Clinical Features and Radiological Findings in Large Vessel Vasculitis: Are Takayasu Arteritis and Giant Cell Arteritis 2 Different Diseases or a Single Entity?

Shunsuke Furuta, Claire Cousins, Afzal Chaudhry, and David Jayne

ABSTRACT. ***Objective.*** Takayasu arteritis (TAK) and giant cell arteritis (GCA) are 2 major variants of large vessel vasculitis (LVV). The frequent involvement of large vessels in GCA has raised the possibility that TAK and GCA should be regarded as 1 disease. By detailed phenotyping of a single-center cohort, we aimed to define the differences between TAK and GCA.

Methods. Forty-five patients (23 TAK, 22 GCA) were identified. Baseline characteristics, clinical symptoms, laboratory data, enhanced computed tomography/magnetic resonance imaging, treatments, and clinical courses were retrospectively assessed with descriptive statistics. In addition, latent class analysis of the 45 patients was performed to explore phenotypic differences.

Results. Patients with GCA had more frequent headache ($p < 0.01$), higher C-reactive protein levels ($p = 0.01$), and higher erythrocyte sedimentation rates ($p = 0.03$) than did patients with TAK at diagnosis. With the exception of subdiaphragmatic lesions, the distributions of vessel lesions were not different between TAK and GCA. However, focusing on subclavian and carotid arteries, long tapered-type stenotic lesions were more frequent in GCA than in TAK ($p < 0.01$). The proportion of patients without relapse was higher in GCA (60%) than in TAK (22%, $p = 0.01$). Latent class analysis also divided patients with LVV into 2 separate groups consistent with TAK and GCA.

Conclusion. The differences observed in clinical symptoms, inflammatory markers, radiological findings, and clinical courses suggested that TAK and GCA were 2 different diseases. Latent class analysis supported these results. The shape of stenotic lesions in the subclavian and carotid arteries is a useful discriminator between TAK and GCA. (J Rheumatol First Release Nov 15 2014; doi:10.3899/jrheum.140562)

Key Indexing Terms:

TAKAYASU ARTERITIS | GIANT CELL ARTERITIS | IMAGING
PHENOTYPE | PROGNOSIS | LATENT CLASS ANALYSIS

In the Chapel Hill Consensus Conference 2012 definition[1], large vessel vasculitis (LVV) is defined as a disease affecting large arteries more often than other vasculitides, with 2 major variants, Takayasu arteritis (TAK) and giant cell arteritis (GCA). Historically, TAK and GCA have been considered different diseases with different onset age, ethnic distribution, and distribution of affected arteries. In the 1980s–1990s, TAK was recognized to affect mainly the aorta and primary branches, while GCA affected mainly the cranial arteries[2,3]. More recent reports showed the frequent involvement of the aorta (45–65%) and primary branches (29–74%) in GCA[4,5,6,7,8,9,10]. A prospective study revealed 67.5% large vessel involvement in newly diagnosed biopsy-proven GCA[11]. In addition, histopathology from arterial biopsies may be indistinguishable between TAK and GCA[12,13]. Thus, it is unclear whether TAK and GCA are truly 2 separate diseases or the same one.

In 2012, Grayson, *et al* performed a latent class analysis focused on the distribution of arterial lesions in TAK and GCA[14]. They showed that the majority of patients with TAK and patients with GCA had an overlapping distribution, and suggested that they were the same disease. However, their study was limited to radiographic data, mainly the distribution of affected vessels, and lacked detail of other components such as clinical symptoms, laboratory data, and clinical outcomes. In our retrospective observational study, we aimed to investigate whether TAK and GCA were the same disease by using a more detailed clinical and radiological dataset in patients with LVV below the head and neck.

