

## CASE REPORT

# Persistent severe cow's milk protein allergy on strict dietary elimination: A case report and literature review

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**Objective:** Cow's milk protein allergy is among the most common food allergies in early childhood, yet its clinical spectrum can range from mild intolerance to life-threatening anaphylaxis. Rarely, affected children may react not only to ingestion but also to skin contact or inhalation of trace milk proteins. This report presents a detailed case of persistent and extreme hypersensitivity, illustrating the complex immunologic and psychosocial impact of the disease and highlighting the unmet need for refined preventive and therapeutic approaches.

**Methods:** A single pediatric case was analyzed through continuous clinical observation from infancy to seven years of age. The report integrates serial measurements of milk protein-specific immunoglobulin E, documentation of allergic reactions, dietary and environmental management, and psychosocial outcomes. The case description is complemented by a concise review of scientific literature on severe and airborne food allergies.

**Results:** The child exhibited immediate allergic reactions to early milk exposure and developed progressive sensitization over time, culminating in multiple anaphylactic episodes caused by minimal oral, contact, and airborne exposure. Laboratory assessments confirmed rising immunoglobulin E levels despite prolonged elimination of milk from the diet and environment. The literature review identified few comparable cases, confirming the rarity of such severe and persistent allergic phenotypes.

**Conclusions:** Extreme hypersensitivity to cow's milk proteins challenges current concepts of allergy management and tolerance development. This case emphasizes the need for multidisciplinary care, structured education on anaphylaxis response, and greater community awareness to safeguard children with life-threatening food allergies.

**Keywords:** cow's milk protein allergy, anaphylaxis, IgE-mediated allergy

Received 21 November 2025 / Accepted 11 February 2026

## Introduction

Food allergy prevalence has risen in recent decades, with cow's milk protein allergy (CMPA) among the most common in children. CMPA is defined as a reproducible, immune-mediated adverse reaction to one or more cow's milk proteins—most often caseins or the whey protein  $\beta$ -lactoglobulin [1]. CMPA is distinguished from non-immune adverse reactions to cow's milk, such as lactose intolerance, by its immunologic mechanism, timing of symptom onset, and target organs involved [2]. CMPA typically manifests in the first two years of life, most often within the first year, whereas allergies to peanuts, tree nuts, fish, or shellfish more commonly emerge later in childhood or even adulthood [3].

Cow's milk contains approximately 30 to 35 grams of protein per liter, consisting of about 80% caseins and 20% whey proteins. The main whey allergens include alpha lactalbumin and beta lactoglobulin. Smaller amounts of immunoglobulins, serum albumin, and lactoferrin are also present. Caseins comprise alpha S1, alpha S2, beta, and kappa casein, with alpha S1 and beta casein predominant.

Both whey and casein fractions contain clinically relevant allergens, and whey proteins are most often implicated in CMPA. Many patients are sensitized to multiple milk components [4]. The 2015 EuroPrevall cohort study reported a 0.54% incidence of confirmed CMPA across nine European countries, with higher rates in Western Europe, and found that infants lacking milk-specific IgE developed tolerance more rapidly than those with detectable antibodies [5].

CMPA is a reference model for pediatric food allergy. Many food allergies remit in childhood, but CMPA shows variable resolution across cohorts: about half of children achieve tolerance by around 5 years of age, and as many as three quarters by adolescence. More recent cohorts, however, report lower remission, roughly 57% by 4–5 years in one study and about 41% by 10 years in another, suggesting heterogeneity by design and population and raising the possibility that a larger share of cases now persist into later childhood [4].

To prevent inappropriate immune activation from dietary antigens, the gastrointestinal tract employs both non-immunological barriers, (including mucosal integrity, motility, mucus secretion, gastric acidity and digestive enzymes) and immunological mechanisms, such as

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secretory IgA production and antigen processing by the Gut-Associated Lymphoid Tissue. In healthy individuals, dendritic cells within the Gut-Associated Lymphoid Tissue play a central role in promoting a tolerogenic immune response [6].

A temporary dysfunction of intestinal protective mechanisms may lead to loss of tolerance and sensitization to food antigens. Enterocytes regulate antigen absorption, while mucus, proteolytic enzymes, and gastric acidity normally prevent immune activation. Thus, reduced gastric acidity in infants or use of proton pump inhibitors may contribute to the development of food allergies, including CMPA [7].

