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ORIGINAL ARTICLE

Differences in clinical manifestations and prognosis of Chinese giant cell arteritis patients with or without polymyalgia rheumatica

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Abstract

Background The symptoms of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) frequently overlap in the elderly. Whether there are differences in clinical features or prognosis between GCA patients with or without PMR remains unknown.

Aims To identify differences in clinical manifestation and prognosis between Chinese GCA patients with or without PMR.

Methods A retrospective study of patients diagnosed with GCA in Peking Union Medical College Hospital (PUMCH) during the last 20 years was conducted. Clinical data was collected and analyzed accordingly, and follow-up was performed.

Results A total of 50 patients had PMR, while 41 patients did not, with no significant differences in age, gender, and disease course between the two groups. GCA patients with PMR presented with higher risks of family history of malignancy ($p = 0.048$). Patients without PMR had higher proportion of hearing loss ($p = 0.006$), ANCA positive ($p = 0.024$), and abnormal imaging findings illustrating the involvement of arteries under aortic arch ($p = 0.018$). Before treatment, total lymphocyte counts in patients without PMR were lower than those with PMR, and monocyte counts in both groups were higher than normal. Acute phase reactants in patients without PMR were higher than the other group. No significant differences were found in prognosis during follow-up.

Conclusions GCA patients with or without PMR have different clinical characteristics. Patients with PMR present myalgia or arthralgia more frequently, while those without PMR have higher inflammatory markers, lower lymphocyte counts, and wider involvement of arteries under aortic arch.

Keywords Giant cell arteritis · Glucocorticoids · Polymyalgia rheumatica · Temporal artery biopsy

Introduction

Giant cell arteritis (GCA), also known as temporal arteritis, predominantly affects European and American populations, and mostly affects people over 50. The occurrence is expected to increase with age [1, 2]. Large arteries such as aorta and its primary branches as well as cranial vessels are frequently affected, with main symptoms of ischemic manifestation in blood supply area of involved vessels. PMR is one of the most common inflammatory rheumatic disease in the elderly [3]. PMR is an inflammatory rheumatic disorder with typical symptoms of shoulder, neck, pelvic, and girdle muscle involvement as well as joint symptoms and is usually accompanied by constitutional symptoms such as fever and an increase in ESR [4]. Symptoms of GCA frequently overlap with those of PMR in the elderly. About 40–60% patients diagnosed with GCA have PMR manifestations, and 16–21% of PMR patients have GCA, especially in untreated patients. GCA and PMR can occur simultaneously, independently or in succession [2]. The causes and mechanisms of PMR remain unclear. PMR could be a type of limited or early stage GCA without remarkable inflammation of vasculitis due to unknown regulation pathways [2, 4–6]. The epidemiological features of GCA and PMR in China remain unclear. Poor recognition, lack of serological markers, absence of temporal artery biopsy,

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and false negative biopsies due to missed lesions lead to frequent misdiagnosis of GCA/PMR. This paper reviews all GCA patients diagnosed in PUMCH over the past two decades and focuses on differences in manifestations between GCA patients with or without PMR.

Materials and methods

Patients

We reviewed 117 patients at PUMCH with a discharge diagnosis of GCA between January 1998 and December 2017. After medical history review and telephonic follow-ups, patients with missing data were excluded. Also, we reconfirmed the diagnosis according to the classification criteria below:

GCA was diagnosed according to the American College of Rheumatology (ACR) 1990 classification criteria [7]: (1) age at onset ≥ 50 years of age; (2) headache of new onset or new type; (3) tenderness or decreased pulsation of the temporal artery; (4) elevated erythrocyte sedimentation rate (ESR ≥ 50 mm/h); (5) histological changes of arteritis: either granulomatous lesions, usually with multi-nucleated giant cells, or diffuse mononuclear cell infiltration. GCA was confirmed by the presence of ≥ 3 of the above five diagnostic criteria. Temporal artery biopsy (TAB) was previously considered the only reliable diagnostic test for GCA [8]. But according to European League Against Rheumatism (EULAR) 2018 recommendations for the use of imaging in large vessel vasculitis, early imaging modalities (including ultrasound, MRI, CT, and PET) are recommended to complement the clinical criteria to diagnose GCA and for patients with high clinical suspicion of GCA and a positive test, the diagnosis may be made without an additional test (biopsy or further imaging) [9]. Furthermore, ultrasound of temporal ± axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA [9]. Because of the simplicity and popularity, about 85.7% (78/91) of the patients in this study underwent vascular ultrasound examination. With the improvement of knowledge and economic situation, the proportion of patients who chose CTA and MRA (based on renal function, age, and frequency of recent radiographic examination) in the last 5 years was significantly higher (73.0% 27/37 vs 27.8% 15/54). The cost of PET/CT was relatively high for Chinese patients and it needs to discuss carefully with patients before order of this examination, so the overall ratio was about 25.3% (23/91). Furthermore, due to lack of knowledge about diseases and economic conditions, in this study group of patients, TAB ratio is still very high.

