Pauci-immune Crescentic Glomerulonephritis Associated With ANCA of IgA Class

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Pauci-immune renal vasculitis is associated strongly with antineutrophil cytoplasmic antibodies (ANCAs) of the immunoglobulin G (IgG) class, which are detected in 80% to 90% of affected patients. IgA ANCAs have been reported in association with various conditions, but never in the setting of pauci-immune vasculitis. A 28-year-old man with unexplained polyclonal hyper-IgA1 diagnosed in childhood presented with decreased kidney function, nephrotic syndrome, and microscopic hematuria. Kidney biopsy showed pauci-immune crescentic glomerulonephritis. Serum test results were negative for IgG ANCA by means of both indirect immunofluorescence and enzyme-linked immunosorbent assay techniques. Conversely, indirect immunofluorescence performed using anti-IgA antibody was strongly positive with a cytoplasmic ANCA pattern, and an enzyme-linked immunosorbent assay test had positive results for both antimyeloperoxidase and anti–proteinase 3 IgA. IgA ANCAs were not detected in 2 control serum samples from 1 patient with polyclonal hyper-IgA and 1 patient with monoclonal hyper-IgA. The patient received corticosteroids and 4 weekly perfusions of rituximab (375 mg/m^2). After a 6-month follow-up, decreased kidney function and nephrotic syndrome persisted and IgA ANCA titers were unchanged. However, a control kidney biopsy showed a decrease in vasculitis activity. This first case of pauci-immune vasculitis associated with ANCA of the IgA class suggests the potential pathogenetic role of these peculiar antibodies. Additional studies are needed to determine whether IgA ANCAs, which are not routinely screened for, can be detected in patients with pauci-immune vasculitis either alone or in association with IgG ANCA.

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Pauci-immune crescentic glomerulonephritis (CrGN) is one of the most severe forms of glomerulonephritis, typically resulting in rapid kidney failure. CrGN, as a part of a systemic small-vessel vasculitis or limited to the kidney, is associated with circulating antineutrophil cytoplasmic autoantibodies (ANCAs) in 80% to 90% of patients.[1] Based on indirect immunofluorescence (IIF), 2 main distinct patterns, cytoplasmic ANCA and perinuclear ANCA, are observed. Determined by means of antigen-specific enzyme-linked immunosorbent assays (ELISA), most cytoplasmic ANCAs usually are directed against proteinase-3 (PR3), whereas perinuclear ANCAs are directed against myeloperoxidase (MPO). Accumulating data support the concept of a pathogenetic role of ANCAs in small-vessel vasculitis.[2] ANCAs detected and largely described in patients with renal vasculitis typically are of the immunoglobulin G (IgG) class. IgA ANCAs have never been reported in the setting of pauci-immune small-vessel vasculitis. Therefore, the significance of IgA ANCA has been largely elusive to date. We report 1 case of pauci-immune CrGN associated with IgA ANCAs directed against both PR3 and MPO. This observation suggests that IgA ANCAs may have a pathogenetic role.

CASE REPORT

A 28-year-old man was referred for decreased kidney function detected on routine blood tests. His medical history was remarkable for a major polyclonal hyper-IgA1 (4.5 g/dL) discovered in childhood that remained totally stable and unexplained despite exhaustive investigations. During the last 5 years, he had presented with recurrent purpuric

