



Giant Cell Arteritis: Does Perivascular Inflammation on Biopsy Lead to Clinical Disease?

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i331278

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/83501>

Original Research Article

Received 27 December 2021

Accepted 01 March 2022

Published 09 March 2022

ABSTRACT

Background and Objective: Transmural inflammation of the temporal artery on biopsy is considered strongly suggestive of giant cell arteritis (GCA). Occasionally other inflammation patterns are seen. It is controversial whether these findings predict GCA-like disease. Our objective was to describe the clinicopathologic features in a cohort of patients with temporal artery biopsies to examine outcomes of patients with non-transmural inflammation.

Methods: We examined through retrospective chart review the clinical course from 2010-2020 of patients with temporal artery biopsies from 2010-2012. Biopsy results were divided into 3 groups: GCA transmural inflammation, non-GCA perivascular inflammation and negative. Non-GCA perivascular inflammation included small vessel, vasa vasorum and adventitial inflammation. Endpoints included constitutional and craniofacial symptoms, CRP and ESR levels, ASCVD, large vessel complications, and length of steroid treatment.

Results: 95 patients were included. Transmural patients had more visual loss compared with perivascular patients (55.5% vs 15.7%, p=0.004). Transmural patients had more jaw claudication or

headache/jaw claudication compared with perivascular patients (44.5% vs 12.6%, $p=0.01$). Weight loss was more common in transmural patients compared with perivascular (27.8% vs 3.1%, $p=0.02$). Night sweats, PMR symptoms, and temporal artery tenderness were similar between groups. CRP was higher in transmural patients though not significantly. ESR levels were similar between groups. Transmural patients had a longer steroid duration with a median of 24 months vs 1.5 for perivascular, $p=0.001$.

Conclusion: Patients with non-transmural inflammation on temporal artery biopsies had improved outcomes when compared with transmural patients. This raises the question of whether steroids should be continued after a biopsy returns with perivascular inflammation.

Keywords: Giant cell arteritis; inflammation; vasa vasorum; vasculitis.

1. INTRODUCTION

Giant cell arteritis (GCA) is one of the most common vasculitides, often affecting older adults. Classification criteria from the American College of Rheumatology in 1990 for GCA include: age 50 or older, new localized headache, temporal artery tenderness/decreased pulsation, erythrocyte sedimentation rate (ESR) of 50 mm/h or higher, positive arterial biopsy showing mononuclear infiltration or granulomatous inflammation; with the presence of three out of these five criteria equating a diagnosis [1]. However, later studies suggested that these criteria function poorly to identify patients with GCA with there still not being a widely agreed-upon diagnostic criteria for GCA [2]. In clinical practice, transmural inflammation of the temporal artery on biopsy is considered strongly suggestive of GCA. However, occasionally other inflammatory patterns are seen on temporal artery biopsy, for example inflammatory infiltrates in the adventitia, surrounding small vessels or vasa vasorum only, without any transmural inflammation.

It is an area of clinical controversy as to whether these histopathologic findings predict GCA or GCA-like disease. Current literature is mixed. A study in 2011 looked at patients with isolated vasa vasorum or small-vessel vasculitis compared with transmural vasculitis [3]. This study found that headache, scalp tenderness, jaw claudication, constitutional symptoms, ESR levels and cumulative doses of prednisone were lower in small vessel vasculitis patients, but similar in vasa vasorum vasculitis patients with both groups having a similar frequency of vision loss when compared to transmural inflammation histopathology [3]. Another study in 2014 looked at clinical outcomes in patients with classic transmural inflammation vs only small vessel, adventitial or vasa vasorum inflammation [4]. This study found that patients with vasa vasorum

or small vessel inflammation had a significantly lower frequency of cranial manifestations, lower serum ESR levels, and reduced use of prednisone therapy [4]. Polymyalgia rheumatica and blindness were similar in all patient groups with adventitial inflammation being overall more similar to classic transmural inflammation [4].

