

Poor Predictive Value of Isolated Adventitial and Periadventitial Infiltrates in Temporal Artery Biopsies for Diagnosis of Giant Cell Arteritis

Claire Le Pendu, Véronique Meignin, Solange Gonzalez-Chiappe, Adrian Hij, Françoise Galateau-Sallé, and Alfred Mahr

ABSTRACT. Objective. We investigated the diagnostic value of inflammation limited to the adventitia (ILA), and isolated vasa vasorum or small-vessel vasculitis (VVV, SVV) in temporal artery biopsies (TAB) for giant cell arteritis (GCA).

Methods. Two pathologists reviewed consecutive first TAB. Using the clinical diagnoses as the gold standard, positive predictive values (PPV) were calculated.

Results. Among the 75 patients without classic TAB features of GCA, 8 had GCA diagnoses. The PPV of ILA, VVV, and SVV seen by either or both pathologists were 17%, 0%, and 7%, and 17%, 0%, and 10%, respectively.

Conclusion. (Peri)adventitial infiltrates in TAB poorly predict GCA. (J Rheumatol First Release May 1 2017; doi:10.3899/jrheum.170061)

Key Indexing Terms:

GIANT CELL ARTERITIS TEMPORAL ARTERY BIOPSY SMALL-VESSEL VASCULITIS

Temporal artery biopsy (TAB), showing a mononuclear cell infiltrate with occasional giant cells involving the media or all vessel layers, is a major criterion to establish a secure diagnosis of giant cell arteritis (GCA)^{1,2}. Increasing attention is paid to the diagnostic relevance of more subtle histological anomalies, variably described as periarterial lymphocytic infiltration³, chronic perivascular inflammation⁴, vasa vasorum vasculitis (VVV)⁵, or arteritis of a surrounding vessel^{6,7}. These anomalies were unified in a classification system consisting of inflammation limited to the adventitia (ILA), VVV, and small-vessel vasculitis (SVV)⁸, each of which was suggested as the sole finding in up to 10% of patients with clinically diagnosed GCA^{8,9}.

From the Department of Internal Medicine, Unit for Systemic Diseases (UF07), and Department of Pathology, and Department of Internal Medicine, Unit for Autoimmune and Vascular Diseases (UF04), Saint-Louis University Hospital; ECSTRA Team, Epidemiology and Biostatistics, Sorbonne Paris Cité Research Center UMR 1153, INSERM, Paris; Department of Pathology, University Hospital Caen, Caen; Department of Biopathology, Léon-Bérard Cancer Center, Lyon, France. C. Le Pendu, MD, Department of Internal Medicine, Unit for Systemic Diseases (UF07), Saint-Louis University Hospital; V. Meignin, MD, Department of Pathology, Saint-Louis University Hospital; S. Gonzalez-Chiappe, MD, MPH, Department of Internal Medicine, Unit for Systemic Diseases (UF07), Saint-Louis University Hospital; A. Hij, MD, Department of Internal Medicine, Unit for Autoimmune and Vascular Diseases (UF04), Saint-Louis University Hospital; F. Galateau-Sallé, MD, PhD, Department of Pathology, University Hospital Caen, and Department of Biopathology, Léon-Bérard Cancer Center; A. Mahr, MD, MPH, PhD, Department of Internal Medicine, Unit for Systemic Diseases (UF07), Saint-Louis University Hospital, and ECSTRA Team, Epidemiology and Biostatistics, Sorbonne Paris Cité Research Center UMR 1153, INSERM.

Address correspondence to Professor A. Mahr, Department of Internal Medicine, Hospital Saint-Louis, AP-HP, 1 avenue Claude-Vellefaux, 75475 Paris Cedex 10, France. E-mail: alfred.mahr@aphp.fr

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Thus, the clinical significance of isolated (peri)adventitial infiltrates in TAB is uncertain, mainly because of the dearth of data on how well (peri)adventitial TAB infiltrates predict a diagnosis of GCA. Our study was carried out to assess the positive predictive value (PPV) of ILA and isolated VVV or SVV in TAB for diagnosis of GCA.

MATERIALS AND METHODS

Study setting. We did our study in an academic hospital in which TAB is routinely performed as a first-line diagnostic test for suspected GCA. TAB lengths are measured after formalin fixation, and tissue processing involves paraffin embedding, cutting of multiple 4 µm-thick cross sections, and staining with H&E. The electronic database of the hospital's Pathology Department was searched to identify about 100 consecutive TAB performed from 2009 to 2015. Only TAB performed during the initial assessment were retained for our study; repeated TAB performed to diagnose GCA relapse were discarded. Ethical approval was not required in accordance with the French policy on noninterventional studies.

