Dupilumab provides rapid improvement for morphologic variants of paediatric atopic dermatitis: A case series

Sir,

Recent studies have demonstrated that Th2 immune mediators, interleukin-4 and interleukin-13, may play a key role in the development of atopic dermatitis. This has led to the advent of dupilumab for the targeted treatment of refractory atopic dermatitis.[1] Morphological variants of atopic dermatitis including nummular eczema and prurigo-nodularis, deviate from the classic flexural dermatitis.[2] These variants are particularly resistant to conventional treatments including systemic immunosuppressive agents.[3,4] Dupilumab has demonstrated excellent treatment response in adults with nummular eczema and prurigo-nodularis.[3,4] Although the indication of dupilumab was extended from adult patients to paediatric atopic dermatitis patients,[5] there is limited evidence regarding dupilumab effectiveness in paediatric patients with morphologic variants of atopic dermatitis. We present four paediatric cases with morphological variants of atopic dermatitis, who demonstrated dramatic improvement with dupilumab.

Overall four patients (aged 6–8 years, three males and one female) received dupilumab for atopic dermatitis between July 2020 and June 2021, in the dermatology clinic at Seoul National University of Bundang Hospital in Korea. The diagnosis of atopic dermatitis was confirmed by Hanifin and Rajka criteria and classified into specific morphologic phenotypes by an experienced dermatologist of the reference hospital.

Atopic dermatitis onsets for most patients were reported before the age of four months. All patients had generalised multiple eczematous lesions that were either refractory or minimally responsive to conventional treatments ranging from topical agents to systemic agents including cyclosporine and narrow-band ultraviolet-B therapy. Initial Eczema Area and Severity Index (EASI) of the subjects ranged from 17.1 to 24.7. Initial Investigator Global Assessment (IGA) scored 4 in all patients [Table 1]. All patients were treated with dupilumab at a starting dose of 600 mg subcutaneously followed by 300 mg every four weeks. All patients demonstrated remarkable clinical improvement after their first injection [Figures 1–4]. Based on IGA, all of our patients showed at least a 2-point

Table 1: Baseline characteristics and treatment response of paediatric AD patients treated with dupilumab

Patient no.	Age at DPLM initiation (y)	Gender	Onset of AD	Other atopic/ allergic conditions	Initial total IgE (IU/mL)	Phenotype of AD	EASI				IGA				Weight(kg)	Previous therapies
							Wk 0	Wk 4	Wk 16	Wk 24	Wk 0	Wk 4	Wk 16	Wk 24		
1	7	M	3 mo	Food allergy	>2500	Nummular eczema	24.7	2.8	1.2	0	4	2	1	0	20.0	TCSs, TCIs, CsA
2	6	M	4 mo		98.85	Prurigo nodularis	21.6	2.9	0	0	4	2	0	0	19.0	TCSs, TCIs, NB-UVB, CsA
3	8	F	Infancy		NA	Prurigo nodularis	17.1	2.3	0	0	4	1	0	0	26.0	TCSs, TCIs
4	7	M	1 mo	Food allergy, allergic rhinitis	20,000	Prurigo nodularis	20.2	4.8	NA	NA	4	1	NA	NA	22.0	TCSs, TCIs, NB-UVB

DPLM: Dupilumab, AD: Atopic dermatitis, y: Year, mo: Month, wk: Week, IgE: Immunoglobulin E, IGA: Investigator's global assessment, EASI: Eczema area and severity index, TCS: Topical corticosteroid, TCI: Topical calcineurin inhibitor, NB-UVB: Narrow band ultraviolet B, CsA: Cyclosporine, NA: Not assessed