PMR was diagnosed according to the ACR 1982 classification criteria [10]: (1) age ≥ 50 years; (2) pain and morning stiffness of ≥ 2 of three predilection sites (neck, shoulders, and pelvic girdle) for > 1 month; (3) obviously elevated ESR (ESR ≥ 50 mm/h); (4) absence of redness, swelling, heat, or weakness of affected muscles; (5) exclusion of other diseases such as rheumatoid arthritis, chronic infection, polymyositis, tumor, etc. (6) response to small dose of glucocorticoid (prednisone 10–15 mg/day). Patients who fulfill all six criteria were diagnosed as PMR.

Methods

Medical history of patients, including symptoms and signs, physical examinations before and after diagnosis, accompanying diseases, laboratory results and imaging results before and after treatment, as well as telephonic interview information were collected and summarized. Decreased vision and hearing loss were defined as patients' self-reported significant decreased vision and hearing loss after the onset of GCA, or specialist examination, specialist consultation found disease-related visual and hearing impairment. Stabilization was defined as manifestations relieved after treatment and no symptom relapse after reduction of glucocorticoid and other immunosuppressive agents. Unstable disease was defined as symptoms relieved after treatment, but symptoms relapsed or complications associated with treatment such as infection occurred after reduction of glucocorticoid and other immunosuppressive agents. Patients were divided into two groups, GCA with PMR and GCA without PMR, according to 1982 ACR criteria for PMR. This retrospective research was approved by the Ethics Committee of PUMCH.

Statistical analysis

Data analysis was performed with SPSS 19.0 software (IBM SPSS Statistics 19). General information was analyzed by descriptive statistics. Mean value and standard deviation were calculated for continuous variables, while frequency and percentage were used for categorical variables. Independent sample *t* test was applied for continuous variables, paired sample *t* test was applied for comparing continuous variables before and after treatment, and Chi-square test was applied for categorical variables. All tests were two-sided, and $p < 0.05$ was considered to be significant.

Results

Population analysis and clinical manifestations

A total of 91 cases met the inclusion criteria. The average follow-up time was 86.04 (3–218) months. Among the 91 cases, 46 patients were biopsy-positive GCA, comprising > 50% of total cases; 50 patients (54.9%) were female, and the male/female ratio was 1:1.22.

Patients were divided into two groups, of which 50 patients had GCA accompanied by PMR and 41 patients had isolated GCA. No significant differences were found in age, disease course, and gender between the two groups. Patients with GCA accompanied by PMR had a higher prevalence of myalgia or arthralgia ($p < 0.001$), which is consistent with the clinical manifestation of PMR. Given the clinical manifestation, GCA patients with PMR presented with higher risks of a positive family history of malignant disease ($p = 0.048$). Meanwhile, patients without PMR had a higher prevalence of hearing loss ($p = 0.006$) (Table 1).

Laboratory results

Comparison of blood cell counts of the two groups before treatment illustrated that GCA patients with PMR had higher lymphocyte count than patients without PMR ($p = 0.020$), while the lymphocyte count of both groups increased significantly after treatment ($p < 0.001$), showing no significant difference between the two groups. The monocyte count of both groups was higher than normal before treatment, but decreased significantly after treatment ($p < 0.001$), with no significant difference between the two groups. Besides, hemoglobin and platelet levels

