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Case Report

Bullous Pemphigoid With a Dual Pattern of Glomerular Immune Complex Disease

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A 75-year-old man presented with a blistering skin disease and nephrotic syndrome. Bullous pemphigoid was diagnosed by linear immunoglobulin G (IgG) and C3 staining along the basement membrane zone of a skin biopsy specimen and by the presence of circulating IgG recognizing the 180-kDa bullous pemphigoid antigen (BP180; type XVII collagen). A kidney biopsy specimen showed endocapillary inflammation without crescents. Direct immunofluorescence showed strong IgG and C3 staining in a combined granular and linear pattern along the glomerular basement membrane. Electron microscopy showed subepithelial deposits. In serum, no antibodies against the Goodpasture antigen (type IV collagen) or phospholipase A_2 receptor were detected. Indirect immunofluorescence studies using the patient's serum showed a strikingly linear but not granular IgG pattern along the epithelial basement membranes of monkey esophagus and kidney. Although type XVII collagen was recently identified in the glomerulus, the patient's serum did not produce a 180-kDa band on immunoblot of kidney tissue and still stained glomeruli of BP180 knockout mice by indirect immunofluorescence. The patient was treated with prednisone and azathioprine, which resulted in complete remission of skin and kidney manifestations. Although bullous pemphigoid has been reported previously in association with anti–glomerular basement membrane disease or membranous nephropathy, this case demonstrates both elements in 1 patient. This concurrence and the linear pattern on indirect immunofluorescence support the possibility of cross-reactive or parallel autoantibodies to basement membranes with a secondary membranous component.

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INDEX WORDS: Bullous pemphigoid; 180-kDa BP antigen; type XVII collagen; glomerular basement membrane (GBM); anti-GBM disease; membranous nephropathy; autoantibody; nephrotic syndrome; renal biopsy.

Bullous pemphigoid is the most common subepithelial blistering skin disease of autoimmune origin.[1] Two antigens have been linked to the disease, the 180-kDa minor bullous pemphigoid antigen (BP180, also known as type XVII collagen) and the 230-kDa major bullous pemphigoid antigen (BP230). BP180 and BP230 derive from basal keratinocytes and are part of the hemidesmosome, which links the keratin intermediate filaments with the basement membrane zone. Both antibodies can be measured in serum to establish the diagnosis; BP180 autoantibodies also correlate with disease activity and are pathogenic.[2,3] The mechanism for lesion formation in bullous pemphigoid appears to be antibody-mediated activation of the complement cascade, although autoantibody-mediated disruption of hemidesmosome structural integrity has also been suggested.[4] Bullous pemphigoid has been reported to occur in association with glomerular disease, including anti–glomerular basement membrane (anti-GBM) disease and membranous nephropathy.[5,6] We present a patient with bullous pemphigoid and nephrotic syndrome in whom the glomerular disease had characteristics of both anti-GBM disease and membranous nephropathy. We suggest that this concurrence may shed light on the pathogenesis of glomerular disease in bullous pemphigoid.

CASE REPORT

A 75-year-old man presented with a blistering skin disease (Fig 1A). His medical history was unremarkable, and he used no medication. A perilesional skin biopsy was performed and immunofluorescence microscopy showed linear immunoglobulin G (IgG) and C3 staining along the basement membrane zone, findings that supported the diagnosis of bullous pemphigoid. The diagnosis was confirmed by positive staining (3+) for roof-binding IgG using indirect immunofluorescence of the patient's serum on salt-split human skin; an enzyme-linked immunosorbent assay (ELISA) detecting antibodies against NC16A, a non-collagenous extracellular domain of BP180 (index value for NC16A, 100 U/mL; threshold for positivity, 9 U/mL); and by the

