Outcome of Takayasu Arteritis with Inactive Disease at Diagnosis: The Extent of Vascular Involvement As a Predictor of Activation

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ABSTRACT. ***Objective.*** Some patients with Takayasu arteritis (TA) have inactive disease at the time of diagnosis. The objective of our study was to investigate the clinical outcomes and factors that predict disease activation in patients with clinically inactive TA.

Methods. The medical records of patients diagnosed with TA between 1990 and 2012 were reviewed. At the time of diagnosis, patients were identified as having inactive disease according to the National Institutes of Health definition. Patients who went on to develop active disease during followup were classified as the "activation group". The pattern of vascular involvement was classified according to the International Conference on TA, 1994.

Results. A total of 59 patients with TA were classified as having inactive disease at the time of diagnosis. During the followup, 13 (22.0%) of these experienced TA activation (median followup, 37.0 mos; activation group). The remaining 46 (78.0%) did not experience disease activation (stable group). Renovascular hypertension was more common in the activation group than in the stable group (5/13, 38.5% vs 4/46, 8.7%, p = 0.019). Further, type V, which is the most extensive, was more common in the activation group (12/13, 92.3%) than in the stable group (18/46, 39.1%, p = 0.008). Multivariate analysis identified type V disease (OR 10.969, 95% CI 1.144–105.182, p = 0.038) as being significantly associated with an increased risk of disease activation.

Conclusion. Substantial portions of patients with clinically inactive TA at the time of diagnosis experienced disease activation during followup. Type V disease may be an important predictive factor for disease activation in patients with clinically inactive TA. (J Rheumatol First Release Dec 15 2014; doi:10.3899/jrheum.140981)

Key Indexing Terms:
TAKAYASU ARTERITIS
RENOVASCULAR HYPERTENSION
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ANGIOGRAPHIC CLASSIFICATION

Takayasu arteritis (TA) is a large vessel vasculitis that primarily affects the aorta and its main branches[1,2]. It occurs most commonly in young women, resulting in considerable morbidity and mortality because of major vessel involvement. Inflammation in the vessel wall can lead to stenosis or occlusion, causing ischemic symptoms. In some cases, the disease presents with constitutional symptoms, such as fever, associated with systemic inflammation[1,2,3]. TA typically exhibits a chronic, persistent nature, with some patients experiencing frequent relapse during followup[4]. Thus, patients with TA are usually treated with immunosuppressants, including glucocorticoids.

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However, some patients show a monophasic pattern in which the disease is quiescent after initial diagnosis[1,5,6]. At the time of diagnosis, about 10–20% of patients with TA show no symptoms or signs suggestive of active inflammation or ischemia[1,6,7,8], and such patients do not usually receive immunosuppressive treatment. However, data regarding the longterm outcome of patients with clinically inactive disease at the time of diagnosis are quite limited. Indeed, it is unclear whether clinically quiescent patients will experience activation throughout the natural course of the disease.

Therefore, we examined the longterm outcome of patients with clinically inactive TA, and addressed whether baseline clinical variables, including the pattern of angiographic involvement, were associated with disease activation.

MATERIALS AND METHODS

The medical records of patients with TA at a tertiary hospital in South Korea between January 1990 and December 2012 were retrospectively reviewed. All patients fulfilled the 1990 revised American College of Rheumatology classification criteria for TA[9] except age of onset before 40

years, because delayed diagnosis of TA was possible in patients with clinically inactive disease. Patients were excluded from the analysis if clinical outcome data were not available at followup. All patients underwent an aortic angiography and/or an aortic computed tomography (CT) scan at the time of TA diagnosis. Clinical manifestations such as abnormal vascular findings (e.g., decreased pulse, asymmetric blood pressure, and vascular bruit) were addressed. Laboratory data, including complete blood cell counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and creatinine levels were collected. Disease activity was classified according to the US National Institutes of Health (NIH) definition of active TA[1]. This definition included the following systemic features: fever and musculoskeletal symptoms; elevated ESR; features of vascular ischemia or inflammation, including claudication, diminished or absent pulse, bruit, vascular pain, and asymmetric blood pressure in either the upper or lower extremities; and typical angiographic findings. New onset or worsening of 2 or more of the above features was defined as active disease.

The pattern of vascular involvement was classified according to the International Conference on TA in Tokyo 1994 angiographic classification[10]. There are 5 types: type I (branches of the aortic arch), type IIa (ascending aorta, aortic arch, and aortic arch branches), type IIb (ascending aorta, aortic arch and its branches, and descending thoracic aorta), type III (descending thoracic aorta, abdominal aorta, and/or renal arteries), type IV (abdominal aorta and/or renal arteries), and type V (combined features of types IIb and IV). The medical records, including imaging studies, were reviewed and the longterm outcomes during followup were assessed. During followup, TA activation was defined if the patients met any of the criteria for active disease according to the NIH definition of active TA[1].

