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Single Case

Nephropathy in a Child with Severe Recessive Dystrophic Epidermolysis Bullosa Treated with Cyclophosphamide: A Case Report

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Keywords
COL7A1 · Cyclophosphamide · Hematuria · Immunoglobulin A nephropathy · Immunosuppression · Proteinuria · Steroid-resistant children

Abstract
Long-term inflammation and recurrent skin infection in recessive dystrophic epidermolysis bullosa (RDEB) are associated with the presence of immunoglobulin A (IgA)-containing immune complexes in the glomerulus. Only eight pediatric RDEB cases with IgA nephropathy (IgAN) have been documented in English-language literature. Most RDEB patients with IgAN progress to kidney failure within 5 years of diagnosis, indicating that these patients may require more intensive early treatment compared to those with primary IgAN. However, diagnosing IgAN in RDEB cases with severe cutaneous manifestations can be challenging. Herein, we report a rare case of nephropathy in an 11-year-old boy with severe RDEB and a frameshift mutation on the *COL7A1* gene, which may manifest as kidney disorders. He presented with persistent hematuria and progressing proteinuria. A presumptive IgAN diagnosis was based on clinical features and increased IgA serum levels, as kidney biopsy was refused by his parents. Nephrotic-range

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proteinuria persisted despite initial steroid and lisinopril treatment. Monthly intravenous cyclophosphamide (IV CPA; 500 mg/m^2) led to proteinuria remission and preservation of kidney function for 2 years posttreatment. We conclude that *COL7A1* mutations may result in extracutaneous manifestations, including kidney disorders. The association between IgA-containing immune complex deposits in the glomerulus and recurrent skin infection in RDEB may indicate IgAN, particularly when kidney biopsy is infeasible due to severe skin manifestations. In our case, positive results with IV CPA suggest further investigation is needed to explore its potential role in non-rapidly progressing IgAN in children with RDEB.

Introduction

Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic skin disorder causing widespread blisters, scarring, and recurrent skin infection [1]. Only eight pediatric RDEB cases with immunoglobulin A (IgA) nephropathy (IgAN) have been documented in English-language literature [2–5]. Consistent with data from the largest epidermolysis bullosa (EB) registry [6], most reported cases progressed to kidney failure or death within 5 years of IgAN diagnosis. In contrast, only 5% of pediatric IgAN cases required kidney transplantation initially, and 20–25% of children with primary IgAN progressed to kidney failure within 20–30 years post-diagnosis [7–9]. Consequently, early detection and appropriate treatment of IgAN are crucial for RDEB patients [6].

The role of immunosuppressants in pediatric IgAN remains controversial [10]. In this report, we present a case illustrating the potential effectiveness of intravenous (IV) cyclophosphamide (CPA) in delaying nephropathy progression in a child with RDEB and IgAN.

Case Presentation

An 11-year-old Indonesian boy with RDEB from a remote island was referred to our pediatric nephrology clinic in Jakarta due to persistent hematuria and worsening proteinuria. He developed generalized blisters at 1 week old and lost his nails by age one. A skin biopsy at 6 months confirmed an EB diagnosis, and his EB subtype was identified at age seven using a clinical diagnosis matrix [11]. He regularly visited a local dermatologist for wound care.

Six months before being referred to our hospital, the patient developed macroscopic hematuria with dark-colored urine but no proteinuria. Although the gross hematuria resolved, microscopic hematuria persisted, and proteinuria developed. His blood pressure and kidney function remained normal. He had a history of recurrent skin infection requiring antibiotics, which had increased in frequency over time. He received packed red blood cell transfusions for anemia due to chronic blood loss from skin lesions. His vision, hearing, and family medical history were normal, and his parents were not closely related. Genetic analysis using whole-exome sequencing [12] revealed a frameshift mutation in the *COL7A1* gene (exon51: c.4889_4890insTTGGCCCCCG), predicted to cause an absence of type VII collagen within the anchoring fibrils between the epidermis and dermis (p.R1630fs).

