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Glomerulonephritis in Youth With Dystrophic Epidermolysis Bullosa

Erica Hughley[1], Edward J. Nehus[1], Katherine VandenHeuvel[2], Bret D. Augsburger[3], Namrata G. Jain[4] and Anne W. Lucky[3]

[1]Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [2]Division of Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [3]Division of Dermatology and Cincinnati Children's Epidermolysis Bullosa Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; and [4]Division of Pediatric Nephrology, Columbia University Medical Center, New York, NY, USA

Correspondence: Erica Hughley, Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7022, Cincinnati, OH 45229-3026, USA. E-mail: Erica.Hughley@cchmc.org

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INTRODUCTION

Epidermolysis bullosa (EB) is a rare group of genetic conditions involving mutations in genes such as *COL7A1* that encode structural proteins required to maintain skin integrity. These mutations lead to skin fragility and subsequent nonhealing erosions and scarring. Because these mutations are also partially expressed in other epithelial and mesenchymal tissues, patients with EB may have secondary consequences, such as malnutrition and extracutaneous manifestations involving the renal system. Those with junctional EB generalized severe and recessive dystrophic EB generalized severe are particularly susceptible to renal involvement and may progress to renal failure.[1] For example, the National Epidermolysis Bullosa Registry reported renal failure was the attributed cause of death in 3.6% of adults with recessively dystrophic EB generalized severe (RDEB) with a mean age at death of 24 years, and a cumulative risk of death from renal failure of 12.3% at age 35 years.[1] Renal involvement in both the adult and pediatric EB population has also been described in case reports owing to a variety of causes, predominantly postinfectious glomerulonephritis (GN), immunoglobulin (Ig) A nephropathy, chronic interstitial nephritis, secondary amyloidosis, and congenital nephrotic syndrome.[2–6] However, much remains unknown about the pathophysiology of renal disease in patients with EB. This case series describes 5 pediatric patients treated at our institution for dystrophic EB in whom GN developed and who underwent renal biopsy. We describe their unique clinical presentation and histopathologic findings.

CASE DESCRIPTION

Patient 1

Patient 1 was a Caucasian male with a tentative diagnosis of dominant dystrophic EB (Table 1). He had many signs of RDEB, so it is possible that he had a cryptic second *COL7A1* mutation that was not detected. He also had a history of chronic cutaneous *Staphylococcus* infections and a baseline C-reactive protein (CRP) level of approximately 5 to 7 mg/dl. At age 18 he had coffee-colored urine and an elevated serum creatinine (SCr) level of 1.5 mg/dl. He was referred to a pediatric nephrologist, who obtained a renal profile with similar results: a urinalysis with >300 mg/dl of protein and large blood; urine microscopy with red blood cells too numerous to count per high-power field; normal complement levels (C3 level 148 mg/dl and C4 level 27 mg/dl); normal anti-DNAse B level; normal antistreptolysin O titer; negative antinuclear antibody; negative perinuclear antineutrophil cytoplasmic antibody; and negative cytoplasmic antineutrophil cytoplasmic antibody. A urine protein-to-urine creatinine (UPC) ratio was not available for review. Renal ultrasonographic images showed normal results. Because of the persistence of hematuria and proteinuria, he underwent a renal biopsy 1 month after presentation. Histopathologic study showed 21 glomeruli, all with mesangial hypercellularity on light microscopy and globular mesangial staining for C3 (3+) and IgA (2+) on immunofluorescence (IF). Staining for C1q was negative. Electron microscopy showed thickened glomerular basement membrane owing to multifocal subendothelial electron-dense immune complex deposits. A diagnosis of IgA nephropathy was made,

Table 1. Summary of renal histopathology, treatment, and clinical outcome of patients with dystrophic EB

