SHORT COMMUNICATION

Cardio-facio-cutaneous Syndrome with Severe Inflammatory Cutaneous Lesions: Dramatic Effect of Dupilumab

Sara A. ALTANDI[1], Pol A. APOIL[2], Juliette MAZEREEUW-HAUTIER[1]* and Maella SEVERINO-FREIRE[1]
*[1]Department of Dermatology, Reference Center for Rare Skin Diseases, Paul Sabatier University, Larrey Hospital, 24 Chemin de Pouvourville, FR-31059 Cedex 09 Toulouse, and [2]Institut Fédératif de Biologie (IFB) Paul Sabatier University, Toulouse, France. *E-mail: mazereeuwhautier.j@chu-toulouse.fr*
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Cardio-facio-cutaneous syndrome (CFC) is a rare autosomal dominant monogenic disease due to mutations of several genes implicated in the RAS signalling pathway. Patients present with various anomalies including dysmorphic facial features, psychomotor and neurodevelopmental delays, growth retardation, cardiac abnormalities, and skin anomalies. The latter include scarce scalp/eyebrow hair, diffuse keratosis pilaris, ulerythema ophryogenes, multiple melanocytic naevi, palmoplantar keratosis, and a not well characterized inflammatory dermatitis. We herein present the first case of CFC with severe inflammatory dermatitis dramatically improved by dupilumab.

CASE REPORT

A 25-year-old woman presented with an inflammatory dermatitis present since 2 years of age. She was born at term with low birthweight, dysmorphic facies, macroglossia, very thin eyebrows, and scarce hair. Family history included bronchial asthma (father and paternal grandmother). A diagnosis of CFC was made, based on the presence of hypertrophic cardiomyopathy, failure to thrive, delayed psychomotor development, and neurological anomalies. Molecular analysis revealed a heterozygous mutation of *BRAF* (c1406G>A (p.GGly469Glu)). Skin lesions consisted of diffuse erythematous lesions covered by thick scales (**Fig. 1**a), yellowish palmoplantar keratoderma, coarse and unruly hair, and thick hyperkeratotic scalp plaques. Quality of life was severely impacted by severe itching and sleep disturbance. Over the years, she presented with multiple episodes of worsening of skin findings, together with pustules/blisters and staphylococcus superinfections. Her skin condition continued to worsen with time. We noticed a failure of all topical (steroids, calcineurin inhibitors, and vitamin D3 analogues) or systemic medications (acitretin up to 0.5 mg/kg, methotrexate 20 mg/week, subcutaneous injections of ustekinumab 45 mg every 12 weeks). Subcutaneous injections of dupilumab 300 mg every 15 days were started at the age of 24 years: time before treatment (T1). After 3 months (T2) there was a dramatic reduction in skin lesions and pruritus, permitting a complete cessation of topical steroid use (**Fig. 1**b). Palmoplantar keratoderma remained unchanged. The patient did not experience any side effects. The treatment is still ongoing and the improvement is maintained after 24 months of follow-up.

At T1, and as frequently observed in patients with chronic inflammatory dermatitis, the patient had an extended sensitization profile, with presence of specific immunoglobulins (Ig) against 26 of the 112 molecular allergens displayed on ImmunoCAP™ ISAC. At T2, sensitization against these allergens had decreased by a mean value of 83% (**Fig. 2**). However, specific IgE measurements with biochips are influenced by competition from specific IgG, and thus can show falsely low IgE (1). Indeed, total IgE concentration in the patient's serum diminished by only 58%, from 4,539 kU/L at T1 to 1,924 kU/L at T2. This was paralleled by singleplex specific IgE measurements for 9 molecular allergens, which decreased by 51% (86% for the same 9 allergens on ISAC (**Fig. 3**).

