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Giant cell arteritis and its mimics: A comparison of three patient cohorts

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ABSTRACT

Objective: To compare temporal artery biopsy (TAB)-positive giant cell arteritis (GCA) to TAB-negative GCA and patients with GCA mimics

Methods: Patients diagnosed with TAB-positive and TAB-negative GCA between 1/1/1998 and 12/31/2013 were: retrospectively identified. These two groups were compared to a cohort of patients with TAB performed between 1/1/2009 and 12/31/2010 in which the TAB was negative and alternative diagnosis was provided after a minimum of 6-months of follow-up. Baseline characteristics were compared between groups using chi-square and rank sum tests.

Results: 591 study subjects were identified (286 TAB-positive, 110 TAB-negative GCA and 195 TAB-negative GCA mimics) during the respective study periods. Compared to TAB-negative GCA, GCA mimics had similar rates of headache and vision loss but significantly less frequent jaw/limb claudication, arterial bruits and constitutional symptoms, as well as lower platelet levels. Compared to TAB-positive GCA patients, TAB-negative GCA were younger, had shorter time to diagnosis, met fewer 1990 ACR classification criteria and had lower frequencies of polymyalgia rheumatica, jaw claudication and temporal artery abnormalities; but, higher frequency of arm claudication and constitutional symptoms. Among 61 TAB-negative patients with advanced arterial imaging, 43 (69%) had at least one abnormality consistent with GCA.

Conclusion: Consideration of alternative diagnoses is requisite in evaluating patients with negative TAB. Advanced imaging assists in identifying occult large-vessel vasculitis and should be employed in all TAB-negative patients with suspicion for GCA.

Introduction

Temporal artery biopsy (TAB) has been a cornerstone in the evaluation of suspected giant cell arteritis (GCA) from the time of Horton and colleagues' original description of the initial TABs confirming histopathological identification of temporal arteritis in two patients in the early 1930s [1]. Over the past two decades, non-invasive imaging studies, particularly color Doppler ultrasonography (CDUS), have been proposed as potential diagnostic surrogates for TAB [2]. However, while some experts suggest CDUS should supersede TAB as the initial diagnostic procedure of choice [3], this has not been universally accepted [4,5]. The sensitivity and specificity of CDUS is operator dependent, and expertise in this imaging modality for GCA is not widely available. As such, TAB continues to remain a key method of GCA diagnosis.

Although the specificity of TAB is 100%, its sensitivity can range from 39 to 77%; resulting in observed false-negative rates between 5 and 40% [6–9]. Given the lack of diagnostic criteria for GCA, diagnosis of TAB-negative GCA is challenging and is based on the appropriate clinical context and exclusion of mimicking conditions. This diagnostic dilemma is further complicated by the more recent understanding that there may be multiple phenotypic patterns present within the spectrum of GCA [10,11] and the clinical presentation of patients with TAB-negative GCA can vary from their TAB-positive counterparts [9,10,12–16]. Furthermore, limited guidance is available to assist clinicians in differentiating TAB-negative GCA from non-GCA alternative diagnoses because few studies [16–19] have focused on distinguishing features between these two groups.

The purpose of this study was to identify patients from a large, single-institution, referral center with TAB-negative GCA as well as patients undergoing TAB for which an alternate diagnosis was obtained and compare them to patients with TAB-positive GCA, in order to identify distinctive clinical, laboratory and radiographic features.

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Patients and methods

All patients with a current procedural terminology (CPT) code for TAB excision and/or code for TAB pathology review plus at least one ICD-9 (446.5) or ICD-10 (M31.5, M31.6) code for GCA between 1/1/1998 and 12/31/2013 were retrospectively reviewed. Per standard practice, all biopsies were reviewed by Mayo Clinic pathologists with expertise in vascular histopathology. If the TAB was performed at an alternate institution, patients were only considered eligible if the biopsy specimen was obtained and over-read by the Mayo Clinic pathology department.

Three patient cohorts were established for comparison. The first cohort consisted of patients with TAB-positive GCA, which has been previously reported in detail [20]. The second cohort consisted of patients with TAB-negative GCA. Diagnosis of TAB-negative GCA was determined if the TAB was negative for GCA but the patient met three or more 1990 ACR classification criteria for GCA [21] without an alternate rheumatic or non-rheumatic diagnosis identified. Patients meeting less than three 1990 ACR classification criteria for GCA were included if they met all of the following criteria: 1) had a negative TAB, 2) were $\geq$ 50 years of age at onset of symptoms, 3) had an ESR $\geq$ 30 mm/hr and/or CRP $\geq$ 10 mg/L and 4) had characteristic radiographic evidence of large-vessel GCA involvement [22]. Diagnosis was confirmed by consensus among two physicians (K.Y. and M.J.K.). In cases for which agreement was not initially met, review by a third physician (K.J.W.) was performed.

The third cohort of patients consisted of subjects that had undergone a TAB for suspected GCA, but for which another diagnosis was identified. This cohort, termed "GCA mimics", was developed by direct medical chart review of all patients with a TAB performed at Mayo Clinic, Rochester, Minnesota between 1/1/2009 and 12/31/2010. Patients were required to have a minimum of six months of follow-up to determine the presence or absence of GCA. Patients were excluded from this cohort if they had a positive biopsy, a biopsy with findings of "healed arteritis" or if they were diagnosed with TAB-negative GCA.