Patient characteristics	Case Number				
	1	2	3	4	5
Sex	Male	Male	Male	Female	Female
Epidermolysis bullosa type	DDEB	RDEB-GS	RDEB-GS	RDEB-GS	RDEB-GS
Age at biopsy (y)	18	17	10	14	14/15
Histopathologic findings	Mesangial staining for C3 and IgA; subendothelial, subepithelial, mesangial, and paramesangial deposits	Mesangial staining for C3; mesangial deposits	Mesangial staining for C3; mesangial and paramesangial deposits	Mesangial staining for C3; mesangial and paramesangial deposits	Mesangial staining for C3; mesangial and paramesangial deposits
Renal diagnosis	IgA-dominant infection- associated GN	GN with dominant C3	GN with dominant C3	GN with dominant C3	GN with dominant C3
Preceding cutaneous infections	*Staphylococcus*	*Staphylococcus Streptococcus Pseudomonas*	*Staphylococcus*	*Staphylococcus Streptococcus Pseudomonas*	*Staphylococcus Streptococcus*
Preceding C-reactive protein level (mg/dl)	7.5	10.1	21.2	9.6	15.0
Treatment	Steroids, ACEI	Antibiotics	Steroids, mycophenolate	Antibiotics	ACEI, antibiotics
Clinical outcome	Mildly improved proteinuria and renal function	Significantly improved proteinuria and normalized renal function	Significantly improved proteinuria and improved renal function	Improved renal function, hematuria, and proteinuria	Death from renal failure at age 18 in the setting of preceding sepsis

ACEI, angiotensin converting enzyme inhibitor; DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; GN, glomerulonephritis; IgA, immunoglobulin A; RDEB-GS, recessive dystrophic epidermolysis bullosa-generalized severe

and the patient was treated with long-term steroid and lisinopril therapy. Initially there was improvement in the SCr level (0.86 mg/dl), hematuria (31 red blood cells per high-power field on microscopy), and proteinuria (30 mg/dl), but he experienced a relapse of gross hematuria, nephrotic-range proteinuria, and renal dysfunction (SCr, 1.9 mg/dl) while being weaned from steroids. Repeat renal biopsy at age 21 years showed IgA dominant (3+ to 4+) immune complex proliferative GN with crescents plus strong (3+) C3 deposition. In addition, electron microscopy showed hump-like subepithelial deposits, suggesting a possible component of infection-associated GN superimposed on chronic IgA nephropathy. Because of concern that the chronic cutaneous *Staphylococcus* infections represented a possible antigenic stimulus for his GN, he was treated with cephalexin and steroid therapy was resumed. Although he did not complete the antibiotic course, there was resolution of gross hematuria and some improvement in the SCr level (to 1.5 mg/dl), so he was again weaned from steroids. Three months after steroid discontinuation, he was admitted for acute kidney injury with an SCr level of 3.8 mg/dl in the setting of lower extremity cellulitis. He received antibiotics and lisinopril was held because of his acute kidney injury. His primary nephrologist believed he had postinfectious GN that would improve after resolution of the infection. A repeat renal profile obtained 3 months later (at age 22) showed no improvement in the SCr level (3.3 mg/dL), so the patient came to our institution for a second opinion. He was noted to have nephrotic-range proteinuria (UPC ratio, 9.2 mg/mg) and microscopic hematuria. The IgA level was mildly elevated (396 mg/dl), and both C3 and C4 levels were normal. He underwent a third renal biopsy, which showed signs of chronic GN with crescents, segmental sclerosis, and mesangial proliferation. There was no definitive evidence of immune complex deposition in the 1 glomerulus available for IF, and electron microscopy showed mesangial, paramesangial, and subepithelial hump-like deposits. It was ultimately considered he had IgA nephropathy based on review of his previous biopsy findings. He received intravenous pulse and oral steroids in addition to mycophenolate, with some improvement in SCr (to 2.5 mg/dl) and reduction in proteinuria (UPC ratio 4.0 mg/mg). As of the date of writing, the goal was to continue mycophenolate therapy and with gradual weaning from steroids.