The physical examination found the patient's vital signs to be normal, including a blood pressure of 90/60 mm Hg (<90th percentile). He appeared pale and had widespread blisters, erosions, and mitten deformities on his hands and feet, with no edema present (Fig. 1a–e). He was severely malnourished (body weight 18 kg, <50th percentile) and exhibited a short

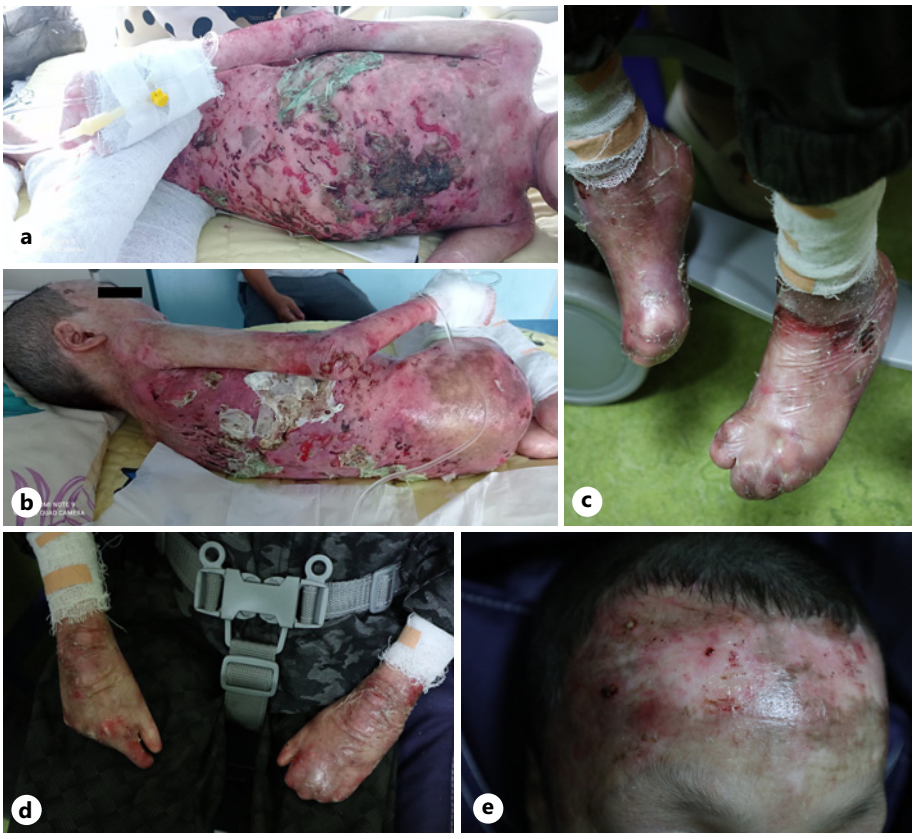

Fig. 1. Extensive skin ulcers in his abdomen (**a**) and back (**b**); mitten deformity of his feet (**c**) and hands (**d**); infected skin lesions (**e**).

stature (body height 110 cm, <5th percentile). Blood tests indicated normocytic normochromic anemia, hypoalbuminemia, and elevated inflammatory markers and IgA levels. However, kidney function, serum electrolytes, serum complement, antistreptolysin O titer, antinuclear antibodies, and anti-double-stranded DNA antibody levels were normal. Urinalysis showed microscopic hematuria and nephrotic-range proteinuria (Table 1). *Enterobacter cloacae* was detected in a skin swab culture. Abdominal ultrasound indicated normal kidneys and urinary bladder. Due to infected skin ulcers in the biopsy area, a kidney biopsy was not performed (Fig. 1a, b). However, the patient's clinical features led to a presumptive diagnosis of IgAN with significant proteinuria. The patient was prescribed oral prednisone (2 mg/kg/day) and lisinopril (10 mg/day), discharged, and advised to continue treatment under a local pediatric nephrologist's care.

