

Clinical and Pathological Features of Microscopic Polyangiitis in 20 Children

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ABSTRACT. Objective. To explore the clinical and pathological features of microscopic polyangiitis (MPA) in children.

Methods. A retrospective analysis was performed of patients with pediatric MPA in our hospital over 10 years.

Results. Data for 20 patients were collected; 16 patients had primary MPA (4 boys, 12 girls), with a median age of 8.9 years at the time of disease onset; 4 patients, all female, had antithyroid drug (ATD)-associated MPA, with an age range of 12.5 to 16.2 years at the time of disease onset. All patients exhibited renal involvement. Renal biopsies were performed in 14 patients. Fibrinoid exudation and necrosis of the glomerular capillaries were observed in all biopsy specimens. Crescents and scleroses were noted in 92.9% and 85.7% of these cases, respectively. The most frequent extrarenal organs involved were lungs, followed by the central nervous system (CNS), skin, and digestive system. Ninety percent of patients were positive for perinuclear antineutrophil cytoplasmic antibody, 94.1% were positive for myeloperoxidase, and 88.2% were positive for both. Forty-five percent of the patients had received steroid plus cyclophosphamide (CTX) pulse therapy for more than 3 months, and varying degrees of remission had been achieved in 88.9% of the patients.

Conclusion. Both primary and ATD-associated MPA showed a female predisposition. Renal involvement was the most frequently observed condition, followed by involvement of lungs. CNS involvement was not rare in these pediatric patients. The efficacy of steroid plus CTX as induction therapy was evident in these patients. (First Release July 1, 2014; *J Rheumatol* 2014;41:1712–19; doi:10.3899/jrheum.131300)

Key Indexing Terms:

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES
MICROSCOPIC POLYANGIITIS

GLOMERULONEPHRITIS
SYSTEMIC VASCULITIS

Microscopic polyangiitis (MPA) is a small-vessel vasculitis associated with antineutrophil cytoplasmic antibody (ANCA)¹. MPA typically exhibits multiple organ involvement, affecting kidneys, lungs, skin, gastrointestinal tract, and the nervous system. MPA can be divided into primary and secondary forms based on its causative factor. The latter form is primarily caused by treatment with antithyroid drugs

(ATD), particularly propylthiouracil (PTU)². MPA rarely occurs in children³.

MATERIALS AND METHODS

Children with MPA who were treated in our hospital between 2003 and 2013 were evaluated in our study. The diagnosis of primary MPA was based on the 2012 revised Chapel Hill Consensus Conference Nomenclature of Vasculitides¹, and ATD-associated MPA has been defined⁴. Renal involvement was defined by hematuria (≥ 3 red blood cells/high-power field) and proteinuria (> 150 mg/day)⁵.

Definitions. Renal insufficiency was diagnosed as described⁶. Chronic kidney disease (CKD) was defined using Kidney Disease Outcomes Quality Initiative staging (stage 1 to 5)⁷, and glomerular filtration rate was calculated according to the Schwartz formula⁸. We defined hypertension (HTN) as office-measured systolic or diastolic blood pressure ≥ 95 th percentile for sex, age, and height, according to international guidelines⁹. The grade of proteinuria was classified as mild to moderate proteinuria (< 50 mg/kg/24 h) or severe proteinuria (nephrotic range, ≥ 50 mg/kg/24 h). Disease activity was scored according to the Birmingham Vasculitis Activity Score (BVAS)¹⁰. Irreversible damage was assessed using the Vasculitis Damage Index (VDI)¹¹.

Treatment protocols⁴. Induction therapy consisted of a corticosteroid (prednisone: 1–2 mg/kg/day, tapered gradually at 4–8 weeks) plus cyclophosphamide (CTX: 0.75 g/m²/month for 6 mos). For patients with severe organ involvement [pulmonary hemorrhage, rapidly progressive glomeru-

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Supported by Fundamental Research Funds for the Central Universities (Grant No. 09ykpy40), the Science and Technology Planning Project of Guangdong Province (Grant No. 2011B031800126), and the Natural Science Foundation of Guangdong Province (Grant Nos. S2012010009405 and S2013010015536).

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Accepted for publication March 26, 2014.

lonephritis, digestive tract hemorrhage, central nervous system (CNS) involvement], methylprednisolone pulse therapy (7.5–15 mg/kg qod, 3 to 6 administrations per course) was initially used, followed by prednisone plus CTX.

