Antineutrophil Cytoplasmic Autoantibody–Associated Glomerulonephritis in Children

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Abstract. A retrospective investigation was conducted by members of the Japanese Society for Pediatric Nephrology from 1990 to 1997 to define the clinical features and outcome of antineutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis in children. Thirty-four ANCA-seropositive Japanese pediatric patients with biopsy-proven pauci-immune necrotizing crescentic glomerulonephritis were identified. Of these, 3 cases associated with Wegener’s granulomatosis were excluded because of the small sample size. Among the 31 patients studied, 10 had a diagnosis of necrotizing crescentic glomerulonephritis alone and 21 had microscopic polyangiitis. Females predominated (87%), and the median age at onset was 12 yr. Twenty-six patients received treatment with cyclophosphamide and corticosteroids, and five patients received treatment with corticosteroids alone; 84% of patients achieved remission, and 39% of responders relapsed in a median of 24 mo. ANCA titers correlated with response to treatment and disease activity, with some exceptions. Patients were followed for a median of 42 mo (range, 3 to 96 mo). Nine of 31 patients (29.0%) progressed to end-stage renal disease, 6 (19.4%) had reduced renal function, and 15 (48.4%) had normal renal function at the last observation. One patient (3.2%) died from cytomegalovirus infection 3 mo after initiation of therapy. Life-table analysis showed 75% renal survival at 39 mo. Patients who subsequently developed end-stage renal disease (n = 9) had significantly higher average peak serum creatinine levels and more chronic pathologic lesions at diagnosis compared with patients with favorable renal outcome (n = 15). In conclusion, our clinical experience suggests that the clinical disease spectrum of ANCA-associated glomerulonephritis is similar in pediatric and adult patients, but there is a female predominance in children.

Antineutrophil cytoplasmic autoantibodies (ANCA) constitute a family of autoantibodies directed against various components of the neutrophil cytoplasm (1). ANCA first were reported in 1982 by Davies et al. (2), in patients with pauci-immune necrotizing glomerulonephritis with crescents, and now are regarded as a serologic marker for active pauci-immune necrotizing crescentic glomerulonephritis (NCGN), either in the renal-limited form or associated with systemic vasculitis such as Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (3). The association of pauci-immune NCGN with ANCA and the greater availability of these markers have contributed to increased interest and attention given to diagnosis of these diseases. Although an extensive literature on ANCA-associated diseases in adult patients has been published (4,5), studies in children are limited (6).

In this study, we report the results of our analysis of ANCA-associated glomerulonephritis and systemic vasculitis in children in wide geographic areas in Japan during 1990 to 1997 in an attempt to define further the clinical features and outcome of ANCA-associated glomerulonephritis and systemic vasculitis in children.

Materials and Methods

Patients

A retrospective study on Japanese pediatric patients with ANCA-associated glomerulonephritis and systemic vasculitis was conducted in all member hospitals of the Japanese Society for Pediatric Nephrology (JSPN) for the period between January 1990 and December 1997. In January to March 1998, pediatric nephrologists of the member hospitals of JSPN reviewed and selected all patients who renal biopsy specimens showed pauci-immune NCGN and who were seropositive for ANCA. A total of 34 pediatric patients were identified as eligible for the study. “Pauci-immune” was defined as a score of 2+ or lower in staining for any Ig (on a scale of 0 to 4+) observed by immunofluorescence microscopy (4). The period 1990 to 1997 was chosen because ANCA tests became commercially available in Japan in December 1989.

ANCA Analysis

All patients included in this study were positive for ANCA by either indirect immunofluorescence microscopy or enzyme-linked immunosorbent assays (ELISA) for proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA.
Before November 1993, ANCA were analyzed only by IIF with the use of ethanol-fixed normal peripheral blood neutrophils and FITC-conjugated rabbit antihuman IgG (Dako, Copenhagen, Denmark), according to the guidelines of the First International ANCA Workshop (7). Positive reactions were classified into two subsets: perinuclear-staining ANCA (P-ANCA) and cytoplasmic-staining ANCA (C-ANCA). To differentiate P-ANCA from antinuclear antibodies, formalin-fixed neutrophils also were tested. Perinuclear fluorescence in ethanol-fixed neutrophils together with only cytoplasmic fluorescence in formalin-fixed cells was taken to indicate P-ANCA.

