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Complete blood count reflecting the disease status of giant cell arteritis

A retrospective study of Chinese patients

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Abstract

Giant cell arteritis (GCA) is the most common vasculitis in elderly, with ischemic and constitutional symptoms caused by vascular involvement and systemic inflammation. Early initiation of therapy results in prompt remission, while patients may still experience flares or severe complications during glucocorticoid tapering. This study was to identify the characteristics of Chinese GCA patients with different prognosis.

Ninety-one patients diagnosed with GCA in Peking Union Medical College Hospital in the last 20 years were followed up. Those who were lost to follow up or were followed up for less than 1 year were excluded. According to the prognosis, patients were divided into the group of favourable prognosis (patients who sustained disease remission for over 1 year) and unfavorable prognosis (patients who had relapses or severe complications). Clinical data at disease onset and after treatment were collected and analysed between the 2 groups.

Thirty-seven patients with favourable prognosis and 40 patients with unfavourable prognosis were admitted into the study. Fever as an onset symptom was less common in favourable group (P=.016). As for presentations of GCA, fever, tenderness and abnormal pulsation of temporal artery and jaw claudication were less frequently observed in patients with favourable prognosis (P=.029, .049, .043, respectively). At onset, medium-size arteries were affected more in unfavorable prognosis group (P=.048), and involvement of branches below the aortic arch were more common in favorable prognosis group (P=.034). Erythrocyte sedimentation rate in group of favourable prognosis were significantly lower after treatment (P=.041). Compared with healthy subjects, GCA patients had increased monocytes and decreased lymphocytes at disease onset (P<.01). Monocyte counts were higher in patients with favourable prognosis at disease onset (P=.043), while no significant differences were seen between the 2 groups after treatment. Lymphocyte counts were lower in patients with unfavourable prognosis (P=.014) after treatment.

Complete blood count may reflect the disease status of GCA. Little change in monocyte during treatment and lower lymphocytes after treatment may serve as potential predictors of unfavourable clinical prognosis.

Abbreviations: ESR = erythrocyte sedimentation rate, GC = glucocorticoid, GCA = giant cell arteritis, MTX = methotrexate.

Keywords: complete blood counts, giant cell arthritis, lymphocyte, monocyte, prognosis

1. Introduction

Giant cell arteritis (GCA), also known as temporal arteritis, is the most common primary systemic vasculitis in elderly, which affects medium-size and large arteries. The pathogenesis of GCA includes activation of resident dendritic cells of the adventitia, recruitment, activation and polarization of CD4+ T cells, recruitment of CD8+ T cells and monocytes,[1] resulting in intimal hyperplasia and occlusion due to inflammatory cells infiltration and granulomatous lesions, which in turn leads to occlusion and stenosis of the involved vessels.

Patients with GCA usually present with ischemic and constitutional symptoms caused by vascular involvement and

systemic inflammation, including fever, fatigue, weight loss and other constitutional symptoms; tenderness and abnormal pulsation of temporal artery; jaw claudication, scalp tenderness, transient ischemic attack, hearing loss, vision loss and other cranial symptoms; myalgia, arthralgia and so on. Among these, cranial symptoms and fever are the most common.[2] Polymyalgia rheumatica and GCA represent either different manifestations of the same disease or overlapping conditions. Approximately 40% to 60% patients diagnosed with GCA also have polymyalgia rheumatica,[3] which is characterized by myalgia and arthralgia.

The primary aim of treatment for GCA is to prevent progression of vascular damage and related complications by suppression of inflammation. Glucocorticoids (GC) remain the mainstay of treatment in GCA, with an initial prednisone dose of 40 to 60 mg per day for most patients.[1] The most severe complications of GCA are ischemic manifestations, such as permanent visual loss and stroke, which constitute 15%-30% of GCA cases[4] and leads to chronic disabilities among GCA patients.[2] For these patients, early initiation of high-dose GC therapy results in prompt remission of symptoms.[1] However, some patients show GC-resistant potential, that is, they have inadequate response to standard GC for induction of remission. Also, those who have had successful induction of remission may present with relapses or recurrences during GC tapering,[5] which is called flares of GCA. Flares were observed in 34% to 62% of patients[6] and were related to dose and duration of GC therapy. Long-term use of GC results in many complications,[7] among which infections present the most severe problems. Both flares and severe complications implicate a poorer prognosis.

