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Clinical Features and Outcomes in Children with Antineutrophil Cytoplasmic Autoantibody–Positive Glomerulonephritis Associated with Propylthiouracil Treatment

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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 outcomes in children with antineutrophil cytoplasmic autoantibody (ANCA)–positive glomerulonephritis associated with propylthiouracil treatment. Seven Japanese pediatric patients who had myeloperoxidase-specific ANCA-positive biopsy-proven pauci-immune necrotizing crescentic glomerulonephritis associated with propylthiouracil administration were entered in the study. Three patients had nephritis alone, and four had nephritis and extrarenal organ system vasculitis. Females predominated, and the mean age at onset was 14 yr. Propylthiouracil was reduced or discontinued in all patients and was switched to methimazole in three patients. For the treatment of nephritis, five patients received corticosteroids; three had pulse methylprednisolone, one had plasma exchange, and one had plasma exchange and pulse methylprednisolone before initiating oral prednisolone. The remaining two patients received cyclophosphamide and corticosteroids, one of whom had pulse methylprednisolone before initiating oral prednisolone and cyclophosphamide. All patients achieved remission. In general, ANCA titers correlated with the response to treatment and disease activity, with some exceptions. No patient progressed to end-stage renal disease, renal dysfunction, or death during the follow-up period (58 ± 25 mo; range, 32 to 108 mo). All but one patient remained euthyroid. In conclusion, this experience suggests that the clinical disease spectrum of ANCA-positive disease associated with propylthiouracil treatment is similar in pediatric and adult patients and that the overall prognosis may be better than that in the non–drug-induced ANCA-positive disease.

Circulating antineutrophil cytoplasmic autoantibody (ANCA) was first reported in 1982 by Davies *et al.* (1) in patients with pauci-immune necrotizing glomerulonephritis with crescents, and is now regarded as a serologic marker for active pauci-immune necrotizing crescentic glomerulonephritis (NCGN) and systemic vasculitis such as Wegener's granulomatosis, microscopic polyangiitis (MPA), and Churg-Strauss syndrome (2). Furthermore, ANCA is detected in a number of other vasculitic diseases, including drug-induced systemic vasculitis.

Propylthiouracil (PTU) has been known to induce ANCA-positive vasculitis in adult patients since the reports of Stankus *et al.* (3) and Dolman *et al.* (4). We first described a teenage girl with ANCA-positive NCGN associated with PTU treatment in 1993 (5). Although 15 case reports and literature review on PTU-induced ANCA-positive NCGN or NCGN with extrarenal organ system vasculitis have been published (6–17), only 4 cases, including 2 in this study, have been reported in children (5,18,19).

In this study, we attempted to define further the clinical features and outcome of ANCA-positive glomerulonephritis and systemic vasculitis associated with antithyroid drug treatment in children. We report the results of our analysis of seven cases identified in a nationwide survey covering wide geographic areas of Japan during 1990 to 1997.

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Materials and Methods

Patients

A retrospective study on Japanese pediatric patients with ANCA-positive glomerulonephritis and systemic vasculitis associated/unassociated with antithyroid drug treatment was conducted in all member hospitals of the Japanese Society for Pediatric Nephrology for the

period between January 1990 and December 1997. In January to March 1998, pediatric nephrologists of the facilities reviewed and selected patients who had renal biopsy specimens showing pauci-immune NCGN and who were seropositive for ANCA. Thirty-one pediatric patients with non–drug-induced ANCA-positive NCGN or MPA were analyzed in our previous report (20). In the present study, a total of seven pediatric patients who were administered PTU for Graves' disease were identified as eligible. "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 (21). The period 1990 to 1997 was chosen because ANCA test kits became commercially available in Japan in December 1989.

Other small-vessel vasculitic diseases, such as systemic lupus erythematosus, cryoglobulinemia, Henoch-Schönlein purpura, hepatitis-related small-vessel vasculitis, vasculitis, and other identifiable conditions induced by medications other than antithyroid drugs, were excluded from the study, as were patients with Goodpasture's syndrome.