DISCUSSION

This is the first report of the efficacy of dupilumab on the inflammatory dermatitis of CFC. Dupilumab is approved for the treatment of atopic dermatitis (AD), and there is now growing evidence in the literature supporting its off-label use in the treatment of other dermatological diseases such as Netherton syndrome (2, 3), dermatitis related to immunodeficiency disorders such as TTC7A (4) and DOCK8-deficiency (5), as well as acantholytic disorders (6, 7). The inflammatory dermatitis of CFC has not been well described and was named "eczematous dermatitis, ichthyosis or 'ichthyosiform hyperkeratosis' in some patients" (8–11).

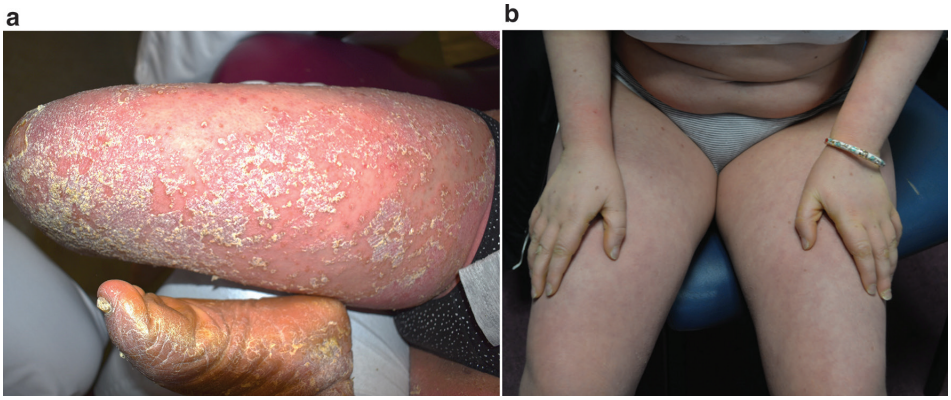

Fig. 1. (A) Diffuse erythematous lesions covered by thick scales at T1 before treatment. (B) Resolution of skin lesions after 3 months of dupilumab (T2).

