Temporal Small-Vessel Inflammation in Patients with Giant Cell Arteritis: Clinical Course and Preliminary Immunohistopathologic Characterization

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ABSTRACT. ***Objective.*** To investigate the occurrence, clinical correlates, and immunohistochemical phenotype of temporal small-vessel inflammation (TSVI) in temporal artery biopsies from patients presenting with clinical features of giant cell arteritis (GCA).

Methods. We retrospectively reviewed 41 temporal artery biopsy specimens for the presence of inflammatory infiltrates in small vessels external to the temporal artery adventitia (TSVI); 33 had sufficient clinical and pathological data for detailed analysis. Clinical and laboratory features at presentation and corticosteroid treatment patterns of patients with isolated TSVI were compared to those of patients with positive and negative biopsies. The cellular composition of the infiltrates was further characterized by immunohistochemistry.

Results. Twenty-three (70%) specimens had evidence of TSVI including 10 with concurrent GCA and 13 (39%) with isolated TSVI. TSVI was found in all positive temporal artery biopsies. The proportion of macrophages and of lymphocyte subpopulations differed between infiltrates observed in TSVI and those of the main temporal artery wall. Initial erythrocyte sedimentation rate (ESR) was similar in the TSVI and positive biopsy groups and was significantly higher than in the negative biopsy group. Patients with isolated TSVI more often had symptoms of polymyalgia rheumatica compared to the positive biopsy group. Patients with TSVI received corticosteroid doses that were intermediate between patients with positive and those with negative biopsies.

Conclusion. A significant number of patients with clinical features of GCA demonstrated isolated TSVI. Differences in the clinical presentation and cellular composition suggest that TSVI may represent a subset of GCA and should be considered in the interpretation of temporal artery biopsies and treatment decisions. (J Rheumatol First Release Dec 1 2010; doi:10.3899/jrheum.100455)

Key Indexing Terms:
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A positive temporal artery biopsy is considered by many clinicians to be the most definitive way to diagnose giant cell arteritis (GCA). However, it is well established that there are important limitations to temporal artery biopsy, including false negatives, skip areas, and lack of complete agreement on what constitutes a positive biopsy. Mononuclear infiltrates limited to the adventitia have been considered to constitute a positive biopsy[1]. In addition to the classic histopathologic findings described in the American College of Rheumatology (ACR) classification criteria for GCA[2], other histologic findings of unclear clinical significance have been described. In studies by Chakrabarty and Franks, periarterial lymphocytic infiltration was observed in 8.9% of biopsies following examination of additional sections in specimens interpreted as negative for GCA on initial examination[3]. Corcoran, *et al* reported a subset of temporal artery biopsy specimens without evidence of definite vasculitis but displaying perivascular-based chronic inflammation primarily consisting of lymphocytes[4]. Esteban, *et al* reported a series of patients in whom small-vessel vasculitis surrounding a spared temporal artery was the initial histologic evidence of systemic necrotizing vasculitis as well as the sole histopathologic finding in GCA[5]. Chatelain, *et al* described small-vessel vasculitis surrounding an uninflamed temporal

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The authors note with sorrow the passing of our coauthor, Lucien Nochomovitz, MD.

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artery in 7% of 490 patients with a clinical diagnosis of GCA and/or polymyalgia rheumatica (PMR)[6]. In a study designed to determine the effect of corticosteroid treatment on the interpretation of temporal artery biopsies, Font and Prabhakaran demonstrated the presence of inflammation restricted solely to small vessels (branches) in the presence of a normal temporal artery in some patients treated with corticosteroid[7]. Thus, inflammation of small vessels surrounding a normal temporal artery may represent part of the spectrum of GCA and may be of diagnostic importance.

The objective of our study was to determine the prevalence, immunohistochemical features, associated clinical manifestations, and treatment course of patients with inflammation of small vessels external to the temporal artery. Clinical and pathologic features of patients with isolated temporal small-vessel involvement adjacent to an uninvolved temporal artery were compared to those with positive and negative temporal artery biopsies in patients with a clinical diagnosis of GCA.