However, a 2016 study looking at outcomes of stroke, cardiovascular events, blindness, and death in patients with adventitial, small vessel, or vasa vasorum inflammation, found no increased risk of events compared to healthy controls [5]. Still another group in 2016 theorized a dynamic model of arterial invasion, suspected to reflect sequential steps in the progression of inflammation and injury [6]. They did not find a clear relationship between these biopsy patterns and clinical or laboratory findings except for abnormalities on temporal artery palpation, jaw claudication, and scalp tenderness being more common among patients with a finding of transmural inflammation on biopsy [6].

Given this controversy, we aimed to perform a retrospective review on a cohort of patients at our institution with temporal artery biopsies and to compare clinical outcomes between patients with and without transmural inflammation. We also aimed to explore whether treatments could differ between patients found to have non-transmural inflammation on temporal artery biopsies compared to those with transmural inflammation.

2. METHODS

Our study had approval through the Institutional Review Board at the University of Pittsburgh, where all temporal artery biopsies were performed. This study was a retrospective chart review evaluating the clinical course from 2010-2020 of patients at our institution who had temporal artery biopsies from 2010-2012. A

single pathologist (RH) reviewed all biopsies personally and compared the findings to the original pathologist report. When this blinded review was discordant with the original interpretation our pathologist performed a second, with this review becoming the final biopsy interpretation. Biopsy results were divided into three groups: GCA transmural inflammation, non-GCA perivascular inflammation, and negative biopsies. Non-GCA perivascular inflammation included small vessel, vasa vasorum and adventitial inflammation on biopsy.

Clinical features recorded included constitutional symptoms, craniofacial symptoms, C-reactive protein (CRP) levels, ESR levels, cardiovascular complications including stroke or coronary artery disease (CAD), large vessel complications (aneurysm, etc.), duration of steroid treatment and use of other immunosuppressant medications. Baseline demographics were also obtained including age, gender, race/ethnicity, statin use, antiplatelet agent use, presence of diabetes, hypertension, presence of other autoimmune conditions, and malignancy. It was specifically recorded whether a patient had polymyalgia rheumatica (PMR) before temporal artery biopsy, or later was diagnosed with PMR, given the association between GCA and PMR. Categorical variables were compared using Chi-Square tests or Fisher's Exact tests among three groups. Continuous variable averages were compared using One-way ANOVA or medians using Kruskal Wallis for skewed data among three respectively. Two pairwise comparisons of the transmural and perivascular inflammation, and perivascular inflammation and negative control groups were made if the overall test for the three groups comparison was significant. Bonferroni correction was applied to adjust for the multiple comparisons. P values of less than 0.05 were considered statistically significant. Our clinical laboratories have a normal reference range for CRP of <0.8 mg/dL and ESR of 0-23 mm/hr. GraphPad Prism and IBM SPSS were used for the analysis.

3. RESULTS

A total of 95 patients were included in the final analysis. Group numbers included 45 patients in the negative biopsy group, 32 in the perivascular group, and 18 in the classic transmural group. Please see details for the demographics of the study population in Table 1. More patients were female overall (82.2%, 59.4%, 55.6% for

negative vs perivascular vs transmural respectively, $p=0.04$), with most patients being Caucasian (80% vs 68.8% vs 77.8% for negative vs perivascular vs transmural respectively, $p=0.02$). Patients with transmural inflammation had less preexisting atherosclerotic cardiovascular disease (ASCVD), less diabetes, and lower statin use though were not statistically different from the other two groups. Otherwise, groups were similar.