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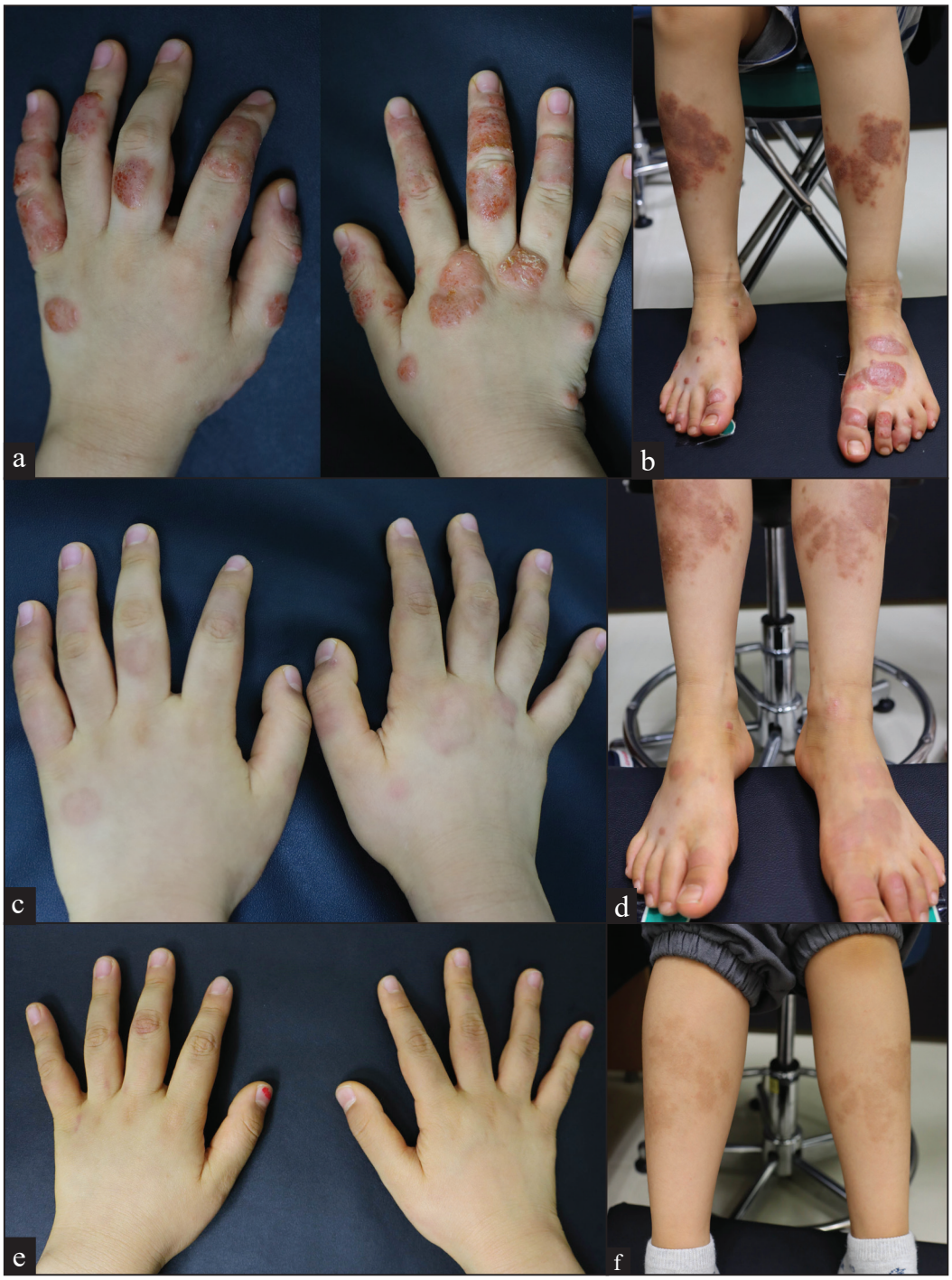

Figure 1a to f: Clinical images of patient 1 (atopic dermatitis with nummular eczema phenotype) at (a and b) baseline, (c and d) four weeks and (e and f) six months after their first injection of dupilumab

reduction in score from baseline by week four and two patients achieved a score of zero by week 16. Based on EASI, all patients achieved at least 75% improvement (EASI–75) by week four. Most patients achieved IGA 0–1 by week 16 and these improvements were maintained over the next six months. Regarding adverse effects, only one patient reported mild conjunctivitis after initiation of dupilumab, which resolved with antihistamine ophthalmic solution.