MATERIALS AND METHODS

Patients. We identified 46 sequential patients with LVV attending a vasculitis clinic in a university medical center. The patients were cate-

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gorized to either TAK or GCA. TAK was defined as arterial lesions of the aorta and/or primary branch vessels attributed to vasculitis, with the patient either younger than 40 years at disease onset or fulfilling the 1990 American College of Rheumatology (ACR) criteria for the classification of TAK[2]. GCA was defined as arterial lesions of the aorta and/or primary branch vessels attributed to vasculitis, with the patient either older than 50 years at disease onset or fulfilling the 1990 ACR criteria for the classification of GCA[3]. An arterial lesion was defined as wall thickness, stenosis/occlusion, or aneurysm attributed to vasculitis, and detected by computed tomography (CT) scan or magnetic resonance imaging (MRI). Two patients between 40 and 50 years at disease onset were included in the TAK group (1 fulfilled the ACR criteria for TAK and 1 did not fulfill the criteria for either diagnosis). We excluded 1 patient diagnosed with the assistance of an 18F-fluorodeoxyglucose-positron emission tomography scan who lacked CT scan or MRI. Thus, 45 patients were further studied (23 TAK and 22 GCA; 42 white, 2 Indian, and 1 Filipino).

Assessment. We retrospectively assessed age at disease onset, age at diagnosis, sex, coexisting polymyalgia rheumatica (PMR), clinical symptoms at diagnosis including ischemic symptoms of large vessels and other vessels, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels at diagnosis. In addition to the distribution of affected vessels, these characteristics were assessed by scanned images of enhanced CT (n = 37) and/or MR angiograms (n = 19): vessel wall thickness, stenosis/occlusion, length of the longest stenotic lesion in the subclavian or carotid artery, and types of stenosis according to length (short < 5 cm, medium 5–10 cm, and long > 10 cm) and shape (tapered, non-tapered, and complete occlusion; Figure 1) at any timepoint during the clinical course. All images were reviewed again for this purpose by a vascular radiologist blinded with regard to clinical diagnosis. Also collated was information on the use of oral glucocorticoids (converted to the equivalent prednisolone dose), immunosuppressants, biologic agents, and vascular surgery. In addition, we categorized patients with more than 6 months of followup into 4 possible clinical courses: "no relapse" defined as maintaining remission without relapse, "relapsing" defined as having 1 or more relapse, "refractory" defined as never achieving remission, and "burn-out" defined as having no immunosuppressive treatment during their clinical course and no worsening of symptoms or radiological progression. The "no relapse" group included both the patients on maintenance treatments and the patients stopping their treatments. Remission was defined as the absence of constitutional symptoms, no worsening of ischemic symptoms, normalization of inflammatory markers, and no progression in radiology with 10 mg/day or less than 10 mg/day of prednisolone for at least 3 months. Relapse was defined as recurrence of at least 1 of these after remission.

Statistics. The distributions of age, CRP, and ESR were described by median and range, and compared by Mann-Whitney U test. Proportions of sex, PMR, clinical symptoms, radiological features, and the defined 4 categories of clinical courses were compared by chi-square test, or Fisher's exact test when the expected frequency was less than 5 in 1 or more cells. Residual analysis[15] for a cell-by-cell comparison of observed and estimated expected frequencies was planned in case there was significant difference between TAK and GCA in the proportions of the clinical courses.

Latent class analysis was done for comparing membership probabilities of LVV (TAK and GCA) based on observed clinical features, laboratory data, and radiological findings. Data regarding treatments and clinical courses was excluded from latent class analysis in our study. A multiple-group latent class model[16] with the optimal number of computer-derived subgroups (latent classes) was determined using model selection criteria, Consistent Akaike Information Criteria, and Bayesian Information Criteria values.

All analyses except latent class analysis used IBM SPSS Statistics version 20 (IBM Corp.) and $p < 0.05$ was taken to indicate statistical significance. Latent class analysis used SAS version 9.3 (SAS Institute Inc.).

RESULTS

Clinical features at diagnosis. Patients with TAK were diagnosed at a younger age than were those with GCA (median 29.2 yrs and 65.8 yrs, respectively, $p < 0.01$) and female sex predominated in both TAK and GCA ($p = 0.70$; Table 1). Delay from symptom onset to diagnosis was longer in TAK than GCA (median 21.4 mos and 2.7 mos, respectively, $p = 0.05$). None of the patients with TAK and only 3 patients with GCA (14%) had a concomitant diagnosis of PMR ($p = 0.10$). Patients with GCA (20/22, 91%) had constitutional symptoms more frequently than did those with TAK (15/23, 65%, $p = 0.07$). Ischemic symptoms attributable to large vessel disease was observed in 17 patients with TAK (74%) and 12 patients with GCA (55%, $p = 0.18$). Headache was more frequent in GCA (6/22, 27%) than in TAK (0/23, 0%, $p < 0.01$), while there were no differences in visual loss, myocardial infarction, or aortic regurgitation ($p = 1.00$, 0.23, and 1.00, respectively). CRP levels at diagnosis were higher in GCA than in TAK (median 65 mg/l and 30 mg/dl, $p = 0.01$). ESR was also higher in GCA than in TAK (median 77 mm/h and 43 mm/h, respectively, $p = 0.03$).