In total, 40/95 (42.1%) of patients had preexisting autoimmune diseases prior to temporal artery biopsy. In all groups, a smaller fraction of patients with no autoimmune disease at baseline would be diagnosed with one post temporal artery biopsy. GCA was not included as an "other" autoimmune condition. No patient with a preexisting autoimmune condition in the transmural inflammation group went on to be diagnosed with another one. In the negative biopsy group and perivascular group combined, PMR made up 8/15 (53.3%) of new autoimmune diagnoses, with the transmural group having no PMR diagnoses. For time to the development of new autoimmune conditions, the average time with standard deviation included 2.1 ± 3 , 15 ± 24.4 , and 2 ± 0 months for the negative, perivascular, and transmural groups respectively. For time to the development of new malignancy average time with standard deviation included 92.4 ± 43.4 , 42.6 ± 17.6 , and 31 ± 0 months for the negative, perivascular, and transmural groups respectively. Please see Table 2 for more details including baseline and future malignancy diagnoses.

For other symptoms, the distribution of craniofacial symptoms did differ amongst transmural, perivascular, and negative patients, with transmural patients having more jaw symptoms either alone or in combination with headache (negative: 2.2% jaw claudication, 68.9% headache, 11.1% both; perivascular: 6.3% jaw claudication, 65.6% headache, 6.3% both; transmural: 27.8% jaw claudication, 33.3% headache, 16.7% both). This distribution was significantly different amongst the three groups ($p=0.037$). However, when comparing transmural and perivascular patients directly this did not meet significance when accounting for Bonferroni correction ($p=0.05$). When comparing the distribution of craniofacial symptoms for perivascular and negative controls this also did not meet significance ($p=0.74$). The presence of jaw claudication alone was significantly different amongst all three groups though not when

transmural patients were compared with perivascular and perivascular was compared with the negative group ($p=0.008$, $p=0.08$, $p=0.56$ respectively). The presence of jaw claudication alone or both headache/jaw claudication was significantly different amongst all three groups and when transmural patients were compared with perivascular though not when perivascular was compared with the negative group ($p=0.01$, $p=0.01$, $p=0.96$ respectively). Overall, these analyses suggested the presence of jaw claudication was more common in transmural patients.

Weight loss was different among all three groups ($p=0.048$), with it also being more common in transmural patients compared with perivascular patients ($p=0.02$). Weight loss was not different for transmural vs negative patients ($p=0.136$). Night sweats, PMR symptoms, and temporal artery tenderness were all similar between groups. Please see Table 4 for more details. CRP levels were higher in transmural patients with medians and associated 25th/75th percentiles being 5.1 (2.3, 16.5) vs 1.7 (0.3, 10.8) vs 1.8 (0.2, 4.2) mg/dl for transmural vs perivascular vs negative groups respectively with $p=0.04$. However, transmural patients were not different from the perivascular group nor were the perivascular group different from the negative group when analyzed in pairs ($p=0.09$ and $p=0.64$ respectively). ESR levels were similar between groups with medians and associated 25th/75th percentiles being 61.5 (55.8, 106) vs 73 (45, 99.5) vs 61.5 (41, 85.3) mm/hr for transmural vs perivascular vs negative groups respectively ($p=0.57$).

For visual symptoms, the negative biopsy and perivascular groups had more visual disturbances (negative: 18.8%, perivascular: 18.8%, transmural 16.7%) with the transmural group having more true loss of vision including either temporary or permanent (Temporary vision loss: Negative 17.8%, perivascular 6.3%, transmural 22.2%; Permanent vision loss: Negative 8.9%, perivascular 9.4%, transmural 33.3%). The differences in overall visual symptom presentations were different among the three groups ($p=0.02$). Transmural patient visual symptoms were distributed differently from perivascular patients ($p=0.009$). Negative controls did not have a different visual symptom distribution compared with perivascular patients ($p=0.53$). Presumed causes of permanent vision loss are noted in Table 3. The amount of vision

loss either permanent or temporary was different amongst all three groups ($p=0.01$). This was also significant when comparing transmural to perivascular ($p=0.004$) but not perivascular to the negative group ($p=0.28$) supporting transmural patients having more vision loss.