Acquisition of data. Two experienced pathologists (VM, FGS), blinded to the clinical diagnoses, independently reviewed the selected TAB. The presence or absence of inflammatory cell infiltrates in the intima, media, adventitia, and/or tissue surrounding the temporal artery was recorded. Using a previously suggested cutoff of 15 cells¹⁰, observed inflammatory infiltrates were additionally categorized as those with < 15 or ≥ 15 cells. Classic GCA was defined as infiltrates of the media or all vessel layers, ILA as more scattered infiltrates involving only the adventitia, VVV as concentrically arranged perivascular infiltrates within the adventitia, and SVV as infiltrates of a periadventitial vessel⁸. The total number of sections was determined by summing the number of sections per slide across all available slides. Information on TAB lengths was extracted from the original pathology reports.

Clinical information was extracted from the patients' medical charts by an investigator (CLP) unaware of the findings of the pathology reviews. The clinical diagnoses were used as gold standards, with a minimum followup of 6 months. For GCA and polymyalgia rheumatica (PMR), we calculated the proportion of patients fulfilling the American College of Rheumatology

(ACR)¹¹ and ACR/European League Against Rheumatism (EULAR) classification criteria¹², respectively.

Statistical analysis. From the TAB that did not show a classic GCA, we calculated the PPV of ILA, VVV, and/or SVV for GCA. Because of the close relationship between GCA and PMR, we also calculated the PPV for the combined GCA/PMR spectrum. For the primary analyses, PPV were calculated for findings by either (at least 1) or both pathologists; in a secondary analysis, the same calculations were based on the findings by either pathologist alone. Cohen's κ statistic was used to measure interpathologist agreement. The nonparametric Wilcoxon test was used to compare continuous variables.

RESULTS

Selection of patients. The search identified TAB from 108 patients; 8 were discarded because they were repeat TAB. During the TAB review process, we excluded TAB of 6 other patients because technical artifacts did not allow for proper histopathological analysis of all vessel layers.

Among the remaining 94 patients, 19 TAB (median TAB length 1.7 cm, range 0.6–3.5) showed classic GCA; all 19 patients (median age 74 yrs, range 54–87, 68% women) also had a clinical diagnosis of GCA. For these TAB, the assessments of both pathologists were perfectly concordant ($\kappa = 1.0$, 95% CI 0.80–1.20). Therefore, the analyses of the diagnostic value of isolated (peri)adventitial anomalies pertained to 75 patients.

Clinical and TAB characteristics of selected patients. Among the 75 patients (median age 69 yrs, range 31–90, 59% women), 8, 7, and 60 had received clinical diagnoses of GCA, PMR, and non-GCA/PMR, respectively. The latter cases included 10 of infectious diseases, 9 malignancies, 3 isolated idiopathic aortitis, 3 rheumatoid arthritis, 3 rheumatoid factor–seronegative arthritis, 2 systemic lupus erythematosus, 1 Behçet disease, 1 isolated cutaneous vasculitis, 1 primary Sjögren syndrome, 11 miscellaneous diagnoses, and 16 with no specific acute illness diagnosed because of spontaneous recovery and negative diagnostic workup. All 8 patients with GCA satisfied the ACR criteria for GCA and all 7 patients with PMR fulfilled the ACR/EULAR criteria for PMR.

The median followup was 13 months (range 1–84); all patients were followed up for ≥ 6 months, except for 2 who died of infectious pneumonia and cutaneous carcinoma at 1 month post-TAB. Overall, 32 patients received longterm treatment (≥ 3 mos) with glucocorticoids (GC) after TAB, including the 15 with a GCA or PMR diagnosis, 3 with isolated idiopathic aortitis, 6 with other inflammatory rheumatisms, and 7 with malignancies or infectious diseases in addition to other specific therapies; 1 patient received longterm GC despite no clear diagnosis being made.

The median TAB length was 1.5 cm (range 0.4–3.5, 13 missing values) and did not differ between patients with and without a GCA diagnosis ($p = 0.75$) or with and without a GCA/PMR diagnosis ($p = 0.65$). The median number of sections analyzed was 27.5 (range 8–90) and did not differ

with and without a GCA diagnosis ($p = 0.13$), or a GCA/PMR diagnosis ($p = 0.35$). Nine patients (12%) received GC before TAB, mostly for < 15 days, including 4 with a diagnosis of GCA, 1 PMR, and 4 non-GCA/PMR conditions.

