IgA Nephropathy in a Patient with Dominant Dystrophic Epidermolysis Bullosa

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Dystrophic epidermolysis bullosa (DEB) is a rare and severe hereditary dermatosis. On the other hand, IgA nephropathy is the most common form of glomerulonephritis in childhood and adults, and clinically characterized by microhematuria and proteinuria and histologically by deposition of immunoglobulin A in mesangial lesions. Several renal complications of recessive DEB including IgA nephropathy and amyloidosis have been reported. However, there have been no reports on dominant DEB associated with IgA nephropathy. We report here for the first time a 17-year-old girl with dominant DEB associated with IgA nephropathy. The patient has suffered from episodes of urinary, upper airway, and skin infections. At 17 years of age, proteinuria and hematuria were detected, with a high value of serum IgA. Renal biopsy was performed, and immunofluorescence microscopic examination revealed segmental deposits of IgA in mesangial lesions, with many glomeruli exhibiting diffuse segmental mesangial-proliferative glomerulonephritis. We diagnosed dominant DEB associated with IgA nephropathy on the basis of proteinuria, hematuria, and deposits of IgA in mesangial lesions on immunofluorescence microscopic examination, and diffuse segmental mesangial-proliferative glomerulonephritis. These findings suggest that repeated skin infections might have contributed to the pathogenesis of IgA nephropathy in this patient.

Dystrophic epidermolysis bullosa (DEB) is a rare genetic disorder of the skin and mucosae, characterized by the formation of severe blisters, which occur as a result of minor mechanical trauma and dystrophic changes (Berger and Hinglais 1968; Cuesta-Estelles et al. 1998; Farhi et al. 2004). All forms of DEB result from mutations of collagen type VII (Fine et al. 2004), a major component of anchoring fibrils that tether the basement membrane and overlying epidermis to its dermal foundation (Cuesta-Estelles et al. 1998; Farhi et al. 2004). Several reports have described renal involvement complicating recessive DEB (Hogg et al. 1994; Koyama et al. 1995; Glazier and Zaonts 1998; Horn and Tidman 2002; Kaneko et al. 2003; Mallipeddi et al. 2003), including amyloidosis, IgA nephropathy, postinfectious glomerulonephritis, hereditary nephritis, and upper and lower urinary tract obstruction. IgA nephropathy is the most common form of glomerulonephritis.
At 17 years of age in July 2003, her family physician discovered that she had proteinuria and hematuria, and she was admitted to Takeda General Hospital (Aizu). Subsequently, the mild proteinuria and hematuria continued. In April 2004, the hematuria and proteinuria were increased and she was admitted to our hospital. She had blisters with erosion and scar formation. There was no pretibial edema and BP was 120/60 mmHg.

Laboratory tests (Table 1) revealed leukocyte count 9,900/μl, erythrocyte count 463 × 10⁴/μl, platelet count 21.3 × 10⁴/μl, erythrocyte sedimentation rate (ESR) 56 mm/hr, serum total protein 7.4 g/dl, serum albumin 3.5 g/dl, serum creatinine 0.6 mg/dl, serum total cholesterol 167 mg/dl, and c-reactive protein 1.3 mg/dl. Urinalysis revealed protein loss of 1.2 g/day, with sediment containing 100 erythrocytes per high-power field, 10-19 leukocytes per high-power field, and 10-19 granular casts in all fields. Creatinine clearance (24-hr) was 163 ml/min/1.73 m². Immunological studies revealed the following: C3 (normal range 69-128 mg/dl) 131 mg/dl; C4 (14-36) 24 mg/dl; CH50 (30-45) 44 U/ml; antinuclear antibody titer < 80; negativity for anti-DNA antibody; IgG 2,533 mg/dl; IgA 440 mg/dl; IgM 234 mg/dl; BUN 10.1 mg/dl; Cr 0.57 mg/dl. IgA nephropathy has never previously been reported in a patient with dominant DEB.