Relapse was defined as either of the following if glucocorticoid therapy was increased with subsequent improvement: (i) new onset or reappearance of signs/symptoms compatible with GCA with an associated increase in inflammatory markers, (ii) new onset or reappearance of signs/symptoms compatible with GCA without an associated increase in inflammatory markers or (iii) isolated increase in inflammatory markers without GCA signs/symptoms or other explainable etiology present (particularly infection). In accordance with local laboratory standard references ranges, inflammatory marker elevation was defined as a CRP level >8 mg/L and/or ESR by the Westergren method >22 mm/h for men and >29 mm/h for women.

Descriptive statistics (means, medians, percentages, etc.) were used to summarize the data. Baseline characteristics were compared between groups using chi-square and rank sum tests. Kaplan–Meier methods were used to estimate the rate of development of outcomes during follow-up. Relapse rates were calculated using person-year methods as the number of relapses divided by the length of follow-up. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

This study was approved by the institutional review board at the Mayo Clinic (14–001179) and the study was conducted in accordance with the ethical standards of the responsible committee on human experimentation as outlined by the Declaration of Helsinki.

Results

Patients

A total of 591 study subjects were identified during the respective study periods; 396 patients with GCA were identified (286 TAB-positive, 110 TAB-negative) and 195 patients with GCA mimics. Baseline and demographic information for patients identified as TAB-positive GCA, TAB-negative GCA, and GCA mimics are presented in Table 1.

TAB-positive versus TAB-negative GCA patients

Compared to TAB-positive GCA, patients with TAB-negative GCA were younger ($p = 0.001$), had a shorter time from first symptom to diagnosis ($p < 0.001$) and met $\geq$ 3 1990 ACR classification criteria less often ($p < 0.001$). TAB-negative GCA patients had lower frequencies of polymyalgia rheumatica (PMR; $p = 0.024$), jaw claudication ($p < 0.001$) and abnormal temporal arteries on examination ($p = 0.004$); whereas, arm claudication, non-PMR musculoskeletal pain, anorexia and fatigue were more commonly observed ($p < 0.001$). ESR values at diagnosis were similar but CRP, platelets, alkaline phosphatase were each significantly lower ($p < 0.001$).

TAB-negative GCA versus GCA mimics

In comparison to patients with TAB-negative GCA, patients with GCA mimics were similar in age and sex but had longer duration between symptom onset and diagnosis ($p < 0.001$) and notable lower frequency of meeting $\geq$ 3 1990 ACR classification criteria ($p < 0.001$). Headache rates were comparable but patients with GCA mimics had higher rates of non-frontotemporal facial pain ($p = 0.001$). Additionally, patients with GCA mimics less often had features of claudication [jaw, $p = 0.005$; arm, $p < 0.001$; leg, $p = 0.001$] or arterial abnormalities on examination [decreased TA pulse, $p = 0.004$; decreased large artery pulse, <0.001; large artery bruit, $p = 0.014$]. Constitutional symptoms of anorexia ($p < 0.001$), fatigue ($p < 0.001$) and fever ($p = 0.02$) were also less commonly reported. CRP values were similar, but ESR ($p = 0.002$), platelets ($p < 0.001$) and alkaline phosphatase ($p = 0.004$) were significantly lower.

TAB-positive GCA versus GCA mimics

Multiple significant differences were observed between patients with TAB-positive GCA and non-GCA patients (Table 1). Notable characteristics that differentiate GCA mimics from TAB-positive GCA include lower female percentage (61% vs 74%; $p = 0.002$) and higher frequency of atypical facial pain ($p < 0.001$) and non-PMR musculoskeletal pain ($p < 0.001$). In addition, laboratory parameters were more markedly discordant between GCA mimics and TAB-positive GCA with lower ESR, CRP, alkaline phosphatase and platelets but higher hemoglobin and albumin seen among GCA mimics.

Biopsy

Characteristics of the biopsies from the TAB-negative GCA and GCA mimics are demonstrated in Table 2. The median number days on glucocorticoids prior to TAB was lower among patients with TAB-positive GCA [0 IQR (0,4) days] but similar between the TAB-negative GCA [3 IQR (0,7) days) and GCA mimics [1 IQR (0,13) day]. Unilateral biopsy was performed in 86% of cases with TAB-positive GCA, 76% of GCA mimics and in 66% of TAB-negative GCA. The median post-fixation length for unilateral, or first biopsy if subsequent biopsy obtained, were shorter in patients with TAB-positive GCA (11 mm) compared to TAB-negative GCA (14 mm, $p = 0.013$) but similar between TAB-negative GCA and GCA mimics. Among patients with second biopsy performed, the median length of the subsequent biopsy was longer in the GCA mimics group (32 mm) compared to TAB-negative GCA (22 mm, $p = 0.003$). Patients with TAB-positive disease had shorter duration of prednisone use prior to biopsy with median of 0 [IQR (0, 4)] days compared to TAB-negative patients [3 days (0, 7)] and GCA mimics [1 day (0,13)].

Table 1
Characteristics of patients based on biopsy findings and presence or absence of giant cell arteritis diagnosis.

