A case of familial focal dermal hypoplasia: A report of 3 cases in consecutive generations

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\section*{ABSTRACT}

Focal dermal hypoplasia (FDH), or Goltz syndrome, is a rare multisystem disorder affecting mesodermal and ectodermal structures, with the skin, eyes, teeth, and musculoskeletal systems most commonly affected. FDH results from mutations in the PORCN gene. Ninety-five percent of cases arise from novo mutations, whereas 5\% are hereditary with an X-linked dominant inheritance pattern. Here, we describe an uncommon presentation of FDH in three consecutive generations. Patient 1 is an 8-month-old female born of non-consanguineous marriage who presented with diffuse alopecia of the scalp, linear hypopigmented, atrophic papules, and plaques with peripheral hyperpigmentation on the right hemiabdomen and right lateral leg along Blaschko’s lines as well as syndactyly of the right second and third toes. Skin biopsy from the abdomen showed a thin epidermis with flattened rete ridges and massive dermal edema within collagen fibers and reactive capillaries. Family history was significant for similar skin lesions and bone deformities in her mother and similar skin lesions in her grandmother. Patient 2 (patient 1’s mother) is a 17-year-old female with similar linear hypopigmented, atrophic plaques with peripheral hyperpigmentation on the abdomen and right axilla, syndactyly of the right hand, patchy alopecia of the scalp, microdontia, teeth fusion, enamel defects, verrucous papillomas in the axillae and onycholysis. Patient 3 (patient 1’s grandmother), presented with similar hypopigmented, atrophic plaques on the abdomen and left arm.

\section*{INTRODUCTION}

Focal dermal hypoplasia (FDH), also known as Goltz syndrome, is a rare genetic disorder that arises from mutations in the PORCN gene.\textsuperscript{1,2} The disorder affects organs derived from ectodermal and mesodermal structures, with the skin, eyes, teeth, and musculoskeletal systems most commonly affected.\textsuperscript{3,4} The classic skin findings are linear hypopigmented papules and plaques with hyper- or hypopigmentation along the lines of Blaschko.\textsuperscript{4} It is known that 95\% of all cases arise from novo mutations, only 5\% are familial cases with an X-linked dominant inheritance pattern.\textsuperscript{3,5,6} Here, we describe an uncommon presentation of 3 family members from consecutive generations with FDH.
Patient 1 is an 8-month-old female born of non-consanguineous marriage who presented with linear hypopigmented, atrophic papules and plaques with peripheral hyperpigmentation along the lines of Blaschko on the right hemiabdomen and right lateral leg (Figure 1A). The patient had diffuse alopecia and syndactyly of the right second and third toes (Figure 1B and 1C). The nails and oral mucosa were normal. The remainder of the physical exam was normal. Prenatal, perinatal, and the remainder of her medical history were unremarkable. Family history was significant for similar skin lesions in both her mother and grandmother. Skin biopsy from an abdominal lesion showed a thin epidermis with flattened rete ridges and massive edema in the dermis within collagen fibers and reactive capillaries (Figure 2).

Patient 2 (patient 1’s mother) is a 17-year-old female that presented with similar skin lesions from birth. She also had dental and scalp defects as well as multiple wart-like lesions on the genital area that had been removed previously. She was born from a non-consanguineous marriage and was the youngest of three children. Physical exam was significant for linear hypopigmented, atrophic plaques with peripheral hyperpigmentation following Blaschko's lines on the left hemiabdomen (Figure 1D) and right axilla. She had alopecia on the frontal and temporal area, microdontia, diastema with teeth fusion and enamel defects (Figure 1E). Further examination revealed syndactyly of the right third and fourth fingers with distal onycholysis of right fifth finger, syndactyly of the right fourth and fifth toes with distal onycholysis (Figure 1F), and verrucous papillomas in the axillae.

