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# A Retrospective Study of Chinese Patients With Giant Cell Arteritis (GCA)

## *Clinical Features and Factors Associated With Severe Ischemic Manifestations*

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**Abstract:** A retrospective study was performed on 70 giant cell arteritis (GCA) patients in Peking Union Medical College Hospital (PUMCH). The aim of this study was to describe the clinical features of these Chinese GCA patients and explore the possible associated factors for severe ischemic manifestations. Medical charts of all patients were reviewed, and the demographic, clinical, and laboratory data were analyzed. The mean age at disease onset was 65.2 years old, and the ratio of male to female was 1:1. Fever and headache were most prominent symptoms at onset, which occurred in 51.4% and 30.0% of patients, respectively. Common manifestations at diagnosis were constitutional symptoms (85.7%), headache (68.8%), visual impairment (38.6%), jaw claudication (30%), scalp tenderness (30%), and concurrent polymyalgia rheumatic (27.1%). No significant difference in clinical manifestations between genders was observed. Comparisons between patients with and without severe ischemic manifestations including jaw claudication, permanent visual loss, or cerebrovascular accident had shown that fever and asthenia were significantly less frequent in patients with severe ischemic manifestations ( $P=0.006$  and  $0.023$ , respectively), and the mean value of erythrocyte sedimentation rate (ESR) was significantly lower in patients with severe ischemic manifestations than patients without ( $P=0.001$ ). History of smoking was more frequent in patients with severe ischemic manifestations ( $P=0.038$ ).

This is the largest group of GCA patients from China so far. When compared our data with patients reported in the literature, this series of GCA patients were younger and without female predominance. The clinical manifestations of patients in this report were similar to other studies except for a higher prevalence of constitutional symptoms. The results of this study indicated that lower systemic inflammatory response and the history of smoking might be associated with severe ischemic damages.

Editor: Raouf Hajji.

Received: October 14, 2015; revised: February 16, 2016; accepted: March 7, 2016.

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The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.00000000000003213

(*Medicine* 95(13):e3213)

**Abbreviations:** CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, Hb = hemoglobin, PLT = platelet counts, PMR = polymyalgia rheumatica.

## INTRODUCTION

Giant cell arteritis (GCA) is the primary systemic vasculitis characterized by inflammatory giant cell infiltration in the large and medium-size arteries, especially the extracranial arteries.<sup>1</sup> Arteritis of these vessels cause intimal hyperplasia, lead to stenosis or occlusion of the involved arteries, and result in a variety of cranial ischemic manifestations. Besides extra-cranial arteries, aorta and other large arteries may also be involved. GCA mainly affects individuals over the age of 50, and women are more frequently involved than men in the reports of most populations. The incidence of GCA varies widely in different ethnical backgrounds and geographic regions. Scandinavians and North Americans of Scandinavian descent have the highest incidence rates, while Southern Europeans have a much lower incidence.<sup>2,3</sup> However, GCA was found to be quite uncommon in Asian populations, and the incidence of GCA in China is unknown.<sup>4</sup> But the general impression is that it is very rare in Chinese. The clinical manifestations of GCA can vary. The typical clinical manifestations of GCA are ischemic symptoms related to vascular involvement, such as temporal headache, scalp tenderness, jaw/limb claudication, stroke, and visual disturbance. Other common manifestations are the constitutional symptoms caused by systemic inflammation including fever, asthenia, weight loss, and anorexia. The severe ischemic complications, such as permanent visual loss and stroke, constitute the major source of chronic disabilities among GCA patients, and are closely related to the outcome of GCA.<sup>5</sup>

So far, there are only several case reports and one prospective study of 16 patients about Chinese GCA patients in the literature.<sup>6-10</sup> Whether the clinical pictures of Chinese patients with GCA are similar to patients of other populations or not is not known. In order to better understand the clinical characteristics of GCA patients in China, we conducted this retrospective study to describe the demographic data, clinical manifestations, and laboratory findings of GCA patients prior to the start of drug therapy. Furthermore, we examined the influence of gender on clinical features and the possible associated factors for the occurrence of disease-related severe ischemic manifestations in this group of GCA patients.