Characteristic, n (%)	TAB-pos GCA (*N* = 286)	TAB-neg GCA (*N* = 110)	GCA mimics (*N* = 195)	TAB-pos vs TAB-neg p-value	TAB-neg vs GCA mimics p-value	TAB-pos vs GCA mimics p-value
Age at diagnosis, yr*	75.0 ± 7.6	72.0 ± 9.0	72.4 ± 9.3	0.001	0.56	0.002
Sex, female	213 (74)	74 (67)	119 (61)	0.15	0.28	0.002
Ethnicity, white	279 (98)	109 (99)	190 (97)	0.24	0.49	0.09
Time from first symptom to diagnosis, mo*	4.0 ± 7.5	1.5 ± 2.1	2.6 ± 2.5	<0.001	<0.001	0.16
Follow-up duration, years*	6.0 ± 3.9	5.8 ± 4.0	3.8 ± 3.0	–	–	–
Abnormal temporal artery biopsy	286 (100)	0 (0)	0 (0)	–	–	–
≥ 3 ACR criteria met	273 (95)	70 (64)	51 (27)	<0.001	<0.001	<0.001
Headache	187 (67)	73 (66)	132 (68)	0.97	0.76	0.73
Other facial pain	17 (6)	10 (9)	47 (24)	0.28	0.001	<0.001
TA tenderness	46 (16)	39 (35)	18 (9)	<0.001	<0.001	0.027
Nodular, erythematosus or swollen TA	50 (18)	7 (6)	9 (5)	0.004	0.52	<0.001
Decreased TA pulse	42 (15)	9 (8)	3 (2)	0.072	0.004	<0.001
Vision loss, transient	20 (7)	5 (5)	12 (6)	0.39	0.58	0.71
Vision loss, permanent	16 (6)	3 (3)	6 (3)	0.23	0.86	0.19
Jaw claudication	149 (52)	21 (19)	16 (8)	<0.001	0.005	<0.001
Arm claudication	7 (2)	14 (13)	1 (1)	<0.001	<0.001	0.10
Leg claudication	6 (2)	6 (5)	0 (0)	0.08	0.001	0.042
Decreased large artery pulses	18 (6)	13 (12)	3 (2)	0.073	<0.001	0.011
Large artery bruit	20 (7)	5 (5)	1 (1)	0.36	0.014	0.001
Polymyalgia rheumatica	125 (44)	35 (32)	41 (21)	0.024	0.04	<0.001
Other musculoskeletal pain	48 (17)	48 (44)	93 (48)	<0.001	0.47	<0.001
Anorexia	54 (19)	47 (43)	23 (12)	<0.001	<0.001	0.035
Fatigue	129 (45)	92 (84)	84 (43)	<0.001	<0.001	0.64
Weight loss (≥5 lb or 10% weight)	91 (32)	38 (35)	53 (27)	0.62	0.18	0.26
Fever	57 (20)	30 (27)	31 (16)	0.14	0.02	0.22
ESR, mm/hr¥	65 (42, 94)	58 (35, 90)	47 (22, 76)	0.30	0.002	<0.001
C-reactive protein, mg/L¥	54.7 (23.0, 100.5)	22.0 (8.0, 59.0)	20.1 (5.0, 48.2)	<0.001	0.39	<0.001
Hemoglobin, g/dL*	11.9 ± 2.4	12.0 ± 1.6	12.3 ± 1.7	0.055	0.43	0.002
Platelets, $x10^9$/L¥	372 (310, 463)	330 (262, 403)	258 (215, 358)	<0.001	<0.001	<0.001
Albumin, gm/dL*	3.2 ± 0.6	3.8 ± 0.5	3.7 ± 0.6	<0.001	0.77	<0.001
Alkaline phosphatase, mg/dL¥	171 (106, 226)	95 (79, 123)	83 (68, 101)	<0.001	0.004	<0.001
Platelets < 400×10^9/L with no constitutional symptoms or extremity claudication€	30 (11)	14 (13)	80 (43)	0.77	<0.001	<0.001
Initial dose prednisone, mg/day¥	60 (40, 60)	50 (40, 60)	40 (15, 60)	0.12	< 0.001	< 0.001

¥ median (interquartile range).
€ missing data resulted in reduced cohort size of 266 in TAB-pos, 109 TAB-neg, 184 GCA mimics; ACR, American College of Rheumatology; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; TA, temporal artery; TAB temporal artery biopsy.
* mean±SD.

Imaging

At least one advanced imaging modality was performed within 7 months of diagnosis in 72 (25%) TAB-positive GCA, 61 (55%) TAB-negative GCA and 43 (22%) patients with GCA mimics. Imaging findings are summarized in Table 3. Comparison of the baseline characteristics between GCA patients with and without imaging is summarized in the supplementary Table S1. Patients with TAB-positive GCA for which large-vessel imaging was performed tended be younger and have higher frequency of extremity claudication as well as more commonly reported anorexia and weight loss. PET-CT was more commonly used in GCA mimics compared to TAB-positive or TAB-negative patients. At least one abnormality was observed in 76% of patients with TAB-positive GCA and in 69% TAB-negative GCA patients. Only one patient in the GCA mimics group with history of seropositive rheumatoid arthritis had moderate narrowing of the left subclavian artery that was focal, associated with atherosclerotic changes and had negative FDG uptake on PET-CT, otherwise arterial abnormalities associated with pathologic aneurysm, stenosis, occlusion, thickening, FDG avidity were not observed. Wall thickening was

Table 2
Biopsy characteristics between patients with temporal artery biopsy negative giant cell arteritis and patients with negative temporal artery with alternate diagnosis.

Characteristic	TAB-pos GCA (*N* = 286)	TAB-neg GCA (*n* = 110)	GCA mimics (*n* = 195)	TAB-pos vs TAB-neg p-value	TAB-neg vs GCA mimics p-value	TAB-pos vs GCA mimics p-value
Prednisone days prior to biopsy¥	0 (0, 4)	3 (0, 7)	1 (0, 13)	<0.001	0.29	0.001
Biopsy location				<0.001	0.042	0.032
Unilateral	245 (86)	73 (66)	149 (76)	–	–	–
Bilateral sequential	7 (2)	10 (9)	6 (3)	–	–	–
Bilateral simultaneous	34 (12)	27 (25)	40 (21)	–	–	–
Length of 1st or unilateral biopsy, mm	11 (8, 20)	14 (10, 28)	12 (8, 22)	0.013	0.054	0.78
Length of 2nd biopsy, mm*¥	16 (11, 30)	22 (10, 30)	32 (22, 37)	0.80	0.003	<0.001

¥ median (IQR); *for patients undergoing 2nd biopsy which was *n* = 42 in TAB-pos GCA, *n* = 34 in TAB-neg GCA and *n* = 32 in TAB-neg non-GCA.