MATEERIALS AND METHODS

Patients. We retrospectively reviewed 41 clinical records and temporal artery biopsy specimens of patients who were evaluated by Rheumatology Department attending faculty and were suspected of having GCA. Eight patients were excluded from the analysis: 7 were lost to followup [3 from the temporal small-vessel inflammation (TSVI) group, 4 from the negative group] and the final diagnosis could not be confirmed; one patient was excluded based on unclassifiable histology (see below). The ACR 1990 classification criteria were utilized to make comparisons among patient subgroups and not to determine a diagnosis of GCA. This research was approved by the Institutional Review Board of Winthrop University Hospital.

Histology. Histologic review of hematoxylin and eosin (H&E) stained temporal artery biopsy specimens was performed by 2 sets of investigators (RK, JK, GT, and LN; and JM, EB, SC, and GT), each consisting of pathologists and rheumatologists. By consensus, specimens were assigned to one of 3 subsets: (1) definitive evidence of temporal arteritis (positive); (2) normal temporal artery with isolated small-vessel inflammation (isolated TSVI); and (3) no evidence of inflammation (negative). Biopsies were considered positive as defined by Hunder, *et al*[2]. In one case, consensus on the classification of the biopsy could not be reached by the investigators and this case was excluded. We define vasa vasorum strictly as capillary vessels within the adventitial layer of the vessel wall. The external limit of the temporal artery adventitia was histologically defined as the site of transition from densely packed collagen with elastic fibers to loose collagen lacking elastic fibers in the surrounding connective tissue. In the isolated TSVI group, inflammation was confined to the small vessels adjacent to but external to the temporal artery adventitia. None of the temporal artery specimens had fibrinoid necrosis or polymorphonuclear infiltration, although immunostaining for neutrophils was not performed.

The mean length of temporal artery specimens was 1.68 ± 0.33 cm for the positive biopsy specimens, 1.71 ± 0.22 cm for TSVI, and 1.20 ± 0.29 cm for the negative group (p = nonsignificant). On average, 182 ± 78 sections were analyzed. The mean numbers of sections for the positive, TSVI, and negative groups were 223 ± 92, 219 ± 43, and 115 ± 18, respectively (p = nonsignificant).

Immunohistochemistry. The cellular phenotype of the inflammatory infiltrates was analyzed immunohistochemically in 7 temporal artery biopsy specimens of patients who met criteria for GCA and had small-vessel inflammation external to the temporal artery (4 isolated TSVI; 3 GCA). Serial sections of the formalin-fixed and paraffin-embedded tissues were prepared and deparaffinized with xylene. Nonspecific binding was blocked with 3% hydrogen peroxide/APK buffer. Subsequently, tissue sections from each patient were incubated with monoclonal antibodies directed against CD20 (L26), leukocyte common antigen, CD3, and CD68 (Dako, Carpenteria, CA, USA). Negative control staining was performed by substituting phosphate buffer for the primary antibody. All sections were sequentially incubated with the corresponding biotinylated secondary antibody followed by peroxidase labeled streptavidin (Dako). Sections of paraffin-embedded lymph nodes were stained as described above as positive controls. Three independent reviewers, including 2 pathologists (JK and GT), analyzed all sections. The cellular composition was assessed using a semiquantitative scale: 0 = no significant expression, +1 = 1%–10% inflammatory cells, +2 = 11%–50% inflammatory cells, +3 = > 50% inflammatory cells. In patients with positive biopsies, inflammatory infiltrates in the adventitia (ADV), the area surrounding the internal elastic lamina (IEL), and the small vessels outside the involved temporal artery (SV) were analyzed.

Clinical course. From chart review, we documented presenting clinical symptoms; presenting laboratory data; relationship of timing of corticosteroid initiation to biopsy; mean corticosteroid dose at Days 1, 30, 60, and 90; number of flares, defined as an increase in corticosteroid dose for recurrence of clinical symptoms with or without an elevated ESR; and the number of ACR classification criteria fulfilled. For one patient in the negative group, the relationship of timing of corticosteroid initiation to biopsy could not be determined. Three patients in the TSVI group were not included in the analysis of corticosteroid duration prior to biopsy because they had been taking longterm low-dose corticosteroid for PMR. One patient in the negative group received a single intravenous dose of 1000 mg methylprednisolone on Day 0 and was excluded from Day 1 corticosteroid dose calculations.