Since December 1993, MPO-ANCA and PR3-ANCA also were examined with the use of ELISA kits. The MPO-ANCA ELISA 96-well plate (Nissho Co., Osaka, Japan) was coated with MPO, which was extracted from human neutrophil cytoplasmic α granules by Wieslab AB (Lund, Sweden). Diluted serum (1:20, 200 μl) was added to each well and incubated for 1 h at 25°C. After washing, 200 μl/well diluted alkaline phosphate-conjugated anti-human IgG was added and left for 1 h at room temperature. After washing, substrate was added and the optical density was read at 405 nm. Titers of MPO-ANCA was calculated with the use of a standard curve obtained from three standards (10, 100, and 1000 EU). The cutoff point was determined with the use of 210 samples from adults, including 40 healthy control subjects. The normal MPO-ANCA titer was below 10 EU. The intra- and interassay coefficients of variability (CV) were 2.5 to 5.9% and 5.6 to 8.1%, respectively (8). The PR3-ANCA ELISA plate was coated with PR3 extracted from human neutrophil cytoplasmic α granules (BioCarb Diagnostics, Lund, Sweden). The procedures were similar to those for MPO-ANCA ELISA. The normal PR3-ANCA titer was below 10 EU. The intra- and interassay CV were 1.2 to 4.4% and 3.3 to 6.5%, respectively (9). Two medical schools (Dr. Y. Arimura; Kyorin University, School of Medicine, and Dr. K. Kaneko, Juntendo University, School of Medicine) and one private laboratory participated in ANCA analyses.

**Clinical Diagnosis**

Patients with ANCA-associated glomerulonephritis and systemic vasculitides were classified into WG and MPA according to the definitions of the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides (3). Nasal septal perforation and/or saddle-nose deformity were regarded as definite upper-respiratory tract involvement of WG. Chest x-ray and/or CT findings showing the presence of nodules and/or nodular infiltrates that have a tendency to cavitate were considered as lower-respiratory tract involvement of WG. The absence of these granulomatous inflammations is taken to indicate MPA. Other small vessel vasculitis diseases such as systemic lupus erythematosus, cryoglobulinemia, Henoch-Schönlein purpura, rheumatoid arthritis, hepatitis-related small vessel vasculitis, drug-induced vasculitis, and other identifiable conditions were excluded from the study, as were patients with Goodpasture’s syndrome.

**Organ Involvement**

Renal involvement was inferred when hematuria or proteinuria or both were present on urinalysis with or without renal insufficiency or hypertension. All of the eligible patients had histologically verified renal involvement. Renal biopsy specimens for light and immunofluorescence microscopy were processed by established methods. All renal biopsies were evaluated as follows (10). Glomerular involvement was expressed as a percentage of the glomeruli affected with cellular crescents with or without necrosis, fibrocellular crescents, fibrous crescents, and global sclerosis. Interstitial lesions, such as interstitial inflammation, interstitial fibrosis, and tubular atrophy, were graded semiquantitatively on a scale of 0 to 3 (absent, mild, moderate, and severe, respectively).

**Definitions**

Hematuria was graded as “gross” or “positive” (five or more red blood cells per high power field) (12). Proteinuria was measured by the pyrogallol red method and evaluated by 24-h quantitative measurement. The nephrotic syndrome was defined as the presence of proteinuria (≥40 mg/g per m²) and serum albumin <2.5 g/dl with or without edema (12). Hypertension was defined as a systolic or diastolic BP greater than the age-specific 95th percentile (13). Clinical syndromes were modified from the World Health Organization clinical syndromes (14). End-stage renal disease (ESRD) was defined as when a patient required chronic dialysis or renal transplantation.

**Criteria for Treatment Response**

Criteria for evaluating treatment responses were based on the report by Nachman *et al.* (15).