Figure 1. Patient 1 (8-month-old female), A: linear hypopigmented, atrophic papules and plaques with peripheral hyperpigmentation on right lateral leg. B: diffuse alopecia. C: syndactyly of the right second and third toes. Patient 2 (patient 1’s mother), D: linear hypopigmented, atrophic plaques with peripheral hyperpigmentation following Blaschko's lines on left hemiabdomen. E: microdontia, diastema with teeth fusion and enamel defects. F: syndactyly of the right fourth and fifth toes. Patient 3 (patient 1’s grandmother), G: linear hypopigmented, atrophic plaques on left hemiabdomen along Blaschko’s lines. H: linear hypopigmented, atrophic plaques on left arm. I: onychodystrophy of the left first finger.

Figure 2. Skin biopsy from an abdominal lesion from patient 1: thin epidermis with flattened rete ridges and massive edema in the dermis within collagen fibers and reactive capillaries.
Patient 3 (patient 1’s grandmother) is a 44-year-old female with similar hypopigmented skin lesions. Her past medical history was unremarkable. Physical examination revealed similar hypopigmented, atrophic plaques on left hemiabdomen and left arm (Figure 1G and 1H), and onychodystrophy of the left first finger (Figure 1I). There were no mucosal, scalp or musculoskeletal findings.

**DISCUSSION**

Focal dermal hypoplasia (FDH), or Goltz syndrome, is a rare genetic disorder resulting from mutations in the PORCN gene. This multisystem disease affects the embryonic development of ectodermal, mesodermal, and endodermal tissues resulting in a wide range of abnormalities with variable expression. When hereditary, FDH is inherited in an X-linked dominant pattern with mosaic distribution in affected tissues. The mutations in the PORCN gene located on the X chromosome result in disruption of Wnt signaling. Ninety percent of patients with FDH are female, 95% of those are due to new mutations, 5% are inherited, and affected individuals may be heterozygous or mosaic. Non-mosaic male PORCN pathogenic variants are presumed to be lethal; therefore, post-zygotic mosaicism allows males with FDH to overcome this consequence. There have been reports of “pseudo-anticipation” in FDH where the affected parent has milder symptoms than that observed in the affected child as was seen in our case series.

The clinical presentation of FDH is often variable, making diagnosis difficult. The characteristic skin manifestations include hypopigmented or depigmented macules with patchy skin hypoplasia and hyperpigmentation following Blaschko’s lines or with a reticulated configuration.

Telangiectasias interspersed between the atrophic plaques are also commonly observed. These features can be present at birth initially as blisters or erosions that heal with atrophic scars anywhere on the body. There have been reports of xerosis, photosensitivity, lipomatous hamartomas, and pruritus within these atrophic areas. The dermal defects permit fat herniation, which appears as soft, pink-brown nodules overlying the thin atrophic skin. Additional cutaneous findings include fibrovascular papillomas which can also arise on mucous membranes, particularly the perineal, vulvar, and perianal regions, and often manifest later in life. Laryngeal and esophageal papillomas have also been described. FDH may cause ridged, dysplastic, or hypoplastic nail, and hair growth can be sparse or completely absent leading to diffuse or patchy alopecia. Extra-cutaneous involvement varies and involves multiple organs and systems. Manifestations of FDH in the eye include iris or chorioretinal colobomas, microphthalmia or anophthalmos, lacrimal duct abnormalities, cataracts, nystagmus, and strabismus.

When genetic testing is not available, as in this case, clinical evaluation is generally sufficient to establish a diagnosis. Bostwick et. al proposed diagnostic criteria for FDH including three or more characteristic skin findings and one or more characteristic limb malformations. Skin findings must be congenital in onset, which helps differentiate FDH from Rothmund-Tomson syndrome, which presents with a similar cutaneous phenotype including patchy skin aplasia, nodular fat herniation, hyper- or hypopigmentation along Blaschko’s lines, telangiectasias, and nail abnormalities. Limb abnormalities seen in FDH include split hand/foot, transverse limb defects (ectrodactyly), syndactyly, oligodactyly, and marked long bone reduction.
We present a rare case series of familial FDH in three consecutive generations. The diagnosis was based on clinical and histopathological features. The clinical presentation of patient 2 and patient 3 illustrates the “pseudo-anticipation” phenomenon and predicts that patient 1 may manifest additional features of FDH later in life and thus should be monitored by a multidisciplinary team including but not limited to a dermatologist, orthopedist, ophthalmologist, and dentist. The goal of treatment is to improve functionality and quality of life.

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