## PATIENTS AND METHODS

### Study Population and Data Collection

A total of 70 inpatients were diagnosed with GCA between August 1992 and May 2014 in Peking Union Medical College

Hospital (PUMCH). Sixty-seven patients were diagnosed according to the American College of Rheumatology criteria.<sup>11</sup> The temporal artery biopsy was performed in 42 (60.0%) cases, and 32 of these 42 (71.4%) patients had characteristic pathological findings of GCA. Three patients neither fulfilled the American College of Rheumatology criteria nor had positive results of temporal artery biopsy, but the 18-fluorodeoxy-glucose positron emission computed tomography showed strong vascular uptake in 2 or more large vessels.<sup>12,13</sup> So, we considered the diagnosis of these 3 patients as GCA and included them into this study. This study was approved by the institutional review board of PUMCH.

We retrospectively analyzed medical records of these 70 patients. Demographic data included sex, age at onset and length of time for diagnosis delay from the initial onset of symptoms. All the clinical features analyzed in this study were prior to steroid therapy. The following clinical data were included: constitutional symptoms (fever, weight loss for at least 4 kg, asthenia, or anorexia), headache, abnormal temporal arteries on physical examination (decreased or absence of pulses, arterial thickening, swelling, or tenderness), scalp tenderness, jaw claudication, visual ischemic manifestations (transient visual loss, permanent visual loss, and blurred vision without other known causes), cerebrovascular accidents (stroke and transient ischemic attacks), limb claudication, and polymyalgia rheumatic (PMR) (marked aching and stiffness of bilateral muscles without other apparent cause in at least 2 of 3 regions: neck, shoulder girdle, or hip girdle).<sup>14–16</sup> As previous studies described, patients were considered to have severe ischemic manifestations if they presented at least one of the following clinical manifestations: jaw claudication, permanent visual loss, and cerebrovascular accidents.<sup>17</sup> Cardiovascular risk factors were also obtained from medical charts, including hypertension, diabetes, hyperlipidemia, history of smoking, and ischemic heart diseases.

A temporal artery biopsy was considered to be positive when inflammatory infiltrates in an arterial wall with or without granuloma and multinucleated giant cells were described upon pathological examination. The following laboratory data at the time of diagnosis confirmation were included: white blood cells (WBC), hemoglobin (Hb) value, platelet counts (PLT), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. The ESR was considered to be elevated when it was higher than 20 mm/hour. Anemia was diagnosed when the Hb level was less than 120 g/L, leukocytosis was considered when WBC count was higher than  $11 \times 10^9/L$ .<sup>18</sup> Thrombocytosis was defined when PLT count was higher than  $400 \times 10^9/L$ .

## Statistical Analysis

Continuous data were described as mean  $\pm$  standard deviation, while categorical variables were expressed as number (or percentage). Comparisons between groups were made using Student's 2-tailed/Mann–Whitney *U*-test for continuous variables. Chi-square tests were performed for categorical data, and Fisher exact tests were performed when the expected frequencies were less than 5. A 2-sided *P*-value less than 0.05 was considered to be statistically significant. Calculations were performed with the SPSS software (version 20.0).

## RESULTS

### Clinical and Laboratory Characteristics

The mean age of these 70 GCA patients at disease onset was  $65.2 \pm 8.0$  years (range: 43–83 years old) and the age at

diagnosis was  $66.4 \pm 8.0$  years. The mean delay between disease onset and diagnosis was 14.4 months. Clinical and laboratory findings of all patients were summarized in Table 1. The most common initial symptom was fever (51.4%), followed by headache which was observed in 30.0% of patients at onset. A total of 18.6% of patients had symptoms that fulfilled the criteria of PMR at disease onset. Other symptoms at onset included asthenia (5.7%), jaw claudication (2.9%), stroke (1.4%), transient ischemic attacks (1.4%), permanent visual loss (1.4%), blurred vision (1.4%), and scalp tenderness (1.4%). When the diagnosis was confirmed, constitutional symptoms were prevalent: fever occurred in 57.1% of patients, weight loss developed in 35 (50.0%) patients, asthenia was observed in 33 (47.1%) patients, and anorexia was seen in 26 (37.1%) patients. The most common ischemic manifestation at diagnosis was headache, and it was observed in 48 (68.6%) patients. Both jaw claudication and scalp tenderness were recorded in 21 (30.0%) patients. Temporal artery abnormalities on palpation at the diagnosis were observed in 17 (24.3%) patients. Twenty-seven (38.6%) patients had visual impairment at diagnosis, including permanent visual loss in 10 (14.3%) transient visual loss in 4

