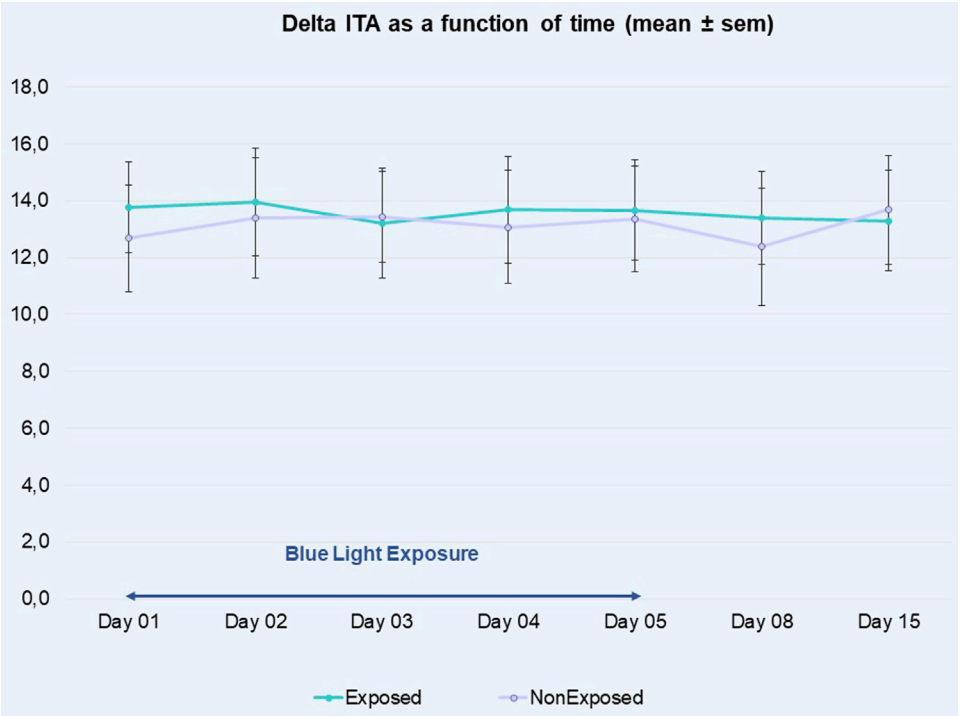

Fig 1. Δ Individual topology angle evolution. Individual topology angle is the colorimetry parameter inversely correlated to pigmentation. The measure of the individual topology angle during the 5 days of exposure and after 1 and 2 weeks showed no significant variation compared with baseline individual topology angle and no significant differences between the exposed and nonexposed half of the face. *ITA*, Individual topology angle; *SEM*, standard error of the mean.

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Histologic features of graft-versus-host disease-associated angiomatosis: Insights into pathophysiology and treatment

To the Editor: Graft-versus-host disease (GVHD)–associated angiomatosis (GVHD-AA) can cause significant morbidity in patients with chronic cutaneous GVHD, and there is no clear treatment.[1] Research is needed to elucidate disease pathobiology and inform treatment options but is hampered by the rarity of the disease. We analyzed 16 GVHD-AA, sclerotic GVHD–non-AA, and healthy