Categorical data between groups were compared using Fisher's exact test. The Student t test was used to compare quantitative variables for univariate analysis. The Mann-Whitney U test was used when continuous variables were expressed as the median or range. Multivariate analysis was performed by Cox regression analysis. After identifying relevant risk factors by univariate analysis, those with p values < 0.30 were entered into multivariate analysis. The results were expressed as OR with 95% CI. The cumulative probability of disease activation during followup was calculated using the Kaplan-Meier method and data were compared using the log-rank test. All significance tests were 2-sided and $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 21.0; SPSS Inc.).

RESULTS

Characteristics of the study subjects. Of the 199 patients diagnosed with TA between 1990 and 2012, 59 (29.6%) showed no evidence of active disease according to the NIH definition of active TA at the time of diagnosis. The baseline clinical characteristics of these clinically inactive patients are shown in Table 1. The mean age of the study patients was 42.9 ± 12.9 years and 50 patients were women (84.7%). Forty-three (72.9%) of the 59 inactive patients were classified as "older age" (above 35 yrs). The median interval from symptom onset to diagnosis was 12.0 months [interquartile range (IQR) 3.0–60.0 mos], and diagnosis was delayed for 2 years more in 28 patients (47.5%). Renovascular hypertension (HTN) was found in 9 patients (15.3%). History of vascular events, such as stroke, transient ischemic attack, and angina, was documented in 4 (6.8%), 3 (5.1%), and 8 (13.6%) patients, respectively. However, no patients showed active symptoms suggestive of ongoing ischemia or systemic inflammation at the time of diagnosis. Imaging studies for diagnosing TA included aortic CT angiography (42, 71.2%), conventional angiography (29, 49.2%), and magnetic resonance angiography (2, 3.4%). Stenosis (51, 86.4%) was the most commonly observed pattern of vascular involvement, followed by occlusion (38, 64.4%), dilatation (13, 22%), and aneurysm (11, 18.6%).

Table 1. Baseline characteristics of the 59 patients with clinically inactive TA. Values are n (%) unless otherwise specified.

Characteristics	Total, n = 59
Age at diagnosis, yrs, mean ± SD	42.9 ± 12.9
Older age, > 35 yrs	43 (72.9)
Sex, male/female	9/50 (84.7)
Weight, kg, mean ± SD	56.7 ± 7.7
Height, cm, mean ± SD	158.6 ± 7.8
Delay in diagnosis, mos, median (IQR)	12.0 (3.0–60.0)
Delay in diagnosis, > 2 yrs	28 (47.5)
ESR, mm/h, mean ± SD	15.5 ± 11.7
CRP, mg/dl, mean ± SD	0.21 ± 0.24
Creatinine, mg/dl, mean ± SD	0.78 ± 0.17
Systemic HTN	28 (47.5)
Renovascular HTN	9 (15.3)
Limb claudication	24 (40.7)
Decreased pulse	46 (78.0)
Asymmetric blood pressure	49 (83.1)
Vascular bruit	19 (32.2)
Vascular involvement	
Stenosis	51 (86.4)
Occlusion	38 (64.4)
Dilatation	13 (22.0)
Aneurysm	11 (18.6)
Aortic regurgitation	4 (6.8)
Classification†	
Type I	13 (22.0)
Type IIa	2 (3.4)
Type IIb	11 (18.6)
Type III	3 (5.1)
Type IV	0 (0.0)
Type V	30 (50.8)
Diagnostic imaging modality	
CT	42 (71.2)
Angiography	29 (49.2)
MRI	2 (3.4)

† Classification based on the International Conference on TA in Tokyo, 1994. IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CT: computed tomography; MRI: magnetic resonance imaging; TA: Takayasu arteritis; HTN: hypertension.

At the time of diagnosis, histopathologic data were available for 3 patients who underwent bypass surgery or valve replacement. Of the 3 patients, 2 showed chronic inflammation with fibrosis and calcification in the vessels. All patients were classified according to the Tokyo 1994 classification, which is based on the distribution of major vessel involvement[10]. Type V (30, 50.8%) was the most common pattern, and the other types were as follows: type I (13, 22.0%), type IIa (2, 3.4%), type IIb (11, 18.6%), type III (3, 5.1%), and type IV (0, 0.0%). At the time of diagnosis, 10 patients underwent a whole-body positron emission tomography (PET) scan. Most of these patients (9/10, 90.0%) showed no evidence of abnormal hypermeta-

bolic lesions in the vessels, whereas 1 patient showed mild hypermetabolic activity in the abdominal aorta. None of the patients received immunosuppressants, including glucocorticoids, after TA diagnosis, since there was no evidence of active inflammation and/or ischemia.

