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Laser-Induced Neocollagenesis in Focal Dermal Hypoplasia Associated With Goltz Syndrome in a Girl

Andrew C. Krakowski, MD; David M. Ozog, MD; David Ginsberg, MD, MS; Carol Cheng, MD; Marsha L. Chaffins, MD

IMPORTANCE Current models of Goltz syndrome cannot estimate the overall neocollagenesis and marked shift in collagen types after ablative fractional laser resurfacing (AFR) within treated areas of focal dermal hypoplasia (FDH).

OBJECTIVES To clinically improve FDH by using AFR to characterize the specific ratio of collagen types associated with observed clinical changes.

DESIGN, SETTING, AND PARTICIPANTS This case report of a girl with Goltz syndrome used extensive laboratory evaluation and multiple observers blinded to the patient’s clinical status. Serial samples of clinically unaffected skin constituted internal control specimens, with clinical and histologic evaluations performed as part of a multicenter investigation. The analysis tested the hypothesis that thermal microtrauma caused by AFR created a unique environment that activated latent genes, inducing neocollagenesis and allowing the patient to adaptively produce the collagen subtype that was specifically deficient at baseline.

INTERVENTIONS Two AFR treatments were administered within an area of FDH. Histologic comparison of the pretreatment and posttreatment skin was performed using serial internal controls.

MAIN OUTCOMES AND MEASURES Histologic changes, including Herovici collagen staining to differentiate between types I and III collagen, within a treated area of mosaically affected FDH compared with clinically unaffected skin.

RESULTS This female patient presented in the second decade of life with self-described red, itchy skin within a large plaque of FDH on her left posterior thigh and calf. After AFR, skin tightening and symptomatic relief were reported. Histologic findings demonstrated objective thickening of the dermal collagen. A marked shift in collagen predominance from type III (fetal/early wound) to type I (adult/mature) was observed.

CONCLUSIONS AND RELEVANCE Although further study is needed, this report shows promising results and raises important questions about gene expression and the epigenetics of Goltz syndrome–associated mutations and the local effects of AFR. Coupled with more rigorous investigation, this novel technique may help reveal molecular workarounds permitting innovative therapies that take advantage of the subtly different collagens that exist within the skin.
Goltz syndrome is an X-linked dominant disorder most commonly affecting the skin, eyes, teeth, and skeleton.1 The condition is caused by heterozygous and mosaic PORCN (HGNC 17652) gene mutations located on Xp11.23.2,3 This region encodes an endoplasmic reticulum membrane protein involved in regulation of the Wnt signaling pathway, which plays a crucial role in mesoderm and ectoderm development.4 Nearly 120 different mutations have been identified; however, owing to the overall complexity of the Wnt pathway and the specific underlying pathophysiologic features of Goltz syndrome, neither severity nor presentation can be estimated based on a specific mutation at this time.5-7 Dermatologic signs are often present at birth and include aplasia cutis congenita, telangiectasias, nodular fat herniations (ie, outpouchings), pigmentedary alterations, dystrophic nails, thin and brittle hair, papillomas, and focal dermal hypoplasia (FDH) in a blaschkoid distribution.1,8

Histologic evaluation of mosaically affected FDH demonstrates an atrophic dermis, increased dermal adipocytes, increased papillary dermal capillaries, abnormal fibroblasts, and sparse, disorganized collagen.9-11 The mechanism by which the excess fat enters the dermis remains controversial; theories include decreased collagen allowing for displacement of subdermal adipocytes into the dermis vs adipocyte overgrowth within the dermis.

To our knowledge, no reports of spontaneous resolution within mosaically affected skin have been published. Likewise, the specific ratio of collagen types within the abnormal network present in patients with Goltz syndrome has yet to be characterized, and no attempts to improve FDH directly through inducement of neocollagenesis have been published.

Ablative fractional laser resurfacing (AFR) has been shown to induce collagen remodeling in burn scars, chronic wounds, and epidermolysis bullosa.12-15 We hypothesized that the local effects of AFR might induce neocollagenesis and help fortify the type III collagen present at baseline in the mosaically affected areas of FDH despite the patient’s genetic predisposition to the contrary.

Methods

A female infant presented with erosion and fat herniation of the left posterior leg, microphthalmia, ocular coloboma and blindness of the left eye, lop ear deformity, left third and fourth finger syndactyly, and left great toe polydactyly. She was subsequently diagnosed with Goltz syndrome by the late Robert Goltz, MD. More than a decade later, she sought treatment for self-described red, itchy skin within a large plaque of FDH on her left posterior thigh and calf (Figure 1A). This area was cosmetically distressful and physically debilitating because the loose skin was easily traumatized, irritated, and extremely pruritic. The possibility of AFR was introduced, and the family elected to proceed with treatment. Informed parental consent and patient assent were obtained.