- Remission was defined as stabilization or improvement of renal function, resolution of hematuria, and resolution of extrarenal manifestations of systemic vasculitis. Persistence of proteinuria was not considered indicative of persistence of disease activity.
- Remission on therapy was defined as the achievement of remission while still receiving immunosuppressive medication or corticosteroids given at a dose greater than 7.5 mg/d of prednisone or its equivalent.
- Treatment resistance was defined as (1) progressive decline in renal function with the persistence of an active urine sediment or (2) persistence or new appearance of any extrarenal manifestation of vasculitis despite immunosuppressive therapy.
- Relapse was defined as occurrence of at least one of the following: (1) rapid rise in serum creatinine concentration accompanied by an active urine sediment; (2) a renal biopsy demonstrating active necrosis or crescent formation; (3) hemoptysis, pulmonary hemorrhage, or new or expanding nodules without evidence of infection; (4) active vasculitis of the respiratory or gastrointestinal tracts as demonstrated by endoscopy with biopsy; (5) iritis or uveitis; (6) new mononeuritis multiplex; or (7) necrotizing vasculitis identified by biopsy of any tissue.

**Statistical Analyses**

Data are presented as mean ± SD, unless otherwise indicated. Statistical analysis was performed by the $\chi^2$ test and nonparametric Mann-Whitney $U$ test, as appropriate. The Kaplan-Meier method was
used to estimate renal (ESRD-free) survival. The starting date of the survival curve was the date on which immunosuppressive treatments were instituted. The end point was the date of initiation of maintenance dialysis. When death occurred within 3 mo after treatment was initiated without recovery of renal function, the patient was censored for the kidney survival analysis. Differences between survival curves were tested with the log-rank test. Statistical calculations were computed with the use of Statview 5.0 (Abacus Concepts, Berkeley, CA). The level of significance was 0.05. All reported $P$ values were two-tailed.

Results

Clinical Diagnosis

By definition, all 34 eligible patients had biopsy-proven pauci-immune NCGN and were seropositive for ANCA. Ten patients presented with NCGN alone. Clinical examinations suggested that 21 patients had MPA with renal and extrarenal organ system vasculitis; the remaining 3 patients had WG. Churg-Strauss syndrome was not found in this study. Because the number of patients with WG was too small to analyze the clinical features and outcome, the three patients with WG were excluded from the present study.

Demographic Characteristics

The mean age at onset of 31 patients with NCGN or MPA was 11.9 ± 2.9 yr (median, 12.0 yr; range, 5 to 17 yr). The study group consisted of 4 males (13%) and 27 females (87%), corresponding to a ratio of 1:6.8 (Figure 1).

ANCA Serology

Twenty-eight of 31 patients (90.3%) with NCGN or MPA had MPO-ANCA/P-ANCA, and the remaining 3 (9.7%) had PR3-ANCA/C-ANCA.

Clinical Manifestations at Onset

Ten patients (7 of 10 patients with NCGN and 3 of 21 patients with MPA) were asymptotically detected by a national urine screening program for hematuria and proteinuria in school children, which has been conducted since 1973 by the Ministry of Education in Japan (16). The remaining 21 patients presented with the following symptoms: macroscopic hematuria in 9, hemoptysis in 7, abdominal pain in 2, arthralgias in 2, and purpura in 1.

The onset of illness might have a seasonal variation in 21 symptomatic patients. The proportions of symptom onset in winter (December to February), spring (March to May), summer (June to August), and autumn (September to November) were 38.1%, 33.3%, 9.5%, and 19.1%, respectively. Although there were no significant differences from the expected value of 25%, the percentages of patients with symptom onset in winter and spring were higher than expected, whereas that in summer was lower than expected (Figure 2).

Clinical Features

The distribution of organ system involvement at presentation is shown in Table 1.

Three of 10 patients with NCGN and 18 of 21 patients with MPA had prodromal flu-like symptoms usually consisting of malaise, fever, anorexia, and weight loss. These systemic symptoms appeared within days to weeks before the onset of overt vasculitic or nephritic disease.

Hemoptysis and pulmonary hemorrhage were the predominant manifestations and often the presenting symptoms in patients with MPA. Eleven of 21 patients with MPA had pulmonary hemorrhage. Purpuric rash, arthralgias, and arthritis involving both large and small joints, and abdominal pain with or without gastrointestinal bleeding also were observed frequently in patients with MPA. Sinusitis was present in two patients. Ocular involvements included bilateral conjunctivitis and episcleritis in one patient each. Although seizures were present in one patient, peripheral neuropathy was not observed in patients who were examined in the present study. All three patients who had MPA and who were asymptotically detected by urine screening developed pulmonary hemorrhage in a mean interval of 13.7 mo after detection of urinary abnormalities. None of the 10 patients who received a diagnosis of NCGN developed extrarenal vasculitic diseases during the follow-up period (median, 3.9 yr; range, 1.3 to 4.9 yr).