Table 1 Clinical features of GCA patients with or without PMR

		GCA with PMR $N = 50$ (%)	GCA without PMR $N = 41$ (%)	P
Age	Years (mean ± SD)	65.24 ± 7.86	65.41 ± 7.52	0.914
Disease course	Months (mean ± SD)	10.34 ± 21.76	6.82 ± 9.40	0.306
Gender	Male	21 (42)	20 (48.8)	0.518
	Female	29 (58)	21 (51.2)	
Initial symptoms				
	Fever	29 (58)	26 (63.4)	0.599
	Symptoms of myalgia and/or arthralgia	35 (70)	9 (22.0)	< 0.001*
	Cranial symptoms	27 (54)	25 (61.0)	0.503
Clinical manifestations				
	Fever	39 (78)	35 (85.4)	0.370
	Headache	36 (72)	28 (68.3)	0.700
	Scalp tenderness or pain	16 (32)	8 (19.5)	0.179
	Abnormal pulsation and tenderness of temporal artery	13 (26)	7 (17.1)	0.306
	Decreased vision	17 (34)	18 (43.9)	0.334
	Myalgia	49 (98)	2 (4.9)	< 0.001*
	CNS symptoms	10 (20)	11 (26.8)	0.442
	Hearing loss	7 (14)	16 (39.0)	0.006*
	Jaw claudication	17 (34)	9 (22.0)	0.206
	Arthralgia	34 (68)	13 (31.7)	0.001*
	GI symptoms	6 (12)	6 (14.6)	0.712
	Unspecific symptoms	34 (68)	27 (65.9)	0.828
	Weight loss	29 (58)	21 (51.2)	0.518
Past medical history				
	Smoking	19 (38)	14 (34.1)	0.704
	Tumor family history	13 (26)	4 (9.8)	0.048*
	Diabetes	6 (12)	8 (19.5)	0.323
	Hypertension	17 (34)	15 (36.6)	0.797
	Dyslipidemia	20 (40)	11 (26.8)	0.187

CNS symptoms: vertigo, transient ischemia attack, and stroke; GI involvement: abdominal pain and abdominal distention; constitutional symptom: fatigue, night sweat, and anorexia

CNS central nervous system, *GCA* giant cell arteritis, *GI* gastrointestinal

*Significantly different

improved after treatment, with no obvious change in white blood cell count. The inflammatory markers in patients without PMR were higher than in patients with PMR before treatment, of which the difference in C-reactive protein (CRP) between the two groups was significant ($p = 0.003$). After treatment (according to the last laboratory result at the hospital), the inflammatory markers of both groups obviously decreased ($p < 0.001$), but the inflammatory markers of patients without PMR were higher than the other group, and the difference in ESR was significant ($p = 0.046$). Meanwhile, albumin (ALB) level of both groups was lower than normal before treatment and improved after treatment, but was obviously lower in patients without PMR ($p = 0.017$) (Table 2).

Table 2 Laboratory results of GCA patients with or without PMR before and after treatment

	GCA with PMR mean ± SD	$N = 50$	GCA without PMR mean ± SD	$N = 41$	P
WBC (*10^9/L)					
Before treatment	9.47 ± 4.52	48	8.62 ± 4.09	41	0.353
After treatment	8.97 ± 3.24	48	8.93 ± 3.08	41	0.945
p	0.487		0.569		
MONO (*10^9/L)					
Before treatment	1.13 ± 1.39	48	0.99 ± 0.69	41	0.547
After treatment	0.65 ± 0.29	48	0.56 ± 0.28	41	0.155
p	0.026*		< 0.001*		
LYM (*10^9/L)					
Before treatment	1.63 ± 0.73	48	1.31 ± 0.55	41	0.020*
After treatment	2.21 ± 0.91	48	1.97 ± 1.01	41	0.245
p	< 0.001*		< 0.001*		
HGB (g/L)					
Before treatment	108.31 ± 18.18	48	105.29 ± 21.10	41	0.476
After treatment	117.64 ± 13.11	48	113.10 ± 18.34	41	0.192
p	0.003*		0.002*		
PLT (*10^9/L)					
Before treatment	381.56 ± 167.56	48	377.51 ± 133.49	41	0.899
After treatment	254.81 ± 123.03	48	312.73 ± 137.93	41	0.042*
p	< 0.001*		< 0.001*		
ESR (mm/h)					
Before treatment	87.62 ± 23.42	50	95.12 ± 32.07	41	0.216
After treatment	31.00 ± 24.44	46	44.93 ± 38.71	40	0.046*
p	< 0.001*		< 0.001*		
CRP (mg/L)					
Before treatment	62.17 ± 55.38	50	101.33 ± 64.71	41	0.003*
After treatment	10.42 ± 17.10	46	19.88 ± 34.37	40	0.120
p	< 0.001*		< 0.001*		
ALB (g/L)					
Before treatment	32.83 ± 4.14	48	32.24 ± 5.16	41	0.558
After treatment	35.90 ± 4.05	41	33.62 ± 4.19	37	0.017*
p	0.527		0.745		

WBC white blood cell, *MONO* monocyte, *LYM* lymphocyte, *HGB* hemoglobin, *PLT* platelet, *ESR* erythrocyte sedition rate, *CRP* C-reactive protein, *ALB* albumin

*Significantly different

Immune markers and artery involvement

The number of patients with low-titer ANA, ANCA positive, and APS positive were 18, 12, and 12, respectively. ANCA positive was more frequent in patients without PMR ($p = 0.024$), and percentage of patients with involvement of arteries under aortic arch was higher in this group ($p = 0.018$) (Table 3).

