Incidence of ANCA-Associated Primary Renal Vasculitis in the Miyazaki Prefecture: The First Population-Based, Retrospective, Epidemiologic Survey in Japan

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Clinicoepidemiological manifestations of the vasculitides differ geographically. According to a nationwide, hospital-based survey in Japan, the prevalence of microscopic polyangiitis (MPA) and/or renal-limited vasculitis (RLV) is much higher than that of Wegener's granulomatosis (WG). However, little is known about the incidence of antineutrophil cytoplasmic autoantibodies (ANCA)-associated primary renal vasculitis (PRV) in Japan. The incidence of PRV was retrospectively determined by a population-based method in Miyazaki Prefecture in Japan between 2000 and 2004. PRV was defined according to the following criteria from the European Systemic Vasculitis Study Group: (*1*) new patients with WG, MPA, Churg-Strauss syndrome (CSS), or RLV, (*2*) renal involvement attributable to active vasculitis, and (*3*) ANCA considered positive if the disease was not histologically confirmed. The numbers of patients with PRV in the years 2000, 2001, 2002, 2003, and 2004 were 9, 9, 9, 16, and 13, respectively. The male to female ratio was 24:32 and the average age was 70.4 ± 10.9 (mean ± SD) yr. The estimated annual incidence of PRV was 14.8 (95% confidence interval [CI] 10.8 to 18.9) and 44.8 (95% CI 33.2 to 56.3) per million adults (>15 yr old) and seniors (>65 yr old), respectively. Ninety-one percent of the patients were myeloperoxidase (MPO)-ANCA positive, but none were positive for proteinase 3 (PR3)-ANCA. There were no WG or CSS patients. The incidence of PRV did not differ between Japan and Europe, but WG was not widespread in Japan. Furthermore, the ratio of serum MPO to PR3-ANCA among Japanese with PRV was much higher than that found among European and US patients.

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Differences among several clinicoepidemiologic manifestations among vasculitides, such as Takayasu arteritis, giant cell arteritis, and Kawasaki arteritis, have been identified between Japan and European and/or American countries (1–3). The incidence of Wegener's granulomatosis (WG) among the anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated systemic vasculitides is higher than that of microscopic polyangiitis (MPA) in northern Europe (4–7). Conversely, two nationwide Japanese surveys demonstrated that the prevalence of patients with WG is very low compared with that of patients with MPA (8) and/or renal limited vasculitis (RLV) (9). The annual prevalence (*i.e.*, the estimated number of patients treated in 1997) of WG is only 2.3 per million, whereas that of MPA and/or RLV is approximately 13.8 per million (8,9). Therefore, the number of patients with MPA and/or RLV is six-fold higher than that with WG in Japan. Furthermore, myeloperoxidase-ANCA (MPO-ANCA) was identified in 79 to 93% of patients with MPA and/or RLV in Japan, whereas reports from Europe described the ratio as being 44 to 69% (6,10–15). Therefore, the ANCA-associated systemic vasculitides epidemiologically and serologically differ between Japan and European countries.

The annual incidence of ANCA-associated vasculitides in Japan remains obscure because the two previous nationwide surveys were conducted using hospital-based, retrospective methods that determined the prevalence but not the incidence of diseases (8,9). Therefore, the precise annual incidence of ANCA-associated vasculitides in Japan should be determined and compared with that of European countries and the United States. We examined whether the incidence of ANCA-associated vasculitides in Japan is lower than that in European counties, whether MPA and/or RLV is more prevalent than WG in Japan, and whether the ratio of MPO-ANCA/proteinase 3-ANCA (PR3-ANCA) among Japanese patients with ANCA-associated vasculitides differs from that among Europeans.

We conducted a population-based survey of primary renal vasculitis (PRV) in Miyazaki Prefecture on the basis of recent

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epidemiologic methods (5,6,16) and the subclassification of ANCA-associated vasculitides by the European Systemic Vasculitis Study Group (EUVAS) (17–19). We also considered the advice and findings from a direct visit and an inspection of the population and of medical facilities in Miyazaki Prefecture in February 2005 by UK collaborators. This is the preliminary study for a prospective, population-based, clinicoepidemiologic investigation that should define the epidemiologic differences between Japanese and European patients with ANCA-associated vasculitides.