The results from our dupilumab study in paediatric atopic dermatitis patients with nummular eczema and prurigo-nodularis phenotypes are consistent with previous findings in adult atopic dermatitis patients. In our resistant cases, dupilumab provided dramatic therapeutic responses as early as four weeks after initial administration. Our findings suggest that dupilumab can be an effective treatment not only for classic, typical atopic dermatitis but also for morphological

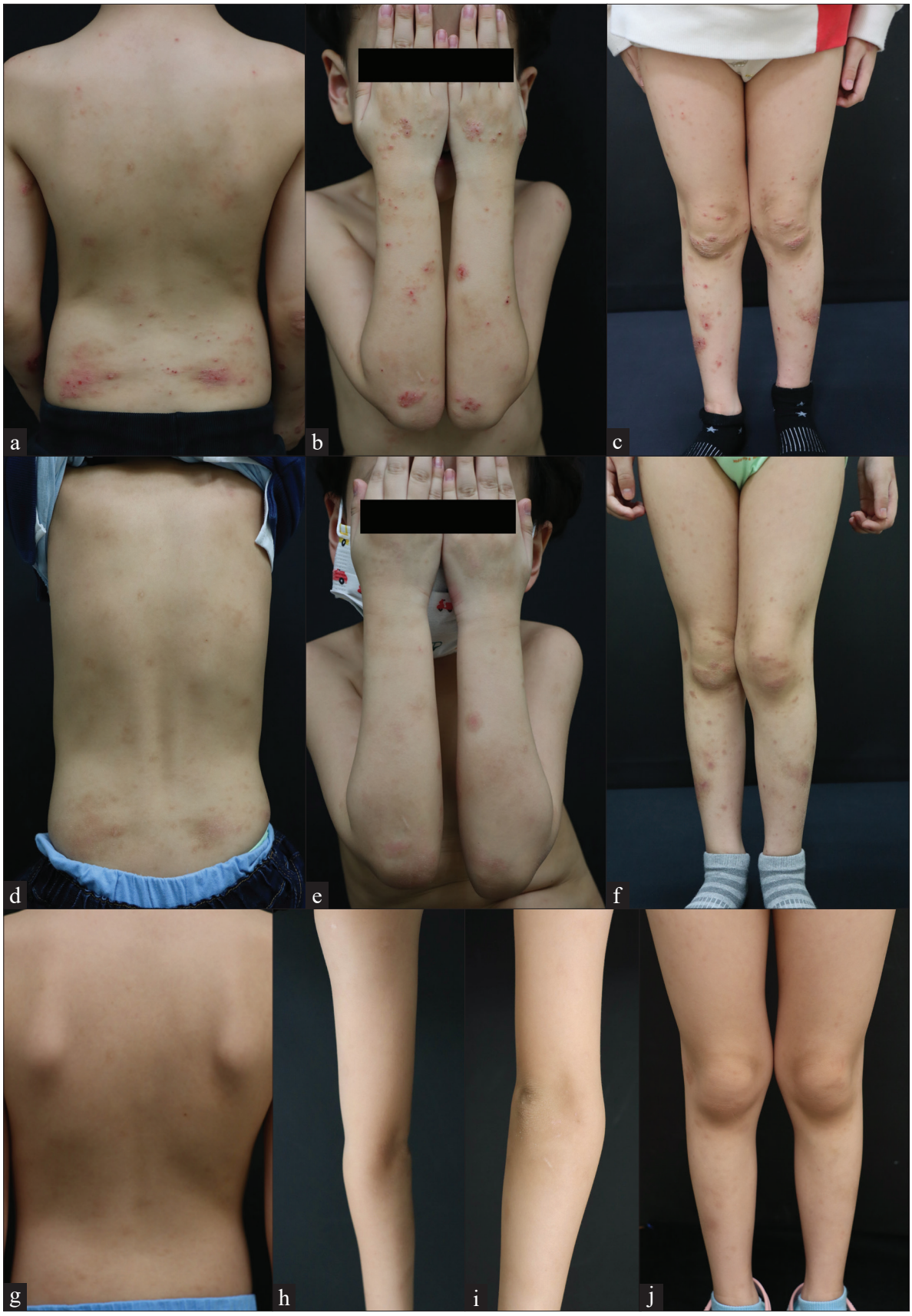

Figure 2a to j: Patient 2 (atopic dermatitis with prurigo nodularis phenotype) at (a–c) baseline, (d–f) four weeks and (g–j) six months after their first injection of dupilumab