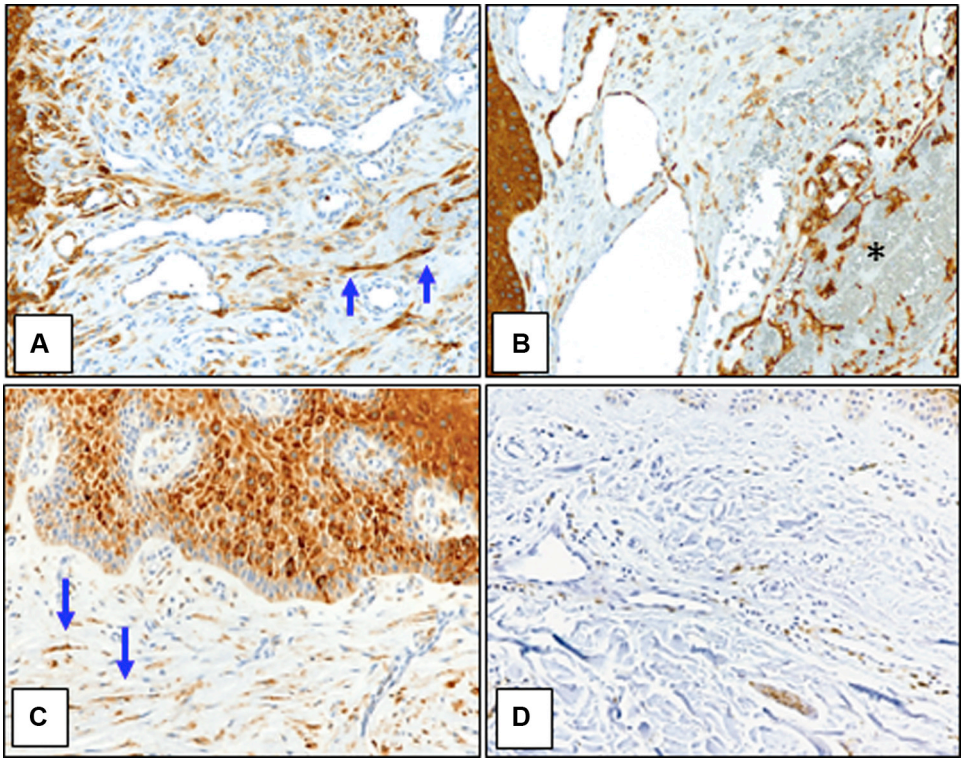

Fig 1. mTORC1 is activated in fibroblasts and epidermis but not endothelium in GVHD-AA. Representative immunohistochemical images of skin samples labeled for pS6 (brown) and counterstained with hematoxylin (blue). **A**, GVHD-AA lesion. **B**, Intralesional Masson's tumor from the same GVHD-AA lesion as in **A**. **C**, Control sclerotic skin adjacent to GVHD-AA lesion. **D**, Healthy skin. Blue arrows point to example pS6-expressing fibroblasts. Black asterisk marks Masson's tumor. (Original magnification: ×200.) *GVHD-AA*, Graft-versus-host disease—associated angiomatosis.

specimens for markers that could provide insight into disease pathogenesis and/or identify specific pathways that are directly or indirectly targetable by currently available treatments.

Methods, patient clinical and treatment data, and lesion histology are detailed in the Supplemental Material (available via Mendeley at https://doi.org/10.17632/nzd6dyc7cb.1). Consistent with previous reports, GVHD-AA lesions represented vascular proliferations composed of thin-walled vessels. Vessels were not lymphatic in origin (D2-40$^-$, data not shown), nor did they result from human herpesvirus 8 infection (data not shown).

Sirolimus has been proposed as a therapy for GVHD-AA, based on the known activation of the mTORC1 pathway in the endothelium of other vascular lesions.[2] mTORC1 signaling was low to absent in the vasculature of GVHD-AA lesions and was comparable to that in the vasculature of healthy control skin, as assessed by phosphorylated S6 (pS6) staining (Fig 1). The endothelium of Masson's tumor—like changes in 3 GVHD-AA lesions stained positively for pS6, despite the remaining GVHD-AA lesion being negative (Fig 1), suggesting that GVHD-AA endothelial cell proliferation uses signaling pathways distinct from other vascular growths. Dermal fibroblasts within both GVHD-AA and control sclerotic GVHD skin displayed increased mTORC1 activity (Fig 1). Although a direct benefit of sirolimus against GVHD-AA lesions is rendered questionable by these findings, it is possible that sirolimus may improve GVHD-AA by suppressing mTORC1 signaling in the surrounding stroma. In our small cohort, there was no clear correlation between response to topical or systemic sirolimus and vascular pS6 staining.