After 4 weeks of full-dose prednisone treatment, the patient's proteinuria did not improve, and his hypoalbuminemia and microscopic hematuria worsened. Despite this, his parents declined a kidney biopsy. The local pediatric nephrologist prescribed monthly IV CPA (500 mg/m^2) while tapering the prednisone dosage and continuing lisinopril. The patient's proteinuria resolved after the third IV CPA dose. The treatment continued for a total of seven doses without side effects. The patient then stopped taking prednisone and continued lisinopril for maintenance (Fig. 2 and Table 2).

The patient experienced recurrent skin infection alongside worsening hematuria throughout our observation period. Serum IgA and inflammatory markers remained consistently high until the end of the follow-up period. Although microscopic hematuria persisted, his proteinuria went into remission, and kidney function remained normal until the final follow-up, 18 months after discontinuing CPA treatment (Fig. 2; Table 2).

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Table 1. Laboratory evaluations at the first presentation of hematuria

Parameter	Unit	Reference range	Results
Complete blood count			
Hemoglobin	g/dL	11.5–15.5	8.9
Hematocrit	%	34.0–45.0	27.5
Erythrocyte	10^6/μL	4.00–5.20	3.57
Thrombocyte	10^3/μL	170–450	566
Leukocyte	10^3/μL	5.00–13.00	17.93
ESR	mm/h	0–15	135
Albumin	g/dL	3.5–5.2	2.6
Immunology profile			
C3	mg/dL	90–180	174
C4	mg/dL	10–40	21
IgA	mg/dL	40–350	536
ANA		Negative	Negative
Anti-dsDNA	IU/mL	<100	2.5
Antistreptolysin O	IU/mL	<408	168
Kidney function			
Ureum	mg/dL	15–36	38.1
Creatinine	mg/dL	0.3–0.6	0.40
eGFR	mL/min per 1.73 m^2		
Urinalysis			
Leukocyte esterase		Negative	Negative
Nitrite		Negative	Negative
Occult blood		Negative	3+
Number of RBCs/HPF		0–2	40–45
Albumin		Negative	Trace
Spot morning uPCR	mg/g	<200	6,252.8

ESR, estimated erythrocyte sedimentation rate; IgA, immunoglobulin A; ANA, antinuclear antibodies; Anti-dsDNA, anti-double stranded DNA antibody; eGFR, estimated glomerular filtration rate (serum creatinine-based calculation using Schwartz formula); RBC, red blood cell; HPF, per high power field; uPCR, urine protein to creatinine ratio.

Discussion and Conclusions

IgAN has been correlated with other diseases with persistent inflammatory states, including inflammatory bowel disease [13]. Besides the onset of IgAN being linked to infective episodes [14], chronic inflammation and recurring skin infection in RDEB may result in the synthesis and deposit of IgA-containing immune complexes in the glomerulus [3, 4, 15]. Furthermore, the *COL7A1* gene is expressed not just in the skin but also in other epithelial and mesenchymal tissues, and patients with mutations in this gene may exhibit extracutaneous manifestations, including kidney disorders [1, 6, 16]. Nevertheless, much of the pathophysiology of kidney involvement in RDEB remains unclear. Therefore, the critical question is how to optimally treat children with both RDEB and IgAN.