Maintenance therapy consisted of low-dose corticosteroid (prednisone: 5–10 mg/day) plus CTX (0.5–0.75 g/m² every 3 mos) pulse therapy. If CTX was not tolerated or not accepted, mycophenolate mofetil [MMF (CellCept): 20–30 mg/kg/day/bid] was used as a substitute. The patients received maintenance therapy for 1 to 2 years¹².

Calcium ion antagonists (nifedipine) were the baseline antihypertension medication. Angiotensin converting enzyme inhibitors (ACEI), such as enalapril, benazepril, and fosinopril; β -receptor antagonists (metoprolol), and α -receptor antagonists (terazosin) were used when HTN could not be controlled by the baseline drug. Antiproteinuric treatment using ACEI was indicated in patients who did not achieve complete remission and whose renal function was not at CKD stage 5.

Treatment response. Definitions of complete remission (CR), partial remission (PR), treatment failure, and relapse were as reported^{13,14}. Damage was assessed according to VDI at the last followup visit if the patients were monitored for more than 3 months.

RESULTS

General data (Table 1). Twenty children (4 boys, 16 girls) were evaluated. For 14 patients, the diagnoses were evident from the patients' renal biopsies. Renal biopsies were not performed in the remaining 6 patients (5 patients with primary MPA, 1 patient with secondary MPA); the diagnoses were based on the clinical manifestations and the serological changes in their disease¹⁵. Granuloma and autoimmune diseases were excluded.

Sixteen of the 20 patients (4 boys, 12 girls) had primary MPA, with a median age of 8.9 years (1.9–16.8 yrs) at disease onset. The median disease course (before diagnosis) was 4 months (0.1–42 mos). The remaining 4 patients with secondary MPA were female, and the age at disease onset ranged from 12.5 to 16.2 years, with disease courses of about 1 month. The duration of PTU administration was 7 months to 6 years. Patient 19 had received PTU and methimazole (MMI) from the time of her hyperthyroidism diagnosis. PTU was discontinued 8 months after improvement in hyperthyroidism, whereas MMI administration continued for an additional 2 years until renal impairment was noted. Moreover, her dizygotic twin sister, diagnosed with hyperthyroidism at the same time, received the same treatment regimen. However, the sister had normal routine urinary test results, normal renal function, and normal levels of perinuclear ANCA (pANCA), cytoplasmic ANCA (cANCA), myeloperoxidase (MPO), and proteinase 3.

Clinical and renal pathological features (Tables 1, 2, and 3). Ninety percent (18/20) of the patients (14 patients with primary MPA and 4 patients with secondary MPA) presented with normocytic normochromic anemia; 2 patients had mild anemia with hemoglobin (Hb) \geq 90 g/l, 14 patients had moderate anemia with Hb 60–90 g/l, and 2 patients had severe anemia with Hb < 60 g/l. Fifty percent (10/20) of the patients (8 patients with primary MPA, and 2 patients with secondary MPA) presented with irregular fever during the

early disease course without apparent infection. The median BVAS in all patients was 14.5 (range, 8–28).

Renal involvement was observed in all 20 patients. Eighty-five percent of all patients (17/20) presented with hematuria and proteinuria; gross hematuria was noted in only 2 patients, and 2 mild cases with isolated hematuria were observed. Fifty-two percent of patients (9/17) showed mild to moderate proteinuria; in 47% of patients (8/17), proteinuria reached a nephrotic range, and 6 patients exhibited signs of nephrotic syndrome. At the time of diagnosis, renal insufficiency was observed in 60% of the patients (12/20), HTN was observed in 45% (9/20), and rapidly progressive glomerulonephritis was observed in 40% (8/20).

Renal biopsies were obtained from 14 patients (Table 3). Crescents were observed in the renal specimens of 92.9% of the patients (13/14). All biopsied patients showed glomerular fibrinoid exudation and glomerular necrosis. Segmental or global glomerular sclerosis was observed in 85.7% of biopsies (12/14). Small amounts of deposits of nonspecific immune complex (IC) were observed in 71.4% of the biopsies (10/14). These deposits typically showed a segmental deposition of IgM and C3. Small amounts of focal IgA deposits were noted in the mesangial area in 2 patients. In the 3 patients with secondary MPA, no IC deposits were noted. Inflammatory cell infiltration and interstitial fibrosis were noted in 71.4% (10/14) and 42.9% (6/14) of the patients, respectively.