Patient 2

Patient 2 was a Caucasian male with RDEB and *chronic Staphylococcus, Streptococcus,* and *Pseudomonas* cutaneous infections (Table 1). His baseline CRP level was approximately 10 to 12 mg/dl. At age 16 gross hematuria and proteinuria developed, so was referred to a pediatric nephrologist, who clinically diagnosed IgA nephropathy and started enalapril therapy. Several months later gross hematuria, worse proteinuria (UPC ratio, 5.4 mg/mg), and an increase in the SCr level from baseline 0.3 mg/dl to 0.8 mg/dl developed. The cystatin C level at the time was 1.3 mg/ (cystatin C–estimated glomerular filtration rate [GFR] 65 ml/min per 1.73 m^2). The C3 level was slightly elevated (171 mg/dl). The patient underwent a renal biopsy, with

pathologic findings showing up to 21 glomeruli with increased proliferation and occasional neutrophils within capillary loops, as well as interstitial inflammation composed primarily of plasma cells and occasional neutrophils (Figure 1). IF showed strong C3 mesangial deposition and no immunoglobulin or C1q deposition. Electron microscopy showed mesangial matrix deposits. He was diagnosed with GN with dominant C3 and prominent interstitial inflammation, possibly infectious in nature. Because of concern that his renal disease may have an infectious etiology, he was empirically treated with cefdinir followed by prophylactic cephalexin. After antibiotic treatment the gross hematuria resolved, although microscopic hematuria persisted (20–29 red blood cells per high-power field). The proteinuria markedly improved, with an UPC ratio nadir of 0.58 mg/mg 6 months after antibiotic treatment. His renal function also markedly improved with an SCr level of 0.23 mg/dl (Schwartz formula–calculated GFR, 273 ml/min per 1.73 m^2) and a cystatin C level of 0.869 mg/L (cystatin C estimated GFR level, 111 ml/min per 1.73 m^2) 6 months after antibiotic therapy. At the time of writing, his renal function remained normal.

Patient 3

Patient 3 is an Emirati boy with RDEB and a history of allogeneic bone marrow transplant at age 19 months in addition to chronic *Staphylococcus* cutaneous infections (Table 1). At age 10 nephrotic-range proteinuria (UPC ratio, 2.3 mg/mg) developed with a rise in the CRP level to 21.2 mg/dl and renal dysfunction with a rise in the SCr level from 0.37 to 0.57 mg/dl in the absence of clinical edema, microscopic hematuria, or red blood cell casts on high-power field microscopy. The cystatin C level was 1.6 mg/l (cystatin C–estimated GFR, 43 ml/min per1.73 m^2). The C3 level was mildly elevated (201 mg/dl) and the C4 level was normal (32 mg/dl). Because of persistent renal dysfunction and nephrotic-range proteinuria, a renal biopsy was performed 4 months after presentation and revealed 12 glomeruli with mesangial hypercellularity and mesangial matrix expansion. IF demonstrated C3 deposition in a discrete granular pattern in the mesangium and no immunoglobulin or C1q deposition. There was no significant tubulointerstitial inflammation. Electron microscopy showed electron dense deposits within the mesangial matrix and paramesangial space. A diagnosis of GN with dominant C3 was made and the patient was with treated with a 6-month course of steroids in addition to low-dose mycophenolate that was gradually titrated up to 1200 mg/m^2 per day. With these therapies renal function improved (SCr level, 0.24 mg/dl; Schwartz formula–calculated GFR, 227 ml/min per 1.73 m^2; and cystatin C, 1.3 mg/l [cystatin C–estimated GFR 67 ml/min per 1.73 m^2). Proteinuria has also improved (UPC ratio 0.63 mg/mg) as has the C3 level (154 mg/dl).