Figure 1. Age at onset and gender of 31 patients with antineutrophil cytoplasmic autoantibody (ANCA)-associated necrotizing crescentic glomerulonephritis (NCGN) or microscopic polyangiitis (MPA). □, male; ■, female.

Figure 2. Seasonal variation in the onset of first symptoms.
The nephrotic syndrome was present in six patients. The mean serum creatinine value was 3.6 mg/dl (range, 0.6 to 14.2 mg/dl). Seven patients had renal failure that required dialysis during diagnostic examinations and initiation of therapy. Hypertension was noted in nine patients. Of 31 patients, 21 presented with rapidly progressive nephritic syndrome, 4 presented with chronic nephritic syndrome, and the remaining 6 had acute exacerbation of nephritis during a median interval of 23 mo (range, 8 to 35 mo) from onset. The histologic data of renal biopsies at diagnosis are summarized in Table 2. The mean percentage of glomeruli with cellular, fibrocellular, and fibrous crescents was 63.5 ± 24.4% (range, 13 to 100%); crescents were found in more than 50% of glomeruli in 22 of 31 biopsy specimens. Extraglomerular vasculitis was present in four cases.

### Response to Therapy and Relapses

Treatment protocols were variable among patients and depended on the decision of the attending pediatric nephrologists. However, patients were treated basically with the following initial protocols. Twenty-four patients received initial treatment with oral prednisone plus oral cyclophosphamide. Of these 24 patients, 10 were given pulse methylprednisolone (15 to 30 mg/kg body wt) and 6 were given plasma exchange before the beginning of the initial therapy. Of the others (n = 7), five were given pulse methylprednisolone, followed by prednisone alone, and two received six monthly intravenous doses of cyclophosphamide in addition to prednisone. Prednisone was given at a dose of 1 to 2 mg/kg for the first 4 to 8 wk, followed by a tapering schedule over the next months. Oral cyclophosphamide was given at a starting dose of 1 to 2 mg/kg for 8 to 12 wk. This dose was adjusted by the pediatric nephrologists according to the patient’s leukocyte count.

On the basis of the criteria for treatment response, 26 of 31 patients (83.9%) responded and remitted, 10 of whom were in remission on therapy. Five patients were considered to be treatment resistant (Figure 3). Dialysis was required in the early stage in seven patients and was discontinued subsequently in three patients as a result of improved renal function.

Ten patients (38.5% of responders) experienced a relapse during diminution of immunosuppressive treatment or at various intervals after stopping treatment (Figure 3). The mean interval between initiation of therapy and relapse was 29.7 ± 22.7 mo (median, 24 mo; range, 6 to 80 mo).

### Changes in ANCA Levels after Initiation of Therapy

Repetitive serum samples were available from 22 patients for measurement of ANCA titers. The titers of MPO-ANCA, determined by ELISA, decreased to the normal range on treatment in 17 patients, accompanied by disease quiescence. Five of 17 patients experienced subsequent relapses together with reappearance of ANCA. Conversely, five patients had persistent positive ANCA titers during treatment despite regression of clinical signs. Only one of the five patients relapsed 18 mo after the initiation of therapy, and the remaining four had long-standing quiescence of clinical disease during the follow-up period (median, 21 mo; range, 19 to 84 mo).

### Outcomes of Patients

Patients were followed for a mean of 45.0 ± 26.9 mo (median, 42 mo; range, 3 to 96 mo). The outcomes of 31 patients are shown in Figure 3. Nine of 31 patients (29.0%) progressed to ESRD; of these 9 patients, 4 required dialysis

### Table 1. Distribution of organ system involvement in 31 pediatric patients with NCGN or MPA

<table>
<thead>
<tr>
<th>Organ System Involvement</th>
<th>NCGN (n = 10)</th>
<th>MPA (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Renal</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ocular</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

a NCGN, necrotizing crescent glomerulonephritis; MPA, microscopic polyangiitis.

