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Clinical Outcome and Prognosis of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis in Japan

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Key Words
Myeloperoxidase-anti-neutrophil cytoplasmic antibody · Vasculitis · Prognosis · Infection · Birmingham Vasculitis Activity Score

Abstract
Background/Aims: We conducted a broad survey of 99 patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and investigated both prognosis and outcomes. ***Methods:*** Clinical data evaluated were age, sex, patient survival, renal survival, serum albumin, serum creatinine, urinary protein, hematuria, C-reactive protein (CRP), ANCA titer, IgG and the Birmingham Vasculitis Activity Score (BVAS). ***Results:*** The patient survival rate at 6 months after onset was 84.8%, and that at 2 years after onset was 82.0%. Most deaths were within 6 months of onset. Infection accounted for 9 deaths (60.0%). Infection together with pulmonary involvement of active vasculitis accounted for 2 deaths (13.3%). Organ-specific involvement of active vasculitis alone caused 3 deaths (20.0%). Others died of cardiac events. At 1 and 3 months after onset, BVAS ($p < 0.0001$, $p = 0.002$), albumin ($p = 0.006$, $p = 0.0004$) and CRP ($p = 0.04$, $p = 0.0002$) were also associated with patient death. ***Conclusion:*** To improve the prognosis of those with ANCA-associated vasculitis, the intensity of initial treatment should be aimed at disease severity. Employing BVAS improved the ability to evaluate therapeutic responses. Finally, prescription with sulfamethoxazole-trimethoprim during the induction therapy with immunosuppressive agents may be advised.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS) are chronic multisystem autoimmune diseases that follow an unpredictable course even with immunosuppressive treatment. Various immunosuppressive drugs and schedules are now used depending on disease activity and the presence of unfavorable prognostic factors. Characteristic features include the presence of ANCA and necrotizing inflammation of small vessels. However, these disorders exhibit important serological and clinical differences.

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ANCA are directed against several myeloid enzymes, of which ANCA to proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) are the most common [1]. PR3-ANCA is present in more than 90% of patients with WG. MPO-ANCA is found in 80% of patients with MPA and 40–60% of those with CSS [2–4]. In PR3-ANCA associated vasculitis, predictive values >50% indicate a relapse within 6–12 months with a >75% increase in the ANCA level [5–7], and PR3-ANCA positivity during early follow-up identified patients at increased risk of relapse [8]. Several studies have described clinical features, performed outcome analyses and attempted to determine prognostic markers in WG, the most common PR3-ANCA-associated vasculitis [9–11].

However, few studies have focused on the prognosis of ANCA-associated vasculitis patients in Japan [12]. To improve the prognosis of patients with ANCA-associated vasculitis, we conducted a broad survey of patients and investigated initial symptoms, laboratory findings, treatment methods and outcomes. We also examined the association between patient survival and the Birmingham Vasculitis Activity Score (BVAS) in ANCA-associated vasculitis, which has not previously been analyzed in detail.

Methods

Patients

Among patients with ANCA-associated vasculitis who were diagnosed at the Department of Medicine of the Kidney Center at Tokyo Women's Medical University, the Department of Nephrology at the Kameda Medical Center, the Department of Nephrology at the Saiseikai Kurihashi Hospital, and the Department of Nephrology at the Tokyo Metropolitan Komagome General Hospital, the data of 99 patients with ANCA-associated vasculitis were reviewed. All patients attending the hospitals as outpatients, hospitalized with a new clinical diagnosis of systemic vasculitis, between January 1, 1995 and December 31, 2006 were identified. The computerized records of the histopathology division were searched for patients with a histological appearance on a renal biopsy consistent with renal vasculitis. The referral policy to the hospital included an increase in serum creatinine (S-Cr) within several weeks and the presence of proteinuria and hematuria.

A diagnosis of ANCA-associated vasculitis was based on a positive titer of MPO-ANCA, clinical findings, and more than one organ-specific involvement of active vasculitis. All patients were also routinely tested for the titers of PR3-ANCA and anti-glomerular basement membrane antibody. Patients fulfilling the inclusion criteria for this study were identified: (1) patients with a new diagnosis of MPA or renal limited vasculitis (RLV), with histological confirmation, and (2) positive serology for ANCA. A negative ANCA was accepted if there was histological evidence of vasculitis. In addition, patients with Henoch-Schonlein purpura, systemic lupus erythematosus or other connective tissue diseases were excluded. We also excluded patients with anti-glomerular basement membrane antibodies and documented episodes of primary renal vasculitis. The study population consisted of 99 patients with ANCA-associated vasculitis, including 73 patients (73.7%) with MPA and 26 (26.3%) with RLV, so-called rapidly progressive glomerular nephritis. The MPA diagnosis was established by the presence of classic features and histological findings, and satisfied the criteria defined by the Chapel Hill Consensus Conference for MPA [13]. Renal biopsies demonstrated that 50 patients were diagnosed as pauci-immune crescentic glomerulonephritis. No patient was diagnosed as WG.

Clinical Data

Clinical data were evaluated with age at the time of diagnosis and laboratory data, including 24-hour urinary protein excretion (U-P, g/day), urinary red blood cell counts (U-RBC/HPF), S-Cr (mg/dl), serum albumin (g/dl), estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) [14], immunoglobulin G (IgG, mg/dl), and C-reactive protein (CRP, mg/dl). MPO-ANCA and PR3-ANCA were measured by enzyme-linked immunosorbent assay (ELISA) (SRL Inc., Tokyo, Japan). Disease activity was scored using BVAS [15]. The patients were followed-up for 2 years at either our institution or affiliated hospitals and a single investigator (M.I.) collected follow-up information.

Treatment

All patients received induction therapy with various corticosteroid doses. Thirty-seven patients with multi-organ involvement MPA received intravenous pulse methylprednisolone (dose 0.5–1.0 g) for 3 consecutive days. Twenty-seven patients with rapidly progressive glomerulonephritis or who were less than 60 years old received more than 0.8 mg/kg/day of prednisolone orally for 4 weeks or more as the subsequent therapy. Cyclophosphamide was administered to 19 patients with steroid-resistant severe disease. Steroid resistance was defined as no decrease in S-Cr levels and persistent nephritic sediment after 1 month of the start of steroid therapy. Among these 19 patients, 13 were given cyclophosphamide intravenously (250–500 mg/day × 1–4 courses) and the others orally (0.5–1.5 mg/kg body weight). Five patients received mizoribine and two received cyclosporine as maintenance therapy. Five patients underwent plasma exchange. No strict protocol was followed as prophylaxis for opportunistic infections. Relapse was defined as a rise in S-Cr levels or worsening/new extrarenal manifestations attributable to active vasculitis with a rise in ANCA titers, and improvement following escalation of immunosuppressive therapy [16].

Statistical Analysis

Data are expressed as means ± SD. The significance of differences between groups was examined using Student's t test for non-paired samples and by the χ^2 test. The evolution of clinical parameters was analyzed in both groups by repeated-measures analysis of variance (ANOVA). When differences could be demonstrated, values were compared with the baseline using the paired-sample t test. $p < 0.05$ was considered statistically significant. Stepwise multiple regression analysis was used to select independent risk factors among parameters selected by univariate analyses. The parameters with an F value of more than 4 were adopted. $p < 0.05$

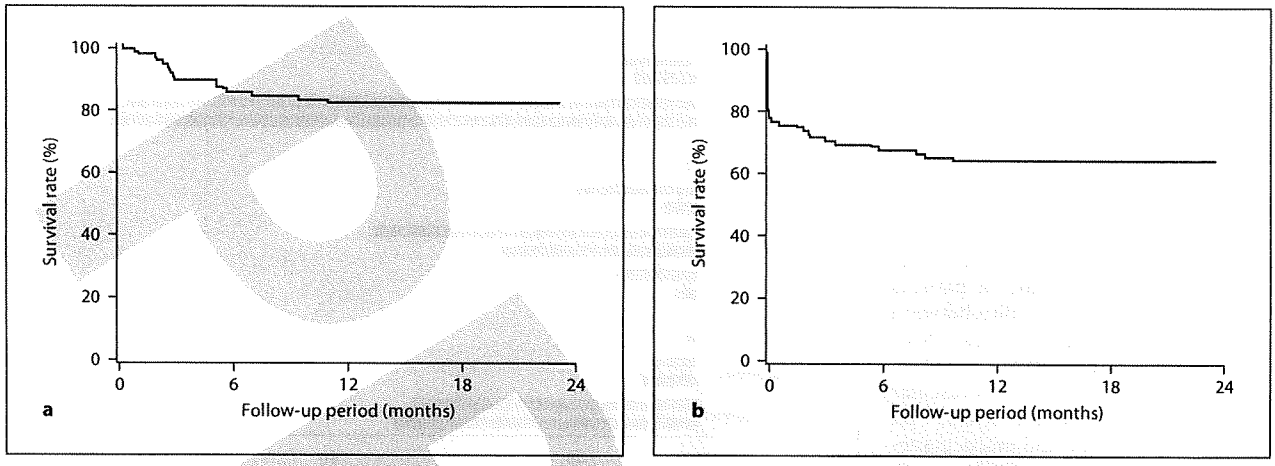

Fig. 1. a Survival of patients with ANCA-associated vasculitis. **b** Renal survival with ANCA-associated vasculitis. X-axis indicates follow-up period (months) and Y-axis indicates survival rate (%).

was considered statistically significant. Survival was assessed by the Kaplan-Meier method. All statistical analyses were performed using JUMP 7 software (SAS Institute, Cary, N.C., USA).