Table 3
Imaging findings in the first 7 months after diagnosis based on biopsy findings and presence or absence of giant cell arteritis diagnosis.

Characteristic, n (%)	TAB-pos GCA (*N* = 72)	TAB-neg GCA (*N* = 61)	GCA mimics (*N* = 43)	TAB-pos vs TAB-neg p-value	TAB-neg vs GCA mimics p-value	TAB-pos vs GCA mimics p-value
Type of imaging						
Conventional angiography	9 (13%)	0 (0%)	1 (2%)	0.004	0.23	0.06
CT angiography	37 (51%)	30 (49%)	20 (47%)	0.80	0.79	0.61
MR angiography	29 (40%)	32 (52%)	12 (28%)	0.16	0.013	0.18
PET	7 (10%)	8 (13%)	13 (30%)	0.54	0.032	0.005
Imaging findings						
Dilatation/ectasia	10/69 (14%)	3/58 (5%)	0/33 (0%)	0.08	0.18	0.021
Aneurysm	6/69 (9%)	3/58 (5%)	0/33 (0%)	0.44	0.18	0.08
Stenosis	34/69 (49%)	12/58 (21%)	1*/33 (3%)	0.001	0.021	<0.001
Occlusion	4/69 (6%)	9/58 (16%)	0/33 (0%)	0.072	0.017	0.16
Wall thickening	20/69 (29%)	22/58 (38%)	0/33 (0%)	0.29	<0.001	0.001
Abnormal FDG uptake	7/7 (100%)	7/8 (88%)	0/13 (0%)	0.33	<0.001	<0.001
Any abnormality	55/72 (76%)	42/61 (69%)	1/43 (2%)	0.33	<0.001	<0.001

CT, computed tomography, GCA, giant cell arteritis; MR, magnetic resonance; PET, positron emission tomography; TAB, temporal artery biopsy.
* one patient with history of rheumatoid arthritis had narrowing of the proximal subclavian with focal atherosclerosis on CT and negative FDG uptake on PET scan.

noted with similar frequencies in TAB-positive and TAB-negative patients (29% and 38%, respectively), as was abnormal FDG uptake when PET-CT was performed (100% and 88%, respectively).

Treatment

Rates of pulse dose glucocorticoids (>125 mg, intravenously administered for ≥ 1 day) were similar between TAB-positive GCA [28/286 (10%)] and TAB-negative GCA [9/110 (9%); $p = 0.62$] patients. Additionally, the median (IQR) daily oral initial prednisone dose for patients with TAB-positive GCA [60 mg (40, 60)] was comparable to those with TAB-negative GCA [50 mg (40, 60); $p = 0.12$]. Cumulative median (IQR) prednisone dose, including pulse dose therapies, at one year was higher in TAB-positive GCA patients [7.0 g (5.6, 8.6)] than in the TAB-negative GCA patients [6.0 g (4.6, 7.7); $p = 0.004$] but were similar at 2 years [9.1 g (7.0, 11.2) vs. 8.3 g (6.4, 11.3); $p = 0.47$] and 5 years [11.8 g (8.3, 15.2) vs. 13.9 (11.6, 15.8); $p = 0.09$]. Patients with TAB-positive GCA had a higher incidence of prednisone discontinuation for ≥ 6 months compared to those with TAB-negative GCA ($p < 0.001$) [Fig. 1A]. Rates of discontinuation for ≥6 months were 18%±2 vs. 9%±3 at 2 years, 49%±4 vs. 28%±5 at 5 years, and 62%±4 vs. 33%±6 at 10 years in TAB-positive and TAB-negative GCA, respectively. During this study period, no patient in either group received tocilizumab.

Outcome

Mean duration of follow-up was similar between TAB-positive GCA (6.0 ± 3.9 yrs) and TAB-negative GCA (5.8 ± 4.0 yrs). The total number of follow-up visits reviewed for TAB-positive GCA patients was 3473 and 1313 for TAB-negative GCA. The median number of follow up visits were comparable between groups with 19 (13, 27) visits for TAB-positive and 20 (13, 27) visits in TAB-negative GCA patients ($p = 0.13$).

At least one relapse occurred in 213/286 (74%) TAB-positive patients and 67/110 (61%) TAB-negative GCA patients. Due to differing lengths of follow-up among patients, the total number of relapses per patient was not compared; rather the relapse rate per person year was calculated. Relapse rates were identical between groups with median of 0.4 (0.2, 0.7) relapses per person per year in both groups, respectively ($p = 0.26$). Time-to-first relapse (Fig. 1B) did not differ between groups. First relapse occurred in 49%±3 at 1 year, 68%±3 at 2 years, and 79%±3 at 5 years in TAB-positive GCA vs. 49%±5 at 1 year, 64%±5 at 2 years and 69%±5 at 5 years in TAB-negative GCA vs. ($p = 0.74$). In total, 69 TAB-positive and 27 TAB-negative GCA patients died during follow-up. Mortality rates were 14%±3 and 16%±4 at 5 years and 31%±4 and 34%±6 at 10 years for TAB-positive and TAB-negative GCA patients, respectively ($p = 0.59$).