Except for the age difference because of the criterion, patients with GCA had more frequent headache and higher inflammatory markers at diagnosis than did patients with TAK.

Radiological findings. Stenosis was more frequent in TAK (22/23, 96%) than in GCA (11/22, 50%, $p = 0.01$; Table 2). There were no differences in the proportions of patients with aneurysm or in wall thickness ($p = 0.41$ and 0.14, respectively).

No differences were observed in the frequency of lesions in the thoracic and abdominal aorta, carotid, vertebral, brachiocephalic, subclavian, axillary, and iliofemoral arteries ($p = 0.10$, 0.86, 0.45, 0.61, 0.92, 0.07, 0.26, and 1.00, respectively). Subdiaphragmatic lesions in the celiac, superior mesenteric, and renal arteries were more frequent in TAK than in GCA ($p = 0.02$, 0.02, and 0.01, respectively).

Focusing on stenotic lesions in the subclavian or carotid arteries, the length of lesion was longer in GCA than in TAK (medians 15 cm and 4.5 cm, respectively, $p = 0.02$). Long tapered-type stenotic lesions were a dominant form in GCA (8/11, 73%), and were more frequent in GCA than in TAK (1/16, 6%, $p < 0.01$). Conversely, short non-tapered-type stenotic lesions were a dominant form in TAK (11/16, 69%), and were more frequent in TAK than GCA (1/11, 9%, $p < 0.01$).

Treatments and clinical courses. Treatments during followup are shown in Table 3. Eighteen patients with TAK (78%) and 21 patients with GCA (95%) had glucocorticoids; median initial dose was 40 mg/day in both groups. Eighteen patients with TAK (78%; 9 had cyclophosphamide, 11 azathioprine, 11 mycophenolate mofetil, 9 methotrexate, and 2 cyclosporine A) and 18 patients with GCA (82%; 1 cyclophosphamide, 11 azathioprine, 9 mycophenolate mofetil, and 8 methotrexate) had immunosuppressants. Nine