Results

The mean age at diagnosis was 67.7 ± 12.4 (range 28–90) years. There were 35 males and 65 females. The patient life-survival rate and the renal survival rate, which was defined as the start of renal replacement therapy due to developed end-stage renal disease or the death of the individual, are shown in figure 1. The patient survival rate at 6 months after onset was 84.8%, and that at 2 years after onset was 82.0%. Fifteen of the 99 patients died and 32 patients (32.3%) received maintenance renal replacement therapy during the 6-month follow-up period. Six patients avoided renal replacement therapy, due to improvement of renal function with treatment, though temporary hemodialysis was necessary because of transient renal failure at 1 month. Most deaths occurred within 6 months of the onset and all deaths occurred within 11 months. Infection alone accounted for 9 deaths (60.0%). The underlying infections were *Pneumocystis carinii* pneumonia in 4 patients, cytomegalovirus infection in 2, sepsis due to *Enterobacter cloacae* in 1, *Nocardia pneumonia* in 1 and *Candida* infection in 1. Infection together with pulmonary involvement of active vasculitis such as interstitial pneumonia and pulmonary bleeding accounted for 2 deaths (13.3%). Organ-specific involvement of active vasculitis alone caused 3 deaths (20.0%). Others died of cardiac events. During follow-up, 3 patients (3.0%) experienced relapse.

The clinical characteristics of patients at the time of diagnosis are shown in table 1. They were positive CRP (6.5 ± 6.8 mg/dl) and surrogate markers of renal vasculitis, such as elevated S-Cr (4.1 ± 2.9 mg/dl), proteinuria (1.6 ± 1.3 g/day), and hematuria (57.7 ± 37.9/HPF). The serum albumin levels were decreased (3.0 ± 0.7 g/dl), while IgG was not. The mean BVAS at the time of diagnosis was 14.9 ± 5.5. The kidney (96%), systemic organs (49%) and the lungs (32%) were the most frequently damaged systems at baseline (fig. 2). Systemic organs were defined as more than three organs including kidney and lungs. To clarify factors influencing the risk of mortality, we divided the patients into two groups, namely, the surviving and the mortality group, and examined them at the time of diagnosis, i.e. baseline, and then at 1, 3 and 6 months. The comparative clinical characteristics of the two groups at the baseline are shown in table 1. The surviving group included 84 patients (males 32, females 51) with a mean age of 67.0 ± 12.7 years at the time of diagnosis, while the 15 patients (males 3, females 12) who died had a mean age of 74.4 ± 8.2 years. Significantly higher ages were observed in those who died than in the surviving group ($p = 0.02$). There were no significant differences in eGFR, albumin, CRP, S-Cr, MPO-ANCA titer, IgG, U-P, U-RBC or BVAS at baseline. There were no changes in MPA and RLV in either group.

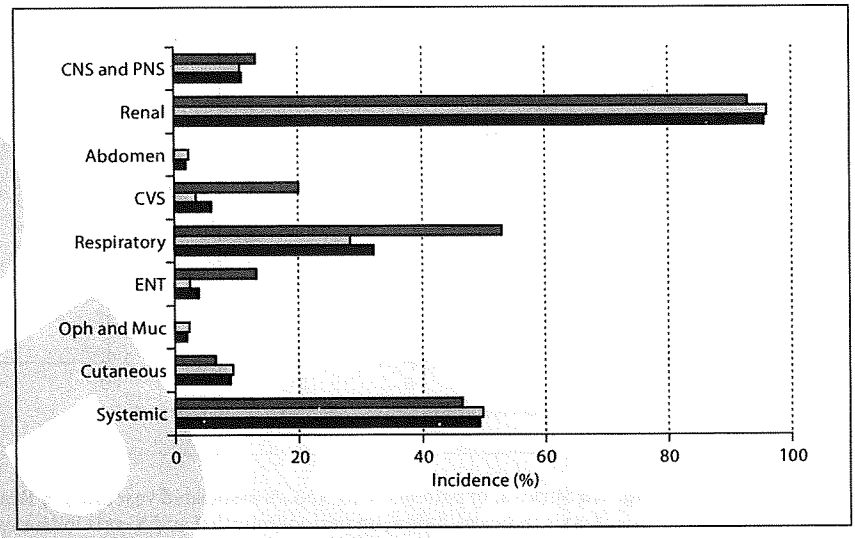

Fig. 2. Comparison of the incidence of organ involvement at baseline in patients with ANCA-associated vasculitis between the surviving and mortality groups. CNS = Central nervous system; PNS = peripheral nervous system; CVS = cardiovascular system; ENT = ear, nose and throat; Oph and Muc = ophthalmic and mucocutaneous. Dark gray bar denotes total, light gray bar denotes surviving group, and black bar denotes mortality group.

Table 1. Clinical findings of ANCA-associated vasculitis patients and differences between survivor group and mortality group at baseline

	Total (n = 99)	Survivor group (n = 84)	Mortality group (n = 15)	p value
Age	67 ± 12	67 ± 13	74 ± 8	0.02
Sex (male:female)	35:64	32:51	3:12	NS
S-Cr, mg/dl	4.1 ± 2.9	4.0 ± 2.9	4.6 ± 2.8	NS
eGFR, ml/min/1.73 m^2	18.2 ± 16.7	19.2 ± 17.4	12.6 ± 11.3	NS
Albumin, g/dl	3.0 ± 0.7	3.1 ± 0.6	2.8 ± 0.8	NS
CRP, mg/dl	6.5 ± 6.8	6.0 ± 6.6	9.5 ± 7.3	NS
IgG, mg/dl	1,529.6 ± 506.1	1,528.9 ± 520.9	1,533.4 ± 423.0	NS
MPO-ANCA, EU	355.8 ± 547.4	380 ± 586	222 ± 189	NS
U-P, g/day	1.6 ± 1.3	1.5 ± 1.3	1.7 ± 1.4	NS
U-RBC, n/HPF	57.7 ± 37.9	57.2 ± 38.1	66.2 ± 36.3	NS
Cyclophosphamide, n	19	15	4	NS
Plasma exchange, n	5	4	1	NS
Hemodialysis, n	32	21	11	NS
BVAS	14.9 ± 5.5	14.5 ± 5.6	17.5 ± 4.1	NS
MPA:RLV	73:26	59:25	14:1	NS

Values are expressed as means ± SD. S-Cr = Serum creatinine; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein; U-P = proteinuria; U-RBC = urinary red blood cells; BVAS = Birmingham Vasculitis Activity Score; MPA = microscopic polyangiitis; RLV = renal limited vasculitis; NS = not significant.

There were no significant differences in organ involvement between those who survived and the patients who died (fig. 2). Furthermore, because most deaths were within 6 months of onset, the changes in clinical data at 1 and 3 months were also compared between these two groups. As shown in table 2, CRP decreased in both groups (9.5 ± 7.3 mg/dl, 6.0 ± 6.7mg/dl to 2.2 ± 4.5 mg/dl, 0.7 ± 1.6 mg/dl; $p = 0.002$, $p < 0.0001$ in the mortality and surviving group, respectively), at 1 month as compared to baseline, while CRP in the surviving group decreased significantly as compared to that in the mortality group at 1 month (0.7 ± 1.6 mg/dl vs. 2.1 ± 4.4 mg/dl;

Table 2. Clinical characteristics between survivor group and mortality group during the 6 months follow-up period

	Survivor group		Mortality group		p value	
	1 month	3 months	1 month	3 months	1 month	3 months
S-Cr, mg/dl	3.1 ± 2.4	2.5 ± 1.8	3.2 ± 2.4	3.0 ± 1.5	NS	NS
eGFR, ml/min/1.73 m^2	22.5 ± 18.0	24.9 ± 17.4	13.9 ± 9.1	12.6 ± 7.9	NS	NS
Albumin, g/dl	3.3 ± 0.5	3.4 ± 0.5	2.8 ± 0.4	2.7 ± 0.6	0.006	0.0004
MPO-ANCA, EU	139.1 ± 182.1	41.4 ± 86.3	59.3 ± 61.3	11.1 ± 8.1	NS	NS
CRP, mg/dl	0.7 ± 1.6	0.6 ± 1.3	2.2 ± 4.5	3.6 ± 4.4	0.04	0.0002
U-P, g/day	1.0 ± 1.0	0.8 ± 1.3	1.3 ± 2.0	0.5 ± 0.6	NS	NS
U-RBC, n/HPF	38 ± 39	16 ± 24	35.6 ± 41.7	16.5 ± 20.5	NS	NS

Values are expressed as means ± SD. S-Cr = Serum creatinine; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein; U-P = proteinuria; U-RBC = urinary red blood cells.