Materials and Methods

Before the study, several candidate areas were considered for investigation. We conferred with our UK collaborators as to whether the area population was suitably defined and whether the area has only a few medical facilities to which patients could be referred. After inspecting the medical facilities with UK collaborators Drs. D. Scott, R. Watts, and D. Jayne during February 2005, central, west, and south Miyazaki Prefecture, Kyushu, Japan, was considered suitable (Figure 1). The case records of all patients who had received a diagnosis of PRV at four hospitals in central Miyazaki Prefecture (Miyazaki Medical College, Miyazaki Prefectural Hospital, Koga General Hospital, and Miyazaki Social Insurance Hospital) from January 2000 through December 2004 were reviewed. These institutions are the only referral centers in Miyazaki Prefecture for patients with renal diseases that require investigation, renal biopsy, and introduction into dialysis therapy. We identified patients with PRV from the renal biopsy registers and discharge summaries of the Departments of Internal Medicine and Otorhinolaryngology, as well as the pathologic specimen records at each hospital. The dialysis center belongs to the Department of Internal Medicine in all four hospitals. The population in these areas seldom undergoes medical examinations in the other parts of Miyazaki or other prefectures. In fact, only one "cross-boundary" referral from the north of Miyazaki Prefecture or adjoining prefectures was identified during 5 yr, and that patient was excluded from the study.

Patients with PRV were defined according to the following criteria (Table 1) in accordance with EUVAS (17–19): New patients with WG, MPA, Churg-Strauss syndrome (CSS), or RLV and renal involvement (elevated serum creatinine, hematuria, proteinuria, or red cell casts) attributable to active vasculitis with or without other organ involvement. The Chapel Hill Consensus Conference (CHCC) nomenclature (20) was used to define MPA, and American College of Rheumatology (ACR) criteria were (21) to define WG and CSS. RLV was defined as necrotizing vascular injury confined to the kidneys (11,18,22,23). All patients underwent serology tests for PR3-ANCA, MPO-ANCA, and anti–glomerular basement membrane (anti-GBM) antibody using an ELISA. When the ELISA results were negative, both cytoplasmic ANCA (C-ANCA) and perinuclear ANCA (P-ANCA) were tested further using indirect immunofluorescence. We excluded patients with anti-GBM antibodies and documented episodes of PRV before 2000. In addition, patients with Henoch-Schönlein purpura, systemic lupus erythematosus, or other connective tissue diseases were excluded. The month of symptom onset was taken as the date of PRV onset.

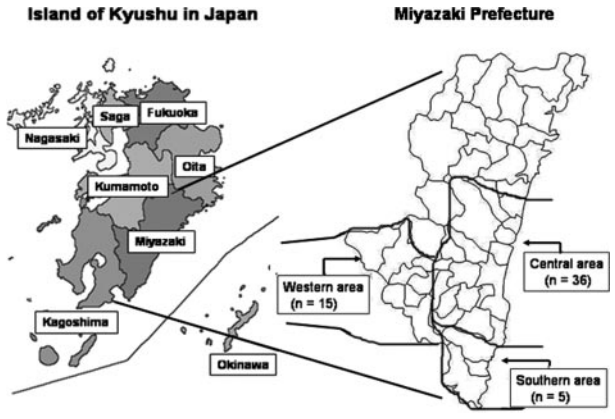

Figure 1. Map of study region and number of patients with primary renal vasculitis (PRV) between 2000 and 2004. Central, west, and south Miyazaki Prefecture.

Table 1. Inclusion criteria[a]

1. New patients with WG, MPA, CSS, or RLV, with or without histologic confirmation[b]
2. Renal involvement[c] with or without other organ involvements, attributable to active WG, MPA, CSS, or RLV
3. Positive serology for ANCA[d]

[a]1, 2, and 3 are required. CSS, Churg-Strauss syndrome; MPA, microscopic polyangiitis; RLV, renal limited vasculitis; WG, Wegener's granulomatosis.
[b]Histologic confirmation: Findings of necrotizing vasculitis and pauci-immune necrotizing, crescentic glomerulonephritis.
[c]Renal involvement: Elevated serum creatinine (>1.3 mg/dl), or hematuria (>30 red blood cells per high-power field), or proteinuria (>1 g/24 h), or red cell casts.
[d]ANCA negativity is allowed if the disease is confirmed histologically.