**TABLE 1.** Clinical and Laboratory Features at Onset and at Diagnosis of All Patients With GCA (n = 70)

Variables	At Onset	At Diagnosis
General characteristics		
Female, n, %	35 (50.0)	35 (50.0)
Age, (mean $\pm$ SD), years	65.2 $\pm$ 8.0	66.4 $\pm$ 8.0
Constitutional symptoms, n, %		
Fever	36 (51.4)	40 (57.1)
Weight loss	0 (0.0)	35 (50.0)
Asthenia	4 (5.7)	33 (47.1)
Anorexia	0 (0.0)	26 (37.1)
Ischemic manifestations, n (%)		
Jaw claudication	2 (2.9)	21 (30.0)
Headache	21 (30.0)	48 (68.6)
Scalp tenderness	1 (1.4)	21 (30.0)
Abnormal temporal artery	0 (0.0)	17 (24.3)
Visual manifestations		
Permanent visual loss	1 (1.4)	10 (14.3)
Transient visual loss	0 (0.0)	4 (5.7)
Blurred vision	1 (1.4)	19 (27.1)
Cerebrovascular accidents		
Stroke	2 (2.9)	4 (5.7)
Transient ischemic attacks	1 (1.4)	1 (1.4)
Limb claudication	0 (0.0)	2 (2.9)
Severe ischemic manifestations	5 (7.1)	29 (41.4)
PMR, n, %	13 (18.6)	19 (27.1)
Laboratory parameters, mean $\pm$ SD		
ESR mm/hour	NR	92.9 $\pm$ 25.3
CRP, mg/L*	NR	80.2 $\pm$ 57.4
Hb, g/L	NR	109.3 $\pm$ 20.7
PLT, $10^9/L$	NR	363.8 $\pm$ 139.0
WBC, $10^9/L$	NR	9.3 $\pm$ 3.6

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, Hb = hemoglobin, NR = not recorded, PLT = platelet counts, PMR = polymyalgia rheumatica, WBC = white blood cells.

\* CRP was available for 55 patients.

(5.7%) and blurred vision in 19 (27.1%). Stroke and transient ischemic attacks were seen in 3 (4.2%) and 1 (1.4%) patients at diagnosis, respectively. Nineteen (27.1%) patients developed PMR at diagnosis. Two (2.9%) patients had limb claudication at diagnosis.

The mean values of the laboratory parameters were shown in Table 1. ESR was elevated in all patients with a mean value of  $92.9 \pm 25.3$  mm/hour (range 32–145). The ESR level higher than 50 mm/hour occurred in 67 (95.7%) patients and higher than 100 mm/hour occurred in 25 (35.7%) patients. CRP was available for 55 patients at diagnosis and it was elevated ( $>10$  mg/L) in 49 (88.6%) patients. Anemia was noted in 51 (72.9%) patients, and the median value of Hb was  $109.3 \pm 20.7$  g/L. Leukocytosis and thrombocytosis presented in 15 (21.4%) patients and 16 (22.9%) patients, respectively.

### Comparison of Clinical Features Between Female and Male Patients

The male–female ratio was 1:1 in this series of GCA patients. As male–female ratio in this present study was higher than most previous studies, we analyzed the influence of gender on the spectrum of clinical features of the disease. We compared the demographic, clinical, and laboratory data of GCA patients for different gender. However, male and female patients did not show any difference neither in age, delay to diagnosis nor clinical manifestations or laboratory findings (Table 2).

### Comparison Between Patients With and Without Severe Ischemic Manifestations at Diagnosis

Severe ischemic manifestations occurred in 29 (41.4%) patients. The comparisons of patients with and without severe ischemic manifestations were summarized in Table 3. Patients with severe ischemic manifestations had lower frequencies of fever ( $P=0.006$ ) and asthenia ( $P=0.023$ ). Levels of ESR at diagnosis were significantly lower in patients with severe ischemic manifestations ( $P=0.001$ ) than patients without. A tendency of difference in serum level of CRP was observed between groups but the difference was not statistically significant ( $P=0.074$ ). Patients with severe ischemic manifestations had a significantly higher frequency of smoking than those patients without severe ischemic manifestations ( $P=0.038$ ). No statistical significant difference between patients with or without severe ischemic manifestations was found in other variables.