β-Blockade is another therapy used in GVHD-AA based on its success in infantile hemangiomas.[3] Infantile hemangiomas are reported to express GLUT1[4]; in contrast, GVHD-AA vasculature lacked GLUT1 expression (data not shown). This finding suggests that the 2 diseases are mechanistically distinct, raising the possibility that β-blockade may not be effective in GVHD-AA. Importantly, β-blocker function in infantile hemangiomas is likely independent of GLUT1,[5] so the lack of GLUT1 on

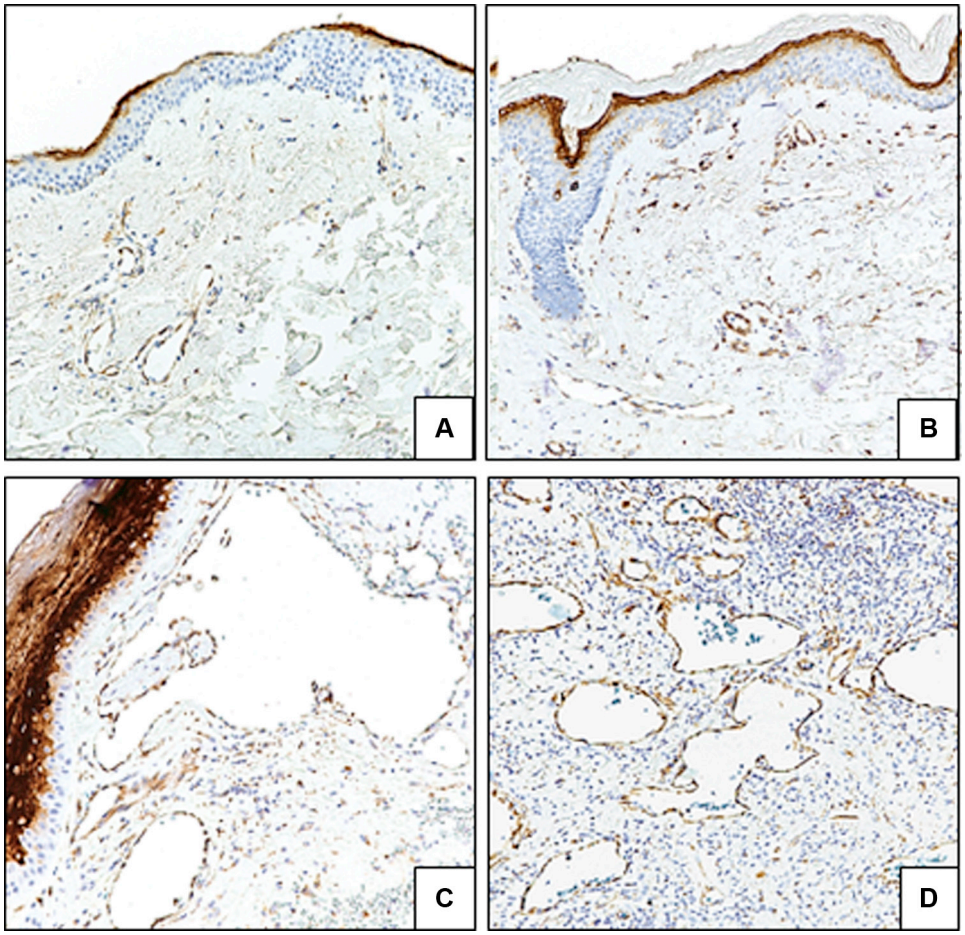

Fig 2. VEGF shows variable upregulation in GVHD-AA. Representative immunohistochemistry images of skin samples labeled for VEGF (brown) and counterstained with hematoxylin (blue). **A**, Healthy skin. **B**, Control sclerotic GVHD−non-AA skin. **C** and **D**, Two different GVHD-AA lesions showing (**C**) increased epidermal VEGF expression and (**D**) increased VEGF expression on dermal vasculature. (Original magnification: ×200.) *GVHD-AA*, Graft-versus-host disease−associated angiomatosis; *VEGF*, vascular endothelial growth factor.

GVHD-AA vasculature does not exclude a potential benefit of β-blockade. In our cohort, not all patients treated with β-blockade experienced benefit, and in those with reported improvement, interpretation was confounded by the combination of other therapies.