The numbers of adults (older than 15 yr) and seniors (older than 65 yr) who lived in Miyazaki Prefecture were 987,186 and 264,802, respectively, during 2004. In central, west, and south parts of the prefecture, the two populations comprised 767,988 (male *versus* female, 356,247 *versus* 411,741) and 200,962 people, respectively. The study population was relatively static during the study period, and we estimated the total immigration rate out of the study area during 2000 to 2004 to be <5%. However, for those who were older than 50 and older than 65 yr, the estimates fell to <1.5 and <0.8%, respectively. The 5-yr population decreased by only 7057 people. Urban areas were defined as cities (resident population >30,000), and rural areas were those that surrounded the urban areas. Agriculture is the main occupation of 19.1% of the rural adults and seniors and of 9.2% of these groups in the urban areas. These demographic data were obtained from the home page of the Miyazaki Prefectural office (http://www.pref.miyazaki.lg.jp/contents/org/honbu/toukei/jinko-setai/index.htm).

Continuous data are presented as means ± SD. Annual incidences are presented as simple proportions with 95% confidence intervals (CI). Seasonal differences were considered with the use of a Poisson regression model with covariates including season (February through April, May through July, August through October, and November through January), place of residence (rural/urban), and year (2000 through 2004). Incidence rate ratios across seasons and their 95% CI were estimated. The Poisson model was calculated by S-Plus (Insightful Corp., Seattle, WA).

Results

Fifty-six new patients with PRV were identified during the period from January 1, 2000, to December 31, 2004. All of them

Table 2. Laboratory data at admission ($n = 56$)[a]

CRP (mg/dl)			Creatinine (mg/dl)			Proteinuria (g/d)		
<0.5	0.5 to 2.0	>2.0	<1.0	1.0 to 3.0	>3.0	<1.0	1.0 to 2.0	>2.0
6	12	38	5	20	31	15	24	17

[a]C-reactive protein (CRP) normal range <0.5 mg/dl; creatinine normal range <1.0 mg/dl; proteinuria normal range <0.3 g/d.

Table 3. Glomerular lesions on renal biopsy specimens ($n = 33$)

Global Sclerosis				Crescents			
<10%	10 to 20%	20 to 30%	>30%	<25%	25 to 50%	50 to 75%	>75%
14	6	6	7	1	7	13	12

had systemic manifestations of vasculitis, such as fever of unknown origin, weight loss, myalgia, arthralgia, and malaise with or without multisystem involvement. C-reactive protein was elevated (5.8 ± 6.2 mg/dl), and surrogate markers of renal vasculitis, such as elevated serum creatinine (3.9 ± 2.8 mg/dl), proteinuria (1.8 ± 2.3 g/d), hematuria, and/or red cell casts, are outlined in Table 2. However, the kidneys, measured using abdominal echo and/or computed tomography, were not decreased in size. At the first admission, dialysis therapy was introduced into 17 patients, three of whom recovered and did not require further dialysis. Twenty-three patients had pulmonary symptoms with abnormal findings on chest x-ray films, three had mononeuritis multiplex, two had gastrointestinal bleeding, and one had otitis media. None had nasal lesions. Ten patients died at the first admission. Histologic evidence of pauci-immune, necrotizing, and crescentic glomerulonephritis and/or vasculitis was obtained from 35 patients, 33 of whom had undergone renal biopsy (Table 3). Five of the 33 patients who underwent biopsy were proved to be C-ANCA and P-ANCA/MPO-ANCA negative, whereas the other 51 patients were positive for MPO-ANCA. None of the patients was positive for either C-ANCA or PR3-ANCA (Table 4). The ACR criteria and/or CHCC definition did not uncover any patients with WG or CSS.