## DISCUSSION

The incidence of GCA in China is generally unknown and reports about Chinese GCA patients are very limited. Only 70 in-patients were admitted and diagnosed as GCA during the past 23 years in PUMCH, it is rare when compared to 688 admissions for Takayasu’s arteritis during the same period. So this data confirms the generally impression that GCA is a rare disease in Chinese. Here, we conducted a retrospective study of these 70 Chinese GCA patients on their demographic, clinical, and laboratory findings. This is the largest series of Chinese GCA according to our knowledge.

The demographic data of our patients are somewhat different from the most previous reports in the literature. First, the average age at onset of all GCA patients in present study is 65.2 years, which is younger than the reported 70 and 80 years of age in other populations.<sup>3,19</sup> Second, females predominance reported in previous GCA studies was not observed in our patients. According to the literature, women are about 2 to 3

**TABLE 2.** Comparisons of Clinical and Laboratory Data at Diagnosis Between Female and Male Patients

Variables	Males (n = 35)	Females (n = 35)	P Value
<b>General characteristics</b>			
Age at onset, (mean $\pm$ SD), years	64.5 $\pm$ 8.5	65.8 $\pm$ 7.5	0.503
Delay in diagnosis, (mean $\pm$ SD), months	14.7 $\pm$ 40.5	14.1 $\pm$ 41.1	0.954
<b>Constitutional symptoms, n, %</b>			
Fever	23 (65.7)	17 (48.6)	0.147
Weight loss	19 (54.3)	16 (45.7)	0.473
Asthenia	17 (48.6)	16 (45.7)	0.811
Anorexia	14 (40.0)	12 (34.3)	0.621
<b>Vascular ischemic manifestations, n, %</b>			
Jaw claudication	9 (25.7)	12 (34.3)	0.434
Headache	25 (71.4)	23 (65.7)	0.607
Scalp tenderness	10 (28.6)	11 (31.4)	0.794
Abnormal temporal artery	6 (17.1)	11 (31.4)	1.942
Visual manifestations	15 (42.9)	12 (34.3)	0.461
Permanent visual loss	6 (17.1)	4 (11.4)	0.734
Transient visual loss	1 (2.9)	3 (8.6)	0.614
Blurred vision	11 (31.4)	8 (22.9)	0.420
Cerebrovascular accidents	2 (5.7)	2 (5.7)	0.172
Stroke	1 (2.9)	2 (5.7)	1.000
Transient ischemic attacks	1 (2.9)	0 (0.0)	1.000
limb claudication	0 (0.0)	2 (5.7)	0.493
Severe ischemic manifestations, n, %	15 (42.9)	14 (40.0)	0.808
PMR	8 (22.9)	11 (31.4)	0.420
<b>Laboratory parameters (mean <math>\pm</math> SD)</b>			
ESR, mm/hour	89.74 $\pm$ 24.98	96.1 $\pm$ 25.6	0.294
CRP, mg/L*	78.4 $\pm$ 57.2	82.0 $\pm$ 58.4	0.802
Hb, g/L	113.0 $\pm$ 25.0	105.4 $\pm$ 14.3	0.130
PLT, $10^9/L$	353.4 $\pm$ 135.5	374.2 $\pm$ 143.7	0.541
WBC, $10^9/L$	9.8 $\pm$ 4.4	8.8 $\pm$ 2.6	0.313

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, Hb = hemoglobin, NR = not recorded, PLT = platelet counts, PMR = polymyalgia rheumatica, WBC = white blood cells.

\*CRP was available for 27 male patients and 28 female patients.

times more prevalent than men in other populations, but men and women are equally involved in present study.<sup>3,20–22</sup> However, these demographic features of our patients are consistent with another study of GCA in China, in which the mean age at disease onset was even younger than our patients and the majority of GCA cases were male.<sup>6</sup> These findings may indicate that Chinese patients with GCA may be different from western countries in susceptible population. Genetic background, environmental exposures, and lifestyle may play roles in the susceptibility to GCA, but it needs further investigation to be verified.