For those indicating poorer prognosis, timely recognition, standardized treatment and close follow-up should be given, which may improve the prognosis of patients. In this retrospective study, clinical and laboratory features of GCA patients were reviewed to assess the potential clinical predictors that may be associated with the prognosis of GCA.

2. Materials and methods

2.1. Patients

Patients diagnosed with GCA were enrolled at Peking Union Medical College Hospital (PUMCH) between November 1998 and October 2017. Patients' clinical data of disease onset were retrospectively reviewed. The diagnosis of GCA were reconfirmed according to the 1990 American College of Rheumatology classification criteria for GCA. That is, the presence of 3 or more criteria (age at disease onset ≥ 50, new headache, temporal artery abnormality, elevated erythrocyte sedimentation rate (ESR), abnormal artery biopsy) were enough to make a diagnosis of GCA (sensitivity 93.5%, specificity 91.2%).[8]

Longitudinal changes in clinical prognosis were followed up for an average of 86.04 (range 3–218) months through outpatient medical records and telephone. Those who were lost to follow up or were followed up for less than 1 year were excluded. Based on the outcomes, patients were divided into 2 groups. Those who underwent therapy and sustained disease remission for more than 1 year were grouped to the favourable prognosis group. Those who had relapse/recurrence (defined as the recurrence of signs or symptoms of GCA and/or ESR≥30 mm/h attributable to GCA) or severe complications including infections, deaths or neoplasms during treatment were placed under the unfavourable prognosis group. Those who were stable but were followed up for less than 1 year were excluded from this study.

2.2. Clinical data collection

Clinical data at disease onset and comorbid diseases were retrieved from medical records, including signs and symptoms, laboratory and angiographic findings (at disease onset). During the follow-up, symptoms of GCA, laboratory findings (after treatment for 1 week), medication, functional status, and time to first relapse were evaluated. Clinical data of patients in the 2 groups before and after treatment were compared and analysed.

For vascular evaluation, radiologic data, including digital subtraction angiography, ultrasonography, computed tomography angiography, magnetic resonance MR angiography, and positron emission tomography were reviewed. The distribution of the involved vessels was also compared in the 2 groups. The large vessels are defined as the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches.[9]

Healthy subjects were selected to examine the distribution characteristics of lymphocytes and monocytes in the peripheral blood compared with those of GCA patients. After strict screening, 182 healthy controls were selected and matched as a ratio of 1:2 in age and sex. The complete blood counts were collected from all patients.

2.3. Statistical analysis

All data analyses were conducted using the SPSS 20.0 software (SPSS, IL). Continuous variables were summarized by mean and standard deviation, and the categorical variables by absolute frequencies and percentages. GCA patients were divided into 2 groups according to their follow-up outcomes. The 2 categories were compared using Student t-test for continuous variables. Chi-square tests were used to compare the categorical variables. For patients who had relapse, their clinical outcomes were analyzed using Kaplan-Meier curve. All statistical tests were 2-sided and P-values < .05 was considered statistically significant.

This study has been approved by the Ethics Board of PUMCH and the approval number is S-K437. Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

3. Results

3.1. Study population

Ninety-one patients were diagnosed with GCA, among whom 46 patients underwent temporal artery biopsy and 29 patients (63%) were positive. Fourteen patients were lost to follow-up or were followed up for less than 1 year. Finally, seventy-seven patients were admitted into this study. Among the 40 patients in the unfavourable prognosis group, twenty-three patients experienced flares of the disease, twelve patients died of complications, 5 patients had severe infections, 2 patients were diagnosed with neoplasms, and 2 patients had both infection and disease flares. Patients' demographic data are shown in Table 1. No statistical differences in sex, age, and delayed time from disease onset to diagnosis were found between the 2 groups.

Table 1

Clinical features and comorbid diseases of GCA patients with or without favourable prognosis.

