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Successful dupilumab therapy for atopic dermatitis in a patient with X-linked agammaglobulinaemia

A 19-year-old man with X-linked agammaglobulinemia (XLA) presented to the dermatology clinic with a four-month history of exacerbation of dermatitis and impetigo. He was diagnosed with XLA at one month of age and received immunoglobulin replacement therapy regularly. Moreover, since he was an infant, he had mild atopic dermatitis (AD), which responded to oxytetracycline hydrochloride and hydrocortisone ointment, and allergic rhinitis. His sister also had AD. However, four months before presentation, the dermatitis worsened, and refractory impetigo developed. Two weeks before presentation, he was evaluated by his primary care paediatrician and started on parenteral acyclovir for one week for a presumed diagnosis of Kaposi varicelliform eruption, however, there was no improvement. On examination, there was a diffuse erythematous rash and numerous itchy dark red nodules over the patient's head, trunk, and extremities (*figure 1A*). He had no respiratory or gastrointestinal symptoms. Laboratory tests revealed eosinophilia (white blood cell count of $14.9 \times 10^3/\mu L$ with 20.0% eosinophils; reference range: $3.3\text{-}8.6 \times 10^3/\mu L$, 2.0–5.0%, respectively) and elevated levels of C-reactive protein (0.43 mg/dL; reference range: 0.00–0.14 mg/dL) and thymus and activation-regulated chemokines (TARC; 20,810 pg/mL; reference range: <450 pg/mL). The levels of immunoglobulin (Ig) G, IgA, IgM, and IgE were low (494 mg/dL, <3 mg/dL, 1 mg/dL and 1 IU/mL, respectively; reference range: 861–1,747 mg/dL, 93–393 mg/dL, 33–183 mg/dL and ≤173 IU/mL, respectively). A biopsy specimen of the skin of the abdominal wall showed irregular epidermal hyperplasia, mild spongiosis with lymphocytic infiltration, and a perivascular lymphocytic infiltration in the upper dermis (*figure 1B*). No atypical cells were seen among these infiltrating cells. Immunohistochemical examination using mouse anti-human C-C chemokine receptor type 4 (CCR4) monoclonal antibody (Poteligeo Test IHC, Minaris Medical Co., Ltd., Tokyo) revealed that CCR4 was expressed by the infiltrating lymphocytic cells (*figure 1C*). A diagnosis of exacerbation of AD was made. The erythematous lesions resolved with the administration of difluprednate ointment, however, acneiform eruptions and small pustules developed on the patient's back one week later. The pus taken from the lesions yielded methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (*S. aureus*). The patient was started on oral trimethoprim-sulfamethoxazole (TMP-SMX) and instructed to apply the topical steroid only to itchy lesions, however, this resulted in re-exacerbation of dermatitis. Subcutaneous dupilumab was then administered three weeks after presentation. Ever since, the symptoms of AD have been well controlled, and the eczema area and severity index dropped from 20.5 (three weeks after the presentation) to 3.1 (14 months after the presentation) (*figure 1D*) using dupilumab (dose of 300 mg every two weeks), TMP-SMX, and topical steroids.

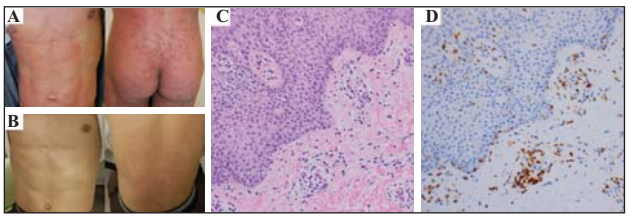

Figure 1. A) A diffuse erythematous rash and numerous itchy dark red nodules over the head, trunk, and extremities at presentation. **B**) A biopsy specimen of the skin of the abdominal wall shows irregular epidermal hyperplasia, mild spongiosis with lymphocytic infiltration, and perivascular lymphocytic infiltration in the upper dermis (haematoxylin-eosin; original magnification: ×100). **C**) CCR4 expressed by the infiltrating lymphocytic cells (immunohistochemistry; original magnification: ×100). **D**) Fourteen months after the initial presentation, skin symptoms resolved after dupilumab therapy.