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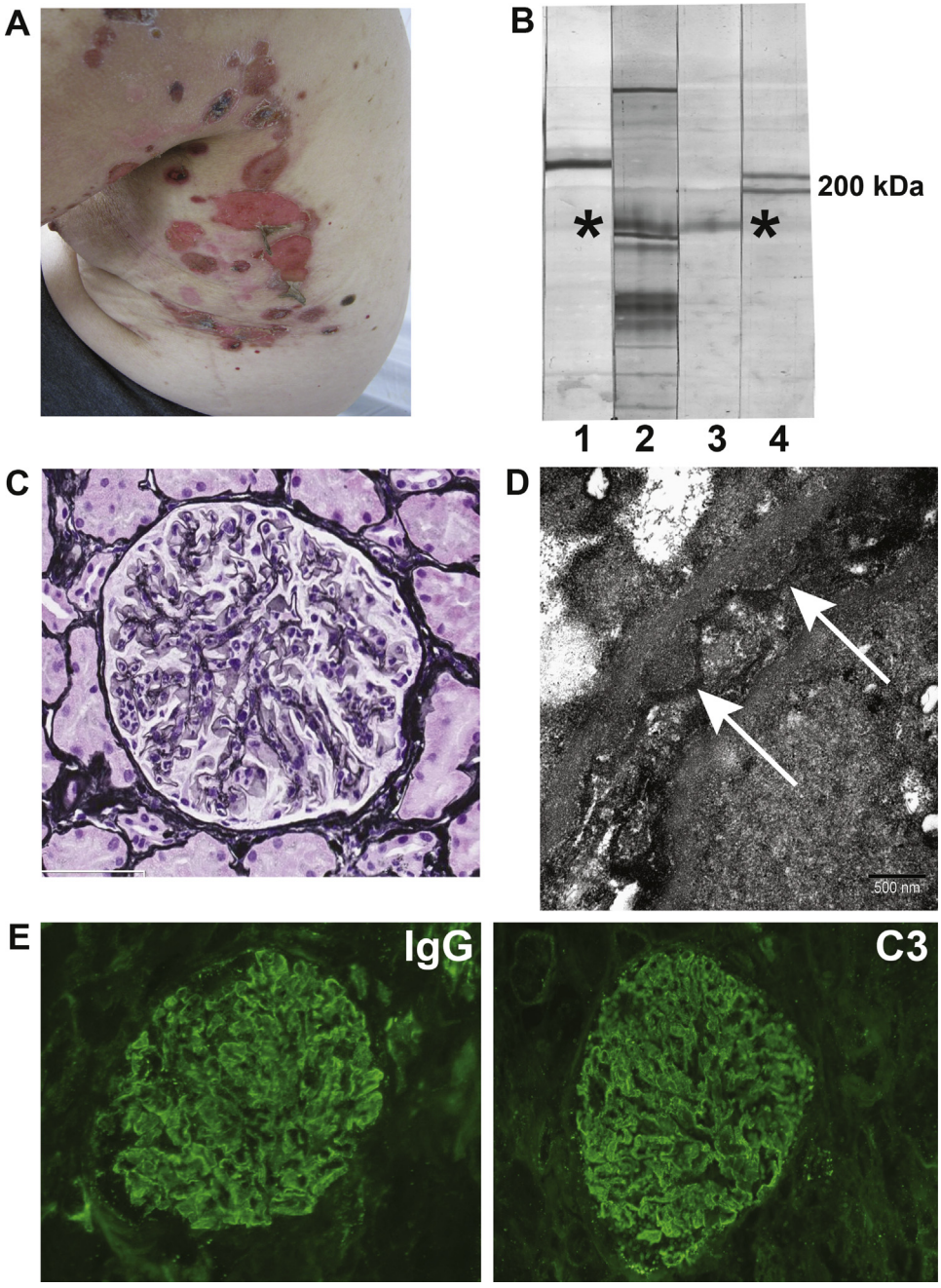

Figure 1. (A) Photograph of the patient's left flank shows multiple blistering skin eruptions secondary to bullous pemphigoid. (B) Immunoblots of electrophoresed human keratinocyte extract probed with (1) mouse monoclonal antibody against laminin γ1 (D-3 antibody; Santa Cruz Biotechnology), (2) patient serum, (3) goat polyclonal antibody against the 180-kDa bullous pemphigoid antigen (BP180; N18 antibody; Santa Cruz Biotechnology), and (4) goat polyclonal antibody against type IV collagen (Southern Biotech). *A band that reacts with patient serum (2) migrates as the same size as BP180 (3). (C-E) Microscopic images from kidney biopsy specimens from the patient. (C) Light microscopy shows a glomerulus with an influx of neutrophils (original magnification, ×400). (D) Electron microscopy shows subepithelial deposits (white arrows; original magnification, ×12,000). (E) Immunofluorescence microscopy shows a combined linear and granular staining pattern for immunoglobulin G (IgG) and C3 along the glomerular capillary walls (original magnification, ×400).

presence of a band migrating at 180 kDa when patient serum was used to immunoblot an epidermal extract (Fig 1B). No BP230 antibodies were identified by ELISA (index value, 7 U/mL; threshold for positivity, 9 U/mL) or immunoblot.

In addition to bullous pemphigoid, the patient was noted to have nephrotic syndrome, including edema, hypoalbuminemia (serum albumin, 19 g/L), and proteinuria (protein excretion, 12 g/d). He had no erythrocyturia. Kidney function was normal (serum creatinine, 1.0 mg/dL, corresponding to an estimated glomerular filtration rate of 74 mL/min/1.73 m^2 using the isotope-dilution mass spectrometry–traceable 4-variable MDRD [Modification of Diet in Renal Disease] Study equation). The patient did not have