Follow-up information

Nine and five patients were lost to follow-up in the GCA with PMR and GCA without PMR groups, respectively. The percentage of patients who were stable, unstable, developed a tumor, or died were not statistically significant between the two groups (Table 4). Comparison of the unstable patients in the GCA with PMR group and without PMR group showed that six patients (37.5%) versus seven (70%) relapsed with reduction of glucocorticoid, and 11 cases (68.8%) versus two (20%) developed infections when immunosuppressive therapy was applied. Among patients without PMR, one patient had acute cerebral infarction and one patient had deep venous thrombosis of lower extremity and pulmonary embolism (DVT-PE).

Discussion

GCA and PMR occurred in 35–55% of elderly patients with fever of unknown origin (FUO) who were finally diagnosed with immune disorders in European and American populations. With the increase in elderly population, the prevalence was most likely to increase [2, 5, 6]. There is no authentic epidemiological data of GCA and/or PMR among Chinese population. Only a few case series were reported, but GCA and PMR might be more common than expected. Our colleagues have repeatedly reported the constitution of different causes of FUO over the past 30 years at PUMCH. The results illustrated that GCA composed of < 4% of all CTD-caused FUO cases and < 12% of elderly FUO cases [11]. This single-center study at PUMCH revealed similar age of disease onset to previous foreign reports. The male/female ratio (1:1.22) was lower than that in European and American populations, but similar to previous Chinese reports [1, 2, 4], indicating potential racial differences.

According to a previous study, GCA and PMR patients had higher prevalence of tumors, and PMR was frequently seen in paraneoplastic immune syndrome [1]. This study showed that patients diagnosed with GCA accompanied by PMR were more likely to have symptoms of myalgia or arthralgia, and family history of tumor, indicating that physicians should pay attention to the family history of these patients and even more, should screen for tumors during diagnosis, treatment, and follow-ups of GCA patients with PMR.

GCA patients may have different clinical subtypes. Some patients present as large artery involvement, some as cranial symptoms and some as PMR and other systemic symptoms [12–18]. This study found that hearing loss, decreased vision, and CNS manifestations were more frequently seen in patients without PMR (the differences in decreased vision and CNS symptoms were not significant) suggesting that cranial vessels were more likely to be affected in patients without PMR. Clinical manifestations were likely to differ between the two groups. It is important to further investigate potential GCA symptoms for early recognition and diagnosis.

Table 3 Immune markers and artery involvement of GCA patients with or without PMR

	GCA with PMR *n* (%)	Number of patients undergoing the test	GCA without PMR *n* (%)	Number of patients undergoing the test	*P*
Immune markers					
Low-titer ANA	9 (19.1)	47	9 (22.0)	41	0.745
ANCA positive	3 (6.3)	48	9 (23.1)	39	0.024*
APS positive	6 (26.1)	23	6 (25)	24	0.932
RF↑	11 (31.4)	35	8 (27.6)	29	0.738
IgG↑	10 (25)	40	11 (32.4)	34	0.484
Vessel involvement assessed by imaging (ultrasound, CTA, PET/CT, MRA)					
Intracranial arteries	16 (53.3)	30	18 (50)	36	0.787
Aortic arch and extracranial arteries above aortic arch	28 (93.3)		30 (88.9)		0.215
Arteries under aortic arch	14 (46.7)		27 (75)		0.018*

ANA anti-nuclear antibody, *ANCA* anti-neutrophil cytoplasmic antibody, *APS* anti-phospholipid antibody, *RF* rheumatic factor, *Ig G* immunoglobin G
*Significantly different

Table 4 Follow-up information of GCA patients with or without PMR

	GCA with PMR *n* (%)	Number of patients[a]	GCA without PMR *n* (%)	Number of patients[a]	*p*
Stable	20 (48.8)	41	17 (47.2)	36	0.891
Unstable	16 (39.0)		10 (27.8)		0.298
Tumor	0		2 (5.6)		0.126
Death	5 (12.2)		7 (19.4)		0.381

