JOURNAL OF
CUTANEOUS IMMUNOLOGY
AND ALLERGY

TYPE Case Report
PUBLISHED 31 August 2026
DOI 10.3389/jcia.2026.17346

OPEN ACCESS

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RECEIVED 10 July 2026
REVISED 29 July 2026
ACCEPTED 04 August 2026
PUBLISHED 31 August 2026

CITATION
Nonaka T, Kido J, Ogata M, Miyake T, Yoshida T, Fukushima S, Seyama R, Uchiyama Y, Matsumoto N and Nakamura K (2026) Case Report: Successful dupilumab treatment for refractory atopic dermatitis-like eczema in a patient with Costello syndrome. *J. Cutan. Immunol. Allergy* 9:17346. doi: 10.3389/jcia.2026.17346

Case Report: Successful dupilumab treatment for refractory atopic dermatitis-like eczema in a patient with Costello syndrome

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Costello syndrome is a rare RASopathy caused by pathogenic variants in *HRAS* and is characterized by distinctive craniofacial features, growth failure, cardiac abnormalities, tumor predisposition, and various cutaneous manifestations. Although eczema has been reported in patients with Costello syndrome, reports of severe AD-like eczema accompanied by clinically significant allergic manifestations, including food allergy, remain limited. We report a female patient with Costello syndrome caused by a heterozygous *HRAS* variant, NM_005343.4: c.37G>T, p.(Gly13Cys), who developed severe atopic dermatitis-like eczema and hen's egg and cow's milk allergies from infancy. Despite treatment with topical anti-inflammatory agents and emollients, her AD-like eczema remained refractory. Add-on dupilumab therapy was initiated in adolescence, resulting in marked improvement in her skin manifestations within 1 month, and clinical improvement was maintained during subsequent follow-up. This case suggests that dupilumab may be an effective therapeutic option for refractory atopic dermatitis-like eczema associated with Costello syndrome. The clinical course also supports the possible contribution of epithelial-driven type 2 inflammation to severe allergic manifestations in Costello syndrome, although direct mechanistic evidence was not obtained.

KEYWORDS
atopic dermatitis, case report, costello syndrome, dupilumab, *HRAS*

Introduction

Costello syndrome (CS) is a RASopathy caused by heterozygous activating germline variants in the proto-oncogene *HRAS* located on chromosome 11p15.5. The RAS–MAPK signaling pathway plays a critical role in regulating cell proliferation and differentiation [1].

Patients with CS exhibit multisystem involvement affecting the skin, cardiovascular, neurological, musculoskeletal, and gastrointestinal systems. Characteristic clinical features

include distinctive craniofacial features, curly hair, cardiac abnormalities such as hypertrophic cardiomyopathy, pulmonary valve stenosis, and arrhythmias, developmental delay, deep palmar and plantar creases, papillomas of the nose and perianal region, and feeding difficulties with failure to thrive beginning in infancy [2]. In addition, CS is associated with an increased risk of malignancies, including rhabdomyosarcoma, neuroblastoma, and bladder carcinoma.

Activation of the RAS–ERK/MAPK pathway promotes type 2 helper T (Th2) cell differentiation through stabilization of GATA3 in T cells [3], and has been proposed as one of the mechanisms underlying the increased susceptibility to allergic diseases presented in RASopathies. Furthermore, *HRAS* variants lead to hyperactivation of the RAS–ERK pathway in keratinocytes, resulting in impaired skin barrier function and the induction of Th2-type inflammation through increased production of epithelial-derived alarmins, including interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP). Consequently, patients with CS are considered predisposed to developing atopic dermatitis-like skin lesions [4].

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic eczema with a typical symmetrical distribution and a relapsing–remitting course. Most patients have an atopic predisposition characterized by a tendency to produce immunoglobulin E (IgE) [5, 6]. Skin barrier dysfunction facilitates allergen entry and induces type 2 inflammation, leading to the production of allergen-specific IgE and contributing to the development of sensitization [7, 8].