Finally, systemic and intralesional anti−vascular endothelial growth factor (VEGF) therapies have been approved by the US Food and Drug Administration for other diseases,[6] and VEGF was reportedly elevated in serum of a patient with GVHD-AA.[7] In our study, VEGF staining in endothelium was variable among GVHD-AA specimens, although overall it was higher than in control sample vasculature (Fig 2). Expression was also increased within lesional epidermis (Fig 2).

It is reasonable to trial β-blockers and mTORC1 inhibitors for GVHD-AA, although ideally as monotherapy (if clinically appropriate) and with rigorous recording/reporting of clinical outcomes to better evaluate efficacy. Local anti-VEGF treatment may be worth considering, particularly for larger or recalcitrant lesions shown to have high VEGF expression.

For detailed results, refer to the Supplemental Material.

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Frequent corneal abrasions precede scarring and vision loss in epidermolysis bullosa: An international patient survey

To the Editor: Patient-reported outcomes are essential for drug development. Symptomatology of epidermolysis bullosa (EB)—related corneal abrasions is not published. We developed a 62-question, internally validated survey to characterize EB-related abrasions and investigate the relationship of abrasion symptoms, scarring, and vision loss. The survey was written in English and electronically distributed through EB foundations. Ninety-five respondents completed the survey, 88% (84/95) from the United States and 12% (11/95) from other countries, including Canada, Ethiopia, France, India, Pakistan, Saudi Arabia, and Trinidad/Tobago. Questions were generated by a pediatric ophthalmologist, a pediatric dermatologist, and an EB-family focus group.

Abrasion and scarring incidences were 68% (69/95) and 44% (42/95), respectively (Table I). Vision loss occurred in 35% (33/95); the cause was amblyopia (potentially reversible vision loss) in 30%. Respondents with frequent abrasions (every 0-4 months, 43%) were 5.18 times more likely to scar (odds ratio) ($P = .001$) than those with infrequent abrasions. Of those with infrequent abrasions, 59% reported a remote prior history of frequent abrasions. Pain scores averaged 8.0 ± 2.0 out of 10, double the values of patients without EB in emergency departments (3.9-5.7/10).[1,2] For 70% (66/95), pain lasts 3 days or more. Factors that worsen abrasions are dry air (42%, 40/95), dry places (41%, 39/95), and antihistamines (11%, 10/95). Factors that improve abrasions are eyedrops (49%, 47/95), use of a humidifier (32%, 30/95), and drops used during screen time (27%, 26/95). Only 5% (2/37) reported no impact on activities of daily living; the remainder reported inability to open eyes (57%, 21/37), use screens (57%, 21/37), read (51%, 19/37), or drive (35%, 16/37). The impact on family emotions was high, with 73% (48/66) reporting that abrasions are moderately to extremely upsetting (on a 5-point scale). Emotional impact correlated with pain severity (0.486; $P < .001$). Despite the adverse impact, 67% (44/66) do not routinely seek medical attention because 56% (37/66) have adequate treatments at home, whereas 23% (15/66) reported "too much pain to go outside." Treatments tried included moisture drops (51%, 48/95), ointment (45%, 43/95), and dim lighting (45%, 43/95). Only 15% (10/68) of respondents found these treatments to be *a good amount* or *completely* helpful, whereas 81% (55/68) reported that these were *somewhat*, *a little*, or *not at all* helpful. Patients commented that abrasions "usually completely shut down my life" and "are one of the worst secondary issues associated with EB, if not the most painful."

Limitations include sample size, and response, nonresponse, and recall biases. Patients with ophthalmic symptoms shared their experiences; therefore, both the percentage with eye involvement and the severity of disease reported are higher in our study population than previously reported in the dermatologic literature.[3]

We highlight the finding that frequent corneal abrasions raise the risk of corneal scarring by 5-fold (Fig 1). Dermatologists who inquire about the frequency of ophthalmic symptoms have the opportunity to intervene earlier and prevent scarring, amblyopia, and subsequent vision loss. The duration, severity, and impact of pain should be queried and addressed because abrasion pain is typically severe and prolonged and interferes with