XLA, a primary humoral immunodeficiency due to defects in Bruton's tyrosine kinase, is characterized by impaired B cell development, severe hypogammaglobulinaemia, and increased susceptibility to infections [1, 2]. AD in patients with XLA without elevated IgE levels has been described in a few studies [1, 2]. Inflammation in AD is thought to be initiated by a disruption of the skin barrier and activation of epidermal dendritic cells and innate lymphoid cells, which leads to the activation of the T helper type 2 (Th2) pathway [3]. Our case further validates the notion that IgE production is not necessary for the onset and maintenance of AD. Additionally, CCR4 -a receptor for a Th2 type chemokine, TARC [4]- was expressed by the infiltrating lymphocytic cells in this case, suggesting the involvement of type 2 inflammatory response in AD in patients with XLA. This is the first report to show the efficacy and safety of dupilumab,

a human monoclonal antibody for the α subunit of interleukin (IL) -4 receptor, for treating AD in a patient with XLA. Several studies have demonstrated that colonization with *S. aureus* is associated with the severity of AD, and *S. aureus* can exacerbate AD by triggering inflammatory responses [5, 6]. In this case, cutaneous *S. aureus* was isolated from the lesional skin, indicating that susceptibility toward *S. aureus* may either be due to and/or may have facilitated the development and exacerbation of AD. While conventional AD treatment can cause immunosuppression, dupilumab specifically targets the Th2 axis by blocking IL-4 and IL-13 signals and rather reduces the risk of skin infections probably by improving skin barrier function and changing the microbiome [7].Therefore, dupilumab is a promising option for treating AD in patients with XLA.

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Conflicts of interest: none. Ethical approval and informed consent: All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee, and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Previous presentation: An oral presentation of this case was presented at the 44th Annual Meeting of the Japanese Society of Pediatric Dermatology. ■

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Successful hybrid grafting of autologous cultured epidermis carrying a revertant mutation and split mesh skin in a patient with recessive dystrophic epidermolysis bullosa

We herein report successful re-epithelization of refractory ulcers using an autologous cultured epidermal sheet carrying a revertant mutation and concomitant mesh skin grafting in a patient with recessive dystrophic epidermolysis bullosa (RDEB).

A 41-year-old man diagnosed with RDEB had been suffering from erythematous hypertrophic scars and ulcers, especially on the extremities and upper back to nape (*figure 1A*). Repeated scratching due to severe itching, resistant to any medication, resulted in an insufficient cure of ulcers over a decade. According to a recent proposal concerning revertant mosaicism (RM), defined as the recovery of mutated type VII collagen gene by conversion or double crossover [1], we attempted to detect a revertant mutation in a skin specimen from the right shoulder, where he had developed fewer blisters and ulcers (*figure 1A; inset*). Our gene mutation analyses of the affected skin by Sanger sequencing revealed heterozygous pathogenic mutations in *COL7A1*, c.8440C > T (p.R2814X) and c.8569G > T (p.E2857X) (*figure 1B, upper panels*) [4]. In contrast, samples of the revertant skin revealed that c.8440 C > T was much less represented, while the c. 8569 G > T mutation was detected as expected (*figure 1B, lower panels*). Since we detected the revertant normal sequence at nucleotide 8440 in 21 out of 56 clones examined by the previous method [2], we used this skin to establish an autologous cultured epidermal sheet (brand name JACE®, J-TEC Co., Ltd., Japan), produced by the modified Green method [3]. In brief, keratinocytes isolated with trypsin from the patient's skin were inoculated on the irradiated feeder layer of 3T3-J2 and cultivated in medium at 37 °C in 10% CO_2. After passaged cultures reached confluence, the keratinocyte sheets were detached from the flask using dispase and sealed in packages (*figure 1C, inset*).

Controlling lesional skin infection, we successfully transplanted split-thickness 1:6 mesh skin graft and applied concomitant JACE® to refractory ulcers from the nape to upper back after removing the residual blister roof (*figure 1C*). While tiny ulcers recurred, the severe itching experienced prior to surgery improved considerably, and long-lasting erythema at the scar site had almost disappeared eight months after grafting (*figure 1D*). An immunohistochemical analysis confirmed a linear expression of type VII collagen along the basal membrane on the grafted recipient site (*figure 1E*).

RDEB is classified as the most severe type of congenital epidermolysis bullosa. This disease carries a type VII collagen gene mutation causing incurable cycles of ulceration, scarring, and further high incidence of squamous cell carcinoma. The phenomenon of RM, found in certain epidermolysis bullosa patients, reflects the acquired repair of genetic abnormalities which leads to re-establishment of protein function [1]. Regarding the revertant mosaicism seen in this case, we speculate that wild-type *COL7A1* in one allele could have been restored by one of two mechanisms: chromosome recombination (two mutations onto one chromosome) or somatic mutation (correction of a pathogenic mutation via a somatic point mutation) [1]. Given that we detected fewer c.8440 C > T mutations in revertant skin, somatic mutations may have occurred in revertant skin, however, further detailed analyses are required. The clinical application of autologous cultured epidermal sheets carrying a revertant mutation has been