The ultimate diagnoses of patients in the GCA mimics group are represented in Table 4. Neurologic conditions were the most common alternate diagnoses (39%) with the majority determined to be unspecified/non-inflammatory headache ($n = 61$). Polymyalgia rheumatica accounted for 19% and non-GCA/PMR rheumatic conditions 13%. Among this latter group rheumatoid arthritis was most common ($n = 11$). Non-GCA vasculitides were identified in 6 patients, four of which had ANCA-associated vasculitis. Malignancies were uncommon, being seen in only 6 patients, three of which had brain tumors.

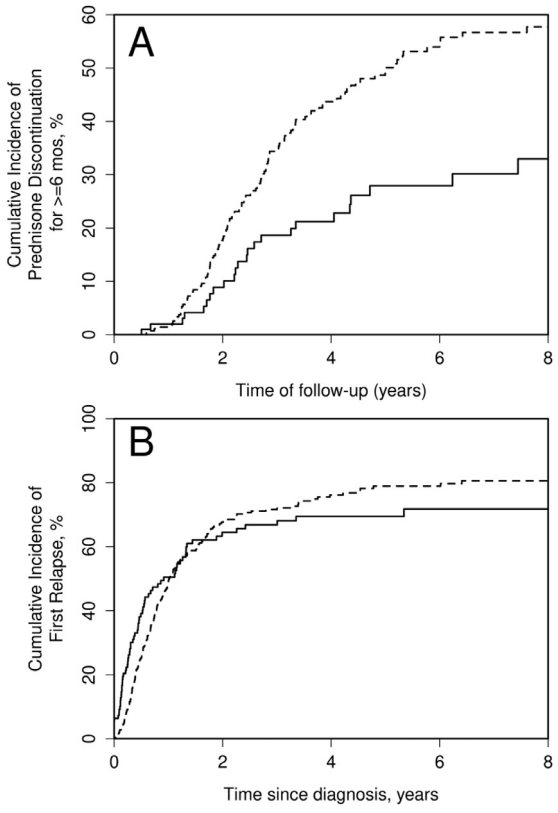

Fig. 1. (A) Cumulative incidence of prednisone discontinuation for ≥ 6 months and (B) cumulative incidence of first-relapse between patients with biopsy-proven (dashed line) and biopsy-negative (solid line) giant cell arteritis.

Table 4
Final diagnoses of patients undergoing temporal artery biopsy for which giant cell arteritis was not identified.

Diagnosis, n (%)	Current study *N* = 195	Bornstein 2018 *N* = 121	Muratore 2016 *N* = 31	Breuer 2008 *N* = 47	Younge 2004 *N* = 703	Chmelewski 1992 *N* = 54	Roth 1984 *N* = 33	Hedges 1983 *N* = 60
Neurologic condition	**76 (39)**	**20 (17)**	–	**6 (10)**	**132 (19)**	**12 (22)**	–	**30 (50)**
Headache, unspecified	69 (35)	–	–	–	93 (13)	–	–	–
Migraine	5 (3)	–	–	–	–	6 (11)	–	–
Tension headache	1 (0.5)	–	–	–	–		–	–
Neuro, other	1 (0.5)	–	–	–	39 (6)	6 (11)	–	–
Polymyalgia rheumatica	**38 (19)**	**22 (18)**	**11 (35)**	**5 (11)**	**198 (28)**	**14 (26)**	–	–
Rheumatic disease other than GCA/PMR	**26 (13)**	**8 (7)**	**10 (32)**	**6 (13)**	**33 (5)**	**7 (13)**	**8 (24)**	**5 (8)**
Rheumatoid arthritis	11 (6)	–	5 (16)	4 (9)	–	3 (6)	–	–
Sjögren's syndrome	5 (3)	–	–	–	–	–	–	–
Spondyloarthritis	4 (2)	–	–	–	–	–	–	–
Inflammatory myositis	2 (1)	–	–	–	–	–	–	–
Rheumatic, other	4 (2)	–	5 (16)	2 (4)	–	4 (6)	–	–
Vasculitis other than GCA	**6 (3)**	**8 (7)**	**2 (6)**	**1 (2)**	**27 (4)**	**3 (6)**	**1 (3)**	–
ANCA-associated vasculitis	4 (2)	–	2 (6)	1 (2)	–	–	–	–
Polyarteritis nodosa	1 (0.5)	–	–	–	–	–	–	–
Cryoglobulinemic vasculitis	1 (0.5)	–	–	–	–	–	–	–
Non-arteritic anterior ischemic optic neuropathy	**10 (5)**	**12 (10)**	**5 (16)**	**3 (6)**	**32 (5)**	**3 (6)**	**5 (15)**	–
Fever of unknown origin	**9 (5)**		**2 (6)**	**3 (6)**	**75 (11)**	**4 (67**	**1 (3)**	
Infectious disease	**7 (4)**	**6 (5)**	–	**3 (6)**	**12 (2)**	**3 (4)**	**1 (3)**	**1 (2)**
Hematologic (non-malignant)	**7 (4)**	–	–	**9 (19)**	**16 (2)**	–	–	–
Malignancy	**6 (3)**	**3 (2)**	–	**5 (11)**	**22 (3)**	**4 (7)**	**6 (18)**	**13 (22)**
Brain tumor	3 (1.5)	–	–	–	–	–	–	–
Solid organ/bowel tumor	2 (1)	–	–	–	–	–	–	–
Lymphoma	1 (0.5)	–	–	–	–	–	–	
Cervical arthritis	**5 (3)**	–	–	–	–	–	–	
Systemic disease of undetermined cause	**5 (3)**	–	**1 (3)**	–	**29 (4)**	–	–	
Other etiology	–	**42 (35)**	–	**6 (13)**	**127 (18)**	**4 (7)**	**11 (33)**	

Fever of unknown origin (n = 9) and systemic disease of undetermined cause (n = 5) were infrequent among this cohort.

