SHORT COMMUNICATION

Non-invasive Analysis of Skin in Recessive Dystrophic Epidermolysis Bullosa Using High-Frequency Ultrasound: A First Case Report

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Epidermolysis bullosa (EB) comprises a group of rare inherited disorders with early onset, characterized by skin fragility and blistering induced by minimal trauma (1, 2). After diagnostic confirmation and subclassification by immunohistochemistry and genetic testing, patients require lifelong monitoring, as severe forms are associated with chronic wounding, infections, local and systemic inflammation, and an increased risk of aggressive skin cancer (1, 3). A major challenge in EB research and care is the lack of objective measures of local disease severity, which hampers longitudinal monitoring and evaluation of new treatments. Conventional methods are limited: histopathology is invasive and unsuitable for repeated assessments, whereas visual examination is subjective and may lack sensitivity to subtle dermal changes.

High-frequency ultrasound (HFUS) addresses these limitations by enabling non-invasive visualization and quantification of skin layers. HFUS utilizes probes above 15 MHz and has demonstrated clinical utility for assessment of skin thickness, inflammation and structural changes in various dermatological conditions, including inflammatory skin diseases, tumours and scarring disorders (4). In particular, the subepidermal low-echogenic band (SLEB) has been validated as a quantitative marker of inflammation, with increased thickness correlating with dermal oedema and inflammatory infiltration (4–10). Here, we present a case report investigating whether HFUS can detect and quantify structural changes associated with recessive dystrophic EB (RDEB).

A DermaScan C HFUS unit (Cortex Technology, Aarhus, Denmark) equipped with a 20-MHz probe (B-scan resolution, 60×150 µm; penetration depth, 13 mm) was used. Imaging was performed using a standardized gain profile (preset gain profile 3, gain level 13), selected based on the manufacturer's recommendations (11).

Epidermal and SLEB thicknesses were measured in A-scan mode by averaging 5 measurements (peak-to-peak):

Epidermal thickness: start to end of the epidermal entry echo

SLEB thickness: end of epidermal entry echo to the first dermal peak

B-scan quantification was performed using pixel intensity segmentation within a fixed rectangular region of interest (ROI; preset shape 4, 1.51 mm²). For the measurement of subepidermal hypoechogenicity, the upper border of the ROI was aligned to the base of the epidermal entry echo using thresholds of 0–30, corresponding to low echogenicity (12). Conversely, for epidermal hyperechogenicity, the lower border of the ROI was aligned to the base of the epidermal entry echo using thresholds of 150–255 (high echogenicity). The percentage of segmentation was calculated by dividing the area of pixels within the threshold by the total ROI area. A schematic of ultrasound visualization and quantification is shown in **Fig. 1**a.

CASE REPORT

A 16-year-old male patient with a confirmed RDEB diagnosis (homozygous *COL7A1* mutation confirmed by genetic analysis; absent collagen VII on immunohistochemistry) was examined. The patient has recurrent wounds over large parts of the body, including the eyes and mouth, with clinically challenging chronic wounds, particularly affecting the axillae and knees. Additional manifestations include lifelong pain, pruritus, and gastrointestinal and nutritional complications, requiring surgery for oesophageal stricture and gastrostomy tube placement. The patient is clinically classified as having severe RDEB. At the time of examination, he received standard symptomatic EB treatment in accordance with local and national guidelines. He had not received birch triterpenes (Filsuvez), beremagene geperpavec (Vyjuvek) or other gene therapy.