ANCA Analysis

All sera of patients included in this study were screened for ANCA by indirect immunofluorescence microscopy using normal peripheral blood neutrophils, according to the guidelines of the First International ANCA Workshop (22).

ANCA were also measured using enzyme-linked immunosorbent assay (ELISA) kits for myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA, as previously reported (20). Briefly, the MPO-ANCA ELISA 96-well plate (Nissoh Co., Osaka, Japan) was coated with MPO, which was extracted from human neutrophil cytoplasmic α-granule by Wieslab (Lund, Sweden). Two hundred microliters of 1:20 diluted serum was added to each well and incubated for 1 h at 25°C. After washing, 200 μl/well of diluted alkaline phosphatase-conjugate 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. Titer of MPO-ANCA was calculated using a standard curve obtained from three standards (10, 100, and 1000 ELISA units [EU]). The normal MPO-ANCA titer is below 10 EU/ml. The intra-assay and interassay coefficients of variability (CV) were 2.5% to 5.9% and 5.6% to 8.1%, respectively (23). The PR3-ANCA ELISA plate was coated with PR3 extracted from human neutrophil cytoplasmic α-granule (BioCarb Diagnostics, Lund, Sweden). The procedures were similar to those for MPO-ANCA ELISA. The normal PR3-ANCA titer is below 10 EU/ml. The intra-assay and interassay CV were 1.2% to 4.4% and 3.3% to 6.5%, respectively (24). The ANCA assays were performed in one facility (Dr. Y. Arimura; Kyorin University, School of Medicine).

Antithyroid Antibody Assays

Serum antibodies to thyroid peroxidase and thyroglobulin were measured with commercial RIA kits (RSR Limited, Cardiff, UK) using purified thyroid peroxidase and thyroglobulin, respectively. The detection limit for both was 0.3 U/ml. The intra-assay and interassay CV of antithyroid peroxidase antibody were 2.0% to 3.2% and 3.5% to 5.2%, respectively (25). The intra-assay and interassay CV of antithyroglobulin were 3.3% to 4.0% and 4.1% to 5.7%, respectively (25).

Organ Involvement

Renal involvement was inferred when hematuria, 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 (26). 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).

The presence of extrarenal manifestations of vasculitis was diagnosed as previously reported (20). Systemic involvement included fever, general malaise, and weight loss. Pulmonary involvement was defined by the presence of hemoptysis, pulmonary hemorrhage, respiratory failure, or radiographic infiltrations without evidence of infection. Upper respiratory tract involvement was defined as long-standing sinusitis or otitis media despite antibiotic and anti-allergy therapies, or the presence of ulcers in the nasal passage with or without epistaxis. Musculoskeletal involvements included arthralgias, arthritis, myalgia, and muscle weakness. Cutaneous disease was defined by a characteristic palpable purpuric rash with or without ulcerations and/or pathologically confirmed leukocytoclastic angiitis. Gastrointestinal vasculitis was presumed when abdominal pain and/or gastrointestinal bleeding was present. Neurologic involvement included seizures or multifocal neural deficit (mononeuritis multiplex). Ocular disease was defined by episcleritis, keratitis, uveitis, and retinal vasculitis.

Definitions

Hematuria was graded as "gross" or "positive" (five or more red blood cells per high-power fields) (27). Proteinuria was measured by the pyrogallol red method and evaluated by 24-h quantitative measurement. Creatinine clearance (Ccr) was calculated as follows: Ccr (ml/min per 1.73 m^2) = ([Urine creatinine (mg/dl) $\times$ urine volume (ml/d)]/[serum creatinine (mg/dl) $\times$ 1440]) $\times$ (1.73/body surface area [m^2]). Hypertension was defined as a systolic or diastolic BP greater than the age-specific 95th percentile based on the Pediatric Task Force Recommendation (28). Clinical syndromes were modified from the World Health Organization clinical syndromes (29). End-stage renal disease (ESRD) was defined when a patient required chronic dialysis or renal transplantation. A state of euthyroidism was defined when clinical symptoms associated with hyperthyroidism disappeared and levels of thyroxine, triiodothyronine, and thyroid-stimulating hormone were within normal ranges.