Transmural patients had the longest steroid duration with medians and associated 25th/75th percentiles being 24 (13,31), 1.5 (1,12.5) and 1(1,13) months for transmural vs perivascular vs negative groups respectively with $p=0.002$. Transmural patients had longer steroid duration compared with perivascular ($p=0.001$) and perivascular patients were not statistically different from the negative group ($p=0.54$). For vascular outcomes, transmural patients did have more large vessel disease (aorta, subclavian, carotid disease) being present in 8.9%, 3.1% and 11.1% for negative vs perivascular vs transmural groups respectively though this did not reach statistical significance. Peripheral vascular disease was higher in the perivascular group being present in 11.1%, 18.8% and 0% for negative vs perivascular vs transmural groups respectively, though this did not reach statistical significance ($P=0.154$). No patient had limb claudication. Coronary artery disease occurred more often in the negative biopsy group though did not reach statistical significance (17.8% vs 9.4% vs 5.6% for negative vs perivascular vs transmural groups respectively). Disease modifying anti-rheumatic drug use (DMARD) was similar among all groups being present in 22.2%, 18.8% and 20% for transmural vs perivascular vs negative groups respectively.

4. DISCUSSION

Overall, our results suggest that patients with non-transmural inflammation on temporal artery biopsies have key clinical differences when compared to transmural patients and may not have GCA. However, of note, our study was limited in power due to the small number of patients with traditional GCA with transmural inflammation that was included. The rates of the most feared complication of GCA – permanent blindness – along with temporary vision loss was more common in transmural patients, with a significant difference found in the distribution of visual symptoms, as well as presence of temporary or permanent visual loss among transmural and perivascular patients.

Table 1. Patient demographics and ASCVD risk factors

Variable	Negative biopsy	Perivascular	Transmural
Number of subjects (n)	45	32	18
Age (mean +/- SD)	72.3 +/- 10.3	72.3 +/- 9.7	78.1 +/- 9.8
Female sex	37 (82.2%)	19 (59.4%)	10 (55.6%)
Ethnicity	36 (80.0%) Caucasian 9 (20.0%) African American	22(68.8%) Caucasian 9 (28.1%) African American 1 (3.1%) Unknown	14(77.8%) Caucasian 4 (22.2%) African American
Smoking status	5 (11.1%) current 11 (24.4%) former 29 (64.4%) never	4 (12.5%) current 15 (46.9%) former 13 (40.6%) never	4 (22.2%) current 1 (5.6%) former 13(72.2%) never
Hypertension presence	31 (68.9%)	20 (62.5%)	12(66.7%)
Diabetes presence	12 (26.7%)	11 (34.4%)	2 (11.1%)
Aspirin and/or clopidogrel use at baseline	26 (57.8%)	17 (53.1%)	6 (33.3%)
Statin use at baseline	22 (48.9%)	15 (46.9%)	7 (38.9%)
Preexisting ASCVD [†]	21 (46.7%)	12 (37.5%)	4 (22.2%)

[†] ASCVD=atherosclerotic cardiovascular disease

Table 2. Coexisting Autoimmune disease, both preexisting and after temporal artery biopsy

Variable	Negative biopsy	Perivascular	Transmural
Number of subjects (n)	45	32	18
Other autoimmune conditions [†] : Baseline information	22 (48.9%)	12 (37.5%)	6 (33.3%)
Other autoimmune conditions [†] : Later development	6 (13.3%) and 3 (6.7%)	5 (15.6%) and 1 (3.1%)	1 (5.6%) and 0.0%
with none at baseline and with preexisting autoimmune condition at baseline respectively			
PMR Information: Percent of patients who were later diagnosed with PMR	6 (13.3%)	2 (6.3%)	0 (0.0%)
Malignancy: At baseline and later development respectively	12 (26.7%) and 6 (13.3%)	7 (21.8%) and 5 (15.6%)	1 (5.6%) and 1 (5.6%)