Statistics. Statistical analysis was performed utilizing SPSS software, version 17.0. Data are expressed as means ± standard error. Differences among means of continuous variables were examined using analysis of variance. The Kruskal-Wallis test was used for nonparametric data. Where appropriate, post hoc analyses were performed using Mann-Whitney U tests with Bonferroni corrections. Relationships among categorical variables were examined using chi-square tests with Fisher's exact test where appropriate. Significance was set at the 0.05 level.

RESULTS

Histology. Thirty-three patients with a clinical diagnosis of GCA were available for comparison among the biopsy groups. Temporal artery histopathology revealed that 23 (70%) had evidence of TSVI. Thirteen patients (39%) had evidence of isolated TSVI (Figure 1), 10 (30%) had classically positive biopsies, and 10 (30%) had negative biopsies. All classically positive biopsies were accompanied by TSVI. The proportion of patients that were treated with corticosteroid prior to temporal artery biopsy were similar among the groups (TSVI 11/13; positive 6/10; negative 9/9; p = nonsignificant). Similarly, of those who were treated, the mean number of days of corticosteroid treatment prior to biopsy was not significantly different (TSVI 5.0 days; positive 6.0 days; negative 4.1 days; p = nonsignificant).

Clinical and laboratory comparisons. Clinical manifestations and laboratory features of the patient groups are summarized in Table 1. Mean age and sex distribution were similar among all groups. In the isolated TSVI group, the mean ESR (87 ± 6.6 mm/h) was similar to that in the positive group (92 ± 9.7 mm/h); both were significantly higher than

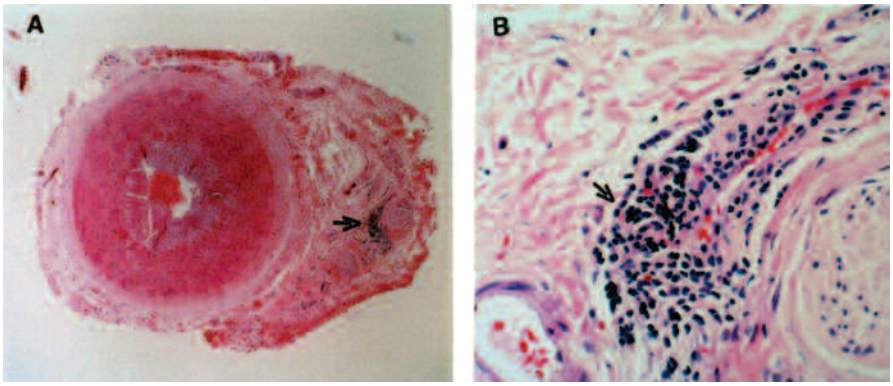

Figure 1. A temporal artery with isolated temporal small-vessel inflammation (TSVI). A. Low power magnification (20×) of isolated TSVI. Note the mononuclear cell infiltration surrounding a small capillary adjacent to a spared temporal artery (arrow). The infiltrate extends into the connective tissue in the vicinity of a nerve bundle. B. Higher power magnification (100×) of A, showing infiltration of the temporal artery small vessels (arrow) (both H&E stain).

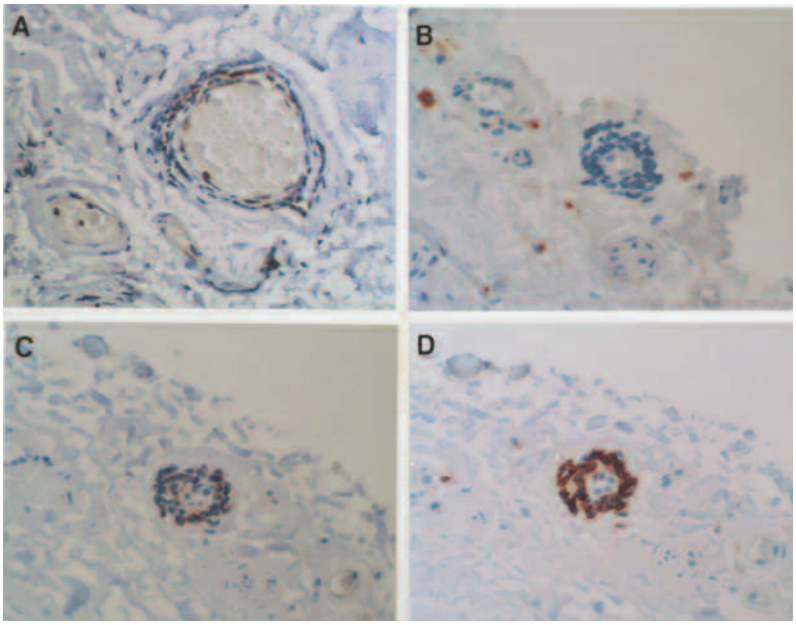

Figure 2. Immunohistochemical staining in isolated temporal small-vessel inflammation (TSVI). Cross-sectional view (100×). (A) CD3 T cells. (B) CD68 macrophages. (C) CD20 B cells. (D) Leukocyte common antigen. Note the comparable proportion of CD3 T cells and CD20 B cells in isolated TSVI infiltrates.