Criteria for Treatment Response

Criteria for evaluating treatment responses in patients with ANCA-positive glomerulonephritis and systemic vasculitis were based on the report by Nachman *et al.* (30).

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 corticosteroid at a dose greater than 7.5 mg/d prednisolone or its equivalent. Treatment resistance was defined as (*1*) progressive decline in renal function with the presence of an active urine sediment or (*2*) persistence or emergence of any extrarenal manifestation of vasculitis despite immunosuppressive therapy.

Relapse of nephritis was defined as occurrence of at least one of the following: (*1*) rapid rise in serum creatinine concentration accompa-

nied 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; and (*7*) necrotizing vasculitis identified by biopsy of any tissue.

Statistical Analyses

Data are presented as mean ± SD, unless otherwise indicated. Statistical analyses were performed by the χ^2 test and nonparametric Mann-Whitney *U* test, as appropriate. Statistical calculations were computed using Statview 5.0 (Abacus Concepts, Berkeley, CA). The level of significance was 0.05. All reported *P* values were two-tailed.

Results

Demographic Characteristics and Clinical Diagnosis

By definition, all seven eligible patients had biopsy-proven pauci-immune NCGN and were seropositive for ANCA. The study group consisted of 1 male and 6 females. The mean age at onset was 14.0 ± 1.8 yr (range, 11 to 16 yr). Three patients presented with NCGN alone (patients 1 to 3), and four patients had NCGN with extrarenal organ system vasculitis (patients 4 to 7; Table 1).

Clinical Manifestations at Onset

Two of seven patients were asymptomatically detected by the national urine screening program for hematuria and proteinuria in school children, which has been conducted since 1973 by the Ministry of Education (31). Presenting symptoms of the remaining five patients are shown in Table 1. No patient had struma.

Clinical Features

The distribution of organ system involvement is shown in Table 1. All patients had clinical evidence of renal disease and biopsy-proven pauci-immune glomerulonephritis. One patient presented with rapidly progressive nephritic syndrome and hypertension (patient 4). Three of seven patients had prodromal flu-like symptoms, including fever and malaise. These systemic symptoms appeared within 2 mo before the onset of overt vasculitic or nephritic disease.

Among four patients with ANCA-positive NCGN and extrarenal organ system vasculitis, three had pulmonary hemorrhage, two had purpuric rash, and two had arthralgia and arthritis involving both large and small joints. Ocular involvement was observed in one patient. No seizure or peripheral neuropathy was observed in patients examined in the present study. None of the three patients whose diagnosis was NCGN alone developed extrarenal vasculitic disease during the fol-

Table 1. Clinical findings of seven ANCA-positive patients with NCGN or NCGN with extrarenal organ system vasculitis associated with PTU treatment[a]

Patient	Age/Gender (yr)	Clinical Manifestations at Onset[b]	Organ System Involvement	Duration of PTU Therapy (mo)	Antithyroid Drug	Therapy	Response to Therapy[c]
1	16/F	None	R	48	PTU reduced	PE + PSL	Remission (46 mo)[d]
2	11/M	None	R	24	PTU discontinued	PE + mPSL + PSL	Remission on therapy
3	15/F	Erythema	R	42	PTU discontinued	mPSL + PSL	Remission (10 mo)
4	14/F	Macrohematuria Edema Hypertension	R,S,P,C	3	PTU discontinued → MMI	mPSL + PSL	Remission (62 mo)
5	16/F	Conjunctivitis Arthralgia	R,S,P,M, O	21	PTU discontinued → MMI	mPSL + PSL	Remission (1 mo)
6	13/F	Hemoptysis	R,S,P	43	PTU discontinued → MMI	mPSL + PSL + CPA	Remission (28 mo)
7	13/F	Purpura Arthralgia	R,C,M	60	PTU discontinued	PSL + CPA	Remission (33 mo)

[a] ANCA, antineutrophil cytoplasmic autoantibody; NCGN, necrotizing crescentic glomerulonephritis; PTU, propylthiouracil; R, renal involvement; S, systemic involvement; P, pulmonary involvement; C, cutaneous involvement; M, musculoskeletal involvement; O, ocular involvement; MMI, methimazole; PE, plasma exchange; PSL, oral prednisolone; mPSL, pulse methylprednisolone; CPA, oral cyclophosphamide.