[†] Other autoimmune conditions included: PMR (polymyalgia rheumatica), Type 1 DM, hypothyroidism, Stills disease vs berylliosis, rheumatoid arthritis, mixed connective tissue disorder, Sjogren/Scleroderma overlap syndrome, idiopathic thrombocytopenic purpura and Guillain-Barré syndrome, Crohn's disease, optic neuritis, multiple sclerosis, microscopic colitis, psoriasis, autoimmune hemolytic anemia, and systemic lupus erythematosus

Table 3. Vision loss severity and causes per group

Symptom	Negative biopsy	Perivascular	Transmural
Number of subjects (n)	45	32	18
Visual disturbance (e.g., blurry vision)	11 (24.4%)	6 (18.8%)	3 (16.7%)
Temporary visual loss	8 (17.8%)	2 (6.3%)	4 (22.2%)
Permanent vision loss	4 (8.9%)	3 (9.4%)	6 (33.3%)
Permanent vision loss causes (clinically suspected)	CRAO [†]	Ischemic optic neuropathy	GCA
	Anterior ischemic optic neuropathy	CRAO	GCA
	Ischemia vs vasculitis	CRAO	GCA
	Corneal ulcer		GCA vs anterior ischemic neuropathy GCA GCA

[†] CRAO=central retinal artery occlusion

Table 4: GCA/PMR symptoms at time of biopsy between groups

Variable	Negative biopsy	Perivascular	Transmural	Overall P value for transmural vs perivascular vs negative (bold where significant)
Number of subjects (n)	45	32	18	
Night sweats	4 (8.9%)	3 (9.4%)	1 (5.6%)	>0.99
Weight loss	6 (13.3%)	1 (3.1%)	5 (27.8%)	p=0.048
				p=0.02 for transmural vs perivascular
PMR symptoms	10 (22.2%)	5 (15.6%)	3 (16.7%)	p=0.136 for transmural vs negative
Craniofacial symptoms (headache, jaw claudication or both)	5 (11.1%) had both 31 (68.9%) with headache 1 (2.2%) with jaw claudication	2 (6.3%) with both 21 (65.6%) with headache 2 (6.3%) with jaw claudication	3 (16.7%) with both 6 (33.3%) with headache 5 (27.8%) with jaw claudication	0.77 p=0.037 p=0.051 for perivascular vs transmural
Temporal artery tenderness	9 (20.0%)	4 (12.5%)	3 (16.7%)	0.72

Transmural patients also had increased frequency of weight loss, longer duration of steroids and increased amount of jaw claudication alone or both jaw claudication with a headache. Jaw claudication is an important symptom to show this difference among groups given a recent study from 2018 showing that jaw claudication, along with headache, seems to best predict which patients truly have GCA [7]. A meta-analysis from 2020 showed that symptoms/clinical factors associated with a diagnosis of GCA included limb claudication (+LR 6.41), jaw claudication (+LR 4.9), temporal artery thickening (+LR 4.7), temporal artery loss of pulse (+LR 3.25), temporal tenderness (+LR 3.14) and ESR greater than 100 mm/h (+LR, 3.11) [8]. No limb claudication occurred in any of our patients, but jaw claudication being more frequent in transmural patients suggests differentiation of transmural and perivascular patients for the development of GCA disease.

It is important to answer the question of whether these non-transmural inflammatory findings on histopathological analysis truly represent GCA-like disease, given the non-benign nature of the standard treatment for GCA being high dose corticosteroids for an extended time. GCA is mainly a disease of the geriatric population, with prolonged corticosteroid use putting patients at risk for osteopenia/osteoporosis with morbidity associated with fractures from this along with delirium, and worsening control of diabetes, among other potential side effects such as increased infection risk and worsening of hypertension [9].