The atopic March refers to the sequential development of allergic diseases, beginning with AD in infancy and followed by food allergy, asthma, and allergic rhinitis [9]. In this process, skin barrier dysfunction during infancy is thought to induce type 2 inflammation and to be closely associated with the development of food allergies. Indeed, infantile AD is strongly associated with food allergy [8], and a systematic review reported that 30%–40% of infants with AD develop food allergy [10].

Here, we report a girl with CS who developed severe AD-like eczema from infancy, accompanied by severe IgE-mediated hen's egg and cow's milk allergies with anaphylaxis, and discuss the possible mechanisms underlying her allergic manifestations and the therapeutic effects of dupilumab.

Case description

She was born to non-consanguineous parents after a pregnancy complicated by polyhydramnios and threatened preterm labor, which required maternal transfer to a tertiary care center. She was delivered vaginally in the cephalic presentation at 37 weeks and 3 days of gestation with a birth weight of 3,980 g, corresponding to large for gestational age according to Japanese neonatal anthropometric standards [11]. Her Apgar scores were 6 and 7 at 1 and 5 min, respectively.

After birth, she was admitted to the neonatal intensive care unit because of transient tachypnea of the newborn. Although mechanical ventilation was not required, supplemental oxygen was needed until day of life (DOL) 22 because of persistent tachypnea. She was discharged on DOL 33; however, vomiting and feeding difficulties persisted thereafter. Tube feeding was required until DOL 40, and feeding difficulties continued until approximately 6 months of age. During the neonatal period, she received mixed feeding with breast milk and standard cow's milk-based infant formula. After discharge, she was fed exclusively with breast milk. Complementary feeding was initiated at 7 months of age.

During infancy, hepatomegaly of unknown etiology, shortening of the extremities, macroglossia, curly sparse hair, and characteristic facial features were noted. Chromosomal analysis, tandem mass spectrometry-based newborn screening, plasma amino acid analysis, echocardiography, brain magnetic resonance imaging, and automated auditory brainstem response testing did not reveal a definitive diagnosis.

At approximately 1 month of age, she developed severe eczematous skin lesions resembling atopic dermatitis (AD). Despite continuous treatment with topical corticosteroids, eczema and pruritus persisted and were occasionally accompanied by bleeding and erosions (Figure 1). Her family history was notable for allergic diseases. Her father had urticaria, and her mother had sensitive skin. Her elder brother had bronchial asthma and cow's milk allergy that resolved at 5 years of age. Another elder brother had bronchial asthma and pollen-food allergy syndrome triggered by melon and tomato. Her younger sister had bronchial asthma and atopic dermatitis.

She fulfilled the Hanifin and Rajka diagnostic criteria for AD [12], including pruritus, typical morphology and distribution of eczematous lesions, a chronic relapsing course, early age of onset, and a family history of atopic diseases.

At 6 months of age, laboratory evaluation demonstrated elevated total immunoglobulin E (IgE) levels (138 kU/L), elevated thymus and activation-regulated chemokine (TARC) levels (4,744 pg/mL), and eosinophilia (9.6%; absolute eosinophil count, 1,325 cells/μL), suggesting marked type 2 inflammation. Serum allergen-specific IgE testing using ImmunoCAP® revealed markedly elevated levels for egg white (57.2 UA/mL) and cow's milk (34.0 UA/mL). Therefore, elimination of hen's egg and cow's milk was initiated. Longitudinal changes in laboratory findings are shown in Figure 2.

Oral food challenges (OFCs) for hen's egg and cow's milk were initiated at 3 years and 10 months of age. Although intake was gradually increased based on the tolerated dose determined by OFCs, she repeatedly experienced immediate allergic reactions during attempts to increase intake. Therefore, an epinephrine auto-injector was prescribed. At 10 years of age, she used the auto-injector for anaphylaxis following accidental ingestion of chocolate containing cow's milk. Hen's egg allergy resolved at 12 years of age; however, cow's milk allergy persisted into adolescence, requiring continued avoidance of amounts exceeding her tolerated dose (Supplementary Data 1).

From approximately 2–3 years of age, she experienced wheezing episodes once or twice annually during respiratory infections, and bronchial asthma was suspected. Regular treatment with a leukotriene receptor antagonist was initiated.

