angiofibromas. Successful treatment of nonangiofibroma cutaneous manifestations of TSC has been sparse. To our knowledge, topical rapamycin has not been used successfully to treat the ungual fibromas of TSC. In our case, the use of topical rapamycin was well tolerated and resulted in the resolution of subungual tumors and rapid normalization of the overlying nail distortion.

The pathogenesis of TSC is characterized by an autosomal dominant mutation in TSC1 or TSC2 resulting in aberrant functioning of hamartin or tuberin, respectively. Tuberin, a GTPase-activating protein for Rheb, functions in a complex formed with hamartin. Rheb, which in turn activates mTOR, is inhibited in the presence of a normal tuberin-hamartin complex. In TSC, the hamartin-tuberin complex is unable to form, resulting in the constitutive activation of the mitogenic mTOR pathway. Rapamycin suppresses this pathway through the direct inhibition of mTOR.

While not entirely understood, an unrestrained mTOR pathway leads to upregulation of vascular endothelial growth factor (VEGF). It is suggested that rapamycin may exert its therapeutic effect on TSC lesions by directly killing tumor cells in addition to inhibiting VEGF production. Therefore, the same mechanism by which rapamycin reduces facial angiofibromas may also apply to nonangiofibroma cutaneous manifestations such as ungual tumors.

Patients with periungual and subungual fibromas associated with TSC are often quite symptomatic and often have significant distortion of the nail plate. Their treatment options have been quite limited to date. While further study is necessary, the experience with our patient suggests that topical rapamycin is a safe, well-tolerated, and potentially efficacious treatment for patients with ungual tumors associated with TSC.

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Somatic Forward (Nonrevertant) Mosaicism in Recessive Dystrophic Epidermolysis Bullosa

Revertant somatic mosaicism is a recognized phenomenon in patients with epidermolysis bullosa (EB) and other inherited diseases. It occurs when spontaneous mutations result in correction of a germline mutation that underlies the genodermatosis, leading to phenotypic reversion and sometimes functional improvement. Revertant mosaicism occurs through several mechanisms, all causing a nonreciprocal transfer of genetic information from the parent cell to the daughter cells. Gene conversions, intragenic crossover, back mutation, and second-site mutation (eg, single-base substitution) have all been described as mechanisms, and multiple mechanisms may occur in different cell populations in the same individual. True forward somatic mosaicism, however, has not to our knowledge been described previously in EB. Forward, or nonrevertant, mosaicism occurs during embryogenesis, when a mutation occurs in mitosis affecting only that subsequent cell line and not the other dividing cells of the embryo. The later it occurs during embryogenesis, the fewer cells will be affected. Dystrophic EB results from mutations in the COL7A1 gene that encodes type VII collagen, the major component of anchoring fibrils at the dermoepidermal junction. Blisters develop below the lamina densa clinically resulting in trauma-induced skin blistering, milia, and scarring, sometimes with nail dystrophy and mucosal involvement.

Report of a Case | A woman in her 20s presented with lifelong skin blistering and clinical features consistent with a mild recessive dystrophic EB. On examination, she had normal hair and teeth but evidence of dystrophic toenails, milia, and scarring. Notably, however, there was segmental sparing of the left side of her trunk (Figure 1) and part of her left arm. There were no other affected family members and no consanguinity.

Following written informed consent, genomic DNA was extracted from peripheral blood leukocytes and used as a template to sequence COL7A1, as described elsewhere. We identified compound heterozygosity for a donor splice site mutation (IVS64 + 1G>A) and a frameshift mutation (c.7787delG; p.Gly2596fs*34). The heterozygous frameshift mutation was identified in her father’s DNA, but the splice site mutation was not present in either paternal or maternal DNA and therefore appeared to have arisen de novo.

Skin biopsy specimens were taken from the affected and unaffected abdominal skin following local anesthesia with 2% lidocaine. Immunofluorescence microscopy labeling with an antibody to type VII collagen (LH7;2; SeraLab) showed a marked reduction in type VII collagen immunostaining intensity in affected skin compared with unaffected skin, the latter resembling normal control skin (Figure 2). Genomic DNA was extracted from the biopsy specimens and used to assess the COL7A1 mutations: both were present in affected skin DNA, but in unaffected skin, although the frameshift mutation was present, the splice site mutation was barely detected.
Figure 1. Clinical Photographs Demonstrating Segmental Nature of the Patient’s Dystrophic Epidermolysis Bullosa

Clinical appearances of the abdomen (A and B), hand (C), and nails (D) showing localized erythema and scarring in contrast to the normal-appearing skin.