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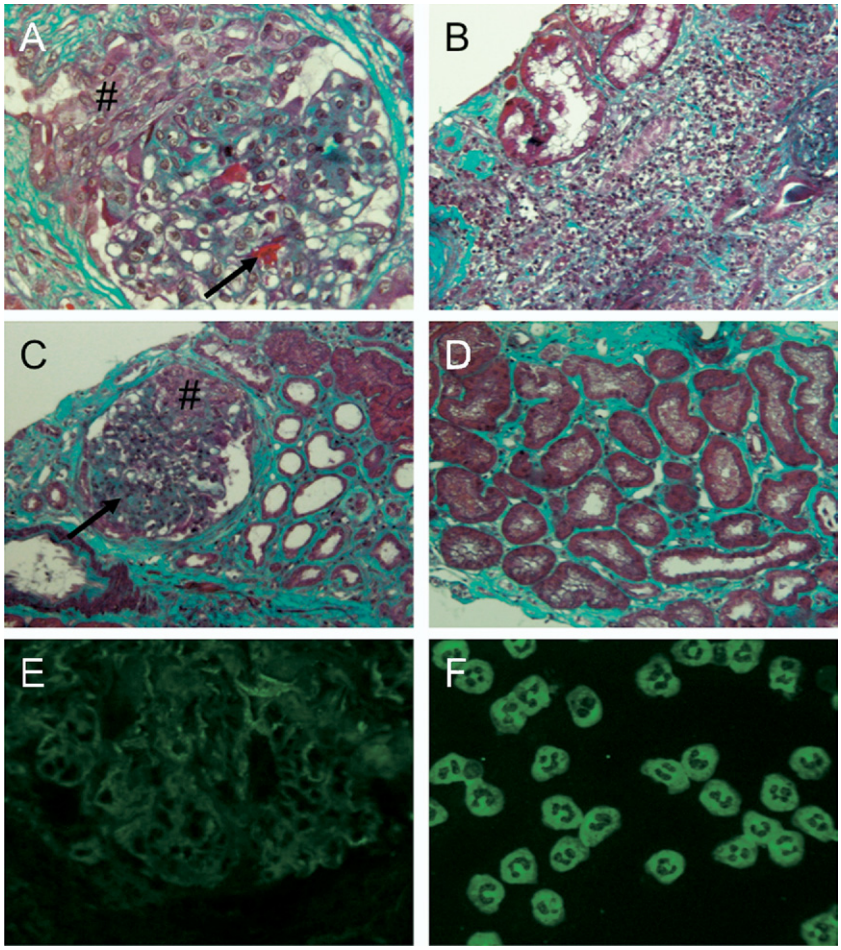

Figure 1. Histological findings in kidney biopsy specimens and serum screening for immunoglobulin A (IgA) antineutrophil cytoplasmic antibodies (ANCAs) by means of indirect immunofluorescence (IIF). (A, B) First kidney biopsy, light microscopy (Masson trichrome stain). (A) Extracapillary cellular proliferation with crescent formation (#) and fibrinoid capillary necrosis (arrow). Neither mesangial nor endocapillary cellular proliferation nor deposits were observed (original magnification ×400). (B) Significant chronic tubulointerstitial changes and widespread interstitial infiltrate by mononuclear cells (original magnification ×200). (C, D) Second kidney biopsy performed at 6 months, after corticosteroid and rituximab therapy, light microscopy (Masson trichrome stain). (C) Only 1 crescentic glomerulus showed extracapillary cellular proliferation (#); all glomeruli showed segmental sclerosis (arrow; original magnification ×200). (D) Interstitial inflammation had almost completely disappeared (original magnification ×20). (E, F) Immunofluorescence study (original magnification ×400). (E) Absence of complement or immunoglobulin (anti-IgA represented here) deposits in glomeruli. (F) IIF using anti-IgA–fluorescein isothiocyanate conjugate on ethanol-fixed human polynuclear neutrophils was strongly positive with a cytoplasmic ANCA pattern.

eruptions of the lower limbs. Skin biopsy showed nonspecific leukocytoclastic vasculitis without immune deposits. On admission, physical examination findings were unremarkable. Blood pressure was 125/80 mm Hg. Laboratory tests on admission showed the following values: serum creatinine, 1.6 mg/dL (142 μmol/L; estimated glomerular filtration rate, 55 mL/min/1.73 m^2 [0.92 mL/s/1.73 m^2]), serum albumin, 2.4 g/dL (24 g/L); serum protein, 8.7 g/dL (87 g/L); and polyclonal hypergammaglobulinemia with gamma globulin of 4.5 g/dL. Urinalysis showed red blood cells, 200/μL, and proteinuria with protein of 11 g/24 h. No monoclonal component was detected in urine and serum by means of immunofixation.

A kidney biopsy was performed (Fig 1A and 1B). On light microscopy, 8 glomeruli were observed, of which 4 were sclerotic. Of the 4 nonsclerotic glomeruli, 3 showed extracapillary cellular proliferation with crescent formation and 1 showed focal capillary necrosis. Neither glomerular mesangial nor endocapillary cellular proliferation or deposits were noted. Significant chronic changes consisting of inflammatory interstitial fibrosis and tubular atrophy also were observed. Immunofluorescence study showed the absence of