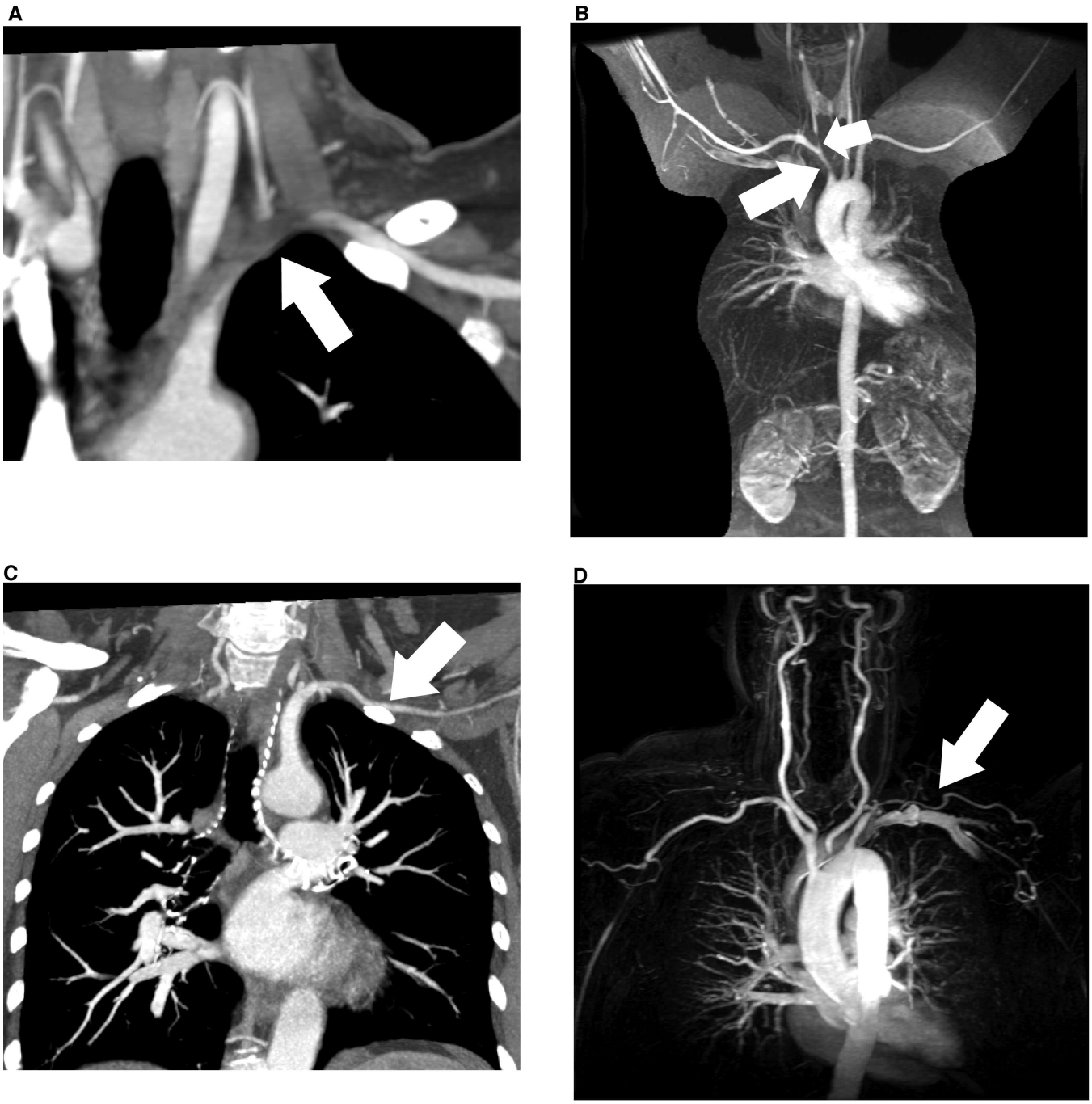

Figure 1. Typical images of TAK and GCA in subclavian artery lesion. A. Tight and short stenosis of subclavian artery in TAK by CT. B. Short stenosis of proximal common carotid and brachiocephalic arteries in TAK by MRI. C. Long tapered stenosis of subclavian artery in GCA by CT. D. Long tapered stenosis of subclavian artery in GCA by MRI. TAK: Takayasu arteritis; GCA: giant cell arteritis; CT: computed tomography; MRI: magnetic resonance imaging.

patients with TAK (39%) took biologic agents (infliximab, etanercept, adalimumab, certolizumab, and rituximab) compared to 1 patient with GCA (5%) who took infliximab. Eight patients with TAK (35%) and 2 patients with GCA (9%) underwent interventional vascular procedures; 4 patients with TAK and 1 patient with GCA had surgery, while the remaining 4 patients with TAK and 1 patient with GCA had endovascular procedures, angioplasty, or stenting by interventional radiologists.

Death occurred in 1 patient with TAK (4%) and 2 patients with GCA (9%, p = 0.61). The patient with TAK was 64.9 years old, and the patients with GCA were 78.0 and 83.5 years old. Causes of death were cerebral infarction, acute myeloid leukemia, and pneumonia.

Table 1. Clinical features at diagnosis in patients with TAK and GCA. Variables were described by median.

Characteristics	TAK, n = 23	GCA, n = 22	p
Baseline characteristics			
Male:female (female rate %)	5:18 (78)	3:19 (86)	0.70
Age at diagnosis, yrs (range)	29.2 (6.9–64.1)	65.8 (54.5–79.7)	< 0.01
Delay from onset to diagnosis, mos (range)	21.4 (0–198.5)	2.7 (0–211.7)	0.05
Patients with PMR, n (%)	0 (0)	3 (14)	0.10
Symptoms, n (%)			
Constitutional symptom	15 (65)	20 (91)	0.07
Ischemic symptom of LV	17 (74)	12 (55)	0.18
Loss of vision	1 (4)	0 (0)	1.00
Jaw claudication	0 (0)	1 (5)	0.49
Headache	0 (0)	6 (27)	< 0.01
Myocardial infarction	3 (13)	0 (0)	0.23
Aortic regurgitation	2 (9)	1 (5)	1.00
Laboratory data			
CRP at diagnosis, mg/l (range)	30 (1–114)	65 (1–198)	0.01
ESR at diagnosis, mm/h (range)	43 (2–109)	77 (1–125)	0.03

TAK: Takayasu arteritis; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; LV: large vessels; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 2. Radiological findings of patients with TAK and GCA. Values are n (%) unless otherwise specified.