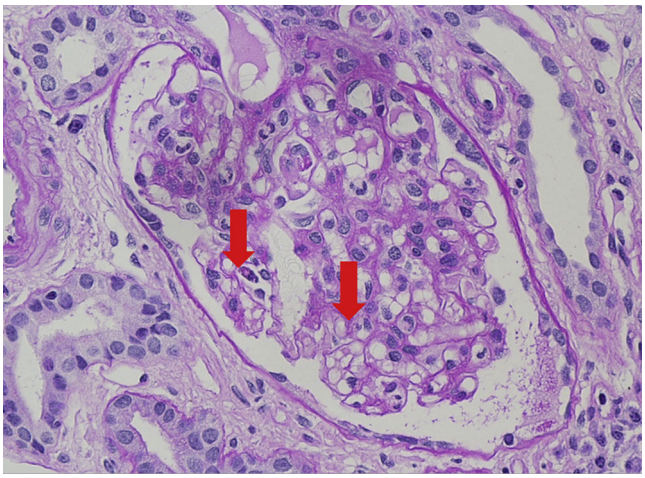

Figure 1. Renal histopathologic findings from patient 2. Glomerulus shows increased mesangial cellularity and matrix, and inflammatory cells in capillary loops (arrows; periodic acid–Schiff stain, original magnification ×400).

Patient 4

Patient 4 was a Caucasian adolescent girl with RDEB and chronic *Staphylococcus*, *Streptococcus*, and *Pseudomonas* infections (Table 1). Her baseline CRP level was approximately 10 mg/dl. Coffee-colored urine developed at age 14. A renal profile was obtained and showed a rise in SCr from 0.3 to 0.68 mg/dl. Urinalysis showed more than 50 red blood cells per high-power field, 30 mg/dL protein, and moderate leukocyte esterase. She was presumed to have a urinary tract infection and began a regimen of sulfamethoxazole-trimethoprim. Further evaluation showed an antistreptolysin O titer elevated at 2669 unit/ml and a mildly low C3 level (56 mg/dl). A nephrology consultation was obtained and postinfectious GN was suspected. Gross hematuria continued and she had nephrotic-range proteinuria (UPC ratio, 3.2 mg/mg), so she underwent a renal biopsy 1 month after initial presentation. Histopathologic findings showed 18 glomeruli with mesangial proliferation and extensive tubulointerstitial inflammation, primarily composed of neutrophils, plasma cells, and lymphocytes (Figure 2). IF showed strong (3+) mesangial staining for C3 and no immunoglobulin, C1q, or C4 deposition (Figure 3). Electron microscopy showed a mild increase in the mesangial matrix with scattered paramesangial and mesangial deposits. At the time of biopsy, urinalysis showed nitrite, moderate leukocyte esterase, and 2+ bacteria. A diagnosis of GN with dominant C3 was

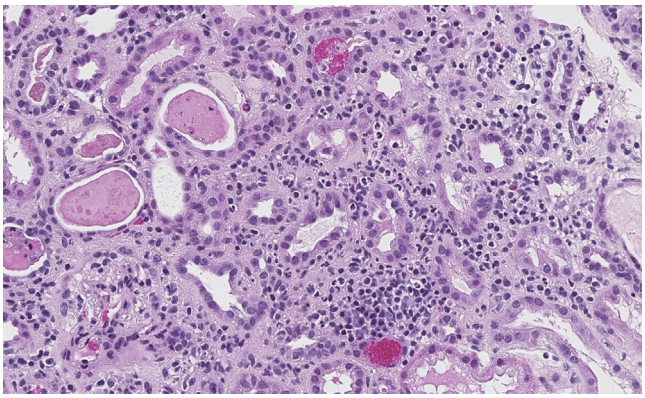

Figure 2. Renal histopathologic findings from patient 4. Prominent mixed interstitial inflammatory infiltrate is present, with lymphocytes, plasma cells, rare eosinophils, and neutrophils (hematoxylin-eosin stain, original magnification 200).

made. Because of concern that there was an infectious etiology given the tubulointerstitial inflammation, she was treated with cefdinir followed by prophylactic amoxicillin. After initiation of antibiotics, she had subsequent resolution of gross hematuria and proteinuria within 12 weeks. At the time of writing, she was doing well from a renal standpoint, maintaining her baseline SCr, and had a normal urinalysis.