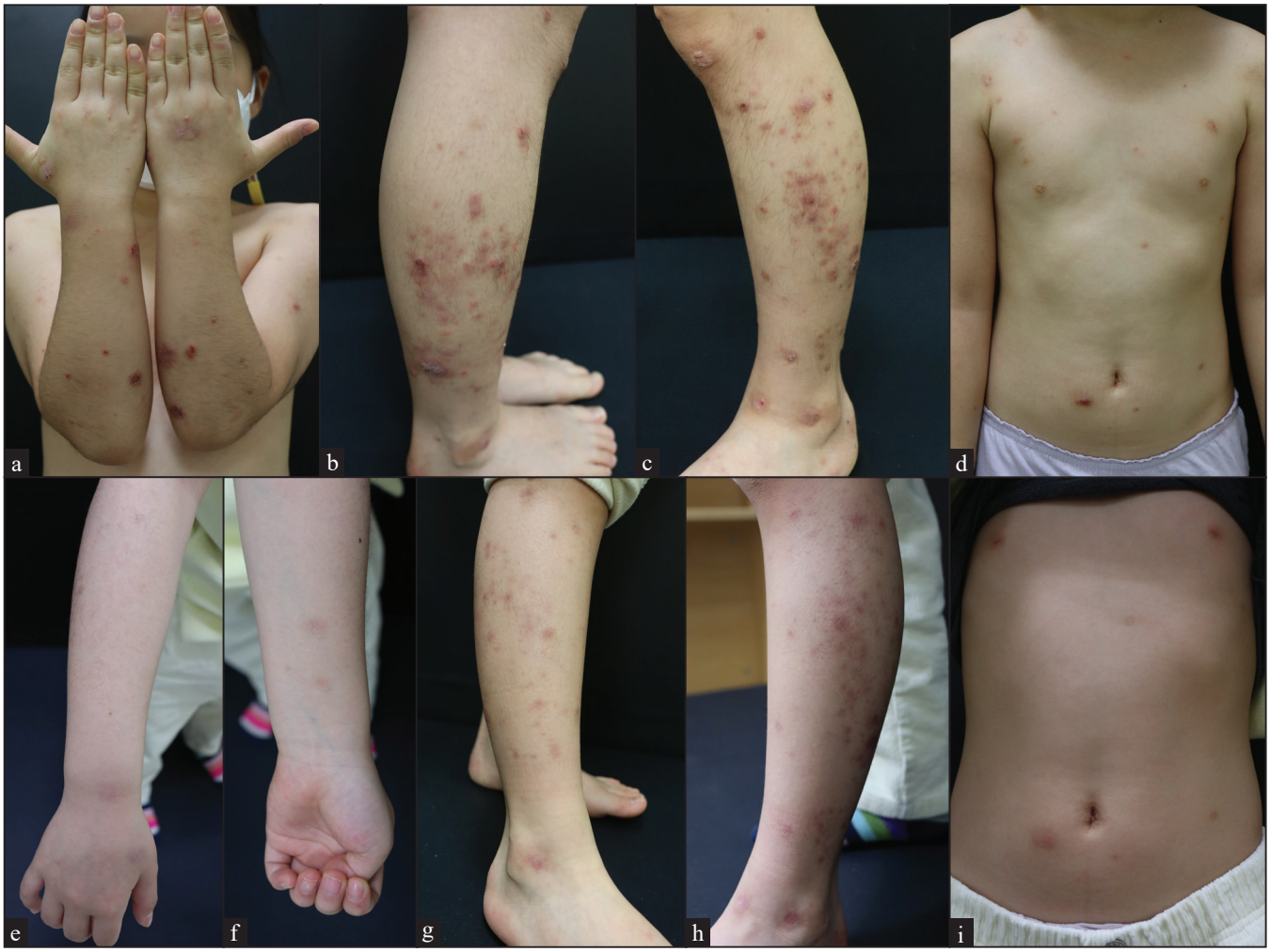

Figure 3a to i: Patient 3 (atopic dermatitis with prurigo nodularis phenotype) at (a–d) baseline and (e–i) four weeks after their first injection of dupilumab

variants of atopic dermatitis, especially in the understudied paediatric patient population.