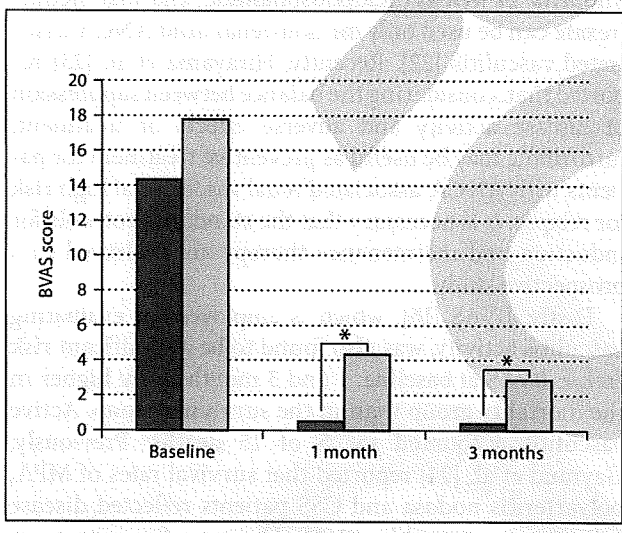

Fig. 3. BVAS changes in the surviving and mortality groups. At baseline, 1 and 3 months, BVAS was significantly higher in the mortality than in the surviving group. Dark gray bar denotes surviving group and light gray bar denotes mortality group, * $p < 0.05$.

Table 3. Multiple regression analysis for risk factors of survival time

Parameter	F value	p value
Age	2.4	NS
Sex	1.7	NS
Albumin	0.9	NS
CRP	0.6	NS
S-Cr	1.1	NS
eGFR	2.1	NS
IgG	0.1	NS
MPO-ANCA	0.6	NS
U-P	0.9	NS
U-RBC	2.6	NS
Cyclophosphamide	0.1	NS
Plasma exchange	0.4	NS
BVAS at baseline	1.5	NS
BVAS at 1 month	4.7	0.03
BVAS at 3 months	14.6	0.0003

CRP = C-reactive protein; S-Cr = serum creatinine; eGFR = estimated glomerular filtration rate; U-P = proteinuria; U-RBC = urinary red blood cells; BVAS = Birmingham Vasculitis Activity Score; NS = not significant.

$p = 0.04$). Similarly, at 3 months, CRP was significantly higher (3.6 ± 4.4 mg/dl) in the mortality group than in the surviving group (0.6 ± 1.3 mg/dl; $p = 0.0002$). Significant decreases in Alb at 1 and 3 months were observed in the mortality group (2.8 ± 0.4 and 2.7 ± 0.6 g/dl) as compared to the surviving group (3.3 ± 0.5 and 3.4 ± 0.5 g/dl; $p = 0.006$, $p = 0.0004$). No significant changes in other parameters, i.e. eGFR, S-Cr, MPO-ANCA titer, IgG, U-P and U-RBC, were observed between the surviving and mortality group within 6 months of the onset. Disease activity was also evaluated at 1 and 3 months. BVAS were significantly higher in the mortality group (4.7 ± 7.5, 3.3 ± 6.0) than in the surviving group (0.5 ± 1.9, 0.4 ± 1.5; $p < 0.0001$, $p = 0.002$) (fig. 3).

In addition, we analyzed independent risk factors for mortality. Multiple regression analysis (table 3) identified

PR3-ANCA at baseline and BVAS at 1 and 3 months as independent risk factors influencing the survival time ($p = 0.01$, $p = 0.03$, $p = 0.0003$). There were no significant risk factors among age, sex, albumin, CRP, S-Cr, eGFR, IgG, MPO-ANCA, U-P, U-RBC, cyclophosphamide, plasma exchange and/or BVAS at baseline.

Discussion

Predicting the clinical course and response to therapy of patients with ANCA-associated vasculitis is a major challenge. In contrast to PR3-associated vasculitis, which has been widely studied, there are few publications on the relevance and outcomes of ANCA-associated vasculitis. In the present study, we aimed to determine the prognosis and outcome of ANCA-associated vasculitis.

Deaths and renal deaths mostly occurred in the early stage, within the first 6 months of follow-up. Later, survival curves reached a plateau. In our study, mortality was significantly associated with disease severity as assessed by BVAS, CRP, and Alb at 1 and 3 months. At baseline, mortality was associated with older age. The main causes of deaths were mainly infection and progressive vasculitis. We could not follow-up the data from the mortality group at 6 months and therefore did not show the comparison of the data between survivor and mortality group.

First, mortality increased significantly with age, confirming previous findings. It has been suggested that disease may be more severe and resistant to treatment in the elderly than in younger patients [17–19]. Five of 9 patients died of infections and 4 patients had *P. carinii* pneumonia, suggesting an increased sensitivity to ateroids in an aging immune system. Because peripheral white blood cell and/or lymphocyte counts were influenced by steroid therapy, we did not analyze the data. In a previous report, when trimethoprim-sulfamethoxazole was administered, a reduction was observed in the occurrence of *Pneumocystis* pneumonia, and *Pneumocystis* pneumonia-related mortality was significantly reduced [20]. Four patients with *Pneumocystis* pneumonia were not treated with trimethoprim-sulfamethoxazole. As this intense immunosuppression increases the risk of infections in association with vasculitis, prescription of trimethoprim-sulfamethoxazole during the induction therapy with immunosuppressive agents may be advised.

Next, concerning ANCA testing, MPO-ANCA levels were not associated with mortality. There have been few reports on mortality in relation to ANCA testing. In the management of patients with anti-MPO-associated vasculitis, Terrier et al. [21] evaluated the relevance of monitoring MPO-ANCA levels. According to their study, MPO-ANCA levels were a very useful and relevant surrogate marker of disease activity. In our study, despite induction therapy in the early stage, after a mean follow-up of 22 ± 2 months, 3 of 99 patients experienced relapses. MPO-ANCA was elevated at the time of relapse. Our relapse patients had never been treated with immune suppressants. One patient had even discontinued steroid therapy. Therefore, the maintenance therapy strategy for ANCA-associated vasculitis is important. Randomized controlled trials focusing on induction and maintenance of remission of ANCA-associated vasculitis have indicated that the rate of remission induction with the standard regimen is approximately 90% at 6 months, that maintenance of remission can be achieved with oral azathioprine as well as cyclophosphamide, and that methotrexate can be used only for non-renal mild ANCA-associated vasculitis [22]. Recently, Hirayama et al. [23] reported that, considering the balance between suppression of disease activity and adverse effects of treatment, mizoribine may be useful as preventive treatment for patients with ANCA-associated renal vasculitis at high risk for relapse. It is necessary that the standard protocols for induction and maintenance therapy are evaluated in a prospective study.

Lastly, BVAS [16], which is employed for evaluating vasculitis activity, was also found to be a significant risk factor. BVAS at baseline, 1 and 3 months were higher in the mortality group than in the surviving group. Active vasculitis accounted for 5 of 15 deaths. Previously, Gayraud et al. [24] reported that survival rates of MPA, polyarteritis nodosa and CSS patients reflected disease severity, as assessed by BVAS. However, few reports on the association of ANCA-associated vasculitis and BVAS have focused on survival rate [25]. In our study, there was no correlation between BVAS and MPO-ANCA levels, or between BVAS and CRP. CRP was significantly higher in the mortality than in the surviving group at both 1 and 3 months. However, CRP might have been influenced by both infection and vasculitis activity. Differentiating infection from active vasculitis has often been difficult [26]. In addition, Alb was significantly lower in the mortality than in the surviving group at both 1 and 3 months. Inflammation decreases albumin synthesis and increases the albumin fractional catabolic rate, providing 2 mechanisms for hypoalbuminemia. Hypoalbuminemia was shown to be a risk factor for cardiovascular mortality in hemodialysis patients [27]. There was no correlation be-

tween BVAS and CRP. Based on this finding, we recommend that the intensity of initial treatment be aimed at disease severity. Employing BVAS improved the ability to evaluate therapeutic responses.

Several limitations of this study, including (1) this is an observational and retrospective study, (2) treatment regimens were not controlled, (3) vasculitis patients involved in this study were mainly from nephrology departments, and (4) the data were collected from ANCA-associated patients in a restricted area, are suggesting the presence of patient bias.

In conclusion, these observations confirm poor survival within 6 months of onset in patients with ANCA-associated vasculitis. BVAS highlights the strong impact on patient survival. Infection was the most common cause of death in patients with ANCA-associated vasculitis. To improve the prognosis of patients with ANCA-associated vasculitis, it may be necessary to detect this disease in earlier stages, to treat infections in association with maintenance of nutritional status, all of which could improve the prognosis of these patients.