Patient 5

Patient 5 was a Caucasian female adolescent with RDEB and chronic *Staphylococcus* and *Streptococcus* infections (Table 1). Her baseline CRP level was approximately 12 to 15 mg/dl. At age 13 microscopic hematuria and proteinuria (UPC ratio, 1.0 mg/mg) developed, so she was referred to a pediatric nephrologist. Further evaluation included a normal renal profile, normal C3 and C4 levels, and a negative antinuclear antibody level. Coke-colored urine developed at age 14 in addition to worsening proteinuria (UPC ratio, 7.3 mg/mg) and a rise in SCr from 0.4 to 0.96 mg/dl. Renal biopsy showed 15 glomeruli with increased mesangial proliferation, 2 small crescentic lesions, and interstitial inflammation. IF showed C3 mesangial deposition and no immunoglobulin, C1q, or C4 deposition. Electron microscopy showed a mild increase in mesangial matrix with scattered paramesangial and mesangial deposits (Figure 4). A diagnosis of GN with dominant C3 was made, and the patient was treated with alisinopril, but her renal function worsened with a rise in SCr to 1.6 mg/dl. Additional evaluation showed elevated antistreptolysin O titer and elevated streptozyme, so clindamycin therapy was started out of concern for a *Streptococcus* cutaneous infection. Subsequently the SCr level and gross hematuria improved and the UPC ratio was mildly decreased to 4.0 mg/mg, but a relapse occurred after switching to rifampin after development of diarrhea during clindamycin use. A second renal biopsy at age 15 showed acute proliferative and exudative GN with cellular and fibrosing crescents, interstitial inflammation, and fibrosis with focal tubular atrophy. IF again showed strong mesangial C3 deposition. A transition was made from rifampin therapy to amoxicillin prophylaxis. At age 16 she was considered to have achieved partial remission of chronic GN because of improvement in SCr to 0.87 mg/dl and improvement in microscopic hematuria. However, at age 17 she was hospitalized for decompensated septic shock in the setting of a

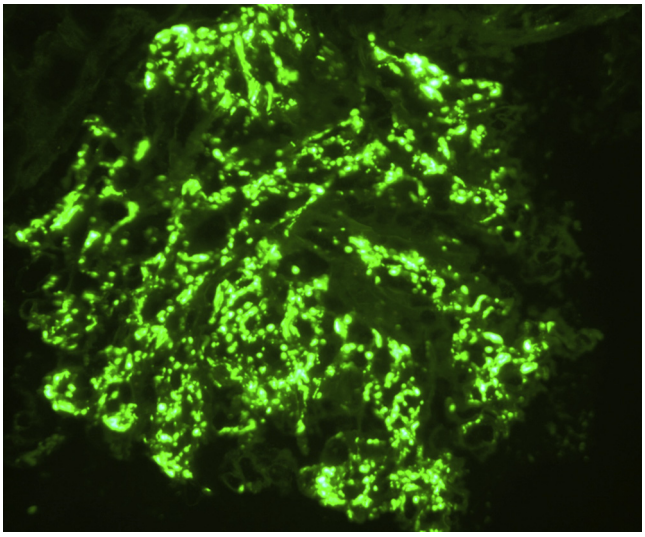

Figure 3. Renal histopathologic findings from patient 4. Strong (3+) C3 staining shows a granular mesangial pattern (immunofluorescence staining, original magnification ×200).