All our cases who received dupilumab showed dramatic improvement in IGA or EASI score by week four, which were usually maintained over the next six months. These results are consistent with previous clinical studies in which atopic children (age 6–11 receiving dupilumab required only four weeks to achieve a significant improvement in EASI–75 response ($P \leq 0.0001$) compared to the placebo group, whereas adult atopic dermatitis patients required 16 weeks to demonstrate a similar statistical difference.[5,6] Another report highlighted a 5-year-old patient with severe atopic dermatitis achieving IGA score 1 only two weeks after dupilumab initiation.[7] These findings support the conclusion that dupilumab may provide more rapid improvement in paediatric atopic dermatitis patients compared to adult atopic dermatitis patients.

This variable therapeutic timing may be attributed to differences in immune phenotypes between paediatric and adult atopic dermatitis patients. Based on previous findings, paediatric atopic dermatitis is characterised by Th2 and Th17 axis-skewing, while adult atopic dermatitis is characterised by Th2, Th22 and Th1 axis-skewing.[8,9] Chronic atopic dermatitis lesions in adults have demonstrated increased Th1 axis activation parallel to intensified Th2 and Th22 responses,[9] while acute or subacute atopic dermatitis lesions in childhood are characterised by a less activated Th1 axis. Additionally, dupilumab significantly reduced the expression of genes involved in type II inflammation and Th17/Th22 activity with no effect on Th1 gene expression.[10] These differences in immune phenotypes may subject atopic dermatitis in early childhood to a more rapid response to dupilumab compared to adult atopic dermatitis. We were unable to find any previous reports demonstrating the clinical efficacy of dupilumab in morphological variants of atopic dermatitis in early childhood. In contrast to conventional treatments which often prove refractory in children with nummular eczema or prurigo-nodularis phenotypes, dupilumab remains effective in managing morphological variants of atopic dermatitis in early childhood.

