

# Cardiac transplant for epidermolysis bullosa simplex with KLHL24 mutation—associated cardiomyopathy



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**Key words:** dilated cardiomyopathy; epidermolysis bullosa; KLHL24.

## INTRODUCTION

Epidermolysis bullosa simplex (EBS) is a rare inherited blistering disease characterized by mutations in several genes encoding for structural proteins within the epidermis. Mutations in kelch-like protein 24 (KLHL24) were recently implicated in a unique subtype of EBS.<sup>1</sup> Features of EBS-KLHL24 include blistering at birth, stellate scarring, hypo- and hyperpigmentation in childhood, nail dystrophy, alopecia, anetoderma, and skin fragility. There is a growing association of dilated cardiomyopathy in EBS-KLHL24 that may be severe and present in early adulthood.<sup>2</sup> Here we report a case to support the current evidence of dilated cardiomyopathy (DCM) associated with EBS-KLHL24. In addition, we report a successful orthotopic heart transplant (OHT) as treatment for severe manifestation of KLHL24 mutation—related cardiomyopathy.

## CASE REPORT

A 14-year-old girl with epidermolysis bullosa (EB) of initially unknown subtype presented with 2 weeks of progressive lower extremity edema, increased abdominal girth, and abdominal pain. Abdominal ultrasound scan was notable for ascites. Brain natriuretic peptide was elevated to 9671 pg/mL, and troponin was elevated at 0.59 ng/mL. Transthoracic echocardiogram (TTE) displayed moderate dilation of all 4 cardiac chambers, moderate-to-severe tricuspid and mitral regurgitation, and a reduced left ventricular ejection fraction of 19%. She had acute congestive heart failure and dilated cardiomyopathy. The patient was stabilized on a milrinone drip and intravenous furosemide.

### Abbreviations used:

DCM:	dilated cardiomyopathy
EB:	epidermolysis bullosa
EBS:	epidermolysis bullosa simplex
KLHL24:	kelch-like protein 24
OHT:	orthotopic heart transplant
TTE:	transthoracic echocardiogram

Thorough investigation into possible etiologies of heart failure was undertaken. Despite evaluation including viral respiratory panel, nasopharyngeal viral cultures, and rectal viral cultures, there was no evidence of viral myocarditis or other inciting event.

Within 1 month of presentation, the patient required implantation of a left ventricular assist device. She was also evaluated and listed for OHT, which was successfully performed. At the time of this writing, she is 5 months post cardiac transplant and doing well with normal systolic function.

EB was initially diagnosed after blisters were noted at birth; they have persisted through early childhood. Biopsy for electron microscopy reported a lack of anchoring fibrils, and a diagnosis of recessive dystrophic EB was posited; those electron micrographs are no longer available for re-evaluation. However, the patient was lost to follow-up after early infancy. The patient was adopted shortly after birth, and the medical histories of her biologic parents are limited. Early clinic notes suggest that the patient's biological father may have displayed mild acral blistering in childhood. Our patient reported improvement in frequency of blister development especially after

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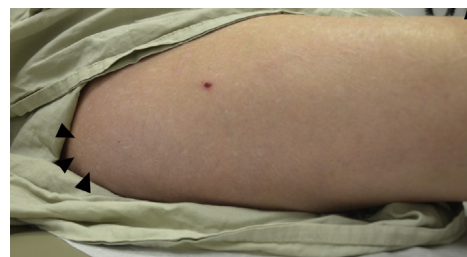
**Fig 1.** **A**, Mottled, hypopigmented macular scars on the shins and knees. Note malalignment of great toenails. **B**, Similar mottled hypopigmented scars on the knees and dorsal hands. **C**, Close-up image of atrophic scars on the shin.

age 4. At the time of presentation, she reported occasional blistering on her hands and feet, at sites of mild friction, and occasionally intraorally. Overall symptoms were mild and did not affect her activities of daily living. On examination of the bilateral shins, thighs, and dorsal hands, there were hypopigmented macular scars (Fig 1, A-C). On the right flank, there was a well-defined annular erosion consistent with an unroofed bulla. On the bilateral upper thighs were several grouped 2- to 3-mm well-defined hypopigmented papules consistent with albopapuloid-type lesions, lesions once believed to be diagnostic of dominant dystrophic EB but now known to occur occasionally in any EB type or subtype (Fig 2). To clarify EB subtype, an EB genetic panel was completed and found a heterozygous mutation in *KLHL24* exon 4 c.1A>T consistent with EBS-KLHL24. The remainder of the EB genetic panel, including *COL7A1*, was unremarkable.

Interestingly, the patient also has a history of left vesicoureteral reflux with resulting decreased left kidney function now post-incision of ureterocele at age 10. The significance of this and any association with *KLHL24* mutation is unclear.

## DISCUSSION

Epidermolysis bullosa encompasses a spectrum of inherited defects in epidermal and dermoepidermal junction ultrastructure. As many as 9 different genes have been associated with EBS.<sup>3</sup> Recently, described mutations in *KLHL24* have been implicated in a novel subtype of EBS. Although the exact mechanism by which *KLHL24* results in skin fragility is unclear, the protein is involved in a ubiquitination and protein degradation pathway.<sup>4</sup> As in our patient, the pathogenic mutations appear to



**Fig 2.** Subtle albopapuloid-type papules on right lateral thigh indicated by black arrows.

consistently involve the initiation codon of the *KLHL24* gene.<sup>5</sup> The same mutation in our patient, c.1A>T, has been reported in one other affected family.<sup>2</sup> In addition to blistering at birth, stellate scarring, and dyspigmentation in childhood, multiple cases of DCM have been described among these patients. Yenamandra et al<sup>6</sup> reported a father and son with EBS-KLHL24. The father also had a history of DCM diagnosed at age 18 requiring OHT.<sup>6</sup> The son had a borderline enlarged left ventricle on TTE, but it was clinically asymptomatic. Schwieger-Briel et al<sup>7</sup> reported the extracutaneous features of 20 patients with EBS-KLHL24. Eight of the 20 patients had DCM including 2 patients who died of cardiac death at ages 39 and 54 before the start of the study.<sup>7</sup> Based on our patient and other reported cases, DCM is a serious extracutaneous manifestation of EBS-KLHL24. Given the potential for early age of onset and rapid progression, as seen in our case, routine cardiac screening (such as TTE and brain natriuretic peptide level) should be performed. Furthermore, cardiac transplantation appears to be a viable treatment option in severe cases of EBS-KLHL24-associated cardiomyopathy.

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