

## CASE REPORT

# Recessive dystrophic epidermolysis bullosa (RDEB) complicated by secondary hepatic amyloidosis

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Epidermolysis bullosa (EB) consists of a heterogeneous group of autosomal dominant or recessive disorders, characterized by epithelial fragility.<sup>1</sup> In dystrophic EB, patients have a genetic defect in the gene encoding collagen VII, COL7A1. Generalized severe recessive dystrophic EB (RDEB) is characterized by large, flaccid bullae present at birth with healing atrophic scars.<sup>2</sup> RDEB is associated with a high mortality and morbidity.

Although no definitive therapy exists, recent advances in medical care have significantly increased the survival of RDEB. This has exposed complications not previously observed, including secondary amyloidosis, which can have fatal outcomes. Secondary amyloidosis, a rare complication, has been scarcely reported in the literature to date, usually solely affecting renal function. We report a case of RDEB with amyloidosis, causing liver hypertrophy and caput medusa.

## CASE REPORT

A 25-year-old woman presented with a 2-month history of gradual-onset right upper-quadrant abdominal pain, with associated abdominal distension and dark urine. She was born to non-consanguineous parents, and diagnosed at birth with RDEB. She had inherited 2 heterozygous deletion mutations in the COL7A1 gene, c [4918del] in exon 52 and [7634del] in exon 102, predicting 2 frameshift mutations, p. [Gly1640fs] and [Gly2545fs], with downstream premature termination codons. This explained the lack of



**Fig 1.** Squamous cell carcinoma identified after multiple biopsy specimens of poorly healing area over left malleolus.

collagen VII expression in her skin on immunofluorescence mapping.

Blistering was extensive from early infancy, causing cutaneous scarring and mitten deformities of hands and feet. She developed associated complications, including squamous cell carcinoma (Fig 1), dental caries, esophageal strictures, anal fissures, osteoporosis, anemia, hypogonadotropic hypogonadism, and bilateral inferior exposure keratopathy. Previous procedures included surgeries to correct hand contractures, right lower lid ectropion repair,

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and regular iron and blood transfusions for anemia. Medications included long-standing phenytoin (50 mg) 3 times daily to aid wound healing, pantoprazole, cholecalciferol, estradiol/norethisterone, pregabalin, tramadol, and oxycodone.

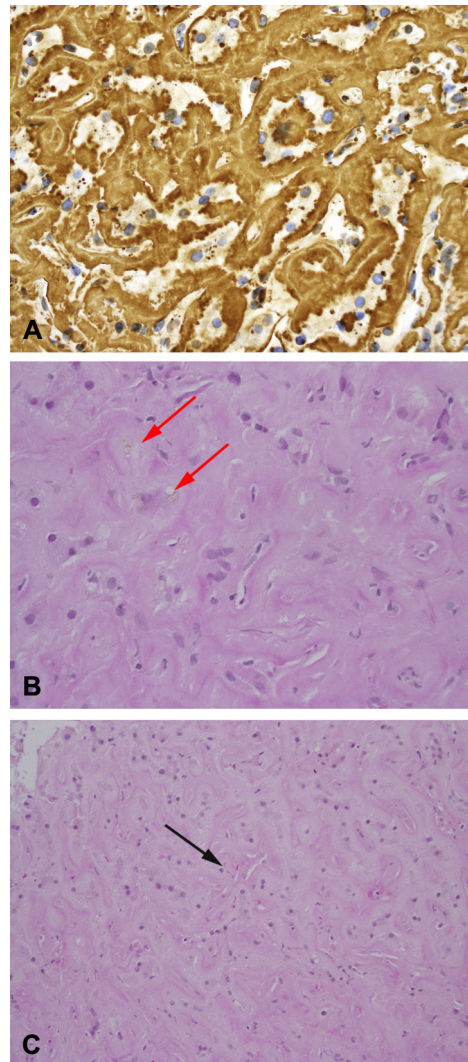
Physical examination revealed weight 27 kg, massive hepatomegaly with caput medusa, and right upper-quadrant tenderness. Investigations revealed normochromic anemia (hemoglobin 8.5 g/dL), hyponatremia (212 g/dL), hypoalbuminemia (2.1 g/dL), creatinine 48  $\mu\text{mol/L}$ , and liver function test results demonstrating a cholestatic picture (GGT 356 U/L, ALP 443 U/L, alanine transaminase 6 U/L, aspartate transaminase 20 U/L, bilirubin 0.1 mg/dL, international normalized ratio 1.4). Total globulins were significantly decreased (9.5 g/dL). Chronic liver disease screen produced negative findings (antinuclear antibody, SMA, anti-LKM, hepatitis B, hepatitis C, alpha-antitrypsin, and ceruloplasmin). Liver ultrasound revealed gross hepatomegaly with “starry-sky” appearance, and no common bile duct dilatation or gallstones.

