Elevated Expression of Pentraxin 3 in Anti-neutrophil Cytoplasmic Antibody-associated Glomerulonephritis with Normal Serum C-reactive Protein

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Abstract

A 20-year-old woman was admitted to our hospital with an elevated serum creatinine level of 1.61 mg/dL and a normal C-reactive protein level of less than 0.1 mg/dL. Her myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA) titer was slightly increased at 9.2 U/mL; a kidney biopsy revealed that 23 of 32 glomeruli had crescents. The expression of pentraxin 3 was detected in her kidney and her plasma pentraxin 3 level was elevated at 63.53 ng/mL. Plasma pentraxin 3 levels may be an activity marker for ANCA-associated glomerulonephritis, particularly when serum C-reactive protein levels are within the normal limits.

Key words: anti-neutrophil cytoplasmic antibody, crescentic glomerulonephritis, pentraxin 3, rapidly progressive glomerulonephritis


Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis is one of the major causes of rapidly progressive glomerulonephritis. A higher serum creatinine level at diagnosis typically indicates a poor prognosis in this disease (1). Early detection and early appropriate treatment are essential for the preservation of kidney function. C-reactive protein (CRP) is generally known as a key marker for early diagnosis and reflects the degree of vasculitis and kidney injury (1-3). Although the underlying mechanism of kidney injury in ANCA-associated glomerulonephritis remains unclear, a novel theory has recently been proposed with neutrophil extracellular traps (NETs) as the prime triggers of ANCA-associated diseases (4). Pentraxin 3 (PTX3) is associated with NETs and is an inflammatory marker from the pentraxin family, which also includes serum CRP and amyloid P component (5, 6). We herein report a case of myeloperoxidase (MPO)-ANCA-associated crescentic glomerulonephritis with normal CRP and elevated PTX3 levels.

Case Report

A 20-year-old woman was admitted to our hospital because of suspected ANCA-associated glomerulonephritis. One month prior to admission, she had an upper respiratory infection from which she recovered in a few days using cold remedies. She had no other medical history. Two weeks after recovery, the patient visited a local hospital complaining of macrohematuria. The laboratory test results showed renal insufficiency with a serum creatinine level of 1.23 mg/dL, proteinuria, and hematuria. Seven days later, her serum creatinine had increased to 1.8 mg/dL, the urinary protein was 3.6 g/gCr, and there were more than 100 red blood cells per high-power field in her urine. She was admitted to another local hospital, but her renal function did not improve with only bed-rest. At that time, her serum MPO-ANCA titer was also elevated. Therefore, she was referred to our hospital.
On admission, her body temperature was 36.6°C, blood pressure was 102/56 mmHg, and pulse rate was 64/min. A general physical examination revealed normal findings. She had anemia with hemoglobin of 11.6 g/dL. Her serum creatinine was 1.61 mg/dL and the creatinine clearance was 36.4 mL/min; however, she had a normal serum CRP level of less than 0.1 mg/dL (Table 1). A serological examination showed a slightly elevated MPO-ANCA at 9.2 U/mL (normal range: <5 U/mL). A chest X-ray showed normal findings, and renal ultrasonography revealed normal kidney size and shape. A kidney biopsy performed on her fourth hospital day showed that 23 out of 32 glomeruli had crescents (eight had cellular crescents and 15 had fibrocellular crescents) and there was no obvious mesangial or endocapillary proliferation (Fig. 1A, B). There was an infiltration of mononuclear cells into the peritubular capillaries and tubulointerstitium (Fig. 1C). Immunofluorescent studies revealed the nonspecific deposition of immunoglobulin G and complement component 3 in the glomeruli. Immunohistochemical staining showed high PTX3 expression in the interstitial inflammatory cells around the glomerular crescents and peri-tubular capillaries (Fig. 1D, E). No characteristic deposits, humps, or foot process effacements were seen in the glomeruli using electron microscopy (Fig. 1F).

The patient was diagnosed with ANCA-associated crescentic glomerulonephritis. Her initial Birmingham vasculitis activity score (7) was 15 (three points for general and 12 points for renal systems), indicating renal-limited vasculitis. The patient was administered oral prednisolone (1 mg/kg/day) after 3 days of intravenous methylprednisolone (500 mg). Her serum creatinine level peaked at 1.9 mg/dL and decreased to 0.9 mg/dL after 4 weeks of treatment. Six months later, her creatinine levels had decreased to 0.74 mg/dL, and the MPO-ANCA titer also returned to the normal limits (0.6 U/mL). The patient’s serum CRP levels remained normal at all times, while her plasma PTX3 level had dropped significantly from 63.53 to 17.12 ng/mL following treatment (Fig. 2).

