Immune complex type crescentic glomerulonephritis and ANCA-positivity in a nine-year-old girl

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We report a nine-year-old girl who presented with the clinical and laboratory findings of rapidly progressive glomerulonephritis. She was found to be positive for both pANCA and cANCA. However, renal histopathology revealed immune complex type of crescentic glomerulonephritis. Thus, although testing for ANCA is an important tool in the prediction of the subtype of crescentic glomerulonephritis, a renal biopsy is still required to establish the diagnosis.

Key words: antineutrophil cytoplasm antibodies (ANCA), childhood, crescentic glomerulonephritis, immune complex.

Crescentic glomerulonephritis (CGN), characterized by extensive proliferation of cells within the Bowman's space, may be idiopathic or occur secondary to a wide variety of systemic diseases including vasculitides. Primary forms of CGN may be associated with anti-GMB autoantibodies, extensive immune complex deposition in the mesangium and capillary walls or with antineutrophil cytoplasm antibodies (ANCA) in the absence of glomerular immune complex deposition (pauci-immune)[1]. The latter subtype is the most common pattern in adults[2], whereas immune complex type of disease is the most commonly observed pattern in childhood[3]. The ANCA-associated CGN, on the other hand, has rarely been reported in children, and it may occur as an idiopathic variety without systemic manifestations or as part of a systemic vasculitis[4-7]. Thus, testing for ANCA has become an important tool in such diseases as Wegener's granulomatosis (WG), microscopic polyarteritis (MPA), and idiopathic CGN[4]. However, despite the usefulness of ANCA serologies, a biopsy, when clinically indicated, is still required to document the presence or absence of a pauci-immune CGN[8].

We report here a pediatric case who presented with a clinical course of rapidly progressive glomerulonephritis (RPGN) and had positive ANCA serology. However, renal biopsy revealed immune complex type CGN.

Case Report

A nine-year-old girl was admitted to the hospital with a history of cough, weakness, abdominal pain and pallor of 10 days' duration. She was reported to have an upper respiratory infection two weeks before admission.

Physical examination revealed pallor and increased pulse rate (110/minute). Other physical findings, including anthropometric measurements and blood pressure, were normal.

Urinalysis showed proteinuria (2+) and microscopic hematuria. Her hemoglobin was 6.2 g/dl, hematocrit 18.6%, mean corpuscular volume (MCV) 85.7 fl, leukocytes 10,900/μl, platelets 404,000/μl, and reticulocytes 1.8%. Peripheral blood smear revealed erythrocytes with mild anisocytosis and poikilocytosis, but no burr cells. Her serum creatinine was 7.9 mg/dl, blood urea nitrogen 101 mg/dl, uric acid 10.3 mg/dl, and albumin 2.8 g/dl. Serum glucose, cholesterol, electrolytes, bicarbonate, transaminases, bilirubin and blood gases were normal. Erythrocyte sedimentation rate was 150 mm/h, C-reactive protein 164 mg/L (range 0-5), rheumatoid factor 202 IU/ml (range 0-10), and ASO 258 IU/ml (range 0-200). Serum C3 and C4 levels were normal, and ANA and direct Coombs' tests were negative. Serum anti-MPO (40 U/ml, range 0-5) and anti-PR3 (29 U/ml, range 0-2) antibodies measured by ELISA were positive, while anti-GBM

antibody and cryoglobulin were negative. Random urinary protein/creatinine ratio was 3. She had been immunized against hepatitis B virus, (HBV) and her anti-HBs antibody level was 118 mIU/ml. Anti-hepatitis C virus (HCV) antibody was negative. Abdominal ultrasonography demonstrated kidneys of normal size with increased echogenicity of the parenchyma and normal pelvicaliceal structures. Chest x-ray was normal.