[a] Number of patients refers to the number of patients with follow-up information

In addition to the factors such as heredity and infection, GCA was generally believed to be a type of vasculitis of T cell infiltration, in which cellular immunity plays a major role. However, some recent studies have suggested that innate immune-related cells, monocytes, and B lymphocytes may also be involved in the pathogenesis of GCA or even PMR [12]. GCA or PMR patients have lower peripheral blood B lymphocyte count than normal populations, and B lymphocyte count can recover soon after treatment with glucocorticoid. Moreover, the degree of this change was negatively related to the level of ESR and CRP before treatment [19–22]. Although this was a retrospective study and most cases lacked data of peripheral blood lymphocyte subtype count, the lymphocyte count improved remarkably after treatment, which was in agreement with the previous studies. Sleen et al. [23] indicated that peripheral blood monocyte count of GCA and PMR patients was higher than normal and decreased after treatment, which was similar to our findings. Some markers (such as matrix metalloproteinase-3, or small-vessel vasculitis and vasa vasorum vasculitis were observed in pathology) could be applied for predicting the presence of PMR or PMR-related symptoms in GCA patients [24, 25]. If applied to clinical performance, these markers might be beneficial for the diagnosis, treatment, and prognosis of GCA patients. Meanwhile, patients without PMR had higher inflammatory markers as compared to the other group before treatment. The markers decreased remarkably in both groups after treatment but remained higher in patients without PMR. The results of previous studies remain controversial. Pathologists reviewed the temporal artery biopsy specimens in patients diagnosed as GCA with/without PMR and observed small-vessel vasculitis (SVV) of monocytic infiltration surrounding large vessels and the lesion of the temporal artery itself was not obvious in patients without PMR, with a more serious systemic inflammation in clinical manifestations [26, 27]. Other scholars believed that the changes of leukocyte subgroups and inflammatory markers were related to the treatment response and prognosis, and GCA patients had a better response when comorbid with PMR [25]. GCA patients comorbid with PMR had higher inflammatory markers [10]. This single-center study was limited by the number of cases, so larger sample size or multicenter study should be conducted in the future. The immune markers, such as ANA, ANCA, or APS, have been rarely studied in GCA patients. After a simple review at PUMCH over the past 20 years, we have found that more patients have accepted ANCA test and the sensitivity of the test is increasing, with a decrease in specificity. Hence, although the proportion of ANCA positive in the PMR group was higher ($p = 0.024$), it does not confirm a correlation between them.

It was previously believed that vessels involved in GCA were mainly large vessels above aortic arch. However, more than one-third of GCA patients were found to have involvement of descending aorta as well as the vessels under descending aorta. Besides, medium-sized arteries such as cranial arteries, arteries supplying the eyes (ophthalmic artery, posterior ciliary arteries, central retinal artery), ears, and even some small vessels are commonly affected [1, 2, 4, 9, 13, 17]. The advances in techniques of PET/CT, CT, and MRI have contributed to better identification and evaluation of vascular involvement in the vasculitis patients [28]. In this study, involvement of arteries under aortic arch was higher in GCA patients without PMR. It is suggested that the diagnosis of GCA should be considered when the symptoms of ischemia of arteries under the aortic arch appear in elderly patients without typical symptoms of myalgia, arthralgia, or fever [29]. To the best of our knowledge, this is the first study in China to follow up and evaluate the prognosis of GCA patients. After follow-ups of patients, we found that coexistence of PMR had no significant influence on prognosis. However, most GCA patients were relatively old with several complications, and due to the adverse effects of treatment, < 50% of patients were stable. Besides, higher percentage of patients relapsed during the reduction of glucocorticoid among those with PMR, while more patients had infections due to immune suppression treatment among those without PMR. Therefore, it is necessary to highlight the importance of follow-up and integrated management of GCA patients, and the reasons for poor prognosis in some GCA patients should be examined [29–31].

In conclusion, GCA is closely associated with PMR. GCA patients combined with or without PMR have different clinical characteristics, inflammatory status, and vessel involvement, indicating different pathologies of the two conditions. Few studies have been conducted in China, and further studies are needed to fully understand the disease and improve the prognosis of patients.

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Compliance with ethical standards

Ethical approval Patients accepted to participate the study were informed about the study, and ethical approval was granted from the hospital Research Ethics Committee. For this type of study, formal consent is not required.

Conflicts of interest The authors declare that they have no conflicts of interest.

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