Focal facial dermal dysplasia type IV: a case series

Laura Gnesotto,[1-3] Mario Cutrone,[4] Giuseppe Ruggiero,[5] Carla Morando,[6] Anna Belloni Fortina,[1,2] Annalisa Patrizi,[7] Luigi Naldi,[8] Andrea Sechi[9]

[1]Dermatology Unit, Department of Medicine, University of Padua; [2]Pediatric Dermatology Regional Center, Department of Women's and Children's Health, University of Padua; [3]Soft-Tissue, Peritoneum and Melanoma Surgical Oncology Unit, Veneto Institute of Oncology IRCCS, Padua; [4]Pediatric Dermatology, Dell'Angelo Hospital, Venice; [5]Dermatology Study Group of the Italian Federation of Pediatricians, Rome; [6]Neonatal Intensive Care Unit, Department of Pediatrics, San Bortolo Hospital, Vicenza; [7]Department of Experimental, Diagnostic and Specialty Medicine, Dermatology, IRCCS Policlinico Di Sant'Orsola, Alma Mater Studiorum University of Bologna; [8]Dermatology Unit, San Bortolo Hospital, Vicenza; [9]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Abstract

Focal facial dermal dysplasias (FFDDs) encompass four rare inherited disorders. FFDD types I, II, and III are characterized by bitemporal scar-like lesions present from birth, while FFDD IV is identified by analogous lesions localized in the periauricular area. Most FFDD IV cases show autosomal-recessive inheritance with mutations in the *CYP26C1* gene. We describe three infants with bilateral, oval-shaped, hypopigmented preauricular lesions indicative of FFDD IV. It is crucial for physicians to recognize these rare conditions at an early stage to ensure proper diagnosis and to rule out associated malformations.

Correspondence: Andrea Sechi, MD, PhD, Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
E-mail: andrea.sechi@policlinico.mi.it

Key words: pediatric dermatology; rare diseases; skin signs of systemic disease.

Conflict of interest: the authors have no conflict of interest to declare.

Ethics approval and consent to participate: no ethics committee approval was required for this case report according to institutional policy. Informed consent was obtained from the patients' relatives.

Consent for publication: informed consent was obtained from legally authorized representatives for anonymized patient information to be published in this article.

Availability of data and materials: all data underlying the findings are fully available.

Received: 24 November 2024.
Accepted: 27 March 2025.

Dermatology Reports 2025; 17:10199
doi:10.4081/dr.2025.10199

Introduction

Focal facial dermal dysplasias (FFDDs) are developmental defects presenting with skin lesions in temporal or preauricular areas, similar to aplasia cutis congenita (ACC). It has been postulated that defects in FFDDs result from the incomplete closure of the ectoderm along facial embryonic fusion lines.[1] These skin defects manifest with temporal lesions situated at the junction between the frontonasal and maxillary facial prominences and preauricular lesions at the confluence of maxillary and mandibular prominences.[2] Consistent histologic abnormalities have been observed: atrophy and flattening of the epidermis, replacement of the dermis by loose connective tissue, reduced elastic tissue with fragmented fibers, and absence of the subcutaneous tissues and adnexal structures.[3,4] Histologic examination of FFDD lesions shows similar features to membranous ACC, supporting the hypothesis that FFDDs and ACC possibly share a similar pathogenesis.[1] FFDD type IV is particularly characterized by bilateral, round or oval preauricular lesions at birth.[5]

Case Report

Patient 1 is a 5-month-old male, born at term after an uneventful pregnancy, labor, and vaginal delivery. He had an unaffected 5-year-old sister. The patient presented since birth with two oval-shaped, whitish, thinned-skin lesions in his right preauricular area along the fusion line of the maxillary and mandibular prominences. In the left preauricular region, we observed a similar slightly atrophic lesion, which also presented mild peripheral hyperpigmentation and vellus hairs (Figure 1). All the lesions measured 7-8 mm. His psychomotor development was normal for his age. Ocular and hearing investigations were performed, without detecting any alteration.

Patient 2 is a 10-month-old female with congenital bilateral facial skin alterations. She was born after a full-term 38-week gestation and delivered by a cesarean section. The parents had an unaffected 4-year-old daughter. On examination, the patient had four round whitish lesions measuring <1 cm on the right preauricular area and two more atrophic and pale lesions on the left, along the line between labial commissure and tragus (Figure 2). Moreover, she presented two small hemangiomas on her trunk and a *café-au-lait* spot on the right shoulder. Her psychomotor devel-

opment was normal, as well as her ocular and hearing functions.