[b] None, two patients were asymptomatically detected by a national urine screening program.

[c] See criteria for treatment response in Materials and Methods section.

[d] Duration of remission after stopping immunosuppressive treatment.

low-up period (patient 1, 108 mo; patient 2, 62 mo; patient 3, 41 mo; Table 1).

Antithyroid Drugs

The mean period of PTU administration was 37 ± 18 mo (range, 3 to 60 mo). PTU was reduced in one patient (patient 1) and discontinued in 6 patients. Three of the six patients were switched from PTU to methimazole (MMI), and the remaining three received no antithyroid drug during the follow-up period (51 ± 14 mo; range, 32 to 65 mo; Table 1).

ANCA Serology

All seven patients in this study had both perinuclear pattern (P)-ANCA and MPO-ANCA, and no patient had cytoplasmic pattern (C)-ANCA or PR3-ANCA. The titers of MPO-ANCA are shown in Table 2.

Laboratory Findings

The laboratory data at the time of diagnosis are shown in Table 2. Hematuria was observed in all patients. The mean protein excretion was 0.7 ± 0.5 g/m^2 per d. One patient (patient 4) had a high serum level of creatinine (3.8 mg/dl). Median Ccr was 90 ml/min per 1.73 m^2 (range, 29 to 130 ml/min per 1.73 m^2). Antithyroid peroxidase and antithyroglobulin antibodies were detected by RIA assays, each in six patients. No significant relationship was detected between MPO-ANCA titer and titer of each of the antithyroid antibody titers (data not shown).

Renal Biopsy Findings

The histologic data of the renal biopsies at diagnosis are summarized in Table 3. The mean percentage of glomeruli with cellular, fibrocellular, and fibrous crescents was 36.9% ± 25.2% (range, 10% to 70%); crescents were found in >50% of the glomeruli in three of seven patients. Extraglomerular vasculitis was present in one patient (patient 4).

Response to Therapy and Relapses

Treatment protocols varied among patients and depended on the decision of the attending pediatric nephrologists. However, patients were basically treated with the following initial protocols (Table 1). Five patients received oral corticosteroids (patients 1 to 5); three had pulse methylprednisolone (15 to 30 mg/kg body wt), one had plasma exchange, and one had plasma exchange plus pulse methylprednisolone before the initiation of oral prednisolone. The other two patients (patients 6 and 7) received oral corticosteroids plus oral cyclophosphamide, one of whom had pulse methylprednisolone before the initiation of oral prednisolone and cyclophosphamide. Prednisolone was given at a dose of 1 to 2 mg/kg for the first 2 to 8 wk, followed by a tapering schedule during the following months. The mean period of prednisolone administration was 32 ± 24 mo (range, 1.0 to 60 mo). Oral cyclophosphamide was started at 2 mg/kg for 8 wk. This dose was adjusted by the pediatric nephrologists according to patients' leukocyte counts. All patients responded, with one patient (patient 2) in remission on therapy and the remaining six patients in complete remission (Table 1).

Changes in ANCA Levels after Initiation of Therapy

The titers of MPO-ANCA, as determined by ELISA, decreased to normal ranges on treatment in two of the seven patients (patients 4 and 6), accompanied by disease quiescence. The remaining five patients had decreased but persistently positive ELISA findings despite quiescence of clinical symptoms during the follow-up period. ANCA titers increased without overt clinical relapse in two patients (patients 1 and 7; Figure 1).