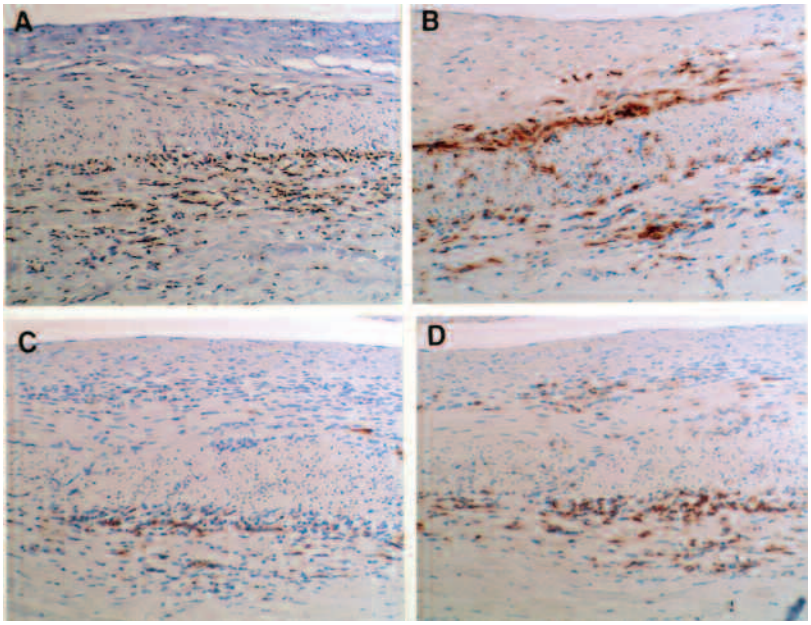

Figure 3. Immunohistochemical staining in vessel wall of giant cell arteritis shows T cell-predominant infiltrates. Longitudinal section (200×). (A) CD3 T cell. (B) CD68 macrophage. (C) CD20 B cell (L26). D. Leukocyte common antigen.

ESR in the negative group (62 ± 9.4 mm/h; p = 0.026 and p = 0.029, respectively). The percentage of patients with PMR symptoms was highest in the TSVI group (63%) and was significantly greater than the percentage with PMR in the positive group (30%; p = 0.040). Compared to patients in the positive group, patients with TSVI tended to have less jaw claudication (15% vs 40% in the positive group) and temporal artery abnormality (39% vs 70%) than patients in the isolated TSVI group (p = nonsignificant). No patient in any of these groups had permanent visual loss attributed to GCA. Specific visual manifestations are listed in Table 1. Although the frequency of visual symptoms at presentation was higher in the isolated TSVI and negative groups than in the positive group, these differences were not significant. One hundred percent of patients with positive biopsies, 70% of patients with negative biopsies, and 62% of TSVI patients fulfilled the ACR 1990 criteria for the classification of GCA[2]. For these purposes, TSVI was not considered to represent a positive biopsy. Patients had a minimum followup of 53 months, during which time no other vasculitic or other inflammatory condition was discovered.