The numbers of recently registered patients with PRV were 9, 9, 9, 16, and 13 in 2000, 2001, 2002, 2003, and 2004, respectively. The male-to-female ratio was 24:32, and the average age was 70.4 ± 10.9 yr. Fifty-five and 45 patients were aged >50 and >65 yr, respectively, and the peak age group was 70 to 74 yr (Figure 2). All patients were from central, west, and south Miyazaki Prefecture (Figure 1). The annual incidence of PRV during the 5-yr period was 14.8 (95% CI 10.8 to 18.9) and 44.8 (95% CI 33.2 to 56.3) per million adults and seniors, respectively. These values increased during the last 2 yr to 18.9 and 57.2 per million people, respectively. The annual incidences per million male and female adults (13.5 [95% CI 11.4 to 15.5] *versus* 15.5 [95% CI 8.9 to 22.2]) did not differ. The annual incidence in urban (population 516,149) and rural (population 251,839) areas did not differ significantly (13.9 per million [95% CI 10.1 to 17.8] *versus* 15.9 per million [95% CI 10.4 to 21.4]).

Twenty-two of the 56 patients were aware of the onset of symptoms during the summer months, and two could not define the time of onset (others noticed symptoms during the following periods: February through April, 18.5%; May through July, 29.6%; August through October, 40.7%; November through January, 11.1%). The seasonal variation in annual incidence of PRV was observed in the result of the Poisson regression analysis. Compared with the incidence rate in November through January, higher rate ratios of 3.67 (95% CI 1.49 to 9.03) in August through October and 2.67 (95% CI 1.04 to 6.81) in May through July were observed, respectively (Figure 3). The annual incidence of PRV, accounting for the seasonal

Table 4. Maximum MPO-ANCA units during admission and results of indirect immunofluorescence assay for C-ANCA ($n = 56$)[a]

MPO-ANCA Titers (EU)				C-ANCA	
<20	20 to 200	200 to 640	>640	−	+
5	21	20	10	56	0

[a]Myeloperoxidase (MPO)-ANCA normal range <20 EU; cytoplasmic ANCA (C-ANCA) normal is negative.

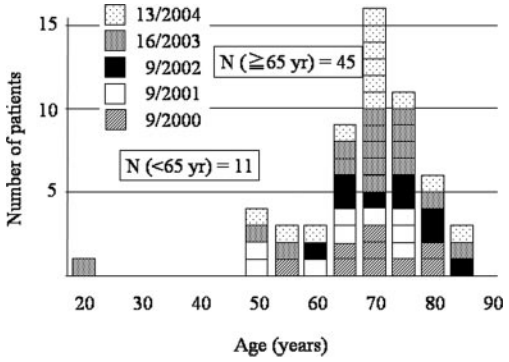

Figure 2. Number and age distribution of new patients with PRV from 2000 to 2004.

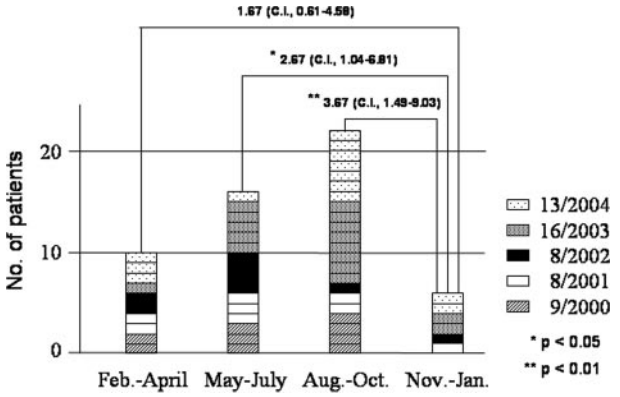

Figure 3. Number of patients with PRV, grouped by the onset time (the month of symptom onset) between 2000 and 2004, and estimated incidence rate ratios across seasons with their 95% confidence intervals by the Poisson regression model.

variation, was not statistically different between urban and rural areas.