Of the 20 patients with MPA, 60% (12/20) showed involvement of more than 1 extrarenal organ. Fifteen percent (3/20) exhibited lung involvement; 3 patients with primary MPA presented with coughing and hemoptysis sputum. The other patient had secondary MPA and presented with coughing and tachypnea; however, her chest radiograph was normal. Fifteen percent (3/20) of patients (1 primary MPA, 2 secondary MPA) showed CNS symptoms, including headaches, convulsions, and symptomatic epilepsy. Cerebral edema, cerebral vasculitis, and focal ischemia were subsequently exhibited on magnetic resonance imaging scans (Figure 1A and 1B). Fifteen percent of the patients (3/20) showed skin involvement; their clinical manifestations included ulcers, necrosis, petechiae, and pinpoint red rash, all of which were present in the lower limbs. Fifteen percent (3/20) of the patients, all of whom had primary MPA, showed digestive system symptoms. One patient showed a recurrent hemorrhage of the lower digestive tract; a colonoscopy revealed ulcers and hemorrhaging in the splenic flexure and sigmoid colon. Pathological examination revealed chronic colorectal inflammation with ulcers. The other 2 patients who presented with abdominal pain had duodenal ulcers and chronic congestive exudative gastritis with antral erosion. In addition to organ involvement, myalgia, arthritis, and eye involvement were observed separately in 1 patient with primary MPA.

Table 1. Summary of clinical features of microscopic polyangiitis in 20 children.

Patient	Sex	Onset Age, yrs	Disease Course, mos	uRBC/uPro	Main Manifestations	GFR at Diagnosis	BVAS	Immuno-suppressive Therapy	Antihyper-tensive Therapy	Antiprotein-uric Therapy	Time of Followup, mos	VDI	Prognosis
1	F	10.0	12	++	Fever, anemia, RI	15.4	13	CTX, MP, P	—	No	Lost	—	CKD 4
2	F	14.3	2	++	Anemia	95.4	12	CTX, MP, P	—	No	Lost	—	Lost
3	F	10.3	5	++	Anemia, arthralgia, gastrointestinal hemorrhage	107.0	9	CTX, MP, P	—	No	78	0	CR
4	F	3.0	42	++	Fever, anemia, HTN, RI, hemoptysis sputum	49.0	17	CTX, MP, P	Yes	Yes	58	1	CKD 3 (PR)
5	F	8.3	8	++	Anemia, photophobia, blurred vision, corneal ulcer, myalgia	156.1	18	CTX, MP, P	—	No	31	1	Initially CR, but progressed to CKD 5 eventually
6	M	7.6	24	++	Anemia, HTN, RI, necrotic skin ulcers	5.18	16	N	Yes	No	4	1	CKD 5
7	F	16.0	1	++	Anemia, HTN, duodenal ulcer	121.7	15	CTX, MP, P	No	No	8	0	CR
8	F	12.1	3	++	Fever, anemia, HTN, RI, alimentary tract hemorrhage	9.3	22	CTX, MP, P, then renal transplantation	Yes	No	16	2	CKD 5 (PR)
9	F	8.5	0.5	++	Anemia, HTN, RI, convulsion	7.5	27	N	Yes	No	4	2	CKD 5, died
10	F	1.9	12	++	Fever, anemia, hemoptysis sputum	58.8	23	CTX, MP, P, MMF	—	No	10	0	CR
11	M	8.8	6	++	Fever, anemia, HTN, RI, rashes	13	28	N	Yes	No	12	2	CKD 5
12	F	5	3	++	Fever, anemia, RI	9.6	13	N	—	No	Lost	—	CKD 5
13	F	2.8	0.5	+/-	Fever	139.7	9	N	—	No	10	—	SR
14	M	3.6	18	+/-	None	165.7	8	N	—	No	Lost	—	SR
15	F	10.3	18	++	Anemia, HTN, RI	10.9	12	N	No	No	Lost	—	CKD 5
16	M	16.8	1	++	Anemia, HTN, RI	24.9	12	N	No	No	Lost	—	CKD 4
17	F	12.5	1	++	Fever, anemia, RI, rashes	49.4	14	CTX, MP, P	—	Yes	79	0	CR
18	F	16.2	1	++	Anemia, tachypnea	104.9	14	CTX, MP, P	—	No	Lost	—	Lost
19	F	13.8	1	++	Fever, anemia, HTN, RI, dizziness, convulsion	12.9	25	CTX, MP, P, PE	Yes	No	12	2	CKD 5 (PR), died
20	F	13.3	1	++	Fever, anemia, RI, convulsion	18.5	25	CTX, MP, PE, IVIG	—	No	4	2	CKD 4, died