Patterns of corticosteroid treatment. One hundred percent of patients received corticosteroid at the initial rheumatologic evaluation. Corticosteroid doses ≥ 40 mg prednisone daily were used at Day 1 in 100% of positive biopsy patients, 85% of isolated TSVI patients, and 90% of negative biopsy patients (p = nonsignificant). There were no differences among the mean dose for the groups at Day 1 (positive group 56 ± 4 mg; TSVI group 61 ± 15 mg; negative group 51 ± 8 mg; p = nonsignificant), but the mean dose diverged by Day 30 (positive group 52 ± 4 mg; TSVI group 42 ± 10 mg; negative group 30 ± 7 mg; p = 0.060) and became significantly different by Day 60 (positive group 39 ± 4 mg; TSVI group 28 ± 6 mg; negative group 21 ± 5 mg; p = 0.018). Patients with positive biopsies received significantly higher doses than patients with negative biopsies at Day 60 (p = 0.008). Overall, patients with TSVI received doses that were intermediate between patients with positive and those with negative biopsies (p = nonsignificant). At Day 60, the TSVI group continued to receive less steroid than the positive group (p = 0.057) and 2 patients experienced flare in the isolated TSVI group between Day 60 and Day 90. The first patient had loss of peripheral vision, bilateral temporal artery tenderness, and jaw claudication on Day 78 while taking prednisone 9 mg. The second patient had a recurrence of headache on Day 86 while taking prednisone 10 mg. Both patients responded to an increase in oral corticosteroid. No flares were noted in the patients in the positive biopsy group.

Table 1. Presenting clinical and laboratory characteristics.

Characteristics	Positive	Isolated TSVI	Negative
No. patients	10	13	10
Age, mean ± SEM yrs	70 ± 2.9	75 ± 2.0	76 ± 3.2
Female:male	6:4	8:5	10:0
Headache, % (n)	70 (7)	54 (7)	90 (9)
Scalp tenderness, % (n)	30 (3)	23 (3)	20 (2)
Temporal artery abnormality, % (n)	70 (7)	39 (5)	40 (4)
PMR*, % (n)	30 (3)	77 (10)	50 (5)
Jaw claudication, % (n)	40 (4)	15 (2)	30 (3)
Any visual symptom, % (n)	10 (1)	38 (5)	50 (5)
Diplopia, % (n)	0	0	10 (1)
Blurred vision, % (n)	10 (1)	23 (3)	30 (3)
Diminished visual acuity, % (n)	0	15 (2)	10 (1)
Fever, % (n)	40 (4)	23 (3)	0
Weight loss, % (n)	20 (2)	31 (4)	20 (2)
ESR, mm/b, mean ± SEM**	92 ± 9.7	87 ± 6.6	62 ± 9.4
Hemoglobin, g/dl, mean ± SEM†	11.8 ± 0.3	12.0 ± 0.6	12.5 ± 0.6

* Isolated TSVI vs positive, p = 0.040. ** Isolated TSVI vs negative, p = 0.026; positive vs negative, p = 0.029. † Hemoglobin was not reported in 1 from the negative group prior to initiating corticosteroid therapy and was not calculated in the mean hemoglobin. TSVI: temporal small-vessel inflammation; PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate.

Immunohistochemistry (Table 2 and Figures 2 and 3). Semiquantitative analysis of immunohistochemical staining was utilized to examine the cellular composition of the inflammatory infiltrates in isolated TSVI compared to infiltrates surrounding small vessels adjacent to positive temporal arteries (SV). In addition, comparisons were made to infiltrates in the adventitia (ADV) and at the IEL region of positive temporal arteries. On H&E staining, the small-vessel infiltrates adjacent to the positive temporal arteries were indistinguishable from the small-vessel infiltrates in isolated TSVI. Overall, CD68-positive macrophages in isolated TSVI displayed approximately one-half the staining intensity seen within the vessel wall of the involved temporal arteries. However, the level of CD68-positive macrophage infiltration was similar in isolated TSVI and the small vessels adjacent to a positive temporal artery. As reported by Banks, *et al*[8], there were significantly greater numbers of T cells as compared to B cells in the involved temporal artery. In a composite analysis of the regions we studied (ADV + IEL + SV), the ratio CD3:CD20 was nearly 2. However, when specific regions were analyzed separately, the T cell predominance was not as strong in the small vessels representing isolated TSVI or in the small vessels surrounding a positive temporal artery (CD3+:CD20+ = 1.33 and 1.60, respectively) compared to the GCA IEL region (CD3+:CD20+ = 2.30; p < 0.05).