Discussion

This report comprises the largest single-institution study comparing TAB-positive and TAB-negative GCA to patients with GCA mimics. The findings from this comparative cohort study highlight several key differences between these subgroups that provide assistance to the evaluating provider.

TAB demonstrating findings of arteritis has been considered a gold-standard [4] for the diagnosis of GCA and this criterion has held a key role in the 1990 ACR classification criteria for this condition, distinguishing it from other forms of vasculitis. Nevertheless, biopsy of the temporal artery may not demonstrate histopathologic evidence of vasculitis in patients with GCA for several reasons including: 1) segmental inflammation ('skip lesions') and inadequate biopsy sample size, 2) involvement of cranial arteries other than the temporal artery (e.g. occipital), 3) involvement of the aorta and arch branches in the absence of cranial vasculitis, 4) prolonged use of glucocorticoids prior to biopsy. Between 3–22% of all patients undergoing TAB and 5–55% of patients with negative TAB are still clinically diagnosed with TAB-negative GCA based on clinical or imaging parameters [8,16–19,23,24]. In the current study, TAB-negative GCA accounted for 28% of the total GCA population during the study period of 16 years. While this frequency is higher than that observed by Gonzalez-Gay and colleagues (15.3%) [15], it is similar to reports observed by Grossman et al. (30%) [14] and Duhaut et al. (29%) [9].

Variance in phenotypic patterns of GCA are being identified [10,25], and it appears that the clinical differences between patients with TAB-negative and TAB-positive GCA extend beyond just the TAB results. In the current study, patients with TAB-positive GCA had notably higher frequency of jaw claudication, a finding that has been confirmed in several other reports as strongly associated with a positive TAB [9,10,12–16]. In addition, as expected, patients with TAB-negative GCA had less frequent TAB abnormalities on examination, as has been noted by others [9,15]. Our study, as well as others, has shown patients with TAB-negative GCA tend to have fewer systemic constitutional symptoms [15] and demonstrate an attenuated acute phase response with lower CRP [9,15] and platelets [9,14,15]. A recent large study evaluating the assessment of GCA from the International Diagnostic and Classification Criteria for Vasculitis (DCVAS) has also similarly depicted different subsets of GCA, finding that patients with positive TAB but negative large-vessel imaging have a 'traditional GCA clinical profile' compared to patients with TAB-negative disease with large-vessel involvement, the latter which had fewer cranial ischemic symptoms and temporal artery abnormalities but more frequent arm claudication [25]. Interestingly, patients with overlapping cranial and large-vessel disease demonstrated a unique clinical presentation compared to isolated cranial or isolated large-vessel patients [25].

Although clinical trial enrollment for patients with diagnosis of GCA has evolved to include radiographic findings indicative of large-vessel vasculitis in patients aged $\geq$ 50 years at symptom onset, regardless of TAB findings [26], there is limited information regarding the frequency of abnormal large-vessel imaging in patients with TAB-negative GCA. Indeed, prior studies have either not included imaging [9,14,15,18,19] or have used large-vessel imaging in less than 25% of TAB-negative GCA patients [17]. In the current report, 55% of patients ultimately diagnosed as TAB-negative GCA had at least one advanced arterial study performed, with 67% of those imaged showing abnormalities consistent with large-vessel vasculitis. The frequency of large-vessel vasculitis observed in our cohort likely explains the findings of a younger age of onset and more frequent limb claudication, as these findings have also been reported by groups comparing large-vessel GCA to cranial (biopsy-positive) GCA patients [10,12,25]. In the large international diagnostic GCA assessment study by Gribbons and colleagues [25] large-vessel imaging was performed in 49% (219/446) of patients with positive TAB, 47% (121/258) of patients with negative TAB and 82% (194/237) of patients that did not have a TAB performed with rates of positive large vessel imaging noted in 31% (68/219), 27% (33/121) and 59% (115/194), respectively [25].The findings from the

aforementioned study in addition to our report highlight the frequency of large-vessel vasculitis in both TAB-positive and TAB-negative GCA patients, and underscores the importance of the 2018 European League Against Rheumatism consensus recommendation that advanced imaging be used as a supplement to assess for vasculitis in the aorta and arch branches to support the diagnosis of large-vessel GCA [3]. It is currently unknown whether the observed phenotypic variants of GCA are a spectrum of disease or potentially separate subgroups of patients. Future observational studies and clinical trials are needed to investigate the clinical features and outcomes between patients with isolated cranial GCA, isolated extra-cranial GCA or mixed phenotypes.

Initial treatment of TAB-positive and TAB-negative patients was similar; however, those with TAB-negative GCA took longer to discontinue glucocorticoids. The reason for this finding is not fully known given the frequency of relapse was similar between groups, and the systemic inflammatory response was initially lower when compared to the TAB-positive patients. Nevertheless, a similar observation has been reported by De Boysson and colleagues, where patients with symptomatic large-vessel GCA had a longer duration of glucocorticoid usage and higher rate of glucocorticoid dependence compared to other GCA phenotypes [10]. Similarly, our group has also previously demonstrated that patients with large-vessel disease, particularly those with subclavian artery involvement, have been associated with both longer duration and higher cumulative glucocorticoid requirements [27]. Given treatment was not standardized and left to the discretion of the managing provider, it is possible that the presence of large-vessel involvement of the aorta or its branch vessels may have led to chronic treatment to prevent disease progression or aneurysm development. Further investigation into the causes of longer treatment durations in patients with large-vessel vasculitis is needed.