BVAS: Birmingham Vasculitis Activity Score (at time of diagnosis); CKD: chronic kidney disease; CNS: central nervous system; CR: complete remission; CrGN: crescentic glomerulonephritis; CTX: cyclophosphamide; GFR: glomerular filtration rate; HTN: hypertension; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; MMI: methimazole; MP: methylprednisolone; N: no specific therapy; P: prednisone; PE: plasma exchange; PR: partial remission; RI: renal insufficiency; SR: spontaneous remission; uPro: urine protein; uRBC: uric red blood cells; VDI: Vasculitis Damage Index; +: positive; -: negative.

ANCA and other laboratory results (Table 2). Positive pANCA results were observed in 90% of patients (18/20), and 94.1% of patients (16/17) analyzed were positive for MPO. Positive results for both pANCA and MPO were observed in 88.2% (15/17) of patients analyzed [84.6% (11/13) of primary MPA cases, 100% (4/4) of secondary MPA cases].

Sixty-three percent of the patients tested (12/19) were positive for ANA (8 patients with primary MPA and 4 patients with secondary MPA), whereas 42.1% of the patients tested (8/19) were positive for both ANA and dsDNA. Seventy-five percent (15/20) had normal comple-

ment 3 (C3) levels, and 1 (patient 1) had an elevated C3 level. Four patients showed decreased C3 levels (3 patients with primary MPA and 1 patient with secondary MPA); of those 4 patients, 3 were negative for both ANA and dsDNA, and 1 (patient 20) was ANA-positive but dsDNA-negative. Ninety-five percent of patients tested (18/19) showed increased erythrocyte sedimentation rates (ESR). Apart from those with infections, 61.1% of tested patients (11/18) had normal ranges of serum C-reactive protein (CRP) levels; elevated CRP levels were observed in 38.9% of the patients (7/18), and 3 patients had only mildly elevated CRP levels.

Table 2. Summary of laboratory tests for microscopic polyangiitis in children.

Patient	p-ANCA/c-ANCA/ MPO/PR3	ANA/dsDNA	C3 (0.77–1.95 g/l)	ESR (≤ 20 mm/h)	CRP (≤ 3 mg/l)
1	+/-/ND/ND	+/-	2.25	128	2.21
2	+/-+/+	-/-	1.04	27	4.8
3	+/-+/+	-/-	1.43	44	5.8
4	+/-+/+	+/+	0.94	28	1.0
5	+/-+/+	+/+	1.35	33	8.32
6	+/-+/+	+/+	0.9	41	ND
7	-/+/-/+	-/-	0.73	19	32.5
8	+/-+/+	+/+	1.0	46	1.79
9	+/-+/+	-/-	0.86	45	2.22
10	+/-+/+	+/+	0.91	15	< 1
11	+/-+/+	+/-	0.9	76	2.7
12	+/-+/+	+/+	1.1	36	2.53
13	+/-+/+	-/-	0.25	8	< 1
14	-/++/+	-/-	0.69	ND	0.73
15	+/-/ND/ND	-/-	1.26	105	ND
16	+/-/ND/ND	ND	1.42	108	10.9
17	+/-+/+	+/-	1.23	90	43.3
18	+/-+/+	+/+	0.9	40	4.29
19	+/-+/+	+/+	0.81	53	< 1
20	+/-+/+	+/-	0.63	24	2.3

ANA: antinuclear antibody; CRP: C-reactive protein; C3: complement 3; ESR: erythrocyte sedimentation rate; ND: not detected; +: positive; -: negative; MPO: myeloperoxidase; p-/c-ANCA: perinuclear/cytoplasmic antineutrophil cytoplasmic antibodies.

Table 3. Renal pathological features of 14 patients who underwent biopsies to diagnose microscopic polyangiitis (MPA).

