a temporal relationship between initiation of the drug and symptoms of edema (that can vary from a few months to years) may suggest this association.\textsuperscript{4} The anatomical correlation between lymphedema and the site of previous surgery (or the area of the AVF used for hemodialysis) may be explained because trauma to local lymphatics by previous surgery can cause failure of lymphangiogenesis as a part of wound healing. The mechanism by which sirolimus interferes with lymphatic drainage is unclear, but it has been postulated that use after surgery inhibits lymphangiogenesis, prevents lymphatic endothelial cell migration, and causes lymphatic endothelial cell proliferation. Interference with lymphatic integrity has also been hypothesized.\textsuperscript{5}

In conclusion, we describe herein 2 renal transplant patients with chronic lymphedema attributable to sirolimus at the same area where the AVF for hemodialysis was located. Patients taking inhibitors of mTOR should be carefully monitored for this complication at an early stage, so that dose reduction or discontinuation of treatment might prevent an irreversible lymphedema.

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Successful Treatment of Subungual Fibromas of Tuberous Sclerosis With Topical Rapamycin

Ungual tumors, a major diagnostic criterion for tuberous sclerosis complex (TSC), are often symptomatic and have posed a therapeutic challenge.\textsuperscript{1} We present a case of successful treatment of a subungual fibroma with topical rapamycin.

Report of a Case | A female toddler with known TSC presented with multiple skin lesions characteristic of TSC; these included 5 facial collagenomas, more than 20 hypopigmented macules and patches consistent with ash leaf macules, and bilateral subungual tumors of the first toenails with associated nail plate dystrophy (Figure, A). Facial angiofibromas were not present. Other manifestations of TSC included known cardiac rhabdomyoma diagnosed prenatally and multiple daily seizures since infancy. Genetic testing had revealed mutations in both TSCI and TSC2.

The patient was having pain associated with the subungual fibromas and nail plate distortion. Surgical intervention had previously been offered for treating the facial collagenomas and the subungual fibromas, but the parents had declined. After presentation to our clinic, topical rapamycin in a 1-mg/mL solution was prescribed to be applied twice daily to the collagenomas and under occlusion to the periungual and subungual areas of the first toenails. While there was minimal to no improvement in the facial collagenomas, improvement in the subungual tumors was observed at the 2-month follow-up. At the 6-month follow-up, the subungual tumors were no longer noticeable, and dystrophy of the nail plate had subsided (Figure, B). Treatment was then discontinued. There were no signs of recurrence of the fibromas 6 months later, at most recent follow-up. The topical rapamycin was well tolerated without complications.

Discussion | Cutaneous stigmata of TSC can be very difficult to treat successfully, and, historically, primarily surgical interventions were considered to be the only options. Recently, several reports and small studies have demonstrated the safety and efficacy of topical rapamycin for facial angiofibromas in patients with TSC.\textsuperscript{2,3} A recent left vs right side of the face comparative study also demonstrated efficacy and good tolerability of topical rapamycin for the treatment of facial

Figure 1. Subungual Tumor of Right Great Toenail With Associated Nail Plate Dystrophy

A, At presentation, subungual tumors involving the patient’s right great toe were causing distortion of the nail. B, At the 6-month follow-up after treatment with topical rapamycin, the subungual tumors were no longer noticeable, and dystrophy of the nail plate had subsided.
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 mosaic 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 (IVS6 + 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.