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Case Report

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Renal Amyloidosis Secondary to Dystrophic Epidermolysis Bullosa: A Case Report and Review of Literature

Dilek Barutçu Ataş[1], Mahmut Başar Aykent[1], İzzet Hakkı Arıkan[1], Ebru Aşıcıoğlu[1], Arzu Velioğlu[1], Deniz Filinte[2], Mehmet Koç[1], Zübeyde Serhan Tuğlular[1], İshak Çetin Özener[1]

[1]Division of Nephrology, Department of Internal Medicine, Marmara University School of Medicine, İstanbul, Turkey
[2]Department of Pathology, Marmara University School of Medicine, İstanbul, Turkey

Abstract

Dystrophic epidermolysis bullosa (DEB) is a rare and severe hereditary dermatosis, associated with collagen VII deficiency. A chronic inflammatory syndrome secondary to recurrent cutaneous infections may be responsible for amyloid deposition in this patient population, causing renal amyloidosis. Amyloidosis should be included in the differential diagnosis of DEB patients presenting with edema and proteinuria. Herein, we report a case of DEB complicated by squamous cell carcinoma and amyloid A amyloidosis of the kidneys confirmed with renal biopsy.

Keywords: Amyloidosis, dystrophic epidermolysis bullosa, nephrotic syndrome

Corresponding Author: Dilek Barutçu Ataş ✉ drdilekb@gmail.com

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INTRODUCTION

Dystrophic epidermolysis bullosa (DEB) is a rare and severe hereditary dermatosis. Epidermolysis bullosa (EB) is classified into simplex, junctional, and dystrophic forms if splitting occurs above, at, or below the epidermal basal membrane, respectively. The diagnosis is suspected on the appearance of the skin lesions and is confirmed with skin biopsy, which includes electron and immunofluorescent microscopy and genetic testing squamous cell carcinoma (SCC) of the skin, which is a common complication of DEB.

Patients with DEB may develop genitourinary disorders such as hydroureteronephrosis, recurrent urinary tract infections, renal amyloidosis, immunoglobulin A (IgA) nephropathy, and postinfectious glomerulonephritis (1). These complications may cause chronic renal failure (2), affecting the management and prognosis of the patients. Secondary amyloidosis involving the kidneys is caused by the deposition of amyloid A (AA) amyloid fibrils.

CASE PRESENTATION

A 26-year-old male with a 1-month history of general fatigue and generalized edema was admitted to our hospital. He had severe generalized recessive dystrophic epidermolysis bullosa (RDEB) since birth, and his parents were related. He had one other sibling, a male who also had RDEB and had died a week after birth. No other relatives were reported to have blistering disorders. The patient's blistering had been active and extensive from early infancy, necessitating frequent long-term hospital admissions and continuous nursing care. He also developed squamous cell cancer and had a prosthesis of the left lower knee owing to amputation and a skin graft on the right heel. He was taking zinc, multivitamin complex, sertraline, hydroxyzine, and oral iron therapy.

At presentation, he was normotensive, and the physical examination revealed anasarca edema and bullous skin lesions consistent with DEB.

Laboratory data were as follows: serum creatinine level 0.39 mg/dL, creatinine clearance 183 mL/min, serum to-

tal protein 5.1 g/dL, serum albumin level 1.4 g/dL, total cholesterol 292 mg/dL, low-density lipoprotein cholesterol 209 mg/dL, high-density lipoprotein cholesterol 45 mg/dL, triglyceride 190 mg/dL, white blood cells 11.6x10^3/mL, hemoglobin 11 g/dL, hematocrit 34.4%, mean corpuscular volume (MCV) 71.4/fL, platelet count 798x10^3/mL, and sedimentation rate 75 mm/h. He was evaluated for thrombocytosis. However, erythropoietin level, JAK-2 mutation, and BCR-ABL were all negative. Protein electrophoresis was negative for monoclonal gammopathy; serum and urine immune fixation were normal. Urinalysis was (+4) positive for protein, and 24-hour urine protein excretion was 16.6 g/day. Urinary sediment revealed fatty casts and oval fat bodies. Complement levels were normal. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, hepatitis B and C, and human immunodeficiency virus serology were negative. Ultrasonography examination of the abdomen showed normal sized kidneys and hepatomegaly (178 mm). We performed kidney biopsy, which showed a total of 31 glomeruli with 10% of them globally sclerotic and widespread accumulation of eosinophilic material in the vessel walls and in the glomeruli suggesting amyloidosis. There was also fibrointimal thickening of the vessels and rare tubular atrophy. Direct immunofluorescence examination was negative. Amyloidosis was confirmed with Congo red and amyloid AA staining (Figure 1). The patient was started on essential amino acids and colchicine. During follow-up, proteinuria increased to 24 g/day. Three months after diagnosis of amyloidosis, the patient developed diarrhea and colchicine had to be stopped. Stool examination was consistently unremarkable. Diarrhea persisted, his renal function deteriorated rapidly, and the patient was hospitalized. On the second day of hospitalization, he developed seizures and required intubation. Despite intensive medical support, he died on the same day.