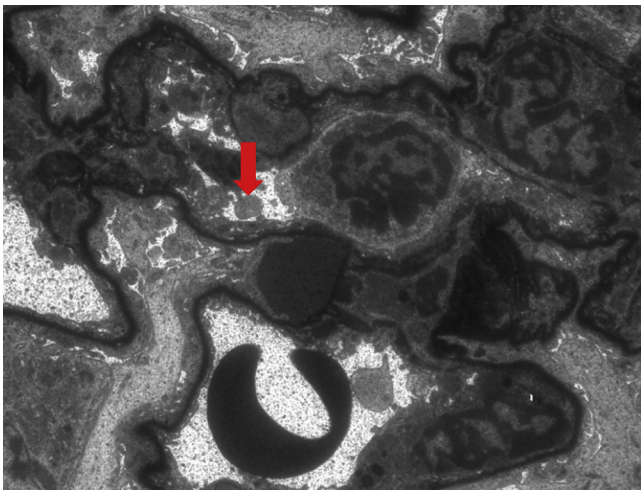

Figure 4. Renal histopathologic findings from patient 5. Electron microscopy shows a mild increase in the mesangial matrix with scattered mesangial and paramesangial deposits (arrow).

diarrheal illness and purulent drainage from cutaneous lesions; vasopressor therapy was started, and she received broad-spectrum antibiotics, including vancomycin and cefepime. On admission she had significantly worse renal function with hyperkalemia and proteinuria (SCr, 4.9 mg/dL; serum potassium, 8.6 mg/dL; UPC ratio, 8.0 mg/mg). Her hyperkalemia was initially medically managed. She ultimately declined dialysis, opting for palliative measures instead. Her renal function continued to decline (SCr, 7.62 mg/dl), and she died 2 weeks after admission as the result of complications of renal failure.

DISCUSSION

We describe the unique renal histopathologic findings in 5 pediatric patients with dystrophic EB and GN. Histologic findings in all patients showed C3 immunofluorescent staining, mesangial proliferation, and mesangial electron dense deposits. Based on the 2013 consensus report,[7] 4 of our 5 patients who underwent biopsy met the criteria for GN with dominant C3, which to the best of our knowledge has not been reported to date in children with EB.

Our patients had histologic variability, rendering a single etiology difficult to determine. Infection may cause GN with dominant C3 staining, more specifically termed infection-associated GN (IAGN). All of our patients had either chronic *Staphylococcus* or *Streptococcus* cutaneous infections, or both, which are known causes of IAGN. In additional, most of our patients had renal interstitial inflammation, a finding suggestive of IAGN. However, other immunofluorescent staining such as IgG and C1q was notably absent in all our cases, which is less consistent with IAGN. Although "masked" Ig deposits may be detectable by IF on paraffin-embedded tissue, this staining was unavailable in our department at the time of our patients' renal biopsies. Regardless, the lack of Ig deposition was not the only inconsistency with IAGN. A predominance of intracapillary neutrophils was not found in all patients, which is also atypical of IAGN. In light of these discrepant findings, we propound that C3 GN due to primary complement dysregulation was a possible contributing etiology in patients 2 through 5. Supportive of this hypothesis is the preponderance of mesangial deposits and lack of co-deposition of immune reactants in 4 of the patients. Patients with EB in whom C3 GN develops may have an underlying genetic abnormality, as has been described in other patients with C3 GN, including mutations in *CFH*, complement factor H–related genes, and the presence of C3 nephritic factor.[8,9] Unfortunately, we did not perform extensive complement-related serologic and genetic testing in our patients, and further research is needed to investigate this possibility. Overall, our patients demonstrated histologic variability and we cannot exclude that both IAGN and C3 GN were involved to varying degrees. Renal disease in patients with EB may represent a spectrum of multifactorial causes, including infectious and immunologic components.

Interestingly, another case series of pediatric EB patients with renal dysfunction described 1 patient with renal pathologic findings similar to those of our patients: mesangial expansion and moderate C3 deposition without Ig deposition in the setting of concurrent *Staphylococcus* and *Streptococcus* cutaneous infections.[2] That patient's renal dysfunction progressed to end-stage renal disease, for which he received dialysis but died a few years later from complications of fluid overload and cardiac failure.[2] The authors similarly opined that his histopathologic findings could be consistent with IAGN or membranoproliferative GN, which includes C3 GN in current classification systems.