During early childhood, marked growth impairment became evident, with height decreasing to approximately −5 SD, while body weight remained around −2 SD (Supplementary Data 2).

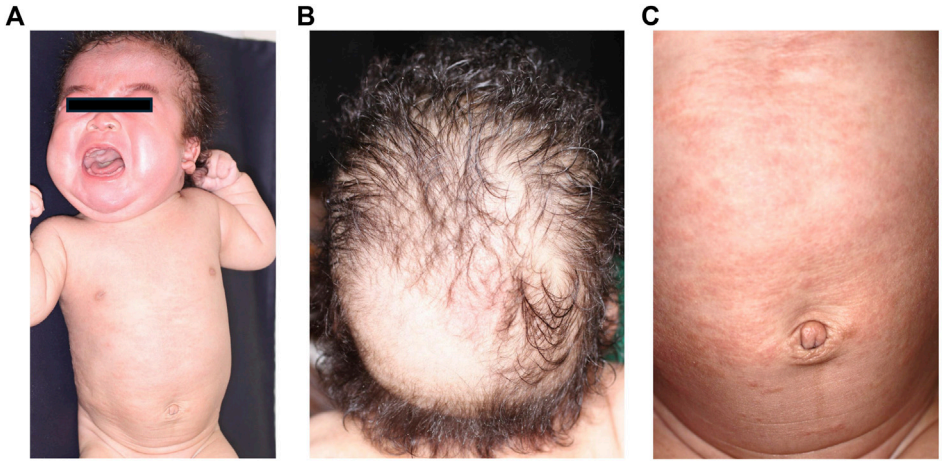


FIGURE 1
Severe AD-like eczema during infancy **(A)** Whole-body appearance. **(B)** Head **(C)** Abdomen. Diffuse erythema, excoriations, and eczematous lesions were observed from infancy, consistent with the early onset of severe AD-like skin manifestations.

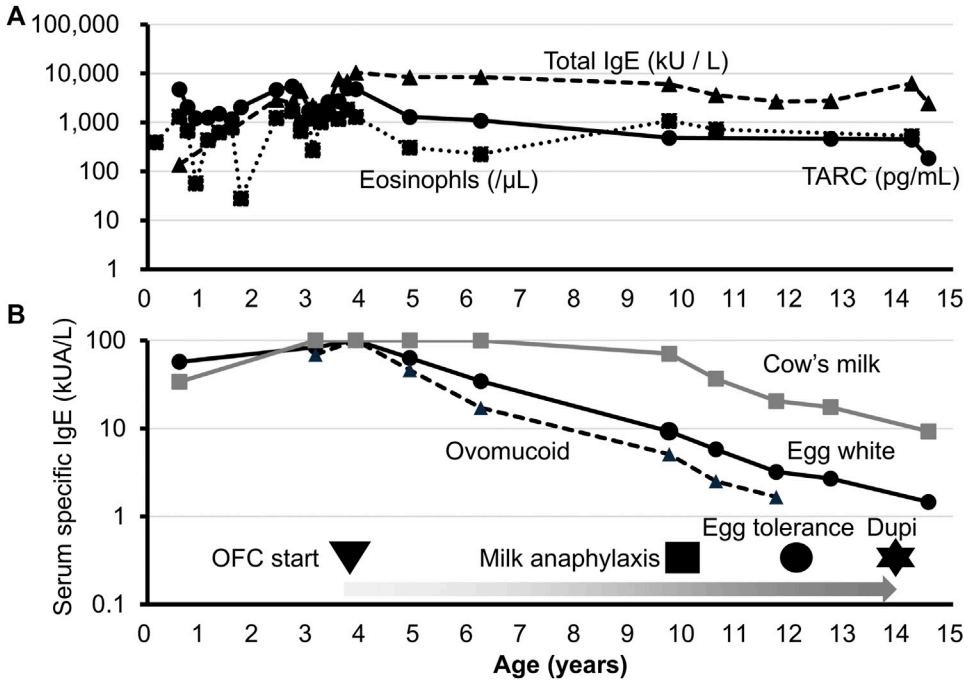
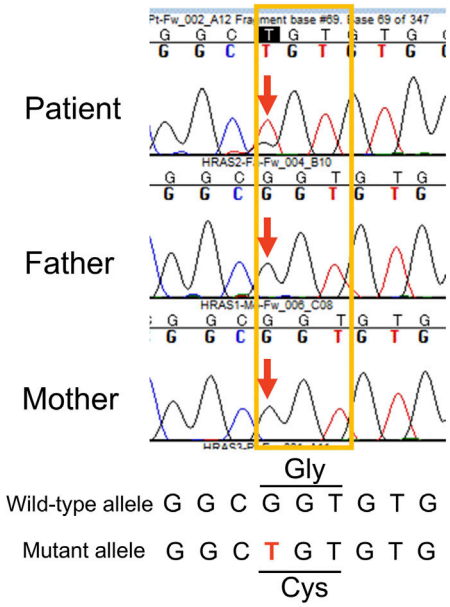


