Case Report

Epidermolysis Bullosa Complicated with Nephrotic Syndrome Due to AA Amyloidosis: A Case Report and Brief Review of Literature

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ABSTRACT. Epidermolysis bullosa (EB) encompasses a clinically and genetically heterogeneous group of rare inherited diseases characterized by marked mechanical fragility of epithelial tissues with blistering and erosions following minor trauma. Amyloidosis is one of the most important complications of EB mostly seen in recessive dystrophic EB (RDEB) patients and can involve the kidney, bowel, liver, and also respiratory system. Herein, we present a child, who is probably the youngest case of genetically diagnosed RDEB, complicated with amyloidosis reported in literature. A 6-year-old boy who was diagnosed with EB was referred to our center with nephrotic-range proteinuria and hypoalbuminemia. He had homozygous mutation in COL7A1 gene. Kidney biopsy was remarkable for amyloidosis with positive Congo red staining, and amyloid fibrils were seen on electron microscopy. Although he did not have any symptoms of autoimmune diseases and mutation in the MEFV gene, he was given colchicine because of positive family history for familial Mediterranean fever and amyloidosis.

Introduction

Epidermolysis bullosa (EB) is an inherited disease characterized by marked mechanical fragility of epithelial tissues with blistering and erosions following minor trauma.¹ The prevalence of EB was estimated to be approximately 11 per million, and the incidence is approximately 20 per million live births.²

Four types are defined upon morphological analysis of a skin sample using transmission electron microscopy or immunofluorescence mapping: (1) EB simplex with intra-epidermal cleavage, (2) junctional EB with cleavage within the lamina lucida of the basement membrane, (3) dystrophic EB with cleavage beneath the basement membrane, and (4) Kindler syndrome with a variable level of skin
The abnormalities in anchoring fibrils mainly formed by Type VII collagen play a pivotal role in the pathogenesis of EB. COL7A1 gene mutations are associated with all forms of EB.

Extracutaneous manifestations are found in different variants of EB, such as corneal erosions, enamel hypoplasia, scarring alopecia, and pseudosyndactyly. Amyloidosis is one of the most important and life-threatening complications of EB, and it is mostly seen in patients with recessive dystrophic EB (RDEB). It can involve the kidney, bowel, liver, and also respiratory system. Herein, we present a patient who is probably the youngest case of genetically diagnosed RDEB complicated with amyloidosis reported in literature.

**Case Report**

Informed consent was obtained from the parents of the child for publication of the case.

A 6-year-old Turkish boy was born from second-cousin parents with C-section at term and was hospitalized due to extensive skin lesions at birth. He was admitted to a local hospital several times because of recurrent skin infections. Six months earlier, he was found to have anemia at a regular checkup and was given red blood cell transfusion once at the local hospital. Two weeks before his admission to our center, he had low serum albumin and nephrotic-range proteinuria. On admission, physical examination revealed failure to thrive with weight of 14 kg (<3 P), height of 101 cm (<3 P), and his vital signs were stable with blood pressure of 90/60 mm Hg (50th percentile) and a heart rate of 108 beats/min. All over his body, multiple fragile blisters, large eroded areas, intact bullae, and deep atrophic and dyschromatic appearance were observed. Loss of nails, contractures in the small joints of the hand and foot, and synechiae in the hands and toes, called as pseudosyndactyly, were also seen (Figure 1). Mild abdominal distension secondary to ascites without pretibial edema was present. He had sparse, short, and dry hair without any dysmorphic facial appearance. The Nikolsky’s sign was also negative. After informed consent, COL7A1 gene mutational analysis was performed by direct DNA sequencing of the whole coding exons and flanking intronic regions and revealed homozygous C>T transversion at c.553 (GenBank accession number NM_000094.3) in exon 5 of the COL7A1 gene. This transversion resulted in premature termination codon (p.Arg185X).

He had a brother with the same skin lesions, and his uncle from the father’s side underwent kidney transplant for chronic renal disease secondary to AA amyloidosis associated with
familial Mediterranean fever (FMF). Laboratory data showed leukocytosis, mild anemia, thrombocytosis, increased inflammatory markers (erythrocyte sedimentation rate: 55 mm/h, C-reactive protein: 61 mg/L, hypoalbuminemia: 1.79 mg/dL, and nephrotic-range proteinuria: 51 mg/m²/h) in 24-h urine collection (Table 1). His estimated glomerular filtration rate (eGFR) was 301 mL/min/1.73 m². Serum amyloid A level was 142 mg/dL (<6 mg/dL). Ultrasound of the abdomen was normal. He underwent kidney biopsy. Light microscopy showed homogeneous amyloid deposits that stained positive with Congo red. Electron microscopy revealed randomly arrayed fibrils (Figure 2). Colchicine treatment was started (0.75 mg/day). Although he did not have any symptoms of autoinflammatory diseases, he had a positive family history for FMF. Therefore, MEFV gene was screened to rule out FMF and was negative. Serum AA level decreased to 36 mg/dL at three months of colchicine, but hypoalbuminemia and proteinuria persisted. He was given albumin infusion to treat refractory edema based on his clinical picture. We thought that amyloidosis in our case possibly occurred secondary to RDEB, but we could not rule out FMF due to the family history for FMF and nationality. Hence, we continued colchicine and thought to give biologic agent to control inflammation and slow amyloid deposition from the point of view of FMF. Since repeated intramuscular/subcutaneous injections or intravenous catheter replacements may worsen skin damage, we thought that he was not a good candidate for biologic agents such as anakinra or canakinumab. At the time of writing this article, he has been on colchicine for six months. We have suggested his family to give him colchicine for another