PPV of isolated (peri)adventitial TAB infiltrates. Among the 75 patients, either pathologist detected ILA, VVV, and SVV in TAB for 12, 7, and 29, respectively, and both pathologists for 6, 1, and 10, respectively. Interpathologist agreement was substantial for ILA ($\kappa = 0.63$) and fair for VVV ($\kappa = 0.21$) and SVV ($\kappa = 0.35$; Table 1). Overall, (peri)adventitial anomalies were detected by either pathologist and both pathologists in 31 and 15 patients, respectively. The 31 patients with findings of ILA, VVV, and/or SVV seen by either pathologist had a variety of diagnoses, including 2 GCA, 5 PMR, and 24 non-GCA/PMR (including 6 without a defined acute illness; Table 2). Examples of the pathology findings are shown in Figure 1.

The PPV for ILA, VVV, and SVV (and their combination) for GCA or GCA/PMR diagnoses were almost uniformly $< 50\%$, even in the analyses restricted to the infiltrates with ≥ 15 cells (Table 1). The analyses of findings for either pathologist alone yielded PPV in the same range (data not shown).

DISCUSSION

Our study indicates that isolated (peri)adventitial infiltrates in TAB poorly predict GCA. Appraisal of data from 5 previous studies that provided information on number of GCA or PMR diagnoses in patients with TAB revealing isolated (peri)adventitial infiltrates also supports this conclusion^{4,5,6,13,14}. Indeed, in 1 study, 36 of 45 patients with TAB showing isolated VVV or SVV had GCA⁵. In another, among 28 patients with TAB showing isolated VVV, only 6 had GCA or PMR¹³. In a study of 81 patients with TAB showing only perivascular inflammation, only 19 fulfilled the ACR criteria for GCA⁴, and among 28 with TAB showing SVV, 12 had a diagnosis of GCA⁶. For 39 patients with isolated small-vessel and/or adventitial inflammation, none had a diagnosis of GCA or PMR at the time of TAB or during followup¹⁴.

In the past, some support for the significance of (peri)adventitial infiltrates for GCA came from studies suggesting that they were associated with a distinct clinical phenotype^{5,8,10}. Thus, (peri)adventitial infiltrates were also hypothesized to be linked with pure PMR⁷ or a larger range of systemic inflammatory rheumatisms^{4,5,13}. In light of our and previous indications that (peri)adventitial anomalies can be seen in infections or cancers⁴ and in people with no health condition diagnosis, it seems unlikely that they represent a characteristic hallmark of certain GCA patterns, PMR, or other inflammatory rheumatisms. The varying frequencies with which isolated (peri)adventitial changes are seen in TAB among studies^{3,4,5,14} may reflect heterogeneous histopathological definitions, but also the often inconspicuous charac-

Table 1. Frequency of ILA, VVV, and SVV and their respective PPV for diagnosis of GCA or GCA/PMR. The results are given for findings by at least 1 of the 2 pathologists or both. κ values express the interpathologist concordance for specific findings.