Characteristics	TAK, n = 23	GCA, n = 22	p
Modalities			
CT and MRI	15 (65)	11 (50)	—
CT alone	3 (13)	8 (36)	—
MRI alone	5 (22)	3 (14)	—
Type of lesions			
Stenosis/occlusion	22 (96)	11 (50)	0.01
Aneurysm	5 (22)	2 (9)	0.41
Wall thickness	16 (70)	20 (91)	0.14
Distribution of lesions			
Thoracic aorta	15 (65)	19 (86)	0.10
Abdominal aorta	13 (57)	13 (59)	0.86
Carotid a.	12 (52)	9 (41)	0.45
Vertebral a.	3 (13)	1 (4)	0.61
Brachiocephalic a.	7 (30)	7 (32)	0.92
Subclavian a.	15 (65)	20 (91)	0.07
Axillary a.	4 (17)	7 (32)	0.26
Celiac a.	9 (39)	2 (9)	0.02
Superior mesenteric a.	8 (35)	1 (4)	0.02
Renal a.	11 (48)	3 (14)	0.01
Iliofemoral a.	2 (9)	1 (4)	1.00
Others	1	0	—
Stenotic/occluded lesions in subclavian or carotid arteries	TAK, n = 16	GCA, n = 11	p
Length of the longest lesion, cm (range)	4.5 (0.6–17)	15 (1.7–23)	0.02
Long tapered type	1 (6)	8 (73)	< 0.01
Short non-tapered type	11 (69)	1 (9)	< 0.01
Other types	4 (25)	2 (18)	—

Numbers of patients with each item were counted when the patient had the positive finding of each item at any timepoint during their clinical course. Wall thickness and occlusion of pulmonary artery were observed in 1 patient with TAK who is classified as "others" in the section of "Distribution of lesions". Length of the longest stenotic lesion in subclavian or carotid artery was measured in those patients with applicable lesions (TAK, n = 16; GCA, n = 11), and is reported as the median value with range from each group. Types of stenotic lesions in subclavian or carotid artery were also assessed according to their length and shapes. Length was classified as short (< 5 cm), medium (5–10 cm), and long (> 10 cm). Shape was classified as tapered stenosis, non-tapered stenosis, and complete occlusion. TAK: Takayasu arteritis; GCA: giant cell arteritis; CT: computed tomography; MRI: magnetic resonance imaging; a.: artery.

Table 3. Treatments and clinical courses in patients with TAK and GCA. Two patients with GCA with short-term followup (< 6 mos) were excluded when assessing clinical courses. The proportions of the 4 categories were different between TAK and GCA (p = 0.02), thus standardized residuals were calculated. Values are n (%) unless otherwise specified.

Variables	TAK, n = 23	GCA, n = 22	Standardized Residual
Median followup period, mos (range)	78.2 (9.9–361.7)	42.7 (0–125.3)	
Treatments			
Glucocorticoids	18 (78)	21 (95)	
Median maximum dose, mg/day	40	40	
≥ 1 immunosuppressants	18 (78)	18 (82)	
≥ 2 immunosuppressants	12 (52)	10 (45)	
Biologics	9 (39)	1 (5)	
Vascular intervention	8 (35)	2 (9)	
No. deaths	1 (4)	2 (9)	
Clinical courses			
No relapse	5 (22)	12 (60)	2.6*
Relapsing	8 (35)	6 (30)	0.3
Refractory	5 (22)	2 (10)	1.0
Burn-out	5 (22)	0 (0)	2.2*

* p < 0.05. TAK: Takayasu arteritis; GCA: giant cell arteritis.