Patient Outcomes

Patients were followed for a mean of 58 ± 25 mo (range, 32 to 108 mo). No relapse of nephritis or vasculitis was observed during the follow-up period. All patients had normal renal function and a state of euthyroidism at the last observation. None of the patients progressed to renal dysfunction or ESRD.

Table 2. Laboratory findings at diagnosis of seven ANCA-positive patients with NCGN or NCGN with extrarenal organ system vasculitis associated with PTU treatment[a]

Patient	MPO-ANCA Titer (EU/ml)	Urinalysis		Serum Creatinine (mg/dl)	Creatinine Clearance (ml/min per 1.73 m^2)	Antithyroid Antibody Titer	
		Hematuria (/HPF)	Proteinuria (g/m^2 per d)			Antithyroid Peroxidase Antibody (U/ml)	Antithyroglobulin Antibody (U/ml)
1	298	Gross	1.4	0.7	126	2.5	2.5
2	859	>100	0.5	0.7	82	6.8	5.7
3	441	20–30	0.3	0.5	130	<0.3	2.5
4	42	Gross	0.6	3.8	29	10.3	1.0
5	121	Gross	0.3	0.6	112	5.4	<0.3
6	27	Gross	0.6	0.8	86	3.7	1.0
7	97	Gross	0.1	0.5	90	70.3	3.0

[a] MPO, myeloperoxidase; HPF, high-power fields.

Table 3. Histologic findings of renal biopsies at diagnosis

Patient	Number of Glomeruli Evaluated	Normal Glomeruli[a] (%)	Glomerular Lesions[a]				Tubulointerstitial Lesions[b]		
			Cellular Crescent (%)	Fibrocellular Crescent (%)	Fibrous Crescent (%)	Global Sclerosis (%)	Interstitial Inflammation (0–3)	Interstitial Fibrosis (0–3)	Tubular Atrophy (0–3)
1	28	40	60	0	0	0	1	0	0
2	24	0	25	10	15	50	1	1	1
3	25	80	10	0	0	10	1	0	0
4	20	30	60	10	0	0	2	0	0
5	16	80	0	14	0	6	1	1	1
6	15	80	10	0	0	10	0	0	0
7	18	56	11	11	22	0	1	1	1

[a] Percentage of total number of glomeruli evaluated.
[b] Semiquantitatively graded on a scale of 0 to 3.

One patient (patient 3) had relapse of Graves' disease 2 wk after cessation of prednisolone that had been administered for 47 mo but regained an euthyroidism state with readministration of prednisolone.

Discussion

The purpose of this retrospective study was to analyze the clinical features and outcomes in pediatric patients with ANCA-positive disease associated with PTU treatment. For this purpose, we reviewed the literature and compared the clinical spectrum of our cases with adults with ANCA-positive disease associated and unassociated with PTU and also children with non–drug-induced ANCA-positive disease identified in the same survey (20). Clinical findings and laboratory data are summarized in Table 4.

The present study showed a clear female predominance of PTU-associated ANCA-positive disease in children. A female predominance was also noted in adult cases associated with PTU treatment (6–17), although a slight predominance of male has been reported in adult patients with non–drug-induced ANCA-positive disease (30,32) (Table 4). Although the reason for this marked gender difference is unclear, this may be because the incidence of Graves' disease is approximately five times higher in girls than in boys.

ANCA-positive NCGN or MPA is considered to be a disease of elderly or middle-aged individuals (30,32). The age at onset