The patient underwent 2 sessions of fractional photothermolysis approximately 2 months apart using general anesthesia for pain management. Both treatments were performed with an ablative microfractionated carbon dioxide laser (Ultrapulse Deep FX; Lumenis, Ltd) at 35 mJ and 10% density for the first treatment and at 20 mJ and 10% density for the second treatment (Figure 1B); microspot size was fixed at approximately 0.12 mm. A petrolatum-based ointment was applied to the wound 3 times daily for 2 weeks. Biopsy specimens of mosaically affected skin and adjacent, unaffected skin (ie, internal control specimens) were obtained before the initial AFR treatment and 8 weeks after the final treatment.

Results

Subjectively, the patient reported decreased pruritus and a reduction in local trauma after AFR. Clinically, tightening and thickening of her treated area were noticeable, with less outpouching and skin laxity (Figure 1C-E). On histologic analysis, both internal controls had findings consistent with normal skin (Figure 2A and B). Before treatment, mosaically affected skin revealed striking attenuation of dermal collagen and loss of elastic tissue, consistent with FDH (Figure 2C). After treatment, mosaically affected skin revealed thickening and fibrosis of the dermal collagen, increased vascularity, and no change in elastin (Figure 2D). Herovici collagen staining of normal skin demonstrated a predominance of type I collagen (Figure 3A). In contrast, mosaically affected skin revealed a baseline predominance of type III collagen before treatment (Figure 3B). After treatment, however, mosaically affected skin showed a marked shift toward type I collagen (Figure 3C). The patient’s subjective improvement and observed clinical changes have persisted more than 6 months postoperatively. We plan to follow up with the patient in 1 year to assess whether retreatment of the affected area is necessary.

Discussion

Ablative fractional laser resurfacing has been shown to induce neocollagenesis, leading to an increased ratio of type III collagen and decreased vascularity.8 This region encodes an endoplasmic reticulum membrane protein involved in regulation of the Wnt signaling pathway, which plays a crucial role in mesoderm and ectoderm development.4

Key Points

Question How might ablative fractional laser resurfacing alter local collagen composition within areas of focal dermal hypoplasia associated with Goltz syndrome?

Findings In this case report of a patient with Goltz syndrome, histologic changes demonstrated that, compared with internal controls, mosaically affected areas of focal dermal hypoplasia treated with ablative fractional laser resurfacing appear objectively thicker. A marked shift in collagen predominance from type III (fetal/early wound) to type I (adult/mature) was found.

Meaning Thermal microtrauma caused by ablative fractional laser resurfacing may create a unique environment that activates latent genes, inducing neocollagenesis and allowing this patient with Goltz syndrome to adaptively produce the collagen subtype that was specifically deficient at baseline.
The mechanism underlying this process has yet to be fully elucidated and involves the induction of growth factors, including increasing transforming growth factor β3 expression, decreasing basic fibroblast growth factor expression, and increasing matrix metalloproteinase-1 expression and involvement of microRNAs (especially miR-18a and miR-19a).12,13 Management of FDH in Goltz syndrome poses a clinical challenge because of the inability to correct or overcome the underlying genetic mutation and elicit neocollagenesis. Histologic features of FDH demonstrate an atrophic dermis, numerous subepidermal adipocytes, and a disorganized, diminished collagen network.9,11 A potential explanation for the defective collagen network based on studies of electron micrographs is that the affected fibroblasts are dysfunctional.9 No published reports, to our knowledge, have defined the specific ratios of type I to type III collagen expression within areas of FDH in patients with Goltz syndrome. Our Herovici collagen stains revealed a baseline predominance of type III collagen that shifted markedly to a type I predominance after AFR. This finding was unexpected for 2 reasons. First, patients with Goltz syndrome, because of their underlying genetic mutation, do not show spontaneous clinical improvement within areas of FDH after normal macrotrauma. Second, AFR has been previously associated with a shift toward type III collagen predominance in treatment of burn scars.13

These clinical and histologic observations could not have been anticipated using current models of Goltz syndrome. We surmise that the thermal microtrauma caused by AFR creates wounds from which the human body has yet to evolve the means for healing normally. In this case, AFR may have induced neocollagenesis through an alternative or as yet unknown pathway, allowing the patient to adaptively produce the type of collagen that was deficient at baseline, effectively overcoming genetic programming in local areas of FDH. This phenomenon, if true, may be analogous to the use of hydroxyurea to increase the ratio of fetal hemoglobin to type I collagen. The mechanism underlying this process has yet to be fully elucidated and involves the induction of growth factors, including increasing transforming growth factor β3 expression, decreasing basic fibroblast growth factor expression, and increasing matrix metalloproteinase-1 expression and involvement of microRNAs (especially miR-18a and miR-19a).12,13

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in patients with sickle cell anemia, with local effects of AFR appearing to stimulate type I collagen production. The patient’s unaffected, adjacent skin served as an internal control throughout the treatment duration. Histologic findings also confirm that the tissue specimens were not switched because the overall Goltz architecture was preserved through the mosaically affected stains albeit to a lesser extent in the post-AFR specimens.