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Clinical Transplantation

Case Report

Two cases of ANCA-associated vasculitis in post-transplant kidney: relapse and *de novo*

Tabata H, Honda K, Moriyama T, Itabashi M, Taneda S, Takei T, Tanabe K, Teraoka S, Yamaguchi Y, Oda H, Nitta K. Two cases of ANCA-associated vasculitis in post-transplant kidney: relapse and *de novo*. Clin Transplant 2009: 23 (Suppl. 20): 49–53.

Abstract: Two cases of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (ANCA-V) occurred in the transplanted kidney were reported. Case 1 was a 57 yr-old female whose original disease was MPO-ANCA-V. A relapse of necrotizing crescentic glomerulonephritis occurred one year after transplantation with positive serum reaction for MPO-ANCA. In spite of several immunosuppressive treatments, the disease progressed and she returned to hemodialysis treatment three yr and seven months after transplantation. Case 2 was a 34 yr-old female whose original disease was IgA nephropathy. She had a stable clinical condition during 13 yr after transplantation; however, *de novo* onset of necrotizing crescentic glomerulonephritis occurred at 14 yr 10 months after transplantation with positive serum reaction for MPO-ANCA. She returned to hemodialysis treatment five yr after the onset of ANCA-V. Urinary abnormities such as microhematuria and proteinuria were useful diagnostic findings but the titers of serum MPO-ANCA were relatively low in both patients. Concerning the treatment, steroid pulse therapy was effective in some extents but the disease progressed to graft failure in both cases. ANCA-V is a severe glomerulonephritis which can occur in kidney allograft in the manner of relapse and *de novo*. Detection of urinary abnormalities and positive serum ANCA combined with histological confirmation of necrotizing crescentic glomerulonephritis and/or vasculitis is required for early diagnosis and effective treatment of ANCA-V in renal transplant patients.

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Key words: *de novo* – kidney transplantation – MPO-ANCA – necrotizing crescentic glomerulonephritis – relapse

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Introduction

ANCA-associated vasculitis (ANCA-V) is a small vessel vasculitis which frequently affects intra-renal small vessels and glomerular capillaries leading to necrotizing crescentic glomerulonephritis. ANCA-V typically presents a rapidly deterioration of renal function and frequently results in end-stage renal failure. In kidney transplantation, a relapse of ANCA-V can occur frequently in transplant patients (1–4). We experienced two cases of ANCA-V in renal allograft; one was a recurrent case and the other was a *de novo* case. Therapeutic interventions including usual immunosuppressive treatment and additional intravenous steroid pulse therapy were not successful and both the patients progressed to graft failure within several years after the onset of the disease. We report here the clinical details of the two cases and discuss some critical points for early diagnosis and treatment for this highly aggressive glomerular disease which can occur after kidney transplantation.

Case 1

A 52-yr-old woman was admitted to our hospital because of anasarca, pleural effusion, and other uremic symptoms in November 2000 (Fig. 1). Laboratory examination showed blood urea nitrogen (BUN) 130mg/dL, Cr11.4 mg/dL, and

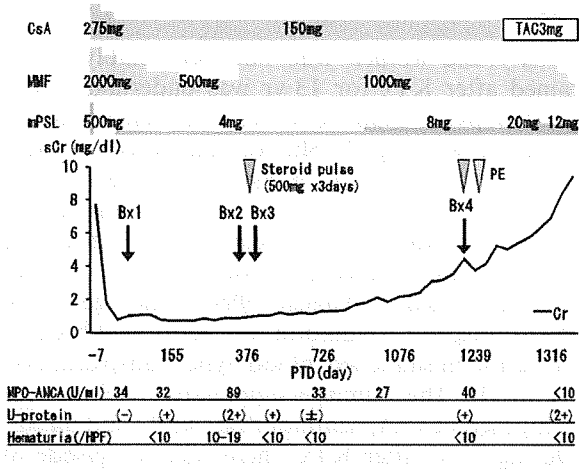

Fig. 1. Clinical course of case 1. CsA: cyclosporine; MMF: mycophenolate mofetile; TAC: tacrolimus; mPSL: methylprednisolone; PE: plasma exchange; Bx: graft biopsy.

MPO-ANCA 590 U/mL (normal range: < 10 ELISA unit). She was diagnosed with renal failure because of ANCA-V and initiated hemodialysis treatment. Intravenous steroid pulse therapy (methyl prednisolone 500 mg/d × 3d) and oral steroid administration (0.8 mg/kg/d) was started, but her renal function did not recover and maintenance dialysis was continued. She received living non-related kidney transplantation (KTx) from her husband in July 2003. Three sessions of double filtration plasma pheresis (DFPP) was performed before KTx and the immunosuppressive regimen using cyclosporine-A (CsA), mycophenolate mofetil (MMF), and methyl prednisolone (mPSL) was started. After KTx, the allograft function was stable and the protocol biopsy performed at post-transplantation day (PTD) 10 showed no signs of rejection. The sCr level had been maintained at 1.0 mg/dL during the next 12 months after transplantation. The second biopsy was performed in July 2004 (358 PTD) because of an increase of s-Cr level (1.3 mg/dL) and urinary abnormalities; proteinuria (2+) and microhematuria (urinary red blood cells: 10–19/high power field (HPF)). The patient provided informed consent before biopsy.

The biopsy (Fig. 2A,B) revealed that two globally sclerotic glomeruli in the total 15 glomeruli and seven glomeruli among the 13 remaining glomeruli showed cellular or fibrocellular crescents with fibrinoid necrosis and inflammatory cells infiltration (Fig. 2B). In the interstitium, a mild degree of tubular atrophy and fibrosis was recognized, but no tubulointerstitial rejection was observed (Fig. 2A). On immunofluorescent exammination, no significant immunoglobulin and complement deposition were observed except a slight deposition of IgM in the mesangial area. These histological finding combined with an increased titer of serum MPO-ANCA (89 U/mL) lead to the diagnosis of relapsing ANCA-V in the kidney allograft.

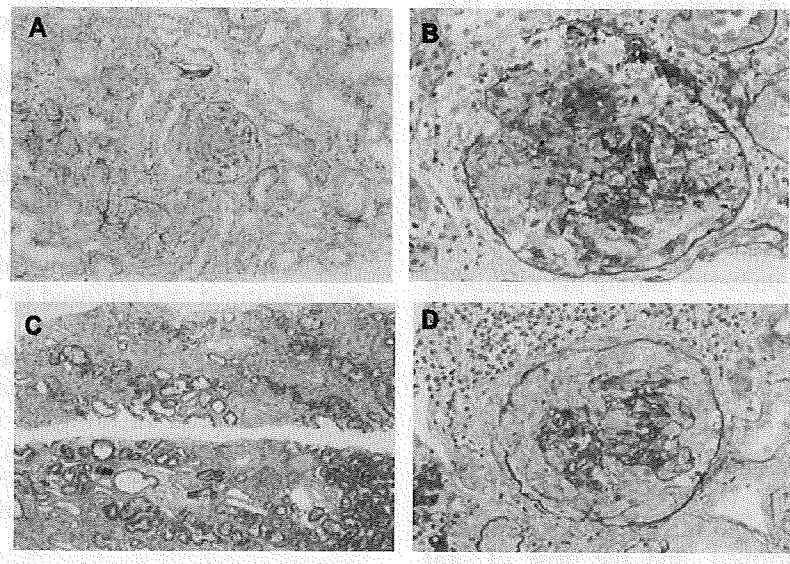

Fig. 2. Renal allograft biopsy findings of case 1. **A and B**: The second biopsy obtained at 358 post-transplantation day (PTD). Two globally sclerotic glomeruli in the total 15 glomeruli and seven glomeruli among the 13 remaining glomeruli showed cellular or fibrocellular crescents with fibrinoid necrosis and inflammatory cells infiltration (B). In the interstitium, a mild degree of tubular atrophy and fibrosis was recognized, but no tubulointerstitial rejection was observed (A). **C and D**: The fourth biopsy obtained at 1183 PTD. Twenty-three out of the 33 glomeruli were globally sclerotic and among the remaining 10 glomeruli eight had crescent formation composed of five cellular (D), two fibrocellular, and one fibrous crescent. Advanced tubulo-interstitial changes was also observed (C). The histological diagnosis was persistent ANCA-V and severe interstitial fibrosis and tubular atrophy (IF/TA).

