthoma was seen. (a) Magnification 10 \times ; (b) magnification 40 \times .

Table 1 Comparison of features of congenital hemidysplasia with ichthyosiform naevus and limb defects (CHILD) syndrome, Conradi–Hunermann–Happle (CHH) syndrome, CK syndrome and our patient

Syndrome	CHILD	CHH	CK	Our patient
Genetics	X-linked dominant disorder caused by heterozygous loss of function mutations in NSDHL	X-linked dominant disorder caused by mutations in EBP	X-linked recessive disorder caused by milder mutations in NSDHL	Heterozygous microdeletion inducing a frameshift and premature stop codon in NSDHL
Cutaneous phenotype	Unilateral ichthyosiform skin lesions with sharp midline demarcation Psychotropic skin lesions	Ichthyosiform erythroderma Linear or whorled pigmentary lesions Striated ichthyosiform hyperkeratosis Patchy cicatricial alopecia	None described	Inflammatory linearichthyotic lesions on both upper limbs, right groin and diffusely bilaterally on cheeks Areas of nonscarring alopecia
Histopathological features	Verruciform xanthoma Hyperkeratosis, parakeratosis and acanthosis Inflammatory and lipid-laden infiltrated within the dermal papillae	Hyperkeratosis and acanthosis Calcium deposits within the stratum corneum Focal pigmentation of basal layer	–	Acanthosis and extension of rete pegs Marked parakeratotic scaling with loss of the granular layer Occasional clusters of neutrophils Perivascular and dermal lymphohistiocytic infiltrates
Associated defects	Congenital hemidysplasia Ipsilateral limb defects Visceral malformations CNS anomalies	Chondrodysplasia punctata Intellectual disability Short stature Cataracts	Cortical malformations Characteristic craniofacial features Asthenic body habitus Behaviour problems	Spinal chondrodysplasia punctata Bilateral hip subluxation Severe neurodevelopmental delay Chronic lung disease Gastro-oesophageal reflux

CNS, central nervous system.

revealed a novel germline heterozygous microdeletion inducing a frameshift and premature stop codon at position 119 of a total translated length of 373 amino acids in NSDHL (c.357_358del, p.Arg119Serfs*1d), predicted damaging *in silico*. This mutation is compatible with the previously reported disease-causing mutations in classical CHILD syndrome,¹ and on the basis of current knowledge confirmed a genetic diagnosis of CHILD syndrome in both the patient and her mother. No other changes in the gene were identified. Previously reported mutations have principally been heterozygous nonsense or missense point mutations, and large heterozygous deletions have been described.^{3,5} This novel microdeletion would be predicted to cause loss of function by truncating the protein before the catalytic site of the gene product.

Traditionally, management of skin lesions in CHILD syndrome has been difficult; however, Paller *et al.* recently reported an innovative and highly successful topical therapy in two patients – co-application of cholesterol 2% and lovastatin 2% – based on the role of NSDHL in cholesterol metabolism.⁶ These results have been replicated in three further reports of

patients using co-application of cholesterol 2% and simvastatin 2%,⁷ and has been successfully trialled in our patient, with complete resolution of erythema and hyperkeratosis in the treated groin area.

Two other conditions are interesting to consider in this atypical case (Table 1). Firstly, the recently described allelic disorder CK syndrome (MIM #300831), caused by milder mutations in NSDHL, is characterized by cortical malformations, typical facial features, asthenic body habitus and no described cutaneous phenotype. Our patient does not exhibit typical features of this syndrome. Secondly, Conradi–Hunermann–Happle (CHH) syndrome is an X-linked dominant disorder caused by mutations in the emopamil-binding protein gene (EBP), which governs the next step in the cholesterol biosynthetic pathway after NSDHL. The presence of chondrodysplasia punctata, intellectual disability and alopecia have all been described in CHH syndrome; however, disproportionate skeletal growth, growth deficiency, characteristic linear/whorled pigmentary lesions and cataracts were lacking in our patient. Furthermore, the histological features in this case support a diagnosis of CHILD syndrome and exclude a diagnosis of CHH.

A clear bilateral presentation in CHILD syndrome has been reported rarely before, once with characteristic skin lesions affecting the body folds in a near-symmetrical distribution, associated with a novel missense mutation in NSDHL,^{8,9} twice with contralateral linear skin lesions,¹ once with bilateral, almost symmetrical, linear lesions on the extremities.¹⁰ Our case confirms this bilateral cutaneous presentation, emphasizes the significant inter- and intrafamilial variation, and extends the noncutaneous phenotype of CHILD syndrome.