Over 6 months, her hepatomegaly worsened. Further investigation revealed negative antimitochondrial antibody, anti-M2, GP210 and SP100, paraprotein, urine Bence-Jones protein, and angiotensin-converting enzyme level. Total IgG was elevated (6.5 g/dL), and other immunoglobulins were normal.

Liver biopsy specimen demonstrated florid secondary amyloidosis (type AA), without fibrosis (Fig 2). The liver parenchyma was extensively obliterated by the deposition of homogenous, eosinophilic material, compressing sinusoids, distorting the architecture, and destroying hepatocytes. There were no portal tracts or fibrosis. Immunostains for amyloid protein P and A showed strong, diffuse staining. Laser capture microdissection and tandem mass spectrometry performed on the liver biopsy demonstrated the amyloid forming protein SAA2 as well as the amyloid associated proteins ApoE, SAP, ApoA4, vitronectin, and clusterin, which was consistent with a diagnosis of AA amyloidosis.

Further investigations for amyloidosis revealed elevated serum amyloid A (34.8 mg/L), kappa light chains (725 mg/L), and lambda light chains (274 mg/L). Paraprotein was negative.

In light of the underlying EB and likelihood of amyloidosis recurrence, hepatic transplantation was not undertaken. The patient was monitored for signs of hepatic decompensation. Over 2 years after biopsy specimen, liver function test results remained stable, and abdominal ultrasound unchanged. Massive abdominal distension and pain remain problematic.



**Fig 2.** Histology of liver biopsy specimen showing positive immunostain for amyloid A protein (A). B, High-power view; black arrow indicates compressed sinusoids. C, Low-power view; red arrows indicate obliterated hepatocytes. (A-C, Original magnifications: A and B,  $\times 400$ ; C,  $\times 100$ .)

Recently, 24-hour urine collection revealed protein/creatinine ratio greater than 300, and testing demonstrated glomerular filtration rate adjusted for body surface area 50.7 mL/min/1.73 m<sup>2</sup>, indicating moderate renal impairment. As no other cause of renal impairment was found, this was attributed to renal amyloidosis. Because of the significant morbidity associated with a renal biopsy, renal amyloidosis has yet to be confirmed histologically.

## DISCUSSION

Amyloidosis consists of a heterogeneous group of disorders where normally soluble plasma proteins are deposited in the extracellular space in an

insoluble, fibrillar form. Secondary amyloidosis (AA amyloidosis) results from the improper processing of serum amyloid A protein, which cannot be broken down beyond an 8.5-kd fragment labeled amyloid A protein.

Recurrent, substantial elevations of serum amyloid A protein are necessary, but not sufficient, for amyloidosis to develop. AA amyloidosis occurs in chronic inflammatory diseases, where serum amyloid A protein concentration can increase greater than 2000 mg/L during the acute-phase response.<sup>2</sup>

Although secondary amyloidosis is a known complication of chronic dermatoses, only 11 sporadic cases of RDEB complicated by secondary amyloidosis have been reported. Bourke et al<sup>3</sup> described fatal systemic amyloidosis in twin sisters with RDEB; in both cases the amyloidosis was rapidly progressive, leading to death. Mann et al<sup>4</sup> reported a case of renal amyloidosis, suggesting that renal involvement negatively alters the course of EB. Dunnill et al<sup>5</sup> reported the first case of dominant dystrophic EB with systemic amyloidosis affecting spleen, liver, and kidney. Csikós et al<sup>6</sup> described a 25-year-old woman with renal and pulmonary amyloidosis.

Kaneko et al<sup>1</sup> reported a 17-year-old boy with RDEB who died as a result of renal amyloidosis; a subsequent retrospective study investigated the incidence of renal amyloidosis in RDEB. They found that 7 of 9 patients with RDEB had nephropathy, however the study was limited as renal biopsy specimens were unable to be obtained for all patients.

There is no definitive treatment for RDEB. Phenytoin is reported to be effective by inhibiting the synthesis and secretion of collagenase from dermal fibroblasts, and has been shown to increase tolerance against trauma.<sup>2</sup> Phenytoin may rarely cause hepatotoxicity, occurring in less than 1% of patients, usually within the first 6 weeks of treatment.<sup>7</sup> It has been associated with amyloidosis in 1 case report, with a 55-year-old man developing renal amyloidosis with a monoclonal gammopathy,

without coexisting multiple myeloma or lymphoproliferative disorders.<sup>8</sup> There have been no reports in any condition associating phenytoin with AA amyloidosis, hence we view it unlikely in this case.

## CONCLUSION

The prevalence of amyloidosis in EB may be underappreciated as these patients have fragile skin, they are susceptible to infections, and organ biopsy is often difficult. As the clinical features of secondary amyloidosis may be nonspecific, diagnosis is often delayed. Hence, we recommend that physicians consider the possibility of amyloidosis, both hepatic and renal, in patients with dystrophic EB.

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