	Favourable Prognosis Group N=37(%)	Unfavourable Prognosis Group N=40(%)	P
Sociodemography			
Age (yr, diagnosis)	65.22±7.82	66.20±6.52	.552
Disease course (month)	5.36±9.40	5.53±4.69	.922
Sex			
Male	15 (40.5)	20 (50)	.405
Female	22 (59.5)	20 (50)	
Onset symptoms			
Fever	19 (51.4)	31 (77.5)	.016*
Myalgia or arthralgia	15 (40.5)	19 (47.5)	.539
Cranial symptoms	24 (64.9)	18 (45)	.080
Clinical signs and symptoms			
Fever	26 (70.3)	36 (90)	.029*
Headache	25 (67.6)	30 (75)	.471
Scalp tenderness or pain	11 (29.7)	10 (25)	.642
Tenderness and abnormal pulsation of temporal artery	5 (13.5)	13 (32.5)	.049*
Visual loss	15 (40.5)	14 (35)	.616
Myalgia	20 (54.1)	22 (55)	.934
CNS symptoms	9 (24.3)	8 (20)	.648
Hearing loss	13 (35.1)	7 (17.5)	.078
Jaw claudication	7 (18.9)	16 (40)	.043*
Arthralgia	18 (48.6)	21 (52.5)	.736
GI symptoms	4 (10.8)	6 (15)	.585
Constitutional symptoms	26 (70.3)	28 (70)	.979
Weight loss	22 (59.5)	20 (50)	.405
Past medical history			
Smoking	11 (29.7)	17 (42.5)	.244
Diabetes	8 (21.6)	5 (12.5)	.286
Hypertension	14 (37.8)	15 (37.5)	.976
Dyslipidemia	13 (35.1)	15 (37.5)	.829

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.

3.2. Clinical differences between GCA patients with favourable and unfavourable prognosis

Main clinical features and comorbid diseases at disease onset are summarized in Table 1. Lower frequency of fever as the symptom at disease onset was observed in patients with favorable prognosis (P=.016), while cranial symptoms, myalgia and arthralgia had no significant differences between the 2 groups. As for presentations of GCA, fever, tenderness and abnormal pulsation of temporal artery, and jaw claudication were less frequently observed in patients with favourable prognosis (P=.029, .049, .043, respectively). Other common symptoms, such as cranial symptoms, myalgia, arthralgia, gastrointestinal syndromes, constitutional symptoms and comorbid diseases were similar between the 2 groups.

All patients received GCs for treatment. For those who had relapse, 12 patients received cyclophosphamide (CYC) while 4 patients were treated with methotrexate (MTX). According to the follow-up outcomes, they were divided into the group of CYC and group of MTX. However, analysis of time to relapse indicated no significance between the 2 groups (P=.142) (Fig. 1).

3.3. Differences of vessels involvement between GCA patients with favourable and unfavorable prognosis

Vascular angiograms from totally 56 patients were reviewed and analysed (Table 2). Twenty-nine patients had favourable prognosis, while the others were in the group of unfavourable prognosis. Patients with unfavourable prognosis showed higher frequency in the involvement of medium-size artery (P=.048). The distribution of the involved vessels in showed involvement of branches below the aortic arch was more common in patients with favourable prognosis (P=.034), while the other arteries including extra-cranial, aorta, and branches above the aortic arch revealed no significant differences between the 2 groups.
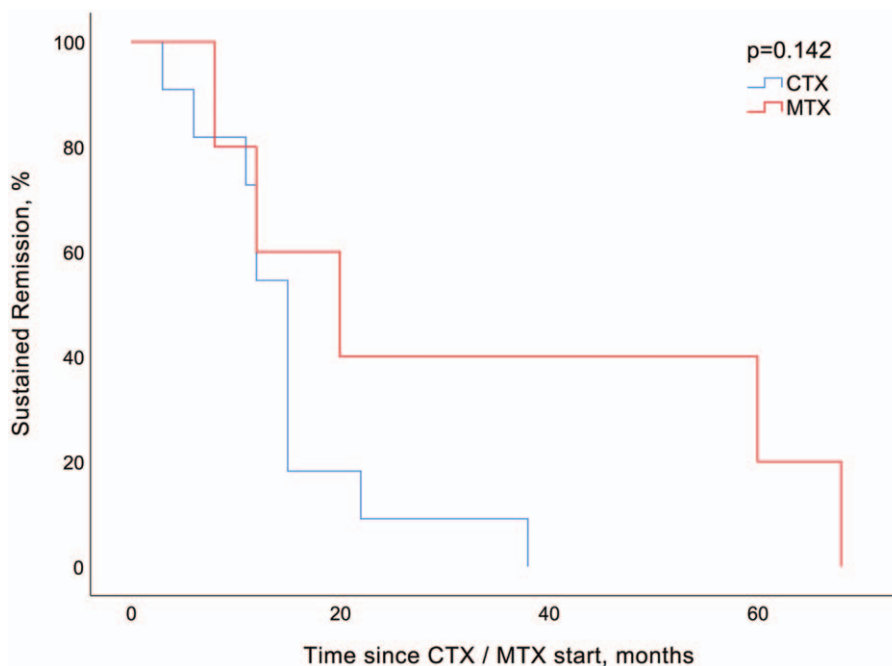