Variable	κ (95% CI)	GCA, n = 8, vs Non-GCA, n = 67		GCA/PMR, n = 15, vs Non-GCA/PMR, n = 60	
		Frequency	PPV % (95% CI)	Frequency	PPV % (95% CI)
Any infiltrate					
ILA	0.63 (0.42–0.84)				
Either pathologist		2/8 vs 10/67	17 (2–48)	4/15 vs 8/60	33 (10–65)
Both pathologists		1/8 vs 5/67	17 (0–64)	1/15 vs 5/60	17 (0–64)
VVV	0.21 (–0.01 to 0.43)				
Either pathologist		0/8 vs 7/67	0 (0–41)	0/15 vs 7/60	0 (0–41)
Both pathologists		0/8 vs 1/67	0 (0–98)	0/15 vs 1/60	0 (0–98)
SVV	0.35 (0.14–0.57)				
Either pathologist		2/8 vs 27/67	7 (1–23)	7/15 vs 22/60	24 (10–44)
Both pathologists		1/8 vs 9/67	10 (0–45)	4/15 vs 6/60	40 (12–74)
ILA, VVV, and/or SVV	0.50 (0.29–0.72)				
Either pathologist		2/8 vs 29/67	6 (1–21)	7/15 vs 24/60	23 (10–41)
Both pathologists		2/8 vs 13/67	13 (2–40)	5/15 vs 10/60	33 (12–62)
Infiltrate \geq 15 cells					
ILA	0.57 (0.35–0.79)				
Either pathologist		1/8 vs 6/67	14 (0–58)	1/15 vs 6/60	14 (0–58)
Both pathologists		1/8 vs 2/67	33 (1–100)	1/15 vs 2/60	33 (1–91)
VVV	0 (NC)				
Either pathologist		0/8 vs 1/67	0 (0–98)	0/15 vs 1/60	0 (0–98)
Both pathologists		0/8 vs 0/67	NC	0/15 vs 0/60	NC
SVV	0.25 (0.10–0.40)				
Either pathologist		1/8 vs 16/67	6 (0–29)	3/15 vs 14/60	18 (4–43)
Both pathologists		1/8 vs 2/67	33 (1–100)	2/15 vs 1/60	67 (9–100)
ILA, VVV, and/or SVV	0.39 (0.21–0.57)				
Either pathologist		1/8 vs 16/67	6 (0–29)	3/15 vs 14/60	18 (4–43)
Both pathologists		1/8 vs 4/67	20 (1–72)	2/15 vs 3/60	40 (5–85)

ILA: inflammation limited to the adventitia; VVV: vasa vasorum vasculitis; SVV: small-vessel vasculitis; PPV: positive predictive values; GCA: giant cell arteritis; PMR: polymyalgia rheumatica; NC: not calculable.

teristics of (peri)adventitial infiltrates. Our calculated interpathologist concordance rates for (peri)adventitial anomalies reached mediocre values, but are in line with the κ values of 0.58 to 0.64 for ILA reported by others⁹.

PPV are intrinsically prevalence-dependent, and a study population in which the disease group is artificially under-represented results in an inaccurately low estimate of this metric. In our sample, the 20% rate (19/94) of TAB-positive GCA among all patients who underwent TAB and the 70% rate (19/27) among those with a clinical diagnosis of GCA indicate that our study population was representative of other study populations undergoing TAB^{3,14,15,16} or with GCA^{9,10,17,18}. The fairly large non-GCA control group, with a minimum required followup of 6 months, allows rejecting with reasonable certainty the concept that such histopathological findings reach high PPV for GCA. Also, it seems highly improbable that our results were influenced by variations between patients with GCA and those without GCA in the amount of periadventitial tissue available for review.

Our data raise caution in diagnosing GCA on the basis of isolated (peri)adventitial infiltrates in a TAB and highlight the need for more general consensus on the histological changes in TAB and their diagnostic relevance for GCA.

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Table 2. Demographics, TAB findings, clinical diagnoses, and post-TAB treatment with GC for 31 patients (among the 75 patients analyzed) in whom TAB revealed (peri)adventitial infiltrates seen by at least 1 of 2 pathologists.

No.	Sex, Age, Yrs, at TAB	ILA, VVV, and/or SVV, Identified by Either /both Pathologists		Clinical Diagnosis	Followup after TAB, Mos	GC Therapy ≥ 3 Mos
		Any	With ≥ 15 Cells			
1	M, 66	Y/Y	N/—	GCA	7	Y
2	M, 70	Y/Y	Y/Y	GCA	6	Y
3	M, 65	Y/Y	Y/N	PMR	21	Y
4	F, 75	Y/Y	N/—	PMR	27	Y
5	M, 85	Y/Y	Y/Y	PMR	6	Y
6	F, 72	Y/N	N/—	PMR	18	Y
7	F, 75	Y/N	N/—	PMR	14	Y
8	F, 52	Y/N	N/—	Isolated idiopathic aortitis	16	Y
9	F, 55	Y/N	Y/N	Seronegative arthritis	32	N
10	F, 35	Y/N	Y/N	Primary Sjögren syndrome	17	N
11	M, 56	Y/N	Y/N	Behçet disease	50	Y
12	M, 68	Y/Y	Y/N	Systemic lupus erythematosus	15	N
13	F, 62	Y/N	N/—	Drug-induced fever	15	N
14	F, 63	Y/Y	Y/N	Buerger disease	6	N
15	M, 84	Y/Y	N/—	Metastatic rectal adenocarcinoma	9	N
16	F, 77	Y/Y	Y/Y	Metastatic breast adenocarcinoma	7	N
17	M, 69	Y/Y	Y/Y	Prostate adenocarcinoma	67	N
18	M, 77	Y/Y	Y/N	Cutaneous carcinoma	1	N
19	F, 90	Y/N	N/—	Urinary tract infection	6	N
20	M, 78	Y/N	N/—	Bronchitis	29	N
21	M, 88	Y/Y	Y/N	Pneumonia	1	N
22	M, 77	Y/Y	Y/Y	Ischemic stroke	6	N
23	M, 69	Y/N	N/—	Adrenal insufficiency	84	N
24	F, 86	Y/N	N/—	GC-induced myopathy	6	N
25	F, 85	Y/N	Y/N	Amyloidosis	13	Y
26	M, 77	Y/N	Y/N	No acute disease diagnosed	10	N
27	F, 62	Y/N	N/—	No acute disease diagnosed	6	N
28	F, 60	Y/N	N/—	No acute disease diagnosed	6	N
29	F, 61	Y/N	Y/N	No acute disease diagnosed	6	N
30	F, 61	Y/Y	Y/N	No acute disease diagnosed	22	N
31	M, 88	Y/N	N/—	No acute disease diagnosed	6	N