Our patient 1 was initially diagnosed with IgA nephropathy and was the only patient who did not meet criteria for GN with dominant C3. Ours is not the first report of a patient with dystrophic EB whose biopsy findings were suggestive of IgA nephropathy; a similar patient case was published in 2008.[S1] However, our patient differs in that he additionally had strong C3 IF staining and both subepithelial and subendothelial deposits, findings atypical of IgA nephropathy. His renal disease was likely due to *Staphylococcus* IAGN, a disease entity in which varying degrees of both IgA and C3 deposition may be present.[S2] Alternatively, it is possible our patient's renal disease was due to primary IgA nephropathy with associated complement dysregulation. Studies have shown an association between complement activation and IgA nephropathy activity,[S3] with C3 and C4d mesangial deposition an independent risk factor for progression of IgA disease.[S4] Therefore, it is possible that underlying complement dysregulation contributed to the aggressive form of IgA nephropathy witnessed in our patient.

Infections, either as the primary cause or as a trigger for complement dysregulation, were suspected to play a

Table 2. Teaching points

- Glomerulonephritis may be an unrecognized cause of renal disease in children with epidermolysis bullosa.
- Preceding cutaneous bacterial infections may play a role in the development of glomerulonephritis with dominant C3 in children with epidermolysis bullosa. Therefore, antibiotics targeting cutaneous bacterial infections should be considered as a potential-first line therapy in these patients.
- Cystatin C is likely a more accurate marker of renal function in malnourished patients with epidermolysis bullosa compared with serum creatinine.

role in the onset of GN in our patients. Three patients therefore received a trial of antibiotic therapies targeting pathogenic bacteria previously cultured from their cutaneous tissues. In patients 2 and 4, markers of renal dysfunction improved after antibiotic therapy without use of immunosuppression. In patient 5, markers of renal dysfunction transiently improved after antibiotic therapy and then acutely worsened in the setting of septic shock. Although the correlation of antibiotic use with renal improvement does not prove causation, we believe the antibiotics contributed at least in part to improvement in our patients' conditions. To our knowledge, there have been no reports of antibiotic therapy as a potential curative treatment for EB patients with GN. Immunosuppressive therapies, such as mycophenolate, steroids, and rituximab, have historically been used to treat C3-dominant GN with some success.[S5,S6] These therapies also remain an option to treat C3-dominant GN in patients with EB. It has been our practice to consider this as second-line therapy if signs of renal dysfunction do not first resolve with a course of antibiotics, or if the renal biopsy pathologic findings show severe glomerular proliferative disease.

A final point of interest is the discrepancy between SCr-based (Schwartz formula–calculated) and cystatin C–based estimations of renal function in patients 2 and 3. For both patients, Schwartz formula–calculated renal function was markedly higher, likely because both patients were malnourished and had low muscle mass as secondary consequences of EB. Overall, these findings suggest cystatin C is a more accurate marker of renal function in EB patients with malnutrition, although additional research is needed to substantiate this hypothesis.

In summary, we describe 5 patients with dystrophic EB in whom GN developed, all of whom had C3 deposition on renal biopsy pathologic findings and 2 of whom had sustained improvement in renal dysfunction after antibiotic treatment targeting chronic cutaneous infections. We postulate that ongoing cutaneous bacterial infections play a role in the development of GN with C3 deposition in patients with EB and propose that antibiotics targeting these infections be considered as a potential first-line therapy for children with EB and GN (Table 2). We additionally hypothesize cystatin C is a more accurate marker of renal function in EB patients with malnutrition compared with serum creatinine.

DISCLOSURE

The authors have nothing to disclose.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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