Figure 1. Sustained remission in time duration from GCA diagnosis to first relapse in patients receiving cyclophosphamide (CYC)/methotrexate (MTX).

Table 2

Distribution of the involved vessels of GCA patients with or without favourable prognosis.

	Favourable Prognosis Group		Unfavourable Prognosis Group		P
	n (%)	N=37	n (%)	N=40	
Size of the vessel involved		29		27	
Large vessel involvement	26 (89.7)		26 (96.3)		.335
Medium vessel involvement	14 (48.3)		20 (74.1)		.048*
Distribution of the involved vessels in imaging (including ultrasound, CTA, PET/CT, MRA)					
Intracranial	13 (44.8)	29	18 (66.7)	27	.100
Aortic arch, extra-cranial and branches above the arch	26 (89.7)		24 (88.9)		.926
Branches below the arch	21 (72.4)		12 (44.4)		.034*

CTA = computed tomography angiography, GCA = giant cell arteritis, MRA = magnetic resonance angiography, PET/CT = positron emission (PET) - computed tomography (CT).

* Significantly different.

3.4. Laboratory differences between GCA patients with favourable and unfavourable prognosis

Compared with healthy subjects, GCA patients had increased monocytes and decreased lymphocytes at disease onset ($P < .01$) (Fig. 2). Laboratory results of GCA patients in the 2 groups are shown in Figure 3. Monocyte counts were higher in patients with favorable prognosis at disease onset ($P = .043$), while no significant differences were seen between the 2 groups after treatment. Lymphocyte counts were lower in patients with unfavourable prognosis ($P = .014$) after treatment. In addition, ESR and C-reactive protein were significantly increased at disease onset and were decreased after treatment in both groups, yet the level of ESR in group of favorable prognosis were significantly lower after treatment ($P = .041$).

4. Discussion

GCA has various manifestations and is usually underestimated, thus better recognition, timely treatment and close follow-up are needed, which is closely related with the prognosis. This
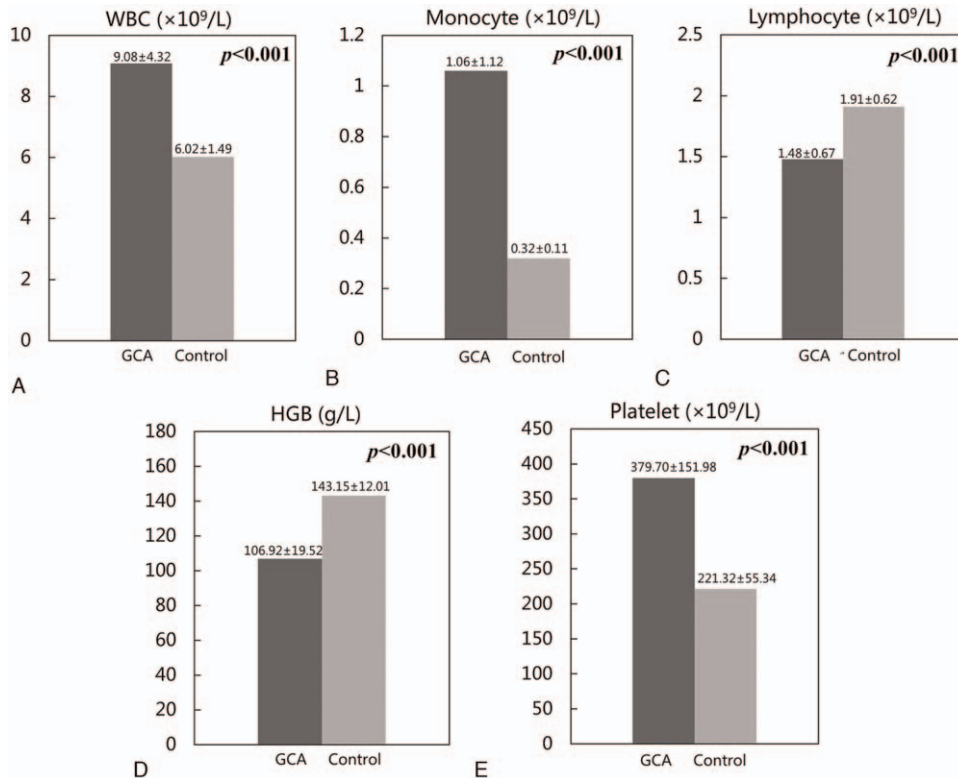