Patient	No. Glomeruli	No. Crescents	Cellular Crescents	Fibrocellular Crescents	Fibrous Crescents	No. Sclerotic Glomeruli	Fibrinoid Exudation or Necrosis	Immune Complex	Interstitial Fibrosis/ Inflammation	Pathology Diagnosis
1	9	3	3	0	0	6	Yes	IgA+~+++, C3+++, focal segmental	Yes/Yes	Necrotic glomerulonephritis
2	7	4	4	0	0	0	Yes	IgA+, IgM±, C3±	No/Yes	Crescentic glomerulonephritis
3	26	2	2	0	0	2	Yes	IgM±~+	Yes/Yes	Necrotic glomerulonephritis
4	24	1	1	0	0	13	Yes	IgM+++, C4+	Yes/No	Proliferative and sclerotic glomerulonephritis
5	29	4	0	2	2	0	Yes	-	No/Yes	Focal segmental glomerular necrosis with crescents
6	44	2	1	1	0	40	Yes	C3+, C1q+	Yes/Yes	Sclerotic glomerulonephritis
7	50	5	4	1	0	3	Yes	IgM+	No/Yes	Focal segmental glomerular necrosis with crescents
8	7	0	0	0	0	5	Yes	C3+	Yes/Yes	Proliferative and sclerotic glomerulonephritis
9	9	5	1	4	0	5	Yes	-	No/Yes	Crescentic glomerulonephritis
10	47	15	1	13	1	0	Yes	IgM+	Yes/Yes	Focal segmental glomerular necrosis with crescents
11	23	5	0	0	5	3	Yes	IgA+, IgG+	No/Yes	MPA
17	23	2	2	0	0	18	Yes	-	No/Yes	Proliferative and sclerotic glomerulonephritis
18	19	5	0	5	0	1	Yes	-	No/Yes	MPA
19	20	12	3	8	1	8	Yes	-	No/Yes	Crescentic glomerulonephritis

-: negative; ±: trace; +: mild; ++: moderate.

Treatment and prognosis (Table 1). Of the 16 patients with primary MPA, 37.5% (6/16) received steroid plus CTX pulse therapy for more than 3 months and achieved varying

degrees of remission, 4 patients (patients 3, 5, 7, and 10) achieved CR; their routine urine tests returned to normal after 3 months, 2 months, 3 months, and 8 months of

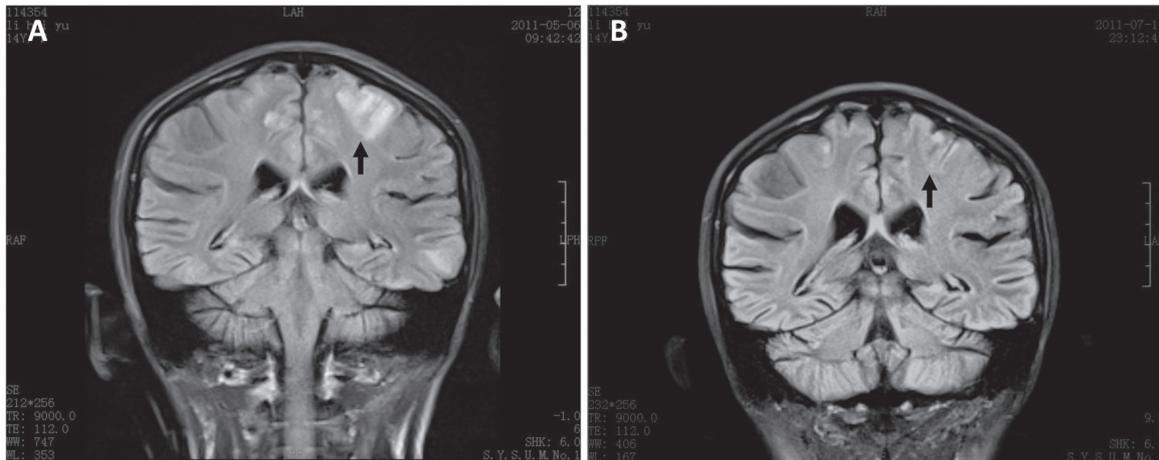


Figure 1. Comparison of encephalic lesions before and after treatment in patient 19. A. Coronal brain magnetic resonance image (MRI) before treatment, on which an abnormal signal of ischemia was observed in the parietal cortex and subcortical white areas (arrow). B. Coronal brain MRI image after treatment showing that the area of the ischemic lesion apparently recovered (arrow).