CMPA involves two main immune pathways: IgE-mediated and non-IgE-mediated. IgE-mediated reactions are classic type I hypersensitivity responses, typically occurring within minutes to up to ~2 hours after exposure, whereas non-IgE mechanisms are less clearly defined and usually present with delayed, predominantly cell-mediated symptoms [8].

IgE-mediated CMPA follows a sensitization–effector sequence: milk proteins drive Th2 polarization and IgE production, which primes mast cells and basophils; subsequent exposure triggers rapid mediator release and acute manifestations ranging from urticaria and angioedema to anaphylaxis. In contrast, non-IgE CMPA is mainly linked to T-cell-driven gastrointestinal inflammation with delayed symptoms (e.g., vomiting, diarrhea, poor weight gain), and recovery of regulatory T-cell activity is associated with spontaneous resolution during childhood [9]. A subset of CMPA is non-IgE-mediated, with negative milk-specific IgE and skin prick tests, and typically presents with delayed gastrointestinal symptoms, including food protein-induced enterocolitis; these reactions are thought to involve predominantly cell-mediated immune pathways rather than immediate IgE-driven mechanisms [10].

Mucosal (oral) tolerance reflects a physiologic attenuation of immune responses to dietary antigens, mediated in part by deletion/anergy of antigen-specific T cells and expansion of regulatory T cells (Treg) that suppress Th2-driven IgE class switching. Impaired Treg function has been implicated in both IgE- and non-IgE-mediated CMPA, whereas tolerance acquisition in childhood correlates with increasing Treg activity [11]. Innate sensing pathways, including Toll-like receptors, shape dendritic-cell programming and downstream adaptive immunity; importantly, intestinal immune priming can imprint effector cells with extraintestinal homing capacity, providing a mechanistic basis for gut–lung immune crosstalk and potentially contributing to severe, low-threshold phenotypes with reactions beyond ingestion [12]. In this context, we report a rare case of persistent, severe IgE-mediated CMPA with clinically significant reactions despite strict avoidance, and we review the literature to highlight implications for multidisciplinary care.

## Case Presentation

### Patient information / Anamnesis:

A female child, born at term in October 2015 with an uneventful perinatal course and exclusively breastfed, began presenting early feeding intolerance during the first months of life. At the age of three months, following pediatric advice for partial weaning, the introduction of cow's milk-based formula resulted in immediate vomiting after ingestion, followed by a brief episode of dyspnea and perioral cyanosis. After switching to a different milk formula, a similar reaction occurred, consisting of regurgitation and shortness of breath within minutes of ingestion. Consequently, exclusive breastfeeding continued.

At approximately 4½ months of age, solid food diversification was attempted. However, the infant showed minimal interest in complementary foods and manifested recurrent episodes of reflux and eczema. Following the pediatrician's suggestion, a small quantity of dairy-based food (cheese) was introduced, which triggered vomiting, rash and respiratory discomfort. These events led to the first suspicion of IgE-mediated CMPA. A strict maternal milk-free diet was subsequently initiated, with the continuation of breastfeeding. Both maternal and infant diets were completely devoid of milk and milk-derived products, resulting in clinical stabilization.

### Clinical findings:

At the age of four years, upon entering kindergarten, the patient experienced her first documented anaphylactic episode. After accidental ingestion of a biscuit containing trace milk proteins, she developed lips swelling, respiratory distress, and cutaneous erythema within minutes. She was treated with oral antihistamines (cetirizine), and symptoms were resolved gradually.

### Diagnostic assessment:

Shortly afterward, allergy testing revealed elevated specific IgE to  $\alpha$ -lactalbumin (2.19 kUA/L; reference < 0.35) and to casein (3.57 kUA/L), while  $\beta$ -lactoglobulin remained undetectable. Minor cross-reactivity to other mammalian milks was also identified — camel (0.64 kUA/L), goat (0.75 kUA/L), and sheep (0.65 kUA/L). Sensitization to the mold *Alternaria alternata* was also detected (2.25 kUA/L). These findings confirmed multiple milk protein sensitizations and an atopic background (Table 1).