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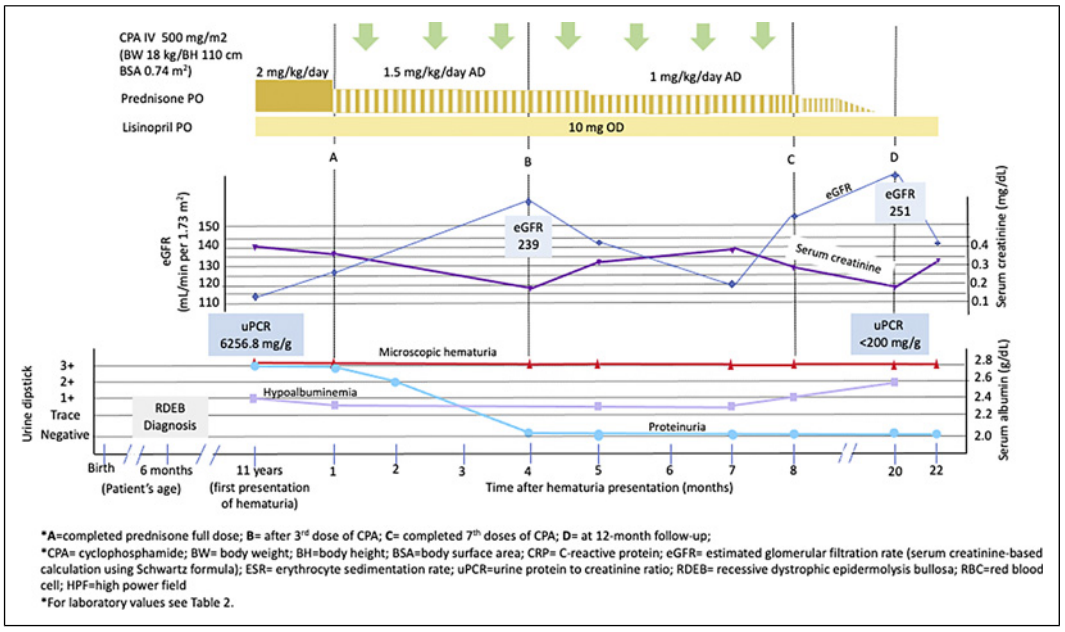

Fig. 2. Clinical course of the case (A, completed prednisone full dose; B, after 3rd dose of CPA; C, completed 7th dose of CPA; D, at 12-month follow-up).

Table 2. Laboratory values during the clinical course as visualized in Figure 2

Parameter	A	B	C	D
	completed prednisone full dose	after 3rd dose of CPA	completed 7th dose of CPA	at 12-month follow-up post-CPA completion
Hematology				
Hemoglobin, g/dL	9.1	9.2	9	8.9
Leukocyte, 10^3/μL	16.9	10.3	11.1	10.4
Thrombocyte, 10^3/μL	581	550	553	549
Urinalysis				
Hematuria (RBCs/HPF)	Too numerous to count	20–30	20–30	5–15

CPA, cyclophosphamide; RBC, red blood cell; HPF, high power field.

Information regarding IgAN in RDEB is largely limited to sporadic case reports or limited case series studies [1, 6]. Many of these reports focus on untreated cases that eventually progressed to end-stage kidney disease (ESKD) [2–4]. The available reports on treated cases reveal diverse treatment preferences and outcomes [5, 15, 16]. Due to this lack of consensus, we opted to treat the present case with oral prednisone and lisinopril, following our hospital's established practices for pediatric primary IgAN.

Antiproteinuric therapy, including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), is recommended for adults and children with primary IgAN [10]. The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend immunosuppressants, particularly steroids, only for adults with persistent proteinuria despite at least 90 days of optimized ACEI or ARB therapy [17]. Despite the paucity of randomized controlled trials, pediatric nephrologists frequently prescribe steroids alongside ACEI or ARB at diagnosis,

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especially in cases with severe clinical features such as proteinuria >1 g/day or urine protein-to-creatinine ratio >1 g/g, as observed in our case [7, 17, 18].

In adults with new-onset IgAN, proteinuria reflects chronic lesion findings on kidney biopsy [19]. Conversely, children typically present with higher estimated glomerular filtration rates (eGFRs), lower proteinuria, and more active kidney lesions [18, 19]. Steroids significantly reduce proteinuria in both age groups, but only children exhibit improved eGFR [19, 20]. A repeated-biopsy study found that steroid treatment reversed active lesions and prevented chronic lesion progression [21]. Consequently, early steroid therapy in children may reasonably treat acute lesions before chronic ones develop [10, 22]. We initially treated our case with adequate doses of prednisone and lisinopril. A clinical trial demonstrated that a once-daily dose of 0.4 mg/kg lisinopril is effective and safe for children with primary IgAN [23].