Discussion

Previous nationwide surveys of ANCA-associated vasculitides in Japan used a retrospective, hospital-based method (8,9). Because the medical expenses of patients with MPA and WG were supported by the Ministry of Health, Labor and Welfare of Japan, previous nationwide government-supported surveys were directed to investigate prevalence (*i.e.*, the estimated number of patients treated in a year) but not the annual incidence of new ANCA-associated vasculitides. However, problems are associated with hospital-based surveys in that patients from tertiary and/or university referral centers usually are based on ill-defined denominator populations, and patients who are seen in tertiary hospitals might not be representative of those who are seen either at district hospitals or in the community, especially in terms of disease severity or age spectrum (5,10). Therefore, we used a population-based survey to investigate the incidence of ANCA-associated vasculitides.

The results showed that the estimated annual incidence of PRV in Miyazaki Prefecture was 14.8 per million, which was similar to that of ANCA-associated systemic vasculitides identified in several European studies (Table 5). The incidence rate in our study does not seem to be lower than expected in comparison with other epidemiologic studies, because it is considered that few patients with PRV died without reaching the hospital in the Japanese medical care system. However, we cannot completely deny a small possibility that patients who had rapidly progressive glomerulonephritis without positive ANCA and did not undergo biopsy would be excluded in this survey. Data from our 1998 nationwide survey showed that the annual prevalence of patients with ANCA-associated vasculitides is 17.1 per million (WG 2.3, CSS 1.0, and MPA/RLV 13.8 per million) (8,9). We therefore predicted a much lower incidence. The reasons could be that disease diagnosis has improved, hospital- and population-based methods differ, and the incidence of PRV has increased over time (5,24).

We also questioned whether MPA and/or RLV is more common than WG among the ANCA-associated vasculitides in Japan. However, the incidence of ANCA-associated vasculitides in Miyazaki Prefecture was very similar to that of the total incidence among European countries, but none of our patients was classified as having WG and CSS. A geographic difference in the incidence of systemic vasculitides has been suggested (1–3), and this theory seems to explain our results. The latitude of Miyazaki Prefecture is almost 30°, which is located south of Lugo, Spain (latitude 43°), where the incidence of WG, MPA, and CSS is 3.0, 7.9, and 1.3 per million, respectively (10). The incidence of WG and MPA might be latitudinal (7,10,25) (Table 5). To our knowledge, there are no reports regarding the incidence of WG in a more southern area than latitude 40° N. In the Middle East country of Bahrain, Saudi Arabia (latitude 26° N; population approximately 500,000), the very first case of WG was reported only in 1998 (26). Race differences also might

Table 5. Incidence of ANCA-associated vasculitides with renal involvement[a]

Location, Country (Reference)	Latitude	Annual Incidence (per million)				Population (millions)	Study Period
		MPA	WG	CSS	Total		
1. Orebro, Sweden (12)	59°N	ND	ND	ND	16.0	0.20 to 0.21	1975 to 1995
2. Lund, Sweden (16)	55°N	2.5[b]	2.1[b]	ND	4.6[b]	1.2	1971 to 1993
3. Norfolk, UK (7)	52°N	7.5	7.9	1.3	18.0	0.41	1992 to 1997
4. Schleswig-Holstein, Germany (8)	51°N	2.7[c]	7.9[c]	1.1[c]	11.7[c]	2.78	1988 to 2002
5. Devon, UK (25)	50°N	ND	ND	ND	12.4	0.85	2 yr
6. Lugo, Spain (11)	43°N	7.9[c]	3.0[c]	1.3[c]	12.2[c]	0.21	1988 to 2001
7. Miyazaki, Japan (this study)	30°N	14.8	0	0	14.8	0.77	2000 to 2004
8. Al-Jahra, Kuwait (14)	26°N	20.9	ND	ND	ND	0.12	1993 to 1996

[a]1, 5, 7, and 8 include RLV; 2, 3, 4, and 6 may not include RLV. 1, 2, 6, and 8 are hospital-based studies; 3, 4, 5, and 7 are population-based studies. ND, not done.
[b]All cases with biopsy-proven renal involvement.
[c]ANCA-associated vasculitides without renal involvement are included.

contribute to the proportion of type of vasculitis. In a US cohort study, white individuals composed >90% of all patients with WG, whereas black, Hispanic, and Asian individuals together represented only 1 to 4% of patients (27,28). The population in the European studies was white (10,25). We reported that the prevalence of Japanese patients with ANCA-associated vasculitides is 2.3, 13.8, and 1.0 per million with respect to WG, MPA/RLV, and CSS, respectively (9). Therefore, WG is not widespread in Japan. The incidence of WG and MPA and/or RLV among Europe, the United States, and Japan should be differentiated by the prospective study.