DISCUSSION

In our study, all patients with positive biopsies, i.e., intramural inflammation, exhibited inflammation in the small vessels external to the temporal artery. Importantly, we also observed this finding entirely external to uninvolved temporal arteries in a significant percentage (39%) of biopsies in patients clinically diagnosed with GCA. In this report we refer to this small-vessel involvement in the absence of temporal arteritis as isolated temporal small-vessel inflammation (TSVI) rather than vasculitis because intramural infil-

Table 2. Immunohistochemistry of inflammatory cell infiltrates surrounding small vessels in isolated temporal small-vessel inflammation (TSVI), small vessels surrounding a positive temporal artery (GCA SV), and intramural regions within a positive temporal artery. Surface marker expression was measured by a semiquantitative scale and reported as relative intensity: 0 = no infiltration; +1 = 1%-10% inflammatory cells; +2 = 11%–50% inflammatory cells; and +3 ≥ 50% inflammatory cells. Data represent the mean of 7 specimens (4 isolated TSVI and 3 GCA).

Location	Relative Intensity				
	CD68 Macrophages	CD3 T Cells	CD20 B Cells	LCA	T:B cell Ratio
Isolated TSVI	+0.75	+2.33	+1.75	+3.00	1.33*
GCA SV	+0.66	+2.66	+1.66	+3.00	1.60*
GCA ADV	+2.00	+3.00	+1.66	+3.00	1.81
GCA IEL	+2.00	+2.30	+1.00	+2.30	2.30
SV + ADV + IEL (GCA composite)	+1.55	+2.65	+1.44	+2.77	1.90

* $p < 0.05$ for isolated TSVI and GCA SV compared to GCA IEL. GCA: giant cell arteritis; SV: small vessels (surrounding involved temporal artery); ADV: adventitia; IEL: internal elastic lamina; LCA: leukocyte common antigen.

tration and/or wall damage of the small vessels was not noted. Nonetheless, certain aspects of the clinical profile and treatment course suggest that isolated TSVI behaves as a subset of GCA.

In a retrospective study of temporal artery biopsies, Chakrabarty and Franks described periarterial lymphocytic infiltration[3]. These authors included cases examined utilizing routine histologic levels, those examined by single section, and those in whom additional levels were obtained if periarterial lymphocytic infiltration was observed on single section. Importantly, 2 patients who were initially considered to have only periarterial lymphocytic infiltration were found to have GCA on further review of the biopsy. In the biopsies studied by these authors, periarterial lymphocytic infiltration was ultimately seen in 16%; GCA was identified in 14%[3]. These data contrast with the 39% and 30% of isolated TSVI and positive biopsies, respectively, seen in our cohort. These differences in prevalence rates may be due in part to patient selection and subspecialty referral bias. One important distinction between TSVI and the findings described by Chakrabarty and Franks is that their description also includes involvement of vasa vasorum in the adventitia.

In a retrospective study, Corcoran, *et al* compared temporal artery biopsies displaying chronic perivascular inflammation without evidence of temporal arteritis to a group of specimens without inflammation[4]. None of the patients had evidence of systemic vasculitis. The study concluded that patients with isolated small-vessel inflammation lacked significant differences in clinical and treatment variables compared to patients with negative temporal artery biopsies, thus making the clinical significance of isolated small-vessel inflammation somewhat uncertain. Our TSVI study population contrasted with the population of Corcoran, *et al* in headache frequency, ESR, PMR, and temporal artery abnormality (Table 3). One hundred percent of our TSVI group responded to steroid treatment compared to 60% of the small-vessel vasculitis group described by Corcoran, *et al*[4]. An important difference is that our study population was evaluated by rheumatologists. Indeed, fulfillment of > 3 ACR criteria for GCA was observed in 62% of our TSVI group compared to 23% described by Corcoran, *et al*[4]. Thus, these differences suggest that our study population was more likely to have had clinical features in common with biopsy-proven temporal arteritis and may account for the difference in treatment response.

Disdier, *et al* described 28 patients in whom temporal artery biopsy revealed isolated vasculitis of vasa vasorum[9]. PMR/GCA was diagnosed or strongly suspected in 6. The others had a variety of systemic disorders that included rheumatologic and infectious diagnoses; these patients, however, presented with diffuse systemic inflammatory disease and did not display clinical characteristics of GCA. In addition, there have been case reports of lymphomatous involvement of small vessels surrounding the temporal artery[10,11]. Chiu, *et al*[12] found evidence of granulomatous arteritis in a branch artery adjacent to a normal temporal artery in a patient undergoing evaluation for symptoms suggestive of PMR/GCA; the patient was ultimately found to have Wegener's granulomatosis. In a study of patients with GCA and/or PMR[6], the authors included a control group; these controls all had negative temporal artery biopsies and did not have either GCA or PMR. These 49 controls had various diagnoses and small-vessel vasculitis was seen in only 1 specimen (2%). Thus, while small-vessel involvement may not be entirely specific for GCA, its occurrence appears to be very low in a sample where GCA/PMR was carefully excluded.