**Clinical Findings**

The patient had blister formation on the skin at birth. The blistering had led to scar formation, which led in turn to digital fusion. The Nikolsky sign was positive. Her toenails and fingernails were thickened and dystrophic. She had visited Tohoku University Hospital (Sendai) at the age of 7 months and skin biopsy was performed, which revealed blister cleavage below the basal lamina and within the papillary dermis. She was diagnosed with dominant DEB, on the basis of clinical and histological findings. Since birth, the patient had been having episodes of urinary or upper airway or skin infection. There was no consanguineous marriage or renal disease in her family history.

<table>
<thead>
<tr>
<th>RBC</th>
<th>463 × 10⁴/μl</th>
<th>TC</th>
<th>150 mg/dl</th>
<th>C3</th>
<th>131 mg/dl</th>
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<tbody>
<tr>
<td>Hb</td>
<td>11.6 g/dl</td>
<td>TG</td>
<td>64 mg/dl</td>
<td>C4</td>
<td>24 mg/dl</td>
</tr>
<tr>
<td>Hct</td>
<td>36.7%</td>
<td>Na</td>
<td>138 mEq/l</td>
<td>CH50</td>
<td>44 U/ml</td>
</tr>
<tr>
<td>PLT</td>
<td>21.1 × 10⁴/μl</td>
<td>Cl</td>
<td>4.4 mEq/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>9,900/μl</td>
<td>Ca</td>
<td>9.6 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neu</td>
<td>65%</td>
<td>P</td>
<td>4.6 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lym</td>
<td>28%</td>
<td>CRP</td>
<td>1.32 mg/dl</td>
<td></td>
<td>1.2 g/day</td>
</tr>
<tr>
<td>Mono</td>
<td>6%</td>
<td>ESR</td>
<td>56-102 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eos</td>
<td>1%</td>
<td>(1h-2h)</td>
<td></td>
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</tbody>
</table>

**Table 1. Results of laboratory investigations on admission to our hospital.**

**Sediment**

<table>
<thead>
<tr>
<th>AST</th>
<th>14 IU/l</th>
<th>RBC ≥ 100/HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>7 IU/l</td>
<td>WBC 10-19/HPF</td>
</tr>
<tr>
<td>LDH</td>
<td>158 IU/l</td>
<td>Cast 10-19/LPF</td>
</tr>
<tr>
<td>ALP</td>
<td>194 IU/l</td>
<td></td>
</tr>
<tr>
<td>BUN</td>
<td>10.1 mg/dl</td>
<td>24hCcr</td>
</tr>
<tr>
<td>Cr</td>
<td>0.57 mg/dl</td>
<td>162.8 ml/min/1.73 m²</td>
</tr>
</tbody>
</table>
IgA Nephropathy in a Patient with DEB

(158-358), IgM 214 mg/dl (72-216); titer of antibody to hepatitis B virus, negative; titer of antibody to hepatitis C virus, negative; and titer of antibody to syphilis, negative. Staphylococcus aureus was detected on culture of skin erosion. A percutaneous renal needle biopsy was performed after she had been in the hospital for 7 days. Immunofluorescence microscopic examination revealed segmental deposits of IgA in mesangial lesions. On light-microscopic examination (Fig. 1A, B), there were 18 glomeruli with diffuse segmental mesangial-proliferative glomerulonephritis and 2 glomeruli with global sclerosis, and mild invasion of inflammatory cells and tubular atrophy in interstitial lesions. We diagnosed IgA nephropathy on the basis of the pathological findings. She was therefore administered steroid treatment, mizoribine, dilazep dihydrochloride, and warfarin. Urinary excretion of protein subsequently deceased. At 4 months after initiation of therapy, her proteinuria had disappeared and her hematuria was improved, and she was discharged. No proteinuria or mild hematuria has been observed in the subsequent 1-year period.

**DISCUSSION**

We have reported here a patient of dominant DEB associated with IgA nephropathy. The diagnosis was confirmed by renal biopsy.