After 4 weeks of treatment, our patient's nephrotic-range proteinuria remained unchanged, and his microscopic hematuria and hypoalbuminemia worsened. Ideally, a kidney biopsy would have guided treatment, but his parents refused. A recent prospective trial by Kang et al. found that only 20% of children with primary IgAN and nephrotic-range proteinuria achieved complete remission with prednisone. After additional treatment with mycophenolate mofetil (MMF) and prednisone, only 60% of steroid-resistant children achieved complete remission, with those having kidney impairment (eGFR <90 mL/min/1.73 m^2) and tubular atrophy/interstitial fibrosis remaining unresponsive [24]. The role of immunosuppression in IgAN with RDEB is unclear.

In 2018, Cavagnaro et al. reported a favorable response to prednisone in a child with RDEB and IgAN [5], although their case never developed significant proteinuria, unlike our current case. Conversely, Ceuppens et al. reported an RDEB case with IgAN that progressed to ESKD despite 4 years of prednisone therapy [15]. Recently, Hughley et al. [16] observed sustained improvements in kidney function and proteinuria in pediatric patients with RDEB and IgAN after IV methylprednisolone, oral prednisone, and MMF treatment. Unlike our case, their cases showed some reduction in proteinuria with prednisone and ACEI but repeatedly relapsed when weaned from prednisone. Although these case reports differed from ours, we added another immunosuppressive agent, IV CPA, since MMF was unavailable locally. Indonesian rural hospitals have previously reported shortages of essential medications and diagnostic tools [25, 26], leading to poor outcomes due to treatment delays [27–29]. Furthermore, a published case of IgAN associated with inflammatory bowel disease responded favorably to CPA and steroids [13].

According to KDIGO guidelines, CPA is only indicated for rapidly progressing IgAN [17]. However, our case, although not displaying rapid eGFR deterioration, had severe proteinuria unresponsive to treatment, a known risk factor for ESKD in pediatric primary IgAN [7, 30]. Kidney disease appears to progress more quickly in RDEB patients compared to primary IgAN patients [6]. When making treatment decisions for pediatric IgAN patients, it is essential to consider clinical prognostic factors and local healthcare constraints, such as drug availability. In our case, IV CPA proved to be a viable treatment option, achieving and maintaining proteinuria remission until the final follow-up.

Recent case reports have associated recurrent skin infection in RDEB with kidney amyloidosis and infection-associated glomerulonephritis (IAGN) [16, 31]. Kidney amyloidosis often presents with elevated serum amyloid A levels [29], but serum amyloid A testing is unfortunately unavailable in Indonesia. In RDEB patients, kidney amyloidosis typically causes rapid deterioration of kidney function, leading to ESKD or death within 2 years of detecting urinary abnormalities [16]. However, given the normal complement levels and lack of improvement in proteinuria and hematuria following targeted antibiotic administration, IAGN seemed an unlikely cause of nephropathy in our case. Nevertheless, IgA-dominant IAGN, which can present as increased IgA and normal complement levels, could not be entirely ruled out.

One notable aspect of our case was the sudden increase in eGFR recordings after the third CPA dose and at the 1-year follow-up (Fig. 2; Table 2). In malnourished RDEB cases with low muscle mass, cystatin C-based eGFR has been reported as a more reliable kidney function parameter [16]. However, in our case, serum creatinine-based eGFR (Schwartz formula-calculated) yielded a markedly higher result. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530875).

In conclusion, favorable outcomes were observed when administering IV CPA to a child with RDEB and IgAN, even though the disease course was not rapidly progressing. Additional research is warranted to explore the potential role of IV CPA in treating non-rapidly progressing IgAN in children with RDEB.

Acknowledgment

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Statement of Ethics

The study was ethically conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the mother of the patient for publication of the details of the medical case and any accompanying images. Copies of the written consents are available for review from the editor of this journal.

Conflict of Interest Statement

The authors have no competing interests to report.

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Author Contributions

C.G.A. and F.A.G.S. performed the literature search, data collection, analysis, and interpretation and wrote the first draft of the manuscript. R.P. and S.W. performed data collection and analysis. E.S. and E.W. performed data collection. C.G.A., R.P., F.A.G.S., E.S., E.W., and S.W. critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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