**Discussion**

We herein reported a thought-provoking case of ANCA-associated crescentic glomerulonephritis with normal serum CRP and elevated plasma PTX3 levels in a young woman. Immunostaining for PTX3 was positive in the interstitial inflammatory cells of the kidney tissue. Her creatinine, MPO-ANCA, and PTX3 levels decreased to normal limits after steroid therapy.

ANCA-associated glomerulonephritis has a high mortality rate and poor kidney prognosis (1-3). A nationwide survey in Japan showed that higher creatinine, advanced age, lung involvement, and higher CRP levels predict a poor prognosis in ANCA-associated crescentic glomerulonephritis (1). In that survey, the serum CRP levels were widely distributed (mean ± standard deviation, 6.2 ± 6.4 mg/dL); however, the details were not described. We also reviewed 35 consecutive cases of ANCA-associated glomerulonephritis from January 2009 to April 2013 in our hospital. The ANCA titers and symptoms classified according to the Birmingham vasculitis activity score (BVAS) were comparable among the CRP quartiles. The patients with the lowest quartile of serum CRP levels were significantly younger than the patients with 2nd and 3rd quartile levels (Table 2). In younger patients, the CRP levels tend to be lower and appear to be unreliable as an inflammatory marker for the early diagnosis of ANCA-associated glomerulonephritis. Our patient’s CRP levels remained within the normal range, whereas the kidney histology revealed severe cellular crescent formation and cell infiltration into the interstitial area.

Previous reports have suggested that some other biomarkers of vasculitis may be more reliable than CRP, such as soluble CD40 ligand, P-selectin, monocyte chemotactic protein 1, B cell-attracting chemokine 1, matrix metalloproteinase-3, tissue inhibitor of metalloproteinases-1, or PTX3 (8-12). CRP is a systemic inflammatory marker protein that is induced by interleukin-6 and is produced in the liver, whereas PTX3 is induced by interleukin-1 or tumor necrotic factor-α and is produced in cells such as macrophages and endothelial cells (8, 9). Although variations in cytokine activation may cause a discrepancy between serum CRP and PTX3 levels, we could not confirm this due to the lack of appropriate samples. A novel mechanism of NETs has been reported as a trigger of vasculitis and ANCA-associated diseases (4, 5, 13). The extrusion of NETs, which are decondensed chromatin of neutrophils, is a novel mechanism of pathogen removal (5) and may trigger
ANCA-associated glomerulonephritis. PTX3 and MPO are structural proteins in NETs (4, 13); this may lead to different roles for CRP and PTX3, particularly in ANCA vasculitis that does not have systemic involvement. The concentration of PTX3 in patients with active vasculitis was higher than those with quiescent vasculitis; how-
ever, the PTX3 levels in chronic systemic inflammatory disease (e.g., systemic lupus erythematosus and rheumatoid arthritis) were not increased even in active phases (8). Furthermore, the production of PTX3 during acute renal allograft rejection (14) and ischemia-reperfusion injury (15) has been demonstrated. Although the detailed mechanism remains unclear, PTX3 may be useful for estimating vascular injury in such cases including those with ANCA-associated disease.

Our patient had normal CRP levels, instead of decreased kidney function, and severe pathological injury associated with MPO-ANCA. PTX3 was elevated in her plasma and expressed in kidney specimens prior to steroid treatment. After the treatment, her PTX3 plasma levels decreased. PTX3 may be a significant marker of activity in ANCA-associated glomerulonephritis, particularly in cases with normal CRP levels. Further studies are necessary to clarify the role of PTX3 in ANCA-associated glomerulonephritis.

The authors state that they have no Conflict of Interest (COI).

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References


Table 2. Distribution of Clinical Characteristics in Patients with ANCA-associated Glomerulonephritis according to Quartiles of Serum C-reactive Protein Levels.

<table>
<thead>
<tr>
<th>Variables</th>
<th>1st Quartile</th>
<th>2nd Quartile</th>
<th>3rd Quartile</th>
<th>4th Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ± 22*</td>
<td>68 ± 11</td>
<td>71 ± 7</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.9 ± 2.4</td>
<td>9.1 ± 2.6</td>
<td>9.4 ± 1.8</td>
<td>9.5 ± 1.1</td>
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<tr>
<td>MPO-ANCA (U/mL)</td>
<td>145.4 ± 184.5</td>
<td>435.1 ± 398.5</td>
<td>685.0 ± 1,055.9</td>
<td>185.3 ± 150.8</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.23 ± 1.85</td>
<td>4.57 ± 3.23</td>
<td>3.12 ± 1.61</td>
<td>2.25 ± 1.95</td>
</tr>
</tbody>
</table>

Variables are given as mean ± SD. A significant difference at the p < 0.05 level was calculated using the Tukey–Kramer HSD test (JMP 7.0.1, SAS Institute, Cary, USA).

* p < 0.05 versus 3rd and 4th quartiles. MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody.
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nous pentraxin-3 limits postischemic acute and chronic kidney in-

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