Activation of clinically inactive TA. The median followup time until last visit was 58 months (IQR 37.0–107.0). During followup, 13 patients (22.0%) experienced disease activation (median followup time 37.0 mos, IQR 23.5–46.5; activation group). The remaining 46 (78.0%) did not experience disease activation (stable group). Manifestations apparent at the time of TA activation included the development of constitutional symptoms, such as malaise and mild fever (n = 5). New-onset vascular ischemia presented as limb claudication (n = 3) and stroke (n = 2). TA activation was also manifested by abdominal aortic aneurysm (n = 2) and aortic regurgitation (n = 1). All patients showed an increase in the levels of acute-phase reactants, including ESR, when they experienced active symptoms, suggesting the development of an active inflammatory response. Pathologic data obtained from patients who had surgical procedures showed the chronic lesion consisting of fibrosis rather than active vasculitis (n = 3). Baseline factors associated with activation were determined by comparing the baseline characteristics of the activation and stable groups (Table 2). There were no significant differences in baseline demographics, including age and sex, between the 2 groups. Both groups were similar in terms of the proportion of older age patients (> 35 yrs at diagnosis) and delay in diagnosis (> 2 yrs until diagnosis). Also, there was no difference in the ESR and CRP levels between patients who developed active TA and those who did not. However, renovascular HTN was more common in the activation group than in the stable group (5/13, 38.5% vs 4/46, 8.7%, p = 0.019).

It is notable that there was a significant difference in the vascular involvement depending on the angiographic classification of TA (p = 0.008). Type V, which is the most extensive type, was more common in the activation group (12/13, 92.3%) than in the stable group (18/30, 39.1%). Next, we performed multivariate analysis to identify factors associated with TA activation. Variables such as age and CRP were categorized and analyzed using a Cox propor-

Table 2. Comparison of baseline characteristics between patients with (n = 13) and without (n = 46) disease activation. Values are n (%) unless otherwise specified.

Characteristics	Active, n = 13	Stable, n = 46	p
Age at diagnosis, yrs, mean ± SD	48.1 ± 12.6	41.4 ± 12.7	0.097
Older age, > 35 yrs	11 (84.6)	32 (69.6)	0.481
Sex, male/female	2/11	7/39	1.000
Weight, kg, mean ± SD	56.1 ± 6.1	56.9 ± 8.2	0.745
Height, cm, mean ± SD	158.7 ± 6.8	158.6 ± 8.2	0.969
Delay in diagnosis, mos, median (IQR)	12 (7.5–24)	17 (1.75–72)	0.639
Delay in diagnosis, > 2 yrs	5 (38.5)	23 (50.0)	0.540
ESR, mm/h, mean ± SD	16.3 ± 9.7	15.3 ± 12.3	0.792
CRP, mg/dl, mean ± SD	0.28 ± 0.30	0.20 ± 0.22	0.293
Creatinine, mg/dl, mean ± SD	0.79 ± 0.14	0.77 ± 0.18	0.740
Systemic HTN	8 (61.5)	20 (43.5)	0.348
Renovascular HTN	5 (38.5)	4 (8.7)	**0.019**
Limb claudication	5 (38.5)	19 (41.3)	1.000
Decreased pulse	10 (76.9)	36 (78.3)	1.000
Asymmetric blood pressure	10 (76.9)	39 (84.8)	0.676
Vascular bruit	4 (30.8)	15 (32.6)	1.000
Vascular involvement			
Stenosis	12 (92.3)	39 (84.8)	0.671
Occlusion	10 (76.9)	28 (60.9)	0.344
Dilatation	4 (30.8)	9 (19.6)	0.455
Aneurysm	3 (23.1)	8 (17.4)	0.693
Aortic regurgitation	1 (7.7)	3 (6.5)	1.000
Classification†			**0.008**
Type I, n = 13	0/13	13/13	
Type IIa, n = 2	1/2	1/2	
Type IIb, n = 11	0/11	11/11	
Type III, n = 3	0/3	3/3	
Type IV, n = 0	0/0	0/0	
Type V, n = 30	12/30	18/30	

Significant data are in bold face. † Classification based on the International Conference on TA in Tokyo, 1994. IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TA: Takayasu arteritis; HTN: hypertension.

tional hazards model (Table 3). The presence of renovascular HTN and high CRP levels were associated with TA activation, but the data did not reach statistical significance (OR 3.446, 95% CI 0.900–13.201, p = 0.071 and OR 7.668, 95% CI 0.725–81.042, p = 0.090, respectively). Notably, type V (OR 10.969, 95% CI 1.144–105.182, p = 0.038) was significantly associated with an increased risk of disease activation in patients with clinically inactive TA. In addition, the cumulative probability of disease activation was significantly higher in patients with TA with type V than in those without type V (p = 0.005; Figure 1).