Histopathological examination of renal biopsy tissue revealed 16 glomeruli in light microscopy. Of these, 11 had cellular crescents, and two were globally sclerotic. Glomerular basement membranes were markedly thickened and there was patchy mesangial hypercellularity. There was no prominent polymorphonuclear leukocytic infiltration of the glomeruli. Interstitium showed marked inflammation and severe fibrosis (Fig. 1). Direct immunofluorescence microscopy exhibited diffuse peripheral granular capillary wall and patchy mesangial deposits of C3, membranous deposits of IgG, and small deposits of IgM, and to a lesser extent of IgA and C1q (Fig. 2).

Fig. 1. Vasculitic lesions involving two glomeruli. Interstitium is also densely infiltrated by lymphocytes (H&E, x200).

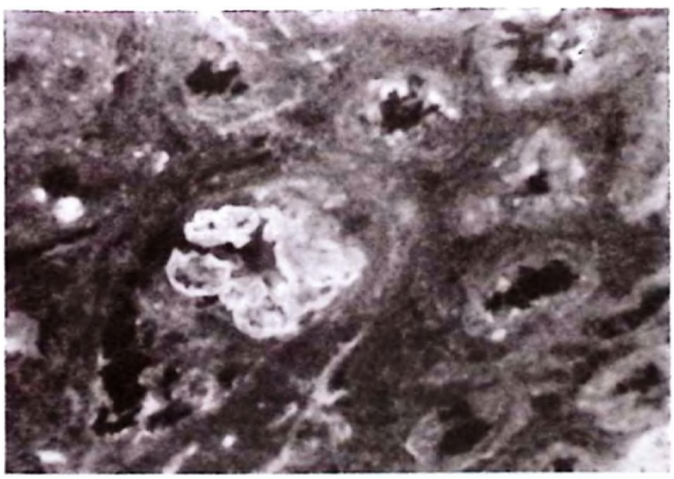

Fig. 2. A glomerulus having peripheral granular capillary wall staining pattern with anti-C3 antibody. Note crescentic proliferation in the Bowman's capsule (DIF, anti-C3, x200).

The patient was monitored for vital signs and given furosemide to increase urine output. However, on the second day of admission, acute peritoneal dialysis was initiated due to increasing BUN (117 mg/dl) and creatinine (10.2 mg/dl) levels. In addition, pulse methylprednisolone therapy (30 mg/kg/day for 3 days) was started. On the fourth day, percutaneous renal biopsy was performed, and histopathological examination was consistent with CGN. Thus, immunosuppressive treatment including cyclophosphamide 1 mg/kg/day prednisolone 2 mg/kg/day was instituted. As renal function did not improve, however, permanent peritoneal catheter was inserted and continuous ambulatory peritoneal dialysis was started on the 14th day of admission. In addition, plasma exchange therapy was added, and a total of six exchanges were performed. She was also given antihypertensive therapy, including a beta blocker and a diuretic, upon development of hypertension. After one month of treatment, anti-MPO and anti-PR3 were still positive (8 and 5 U/ml, respectively). Immunosuppressive therapy was continued for three months with no improvement in renal function. This treatment was stopped at this point due to recurrent peritonitis attacks, and the course of the kidney disease finally terminated with end-stage renal failure.

Discussion

A variety of disorders of different etiology and pathogenesis might result in crescentic glomerulonephritis that is characterized histologically by extensive proliferation of cells within the Bowman's space[2]. Crescentic glomerulonephritis may be a primary renal disease, termed idiopathic, or occur secondary to a wide variety of etiologic events and pathogenetic mechanisms. Primary forms of CGN have several pathogenetic subtypes. Type I is associated with anti-GMB autoantibodies. Type II is characterized by extensive immune complex deposition in the mesangium and capillary walls. These patients

usually do not have anti-GBM antibodies or ANCA. Type III is associated with the absence of glomerular immune complex deposition (pauci-immune) and is associated with ANCA[1]. The latter subtype is the most common pattern in adults[2]. On the other hand, the most commonly observed pattern in childhood is immune complex[3].