FIGURE 2
Temporal changes in laboratory findings and major clinical events. **(A)** Total immunoglobulin E (IgE), thymus and activation-regulated chemokine (TARC), and absolute eosinophil count. **(B)** Allergen-specific IgE levels for egg white, ovomucoid, and cow's milk. Values reported as >100 kUA/L were plotted as 100 kUA/L. The y-axes are shown on a logarithmic scale. The gray arrow indicates the period of OFC-guided intake increase based on tolerated doses. Symbols indicate OFC initiation (▼), cow's milk–induced anaphylaxis (■), hen's egg tolerance (●), and initiation of dupilumab therapy (★; Dupi).

At 4 years of age, Netherton syndrome was suspected because of her curly sparse hair and refractory AD-like eczema; however, no pathogenic variants were identified in *SPINK5*. At 7 years and 10 months of age, she participated in the Initiative on Rare and Undiagnosed Diseases (IRUD) project in Japan [13] and underwent whole-exome sequencing, which identified a heterozygous *de novo HRAS* variant, NM_005343.4: c.37G>T, p.(Gly13Cys) (Figure 3), confirming the diagnosis of CS.

At 14 years of age, dupilumab therapy was initiated for refractory AD-like eczema that remained inadequately controlled despite the appropriate use of high-potency topical corticosteroids. Her history of elevated total IgE and TARC levels, peripheral blood eosinophilia, and food allergy suggested a prominent type



Gene	Chr	Position	AAChange	SIFT	Poly-phen2	Mutation taster	CADD	In-house JPN	Tommo 3.5K	gnomAD
HRAS	11	534286	c.37G>T p.(Gly13Cys)	0	0.448	Prediction disease causing	27.9	0/575	-	-

FIGURE 3
Genetic analysis of the patient. Sanger sequencing identified a heterozygous *HRAS* c.37G>T (p.Gly13Cys) variant in the patient. Neither parent carried the variant, indicating a *de novo* occurrence.

2 inflammatory component. At dupilumab initiation, her body weight was 37 kg, her Eczema Area and Severity Index (EASI) score was 16, her Investigator's Global Assessment (IGA) score was 4, and approximately 20% of her body surface area was affected.

The treatment was started with a loading dose of 400 mg, followed by 200 mg every 2 weeks. Her skin manifestations improved rapidly and markedly within 1 month after initiation of add-on dupilumab therapy, with almost complete resolution of the eczematous lesions (Figure 4), and clinical improvement was maintained during the available 6-month follow-up period. No serious adverse events related to dupilumab were observed during this period.

The patient and her family reported a substantial reduction in the burden of daily skin care and pruritus after the initiation of dupilumab therapy, along with improved participation in school activities.

Discussion

We report a patient with CS who developed severe AD-like eczema, as well as cow's milk and hen's egg allergies. Although the clinical findings fulfilled the diagnostic criteria for AD, we used the term "AD-like eczema" because the underlying CS may have modified or aggravated the eczematous phenotype in this patient.