### Table 2. Histologic findings of renal biopsies at diagnosis (n = 31)

<table>
<thead>
<tr>
<th>Normal Glomeruli (%)</th>
<th>Cellular Crescent (%)</th>
<th>Fibrocellular Crescent (%)</th>
<th>Fibrous Crescent (%)</th>
<th>Global Sclerosis (%)</th>
<th>Tubulointerstitial Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.3 ± 23.7 (0–82)</td>
<td>29.5 ± 24.1 (0–91)</td>
<td>17.2 ± 14.8 (0–48)</td>
<td>16.7 ± 22.8 (0–90)</td>
<td>11.2 ± 12.3 (0–38)</td>
<td>Interstitial Inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interstitial Fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tubular Atrophy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.4 ± 0.5 (1–2)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1 ± 0.8 (0–3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7 ± 0.8 (0–2)</td>
</tr>
</tbody>
</table>

a Results are expressed as mean ± SD (range).

b Percentage of total number of glomeruli.

c Semiquantitatively graded on a scale of 0 to 3.
during the initial phase of therapy and did not recover renal function, 3 progressed to ESRD with relapse episodes, and the remaining 2 progressed to ESRD without active disease or relapse. ESRD was developed in these individuals in a median of 10 mo (range, 1 to 61 mo) after the initiation of therapy. Six patients (19.4%) had reduced renal function (mean serum creatinine value, 2.4 ± 1.7 mg/dl; range, 1.4 to 5.8 mg/dl) at the last observation. One patient (3.2%) died as a result of cytomegalovirus infection at 3 mo after the start of therapy. There was no disease-related death in this study. The remaining 15 patients (48.4%) had normal renal function at the last observation.

Renal Survival and Prognostic Factors for Renal Survival

By life-table analysis, unadjusted renal survival rates for the entire cohort were 0.87 at 6 mo and 0.80 at 12 mo, with 75% renal survival at 39 mo.

To elucidate factors that contributed to renal outcome, patients were categorized into one group that developed ESRD (n = 9) and another group with normal renal function (n = 15), and clinical and pathologic features at the time of diagnosis were compared (Table 3). Patients who developed ESRD had significantly higher average peak serum creatinine levels and more chronic glomerular lesions, such as fibrous crescent and global sclerosis, compared with patients with favorable renal outcome. Patients who developed ESRD tended to have a longer interval from onset to diagnosis and lower frequency of detection by urine screening, although the differences were not significant. There were no differences in age at onset (data not shown), amount of proteinuria at diagnosis, and acute glomerular lesions between the two groups.

As shown in Figures 4 and 5, patients who presented with serum creatinine of less than 2.5 mg/dl had a significantly better renal survival rate compared with those with higher levels (P < 0.001). Likewise, chronic glomerular lesions were a significant contributing factor for renal survival (P = 0.003).

Discussion

We found 31 pediatric patients with ANCA-associated NCGN or MPA in a multicenter survey covering all member hospitals of JSPN. The purpose of this retrospective study was to analyze the clinical features and outcome in pediatric patients and to compare the clinical spectrum of ANCA-associated diseases in children with that in adults. Unfortunately, an analysis of pediatric patients with WG was not possible in the present study because the number of patients with WG was too small to analyze the clinical features and outcome. In the present study, WG was excluded in one PR3-ANCA–positive patient with chronic sinusitis on the basis of other diagnostic features, although WG cannot be excluded in the patients with chronic sinusitis. The reason for a low frequency of WG in our pediatric population is unclear, but a low frequency of WG among adult patients with ANCA-associated glomerulonephritis and systemic vasculitis also was reported in Japan (17).

The present study showed a clear female predominance of ANCA-associated NCGN or MPA in children with a female: male ratio of 6.8:1. This is opposite to the findings reported for adult patients, which showed a slight preponderance of males in most series (15,18,19). Although the reason for this marked gender difference is unclear, a female predominance also was