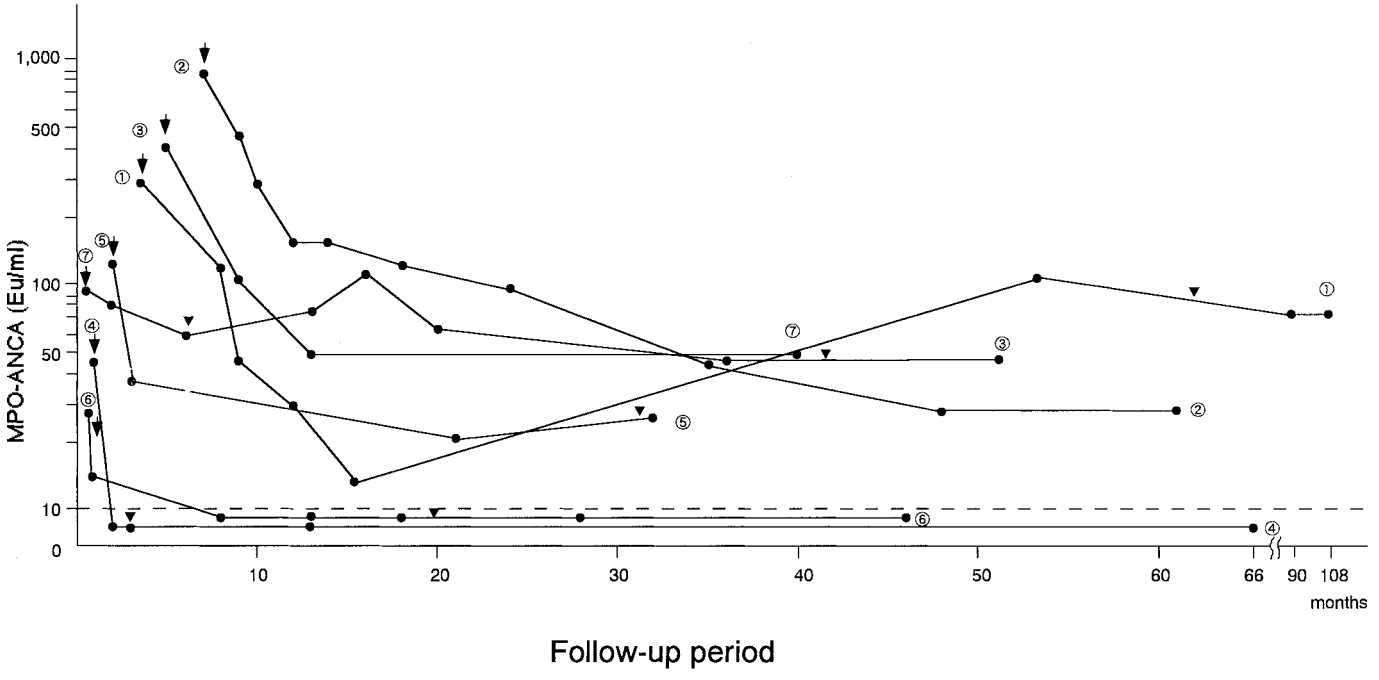

Figure 1. Serial changes of serum levels of MPO-ANCA titers in seven patients with ANCA-positive NCGN or NCGN and extrarenal organ system vasculitis. ① to ⑦, patients 1 to 7, respectively; ↓, the start of immunosuppressive treatment; ▼, the end of immunosuppressive treatment.

in this study (14.0 ± 1.8 yr) is slightly higher than that in pediatric patients with non–drug-induced ANCA-positive disease (20) (11.9 ± 2.9 yr). Because the peak incidence of Graves' disease in children occurs during adolescence, adolescent females may be preponderately affected by PTU treatment.

The period of administration of PTU was similar in both pediatric and adult cases (6–17) (Table 4). The development of vasculitis may appear any time after treatment has begun, as previously reported (33).

PTU was discontinued in six of seven patients in this study, with three patients being switched to MMI. Similarly, PTU was discontinued in 14 of 15 adult patients (6–17), 6 of whom were given another antithyroid treatment and 8 had no further antithyroid treatment. It may be reasonable to recommend discontinuation of PTU because clinical symptoms such as fever, scleritis, and rash quickly resolved after discontinuation of PTU in some adult cases (6,10,11). Whether another antithyroid treatment should be substituted for PTU is not clear. No relapse of Graves' disease was observed despite no antithyroid treatment during administration of prednisolone in both pediatric and adult patients (8–10,12–16). These findings suggest that prednisolone suppresses the activity of Graves' disease, probably via suppression of antibody production.