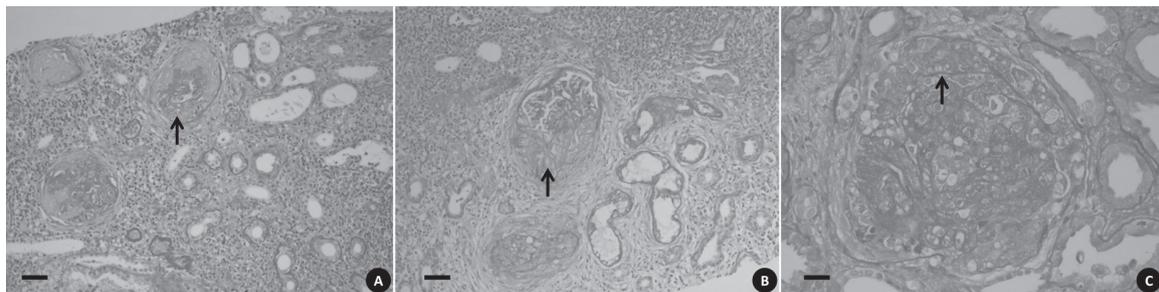


Figure 2. Renal histology of patient 19 (A, B, C: periodic acid-Schiff staining; original magnification of A, B: $\times 200$; C: $\times 400$). Cellular crescents, fibrocellular crescents, and fibrous crescents coexisted in the same patient. A. Globe glomerular sclerosis, a fibrous crescent (arrow), and lymphocytic infiltration in the interstitial space. B. A fibrocellular crescent (arrow), atrophy of the renal tubers, and interstitial fibrosis. C. Fibrinoid necrosis and a fibrous crescent (arrow). Bar: A and B: $60\ \mu\text{m}$; C: $30\ \mu\text{m}$.

treatment, respectively. Hb levels returned to normal, and sera samples were pANCA-negative after 11 months for patient 3 and after 8 months for patient 10. ANCA was not reexamined for patient 5. The gastrointestinal ulcer in patient 7 improved; the patient became ANCA-negative at 4 months after treatment, and routine urine tests were normal after 1.5 years of treatment. In patient 3, the initial renal pathological change noted was focal necrotic glomerulonephritis with crescents. At 1 year after treatment, a repeat renal biopsy revealed minimal change in disease, with focal glomerular sclerosis. The patient was followed up for 6.5 years; an occasional relapse was observed, with mild urinary changes (red blood cell-positive, protein-negative). Although CR was achieved in patient 5 after inductive treatment, she progressed to CKD stage 5 after 2 years and 7 months. MMF with low-dose prednisone was used for maintenance therapy after 6 months of inductive therapy for patient 10; this patient achieved CR by the eighth month of treatment. However, hemoptysis, hematuria, and proteinuria were recurrent during maintenance therapy, and CR was again

achieved after MP pulse therapy. PR was observed in 2 patients (patients 4 and 8), and the VDI scores were 1 for patient 4 and 2 for patient 8. In patient 4, extrarenal symptoms were ameliorated, and the patient became ANCA-negative at 10 months after treatment, whereas the renal function and urinary sediment levels did not return to normal levels (CKD stage 3, urine protein-positive). All gastrointestinal symptoms, hematuria, and proteinuria disappeared in patient 8 after the treatment regimen; however, her renal function did not recover. She subsequently underwent renal transplantation and recovered well afterward. Of the patients with primary MPA, 62.5% (10/16) did not follow the default treatment: 2 patients progressed to CKD stage 4; 5 patients progressed to CKD stage 5; and 2 patients, whose clinical manifestations were mild with only isolated hematuria and who had no extrarenal organ involvement, recovered spontaneously without any specific treatment; the remaining 1 patient was lost to followup.

For the 4 patients with secondary MPA, ATD was discontinued, and corticosteroid plus CTX treatment was adminis-

tered after diagnosis of MPA. Three subjects (patients 17, 19, 20) were treated for more than 3 months. Patient 17 had mildly impaired renal function at the time of admission. That patient's pANCA and MPO levels became negative, and CR was achieved 7 months and 14 months after treatment, respectively. However, pANCA, MPO, and urinary sediment tests were occasionally positive during maintenance therapy. Patient 19 was in acute renal failure when she was admitted. Plasma exchange was administered during the earlier treatment. ANCA disappeared at 2 months after the treatment regimen, CNS symptoms were relieved, and cerebrovascular inflammation and cerebral ischemia also improved (Figure 1). However, the hematuria, proteinuria, and renal insufficiency remained. The patient acquired a severe infection (pneumonia and septicemia) during induction treatment and died 1 year later from a pulmonary infection. Patient 20 was in CKD stage 5 when she was admitted to the hospital. She had pneumonia during the course of induction treatment and died 4 months after admission because of her poor physical condition. Patients 19 and 20 had VDI scores of 2 before death. Patient 18 had mildly impaired renal function and was lost to followup at 1 month after treatment.