<table>
<thead>
<tr>
<th>Groups</th>
<th>Onset to Diagnosis (Mo)</th>
<th>% of Patients Detected by Urine Screening</th>
<th>Serum Creatinine (mg/dl)</th>
<th>Urine Protein (g/m² per d)</th>
<th>Acute Glomerular Lesions (%)</th>
<th>Chronic Glomerular Lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD (N = 9)</td>
<td>3.8 ± 3.1</td>
<td>11.1</td>
<td>7.0 ± 4.7</td>
<td>2.5 ± 1.9</td>
<td>33.7 ± 7.8</td>
<td>52.6 ± 25.0</td>
</tr>
<tr>
<td>Normal (N = 15)</td>
<td>1.5 ± 0.9</td>
<td>53.3</td>
<td>1.3 ± 0.9</td>
<td>1.2 ± 0.6</td>
<td>52.7 ± 25.4</td>
<td>14.1 ± 13.5</td>
</tr>
<tr>
<td>P value&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.052</td>
<td>0.080</td>
<td>&lt;0.001</td>
<td>0.104</td>
<td>0.153</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are expressed as mean ± SD. ESRD and Normal indicate patients who developed ESRD and who had normal renal function during follow-up, respectively.

<sup>b</sup> Values were obtained from each patient at the time of diagnosis.

<sup>c</sup> Acute glomerular lesions include cellular and fibrocellular crescent, and chronic glomerular lesions include fibrous crescent and global sclerosis, respectively. Data indicate the percentage of total number of glomeruli.

<sup>d</sup> Comparison between groups was done by Mann-Whitney U test for continuous variables and Fisher’s exact test for a categorical variable.
noted in another study of children (20). ANCA-associated NCGN or MPA is considered to be a disease of elderly or middle-aged people (15,18,19), although patients of any age may develop this disease. The age at onset in pediatric patients who were examined in this study averaged 11.9 ± 2.9 yr, and the incidence was highest in the early adolescent years. A similar result also was reported in another study in children (20). Thus, ANCA-associated NCGN or MPA in children affects predominantly early adolescent females.

Twenty-eight of 31 patients (90.3%) with NCGN or MPA had MPO-ANCA/P-ANCA, and the remaining 3 patients (9.7%) had PR3-ANCA/C-ANCA. This predominance of MPO-ANCA/P-ANCA patients would be expected in a study population in which patients with WG are excluded. However, the prevalence of MPO-ANCA/P-ANCA was higher in our patients with NCGN or MPA than in the series presented by Hogan et al. (21), who found that 64% of patients had MPO-ANCA/P-ANCA in a similar subject population. Because a high prevalence of MPO-ANCA/P-ANCA in Japanese patients has been reported (22), our findings may reflect the racial difference between Japanese and Caucasians.

There was a higher incidence of symptom onset in winter and early spring and a lower incidence in summer, which are in accordance with the findings in adults (18,23). Hemoptysis and pulmonary hemorrhage were the predominant manifestations and often the presenting symptoms in pediatric patients with MPA in this study, also in accordance with the findings in adults (11,15). Purpuric rash, joint symptoms, and abdominal pain also were observed frequently in pediatric patients with MPA. Because Henoch-Schönlein purpura typically is characterized by these symptoms and is much more frequent in children than in adults, differential diagnosis for pediatric patients with MPA should include Henoch-Schönlein purpura. In fact, pediatric patients with MPA, who initially were considered as having Henoch-Schönlein purpura, were observed in this study as well as in the literature (24,25). Because MPA in pediatric patients can clinically mimic Henoch-Schönlein purpura, appropriate studies, including ANCA titers and a kidney biopsy with immunofluorescence microscopy studies, should be performed to confirm the diagnosis in children.

Clinical improvement was seen in 84% of the patients, and 39% of the responders experienced a relapse in our study. These results corresponded well with the data of Nachman et al. (15), who found a remission rate of 77% and a relapse rate of 29% in a similar population. The present study was retrospective, and therapeutic regimens among patients were heterogeneous and depended on the decision of the attending pediatric nephrologists. Therefore, the relation between treatment and outcome could not be evaluated fully in this study. However, the effects of treatment on morbidity, relapse, and mortality in patients with ANCA-associated NCGN or MPA have been analyzed in prospective studies published elsewhere (15,21). These studies pointed to the beneficial effects of cyclophosphamide over corticosteroids alone on the remission rate, risk of relapse, and patient survival but cautioned an association with severe and potentially lethal side effects (4). Although the optimal duration of cyclophosphamide therapy has not been determined in children, the treatment protocol that has been established in adult patients (26,27) can be extrapolated to pediatric patients with ANCA-associated NCGN or MPA.