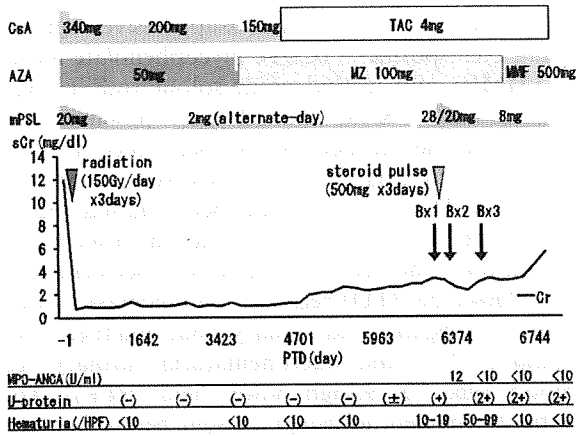

Fig. 3. Clinical course of case 2. CsA: cyclosporine A; MMF: mycophenolate mofetile; TAC: tacrolimus; mPSL: methylprednisolone; AZA: azathioprine; MZ: mizoribine; Bx: graft biopsy.

Intravenous steroid pulse therapy was performed resulting decreased proteinuria(+) and disappearance of microhematuria. The third renal biopsy (not shown) was performed one month after the treatment to evaluate the effect of the treatment. Five glomeruli were globally sclerotic among the total 21 glomeruli, and cellular crescent formation was observed in the two of the remaining 16 glomeruli showing fibrosing tendency and adhesion to Bowman's capsule. The overall activity of the necrotizing glomerulonephritis was slightly decreasing by the intravenous steroid pulse therapy.

During the next two yr, the sCr level increased gradually and reached to 3.0 mg/dL at the time of 39 months after transplantation with complication of urinary tract infection and enterocolitis, the fourth biopsy (Fig. 2C,D) was performed to evaluate the cause of progressive graft dysfunction. Twenty-three out of the 33 glomeruli were globally sclerotic and eight glomeruli among the remaining 10 glomeruli had crescent formation composed of five cellular, two fibrocellular, and one fibrous crescent (Fig. 2D). Advanced tubulo-interstitial changes and severe arteriosclerosis were also observed (Fig. 2C). The histologic diagnosis was persistent ANCA-V and severe interstitial fibrosis and tubular atrophy (IF/TA). The intravenous steroid pulse therapy and three sessions of plasma pheresis were performed, and the dose of oral mPSL administration was increased to 20 mg/d with replacement of CsA to tacrolimus (TAC). In spite of these intensive treatments, sCr progressively increased and she returned to maintenance hemodialysis treatment at 42 months after the KTx.

Case 2

A 34 yr-old women who had been stably maintained after KTx for 13 yr was undertaken allograft biopsy to examine proteinuria, hematuria and increased sCr (Fig. 3). She was diagnosed with IgA nephropathy by renal biopsy at the age of 15 yr old. She progressed to end-stage renal failure and started hemodialysis treatment at 17 yr old. Living related kidney transplantation from her mother was performed in August 1989 at the age of 19. Post-transplant irradiation was performed because of minor mismatched blood type transplantation (A to O). The immuno-suppressive regimen was composed of CsA, azathioprine (AZA) and mPSL. During 13 yr after KTx, there was no episode of rejection and her sCr was stable without any signs of proteinuria or hematuria. In 2003 (33 yr old), sCr was slightly increased with mild proteinuria and hematuria and the first renal biopsy was performed at 5402 PTD. The patient provided informed consent before biopsy.

The first biopsy (Fig. 4A, B) revealed that eight out of the total 22 glomeruli were globally sclerotic and among the remaining 14 glomeruli, nine glomeruli had tuft necrosis with cellular crescents. The crescentic glomeruli accompanied a destruction of the Bowman's capsule and interstitial inflammation (Fig. 4B). Severe tubulointerstitial nephritis with tubular atrophy and interstitial fibrosis were observed with mild peritubular capillaritis (Fig. 4A). No mesangial deposition of IgA or C3 in immunofluorescent examination and no electron dense deposit in the mesangium under electron microscopy were likely to rule out a possibility of recurrent IgA nephropathy with crescent formation. A slight increase of serum MPO-ANCA (12 U/mL) and the histological findings of necrotizing crescentic glomerulonephritis suggested us a *de novo* onset of ANCA-V. Intravenous steroid pulse therapy (mPSL 500mg/d × 3) was performed and followed by oral mPSL administration (0.6 mg/kg/d).

Two months later, the second renal biopsy (not shown) was performed to evaluate the effectiveness of the treatment. In the total 14 glomeruli, eight were globally sclerotic and four had tuft necrosis with fibrocelluar or fibrous crescent formation, suggesting a tendency of inactivation of glomerular inflammation although tubulointerstitial nephritis and peritubular capillaritis were still persistent. Thereafter, the proteinuria and hematuria persisted and sCr increased at the level of 2.41 mg/dL. In December 2005, the third biopsy (Fig. 4C, D) was performed at 5962 PTD to evaluate the cause of graft dysfunction. Seven

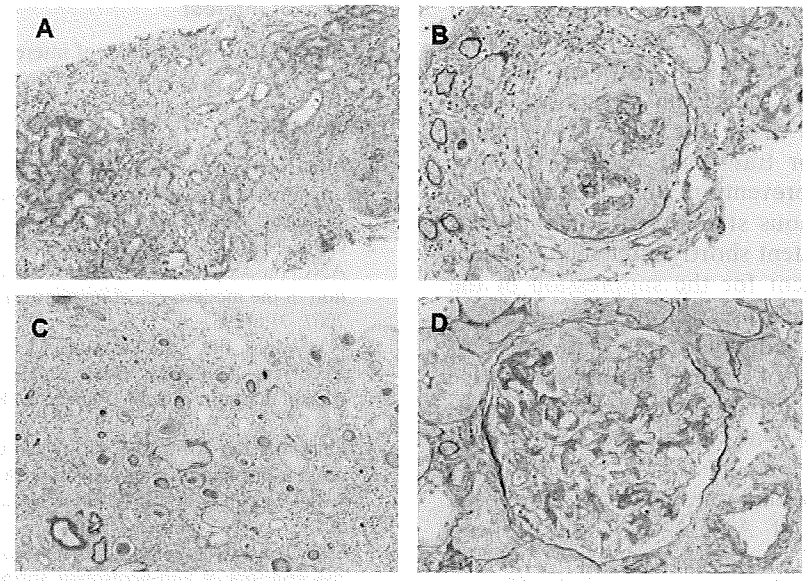

Fig. 4. Renal allograft biopsy findings of case 2. **A and B**: The first biopsy obtained at post-transplantation day (PTD) 5402. Eight out of the total 22 glomeruli were globally sclerotic and among the remaining 14 glomeruli, nine glomeruli had tuft necrosis with cellular crescents. The crescentic glomeruli accompanied a destruction of the Bowman's capsule and interstitial inflammation (**B**). No mesangial deposition of IgA or C3 in immunofluorescent examination was likely to rule out a possibility of relapsing IgA nephropathy. Severe tubulointerstitial nephritis with tubular atrophy and interstitial fibrosis were observed with mild peritubular capillaritis (**A**). **C and D**: The third biopsy obtained at PTD 5962. Seven out of total 15 glomeruli were globally sclerotic and among the remaining eight glomeruli, three had crescent formation (one cellular and two fibrocellular). Glomerular changes of transplant glomerulopathy were segmentally observed in some glomeruli (**D**). Severe tubulointerstitial changes with peritubular capillaritis was observed, but C4d in PTC was negative (**C**). Histological diagnosis was persistent ANCA-V and advanced IF/TA with chronic rejection.

out of total 15 glomeruli were globally sclerotic and among the remaining eight glomeruli, three had crescent formation (one cellular and two fibrocellular) (Fig. 4D). Glomerular changes of transplant glomerulopathy were observed in some glomeruli. Tubulointerstitial changes were advanced and mild grade of peritubular capillaritis consisting of mononuclear cell infiltration was still persisting, although no C4d was detected in the peritubular capillary (PTC). Histological diagnosis was persistent ANCA-V and advanced IF/TA with chronic rejection. The graft function gradually deteriorated and hemodialysis treatment was started three yr after the third biopsy (five yr after the onset of ANCA-V). The cause of graft failure was considered to be both the persistent ANCA-V and chronic rejection.

Discussion

ANCA-associated vasculitis (ANCA-V) is also a severe form of glomerulonephritis in kidney allograft which frequently relapses and progresses to renal failure unless proper diagnosis and treatment was performed in the early stage of the disease. Early detection of urinary abnormality and serum ANCA as well as histological confirmation of necrotizing crescentic glomerulonephritis is required for the management of kidney transplanted patients with ANCA-V.

The serum titer of ANCA is pathognomonic and usually correlated with the disease activity. In case 1, MPO-ANCA had been detected in low titer after KTx and increased at the second biopsy by which necrotizing crescentic glomerulitis was diagnosed. On the other hand, the MPO-ANCA in case 2 was only detected in low titer at the onset of the disease and became negative thereafter although the histologic lesions were still active. The discrepancy between the titer of ANCA and disease activity is sometimes observed in the patients with ANCA-V in native kidney (5). A possible explanation of the low ANCA titer in our cases might be related to the immunosuppressive therapy for kidney transplantation.