We examined whether the ratio of MPO-ANCA/PR3-ANCA among Japanese patients with ANCA-associated vasculitides differs from that in European counties. Only five patients were ANCA negative, whereas sera from 51 (91%) of 56 patients were MPO-ANCA positive, and none was serologically positive for C-ANCA or PR3-ANCA. Among Japanese patients with MPA and/or RLV, 79 to 93% are positive for MPO-ANCA (8,9), compared with 44 to 69% of European patients (6,10–15). Our preliminary examination of the type of ANCA in sera from patients with ANCA-associated vasculitides revealed that the results of commercially available ELISA kits that were used in EUVAS and Japan did not differ (Drs. T. Ihara [Department of Medicine, Kyoto University, Graduate School of Medicine, Kyoto, Japan] and E. Muso [Division of Nephrology & Dialysis, Department of Medicine, Kitano Hospital, Osaka, Japan], personal communication, August 2005). Even among European countries with the higher incidence of MPA and/or RLV, the maximal proportion of MPO-/PR3-ANCA was 5.5:1 (5,10,11,13), whereas that in Japan was 9:1. Therefore, MPO-ANCA–positive patients seem to be more widespread than those with PR3-ANCA among Japanese with ANCA-associated vasculitides. The genetic background of the patients should be closely related to the differences in rates of MPO-ANCA *versus* PR3-ANCA between Europe and Japan. Our previous study demonstrated that HLA-DR0901 is much more prevalent among patients with MPA than in healthy control subjects (29,30).

Approximately 80% of our patients were aged at least 65 yr, and the incidence peaked in the 70- to 74-yr age group (Figure 2). The mean age of 70 yr was higher than that in a previous study, which found that the average age of Japanese patients with ANCA-associated vasculitides was 10 yr younger (9). Recent studies revealed an increasing incidence of ANCA-associated vasculitides in the older population (5,24). Compared with European demographic data regarding MPA with renal involvement and/or RLV, our study was consistent with recent findings (12) showing that the mean age was 72 yr at presentation, and there was no significant gender difference (female 57%). Whether this reflects a real increase in incidence among the elderly, more accurate diagnosis, increased recognition, or an increase in the mean population age remains unclear.

Several reports have shown that more patients with C-ANCA and/or WG develop symptoms during the dark winter months (11,31–33). In contrast, this study showed that symptoms developed predominantly during the summer months. A significant association between farming and P-ANCA and/or MPA (odds ratios 4.3 [95% CI 1.5 to 12.7] and 6.6 [1.9 to 21.6], respectively) was identified (33). One explanation may be high silica exposure in the form of agricultural dust, because silica plays a role in the onset of ANCA-associated primary systemic vasculitides (34–38). Crops are harvested during the summer months in the areas of Miyazaki. The mean age of agricultural workers in Miyazaki prefecture is 58.5 yr, and more elderly residents frequently are involved in farming. Furthermore, Miyazaki prefecture is predominantly agricultural with no heavy industry. Further investigation obviously is required to clarify the association between symptom onset and seasonal variations or occupational exposure to silica.

Conclusion

This is the first epidemiologic study to elucidate the annual incidence of PRV in Japan, especially using the population-based survey applied by European investigators. The incidence of PRV did not differ between Japan and European countries. We found that WG was not widespread in Japan and that the ratio of serum MPO-/PR3-ANCA among patients with PRV is much higher than that reported for European and American countries. Our preliminary results will form the basis for a prospective study of Miyazaki prefecture, and our survey will be distributed in northern Japan. We also plan to determine the epidemiology of the ANCA-associated vasculitides in Asian countries.

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