Figure 2. Laboratory findings of complete blood count between GCA patients and healthy subjects. Compared with healthy subjects (N = 182), GCA patients (N = 91) had increased WBC (A), monocytes (B) and platelets (E) with decreased lymphocytes (C) and HGB (D) at disease onset ($P < .01$) (Mean ± SD). The reference range of the parameters: WBC (3.50–9.50) × 10^9/L, Monocyte (0.12–0.80) × 10^9/L, Lymphocyte (0.80–4.00) × 10^9/L, HGB (110–150) g/L, Platelet (100–350) × 10^9/L. GCA = giant cell arteritis, HGB = hemoglobin, SD = standard deviation, WBC = white blood cell.
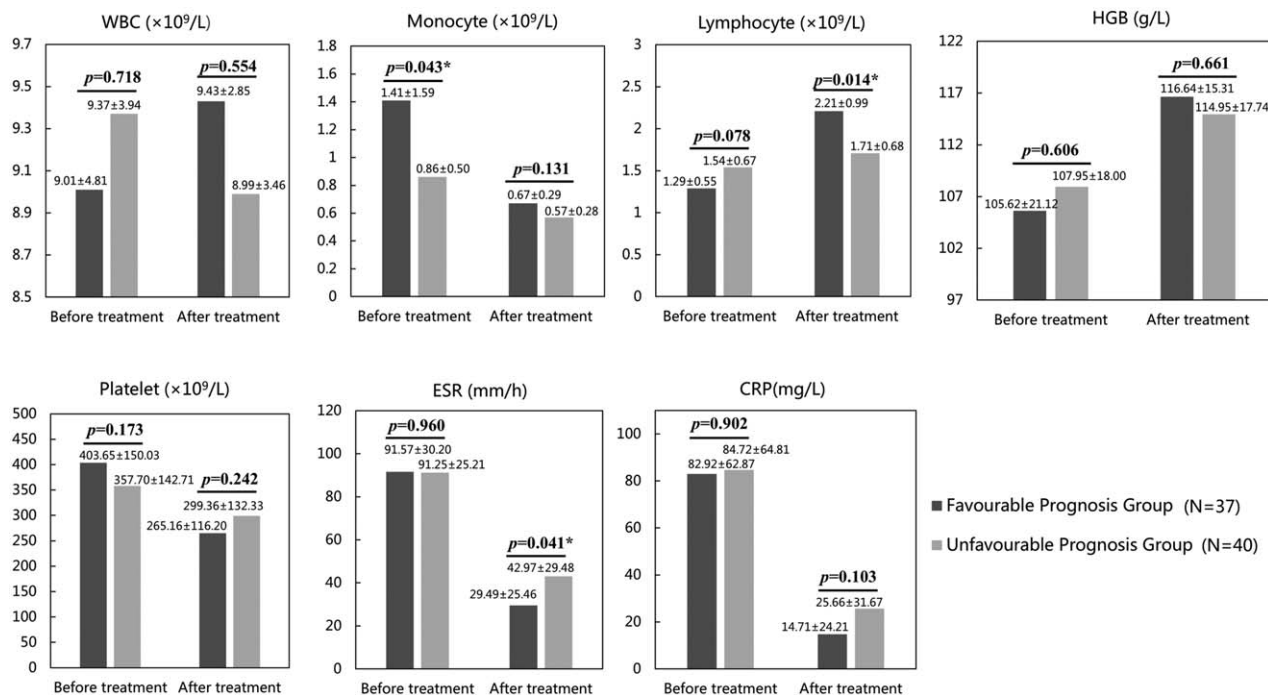
Figure 3. Laboratory findings of GCA patients with or without favourable prognosis. The parameters in 1 group before and after treatment were also displayed (Mean ± SD). The reference range of the parameters: WBC $(3.50–9.50) \times 10^9$/L, Monocyte $(0.12–0.80) \times 10^9$/L, Lymphocyte $(0.80–4.00) \times 10^9$/L, HGB (110–150) g/L, Platelet $(100–350) \times 10^9$/L, ESR (0–15) mm/h, CRP < 3 mg/L. CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GCA = giant cell arteritis, HGB = hemoglobin, SD = standard deviation, WBC = white blood cell. *Significantly different.