Strict avoidance of all milk products was maintained. Nevertheless, at age 6, after consuming pasta contaminated with minute milk residues from shared utensils, the patient experienced a second anaphylactic reaction, characterized by dyspnea, perioral edema, and generalized urticaria. Parents administered oral antihistamines, prepared the epinephrine auto-injector, and sought emergency care. The episode resolved without intubation or systemic corticosteroids. A follow-up immunologic assessment in February 2022 (after more than two years of total dietary

Table 1. Laboratory report, December 2019

Category	Allergen / Name (as reported)	Code / Component	Result
Milk	Cow's milk ( <i>Bos domesticus</i> )	nBos d 4, Alpha-lactalbumin	2.19
Milk	Cow's milk ( <i>Bos domesticus</i> )	nBos d 5, Beta-lactoglobulin	<0.10
Milk	Cow's milk ( <i>Bos domesticus</i> )	nBos d 8, Casein	3.57
Milk	Cow's milk ( <i>Bos domesticus</i> )	—	0.72
Milk	Camel milk ( <i>Camelus dromedarius</i> )	—	1.64
Milk	Goat milk ( <i>Capra hircus</i> )	—	0.75
Milk	Mare's milk ( <i>Equus caballus</i> )	—	<0.10
Milk	Sheep's milk ( <i>Ovis aries</i> )	—	0.65
Molds	<i>Alternaria alternata</i> ( <i>Alternaria alternata</i> )	—	2.25
Molds	<i>Alternaria alternata</i> ( <i>Alternaria alternata</i> )	rAlt a 1, Alt a 1-family	2.31

exclusion) revealed a significant rise in IgE titers, indicating persistent and worsening sensitization despite strict avoidance (Table 2).

Laboratory results showed:

- $\alpha$ -lactalbumin = 14.4 kUA/L;
- casein > 100 kUA/L;
- *Alternaria alternata* = 5.93 kUA/L.

Such progression under total elimination supports a highly persistent phenotype of severe CMPA with ongoing immunologic activation even in the absence of exposure.

At age 7, a third severe episode occurred through cutaneous contact: after being kissed on the forehead by a visitor who had consumed coffee with milk, the patient rapidly developed nasal congestion, cough and periorbital swelling — consistent with *contact-induced anaphylaxis*. The allergist confirmed the event as a non-ingestive reac-

tion, demonstrating extreme hypersensitivity to trace protein exposure. Following this, complete elimination of all potential milk-containing foods was extended to the entire household, including family members' diets, to prevent airborne or contact contamination. In June 2023, at age 7½, a new set of laboratory tests was performed, showing persistent elevation of milk-specific IgE despite continued strict avoidance:

- $\alpha$ -lactalbumin = 5.69 kUA/L;
- $\beta$ -lactoglobulin = 4.76 kUA/L;
- casein = 43.4 kUA/L;
- *Alternaria alternata* = 2.74 kUA/L.

The results again confirmed strong, multi-component milk sensitization and a high risk of anaphylaxis (Table 3).

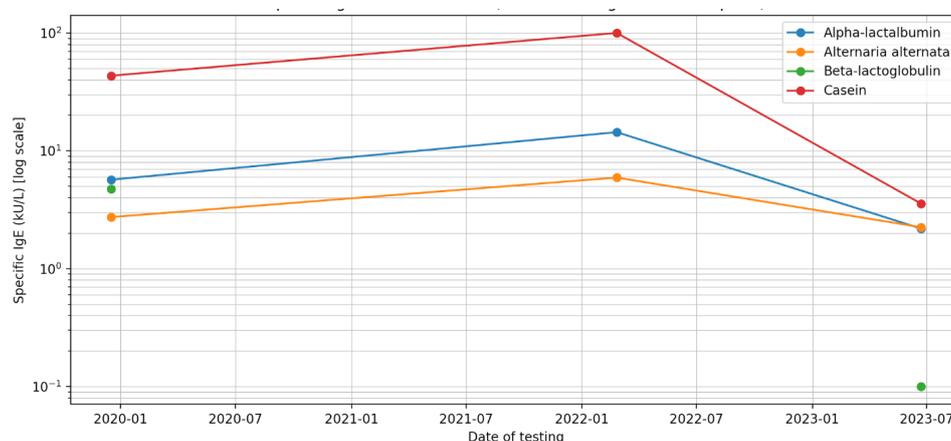
As shown in Figure 1, longitudinal sIgE testing revealed sustained and component-specific sensitization, with ca-