The HFUS examination was performed on the right abdomen in an area with recurrent blistering, erythema and fibrosis bordered by clinically normal-appearing skin. Six sequential scanning positions were assessed across the area and its transition zone (Fig. 1b–c). Sequential scanning from normal to affected skin revealed progressive changes: position 1 (normal-appearing skin) showed a homogeneous, hyperechoic dermis beneath the epidermal entry echo, comparable to the HFUS appearance in healthy individuals. A superficial vessel served as an anatomical landmark

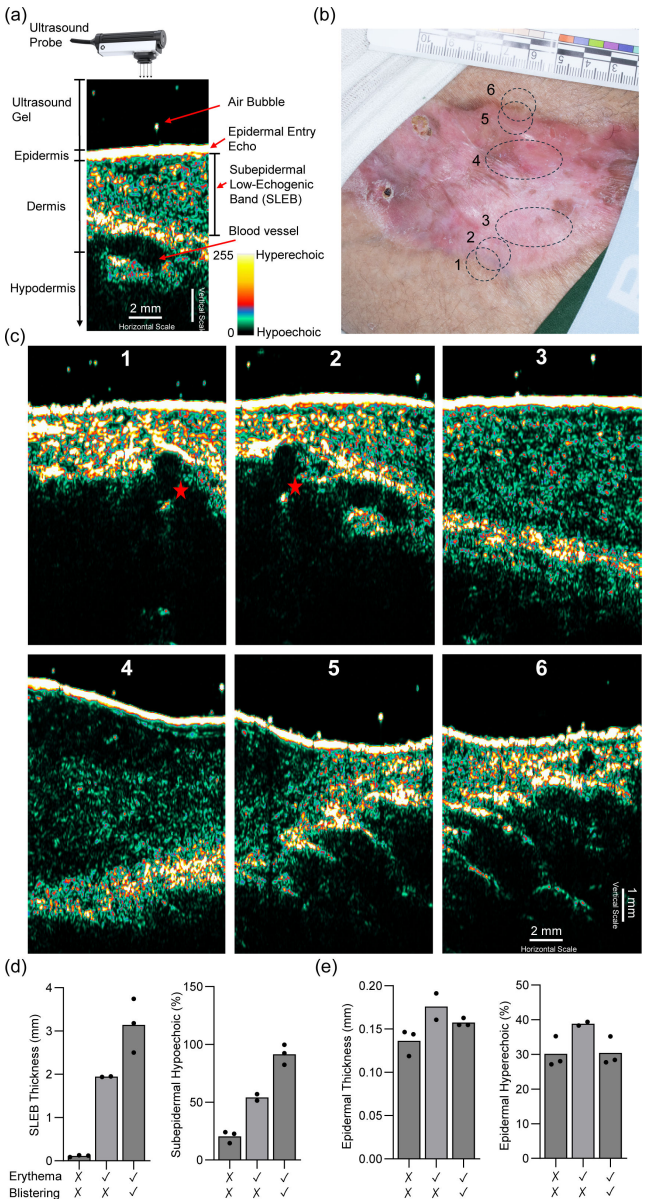

Fig. 1. High-frequency ultrasound (HFUS) assessment of an area with recurrent blistering, erythema and fibrosis in a patient with recessive dystrophic epidermolysis bullosa. (a) Schematic illustration of HFUS skin imaging showing epidermal entry echo, subepidermal low-echogenic band (SLEB), dermis and hypodermis with visualization of basic measurement principles. (b) Clinical photograph of the examined area (right abdomen) showing the approximate location of scanning positions 1–6, spanning the transition from normal to erythematous/blistering skin. (c) Sequential HFUS images at positions 1–6. Red star marks a superficial vessel serving as an anatomical landmark in positions 1–2. Note progressive appearance and thickness of SLEB (dark/hypoechoic band beneath epidermis) from positions 2–4, with abrupt normalization at positions 5–6. (d) Quantification of SLEB thickness and subepidermal hypoechogenicity in normal-appearing skin, erythematous skin and erythematous skin with signs of blistering shows stepwise increases in SLEB thickness and hypoechogenicity. (e) Epidermal thickness and hyperechogenicity showed no consistent differences between skin conditions. Individual data points are shown with bars indicating the mean. Each data point represents a separate image at slightly different locations within the same region. Sample size: n=3 images for normal-appearing skin and erythematous skin with blistering and n=2 for erythematous skin without blistering.

across positions 1–2. At position 2 (erythematous margin), a distinct SLEB began to appear. Position 3 (fully erythematous skin) displayed a prominent SLEB throughout the field of view. Position 4 (erythema and early signs of blistering) showed a large SLEB with even more marked hypoechogenicity as compared with position 3. Positions 5–6, located between the erythematous/blistering area and normal-appearing skin, also showed a gradual normalization towards a homogeneous, hyperechoic dermis beneath the epidermal entry echo, but this was more abrupt than the transition between positions 1 and 2.