study retrospectively reviewed the data of GCA of a Chinese cohort and assessed the characteristics of different prognoses in the follow-ups.

GCs are therapeutically effective in GCA, however, relapses occur frequently during GC tapering or getting discontinued. In previous studies, the frequency of relapses or recurrences were 40.8% to 64% in different population.[7,10] Longer treatment duration and higher cumulative prednisone dose were observed in patients who experienced relapses or recurrences compared to those who did not suffer disease flares.[10] This gives rise to more complications, which is also a factor of poorer prognosis of GCA. In this study, patients were treated with a standard regimen for vasculitis and GC were tapered regularly. 29.9% (23/77) and 51.9% (40/77) had disease flares and unfavourable prognosis respectively, which is in accordance with other reports.

In the past studies, GCA patients presenting with fever as the initial clinical manifestation were younger and with stronger inflammatory response including weight loss, higher ESR and C-reactive protein when compared with other onset symptoms,[11] and the initial systemic inflammatory response is related to disease flares.[12] GCA patients with a strong initial systemic inflammatory response suffer more disease relapses and have higher doses and more prolonged requirements of GC.[13] In the study of Yannick van Sleen, ESR is higher in patients with relapse compared with those in remission.[14] Genetic factors may predispose to persistent chronic inflammation,[15] and interferon-γ expression may cause the relative resistance to corticosteroid therapy,[16] leading to greater requirement and prolonged therapy of GC. In our study, fever was found less frequently as an onset symptom in the subgroup of patients with favourable

prognosis, which may be explained by weaker inflammatory response in these patients. Relatively lower ESR and CR P after treatment were also indicated in patients with favourable prognosis during longitudinal follow-up, which was consistent with previous studies.[14] These results suggest that patients with weaker inflammatory response are predisposed to have favourable prognosis, including less frequencies of flares, less use of GC dosage and further complications.

In previous studies, there were little data on the predictors in clinical presentations. Grossman et al[17] have indicated that patients with severe cranial ischemic events may be related to poor prognosis and are more likely to have jaw claudication. Alba et al reported that polymyalgia rheumatica and scalp tenderness at disease onset were more frequently observed in relapsing patients,[7] while Martinez-Lado et al found no clinical differences in the clinical spectrum of the vasculitis between patients with and without flares.[10] Except for fever, our study indicates that patients with tenderness and abnormal pulsation of temporal artery, and jaw claudication at disease onset are predisposed to poorer clinical courses. Above all, patients with unfavourable prognosis seems to have more cranial presentations. Prospective studies are needed to confirm these results and further explore the underlying mechanisms.

According to the recommendations in the treatment guidelines of GCA from home and abroad, both CYC and MTX are recommended except for GCs.[3,18] However, CYC is more widely used than MTX in China. We compared the clinical prognosis of patients who had relapse receiving CYC or MTX during long-term follow-ups. The Kaplan-Meier curve indicates CYC is not inferior to MTX. Nevertheless, as the cases of relapse

were limited, the results are of limited significance, and more prospective studies are needed.