Epidermolysis bullosa comprises a heterogeneous group of noninflammatory blistering disorders in which intraepidermal or subepidermal blisters form spontaneously or following minor trauma (Berger and Hinglais 1968). In autosomal dominant and recessive DEB, epidermal separation occurs below the basement membrane dense

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**Fig. 1.** Clinical course of the present case.
A: On immunofluorescence microscopic examination of the renal biopsy specimen, IgA deposits are found in mesangial lesions. × 400
B: On Light-microscopic examination of the renal biopsy specimen, some glomeruli exhibit diffuse segmental mesangial-proliferative glomerulonephritis (single arrow). PAS stain, × 400
lamina due to defective anchoring fibrils which lack normal collagen VIIA secondary to COL7A1 gene mutations (Berger and Hinglais 1968; Cuesta-Estelles et al. 1998; Fine et al. 2004). The clinical course of DEB is characterized by severe blistering, repeated skin infection, and healing by scarring.

Several types of renal involvement in recessive DEB have been reported (Hogg et al. 1994; Koyama et al. 1995; Glazier and Zaontz 1998; Horn and Tidman 2002; Kaneko et al. 2003; Mallipeddi et al. 2003). Secondary amyloidosis has been observed during the course of chronic infection or inflammation of skin in a child (Horn et al. 2002). Chronic postinfectious glomerulonephritis due to recurring superinfections of bullous skin lesions were described in a 7-year-old boy (Koyama et al. 1995). Recently, four cases of recessive DEB associated with IgA nephropathy were reported (Mallipeddi et al. 2003). The incidence of renal complication with DEB is unclear. In addition, although there have been a few reports of dominant DEB with renal insufficiency (Kaneko et al. 2003), the dominant inherited form of DEB had not previously been found with IgA nephropathy.

On the other hand, IgA nephropathy is clinically characterized by microhematuria and proteinuria, and histologically by deposition of immunoglobulin A (Mann et al. 1988). IgA nephropathy is the most common form of chronic glomerulonephritis worldwide, and progresses to end-stage renal failure in up to 30% of patients (Motoyama et al. 1999).

Recently, bacterial antigens were detected in renal tissues of patients with IgA nephropathy (Suzuki et al. 1994; Muda et al. 2001; Shimizu et al. 2007). Suzuki et al. (1994) found that H. parainfluenzae outer membranes antigens and the presence of IgA antibody to H. parainfluenzae outer membranes were associated with IgA nephropathy. Furthermore, Koyama et al. (1995) reported that rapidly progressive glomerulonephritis developed among patients infected with methicillin-resistant Staphylococcus aureus (Shimizu et al. 2007), and Suzuki et al. (1994) noted in a review that patients with IgA nephropathy respond strongly through production of IgA against Staphylococcus aureus (Shimizu et al. 2007). These findings suggested that bacterial infections might play an important role in the pathogenesis of IgA nephropathy.

In our patient, there had been many episodes of urinary, upper airway, and skin infection since birth, and Staphylococcus aureus was detected on culture of skin erosion on admission along with a high serum IgA level. We diagnosed dominant DEB associated with IgA nephropathy on the basis of the clinical course and findings of renal biopsy.

The pathogenesis of IgA nephropathy associated with chronic urinary, upper airway, and skin infections has been speculated to be as follows:

1) Circulating immune complexes containing IgA in the circulation may be formed in response to many bacterial skin infections.

2) Deposition of circulating immune complexes in the kidney results in the development of IgA nephropathy.

3) Several cytokines induced by circulating immune complexes and sepsis may play an important role in the pathogenesis of IgA nephropathy.

In conclusion, we have reported a patient of dominant DEB associated with IgA nephropathy, and confirmed the diagnosis by renal biopsy. Since serum IgA concentration persisted at high levels during the clinical course of this patient, repeated skin infections might have played a role in the pathogenesis of IgA nephropathy in this patient.

References