Patients were categorized into 4 possible clinical courses, excluding 2 patients with GCA with < 6 months of followup. The proportions of the 4 categories were significantly different between TAK and GCA (p = 0.02). Thus, residual analysis was done for each category. "No relapse" was more common in GCA (12/20, 60%) than in TAK (5/23, 22%, standardized residual = 2.6). Five patients with TAK (22%) were categorized into "burn-out" compared to no patients with GCA (standardized residual = 2.2).

Latent class analysis. Model selection criteria suggested that a multiple-group latent class model with 2 latent classes was preferable (Appendix 1). In the selected model, membership probabilities with estimate and standard error (SE) were calculated. Patients with TAK had an estimate of 1.00 (SE = 0.00) for Class 1, compared to a GCA estimate of 0.14 (SE = 0.07) for Class 1. Conversely, patients with GCA had an estimate of 0.86 (SE = 0.07) for Class 2 and patients with TAK had an estimate of 0.00 (SE = 0.00) for Class 2. The majority of Class 1 were patients with TAK (86%), and all of the Class 2 were patients with GCA (Figure 2).

Older age at disease onset (≥ 50 yrs) was associated with Class 2, while younger age at disease onset (< 50 years) was associated with Class 1. In addition to the onset age, partial indications of Class 1 were lack of constitutional symptoms, lack of wall thickness, and involvements of celiac, mesenteric, and renal arteries. Presence of headache, lack of stenotic/occluded lesions, and presence of long tapered stenoses in subclavian or carotid arteries indicated Class 2. All of the item-response probabilities in the model are shown in Table 4.

Latent class analysis with a detailed dataset suggested that there were 2 distinct classes, consistent with TAK and GCA.

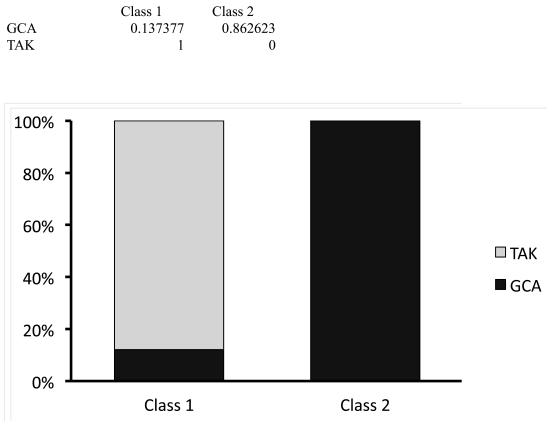

Figure 2. Estimated membership probabilities of TAK/GCA in the 2 classes generated by a multiple-group latent class model. TAK: Takayasu arteritis; GCA: giant cell arteritis.

DISCUSSION

In our study, we investigated whether TAK and GCA were phenotypically different diseases by comparing well-characterized patient cohorts. Apart from age, there were clear phenotypic differences, with patients with GCA having more constitutional symptoms, headache, and higher CRP and ESR levels when compared to patients with TAK at the time of diagnosis. The patterns of radiological examination also differed, with more frequent stenotic lesions in TAK and more frequent wall thickness abnormalities in GCA, while the distributions of large vessel lesions were almost the same except for subdiaphragmatic lesions, as reported[14]. These results suggest TAK and GCA are different diseases with different phenotypes. In latent class analysis with a detailed dataset including not only lesion distribution but

Table 4. Detail of the model with 2 classes.