Nowadays, there were different views between vessel involvement and prognosis in GCA. Some authors consider that extracranial vascular inflammation (large-and medium-size arteries involvement) may have negative impacts on the treatment response in terms of long tapering of GC and more frequent GCA complications such as occlusion and dissection.[19] Espitia and colleagues[20] have reported that patients with signs of aortitis at the initial workup exhibited more chronic or relapsing course of disease. In the study of Czihal et al[21] extensive vascular involvement of both the temporal and subclavian/axillary arteries may be associated with a poor treatment response and relapses in GCA. Our study indicates that patients with the involvement of medium-size artery are predisposed to an unfavourable prognosis, and the involvement of vessel under aortic arch indicates a benign outcome, which provided a brand-new perspective.

As is known, GCA pathology is initiated mainly by infiltration of CD4+ T cells and monocytes/macrophages in vessel walls via the vasa vasorum.[22] Monocytes, the precursors of macrophages, are phagocytes generated in bone marrow from which monocytes are released into bloodstream.[23] Consistent with our result, other studies also revealed a clear monocytosis in newly diagnosed GCA patients,[14] in which monocytes recruited from bone marrow driven by CCL2/CCR2 pathway in response to inflammation, which in turn could be normalized by GCs.[24] In our study, monocyte counts at disease onset were higher in patients with favourable prognosis, and were shift to comparable levels to those with unfavourable prognosis after treatment. The dynamic change in monocyte counts may indicate individual responses to the treatment, and little change in monocyte counts during treatment may serve as a predictor of unfavourable clinical prognosis.

Previous studies indicated a significant decrease of lymphocyte count at disease onset, and it returned to normal ranges when patients went in remission after taking GC,[25–27] which was compatible with our results. Moreover, we reported lower lymphocyte counts in patients with unfavourable prognosis after treatment. As we know, patients with higher disease activity are recommended with higher dose of GC with/without immunosuppressive agents, which may lead to the decrease of lymphocyte counts. As patients with lower lymphocytes may suffer from higher risk of being infected, the lymphocyte counts after treatment may be a predicator of prognosis in GCA patients.

This was a single-center retrospective study based on a small sample size in China, and there was loss for follow-ups, both of which might bias the findings. Future studies should explore the characteristics of subsets of unfavourable prognosis, including relapse, recurrence, complications, deaths, and neoplasms. Also, the changes of specific lymphocyte subsets and the relationships with treatment are urgently needed to better clarify the mechanisms of GCA. Though the sample size seems small compared with that in western countries, it has been the largest cohort in China. This partly due to the less prevalence of GCA in the East compared with the West, which may be correlated with race, genetic background and environmental exposures. However, as manifestations of GCA are various and not specific, early recognition of the disease may be difficult, leading to the underestimation of the incidence, which indicates more attention to the disease are needed, especially in East Asian countries.

This study retrospectively reviewed the data of GCA of a Chinese cohort and indicated some potential predictive factors reflecting disease status of GC. In our study, no fever at disease onset and weaker inflammation after treatment may be potential protective factors in the prognosis of GCA. Little change in monocyte during treatment and lower lymphocytes after treatment may serve as predictors of unfavourable clinical prognosis. In previous studies, the complete blood count has been recognized as a potential indicator of prognosis in several diseases, including cardiovascular disease,[28] subarachnoid haemorrhage,[29] colorectal cancer,[30] and so on. As complete blood count is a readily available and inexpensive routine test for physicians and patients, the monitoring of complete blood count may be a way to reflect disease status of GCA based on our results. These factors could be of help for clinical decision-making and disease management. It can also be used to provide guidelines during the follow-up of patients.

Author contributions

Yue Yin contributed to manuscript writing, data abstracting and performing procedures; Yun Zhang contributed to drafting conception and design, performing procedures, and data analysis; Dongmei Wang contributed to drafting design and data abstracting; Xinxin Han and Xiaotian Chu contributed to data abstracting and performing procedures; Min Shen contributed to drafting conception and design, performing procedures; Xuejun Zeng contributed to drafting conception and design, performing procedures, and data analysis.

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