Quantification was performed on multiple HFUS images from clinically normal-appearing adjacent skin (n=3), erythematous skin without blistering at position 3 (n=2) and erythematous skin with signs of blistering at position 4 (n=3) (Fig. 1d–e). A stepwise increase in SLEB thickness was observed, with mean values of 0.11 mm in normal-appearing skin, 1.95 mm in erythematous skin without blistering and 3.10 mm in erythematous skin with blistering. Correspondingly, the subepidermal hypoechogenicity (percentage area) increased from 19.7% in normal-appearing skin to 54.1% and 91.2%, respectively (Fig. 1d). No apparent differences in epidermal thickness or hyperechogenicity were detected among the regions (Fig. 1e). The quantified images are shown in Fig. S1, and individual data points are given in the Supplementary Material. The patient reported no pain or discomfort during the examination.

DISCUSSION

This case demonstrates that HFUS can non-invasively visualize and quantify dermal changes associated with recurrent blistering, fibrosis and inflammation in EB skin. The SLEB has previously been validated as a marker of dermal inflammation in conditions such as atopic dermatitis, psoriasis and mycosis fungoides (4–10), and our preliminary findings suggest that it may serve a similar role in EB.

We hypothesize that the marked expansion of the SLEB reflects multiple pathological processes: dermal–epidermal separation at the level of the lamina densa due to absent or dysfunctional collagen VII anchoring fibrils, inflammatory cell infiltrate and oedema accumulation in structurally compromised skin following minimal trauma. Supporting this interpretation, a separate study in a murine junctional EB model demonstrated that increased SLEB thickness correlated with both increased immune cell infiltration on histology and severity of visual disease manifestations (13). In the current case, increased SLEB thickness was associated with clinical severity (normal < erythema < blistering), supporting its potential as

an objective marker of local disease activity. However, larger targeted studies are needed to fully elucidate the structural and cellular basis of these HFUS alterations and establish standardized imaging protocols and correlations with clinically meaningful EB outcomes.

Unlike histopathology, HFUS can be performed repeatedly without additional skin trauma, and unlike clinical photography, it provides quantitative subsurface information. Clinically, HFUS could serve multiple roles in EB management, including objective monitoring of disease activity to enable early, focused treatment and evaluation of therapeutic response to guide personalized treatment. These are particularly interesting prospects given recent advancements in EB treatments, especially the approvals of the topical gene therapies beremagene geperpavec (14) and prademagene zamikeracel (Zevaskyn) (15).

In conclusion, HFUS represents a promising non-invasive tool for visualizing inflammatory changes in EB and may facilitate objective disease monitoring and treatment assessment in clinical practice. Validation in larger and more diverse patient cohorts is needed to establish its clinical utility.

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Data Availability Statement: The data supporting the findings of this study are available in the supplementary material. Additional information is available from the corresponding author upon reasonable request, except for information that cannot be shared publicly due to participant privacy protections.

Ethical statement: The HFUS measurements were performed during a clinical study visit for trial NCT05378997. However, they were performed on skin areas not treated with the study drug and served as a pilot study to investigate the feasibility of incorporating HFUS as an outcome measure in future clinical studies. This work was approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten, application 2022-00527-01, amendment 2023-05051-02). Written informed consent was obtained from the patient and parent/legal guardian prior to study inclusion.

Conflicts of interest: AS is a founder of in2cure AB, the parent company of Xinnate AB, which provided partial funding for this study. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The other authors declare no competing interests.

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