DISCUSSION

DEB is a rare, chronic, subepidermal blistering disease, involving the skin and mucous membranes. Clinical findings are mainly due to the skin lesions and typically constitute blisters seen 1 month after birth causing extensive dystrophic scarring on the acral surface such as mitten-hand deformity.

The exact pathophysiology of renal amyloid deposition in patients with RDEB is currently unknown. It is probably associated with the chronic inflammatory state, as in other diseases such as rheumatoid arthritis (3). It has been postulated that increased serum interleukin-1 levels secondary to activation of keratinocytes may lead to systemic amyloidosis in patients with EB with chronic skin disruption (4). In addition, serum amyloid A (SAA) protein levels were to be found high in patients with renal amyloidosis and nephrotic syndrome but not in patients without nephropathy (4). This is likely related to chronic and repeated injuries of the renal parenchyma secondary to repeated cycles of inflammation and infection of the skin.

The most common site of SAA deposition is the kidneys. Renal involvement is found in as many as 90% of patients with AA amyloidosis of any cause. Thus, symptoms reflect the appearance

Main Points

- Dystrophic epidermolysis bullosa (DEB) is a rare and severe hereditary dermatosis.
- Patients with DEB may develop genitourinary disorders such as hydroureteronephrosis, recurrent urinary tract infections, renal amyloidosis, immunoglobulin A (IgA) nephropathy, and post-infectious glomerulonephritis.
- These complications may cause chronic renal failure, affecting the management and prognosis of the patients.
- Secondary amyloidosis involving the kidneys is caused by the deposition of amyloid A (AA) amyloid fibrils. Amyloidosis should be included in the differential diagnosis of DEB patients presenting with edema and proteinuria.
- Despite the severity of skin disease, death from renal failure has been reported excessively. The cumulative risk of death from renal failure was high in the DEB case.

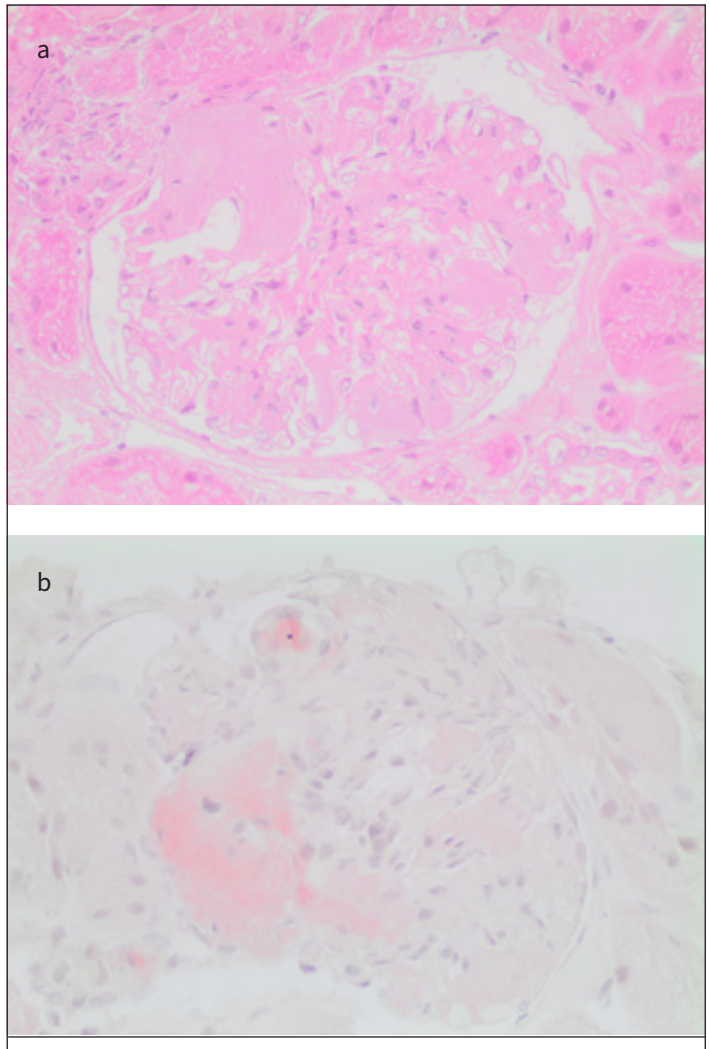

Figure 1. a, b. a) Accumulation of eosinophilic material with hematoxylin-eosin staining (400*). b) Amyloid deposition in the glomeruli (400*), staining with Congo red