All seven patients in this study had MPO-ANCA. A predominance of MPO-ANCA was also noted in adult patients with PTU-associated ANCA-positive disease (6–17) (Table 4). The pathogenesis of this disease is not clearly understood. PTU has been shown to accumulate in neutrophils (34) and bind to MPO, resulting in a change of MPO structure (35). This alteration in configuration may induce ANCA in susceptible individuals. Furthermore, Graves' disease *per se* may contribute to the production of ANCA as the disease is an autoimmune disease, and antibodies to thyroid microsome antigens, which consist mainly of thyroid peroxidase, may cross-react with MPO (36). However, the prevalence of MPO-ANCA is not due to a cross-reaction between MPO and thyroid peroxidase, because no correlation between MPO-ANCA titers and antithyroid peroxidase titers was recognized in either this study or our previous report (37). As ANCA may be induced by other

Table 4. Clinical manifestations and laboratory data of ANCA-positive vasculitis in children and adults[a]

	PTU-GN (This Study $n = 7$)	Non–Drug-Induced GN (20) in Children ($n = 31$)	PTU-GN (Adults $n = 15$) (6–17)	Non–Drug-Induced GN (30,32) in Adults ($n = 107$)
Follow-up period (mo; range)	58.0 ± 25.0 (32 to 108)	45 ± 27 (3 to 96)	9 ± 8 (1 to 29)	30[b] (0.2 to 146)
Gender (M:F)	1:6	1:6.8	1:2.8	1:0.8
Onset age (yr)	14.0 ± 1.8	11.9 ± 2.9	49.5 ± 17.8	57.8 ± 17.0
Duration of PTU administration (mo; range)	37 ± 18 (3 to 60)	—	40 ± 18 (11 to 84)	—
ANCA positivity				
MPO-ANCA/P-ANCA	7/7 (100%)	28/31 (90.3%)	15/15 (100%)	68/107 (63.6%)
PR3-ANCA/C-ANCA	0/7 (0%)	3/31 (9.7%)	2/10 (20%)	39/107 (36.5%)
Laboratory data				
proteinuria (g/m^2 per d)	0.7 ± 0.5	1.6 ± 1.6	2.0 ± 1.6[c] ($n = 6$)	2.7 ± 2.8[c]
median serum creatinine (mg/dl; range)	0.7 (0.5 to 3.8)	2.0 (0.6 to 14.2)	2.0 (0.5 to 4.0)	4.5 (0.8 to 21.6)
median creatinine clearance (ml/min per 1.73 m^2; range)	90 (29 to 130)	43 (5 to 125)	NA	NA
RPNS	1/7 (14.3%)	21/31 (67.7%)	9/15 (60.0%)	NA
CRI and/or ESRD	0/7 (0%)	15/31 (48.4%)	3/15 (20.0%)	23/97 (23.7%)
Mortality	0/7 (0%)	1/31 (3.2%)	0/15 (0%)	12/97 (12.4%)
Relapse	0/7 (0%)	10/31 (32.3%)	0/15 (0%)	22/97 (22.6%)

[a] PTU-GN, propylthiouracil-associated glomerulonephritis; PR3, proteinase-3; RPNS, rapidly progressive nephritic syndrome; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; NA, not available.
[b] Mean follow-up period.
[c] g/d.

drugs, including carbimazole (7) and hydralazine (38), study of the mechanism of developing ANCA associated with PTU should examine other factors, such as HLA (8,39).