Urinary abnormalities such as microhematuria and proteinuria are good indicators for the diagnosis of relapsing and *de novo* glomerulonephritis in kidney allograft in both cases. Combined with the urinary abnormalities, a confirmation of characteristic histological lesions to ANCA-V; necrotizing crescentic glomerulonephritis and/or small vessel vasculitis, by renal biopsy was required for the diagnosis of ANCA-V.

Immune-suppressive treatment including oral and intra-venous steroid have been proposed for ANCA-V, however the ideal treatment has not been established yet. Reviewing the consequences of the present two cases, a calcineurin inhibitor with usual dose for transplant patients was not effective for the prevention and treatment for ANCA-V. Intravenous steroid pulse therapy was effective in some extent shortly after the treatment but was not sufficient for the suppression of the disease in long-term observation. We speculated that the oral steroid administration with a dose of 0.8–1.0 mg/kg/BW of prednisolone must be required after steroid-pulse therapy for the management of ANCA-V as well as the ANCA-V in native kidneys.

Several additional therapies have been proposed for the treatment of ANCA-V. The European Vasculitis Study Group (EUVAS) reported the comparison between intravenous steoroid therapy and plasma pheresis in combination with oral steroid and cyclophosphamide therapy for the treatment of ANCA-V patients with severe renal impairment. It demonstrated that the plasma pheresis was more effective than intravenous steroid pulse therapy (6). Ito-Ihara et al. reported that the effectiveness of the intra-venous immunoglobulin infusion therapy combined with the ordinary immune suppressive treatment (7). We have another renal transplant patient whose original renal disease was ANCA-V, and who was treated with basiliximab, anti-IL2Rα (CD25), for induction of immunosuppressive therapy. The patient has not experienced a recurrence of ANCA-V during 16 months after the kidney transplantation, suggesting that the basiliximab might have a role for the prevention of ANCA-V recurrence. An increase of CD4+ CD25+ regulatory T cell number was reported in the patients with ANCA-V (8). The regulatory T cell is considered to be important for immunological tolerance and to be associated with the etiology of autoimmune animal models (9) and human autoimmune diseases (10–13). Further study is required to establish the effectiveness of these treatments, including basiliximab, for the treatment of ANCA-V in renal transplanted patients.

Conflict of interest

The authors have no conflict of interest to declare.

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LETTER TO THE EDITOR

Mizoribine reduces serum KL-6 levels in ANCA-associated vasculitis

Shogo Fujita · Kouichi Hirayama · Yujiro Ogawa · Homare Shimohata · Masaki Kobayashi

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To the Editor

Interstitial pneumonitis is one of the life-threatening diseases associated with ANCA-associated vasculitis. The measurement of serum levels of KL-6, which is a MUC1 mucin and is expressed on type II alveolar pneumocytes and bronchial epithelial cells [1], may be a good monitoring system for the diagnosis and follow-up of interstitial pneumonitis in ANCA-associated vasculitis patients [2]. Moreover, elevated serum KL-6 levels were reduced during convalescence induced by glucocorticoid therapy [2]. In the present case, the elevated serum KL-6 level was preserved during glucocorticoid therapy, but decreased to within the normal range with additional treatment by mizoribine (MZR).

A 65-year-old woman visited our hospital complaining of a dry cough and low-grade fever. Crepitate sounds were heard in her chest, and chest X-rays and computed tomography showed interstitial pneumonitis in both lower lung fields. On urinalysis, mild proteinuria (urinary excretion of protein, 0.5 g/day), hematuria, and cellular casts were revealed. Mild anemia (hemoglobin concentration, 11.5 g/dl) and leukocytosis (11,000/mm^3) were observed. Although her serum creatinine level (0.66 mg/dl) was within the normal range, her serum cystatin C level was elevated to 0.87 mg/l. Serology revealed elevated levels of C-reactive protein (8.04 mg/dl), MPO-ANCA (208.5 U/ml), and KL-6 (526 U/ml). The major histological finding of renal biopsy was focal necrotizing glomerulonephritis without deposition of immunoglobulins or complements. She was diagnosed with MPO-ANCA-associated vasculitis and treated with an oral corticosteroid (prednisolone 30 mg/day). Although serum C-reactive protein was promptly normalized and MPO-ANCA titers gradually decreased, her high level of serum KL-6 was preserved (Fig. 1). Moreover, her HbA1c level was elevated to 7.0%, and she had been treated with nateglinide. Eighteen months after the initiation of glucocorticoid therapy, the dose of prednisolone was reduced to 7.5 mg/day and MZR was additionally started at a dosage of 150 mg once a day. At the start of MZR administration, no new symptoms of vasculitis or signs of relapse were noted, and ANCA titers were preserved within the normal range (below 9.0 U/ml). In the 6 months after the initiation of MZR therapy, her elevated serum KL-6 level gradually fell to within the normal range (below 500 U/ml). Although the extent of interstitial pneumonitis in both lower lung fields on chest X-rays and computed tomography was not changed after KL-6 was decreased to the normal range, that area was not expanded.

MZR has an immunosuppressive effect equivalent to that of azathioprine, but shows lower hepatic toxicity and myelosuppression. MZR is useful for preemptive treatment of ANCA-associated renal vasculitis patients with a high risk of relapse [3]. MZR caused the delay in the histological development of peribronchial and perivascular lymphocytic infiltrations in the lungs of MRL/lpr/lpr mice [4]. MZR improved renal tubulointerstitial fibrosis in a rat model of unilateral ureteral obstruction by inhibiting the infiltration of macrophages [5]. In this case, MZR may have improved pulmonary fibrosis by inhibiting the infiltration of inflammatory cells, resulting in reduced serum KL-6 levels. The above data indicate that MZR could be useful for the treatment of pulmonary lesions due to ANCA-associated vasculitis. Although MZR may be

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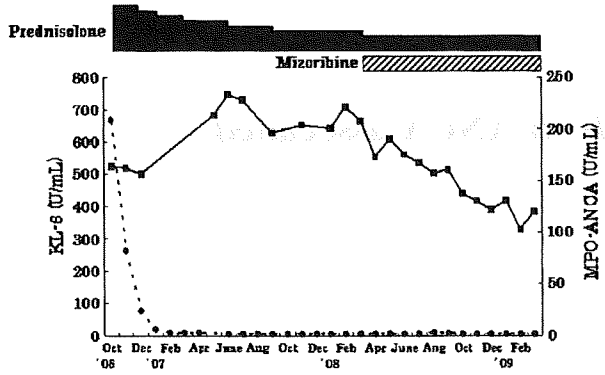

Fig. 1 Clinical course of a patient with MPO-ANCA-associated vasculitis treated with prednisolone and mizoribine. After the addition of mizoribine, her serum KL-6 level gradually decreased to within the normal range (below 500 U/ml). The *straight line* and *filled squares* show serum KL-6 levels, and the *dotted line* and *filled circles* show serum MPO-ANCA titers

effective for chronic or slowly progressive pulmonary fibrosis, the effect of MZR on alveolar hemorrhage or acute interstitial pneumonitis was not verified. Moreover, the possibility of a delayed corticosteroidal effect was undeniable in the present case. Therefore, further controlled study with a larger accumulation of patient data is needed.

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ORIGINAL ARTICLE

Clinicoepidemiological manifestations of RPGN and ANCA-associated vasculitides: an 11-year retrospective hospital-based study in Japan

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Abstract Antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides are major causes of rapidly progressive glomerulonephritis (RPGN). Although recent papers suggest differences in clinicoepidemiological manifestations of ANCA-associated vasculitis between Japan [microscopic polyangiitis (MPA) ≫ Wegener's granulomatosis (WG)] and Europe (WG ≫MPA), little is known about the prevalence and serological pattern. We retrospectively analyzed 27 RPGN patients who were admitted in our hospital over the past 11 years and who could be basically followed for more than 1 year, concerning the incidence of ANCA-related vasculitis, the presence of (MPO)/proteinase 3 (PR3)-ANCA and their clinical outcomes. As there were no PR3-ANCA single positive and/or WG patients, all patients were serologically divided into four groups; Groups I: MPO-ANCA single-positive patients ($N = 11$), II: MPO-ANCA and PR3-ANCA double-positive patients ($N = 3$), III: anti-glomerular basement membrane antibody (anti-GBM Ab)-positive patients ($N = 6$), and IV: all negative patients ($N = 7$). Patients in Groups II/III showed more severe manifestation at admission. However, in Group I, only 36.3% patients avoided death and/or dialysis-dependent end-stage renal disease. Most patients in Group IV were women (85.7%), and 50% of these patients was diagnosed as having rheumatic diseases. Every patient in Groups I–III was treated with oral corticosteroid and/or methylprednisolone pulse therapy. Most patients treated with immunosuppressants showed severe prognosis because of frequent recurrences of vasculitis and infectious episodes after repeated and prolonged treatments with immunosuppressants. Present analysis further confirms the epidemiological and serological differences in ANCA-related RPGN between Japan and Europe, and reinforced the fact that ANCA-associated vasculitis is the most serious causal disease for RPGN.