Table 2. Laboratory report, February 2022

Test	Code	Result	Unit	Reference range	Method
Specific IgE to alpha-lactalbumin	f76	14.400	kU/L	(< 0.100)	Serum, chemiluminescence
Specific IgE to casein	f78	> 100.000	kU/L	(< 0.100)	Serum, chemiluminescence
Specific IgE to <i>Alternaria alternata</i> ( <i>Alternaria tenuis</i> )	m6	5.930	kU/L	(< 0.100)	Serum, chemiluminescence

Table 3. Laboratory report, June 2023

Test (as reported)	Code	Specimen	Result	Unit	Reference interval
Specific IgE to alpha-lactalbumin	f76	Serum	5.69	kU/L	< 0.1 kU/L
Specific IgE to beta-lactoglobulin	f77	Serum	4.76	kU/L	< 0.1 kU/L
Specific IgE to casein	f78	Serum	43.4	kU/L	< 0.1 kU/L
Specific IgE to <i>Alternaria alternata</i>	m6	Serum	2.74	kU/L	< 0.1 kU/L



Notes: Casein reported as >100 kU/L (2022-02-25) is capped at 100 for visualization. Beta-lactoglobulin reported as <0.10 kU/L (2023-06-22) is plotted as 0.10.

Fig. 1. Specific IgE trajectories to alpha-lactalbumin,  $\beta$ -lactoglobulin, casein, and *Alternaria alternata*. Values are plotted on a logarithmic scale to accommodate the wide dynamic range of sIgE concentrations.

sein consistently dominating the immunologic profile and reaching >100 kU/L, compatible with persistent, high-risk CMPA. Alpha-lactalbumin followed a similar but less pronounced pattern, whereas beta-lactoglobulin declined to <0.10 kU/L. Overall, the figure summarizes an IgE pattern characterized by persistent casein-driven sensitization with variable trajectories among individual milk proteins, supporting the severity and persistence of the phenotype despite strict avoidance (Figure 1).

#### **Therapeutic intervention / Management:**

The child's clinical management included continuous dietary avoidance, the permanent prescription of two epinephrine auto-injectors and education of parents and educators on emergency protocols. Despite these precautions, challenges arose due to inadequate understanding of anaphylaxis management among local emergency and school personnel. Episodes of near-anaphylaxis were sometimes dismissed or poorly handled, underlining significant systemic gaps in allergy care education.

#### **Psychosocial/educational impact:**

The condition has also imposed major psychosocial consequences. Due to the impossibility of ensuring a milk-free environment in regular schools and public spaces, the patient has been home-schooled since age 7. Family members adopted a strict allergen-free lifestyle, with the mother leaving her job to supervise the child's education and dietary safety. The family reports significant logistical and emotional strain, as well as financial burden related to medication and food safety requirements.

#### **Follow-up and outcomes:**

Overall, this case represents a rare, life-threatening phenotype of IgE-mediated CMPA marked by systemic reactions to ingestion, cutaneous contact and even airborne exposure. The continuous increase of milk-specific IgE levels under strict dietary avoidance suggests persistent immune activation and an exceptionally low eliciting threshold, underscoring the need for tailored preventive strategies, improved community education, and structured medical protocols for extreme CMPA cases.

#### **Discussions**

There are literature studies evidencing that in genetically susceptible individuals, food antigen presentation can promote Th2 polarization with cytokine release, amplifying downstream IgE production and inflammation that may contribute to morphological and functional mucosal injury [13,14]. The development of food allergies reflects genetics, environmental exposures, and their interactions, including epigenetic modulation. For CMPA, established nonmodifiable risk factors include male sex in childhood, higher prevalence among Asian and Black children compared with White children, and a family history of atopy. Parental atopy is one of the strongest predictors of atopic

risk in the infant [4].

Early-life exposures may further modulate sensitization trajectories: greater dietary diversity in the first year has been associated with lower risks of food allergy and sensitization [15], while reduced microbial exposure, microbiome perturbations, acid-suppressive therapy, and delayed oral introduction may favor sensitization [16].

Vitamin D has also been linked to immune regulation in allergy, although available evidence remains inconsistent; observational studies suggest that both deficiency and excess may be associated with higher risk of food allergy and sensitization [17]. In a cross-sectional study, infants with CMPA had lower serum vitamin D levels than controls, with correlations to bone turnover markers suggestive of deficiency, raising the possibility of altered bone metabolism in affected infants [18].