Neither headache nor vision loss were helpful discriminators between TAB-positive and TAB-negative GCA or between TAB-negative GCA patients and GCA mimics. A possible explanation for this finding is that providers were more likely to perform TAB in patients $\geq$ 50 years of age with headache or vision loss, even when the pretest probability of this condition was low and alternative diagnosis was ultimately identified, in order to avoid missing a possible diagnosis of GCA. While the 1990 ACR classification criteria are not intended for diagnostic purposes, they do appear to have clinical utility in differentiating patients, as 95% of those with positive biopsy met $\geq$ 3 ACR classification criteria, whereas those with TAB-negative GCA reached this threshold in 64% and those with alternative diagnosis in only 27%. Although Muratore et al. noted non-GCA patients fulfilled ACR classification criteria in only 6.5% of cases [17], comparable rates to our report have been shown in a recent study by Bornstein and colleagues investigating 31 patients with TAB-negative GCA and 121 non-GCA patients, with 84% and 36% fulfilling $\geq$ 3 1990 ACR classification criteria, respectively.

Clinical features significantly less frequent in patients with an alternative non-GCA diagnosis were: temporal artery tenderness, jaw claudication, limb claudication and constitutional symptoms of fever, anorexia, and fatigue. ESR was significantly lower in patients with non-GCA compared to TAB-negative GCA but CRP did not differ. This may be due to the already lower CRP observed in TAB-negative GCA compared to TAB-positive GCA. As aforementioned, platelets were significantly lower in TAB-negative GCA patients compared to TAB-positive patients. Interestingly, baseline platelet levels were even further significantly lower in non-GCA patients compared to TAB-negative GCA. Breuer and colleagues [18] noted a similar pattern of significant platelet elevation among their 11 TAB-negative GCA patients ($427{,}000 \pm 145{,}000/\mu l$) compared to 47 non-GCA patients ($310{,}000 \pm 123{,}000/\mu l$; $p = 0.018$) despite similar ESR and CRP values in these groups. They also noted that thrombocytosis (platelets > $400{,}000/\mu l$) was seen in 73% of TAB-negative GCA patients but only 19% of non-GCA patients. Likewise, Bornstein et al. [19] found platelets on multivariate analysis to be one of three features significantly associated with TAB-negative GCA compared to non-GCA with an OR of 1.28 (95% CI 1.07–1.53), whereas ESR was not predictive. In the current study, the combined absence of claudication, constitutional symptoms, and thrombocytosis was seen more frequently in the GCA mimics (43%), compared to TAB-negative (13%) and TAB-positive GCA (11%). Evaluation of this association in larger cohort studies is necessary to determine if the lack of these features are of assistance in predicting a non-GCA diagnosis among patients with a negative TAB.

The most common alternative diagnoses identified on follow-up for non-GCA patients were neurologic/headache and polymyalgia rheumatica without concomitant GCA, which are overall in keeping with other reports [8,13,16–19,23]. Of note, non-GCA rheumatic disease was seen in 13% of cases and an additional 3% of patients had a vasculitis other than GCA. While the frequencies of these alternative diagnoses vary among comparable studies, this highlights that additional evaluation, particularly by a rheumatologist, is strongly suggested in patients with elevated inflammatory markers and negative TAB to assist in distinguishing these clinical entities. Non-arteritic anterior ischemic optic neuropathy was an alternative diagnosis in 5% of our cohort and has been observed in previous studies at frequencies of 6–16% [8,13,16–19,23]. Clinical distinction between non-arteritic anterior ischemic optic neuropathy and arteritic anterior ischemic optic neuropathy, the latter associated with GCA, is often not feasible based on symptoms alone and requires prompt evaluation by a skilled neuro-ophthalmologist to distinguish. The frequency of malignancy among patients with negative-TAB was low (3%) in comparison to older cohorts [8,16] but similar to more recent studies [13,19,23]. Although brain tumor was rare, it did account for 50% of observed cancers. MRI of the cranial arteries is not routinely performed in the evaluation of patients with suspected GCA due to limited availability and cost. However, cranial imaging should be considered particularly in patients with atypical features, cranial nerve palsies, or persistent headache despite high-dose glucocorticoids.

This study needs to be interpreted in the context of its limitations. Given the retrospective nature of this study, data are reliant on documented information and clinical evaluation was not standardized across all providers. Advanced large-vessel imaging was not performed uniformly and therefore observed frequencies may be subject to bias. The majority of TAB were unilateral, and thus it is uncertain if additional contralateral biopsy would have yielded a positive result. Nevertheless, since reports have shown discordant biopsy rates in the total TAB population rate to be approximately 4% [28] and obtaining bilateral biopsy increases sensitivity by a maximum of 5–13% [29,30], we do not anticipate our results would have substantially changed if bilateral biopsies were obtained in all patients. Furthermore, in this cohort, patients with positive TAB actually had a higher frequency of unilateral biopsy and shorter length of biopsy compared to the other groups making laterality and length unlikely contributors towards negative TAB results in this study.

In conclusion, this is the largest single-institution comparative cohort study evaluating TAB-positive, TAB-negative, and non-GCA patients to date. 1990 ACR classification criteria appear to have utility in differentiation between groups but updated classification criteria are needed to assist in identifying patients with extra-cranial presentations. Patients with non-GCA diagnoses have significantly less frequent jaw/limb claudication and lower platelets. Among patients with biopsy-negative GCA imaging of the large arteries demonstrated evidence of large-vessel vasculitis in two-thirds of those evaluated and should be performed to assist in distinguishing patients with TAB-negative GCA from those with alternative diagnoses.