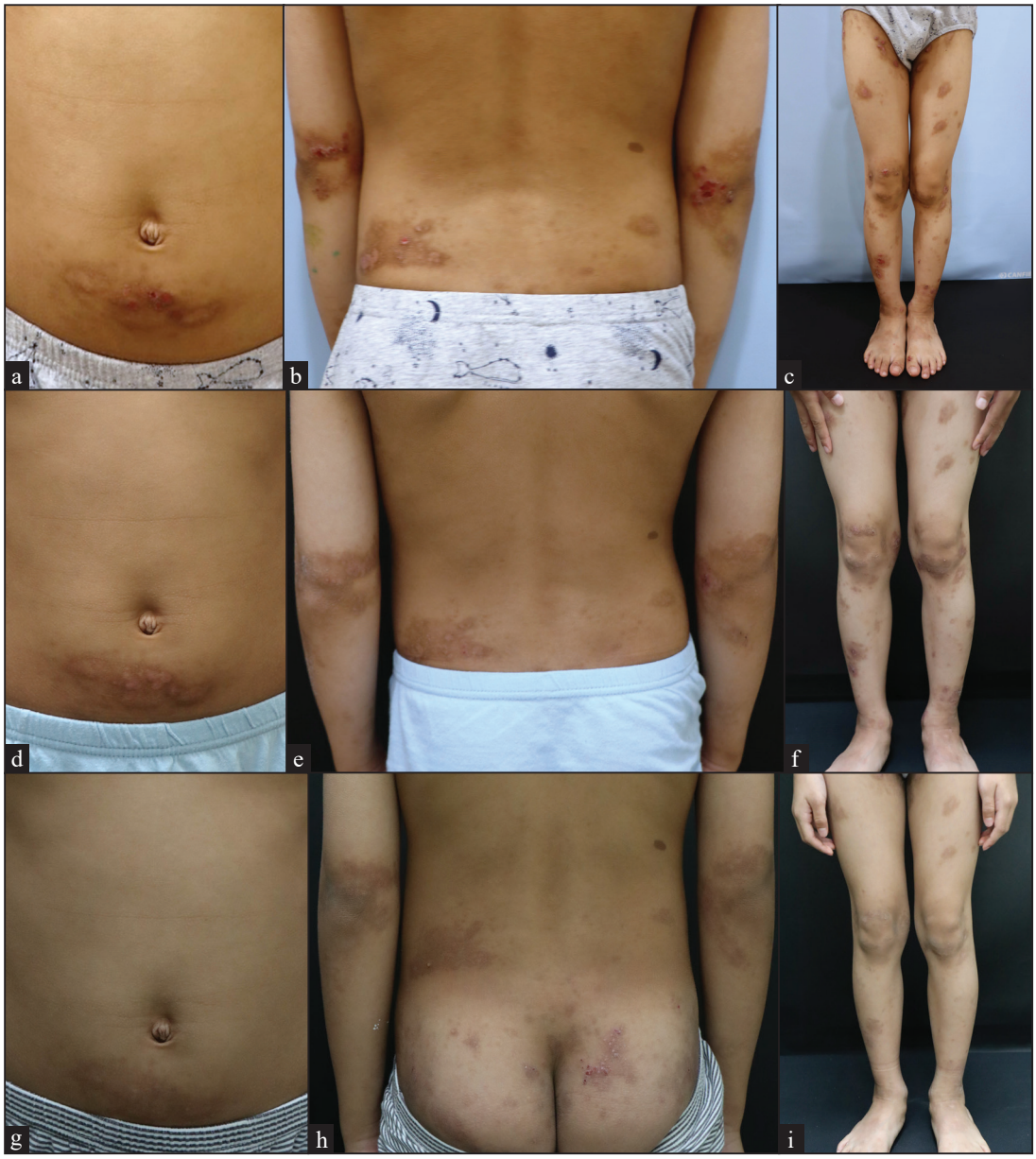

Figure 4a to i: Patient 4 (atopic dermatitis with prurigo nodularis phenotype) at (a–c) baseline, (d–f) four weeks and (g–i) six months after their first injection of dupilumab

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Conflict of interest

There are no conflicts of interest.

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Swift one-stage reconstruction of two adjacent nasal defects with a modified bilobed flap

Sir,

The nasal area, which has complex three-dimensional structures, limited mobility and cosmetic importance, is one of the most difficult areas for dermatologic surgery reconstruction. Although a few possible options are noted for reconstructing multiple skin defects,[1] those involving two adjacent defects ≥1.5 cm on both sides of the nose are challenging. An interesting case of two adjacent nasal defects, where time-saving simultaneous removal with better aesthetic results, with a modified bilobed flap was achieved, is reported in this study.

An 81-year-old female presented with two basal cell carcinomas measuring 1.0 × 1.0 and 0.9 × 0.9 cm on the right nasal sidewall and left nasoalar crease, respectively [Figure 1a]. The patient reported a previous medical history of hypertension, diabetes mellitus, dyslipidemia and coronary artery disease. A physical examination with neck ultrasonography found no evidence of lymph node metastasis. Wide excision with a lateral margin of 3 mm was performed, resulting in a defect measuring 1.7 × 1.3 and 1.5 × 1.4 on the right nasal sidewall and the left nasoalar crease, respectively [Figure 1b].

However, these defects not only spanned over various nose subunits (e.g., dorsum, sidewall and alar lobule), leading to difficulties in achieving esthetic reconstruction, but were also close to the lower eyelid, which could pose a risk of ectropion. Additionally, performing a local flap separately for each defect due to the risk of flap failure was difficult because these defects were located too adjacently, and a two-stage excision and skin grafting or local flap was too time-consuming and labour extensive. To address this problem, designing a bilobed flap and using a redundant tip of the second lobe was essential for reconstruction. First, a pivot point of a bilobed flap, where the two lines connecting the centres of each defect and the pivot point meet at 45°, was set (Figure 2a, red dotted lines). The centre of the first lobe of the bilobed flap was located on the line connecting the centres of the right defect and the pivot point. Due to the right defect, the first lobe obtained a modified short design; therefore, it required a notch on the tip (Figure 2b, red solid line), which lengthened and enlarged it, allowing the left lower defect to be sufficiently covered. Second, the lobe was designed to be long enough to reach the glabella, and a sufficiently long incision towards the pivot point of the lateral margin of the second lobe allowed to overcome the shortness of the first lobe (Figure 2b, black arrow). After removing the Burrow's triangle and undermining the flap, the first lobe covered the lower defect, and the second lobe covered the secondary defect and upper defect at once [Figure 2c]. The flap healed well with a cosmetically good outcome at two months post-surgery [Figure 3].

A bilobed flap is a double transposition flap, usually used for reconstructing defects of the lower third of the nose, where the

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