Breastfeeding may support gut and immune maturation, although findings are mixed and influenced by confounding [19]; early feeding patterns and perinatal factors likely interact with genetic predisposition to shape clinical allergy expression [20,21]

The early-life gut microbiome is increasingly recognized as a key determinant of oral tolerance and CMPA pathogenesis. Dysbiosis, including shifts in bacterial composition such as increased Clostridia and Firmicutes, has been associated with later milk allergy. Microbiota-targeted interventions may influence barrier integrity and mucosal immune programming: probiotic supplementation (including *Lactobacillus rhamnosus* GG and *Lactobacillus casei*) has been reported to alleviate symptoms and may accelerate tolerance acquisition in some infants [22,23]. Prebiotics have shown preventive and immune-modulating effects in allergy development. Studies indicate that early prebiotics can promote beneficial bacterial growth, enhance intestinal barrier function, and modulate immune responses, suggesting an effective intervention strategy for managing allergic disorders, including CMPA [24]. Emerging approaches such as fecal microbiota transplantation have shown the ability to rapidly normalize microbial development in selected contexts (e.g., cesarean-born infants), suggesting a potential future therapeutic avenue; however, evidence in CMPA remains preliminary and requires further validation. [25,26].

Diagnosis of CMPA relies on clinical history, sIgE testing and skin prick tests. Although both provide supportive evidence, oral food challenge remains the diagnostic gold standard in ambiguous cases. Interpretation requires clinical context, and there is no universal agreement on diagnostic thresholds across centers [27].

According to the Diagnosis and Rationale for Action against CMPA guidelines, management relies on strict nutritional monitoring and a complete cow's milk protein elimination diet for 6–12 months, including avoidance of contact and potential inhalational exposure, while maintaining overall nutritional adequacy and avoiding unnecessary restriction of other foods [28]. Current guidelines

recommend continuing breastfeeding with maternal elimination of cow's milk, and in formula-fed infants, starting with an extensively hydrolyzed formula; amino acid-based formulas are reserved for severe or refractory cases. *Lactobacillus rhamnosus* GG-enriched extensively hydrolyzed formula may accelerate tolerance development, especially in non-IgE-mediated CMPA [29]. Hydrolyzed rice protein formulas represent an additional option in selected infants, with careful monitoring of growth and nutritional status [30]. In selected mild phenotypes, supervised baked-milk introduction via a milk ladder may facilitate tolerance by reducing allergenicity and promoting favorable immune shifts (higher IgG4, lower IgE), but it is unsuitable for severe, low-threshold disease such as our patient's [31].

Oral immunotherapy (OIT) may be considered for persistent IgE-mediated CMPA (often  $\geq 4$ –5 years) and can induce desensitization with immunologic changes (decreased sIgE, increased IgG4), yet adverse events—including anaphylaxis—are common and durable benefit is variable. Risk is higher in patients with strong sensitization, asthma, very low reaction thresholds, older age, and prior severe reactions; therefore, OIT requires experienced centers and careful selection [32,33]. Given our patient's extreme phenotype, OIT was deemed inappropriate due to the unacceptable risk of systemic reactions [34].

Airborne food reactions are rare but reported in children exposed to aerosolized food particles (including cow's milk), where minimal exposure (e.g., milk powder or cooking vapors) can trigger rhinoconjunctivitis, cough, wheeze, and occasionally anaphylaxis; our patient fits this exceptional high-risk CMPA phenotype [35]. Roberts et al. reported that 5% of children followed up for food allergy and asthma have respiratory symptoms after inhaling food particles such as milk powder or cooking vapors, highlighting the importance of recognizing inhalation-triggered food allergy [36].

Diagnosis of food-induced respiratory reactions requires confirming the link between inhalation and symptoms through careful history and, when appropriate, controlled

exposure testing. Management includes strict avoidance, family education, and emergency preparedness with self-injectable epinephrine; rapid recognition and treatment with adrenaline and supportive therapy are essential, particularly in patients with asthma [37,38]. Given that lactose-containing dry powder inhalers may contain trace milk protein residues, current recommendations advise avoiding these preparations in confirmed milk protein allergy despite the apparently low incidence of reported reactions [39]. Persistent CMPA into adulthood is uncommon ( $\approx 1$ –3%) but tends to follow a more severe course with increased risk of systemic reactions to minimal exposures [21].