The value of ANCA titers for disease monitoring has been the subject of several investigations. In the present study, the titers of ANCA decreased to the normal level on treatment in two of seven patients (28.6%), accompanied by disease quiescence, but positive ANCA titers persisted in the remaining five patients. ANCA titers increased without overt clinical relapse in two patients. Conversely, the titers of ANCA decreased to the normal level on treatment in 17 of 22 pediatric patients with non–drug-induced ANCA-positive disease (77.3%), and positive ANCA titers persisted in the remaining 5 patients (20). A low rate of normalization of ANCA titers after discontinuation of PTU (33.3%) was also observed in adult patients with PTU-associated ANCA-positive disease (6–17). Furthermore, we observed a high prevalence of MPO-ANCA positivity (64.0%) in childhood-onset Graves' disease treated with PTU without clinical manifestation of vasculitis (37). Thus, the issues of whether ANCA plays a role in the induction of vasculitis and whether ANCA can be used as a guide to therapy remain disputable. ANCA might be examined considering both the titer and epitope recognition profile related to clinical features (39).

Levels of protein excretion and serum creatinine or Ccr at diagnosis in this study were lower than those in pediatric patients with non–drug-induced ANCA-positive NCGN or MPA (20). Similar differences were also reported in adult patients with and without PTU treatment (6–17,30,32). In the present study, only one patient presented with rapidly progressive nephritic syndrome, whereas most patients had more indolent nephritic syndrome. These results suggest that clinical symptoms in pediatric and adult patients with ANCA-positive glomerulonephritis associated with PTU treatment may be less severe compared with pediatric and adult patients with non–drug-induced ANCA-positive disease (Table 4).

Clinical improvement was seen in all seven patients in the present study. Renal function improved and remained well, with an overall good prognosis. Lower rates of ESRD, death, and relapse were noted in pediatric patients with PTU-associated ANCA-positive disease compared with pediatric patients with the non–drug-induced ANCA-positive disease, for comparable follow-up periods (20) (Table 4). In adult cases with PTU-associated ANCA-positive disease, although the follow-up period was short, overall prognosis is better (6–17) compared with the non–drug-induced ANCA-positive disease (30,32), as previously reported (33).

One possible reason for good prognosis is that patients with PTU-associated ANCA-positive disease had mild clinical findings at the time of initiation of therapy compared with the non–drug-induced ANCA-positive disease (Table 4). Moreover, the mean percentages of crescents (36.9 $\pm$ 25.2%) and fibrous crescents (5.3 $\pm$ 9.3%) in the present study were significantly ($P < 0.05$) lower than those (63.5 $\pm$ 24.4% and 6.7 $\pm$ 22.8%, respectively) in non–drug-induced ANCA-positive disease in children (20). Second, discontinuation of PTU may contribute to good prognosis, because vasculitis or nephritis improved after discontinuation of PTU without immunosuppressive therapy in some adult patients with PTU-associated ANCA-positive disease, accompanied with a decrease of ANCA titers (6,11). We also observed normalization of ANCA titers after switching from PTU to MMI in some patients with childhood-onset Graves' disease without clinical vasculitis (data not shown).

Treatment for NCGN should be given appropriately depending on the severity of the illness. Corticosteroids and/or cyclophosphamide are warranted if renal manifestations are severe or rapidly progressive or if biopsy findings show crescentic glomerulonephritis (17). In the present study, five patients were treated with corticosteroids alone and two were treated with corticosteroids plus cyclophosphamide. In adult cases (6–17), 7 of 15 patients were given corticosteroids alone, whereas 6 of 15 patients were given corticosteroids plus cyclophosphamide. The beneficial effects of the corticosteroid-cyclophosphamide combination over corticosteroids alone have been reported in patients with non–drug-induced ANCA-positive disease (20,30,32). These effects are less clear in PTU-associated ANCA-positive disease because the present study and adult studies (6–17) were retrospective and had few subjects. The effects of treatment on prognosis in patients with ANCA-positive disease associated with PTU treatment should be analyzed in a large-scale prospective study.

In conclusion, although only seven pediatric patients with ANCA-positive NCGN or NCGN with extrarenal organ system vasculitis associated with PTU treatment were analyzed in the present study and thus only limited conclusions can be drawn, our experience suggests that the clinical disease spectrum is similar in pediatric and adult patients and that the prognosis may be better than that of non–drug-induced ANCA-positive NCGN or MPA.

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