Her severe AD-like eczema remained inadequately controlled despite topical corticosteroid therapy, but improved dramatically after the initiation of dupilumab therapy. Dupilumab was selected because the patient had marked type 2 inflammatory features, and targeted inhibition of IL-4/IL-13 signaling was considered a rational therapeutic approach for controlling both eczema and type 2 inflammation in this case. Given her underlying CS and the anticipated need for long-term treatment, dupilumab was considered preferable to broader systemic immunomodulatory therapy. A strength of this case is the genetically confirmed diagnosis of CS and the detailed longitudinal clinical follow-up from infancy through adolescence.

CS is characterized by a variety of cutaneous manifestations, among which papillomas, loose skin, and deep palmar and plantar creases are well recognized. In the present patient, thick eyebrows and sparse hair were recognizable in the clinical photographs (Figures 4A,B), and extracutaneous manifestations included polyhydramnios, large for gestational age at birth, feeding difficulty, growth impairment, and developmental delay. Eczema has also been reported in patients with CS. Siegel et al. reported that eczema was present in 23.9% of patients with CS harboring *HRAS* variants [14].

Katata et al. reported that a mouse model of CS harboring the activating *HRAS* c.34G>A p.(Gly12Ser) variant was predisposed to developing AD-like skin lesions following exposure to house dust mites [4]. They demonstrated that this phenotype was mediated by enhanced activation of extracellular signal-regulated kinase (ERK) in epidermal keratinocytes, impaired skin barrier function, and the

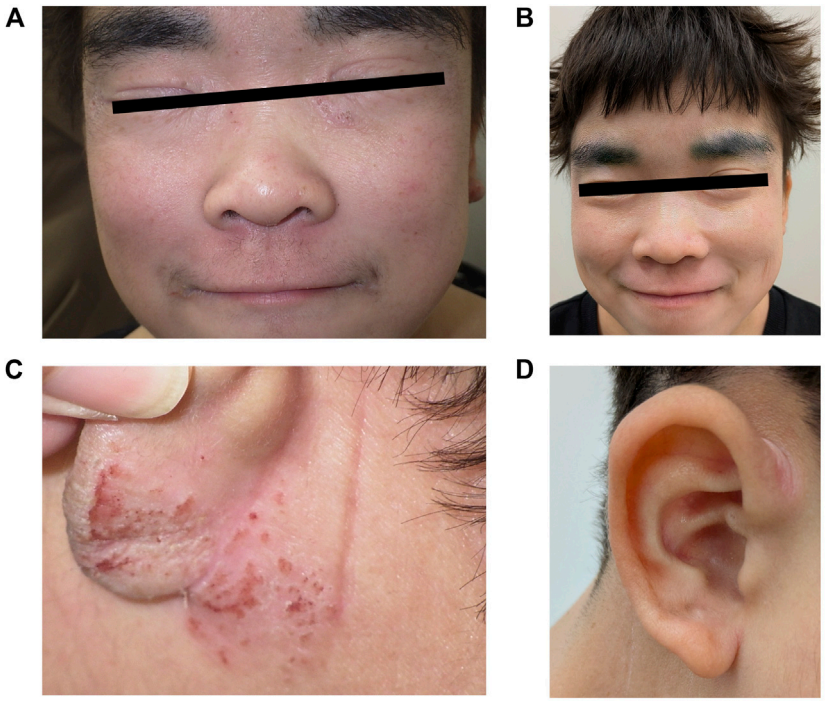


FIGURE 4
Facial and auricular skin manifestations before and after dupilumab therapy. **(A)**. Facial manifestations before dupilumab therapy. **(B)** Facial manifestations 1 month after dupilumab therapy. **(C)** Auricular lesions before dupilumab therapy. **(D)** Auricular lesions 1 month after dupilumab therapy. Marked improvement in facial and auricular erythema, crusting, and excoriations was observed after initiation of dupilumab therapy.

induction of type 2 inflammation through increased production of epithelial-derived alarmins, including IL-33 and TSLP.