Followup imaging of patients who did not experience disease activation. Followup images were available for 24 of the 47 patients who did not experience disease activation (stable group). Aortic CT scanning was performed at a median of 38 months (IQR 21.75–72.25 mos) after the initial diagnosis of TA. There was no significant change in 21/24 patients (87.5%), and improvement of vascular stenosis was observed in 2 patients. A new lesion was detected on the followup imaging scan in only 1 patient (1/24, 4.2%).

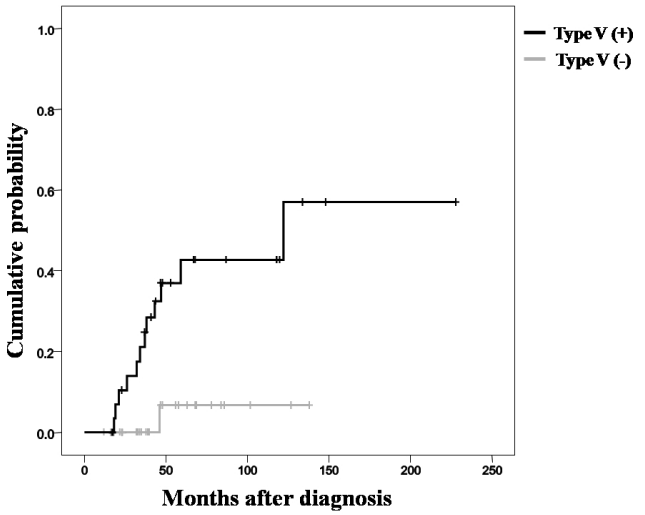

Figure 1. Cumulative probability of activation in patients with Takayasu arteritis (TA) according to type of TA (p = 0.005).

DISCUSSION

Persistent vascular inflammation can lead to vascular dysfunction and ischemia, and the disease often follows a chronic/relapsing course. Therefore, patients with TA are usually treated with longterm immunosuppressants. Nevertheless, some patients have inactive disease at the time of diagnosis[1,6,7,8]. Historically, patients with TA show different patterns in terms of clinical course, with the disease plateauing or following a decreasing pattern[5]. In our present study, 59/199 patients (29.6%) were classified as having inactive disease, which is similar to previous studies reporting that about 10–20% patients are clinically asymptomatic at the time of diagnosis[1,6,7,8]. However, the longterm prognosis and risk factors associated with disease activation in such patients are largely unknown. Ours, to the best of our knowledge, is the first study to report the outcomes of such patients and to identify predictors of TA activation in patients that show no evidence of active disease at the time of diagnosis. None of the patients in our study received immunosuppressants during followup; thus, we were able to observe the natural course of clinically inactive TA. We found that a substantial portion of patients (13/59, 22.0%) with inactive TA at the time of diagnosis went on to experience disease activation, and that angiographic classification may be an important predictor for activation.

Angiographic classification was proposed in TA according to the extent of lesions in the aorta and its major branches[10]. There are 5 categories. Type V is the most extensive and involves major vessels from the ascending aorta to the abdominal aorta. Type V is the most common type observed in patients with TA[7,11,12,13,14]. However, it is unclear whether this angiographic classification plays a role in the longterm outcome of TA[2,15]. Here, we found that type V was a significant independent predictor of TA activation during followup. We can speculate that patients with type V have a more severe disease burden because of more extensive involvement of the vascular lesions. Indeed, it has been suggested that type V may be associated with an unfavorable outcome because it is likely to be accompanied by systemic HTN and aortic regurgitation[7,8,13].

While there is limited data regarding prognosis and the factors that affect the outcome for patients with TA, it is reported that baseline variables, including age at diagnosis, delay in diagnosis, and ESR levels, are associated with a poor prognosis[11,16]. However, we found no significant association between older age at the time of diagnosis (> 35 yrs) or a delay in diagnosis (> 2 yrs) and disease activation. Also, we did not find a significant association between the levels of acute-phase reactants and disease activation, although high CRP levels (> 0.6 mg/dl) tended to increase the risk of activation (Table 3). It is difficult to identify the factors that caused our results to be different from those in previous reports. One important reason, however, may be that our study examined only clinically inactive patients.