Esteban, *et al*[5] described a heterogeneous group of small-vessel vasculitides surrounding a spared temporal artery (SVV-STA), which these authors classified as (1) a GCA-related small-vessel vasculitis, similar to our isolated

Table 3. Studies describing clinical and pathological features of patients with isolated small-vessel (SV) inflammation on temporal artery biopsy (TAB).

Characteristic	Current Report	Esteban[5]	Chatelain[6]	Corcoran[4]
No. (total)	41	58	490	157
Study population	GCA	SVV–STA + comparator GCA	GCA and PMR	SV vasculitis on TAB
SV inflammation, n	13	28	35	81
SV considered GCA, n	13	12	17	27
Clinical features*				
Male:female	0.63	0.5	0.94	0.47
Age, mean yrs	75	71	75	71
Headache, %	54	50	34	40
Jaw claudication, %	15	0	23	6
PMR, %	77	67	86	17
TA abnormal, %	39	8	17	10
Fever, %	23	33	17	16
Weight loss, %	31	25	11	3
Visual symptoms, %	38	33	20	46
ESR, mean mm/h	87 (100% > 50)	96% > 50	72	64% > 50
Pathology*				
Main TA infiltrate	—	—	—	—
Small-vessel mononuclear infiltrate	+	+	+	+
Polymorphonuclear cells	—	+**	—	—
Fibrinoid necrosis	—	—†	—	—
Lymphocyte phenotype	Small vessel T:B cell ratio = 1.33	ND	ND	ND

* Data represent isolated small-vessel involvement in giant cell arteritis (GCA) (this report and Esteban, *et al*[5]); small-vessel involvement in GCA and/or polymyalgia rheumatica (PMR) (Chatelain, *et al*[6]); and small-vessel involvement in a 10-year sample of TAB, multiple diagnoses (Corcoran, *et al*[4]). ** Utilized immunohistochemistry to detect polymorphonuclear cells. † Fibrinoid necrosis seen in small vessels in patients with small-vessel vasculitis but not GCA. SVV-STA: small-vessel vasculitis with spared temporal artery; ND: not done.

TSVI; (2) a systemic necrotizing vasculitis that was associated with polyarteritis nodosa; and (3) unclassifiable. Esteban, *et al* also compared these groups to their cohort with biopsy-proven GCA. Fibrinoid necrosis was found only in the systemic necrotizing vasculitis subgroup. None of our study patients exhibited clinical findings or pathological findings that would be consistent with polyarteritis nodosa or other systemic necrotizing vasculitides.

Our TSVI group shared several clinical characteristics with the subset of patients described by Esteban, *et al* as SVV-STA, whom the authors considered to have GCA[5]. These include PMR, fever, weight loss, age, ESR > 50 mm/h (Table 3), and pre-biopsy fulfillment of ACR criteria (62% and 50%). The clinical and pathologic data displayed in Table 3 are most directly comparable for this report and for the study of Esteban, *et al*, as these data represent only cases of small-vessel involvement that were felt to have GCA. In addition, our study demonstrates similar clinical differences between isolated TSVI and classically positive biopsies in PMR, fever, headache, and jaw claudication when compared to small-vessel vasculitis classified as GCA versus biopsy-proven GCA as reported by Esteban, *et al*[5]. The similarities between our data and those published by Esteban, *et al* support the usefulness of considering isolated small-vessel involvement as a subset of GCA.

Recently, Chatelain, *et al* described small-vessel vasculitis surrounding an uninflamed temporal artery in 7% of 490 patients diagnosed with GCA (biopsy-positive or negative) and/or PMR[6]. Like the data of Chatelain, *et al* our patients with isolated small-vessel involvement had PMR symptoms twice as often as biopsy-positive patients as well as having less frequent headache, temporal artery abnormality, and jaw claudication. Chatelain, *et al* suggest that the findings of small-vessel vasculitis may serve as a pathologic marker for PMR[6]. While there may be an overrepresentation of PMR in our subgroup with isolated TSVI, these patients all had additional signs and symptoms of GCA that led the rheumatologist to obtain a temporal artery biopsy. Thus, it is likely that the threshold for temporal artery biopsy is lower among patients with PMR who report possible GCA symptoms than in such patients without a history of PMR. In this setting, it is possible that TSVI may represent an early manifestation of GCA and may identify a subset of PMR with a higher risk of developing overt GCA. That small-vessel disease might represent an early stage in the development of GCA is supported by studies that suggest leukocytes enter the temporal artery via the periphery of the vessel[13,14].