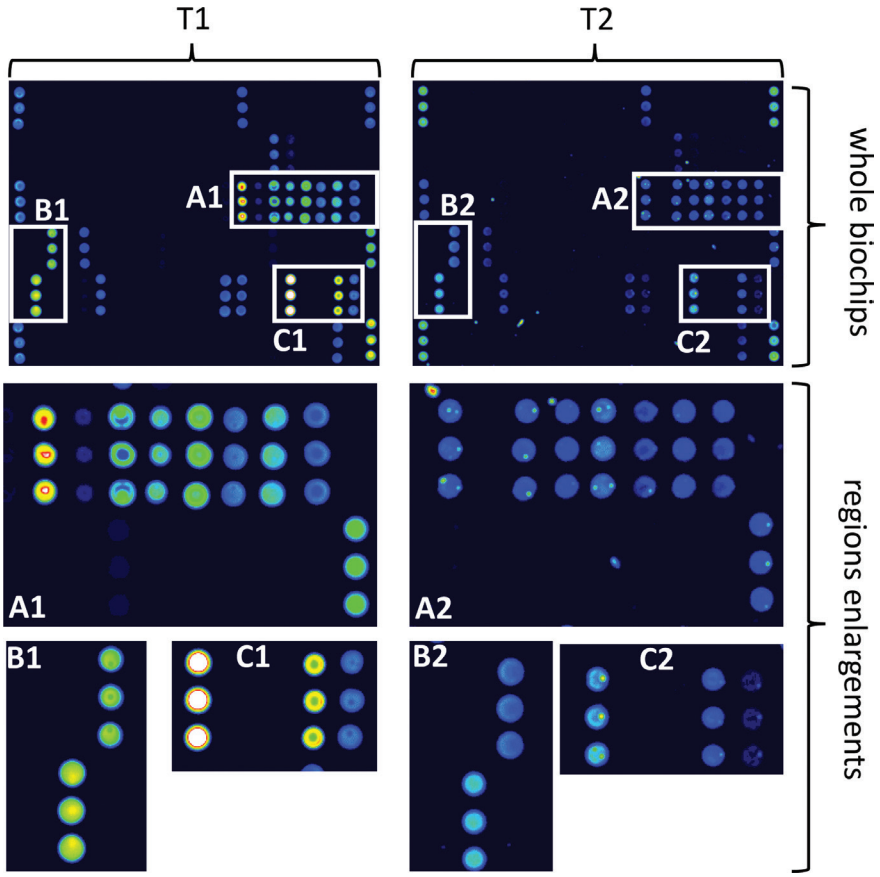

Fig. 2. ImmunoCAP™ ISAC: T1: extended sensitization profile with presence of specific immunoglobulins (Ig) against 26 of the 112 molecular allergens. T2: sensitization against these allergens had decreased by a mean value of 83%. T1: Time before treatment, T2: After 3 months of treatment.

The severity of our patient's dermatitis seems to be unusual (only 2 other comparable severe cases) (10,11). It seems different from psoriasis or AD.

No other treatment has been described as effective in CFC, except for acitretin for palmoplantar keratoderma (12), and topical steroids for the inflammatory dermatitis.

Despite dupilumab therapy being capable of inducing drastic reductions of IgE synthesis in patients with atopic dermatitis (13), the reduction of IgE concentrations at 18 months of treatment is moderate in this case of CFC. This is in contrast with the observed strong and durable improvement of skin symptoms.

Thus, we estimate that our patient's good clinical response to dupilumab therapy can be explained if CFC cutaneous anomalies, as in other chronic skin diseases, are mainly driven by an excessive type 2 immune response. Overactivity of the type 2 pathway, through excessive production of IL-4 and IL-13 by innate type 2 lymphoid cells (ILC2) cells and Th2 lymphocytes, results in additional alterations of skin permeability (14). Overproduction of IgE in individuals with increased skin permeability is well characterized. However, IgE themselves play a reduced role in the severity of skin symptoms and IgE levels are uncoupled from the inten-

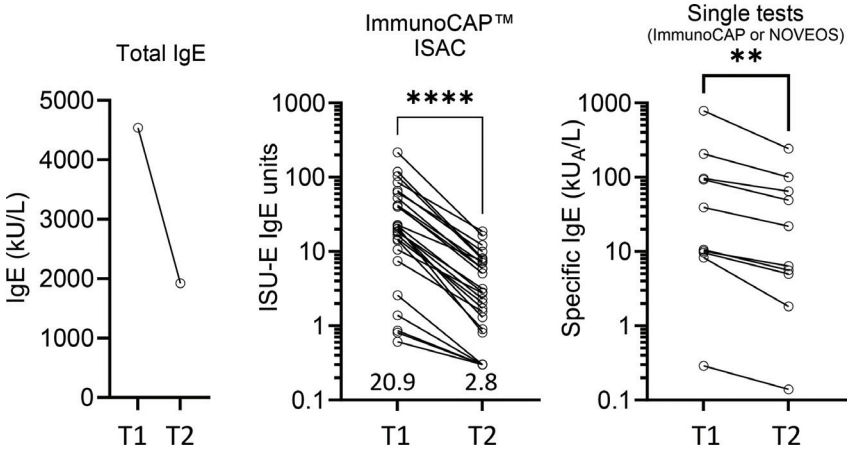

Fig. 3. Total IgE concentration in patient's serum in parallel to singleplex and ImmunoCAP™ ISAC: diminution by only −58%, from 4,539 kU/L at T1 to 1,924 kU:L at T2. This was paralleled by singleplex specific IgE measurements for 9 molecular allergens, which decreased by −51% (−86% for the same 9 allergens on ISAC). T1: Time before treatment, T2: After 3 months of treatment.

sity of skin symptoms (15). The moderate decrease of IgE (total and specific) in our patient after 18 months of dupilumab can probably be explained by the persistence of long-lived IgE-producing plasma cells.

In conclusion, dupilumab induced a dramatic clinical improvement and some biological changes. More cases are needed to conclude and understand the benefit of dupilumab in CFC dermatitis.

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