**TABLE 3.** Clinical Characteristics of Patients With and Without Severe Ischemic Manifestations at Diagnosis

Variables	Group 1 (n = 29)	Group 2 (n = 41)	P Value
General characteristics			
Female, n, %	14 (48.3)	21 (51.2)	0.808
Age at onset, (mean ± SD), years	63.8 ± 9.2	66.1 ± 6.9	0.232
Delay in diagnosis, (mean ± SD), months	17.5 ± 44.9	12.3 ± 37.6	0.607
Constitutional symptoms, n, %			
Fever	11 (37.9)	29 (70.3)	0.006
Weight loss	16 (55.2)	19 (46.3)	0.467
Asthenia	9 (31.0)	24 (58.5)	0.023
Anorexia	13 (44.8)	13 (31.7)	0.263
Vascular ischemic manifestations, n, %			
Headache	21 (72.4)	27 (65.9)	0.560
Scalp tenderness	9 (31.0)	12 (29.3)	0.874
Abnormal temporal artery	8 (27.6)	9 (22.0)	0.588
PMR, n, %	8 (27.6)	11 (26.8)	0.944
Laboratory parameters (mean ± SD)			
ESR, mm/hour	81.6 ± 21.0	101.0 ± 25.3	0.001
CRP, mg/L*	57.6 ± 49.9	83.98 ± 57.00	0.074
Hb, g/L	115.2 ± 14.1	108.4 ± 18.1	0.099
PLT, 10 <sup>9</sup> /L	360.2 ± 121.7	366.4 ± 151.4	0.859
WBC, 10 <sup>9</sup> /L	9.2 ± 3.0	9.3 ± 4.0	0.879
Hypertension, n, %	16 (55.2)	15 (36.6)	0.123
Diabetes mellitus, n, %	5 (17.2)	7 (17.1)	1.000
Hyperlipemia, n, %	14 (48.3)	21 (51.2)	0.808
Smoking, n, %	14 (48.3)	10 (24.4)	0.038
Ischemic heart disease, n, %	3 (10.3)	6 (14.6)	0.726

Group 1: patients with severe ischemic manifestations. Group 2: patients without severe ischemic manifestations. CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, Hb = hemoglobin, NR = not recorded, PLT = platelet counts, PMR = polymyalgia rheumatica, WBC = white blood cells.

\*CRP was available for 27 patients in group 1 and 28 patients in group 2.

It is reported in the literature that male and female patients with GCA may differ in the prevalence of clinical manifestations including visual impairments, jaw claudication, and the concurrence with PMR.<sup>20,23</sup> In order to evaluate whether gender affected clinical manifestations or laboratory findings, comparisons between female and male patients were performed in this study. However, differences in these major clinical presentations could not be detected in this series of Chinese GCA patients.

Fever and headache were the most common initial symptoms in this series of patients at disease onset and the diagnosis of disease. The proportions of GCA patients who had fever and asthenia were higher in present study than those reported in other studies.<sup>19,24</sup> In addition, the prevalence of constitutional symptoms in our patients was higher than the range (60.8–75.0%) previously described.<sup>17,19,24–26</sup> The higher proportion of patients with constitutional symptoms in this study might be partially explained by the fact that patients of this study were

from internal medicine department, while patients in the literature were from departments of ophthalmology, neurology, or others. But other clinical manifestations in our patients are similar to those reported in other studies from western countries.<sup>19,24</sup> Furthermore, we observed that patients in our study had lower incidence of cranial ischemic manifestations and higher proportion of constitutional symptoms than those in another study of GCA patients in China.<sup>6</sup> However, it should be noted that GCA patients in that study from China were from neurology in-patients.<sup>6</sup> Perhaps the differences between our study and that Chinese study were due to patient recruitment difference.