Cow's milk remains a major trigger of pediatric anaphylaxis across cohorts, accounting for a substantial proportion of emergency presentations and occasionally requiring intensive care, with many reactions occurring in early childhood and often in the home setting [40]. Importantly, recent population data also emphasize the potential lethality of food-induced anaphylaxis; although fatal events are rare, cow's milk has been identified as a leading cause of fatal anaphylaxis in individuals under 18 years [41]. Natural history studies suggest that tolerance develops in many children by school age, yet persistence is more likely in those with higher baseline milk-specific IgE, larger skin prick test wheals, and more severe atopic dermatitis—a risk profile consistent with the severe, persistent phenotype observed in our patient [42].

A multicenter European study confirmed that cow's milk is a leading cause of food-induced anaphylaxis in children, most reactions occurring at home and occasionally requiring intensive care (1.3%). These findings emphasize the severity of milk allergy, as also seen in our patient, who developed severe systemic reactions even to airborne exposure [43].

According to the World Allergy Organization Journal (2020), anaphylaxis requires immediate intramuscular epinephrine as first-line therapy, with adjuncts including antihistamines and corticosteroids; observation is rec-

### Key points

1. Layered avoidance: strict dairy elimination plus cross-contact control (clear labeling; dedicated utensils/surfaces; avoidance of shared foods and preparation areas).
2. School/daycare plan: written anaphylaxis action plan, designated safe area, trained staff, and avoidance of high-risk activities (cooking/food handling, shared snacks).
3. Emergency preparedness: two epinephrine auto-injectors available at all times; prompt intramuscular epinephrine for systemic symptoms; call emergency services.
4. Education & communication: train all caregivers/relatives; standardize instructions for visitors; clear protocols for restaurants/travel and medical visits.
5. Follow-up & nutrition: regular allergist review and dietitian support to ensure growth and nutritional adequacy; periodic reassessment of risk.
6. Psychosocial support: address anxiety and social restriction; individualized educational accommodations to reduce family burden.

Box 1. Key practical recommendations for extreme CMPA (very low eliciting threshold)

ommended due to biphasic risks. Collectively, these data underscore that prompt recognition and immediate intramuscular epinephrine are essential, while persistent underuse of auto-injectors highlights the need for structured education, ready access to epinephrine, and coordinated preparedness across families, schools, and healthcare services [44].

## Conclusions

This case highlights an exceptionally severe and persistent phenotype of IgE-mediated CMPA, characterized by systemic reactions not only to ingestion but also to cutaneous and airborne exposure. The progressive rise in milk-specific IgE titers despite long-term strict dietary avoidance suggests continuous immune activation and an extremely low eliciting threshold. Such cases challenge the classical understanding of allergen tolerance and underscore the need for more refined diagnostic and therapeutic approaches.

CMPA remains a major clinical and psychosocial burden for affected families, with implications extending beyond nutrition and emergency preparedness to daily life, education and emotional wellbeing. The case illustrates the limitations of current management based solely on avoidance and emergency intervention and it emphasizes the urgent necessity of multidisciplinary care involving allergists, pediatricians, nutritionists, educators and policymakers.

Future management strategies should prioritize precision-based risk stratification, early immune modulation, and the development of safe, personalized immunotherapies. At the community level, standardized education on anaphylaxis recognition and epinephrine administration is critical, particularly in schools and emergency settings.

Ultimately, this report reinforces that extreme CMPA phenotypes require not only medical vigilance but also systemic adaptations in public health and education, ensuring that patients with life-threatening allergies can live safely and with dignity.

## AI Tools Disclosure

Grammarly (v1.2.182.1722) was used for grammar and clarity improvements. All AI suggestions were reviewed and approved by the authors.

## Authors' contributions

LA – Conceptualization, Resources, Writing – original draft, Writing – review & editing, Methodology  
 TNV – Data curation, Investigation, Methodology  
 SIA – Visualization, Methodology, Resources  
 CU – Supervision, Project administration, Validation

## Conflict of interest

None to declare.

## Ethical Statement

Written informed consent was obtained from the patient's legal guardian for the publication of this case report and

any accompanying images. This report complies with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its subsequent amendments.

## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

## Funding

No external funding was received.

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