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References

- Happle R, Koch H, Lenz W. The CHILD syndrome. Congenital hemidysplasia with ichthyosiform erythroderma and limb defects. *Eur J Pediatr* 1980; **134**:27–33.
- Konig A, Happle R, Bornholdt D et al. Mutations in the NSDHL gene, encoding a 3beta-hydroxysteroid dehydrogenase, cause CHILD syndrome. *Am J Med Genet* 2000; **90**:339–46.
- Bornholdt D, Konig A, Happle R et al. Mutational spectrum of NSDHL in CHILD syndrome. *J Med Genet* 2005; **42**:e17.
- Bittar M, Happle R, Grzeschik KH et al. CHILD syndrome in 3 generations: the importance of mild or minimal skin lesions. *Arch Dermatol* 2006; **142**:348–51.
- Kim CA, Konig A, Bertola DR et al. CHILD syndrome caused by a deletion of exons 6–8 of the NSDHL gene. *Dermatology* 2005; **211**:155–8.
- Paller AS, van Steensel MA, Rodriguez-Martin M et al. Pathogenesis-based therapy reverses cutaneous abnormalities in an inherited disorder of distal cholesterol metabolism. *J Invest Dermatol* 2011; **131**:2242–8.
- Kiritisi D, Schauer F, Wolffe U et al. Targeting epidermal lipids for treatment of Mendelian disorders of cornification. *Orphanet J Rare Dis* 2014; **9**:33.
- Konig A, Happle R, Fink-Puches R et al. A novel missense mutation of NSDHL in an unusual case of CHILD syndrome showing bilateral, almost symmetric involvement. *J Am Acad Dermatol* 2002; **46**:594–6.
- Fink-Puches R, Soyer HP, Pierer G et al. Systematized inflammatory epidermal nevus with symmetrical involvement: an unusual case of CHILD syndrome? *J Am Acad Dermatol* 1997; **36**:823–6.
- Poiars BA, Cortesao JM. [Inflammatory variable epidermal naevus (atypical I.L.V.E.N.? A new entity? (author's transl)]. *Ann Dermatol Venereol* 1979; **106**:443–50 (in French).

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Desmocollin-specific antibodies in a patient with Hailey–Hailey disease

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DEAR EDITOR, Hailey–Hailey disease (HHD) is caused by mutations in the ATP2C1 gene, encoding Ca²⁺/Mn²⁺ ATPase protein 1 (hSPCA1) in the human secretory pathway. We report a case of HHD in which we detected desmocollin (Dsc)-specific antibodies, and discuss a possible mechanism of production of keratinocyte cell-surface-specific autoantibodies in HHD.

In 2010, a 74-year-old Japanese woman presented with a 9-year history of a skin lesion on the left axilla, groin and perineum. The lesion was exacerbated in summer. Topical steroids were effective but the skin eruption recurred. The patient's father and son had similar skin lesions in intertriginous regions. Physical examination revealed oozing plaques on the left axilla (Fig. 1a). A lesional skin biopsy revealed suprabasal acantholysis in the epidermis (Fig. 1b).

On receiving informed consent we extracted genomic DNA from the patient's peripheral blood, and amplified 28 exons of ATP2C1 by polymerase chain reaction (PCR), as described previously.¹ Sequencing of the products of PCR revealed two thymine insertions at the site of an adenine deletion at nucleotide 1216 (Fig. 1c).

Simultaneously, we examined the patient's serum for the presence of autoantibodies against keratinocyte cell surfaces. A direct immunofluorescence (IF) study of perilesional skin was positive for IgG in a net-like pattern (Fig. 1d), but negative for IgA, IgM and C3 after pretreatment with 40% ethanol.²

An indirect IF study revealed cell-surface reactivity positive for IgG in monkey oesophagus, but not in normal human skin (Fig. 1e). Immunoblotting of an extract of normal human epidermis was negative for IgG. Enzyme-linked immunosorbent assays (ELISAs) for desmogleins 1 and 3 gave negative results.

Recently, we developed novel ELISAs for detection of IgG antibodies against Dscs 1–3 using mammalian recombinant proteins (D. Ueo, N. Ishii, T. Hamada, K. Teye, T. Hashimoto, Y. Hatano & S. Fujiwara, submitted for publication). The novel IgG ELISAs for Dscs were extremely specific, and none of 35 normal control sera exceeded the cut-off values in any of the Dsc ELISAs. The ELISAs were positive for antibodies against Dsc1 [optical density (OD) 0.31, cut-off 0.20] and Dsc2 (OD 0.18, cut-off 0.07), but negative for antibodies against Dsc3 (OD 0.10, cut-off 0.12).

We made a diagnosis of HHD with Dsc-specific IgG antibodies. Two years later, during wintertime remission, the level of antibodies against Dsc2 was much reduced (OD 0.07), and ELISAs were negative for antibodies against Dsc1 (OD 0.17) and Dsc3 (OD 0.02). We also performed an