Patient 3 is a newborn male, uneventfully delivered at 36-week gestation, who presented two circular 5-8 mm hypopigmented, atrophic macules linearly arranged on the left cheek. Two similar lesions of 5 mm and 1.5 cm were observed on the right, the latter surrounded by a fine pigmented hair collar (Figure 3). The parents reported that these lesions were present from birth. His neurological development was normal for his age, and no other abnormalities of the skin, hair, or nails were found. At the age of 2 months, the lesions were still appreciable.

In all cases, the clinical features were strongly suggestive of FFDD type IV. As a result, skin biopsies were deemed necessary, especially given the benign course of this condition. Parents decided to postpone genetic analysis due to the early age of their children.

Discussion

A recent classification divides FFDDs into four subtypes.[6] FFDD type I, or Brauer syndrome, features temporal skin depressions and multiple facial abnormalities, including sparse lateral eyebrows, distichiasis, and a flattened nasal tip.[5] FFDD type II, also known as Brauer-Setleis syndrome, is distinguished by bitemporal skin lesions and variable facial anomalies such as puckered periorbital skin, distichiasis, absent eyelashes, and a flat nasal bridge with a broad nasal tip.[7] Both FFDD types I and II follow an autosomal dominant inheritance pattern; however, FFDD type II may be associated with variable expressivity and lack of penetrance.[8] FFDD type III, or Setleis syndrome, exhibits facial characteristics similar to FFDD type II, but with autosomal recessive

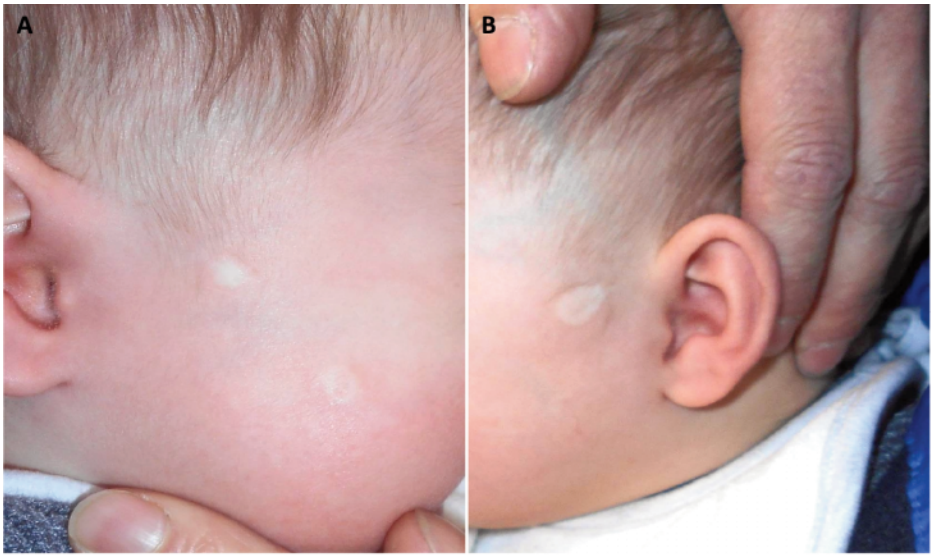

Figure 1. Patient 1: clinical image depicting slightly depressed, hypopigmented, well-defined, oval lesions in the right (**A**) and the left (**B**) preauricular areas at 5 months of age. The lesion on the left also displays peripheral fine pigmented vellus hairs, characteristic of the hair collar sign.