The value of ANCA titers for disease monitoring has been the subject of several investigations. In our study, the titers of ANCA decreased to normal range on treatment in 17 of 22 patients (n = 18; solid line) or higher (n = 13; dashed line) than 2.5 mg/dl at diagnosis. Numbers in the figure represent patients at risk at each time point.

**Figure 4.** Renal survival in patients with serum creatinine levels lower (n = 18; solid line) or higher (n = 13; dashed line) than 2.5 mg/dl at diagnosis. Numbers in the figure represent patients at risk at each time point.

**Figure 5.** Renal survival in patients with chronic glomerular lesions such as fibrous crescent and global sclerosis in fewer (n = 15; solid line) or more (n = 16; dashed line) than 25% of total number of glomeruli at diagnosis. Numbers in the figure represent patients at risk at each time point.

**Figure 6.** Renal survival in patients with serum creatinine levels lower (n = 18; solid line) or higher (n = 13; dashed line) than 2.5 mg/dl at diagnosis. Numbers in the figure represent patients at risk at each time point.
The patients who developed ESRD had significantly higher average peak serum creatinine levels and more chronic lesions, such as fibrous crescent and global sclerosis, at the time of initiation of therapy compared with the patients with favorable renal outcome. Patients who did not respond to initial treatment and were unable to discontinue dialysis had severe irreversible damage to the renal parenchyma. In patients who progressed to ESRD without signs of relapse, the mechanism of underlying renal function loss has been postulated to be hyperfiltration of remnant glomeruli that survive renal vasculitic inflammation (10). Thus, these results emphasize the importance of prompt diagnosis and institution of therapy in pediatric patients, as has already been stressed in adult patients (15).

Although rapidly progressive glomerulonephritis frequently presents in ANCA-associated glomerulonephritis, asymptomatic hematuria with or without minimal proteinuria also is commonly observed (4). In fact, six patients who initially presented with asymptomatic hematuria with or without proteinuria subsequently developed acute exacerbation of nephritis in a median interval of 23 mo. Therefore, when symptoms that suggest systemic vasculitis develop in the clinical course of initially asymptomatic patients, careful clinical and laboratory analyses including ANCA test should be performed, as have been suggested in adult patients (28).

The long time lapse between symptom onset and diagnosis clearly illustrates the difficulty faced in ANCA-associated NCGN or MPA when a single organ is involved. Sometimes, glomerulonephritis progressed by indolent flares before MPA or NCGN was recognized and immunosuppressive therapy was instituted. In our clinical setting, a urine screening program for hematuria and proteinuria in school children, which has been conducted by the Ministry of Education in Japan (16), may contribute to the early diagnosis and initiation of therapy of this disease. In fact, a total of 10 asymptomatic patients (7 of 10 patients with NCGN and 3 of 21 patients with MPA) were detected by this program. Moreover, patients who had been detected by this urine screening system tended to have a favorable renal outcome. Similar beneficial effects of a urine screening program in school children has been reported for childhood IgA nephropathy (29).

Finally, only one patient (3.2%) died from cytomegalovirus infection at 3 mo after the start of therapy, presumably as a consequence of the immunosuppressive therapy. This is lower than the results presented by Hogan et al. (21), who found death in 12 of 97 patients (12.4%) with ANCA-associated NCGN or MPA. A low mortality rate also was noted in another study of children (20). In the present study, all 11 patients who had pulmonary hemorrhage survived. However, Hogan et al. (21) reported that pulmonary hemorrhage was a strong independent risk factor for patient death in their cohort of ANCA-associated NCGN or MPA. Death can result not only from injury caused by the vasculitis but also from infections as a consequence of treatment (19). Massive pulmonary hemorrhage and infection are the most life-threatening complications of ANCA-associated disease in pediatric and adult patients.

In conclusion, although only 31 pediatric patients with ANCA-associated NCGN or MPA were analyzed in the present study and thus only limited conclusions can be drawn, our clinical experience suggests that the clinical disease spectrum is similar in pediatric and adult patients but that there is a female predominance in children. Prompt diagnosis and institution of therapy are important for the prognosis of pediatric patients with ANCA-associated diseases, as has already been stressed in adult patients.

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