Keywords MPO-ANCA · PR3-ANCA · Microscopic polyangiitis (MPA) · Wegener's granulomatosis

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Introduction

More than 80% of patients with active, untreated, necrotizing small-vessel vasculitis associated with an absence or paucity of immunoglobulin (Ig) deposition in vessel walls have circulating antineutrophil cytoplasmic antibody (ANCA) [1]. The major clinicopathological expressions of ANCA-associated small-vessel vasculitis are Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome, and renal-limited vasculitis

(RLV). The incidence of WG among the ANCA-associated small-vessel vasculitides is higher than that of MPA and/or RLV in northern Europe [2–6], whereas conversely, the incidence of MPA/RLV is higher than that of WG in Japan [7]. Two nationwide Japanese surveys demonstrated that the number of patients with MPA and/or RLV is sixfold higher than those with WG in Japan [7–11]. In addition, it is also known that the presence of myeloperoxidase (MPO)-ANCA/proteinase 3 (PR3)-ANCA among Japanese patients with ANCA-associated vasculitides differs from that in European countries [4, 5, 12, 13]. Therefore, recent clinical studies indicate that ANCA-associated systemic vasculitides differ epidemiologically and serologically between Japanese and European countries [7, 11]. However, underlying mechanisms to explain the clinicoepidemiological difference remain unclear.

Vasculitis is a pathological process characterized by inflammation and necrosis of blood-vessel walls. In the kidney, vasculitis preferentially affects the small vessels (arterioles, capillaries, and venules). Therefore, microscopic hematuria with or without proteinuria is consistent with renal vasculitis. Over the past decade, clinical and experimental studies have provided compelling evidence that ANCA is a primary pathogenic factor in renal vasculitis, mainly by augmenting leukocyte–endothelial interactions [14–17]. The renal features of ANCA-associated systemic vasculitis include oliguria, microscopic hematuria, and proteinuria. Its central pathological feature is a pauci-immune focal segmental fibrinoid necrosis with extracapillary proliferation that may become crescentic glomerulonephritis with the accumulation of macrophages and epithelial cells in Bowman's space. This histopathological hallmark is frequently associated with rapid deterioration of renal function, clinically diagnosed as rapidly progressive glomerulonephritis (RPGN). Recent studies revealed an increasing incidence of ANCA-associated vasculitides in the older population [3, 18]. Therefore, RPGN patients with ANCA-associated vasculitides may show poor prognosis. In fact, although the prognosis of patients with RPGN is regarded as having improved over the past 20 years [14–17, 19], the prognosis of older patients with RPGN and their long-term renal survival is still a serious concern [11, 15, 20].

In this study, we retrospectively evaluated RPGN patients over the past 11 years who could be followed for more than 1 year or died within 1 year after onset, and we analyzed the incidence of ANCA-related vasculitis in RPGN, presence of MPO/PR3-ANCA, and their clinical outcomes. This hospital-based analysis may aid the understanding of clinicoepidemiological differences and serve as a baseline for future therapeutic approaches to ANCA-associated systemic vasculitides.

Materials and methods

Patients and assessment of disease manifestation

Twenty-seven patients with RPGN who were admitted to the Division of Nephrology of Juntendo University Hospital from April 1996 to December 2006 and could be followed for at least for 1 year after first admission ($N = 20$) or died within 1 year after onset ($N = 7$) were enrolled in this study. Renal involvement with features of glomerulonephritis, including erythrocyturia, erythrocyte cylindria, and glomerular proteinuria was seen in all patients. Patients with rapid aggravation of renal dysfunction with >30% rise in serum creatinine (Cr) levels over several days to a few months were defined as having RPGN [9, 10]. The hospital Ethical Committee approved the study design.

Age, gender, blood pressure, complete blood count (CBC), and serum markers such as C-reactive protein (CRP), Cr, MPO/PR3-ANCA and antiglomerular basement membrane (anti-GBM) antibody, and urinalysis were assessed at onset and admission and followed for >1 year. For evaluation of lung lesions, chest/abdominal X-rays and/or computed tomography (CT) scans were also examined and followed. Renal biopsies were performed in some patients (three men, four women; age 52.57 ± 12.34 years) who were in relatively good condition at admission. Correlation between clinical outcomes with or without each treatment, such as hemodialysis, plasmapheresis, steroid (oral corticosteroid and/or methylprednisolone pulse therapy), and immunosuppressants (mainly cyclophosphamide), and these clinical markers was evaluated. As most patients treated with immunosuppressants were followed not only by nephrologists but also by rheumatologists, indication of immunosuppressants was typically based on the clinical manual or guidelines of the Committee for Intractable Vasculitides in Japan, Ministry of Health, Labor, and Welfare, Japan. In addition, clinical severity of RPGN in each case was graded by the grading score of the Committee for Guidelines on Diagnosis and Therapy of Rapidly Progressive Glomerulonephritis in Japan, Special Study Group on Progressive Glomerular Disease, Ministry of Health, Labor and Welfare, Japan [9] (Tables 1 and 2). Patients were graded as follows: grade 1: 29.7% ($N = 8$), grade 2: 48.1% ($N = 13$), grade 3: 18.5% ($N = 5$) and grade 4: 3.7% ($N = 1$).

Serological tests for MPO-ANCA, PR3-ANCA, and anti-GBM antibody (anti-GBM Ab) were conducted using enzyme-linked immunosorbent assay (ELISA). MPO or PR3 were immobilized on microplates as antigens for each ELISA. Normal ranges in each MPO-, PR3-ANCA and anti-GBM Ab titers were settled under 10, 10, and 10 EU, respectively. All RPGN patients were serologically divided

into four groups, as follows: Group I: MPO-ANCA single-positive patients ($N = 11$, male:female = 6:5), Group II: MPO-ANCA and PR3-ANCA double-positive patients ($N = 3$, M:F = 3:0), Group III: anti-GBM -Ab-positive patients ($N = 6$, M:F = 2:4) (including MPO-ANCA-positive patients: $N = 4$, M:F = 2:2), and Group IV: all MPO-/PR3-ANCA and anti-GBM-Ab-negative patients ($N = 7$, M:F = 1:6, systemic lupus erythematosus: 3, rheumatoid arthritis: 1, MPA: 1, IgA nephropathy: 1, Henoch-Schonlein purpura: 1).

Statistical analyses

The significance of differences in age between each group (Table 1) was assessed by paired Student's t test using StatView statistical software (Hulinks, Tokyo, Japan).

Results

The number of RPGN patients treated in our hospital has been increasing since 2003 (Fig. 1). Although there was no clear difference in incidence between male and female patients (M:F 12:15), onset age of male RPGN patients ($N = 12$, 67.5 ± 13.55) was older than that of female patients ($N = 15$, 57.6 ± 10.91) ($P < 0.05$).

Serological analyses revealed no PR3-ANCA single-positive patients with RPGN (Table 1). Consistent with this result, WG patients were not included in this study. The age at first medical examination or admission (years old), serum Cr (mg/dl), CRP (mg/dl) and hemoglobin (Hb) (g/dl) were examined. The average age of patients in Group IV (54.3 ± 11.9) was significantly lower than those in other groups ($p < 0.05$) (Table 1). Serum Cr at admission in Group III was higher than that of the other groups (p value; Group III vs. Groups I, II and IV; 0.31, 0.06, and 0.15) (Table 2). There was no clear difference in anemia at admission among the groups (Table 2). CRP at admission in Group IV tended to be low, whereas in other groups, it varied widely (Table 2). Serological changes of MPO- and PR3-ANCA and a-GBM Ab at admission or just before admission/final data after treatments (EU) in each patient is summarized in Table 1.

The severity of RPGN was evaluated by a grading score [9], as shown in Tables 1 and 2. Average grades in each group are shown in Fig. 2 (Groups I vs. II vs. III vs. IV; 1.73 ± 0.65, 2.67 ± 1.53, 2.50 ± 0.55, and 1.57 ± 0.53). Higher grades at admission were observed in Groups II and III (Fig. 2).

Nine of 27 patients (six men: 66.67 ± 16.06 years old; grade 1: 0, grade 2: 4, grade 3: 4, grade 4: 1) showed abnormal shadows suggesting interstitial pneumonitis on X-ray and CT scan analyses summarized in Table 1. Fifty-six percent of those patients showed abnormal shadows indicating alveolar hemorrhage. Only one Group IV (serologically negative) patient had interstitial pneumonitis with alveolar hemorrhage. Average Birmingham Vasculitis Activity Score (BVAS) for patients with lung lesions was 21.33 ± 6.0 at admission. Their BVAS were correlated with grading scores [9] (grade 2: 19.75 ± 6.95, grade 3: 21.5 ± 5.80, grade 4: 27). In particular, three MPO-ANCA/anti-GBM Ab double-positive cases in Group III showed high BVAS (25, 27, and 30) at admission, with severe lung lesions (Table 1). In addition to interstitial pneumonitis, these patients showed vasculitis-related severe eye lesions and cardiovascular complications or stroke with visual disturbance.