| Laboratory parameter     | Patient             | His brother        |
|--------------------------|---------------------|--------------------|
| Complete blood count     |                     |                    |
| Hemoglobin               | 9.8 g/dL            | 10 g/dL            |
| White blood cell         | 9.95 10^3/µL        | 13.63 10^3/µL      |
| Platelets                | 742 10^3/µL         | 841 10^3/µL        |
| MCV                      | 65.3 fL             | 65.1 fL            |
| RDW                      | 20.2%               | 19.8%              |
| Ferritin                 | 26.2 mg/mL          | 25 mg/mL           |
| Serum iron               | 24 Aµg/dL           | -                  |
| Complement C3            | 141 mg/dL           | -                  |
| Complement C4            | 28.6 mg/dL          | -                  |
| IgA                      | 284 mg/dL           | -                  |
| Serum amyloid A          | 142 mg/L            | 32.1 mg/L          |

MCV: Mean corpuscular volume; RDW: Red cell distribution width.
six months.

His brother was 1.5 years old, and he also had EB. He was found to have hypoalbuminemia without proteinuria. His eGFR was 207 mL/min/1.73 m². He did not have any clinical symptoms of FMF. Serum AA level was 32 mg/dL (<6 mg/dL), and R202Q heterozygote/M694V heterozygote mutation was detected on MEFV gene. Although there is no adequate evidence to use colchicine in the prevention of nephropathy in patients with generalized RDEB, we started colchicine based on its efficacy in renal amyloidosis caused by FMF and his positive family history of FMF and compound heterozygous mutation he had.

**Discussion**

EB, a heterogeneous group of inherited disorders with the common finding of epithelial fragility, may result in life-threatening complications such as skin cancer and chronic kidney disease (CKD). The National Epidermolysis Bullosa Registry in 2004 revealed a mortality rate of renal disease as 12.3% at the age of 35 years. In Halleuppe-Siemens recessive EB, the cumulative risk of squamous cell carcinoma (SCC) is 6% by the age of 20 years and 76.5% by the age of 60 years.

In our case, we detected homozygous nonsense mutation in COL7A1 gene. This creates a premature stop codon in exon 5 (p.Arg185X) and is expected to result in formation of a nonfunctional, truncated collagen VII protein. Although the mechanism of renal damage in RDEB patients remains unclear, several factors may be involved. The frequent/chronic skin infections in RDEB are the major source of cytokine release which leads to amyloidosis, nephrotic syndrome, and then chronic renal disease. Furthermore, frequent uses of antibiotic for the treatment of skin and urinary tract infections may result in kidney injury and give rise to CKD. Furthermore, immune-complex diseases such as IgA nephritis, post-infectious glomerulonephritis, or mesangio-proliferative glomerulonephritis may be seen in RDEB patients. In addition to glomerular diseases mentioned above, obstructive uropathy caused by vesicoureteral junction obstruction, urethral stenosis, meatal and labial stenosis, and recurrent urinary tract infections can also worsen the clinical conditions and complicate the management of EB patients.

Amyloid deposition in various tissues and
Table 2. The literature review of the recessive dystrophic epidermolysis bullosa with amyloidosis.