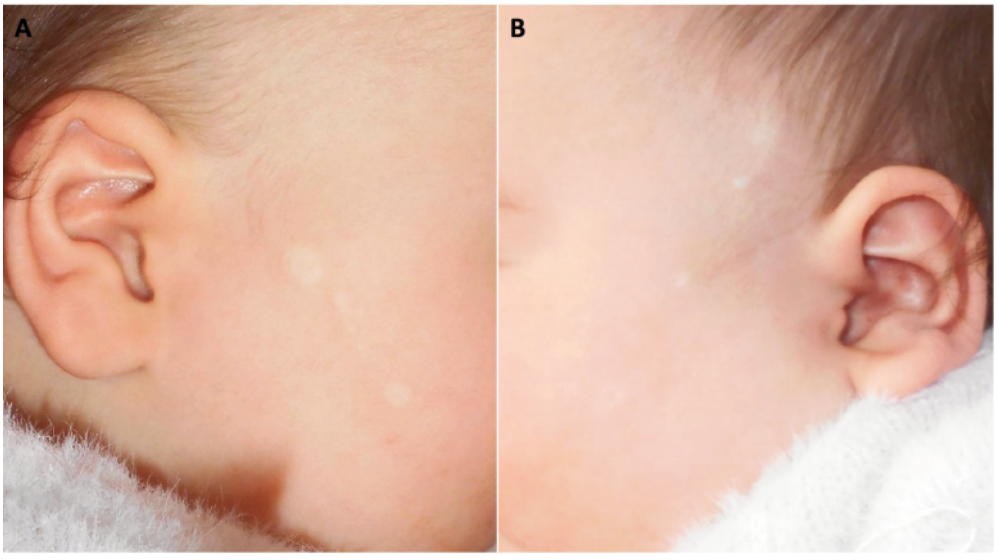

Figure 2. Patient 2: presentation of multiple hypopigmented, roundish lesions of varying sizes, arranged linearly along oblique lines corresponding to the junction between the maxillary and mandibular prominences in the right (**A**) and the left (**B**) preauricular areas, observed at 10 months of age.

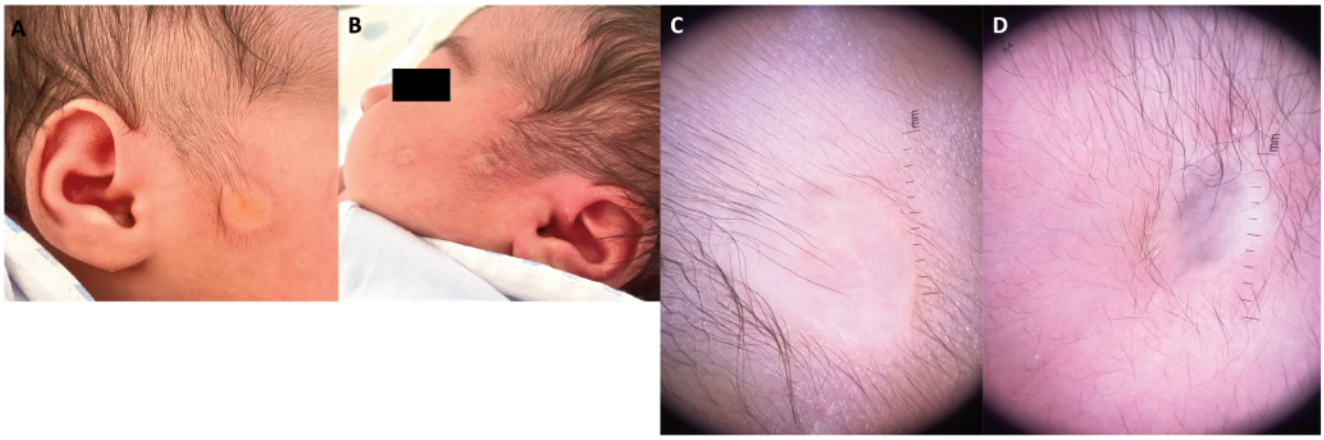

Figure 3. Patient 3: clinical presentation of the lesions in the right (**A**) and the left (**B**) preauricular areas observed at birth. Dermoscopic examination of the right preauricular lesion reveals fine, unmedullated, and pigmented vellus hairs encircling an oval, whitish, structureless area with thin arborizing and linear vessels, along with an absence of follicular openings. A grayish hue is noted around the periphery (**C**), or at the center (**D**) of the lesions.

inheritance.[9] FFDD type IV is identified by isolated preauricular skin lesions without additional facial dysmorphisms. Initially, these defects may appear as vesicles, evolving into hypopigmented macules, occasionally encircled by a hyperpigmented rim with fine hairs, known as the "hair collar sign".[5] The primary differential diagnosis is ACC, a rare condition marked by the congenital absence of skin and sometimes subcutaneous tissue or bone, due to ectodermal fusion defects,[10] with the scalp being the most affected area.[11] In ACC, the "hair collar sign" is considered a specific indicator of a neuroectodermal defect, whereas, in FFDD IV, it has been observed in many cases without associated neurological impairments.[1,4] Additional features of FFDD type IV are infrequent. Still, they could involve buccal mucosa polyps along the same line as the external skin defects, cleft lip and palate, developmental delay, cleft chin, multiple congenital nevi, and cutaneous or cerebral hemangiomas.[2,3,12] Development and cognitive functions are typically unaffected.[3] FFDD IV has been documented in over 20 patients with autosomal recessive or sporadic inheritance patterns.[5] Although the genetic bases of FFDD type I and II remain unknown, recent studies have identified the molecular defect causing FFDD type III and IV.[13] FFDD III patients show loss-of-function mutations in the *TWIST2* gene, which encodes a basic helix-loop-helix transcription factor crucial for craniofacial dermal and bone development; these pathological variants are also seen in ablepharon macrosomia syndrome and Barber-Say syndrome, both featuring similar dermal facial traits.[13,14] For FFDD type IV, homozygous or compound heterozygous recessive loss-of-function mutations in the *CYP26C1* gene have been identified.[3] This gene is part of a trio of mammalian P450 enzymes that modulate retinoic acid metabolism. Although the precise mechanisms by which *CYP26C1* pathological variants lead to atrophic skin lesions are not fully understood, disrupted retinoic acid metabolism during embryonic development is believed to play a pivotal role.[3,5] Specifically, *CYP26C1* is tasked with converting all-trans retinoic acid into an inactive metabolite; thus, mutations in this gene could result in the substrate's accumulation.[5] In mouse embryo studies, *CYP26C1* expression along the maxillary/mandibular fusion line, the location of FFDD IV's preauricular skin lesions, further supports the gene's role in the unique FFDD IV phenotype.[15]