We performed renal biopsies in seven patients (grade 1: 4, grade 2: 3) (Table 1). Patients with IgA nephropathy, lupus nephritis, and Goodpasture syndrome were included. All patients showed cellular and fibrous cellular crescents in >50% of glomeruli. Pauci-immune patterns in immunofluorescence analysis were observed in three patients (Group I/grade 1: 1, Group I/grade 2: 1, Group II/grade 1: 1), whereas one patient in Group III showed cellular crescents with linear IgG deposition in glomeruli. One patient in Group II/grade 2 showed 75% crescent formation (15/20 glomeruli) with not only perinuclear ANCA (P-ANCA) but also anti-hepatitis-C-virus (HCV) antibody and cryoglobulin. The systemic lupus erythematosus (SLE) patient (Group IV/grade I) showed cellular crescent formation with glomerular C1q deposition.

Patient and renal prognoses were divided into four groups: survival, dialysis-dependent end-stage renal disease (ESRD) alone, patient death alone, and ESRD/patient death. The prognosis for each grade of patients is shown in Fig. 3a, whereas the prognosis of each group of patients is summarized in Fig. 3b and Table 2. In MPO-ANCA single-positive Group I, only four patients did die or enter ESRD (4/11; 36.4%). Three patients in Group I who died had sepsis or lethal gastrointestinal bleeding with or without colonic penetration (Table 2). In the other groups, all patient deaths occurred within 1 year after onset. The major causes of patient death were severe infections and subsequent disseminated intravascular coagulation (DIC). Although all cases of death in Group III were due to pneumonia, one death, in a patient 93 years old, was based on aspiration pneumonia (Table 2). One patient in Group IV died because of cerebral hemorrhage.

All patients in Groups I, II, and III were treated with oral corticosteroid and/or methylprednisolone pulse therapy. Hemodialysis therapy was introduced directly without therapy by steroid or immunosuppressants in two of seven patients in Group IV. Methylprednisolone pulse therapy was used for most patients in Groups II and III (Group I: 46%, Group II: 100%, Group III: 83.3%, and Group IV:

Table 1 Diagnosis and disease activity

	Age	Sex	Year of admission	Serological analysis						Diagnosis	Grade	BVAS	Lung lesions	Lung XP/CT	Renal bx	Lesions
				MPO/ ANCA	(EU)	PR3/ ANCA	(EU)	a-GBM	(EU)							
Group I																
1	59	M	1996	+	100/<10	−		−		RLV/HCV	1		−		+	C/F Cres, Pim
3	58	M	1999	+	24/<10	−		−		MPA	2	15	+	RS		
4	84	M	1999	+	660/12	−		−		MPA	3	20	+	RS/EP		
9	65	F	1996	+	831/12	−		−		MPA/HCV/LC	2		−		+	C/F Cres, Pim
12	42	F	1998	+	142/<10	−		−		MPA	2		−			
17	76	F	2003	+	510/<10	−		−		RLV	2		−			
21	74	M	2005	+	640/<10	−		−		RLV	1		−			
22	68	M	2005	+	138/<10	−		−		RLV	1		−			
23	56	F	2006	+	142/<10	−		−		MPA	2	16	+	PH/RS/NO/CV		
24	55	M	2006	+	144/<10	−		−		RLV	1		−			
25	72	F	2006	+	88/<10	−		−		RLV	2		−			
Ave	64.45															
SD	11.9															
Group II																
2	75	M	1997	+	24/<10	+	24/<10	−		PN/RA	3	14	+	RS/PL/GC		
5	69	M	2000	+	175/<10	+	12/<10	−		MPA	4	27	+	RS		
6	63	M	2004	+	920/69	+	24/<10	−		MPA	1		−		+	C Cres, Pim
Ave	69															
SD	6															
Group III																
8	70	M	2002	+	208/<10	−		+	660/<10	RA	2		−			
14	42	F	2003	−		−		+	20/<10	GP s/o	2		−		+	C Cres, linear IgG
18	53	F	2003	+	91/<10	−		+	300/<10	MPA	2	30	+	PH/RS/PL/NO		
20	70	F	2004	+	42/<10	−		+	132/<10	MPA	3	25	+	PH/RS		
21	63	F	2005	−		−		+	117/<10	RLV	3		−			
26	93	M	2006	+	232/<10	−		+	24/<10	MPA	3	27	+	RS/EP/PH		
Ave	65.17															
SD	17.4															
Group IV																
7	42	M	2003	−		−		−		MPA	2	18	+	PH/RS/PL	+	C Cres, IgG±
10	49	F	1998	−		−		−		HSP	2		−			
11	57	F	1998	−		−		−		SLE	2		−			
13	38	F	2001	−		−		−		IgAN	1		−		+	C Cres, IgA3+

Table 1 continued

	Age	Sex	Year of admission	Serological analysis				Diagnosis	Grade	BVAS	Lung lesions	Lung XP/CT	Renal bx	Lesions
				MPO/ANCA (EU)	PR3/ANCA (EU)	a-GBM (EU)								
15	70	F	2002	–	–	–		RA/Cryogl	1		–			
16	58	F	2003	–	–	–		SLE	2		–			
19	66	F	2004	–	–	–		SLE	1		–		+	C Cres, C1q 1+
Ave	54.3	(*$P < 0.05$, vs. Groups I–III)												
SD	11.9													

MPO/ANCA myeloperoxidase antineutrophil cytoplasmic antibody, *EU* equivalent unit, *PR3/ANCA* proteinase 3 antineutrophil cytoplasmic antibody, *a-GBM* antiglomerular basement membrane, *BVAS* Birmingham Vasculitis Activity Score, *XP/CT* X-ray/computed tomography, *bx* biopsy, *MPA* microscopic polyangiitis, *RLV* renal limited vasculitis, *HCV* hepatitis C virus, *RA* rheumatoid arthritis, *LC* liver cirrhosis, *PN* polyarteritis nodosa, *GP* Goodpasture syndrome, *HSP* Henoch-Schönlein purpura nephritis, *SLE* systemic lupus erythematosus, *IgAN* immunoglobulin A nephropathy, *Cryogl* cryoglobulin, *RS* reticular shadow, *EP* emphysema, *PH* pulmonary hemorrhage, *NO* nodular opacity, *CV* cavitation, *PL* pleuritis, *GC* granulomatous change, *C Cres* cellular crescent, *F Cres* fibrous crescent, *Pim* pauci-immune, *Ave* average, *SD* standard deviation, + positive, – negative

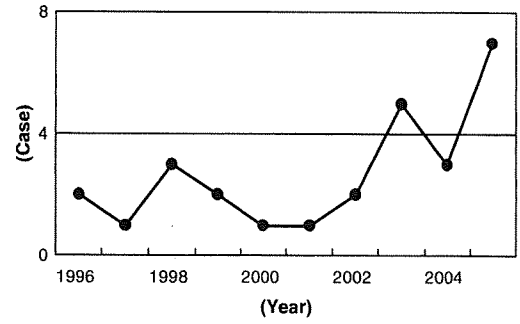

Fig. 1 Annual numbers of rapidly progressive glomerulonephritis (RPGN) patients who were admitted to Division of Nephrology, Juntendo University Hospital, from 1996 to 2006 and could be followed for more than 1 year

57%). Four of six patients in Group III received plasmapheresis therapy. The use of methylprednisolone pulse therapy increased with severity (grade 1: 50%, grade 2: 61.5%, grade 3: 80%, and grade 4: 100%). Only patients in grades 2 (30.7%) and 4 (100%) were treated with immunosuppressants, mainly with cyclophosphamide (Table 2). Eighty percent of patients treated with immunosuppressants died. These patients had strong disease activity and thus showed frequent recurrences of vasculitis and episodes of opportunistic infections, including *Candida albicans* and cytomegalovirus after treatments, even with prophylaxis treatments (Table 2).

Discussion

This study evaluated serological and prognostic outcomes in 27 patients with RPGN at the Division of Nephrology, Juntendo University Hospital, in the past 11 years. Although the average age of all RPGN patients was around 60 years (62.4 ± 13.3), that of male patients was >5 years older than that of female patients. However, this was partly due to the fact that serologically negative patients (M:F = 1:6) included relatively young women with rheumatic diseases and primary glomerulonephritis. In fact, the average age of ANCA-positive cases (66.6 ± 12.2) was older than that of the serologically negative group (54.3 ± 11.9).

Although we did not change the method for measuring ANCA and anti-GBM Ab in the study period, RPGN patients mainly with ANCA-associated vasculitis increased after 2003. In particular, in 2005, we had seven patients. This increment was consistent with the nationwide tendency [9, 10], suggesting that the increasing incidence may be partly due to an aging society, increased opportunity for serological measurement of MPO-/PR3-ANCA, and an increase in referral rates from home doctor to tertiary center hospitals such as university hospitals, based on an