| Literature         | Patient age/sex | EB form | Organ involvement for amyloidosis | Biopsy/autopsy proven | Colchicum treatment | Colchicum response | Prognosis                                                      |
|--------------------|-----------------|---------|----------------------------------|------------------------|---------------------|--------------------|---------------------------------------------------------------|
| Chen et al<sup>5</sup> | 52 years/female | Junctional | Renal, GIS                       | Biopsy− Biopsy+        | Yes                 | Yes                | After 2 months of colchicum treatment, biopsy findings get better |
| Kaneko et al<sup>12</sup> | 27 years/male   | RDEB    | Renal                           | Unknown                | Yes                 | Yes                | Serum creatinine level was stable for 8-year follow-up        |
|                    | 30 years/male   | RDEB    | Renal                           | Unknown                | Yes                 | Yes                | Serum creatinine level was stable for 8-year follow-up        |
|                    | 19 years/female | RDEB    | Renal                           | Unknown                | No                  | -                  | Reach ESRD in 2 years                                         |
|                    | 22 years/male   | RDEB    | Renal                           | Unknown                | No                  | -                  | Reach ESRD in 3 years                                         |
| Csikos et al<sup>7</sup> | 25 years/female | RDEB    | Renal, pulmonary and GIS        | Autopsy+               | No                  | -                  | Mortality due to cardiopulmonary arrest after severe pneumonia and metastasis of SCC |
| Gunduz et al<sup>13</sup> | 15 years/female | RDEB    | Renal, GIS (Rectal)             | Biopsy+ Biopsy+ (negative for amyloidosis) | No | - | The patient received only protein replacement therapy |
| Chaptini et al<sup>6</sup> | 25 years/female | RDEB    | Liver, renal                    | Biopsy+ Biopsy−        | No                  | -                  | Liver function tests were stable after 2 years, but proteinuria was detected |
| Bourke et al<sup>14</sup> | 26 years/female | RDEB    | GIS (duodenal), renal, liver, spleen, adrenal gland, ovaries | Biopsy+ Autopsy+       | No                  | -                  | Reach to ESRD and mortality due to dialysis catheter infection |
|                    | 22 years/female | RDEB    | GIS (rectal), renal, liver and spleen | Biopsy+ Autopsy+       | No                  | -                  | Reach to ESRD after NS and mortality due to dialysis catheter infection |
| Our case           | 6 years/ Male   | RDEB    | Renal, GIS                      | Biopsy+ Biopsy−        | Yes                 | Yes                | Serum amyloid A decrease but proteinuria persisted             |

RDEB: Recessive dystrophic epidermolysis bullosa, ESRD: End-stage renal disease, SCC: Squamous cell carcinoma, NS: Nephrotic syndrome.
organisms is a common and important complication of RDEB; therefore, amyloidosis should be kept in mind in patients with RDEB. It can be detected not only in the kidneys but also in the liver, the gastrointestinal tract, and even the respiratory system. Gastrointestinal involvement should be considered in the presence of malabsorption symptoms and iron-refractory iron-deficiency anemia. Chen et al reported a 52-year-old female patient with abdominal discomfort and diarrhea who was diagnosed with gastrointestinal amyloidosis. They showed that the mucosal amyloid deposition was substantially reduced after two years of colchicine treatment. Liver biopsy performed by Cheptini et al showed hepatic amyloidosis in a 25-year-old woman with hepatomegaly, hypoalbuminemia, nephrotic syndrome, and low glomerular filtration rate. Even though she did not undergo kidney biopsy, her clinical and laboratory findings were likely compatible with renal amyloidosis.

Patients of RDEB with biopsy-proven amyloidosis have rarely been reported in literature. Tammaro et al reported a 6-year-old boy with RDEB and IgA nephropathy, who presented with recurrent macroscopic hematuria and persistent microscopic hematuria. He did not tolerate prednisolone and reached end-stage renal disease (ESRD) at five years of follow-up. They did not have sufficient evidence to claim the relationship between IgA nephropathy and RDEB. Chan et al documented five RDEB patients with kidney involvement. Two of them had glomerulonephritis (IgA nephropathy and postinfectious glomerulonephritis or mesangioproliferative glomerulonephritis), and both reached ESRD. Kaneko et al presented four RDEB patients with renal amyloidosis, of whom two patients taking colchicine preserved stable renal function and two other patients not taking colchicine developed ESRD within three years. With encouraging results obtained from literature, we started colchicine to decrease amyloid deposition and preserve renal functions. At last follow-up, our patient’s serum creatinine was normal with hypoalbuminemia and nephrotic-range proteinuria.

To the best of our knowledge, this child is probably the youngest case of RDEB complicated with amyloidosis reported in literature. The characteristic features of cases with amyloid nephropathy due to RDEB in literature are summarized in Table 2. Early development of amyloidosis may result from recurrent skin infections and uncontrolled chronic inflammation. Renal replacement therapy has many difficulties in patients with EB. Inserting a catheter and its maintenance constitute a big problem due to the integrity of the skin. Infections due to hemodialysis or peritoneal dialysis catheters are a major problem. Therefore, it is necessary to control the disease and prevent and slow the progression of disease to end-stage renal failure.

In conclusion, RDEB patients are prone to the development of renal amyloidosis due to various risk factors. Therefore, urine test should be performed for proteinuria as the earliest clinical manifestation of AA amyloidosis. We did not have enough proof to prescribe colchicine for the treatment of amyloidosis in children with RDEB. Hence, further studies need to be conducted to determine whether colchicine improves proteinuria and prevents chronic kidney disease in patients with amyloid nephropathy due to RDEB.

**Conflict of interest:** None declared.

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