Figure 2. Immunofluorescence and Genetic Sequencing of Affected and Unaffected Skin

The photographic images across the top row represent immunofluorescence (IF) studies (scale bar = 50 μm) in affected (A), unaffected (C), and control skin (D) and a clinical image of the patient’s abdomen (B). Evident in the IF images is a reduction in type VII collagen immunoreactivity at the dermoepidermal junction in affected skin (A) compared with bright, linear labeling in unaffected skin (C) and control skin (D). A-C, The Sanger sequencing graphs of genomic DNA (gDNA) reveal compound heterozygosity for splice site/frameshift mutations in COL7A1, with both mutations clearly evident in DNA from affected skin (A) and blood (B), but the splice site mutation barely detectable in unaffected skin (C), although the heterozygous frameshift mutation is still evident. D, The Sanger sequencing graphs of gDNA from control blood are provided for comparison.
Discussion | We have described a case of recessive dystrophic EB with clinical, immunohistochemical, and molecular data supporting somatic revertant mosaicism. In this patient, the frameshift mutation was inherited from the paternal gamete, and the splice site mutation occurred spontaneously and affected only some areas of skin.

Mosaicism has important connotations for treatment. In revertant mosaicism, punch grafting of small areas of reverted skin to unreverted sites has been successful, although the much larger areas of somatic mosaicism in our patient makes this a more scalable therapy. Other options include culturing the mosaic keratinocytes for grafting or using these cells to generate inducible pluripotent stem cells, as has been attempted for revertant keratinocytes.5

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COMMENT & RESPONSE

Dermatology Mobile Applications: More Than Just Patient Education

To the Editor | We read with interest the research letter by Cohen and colleagues1 that described a mobile application (app) to provide peer-reviewed education to individuals with acne and to identify users’ characteristics. As noted in the research letter2 and accompanying commentary,3 mobile apps have significant potential to provide information to large numbers of dermatology patients. However, these apps can and should go far beyond the role of surveying users and providing information and basic education.3 Dermatology apps should use evidence-based approaches and sophisticated programming to facilitate the promotion, inhibition, and self-monitoring of behaviors (eg, treatment adherence, UV exposure and protection, skin self-examination, and diet), symptoms, and other important outcomes (eg, quality of life). Additionally, apps can provide content that is tailored (ie, personalized to individuals’ behaviors and other characteristics), customized (ie, incorporating user-selected features or content), interactive, and dynamic, which may facilitate user experiences, engagement, and attainment of targeted outcomes. Apps can harness the myriad functions of smartphones and tablets, including taking photographs, video conferencing, text and multimedia messaging, instant messaging, and geographic locating (via global positioning system [GPS]).

In the context of acne education and treatment, a mobile app might incorporate a host of features beyond text-based education and information, including audio, video, graphic, and animated material. The app could promote (eg, via instant or text message, e-mail, or pop-up reminders) and assess adherence to topical and systemic therapies; provide local UV index and weather forecasts (based on the user’s GPS-determined location) while prompting and evaluating appropriate sun protection measures; prospectively track treatment adverse effects and acne status via self-report and more objective metrics such as photographs; track concomitant behaviors and outcomes (eg, diet, stress, distress, social anxiety, and other psychosocial factors); facilitate support via social networking with other patients; and enable the exchange of information to and from health care providers.

Dermatology mobile apps should not only take advantage of current technology but be grounded in science and subject to rigorous evaluation. Hundreds of dermatology mobile apps have already been disseminated through widely used commercial app stores with almost no empirical validity.4 Studies testing these and other newly developed apps should be conducted using randomized and/or nonrandomized research designs with iterative, adaptive, and/or quality improvement methods.5 Research is also needed to examine the dissemination, implementation, sustainability, and cost-effectiveness of such apps. The considerable potential for the role of mobile apps in dermatology will be realized through systematic efforts to develop evidence-based apps and examine their impact on clinical and public health outcomes.

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