Six of the 9 patients with HTN received antihypertensive therapy. Two of 4 patients (patients 4, 16, 17 and 20) who had not achieved CR and whose renal function was not at CKD stage 5 received antiproteinuric treatment (Table 1).

In total, 7 patients were lost to followup; 13 patients had been followed up for 4–9 months, and 9 of these 13 patients received corticosteroid plus CTX therapy for more than 3 months: 88.9% (8/9) achieved varying degrees of remission, 55.6% (5/9) achieved CR, and 33.3% (3/9) progressed to CKD stage 3 to 5, and the remaining 1 patient died. Of the 11 patients who received immunosuppressive medication, 2 (patients 19 and 20) were severely infected during induction therapy, and both died subsequently. Longterm side effects, such as impairment of fertility and tumorigenesis, were not observed in our study. Fifty-five percent (11/20) of all patients progressed to CKD stage 4, CKD stage 5, or death. Moreover, the BVAS was reassessed after induction treatment; the BVAS were 0 in all 5 patients who achieved CR, ranging from 8 to 12 in 3 patients with CKD. The VDI scores were 0 in all patients who achieved CR, and they ranged from 1 to 2 in patients with CKD or those who died (Table 1).

DISCUSSION

According to the literature, MPA is the most frequent form of ANCA-associated vasculitis in children, although the incidence of granulomatosis with polyangiitis in adults is higher than that of MPA in northern Europe^{16,17}. MPA occurs more frequently in female subjects, and the mean age at the time of onset in children is 10 to 12 years^{3,13,18}. Compared with adult MPA, there is a lower prevalence of

HTN and a higher incidence of acute renal failure and CKD¹⁸. In our present study, most patients (80%) were female. Of the patients with primary MPA, 75% were female, with a median age of 8.9 years at the time of disease onset. All 4 patients with secondary MPA were female, with an age range of 12.5 to 16.2 years.

The kidneys are the most frequent organ involved in MPA in children and adults³; hematuria and proteinuria are the primary manifestations¹⁴. In our current study, all patients showed renal involvement, and the majority presented with both hematuria and proteinuria. Mild to moderate proteinuria was frequently noted. However, only a few patients fulfilled the criteria for nephrotic syndrome. These results were similar to those in adults¹⁹. In the present study, renal insufficiency and HTN at the time of diagnosis were not rare, and the majority showed varying degrees of renal interstitial fibrosis, which is an indicator of chronic kidney disease. These data suggested that early diagnosis of MPA in children is difficult and has not yet been achieved in this field of study.

The typical renal histopathology of MPA is pauciimmune glomerulonephritis with glomerular capillary necrosis and crescent formation²⁰. In our present study, typical vasculitis lesions were evident in all of the patients biopsied. Crescents were also evident in the majority of the patients. Another distinctive pathological feature of MPA is the presence of different phases of renal lesions, such as cellular crescents, fibrocellular crescents, and fibrous crescents, which can coexist in the same biopsy specimen (Figure 2). Although MPA is a pauciimmune glomerulonephritis, small amounts of nonspecific IC have been found in many patients. Yu, *et al*^{4,5} reported that IC of IgM, IgG, IgA, C3, and C1q was present in 65% of patients with primary MPA and 60% of patients with PTU-associated MPA. In the present study, we found small amounts of nonspecific IgM, IgA, C3, and C1q deposits in the glomeruli of many patients with primary MPA; however, IC deposits were not observed in the glomeruli of 3 patients with secondary MPA.

Fever and anemia have been commonly noted in patients with MPA³. Consistent with the literature²¹, 50% of our patients presented with irregular fever, and the majority showed varying degrees of anemia. Extrarenal organ(s) involvement was observed in the majority of patients. Lung involvement reportedly occurs in 19.0% of patients with MPA, followed by involvement of the skin, joints, and so on²². Pulmonary involvement was also frequent in our group of patients. Surprisingly, CNS involvement, which has seldom been observed in other studies, was noted in 15% of our patients. Further studies are required to determine whether CNS involvement occurs more frequently in children with MPA (particularly in ATD-associated MPA).