The most important complications in GCA patients were severe ischemic events, and they were closely related to the prognosis of GCA patients. The definition of severe ischemic manifestations was not unified in previous studies, so the incidence of severe ischemic manifestations was somewhat different in various populations. In present study, the proportion of patients who had severe ischemic manifestations was 41.4%, which ranged between 21.1% and 54.6% reported in the literature.<sup>25,27,28</sup> Among these severe ischemic manifestations, jaw claudication was the most common presenting symptom in our patients with GCA (30.0%), followed by permanent visual loss in 14.3% of the patients, and cerebrovascular events in 5.7%. The prevalence of these complications was similar to previous reports on GCA.<sup>19,29,30</sup> A lot of attentions had been paid to identify the risk factors for severe ischemic manifestations in patients with GCA. The reported risk factors in previous studies included scalp necrosis, low inflammatory response, elevated PLT count, absence of anemia, hypertension, and history of ischemic heart disease.<sup>17,28,30–37</sup> However, patients with severe ischemic manifestations in our series had lower incidence of constitutional symptoms (fever and asthenia) and lower levels of inflammatory markers (ESR and CRP) when compared to patients without severe ischemic damages. This finding was consistent with previous studies which suggested that patients with lower inflammatory response were at a higher risk of developing ischemic manifestations.<sup>17,18,28,31–33,35</sup> Gonzalez-Gay et al<sup>17</sup> demonstrated that GCA patients with fever constituted a subgroup of patients with more severe inflammatory response and less ischemic disease. Similarly, in the study by Neshet et al,<sup>33</sup> GCA patients without fever or other systemic symptoms were at increased risk of cranial ischemic complications. In a series of 240 patients in Spain, GCA patients with ESR greater than 100 mm/hour exhibited a statistically significant reduction in the incidence of visual ischemic events.<sup>18</sup> Salvarani et al<sup>32</sup> also observed that the only statistically significant predictor for the development of permanent visual loss was the absence of high levels of ESR at diagnosis. Moreover, previous studies observed the anemia, a result of chronic inflammatory response in GCA, might be a potential protective factor against the development of severe ischemic manifestations.<sup>31,37</sup>

A markedly elevated ESR has long been considered a critical marker for inflammatory response in GCA and has been considered an important criterion for the diagnosis of GCA. However, it seemed that augmented inflammatory response may be negatively correlated with the occurrence of ischemic events. The explanation for this phenomenon remains to be elucidated. The study of Cid et al<sup>38</sup> has provided some clues to the potential mechanisms of this phenomenon. They observed that patients without ischemic complications had higher tissue angiogenesis scores than patients with ischemic events. In addition, angiogenesis was also significantly more prominent

in patients with strong inflammatory response. Based on their findings, it is possible that inflammation-induced angiogenesis may be a compensatory mechanism for ischemia in GCA patients. The relationship between systemic inflammatory response and the occurrence of ischemic events deserves further research.

We also included the presence of cardiovascular risk factors in our analysis since these factors may influence the development of severe ischemic manifestations of GCA as reported in previous studies.<sup>28,30</sup> In present study, univariate analysis showed that GCA patients with severe ischemic manifestations had a higher frequency of smoking history. Machado et al<sup>39</sup> reported an association between smoking and disease development in a case-control study of GCA, and Duhaut et al<sup>40</sup> described a strong association between smoking and GCA in women. However, hypertension, rather than smoking, exhibited increased risk of developing severe ischemic complications in other 2 studies.<sup>28,30</sup> These controversial results need to be confirmed in large GCA patient studies.

The major limitations of this study include the retrospective design and small number of cases. Patients in this study are from a single healthcare center and referral bias may also limit the conclusion of this study. Prospective multicenter or national population-based studies are needed to further verify the findings of present study in Chinese GCA patients.

In conclusion, this largest series of Chinese GCA patients has shown that the onset age of Chinese GCA patients is younger than those of other populations and both male and female are equally susceptible to the disease. Chinese GCA patients have a higher prevalence of constitutional symptoms but similar prevalence of severe ischemic damages. Furthermore, we also find that low systemic inflammatory response and the history of smoking may be associated with the development of severe ischemic manifestations in patients with GCA although further studies are mandatory to confirm this association. Nevertheless, rheumatologists should alert to GCA patients with low ESR levels since they may have unfavorable prognosis. We may suggest that GCA patients with low ESR levels should be treated more aggressively than patients with high ESR levels in order to prevent severe ischemic organ damages.

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