Latent Class	Class 1		Class 2	
	Estimate	SE	Estimate	SE
Membership probabilities				
GCA	0.137	0.074	0.863	0.074
TAK	1.000	0.000	0.000	0.000
Item response probabilities				
Sex				
Male	0.192	0.076	0.159	0.083
Female	0.808	0.076	0.841	0.083
Onset age, yrs				
< 50	0.801	0.078	0.012	0.025
≥ 50	0.199	0.078	0.988	0.025
PMR complication				
No	0.961	0.038	0.896	0.069
Yes	0.039	0.038	0.104	0.069
Clinical symptoms				
Constitutional				
No	0.382	0.094	0.057	0.053
Yes	0.618	0.094	0.943	0.053
Ischemic				
No	0.233	0.082	0.522	0.113
Yes	0.767	0.082	0.478	0.113
Myocardial infarction				
No	0.886	0.062	0.998	0.009
Yes	0.114	0.062	0.002	0.009
Loss of vision				
No	0.962	0.037	0.999	0.005
Yes	0.038	0.037	0.001	0.005
Headache				
No	0.997	0.010	0.689	0.105
Yes	0.003	0.010	0.311	0.105
Jaw claudication				
No	1.000	0.004	0.948	0.050
Yes	0.000	0.004	0.052	0.050
Aortic regurgitation				
No	0.886	0.062	0.998	0.010
Yes	0.114	0.062	0.002	0.010
Laboratory data				
CRP, mg/l				
3	0.090	0.060	0.001	0.009
≥ 3	0.910	0.060	0.999	0.009
ESR, mm/h				
< 10 (male), < 15 (female)	0.129	0.069	0.002	0.011
≥ 10 (male), ≥ 15 (female)	0.871	0.069	0.998	0.011
Radiological findings				
Subclavian/carotid artery lesions				
Long tapered type	0.195	0.098	0.826	0.139
Short non-tapered type	0.682	0.115	0.169	0.137
Occluded type	0.124	0.081	0.006	0.028
Stenosis/occlusion				
No	0.043	0.039	0.572	0.112
Yes	0.957	0.039	0.428	0.112
Aneurysm				
No	0.771	0.082	0.945	0.052
Yes	0.229	0.082	0.055	0.052
Wall thickness				
No	0.306	0.090	0.056	0.052
Yes	0.694	0.090	0.944	0.052
Thoracic aorta				
No	0.344	0.092	0.108	0.071
Yes	0.656	0.092	0.892	0.071

Table 4. Continued.

Latent Class	Class 1		Class 2	
	Estimate	SE	Estimate	SE
Abdominal aorta				
No	0.423	0.096	0.421	0.112
Yes	0.577	0.096	0.579	0.112
Carotid a.				
No	0.463	0.097	0.629	0.110
Yes	0.537	0.097	0.371	0.110
Vertebral a.				
No	0.885	0.062	0.946	0.051
Yes	0.115	0.062	0.054	0.051
Brachiocephalic a.				
No	0.692	0.090	0.684	0.105
Yes	0.308	0.090	0.316	0.105
Subclavian a.				
No	0.306	0.089	0.108	0.070
Yes	0.694	0.089	0.892	0.070
Axillary a.				
No	0.807	0.077	0.686	0.105
Yes	0.193	0.077	0.314	0.105
Celiac a.				
No	0.581	0.096	0.994	0.018
Yes	0.419	0.096	0.006	0.018
Superior mesenteric a.				
No	0.657	0.092	0.995	0.016
Yes	0.343	0.092	0.005	0.016
Renal a.				
No	0.466	0.097	0.992	0.020
Yes	0.534	0.097	0.008	0.020
Iliofemoral a.				
No	0.923	0.052	0.947	0.051
Yes	0.077	0.052	0.053	0.051

SE: standard error; GCA: giant cell arteritis; TAK: Takayasu arteritis; PMR: polymyalgia rheumatica; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; a.: artery.

also clinical symptoms, laboratory data, and other radiological findings, model selection criteria suggested that the model with 2 classes was preferable and the 2 classes were consistent with TAK and GCA, respectively. Latent class analysis supported the results of descriptive statistics, suggesting that TAK and GCA were different diseases. This was especially true for headache and ESR, which are included in the ACR criteria for GCA but not in the ACR criteria for TAK, where the latent class analysis supported that the differences in the 2 items between TAK and GCA were true and not spurious. In addition, latent class analysis also suggested that conventional age criteria between TAK and GCA were legitimate. Considering potential selection bias by age criteria, we reran the model without age as a sensitivity analysis. The results were very similar with the model with age; 2 latent classes were still preferable and they were consistent with TAK and GCA.

Longterm diagnostic delay in patients with TAK appeared to reflect the natural history of the disease rather than the reason for phenotypic difference at diagnosis. TAK tends to start without symptoms and progresses more slowly; thus, there is a longer time to diagnosis and more disease-related damage.