Limitations
This report is limited by the study of a single patient. The field would benefit from rigorous long-term prospective trials.

Conclusions
Although further study is needed to confirm the overall efficacy of an AFR protocol for the treatment of FDH plaques in patients with Goltz syndrome, our report shows promising results and raises important questions about gene expression and the epigenetics of Goltz syndrome-associated mutations and the local effects of AFR. A dearth of treatment options exists for the cutaneous manifestations of Goltz syndrome, and the skin defects may be distressing to affected patients. In addition to the clinical benefits afforded by AFR, this novel technique may help reveal
molecular workarounds that permit innovative therapies to take advantage of the subtly different collagens that exist within the skin. Finally, this report suggests the potential to use AFR for laser-assisted delivery of normal autologous fibroblasts into the dermis through the microablated channels to help dilute the influence of mosaically affected fibroblasts, further bolstering the dermal network and helping to clinically normalize areas of FDH.

Figure 3. Comparison of Types I and III Collagen

Histologic images were obtained from samples of the posterior leg. A, Internal control specimen of skin predominantly contains type I collagen. B, Mosaically affected skin sample obtained before ablative fractional laser resurfacing (AFR) treatment demonstrates a predominance of type III collagen. C, Mosaically affected skin sample obtained after AFR treatment reveals areas of fibrosis with a marked shift to type I collagen. All samples use Herovici collagen staining, with red indicating type I collagen and blue indicating type III collagen (original magnification ×100).

REFERENCES


NOTABLE NOTES

**Dermatology in Epic Poetry—from *Beowulf* to *The Odyssey***

Ajay Kailas, BS

Epic poems have captured the imaginations of readers, listeners, and artists alike for millennia. Michelangelo painted part of the Sistine Chapel after being inspired by Dante’s *Divine Comedy*. Shakespeare’s 1602 play, *Troilus and Cressida*, is based on *The Iliad*, an ancient Greek epic poem attributed to Homer. All told, epic poems are captivating tales full of wonder and adventure. Particularly, they have often integrated dermatology in their unique plots. *Beowulf* is an Old English poem (written circa AD 700-1000) that tells of the powerful Geat hero Beowulf, who visits the mead hall, Heorot, to kill the evil monster Grendel. Grendel, bothered by the sounds of joy, has gruesomely slaughtered Heorot’s inhabitants for years. Owing to his magical gifts, no one has been able to slay him. Grendel not only possesses incredible strength, but his skin is also impenetrable to any blade: “Every nail, claw-scale, of that heathen beast...had magic in it; no one could penetrate it. No sword, no club, could cut his brutal, blood-caked claw.” Beowulf notably does not use a sword, but rather kills Grendel by directly ripping his arm off, causing him to bleed to death. In the 13th century German epic poem *Das Nibelungenlied* (*The Song of the Nibelungs*), the skin of a main character is a weakness rather than a strength. In the beginning of the story, the knight Siegfried is said to have slaughtered a dragon and bathed in his blood—rendering him invulnerable to weaponry. However, a leaf from a linden tree fell between his shoulders during this bath, leaving that area untouched with blood. His wife, Kriemhild, mentions, “There one might stab him, and thence is my care and dole,” indicating that this is his only weakness (similar to Achilles’ heel). Unfortunately, Siegfried is later murdered by Hagen, who spears the unsuspecting knight while he is drinking from a brook. His death inspires Kriemhild’s revenge, which is the focus of the second half of *Das Nibelungenlied*. *The Odyssey*, a Greek epic poem by Homer, details the legendary return of Odysseus to his home of Ithaca after the Trojan war. Arriving after 20 years, he discovers that multiple suitors are courting his wife, Penelope, presuming he is dead. Odysseus is then transformed by Athena (the goddess of war) into an old man as a disguise. However, his housekeeper, Eurycleia, identifies him because of a hunting scar on his leg: “She immediately recognized the scar; which once a boar inflicted upon him.” This discovery demonstrates Eurycleia’s loyalty and allows the Odysseus and Penelope to reunite. Together, they plot to kill the suitors and eventually restore peace to Odysseus’ kingdom. Ultimately, epic poems are full of fantastic details and magical characters. Many tales involve the skin, demonstrating dermatology’s unique significance in literature. Hopefully, epic poetry will continue inspiring many more for ages to come.

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