Conclusions

We reported three uncommon instances of FFDD IV in otherwise healthy newborns characterized by bilateral preauricular lesions that mimic membranous ACC. The discovery of *CYP26C1* gene mutations in these cases underscores the critical role of retinoic acid metabolism in the facial development of the preauricular region along the maxillary and mandibular prominences. *CYP26C1* may be essential to ensure proper embryonic development of these structures, protecting them from retinoic acid exposure. When FFDD is suspected, a thorough physical examination of the child is essential, as the diagnosis is based on clinical manifestations. Furthermore, parents should be carefully visited, too, in the case of autosomal-inherited types.

References

1. Mehrtens SH, Shankar S. A case of focal facial dermal dysplasia type 4. Pediatr Dermatol 2019;36:58-9.
2. Drolet BA, Baselga E, Gosain AK, et al. Preauricular skin defects. A consequence of a persistent ectodermal groove. Arch Dermatol 1997;133:1551-4.
3. Slavotinek AM, Mehrotra P, Nazarenko I, et al. Focal facial dermal dysplasia, type IV, is caused by mutations in CYP26C1. Hum Mol Genet 2013;22:696-703.
4. Wells JM, Weedon D. Focal facial dermal dysplasia or aplasia cutis congenita: a case with a hair collar. Australas J Dermatol 2001;42:129-31.
5. Lee BH, Aggarwal A, Slavotinek A, et al. The focal facial dermal dysplasias: phenotypic spectrum and molecular genetic heterogeneity. J Med Genet 2017;54:585-90.
6. Cervantes-Barragán DE, Villarroel CE, Medrano-Hernández A, et al. Setleis syndrome in Mexican-Nahua sibs due to a homozygous TWIST2 frameshift mutation and partial expression in heterozygotes: review of the focal facial dermal dysplasias and subtype reclassification. J Med Genet 2011;48:716-20.
7. Graul-Neumann LM, Stieler KM, Blume-Peytavi U, Tzschach A. Autosomal dominant inheritance in a large family with

focal facial dermal dysplasia (Brauer-Setleis syndrome). Am J Med Genet A 2009;149A:746-50.
8. Kowalski DC, Fenske NA. The focal facial dermal dysplasias: report of a kindred and a proposed new classification. J Am Acad Dermatol 1992;27:575-82.
9. Rosti RO, Uyguner ZO, Nazarenko I, et al. Setleis syndrome: clinical, molecular and structural studies of the first TWIST2 missense mutation. Clin Genet 2015;88:489-93.
10. Duan X, Yang GE, Yu D, et al. Aplasia cutis congenita: a case report and literature review. Exp Ther Med 2015;10:1893-5.
11. Yang MY, Ha DL, Kim HS, et al. Aplasia cutis congenita in Korea: Single center experience and literature review. Pediatr Int 2020;62:804-9.
12. Prescott T, Devriendt K, Hamel B, et al. Focal preauricular dermal dysplasia: distinctive congenital lesions with a bilateral and symmetric distribution. Eur J Med Genet 2006;49:135-9.
13. Tukel T, Šošić D, Al-Gazali LI, et al. Homozygous nonsense mutations in TWIST2 cause Setleis syndrome. Am J Hum Genet 2010;87:289-96.
14. Marchegiani S, Davis T, Tessadori F, et al. Recurrent Mutations in the Basic Domain of TWIST2 Cause Ablepharon Macrostomia and Barber-Say Syndromes. Am J Hum Genet 2015;97:99-110.
15. Tahayato A, Dollé P, Petkovich M. Cyp26C1 encodes a novel retinoic acid-metabolizing enzyme expressed in the hindbrain, inner ear, first branchial arch and tooth buds during murine development. Gene Expr Patterns 2003;3:449-54.