Although our results suggested that TAK and GCA were different, no single item was specific for TAK and GCA. Long tapered-type stenoses in the subclavian or carotid arteries were characteristic of GCA, with a sensitivity and specificity for GCA of 73% and 83%. However, stenotic lesions in subclavian or carotid arteries were not always observed. Other candidates are temporal artery biopsy and ultrasonography. Positive results in such examinations strongly suggest GCA[17], although older patients with LVV consistent with GCA can lack temporal arteritis. Establishing new specific markers for the 2 diseases, such as anti-ferritin autoantibodies for GCA[18] and anti-endothelial cell antibodies for TAK[19,20], may complement the radiological patterns in further evaluation of LVV subtypes.

In addition to differences in phenotype and radiological findings, the clinical courses may also be different between TAK and GCA. The proportion of patients with a "one-off" clinical course was higher in patients with GCA than in patients with TAK, with the majority of patients with TAK

having chronic active disease. This may influence treatment strategies where combination therapy of glucocorticoids and immunosuppressants or biologic agents from disease onset may be more appropriate in TAK to minimize glucocorticoid toxicity, whereas glucocorticoid monotherapy may remain an acceptable first treatment for GCA, with immunosuppressants or biologic agents used in relapsing or refractory disease. However, the retrospective nature of our observational study with differing treatments and followup periods between TAK and GCA may weaken the reliability of this observation. Patients with TAK had longer terms and more relapses than patients with GCA, although discontinuation of followup in patients with GCA was usually because of longterm drug-free remission. A prospective study will be needed.

The clinical features we observed in patients with GCA (relatively younger age at the disease onset, less frequent PMR, and less frequent ocular involvement) deviate from the classical characteristics of GCA[21,22]. The reasons are not clear, but may be a combination of differences in definition of GCA and referral bias. Classical characteristics were obtained from studies with patients having temporal arteritis with or without LVV (temporal arteritis-type GCA), while our study focused on LVV with or without temporal arteritis in older patients (LVV-type GCA). Indeed, only 6 of the 22 patients with GCA in our study showed temporal headache, and 1 of 6 had biopsy-confirmed temporal arteritis. In addition, in east England, patients with temporal arteritis without LVV tend to be reviewed by local physicians, while patients with LVV are frequently referred to our vasculitis clinic. Interestingly, a prospective study with CT angiography revealed that patients with biopsy-proven temporal arteritis with LVV had less PMR and less ocular involvement than patients with temporal arteritis without LVV[11]. Another report found no ocular involvement in 10 patients with temporal arteritis with aortitis, and suggested a prognostic difference between temporal arteritis with and without aortitis[23]. It is known that patients with temporal arteritis frequently have aortitis and vasculitis of its primary branches, although an association between temporal arteritis and LVV is obvious. To clarify the term *GCA* and to subgroup GCA according to disease distribution may be future issues[4,5,6,7,8,9,10].

Our study had some limitations. Relatively small sample sizes might reduce statistical power, and a single-center study might be influenced by referral bias. The retrospective nature of our study can bias assessment of some clinical symptoms. For example, headache in GCA was regularly assessed as a part of the classification criteria while it might be missed in TAK. Further, we permitted both CT and MRI for disease assessment. Efficacy of both modalities in LVV has already been established[24], but their features such as spatial resolution are different, which might influence the radiological results, although there were no major differences in the results of the assessment items in our study between CT and MRI in patients having both examinations.

Nevertheless, considering the number of observed differences and the results of latent class analysis, the evidence appears strong that TAK and GCA are phenotypically different diseases, answering our primary research question.

The distributions of affected vessels were similar to previous reports. However, the clinical symptoms, laboratory data, radiological findings, and clinical courses were different between patients with TAK and patients with GCA. Latent class analysis with detailed datasets also divided patients with LVV into the 2 definite groups consistent with TAK and GCA. Thus, our results suggested that TAK and GCA are 2 different diseases. The shape of stenotic lesions in the subclavian and carotid arteries is a useful discriminator between TAK and GCA.

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APPENDIX 1. Selection of the number of classes in latent class analysis. The BIC and the CAIC are criterion for model selection. Good models (e.g., the true model or nearly true models) have relatively small BIC and CAIC values.

No. Classes	BIC	CAIC
2	**868.0**	**926.0**
3	895.3	983.3
4	932.4	1050.4
5	1004.8	1152.8
6	1091.4	1269.4

Significant data in bold face. BIC: Bayesian Information Criterion; CAIC: Consistent Akaike Information Criterion.