TAB: temporal artery biopsy; GC: glucocorticoids; ILA: inflammation limited to the adventitia; VVV: vasa vasorum vasculitis; SVV: small-vessel vasculitis; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

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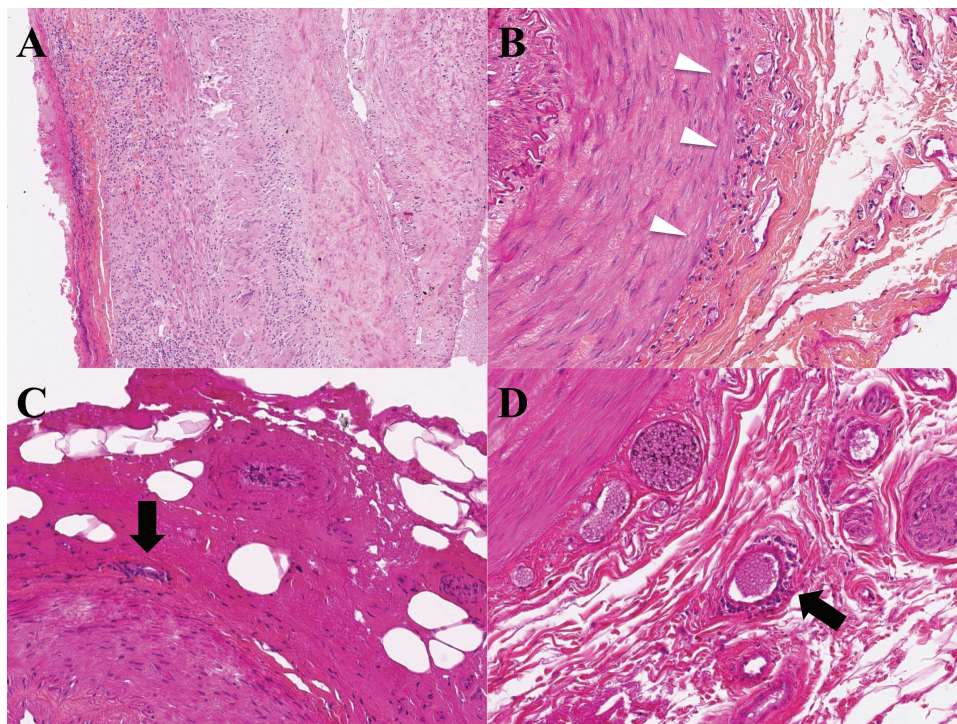


Figure 1. Examples of histopathological features found in the analyzed temporal artery biopsies. (A) Classic giant cell arteritis with prominent mononuclear cell infiltrate of the media, giant cells, and fibrosis. (B) Inflammation limited to adventitia with scattered mononuclear infiltrate (arrowheads) in a 69-year-old man with no acute illness diagnosed and spontaneous recovery. (C) Vasa vasorum vasculitis with mononuclear perivasculitis of an intra-adventitial vessel (arrow) in an 84-year-old man diagnosed with rectal adenocarcinoma. (D) Small-vessel vasculitis with perivascular mononuclear infiltrate of a periadventitial vessel (arrow) in a 77-year-old man with no acute illness diagnosed and spontaneous recovery. H&E staining $\times 100$ (A) and $\times 250$ (B–D) .

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