ANCA are specific hallmarks used for diagnosing vasculitis²³, and pANCA is more specific for MPA. Bakkaloglu, *et al*²⁴ reported that the specificity of a diagnosis

of MPA based on the patient being both pANCA- and MPO-positive was 99%. In our present study, patients who were positive for both pANCA and MPO comprised 88.2% of the tested patients. According to the literature, titers of ANCA decreased to normal levels after treatment in 28.6% of patients with MPA²⁵, and ANCA could be used as an index for assessing MPA relapse^{25,26}. These changes were noted in our study. ANCA were negative in the majority of patients who achieved varying degrees of remission after treatment. Two patients became ANCA-positive during relapse.

With regard to other immunological disorders, we noted that most of our tested patients were ANA-positive, and about 40% were both ANA and dsDNA-positive. Of the ATD-associated patients with MPA, all were ANA-positive and 2 were dsDNA-positive; and 1 patient had a low C3 serum level. These data suggest that the differential diagnosis from systemic lupus erythematosus can be challenging. It has been reported that increased ESR is associated with reduced survival in patients with MPA²². However, in our present study, an increased ESR was observed in the majority of patients, and their levels returned to normal during remission. In our present study, C3 levels were normal in the majority, and most of the patients had normal or only mildly elevated serum CRP levels. Relationships between disease activity and C3 levels and CRP levels were not observed.

The clinical and pathological features of ATD-associated MPA are similar to those of primary MPA²⁵. We also saw these in our study. PTU is the primary medication that induces MPA. MMI-associated MPA typically shows mild manifestations²⁷. In our present study, in patient 19, MPA symptoms were observed 2 years after PTU was discontinued, whereas MMI was taken continuously. Unfortunately, urinary test and renal function were not monitored during her treatment for hyperthyroidism. PTU-associated MPA typically regressed after ATD withdrawal, and MMI-associated MPA should be noted in this child. Fresh crescents were observed in her kidney biopsy, which further supported this hypothesis. However, the clinical manifestations appeared to be too severe for MMI-associated MPA. Thus, the contribution of PTU to the pathogenesis of MPA in this child should also be considered. Moreover, there might be synergistic pathogenesis between PTU and MMI. Interestingly, patient 19 had a dizygotic twin sister who had similarly been treated with PTU and MMI for hyperthyroidism. However, she showed no signs of MPA, which indicated that the genetic background may not play an important role in the pathogenesis of MPA.

Early diagnosis and early and standard treatment are key factors for improving MPA prognosis¹⁴. Steroid plus cytotoxic agents constitute effective therapy for MPA²⁸. In our present study, early diagnosis was not achieved in some patients, as shown by the renal pathological changes.

Although most of the treated patients responded to induction therapy, more than 50% of the children progressed to late CKD stages, including 1 patient who achieved CR initially, but then progressed to CKD 5 in the end. These results might be attributed to the delayed diagnosis and treatment and/or to unoptimized treatment. It has been reported that an initial favorable response to immunosuppressive therapy might not necessarily prevent the occurrence of renal scarring²⁹. Therefore, regular followup is important for improving prognosis. It was a pity that quite a few patients were lost to followup in our study. Nonimmunological interventions, such as antihypertensive and antiproteinuric treatments, are also important in slowing progression of kidney injury. Regrettably, these interventions were not administered in several patients in our present study, which could be attributed to the progression to late CKD stages in those patients.

Fujieda, *et al*²⁵ reported that patients with PTU-induced MPA showed milder manifestations of disease and better prognoses than patients with primary MPA. In the present study, the prognosis of ATD-associated MPA was not better than that of primary MPA, which could be partially attributed to delayed diagnosis and treatment.

Both primary and ATD-associated MPA showed a female predisposition in children. The kidneys were the most frequently involved organ, followed by the lungs. CNS involvement was not rare among these pediatric patients, especially those with ATD-associated MPA. The efficacy of corticosteroid plus CTX treatment was evident in the induction therapy for these patients. Early diagnosis, regular followup, and optimized therapy are also important for improving longterm outcomes.

ACKNOWLEDGMENT

The authors thank all participants for their support.

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