Pallor, abdominal pain, anemia, hematuria, proteinuria and impaired renal function following an upper respiratory tract infection in a nine-year-old girl might suggest some diagnoses as hemolytic uremic syndrome (HUS), systemic lupus erythematosus (SLE), or poststreptococcal acute glomerulonephritis (PSAGN). Absence of hypertension, thrombocytopenia, and microangiopathic hemolytic anemia excluded HUS as a diagnostic possibility in our patient. On the other hand, absence of hypocomplementemia, and negative Coombs' and ANA tests ruled out SLE. Anemia unrelated to the degree of renal failure, as in our patient, has been reported to be seen at presentation in 50% of the patients with membranoproliferative glomerulonehphritis (MPGN)[3]. However, hypocomplementemia, detected in most patients with MPGN, was not present in this case. Although ASO titer was only slightly elevated and serum complement levels were normal, PSAGN could not be exluded in this cases, since 11% of patients had normal complement levels[3]. In addition, presence of rheumatoid factor, although nonspecific, was reported in nearly all patients with PSAGN[3] as in our patient.

Recent onset of clinical symptoms, hematuria, proteinuria, and uremia along with rapidly increasing serum creatinine and BUN levels suggest, whatever the cause, RPGN[3]. This type of presentation is seen in any type of CGN[1]. The testing for ANCA has become an important tool in classification of idiopathic CGN[4]. Evaluation of the patients with CGN having positive ANCA serology reveals anti-MPO p-ANCA in 75-80% of individuals, with the remaining generally being positive for anti-PR3[9,10]. Our patient, on the other hand, had both anti-MPO and anti-PR[3] antibodies, anti-MPO being more pronounced. Thus, clinical and laboratory data of our patient were consistent with ANCA-positive idiopathic CGN, and the expected renal pathology was CGN with sparse or no immune deposition[9,10]. As such, light microscopic examination of renal biopsy specimen demonstrated crescents in 70% of then glomeruli examined. However, immunofluorescence microscopy findings were compatible with immune complex type CGN.

Crescentic glomerulonephritis with immune complex pattern could be primary or secondary to some multisystem diseases (like PSAGN, SLE, cryoglobulinemia, hepatitis C), or superimposed on another primary glomerular disease (like MPGN or IgA nephropathy)[1]. While clinical and serologic findings excluded multisystem diseases, histopathologic findings excluded other primary glomerular diseases in this patient. Thus, she was diagnosed as primary CGN. However, as stated previously, PSAG could not be excluded unequivocally.

Although ANCA were first described in a few patients with necrotizing glomerulonephritis and later gained interest due to their presence in Wegener's granulomatosis. (WG), it has been shown that ANCA are not specific for WG. Thus, diagnostic potential of these autoantibodies has been challenged. In addition to WG, MPA and idiopathic pauci-immune CGN, ANCA has been shown to be present in anti-GBM disease, Churg-Strauss syndrome, connective tissue diseases like SLE and rheumatoid arthritis, inflammatory bowel diseases, autoimmune liver disease, and some drugs and infectious diseases[9]. In addition, presence of ANCA has been demonstrated in PSAGN[11,12]. In fact, ANCA positivity, whether in a perinuclear or cytoplasmic pattern, has been reported to be present in approximately 60% of patients with immune complex glomerulonephritis[13].

The most important factor affecting prognosis is the speed with which treatment is instituted following recognition of disease; intravenous pulse methylprednisolone therapy can be initiated empirically while awaiting the results of diagnostic studies in CGN[1]. Most management protocols of CGN associated with ANCA include cyclophosphamide and prednisolone. In addition, plasma exchange therapy might be of value in those patients dependent on dialysis at presentation[1]. However, our patient did not benefit from these treatment protocols, and progressed to end-stage renal failure, The medications were stopped at the third month of treatment due to recurrent episodes of peritonitis.

In conclusion, this patient had ANCA-associated CGN with immune complex staining pattern and no finding of systemic vasculitis, making

her an interesting case. In addition, presence of ANCA in a child with the clinical course of RPGN is not a specific predictor of renal pathology; a renal biopsy is always needed to determine the nature of the disease and to select the appropriate treatment.

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