Table 1. Demographic, clinical, and laboratory findings of patients with RDEB with amyloidosis

Case number	Age, sex	Proteinuria	Nephrotic syndrome	Serum creatinine level (mg/dL)	AA amyloid with biopsy	Dialysis	SCC	Survival after diagnosis	Cause of death
Case 1 (4)	17, M	6 g/L	+	2.2	Renal-liver-thyroid-spleen-adrenal-GIST (autopsy)	HD	-	2 months	Sepsis
Case 2 (7)	16, M	38 g/day	+	Normal	Renal biopsy	Refused to HD	-	3 months	Renal failure
Case 3 (8)	22, F	3.7 g/day	+	Unreported (ClCr: 8.3 mL min^{-1})	Rectal biopsy				
Renal-liver-spleen (autopsy)	Unavailable for dialysis	-	5 months	Renal failure					
Case 4 (8)	26, F	6.1 g/day	+	Normal	Renal-liver-over-spleen-adrenal-GIST (autopsy)	-	-	18 months	Renal failure
Case 5 (9)	25, F	5-6 g/day	+	0.78	Renal-liver-spleen-lung (autopsy)	-	+	Unreported	Sepsis/ pneumonia
Index case*	26, M	16.6 g/day	+	1.83	Renal biopsy	-	+	3 months	Sepsis/acute renal failure

*The case presented in this study
AA: amyloid A; ClCr: clearance of creatinine; F: female; HD: hemodialysis; GIST: gastrointestinal stromal tumor; M: male; SCC: squamous cell carcinoma

of proteinuria, progressive development of renal insufficiency, or nephrotic syndrome (5). Specifically, glomerular involvement with amyloidosis and fibrosis appears to have clinical course characterized by deteriorating renal function as compared with patients with other types of renal involvement (6). Our patient presented with proteinuria (17 g/day), which was later accompanied by deterioration in renal function.

Although RDEB is known to develop because of hereditary collagen disorders, inflammatory processes secondary to recurrent skin infections also play an important role in the pathogenesis. Therefore, colchicine treatment, which may improve the survey of patients with RDEB, must be used before tissue amyloid deposition occurs. There is no strong evidence to support prophylactic colchicine usage for patients with RDEB with renal amyloidosis.

We did a literature search and found 5 cases diagnosed as RDEB with AA amyloidosis confirmed by histological examination (4, 7-9). Two of them were men and 3 of them were women. As, at diagnosis, age varied between 16 and 26 years, the mean age of renal involvement was 21.2 years. In women, the mean age of renal disease onset was 24.3 years, whereas it was 16.5 years in men (Table 1). All 5 cases presented with the nephrotic syndrome. All cases were verified by histologic examination. One histological diagnosis was verified by renal biopsy when the other 4 histological diagnoses were verified by autopsy. Survival ranged from 2 months to 18 months in patients with AA amyloidosis after diagnosis.

We also found 16 cases diagnosed as RDEB with renal complications in the literature (2, 4, 7-12). In 2 patients, the renal manifestation was hematuria, and they were further diagnosed as IgA nephropathy (10, 11). Both of them were 14 year old and eventually needed dialysis treatment. Three of the patients were diagnosed as post-streptococcal glomerulonephritis (PSGN) (11, 12). Five patients were diagnosed as renal amyloidosis (7-10), and other 6 patients did not have any histologic examination (2, 4, 11, 12).

It can be hypothesized that SCC was the cause of AA amyloidosis in our patient. Generalized and/or local AA amyloidosis was demonstrated in patients with SCC of the lung (13). Localized amyloid deposits accompanied with SCC were also observed in patients with SCC or dysplasia in the oral cavity, pharynx, or larynx (14). However, an association between SCC of the skin and systemic amyloidosis has never been reported. In our patient, SCC in the skin was treated by resection 2 years ago, and he did not develop any new lesions during follow-up. Accordingly, we believe that the systemic amyloidosis in our patient was most likely due to the inflammatory processes in the skin including recurrent skin infections rather than SCC.

CONCLUSION

In conclusion, nephropathy is a serious complication of RDEB. Renal amyloidosis is the best described renal pathology and is the major cause of end stage renal disease (ESRD). Despite

the severity of skin disease, death from renal failure has been reported excessively. The cumulative risk of death from renal failure was high in the RDEB case.

Informed Consent: Informed consent was obtained from the parents of the patient.

Peer-review: Externally peer-reviewed.

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