Declaration of Competing Interest

The authors do not declare any relevant conflicts or interesting pertaining to this research study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2020.05.018.

References

[1] Horton B, Magath T, Brown G. An undescribed form of arteritis of the temporal vessels. Proc Staff Meet Mayo 1932;7:700–1.
[2] Schmidt WA, Kraft HE, Vorpahl K, Volker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med 1997;337(19):1336–42.
[3] Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77(5):636–43.
[4] Bienvenu B, Ly KH, Lambert M, et al. Management of giant cell arteritis: recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). Rev Med Interne 2016;37(3):154–65.
[5] Maldini C, Depinay-Dhellemmes C, Tra TT, et al. Limited value of temporal artery ultrasonography examinations for diagnosis of giant cell arteritis: analysis of 77 subjects. J Rheumatol 2010;37(11):2326–30.
[6] Luqmani R, Lee E, Singh S, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Health Technol Assess 2016;20(90):1–238.
[7] Davies CG, May DJ. The role of temporal artery biopsies in giant cell arteritis. Ann R Coll Surg Engl 2011;93(1):4–5.
[8] Hedges TR, 3rd Gieger GL, Albert DM. The clinical value of negative temporal artery biopsy specimens. Arch Ophthalmol 1983;101(8):1251–4.
[9] Duhaut P, Pinede L, Bornet H, et al. Biopsy proven and biopsy negative temporal arteritis: differences in clinical spectrum at the onset of the disease. Groupe de Recherche sur l'Arterite a Cellules Geantes. Ann Rheum Dis 1999;58(6):335–41.
[10] de Boysson H, Liozon E, Ly KH, Dumont A, Delmas C, Aouba A. The different clinical patterns of giant cell arteritis. Clin Exp Rheumatol 2019;37(2):57–60 Suppl 117.
[11] Dejaco C, Brouwer E, Mason JC, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol 2017;13(10):578–92.
[12] Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum 1999;42(2):311–7.
[13] Younge BR, Cook Jr. BE, Bartley GB, Hodge DO, Hunder GG. Initiation of glucocorticoid therapy: before or after temporal artery biopsy? Mayo Clin Proc 2004;79(4):483–91.
[14] Grossman C, Barshack I, Koren-Morag N, Ben-Zvi I, Bornstein G. Baseline clinical predictors of an ultimate giant cell arteritis diagnosis in patients referred to temporal artery biopsy. Clin Rheumatol 2016;35(7):1817–22.
[15] Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, Gonzalez-Louzao C, Rodriguez-Ledo P. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. Semin Arthritis Rheum 2001;30(4):249–56.
[16] Roth AM, Milsow L, Keltner JL. The ultimate diagnoses of patients undergoing temporal artery biopsies. Arch Ophthalmol 1984;102(6):901–3.
[17] Muratore F, Cavazza A, Boiardi L, et al. Histopathologic findings of patients with biopsy-negative giant cell arteritis compared to those without arteritis: a population-based study. Arthritis Care Res (Hoboken) 2016;68(6):865–70.
[18] Breuer GS, Nesher R, Nesher G. Negative temporal artery biopsies: eventual diagnoses and features of patients with biopsy-negative giant cell arteritis compared to patients without arteritis. Clin Exp Rheumatol 2008;26(6):1103–6.
[19] Bornstein G, Barshack I, Koren-Morag N, Ben-Zvi I, Furie N, Grossman C. Negative temporal artery biopsy: predictive factors for giant cell arteritis diagnosis and alternate diagnoses of patients without arteritis. Clin Rheumatol 2018;37(10):2819–24.
[20] Labarca C, Koster MJ, Crowson CS, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. Rheumatology (Oxford) 2016;55(2):347–56.
[21] Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33(8):1122–8.
[22] Muratore F, Pazzola G, Pipitone N, Boiardi L, Salvarani C. Large-vessel involvement in giant cell arteritis and polymyalgia rheumatica. Clin Exp Rheumatol 2014;32(3 Suppl 82):S106–11.
[23] Chmelewski WL, McKnight KM, Agudelo CA, Wise CM. Presenting features and outcomes in patients undergoing temporal artery biopsy. A review of 98 patients. Arch Intern Med 1992;152(8):1690–5.
[24] Grossman C, Barshack I, Bornstein G, Ben-Zvi I. Is temporal artery biopsy essential in all cases of suspected giant cell arteritis? Clin Exp Rheumatol 2015;33(2 Suppl 89) S–84-9.
[25] Gribbons KB, Ponte C, Craven A, et al. Diagnostic assessment strategies and disease subsets in giant cell arteritis: data from an international observational cohort. Arthritis Rheumatol 2020;72(4):667–76.
[26] Tuckwell K, Collinson N, Dimonaco S, et al. Newly diagnosed vs. relapsing giant cell arteritis: baseline data from the GiACTA trial. Semin Arthritis Rheum 2017;46(5):657–64.
[27] Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford) 2015;54(3):463–70.
[28] Durling B, Toren A, Patel V, Gilberg S, Weis E, Jordan D. Incidence of discordant temporal artery biopsy in the diagnosis of giant cell arteritis. Can J Ophthalmol 2014;49(2):157–61.
[29] Pless M, Rizzo 3rd JF, Lamkin JC, Lessell S. Concordance of bilateral temporal artery biopsy in giant cell arteritis. J Neuroophthalmol 2000;20(3):216–8.
[30] Breuer GS, Nesher G, Nesher R. Rate of discordant findings in bilateral temporal artery biopsy to diagnose giant cell arteritis. J Rheumatol 2009;36(4):794–6.