Table 3. Multivariate Cox regression analysis of factors related to activation in patients with clinically inactive TA.

Factors	OR	95% CI	p
Older age, > 35 yrs	4.321	0.514–36.346	0.178
Renovascular HTN	3.446	0.900–13.201	0.071
CRP, > 0.6 mg/dl	7.668	0.725–81.042	0.090
Type V	10.969	1.144–105.182	**0.038**

Significant data are in bold face. CRP: C-reactive protein; TA: Takayasu arteritis; HTN: hypertension.

TA is often undiagnosed (or the diagnosis is delayed) in many patients, which may contribute to morbidity in young patients that results from major vascular events[3,16,17]. In particular, this might be more problematic in subjects who show no active symptoms. Here, we found that about half of patients had a delayed diagnosis (for 2 yrs more; Table 1). A substantial portion of patients (13/59, 22.0%) with clinically inactive TA experienced disease activation that presented as major vascular events such as stroke. Therefore, it is important that clinicians are aware of a possible diagnosis of TA in young female subjects who present with abnormal vascular findings, such as difference in blood pressure, pulse, and/or HTN[3].

In our present study, patients aged over 40 years were included in our analysis, indicating that it may be indistinguishable from giant cell arteritis (GCA). However, the prevalence of GCA in Asia is much lower than in Western countries[18,19]. In addition, we found that diagnosis was delayed for 2 years more in substantial portions of patients (28/59, 47.5%) in our cases. Thus, some patients may have already developed TA before the age of 40, although they were diagnosed with the disease at the age of 40 years or older. Further, when considering that TA and GCA might be the same disease with different clinical manifestations[20], it is an interesting issue to study the clinical outcome of GCA with inactive disease, such as incidentally detected aneurysm of large vessels[21].

It is challenging to evaluate the disease activity of TA[22,23]. Although new tools have been proposed to assess disease activity in TA[24], validated measure remains under investigation. Here, we classified patients as active or inactive based on the NIH criteria for the definition of active TA[1]. These criteria are simply based on the presence of active (new-onset or worsening) symptoms that are suggestive of inflammation and/or ischemia[1], and thus are not perfect in assessing disease activity in TA. The best way of assessing disease activity in TA may be the integrated use of noninvasive imaging methods, patient symptoms, clinical findings, and acute-phase reactants. Indeed, developed measures such as the Indian Takayasu Clinical Activity Score contained various items including clinical activity, acute-phase reactants, and imaging findings to evaluate disease activity more accurately[24]. Therefore, the NIH criteria, a somewhat ambiguous definition, could include patients who have experienced the recent onset of mild, nonspecific symptoms. However, in our present study, we found that there was a long time between diagnosis and definite disease activation (median 37.0 mos, IQR 23.5–46.5), and no patient experienced activation within 1 year of diagnosis. In addition, while 1 patient had a mild hypermetabolic lesion, the majority (9/10, 90.0%) showed no abnormal hypermetabolic lesions in the vessels when examined using a whole-body PET scan, which might be a more sensitive method of assessing disease activity[25]. Therefore, it is likely that most of the patients with TA included in our present study had quiescent disease at baseline.

Additionally, we studied the progression of vascular lesions in patients who did not show clinically evident activation of TA. It is reported that vascular inflammation might persist or even progress in patients with clinically inactive TA[1,26]. Thus, one of the major concerns in our present study was that even quiescent patients (stable group) may progress without any clinical evidence of activation. However, followup CT imaging showed aggravation of vascular stenosis in only 1 of 24 patients at a median duration of 38 months (IQR 21.75–72.25 mos) after the initial diagnosis of TA. The lesions in this patient mainly involved vessel calcification rather than enhanced thickening. Further, pathologic examination in patients who underwent surgical interventions at the time of disease activation as well as at the time of diagnosis showed chronic lesions rather than active vasculitis. Thus, the majority of patients with inactive TA showed no evidence of chronic and persistent inflammation, indicating a clinical course involving a monophasic pattern[16,27].

The data presented herein show that a substantial portion of patients with clinically inactive TA at the time of diagnosis experienced disease activation during followup. Involvement of type V was significantly associated with an increased risk of TA activation. These findings suggest that a type V angiographic pattern may be an important predictor for disease activation. Thus, careful observation is required, even in patients with clinically inactive TA.

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