The *HRAS* c.37G>T variant identified in our patient differs from the c.34G>A variant used in the mouse model developed by Katata et al. The c.37G>T variant has been associated with a milder clinical phenotype than the c.34G>A variant [2]. Gripp et al. [15] similarly reported that although the phenotype associated with c.37G>T generally resembles that associated with c.34G>A, it is typically milder, with less severe short stature, facial coarsening, and cognitive impairment. Individuals with c.37G>T also have lower frequencies of multifocal atrial tachycardia, papillomata, and neurosurgical interventions, while exhibiting distinctive features such as dolichocilia and loose anagen hair, suggesting variant-specific phenotypic effects. The absence of cardiac complications in our patient was consistent with this relatively mild phenotype. Nevertheless, she exhibited prominent allergic manifestations, including severe, treatment-refractory AD-like eczema and persistent cow's milk allergy.

Therefore, caution may be warranted when extrapolating the mechanisms underlying dermatitis demonstrated in the c.34G>A mouse model to our patient. In addition, several family members of this patient had allergic diseases, suggesting that genetic predisposition and environmental factors related to atopy may also have contributed to the severity of the skin lesions. However, HRAS activation facilitates the development of type 2 inflammation through ERK activation [4]. In the present patient, such epithelial-driven type 2 inflammation may have amplified her atopic predisposition and contributed to the development of severe AD-like eczema.

Egg and cow's milk allergies are commonly associated with infantile AD [7, 10]. In this patient, severe skin barrier impairment associated with severe AD-like eczema is considered to have facilitated epicutaneous sensitization. However, it remains unclear whether HRAS activation directly enhanced the production of egg- or cow's milk-specific IgE antibodies, thereby contributing to the development or persistence of food allergy. Further studies are needed to clarify this issue.

Furthermore, the rapid and marked improvement in the skin lesions following treatment with dupilumab, which blocks IL-4 and IL-13 signaling [16], is consistent with the possibility that HRAS activation-associated epithelial-driven type 2 inflammation contributed to the refractory skin lesions in this patient. Thus, this case suggests a potential role for epithelial-driven type 2 inflammation in the pathogenesis of severe allergic manifestations in CS.

Moreover, this case also suggests that dupilumab may represent an effective therapeutic option for refractory eczema associated with CS. However, reports of dupilumab use in patients with CS remain limited, and its long-term efficacy and safety have not been sufficiently established. Given the increased risk of malignancies and the presence of multisystem complications in CS [2], careful long-term follow-up remains necessary.

In conclusion, we reported on a patient with Costello syndrome who developed severe AD-like eczema and persistent IgE-mediated food allergies and showed a marked clinical response to dupilumab. This case suggests a potential contribution of epithelial-driven type 2 inflammation to severe allergic manifestations in Costello

syndrome and highlights dupilumab as a promising therapeutic option for refractory eczema in affected patients.

Data availability statement

The data supporting the findings of this case report are included in the article and its Supplementary Material. Additional patient-level datasets are not publicly available due to concerns regarding patient anonymity. Further inquiries can be directed to the corresponding author.

Ethics statement

The Ethics Committee of the Faculty of Life Sciences at Kumamoto University approved this study (No. 1574; Genome No. 382). Written informed consent was obtained from the patient's legal representative for publication of this case report and any accompanying images.

Author contributions

TN, JK, TM, and MO contributed to the clinical care of the patient, including therapeutic decision-making. RS, YU, and NM contributed to the genetic diagnosis and interpretation. TN, TM, TY, and MO drafted the manuscript. SF and KN supervised the work. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant-in-Aid for Scientific Research (JP23K07229, 26K10804 to YU, JP24K02230 to NM); the Japan Agency for Medical Research and Development (AMED) (grant numbers JP26ek0109880, JP25ek0109674, JP26ek0109617, JP25ek0109648, JP25ek0109677, and JP26ek0109760 to NM); and the Takeda Science Foundation (to NM).

Acknowledgments

The authors thank the patient and her family for their cooperation in the preparation of this case report. We are grateful to Yohei Misumi and Prof. Mitsuharu Ueda in the Department of Neurology, Graduate School of Medical Sciences, Kumamoto University for their assistance with the Initiative on Rare and Undiagnosed Diseases (IRUD) program.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declared that generative AI was used in the creation of this manuscript. ChatGPT (OpenAI) was used to assist with English language editing and improvement of clarity. All AI-assisted content was reviewed and revised by the authors.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/jcia.2026.17346/full#supplementary-material

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