Other potential tools that could be used to help risk stratify patients undergoing evaluation for GCA include various imaging modalities, and analysis of inflammatory gene expression given temporal artery biopsy its self is an imperfect gold standard. Ultrasound of the temporal arteries is one such tool available, though routine use has been limited by the need for skilled sonographers to be used effectively. Typically ultrasound is considered consistent with GCA if a halo sign is seen, which is a hypoechoic ring around the temporal artery demonstrating inflammation [10]. In a meta-analysis, sensitivity and specificity of the halo sign when compared with temporal artery biopsies was 68% and 81% respectively [10].

Another imaging option is magnetic resonance angiography or MRA of the temporal arteries. MRA is considered consistent with GCA when

mural thickening and enhancement or mural thickening and enhancement with perivascular enhancement are demonstrated [11]. In a prospective cohort study, MRA had a sensitivity of 93.6% and specificity of 77.9% when compared with temporal artery biopsy for the detection of GCA [11]. Notably in this trial a positive temporal artery biopsy was considered intimal, medial and/or adventitial inflammation [11]. Analysis of inflammatory gene expression signature has also shown some promise. One such study evaluated micro RNA (miRNA) expression in temporal artery biopsies from patients and compared them amongst patients with positive biopsies, negative biopsies though felt to have GCA clinically, and negative biopsies in patients not felt to have GCA [12]. Nine proinflammatory miRNA were overexpressed and 6 regulatory micro RNAs were under-expressed in patients with a positive biopsy [12]. Particular miRNA expression profiles were also associated with the presence of jaw claudication and headache in this cohort [12].

As discussed above, while our study is limited by being underpowered to give a definitive answer, our cohort of patients does suggest that non-transmural inflammatory findings do not predict a GCA-like disease when compared with patients with more traditional transmural inflammation. Alternatively, it is possible that non-transmural findings represent a spectrum of GCA disease but a milder form. From a clinical standpoint, this does raise the question of whether corticosteroids should be continued after a biopsy comes back with the perivascular findings, with risks of continued corticosteroids likely outweighing benefits. At the very least one could consider a more rapid taper of corticosteroids as well.

It is also possible that perhaps perivascular inflammation on temporal artery biopsies represents a distinct non-GCA vasculitis with different less serious complications. Regardless, the literature on whether these findings cause GCA disease is mixed, with our study now giving some additional support towards these biopsy findings not leading to GCA. Larger studies involving multiple clinical centers in the future would help to answer this important clinical question.

With the advent of imaging strategies for temporal artery evaluation, and the ability to evaluate inflammatory gene expression in samples combined with the imperfect standard of

temporal artery biopsy histopathology, future directions might include a scoring system as part of a formal diagnostic criteria. Such a system could include imaging such as MRA/ultrasound, clinical factors such as the presence of jaw claudication or loss of temporal artery pulse, and biopsy results including miRNA expression and histopathology. Future studies could investigate how each finding contributes to the prediction of a GCA phenotype and evaluate a numerical cutoff indicating highly likely GCA. This may be the best direction to help decide which patients have GCA and who would benefit from treatment given the current complexity in diagnosis. Similar approaches are already used elsewhere in medicine, with this being an exciting prospect in GCA.

5. CONCLUSION

Patients with non-transmural inflammation on temporal artery biopsies being evaluated for GCA had improved clinical outcomes when compared with transmural inflammation in our patient cohort. This would suggest non-transmural inflammation may represent a distinct milder subtype of GCA, a unique separate vasculitis syndrome or may not be a pathologic finding at all. Steroids may be able to be discontinued for empiric treatment of GCA when such a result is found on temporal artery biopsies during GCA evaluation, or more conservatively a rapid taper could be considered. Our results are, however, limited by small sample size and larger clinical studies are needed to confirm our findings before this should be routinely implemented in clinical practice.

DATA AVAILABILITY

Data used in analysis for our manuscript is available upon request

FUNDING

This project was supported in part by the National Institutes of Health through Grant Number UL1-TR-001857. This funding was used for statistical analysis support.

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Pittsburgh with approval number STUDY20030166

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

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