We observed that the initial mean corticosteroid doses

were similar among all groups, which probably reflected the clinician's desire to treat in order to prevent ischemic complications while awaiting the final laboratory and pathological data. Regardless, patients with isolated TSVI received consistently higher corticosteroid doses throughout the study treatment period than patients with negative biopsies, suggesting that clinicians perceived a higher probability of disease. Despite similar initial mean corticosteroid dose and clinical characteristics, patients with isolated TSVI received corticosteroid doses that were intermediate between the positive and the negative groups. This may in part have been secondary to the clinician receiving a pathology report that was not diagnostic of temporal arteritis. It is interesting that 2 patients with isolated TSVI experienced flare, whereas none of the patients with positive biopsies did so. This suggests that lack of classical histopathologic features on the biopsy report may have influenced the rate of corticosteroid taper in the isolated TSVI cohort and that the TSVI patients may have been tapered too rapidly. Additionally, patients with TSVI may have disease that is more difficult to suppress than biopsy-negative patients. Recently, ter Borg, *et al*[15] suggested that patients with atypical histopathologic features on temporal artery biopsy more closely resembled classical GCA (elevated ESR, anemia, and complications including blindness and cerebrovascular accident) and should be treated with higher doses of corticosteroid; in contrast, patients with histologic evidence of healed arteritis might be adequately treated with lower doses of corticosteroid.

Comparing reports of small-vessel involvement in the literature is hampered by difficulty in identifying the precise nature and/or source of these small vessels. Small vessels in the vicinity of the temporal artery may be small artery branches, arterioles, capillaries, or venules. Some of these vessels may be extensions of those entering or exiting and serving as nutrient vessels for the temporal artery, i.e., vasa vasorum[16], but it is difficult to discern this on standard histopathologic sections. Further, delineation by investigators of the external limit of the adventitia has been variable. In our study, we took particular care to restrict our TSVI group to those specimens that demonstrated inflammation limited to the extramural small vessels.

To begin to determine if inflammatory infiltrates associated with the small vessels external to the temporal artery differ from those found intramurally, we performed immunohistochemical phenotyping. Studies have shown that the inflammatory infiltrate in the temporal artery is composed predominantly of T cells, macrophages, and giant cells, with fewer B cells[17,18]. Our data show significantly fewer macrophages in isolated TSVI as well as in TSVI surrounding a positive biopsy as compared to the intramural infiltrates. The relative paucity of CD68-positive macrophages in this region is not surprising, since it has been shown that a major role of macrophages in GCA is intramural granuloma formation and destruction of internal elastic lamina[19]. Nearly equal numbers of T cells and B cells were found in the infiltrates of isolated TSVI and in TSVI associated with positive biopsies; this is in contrast to the T cell predominance found in the vessel wall of positive biopsies. The potential role of B cells in the inflammatory infiltrates of the extramural small vessels in GCA requires further clarification.

A limitation of this retrospective study is the small sample size. In addition, control biopsies in patients without symptoms of PMR and/or GCA were not available. Review of pathology specimens was limited to sections cut for routine diagnostic purposes; it is possible that inflammation within the main temporal artery wall may have been found if additional sections had been cut on cases categorized as TSVI. Of note, not all surgical specimens may have contained sufficient tissue surrounding the temporal artery to collect equivalent areas for small-vessel analysis. Lastly, in our cohort, the majority of patients had brief exposure to corticosteroid prior to biopsy. Although the mean pre-biopsy corticosteroid treatment period for the entire cohort was only 5 days, we cannot exclude alteration of the histopathologic phenotype[20,21]. However, this effect was likely negligible since no significant differences were noted among the groups in the proportion of patients treated with corticosteroid prior to biopsy, nor were there significant differences in the intervals between initiation of corticosteroid therapy and performance of temporal artery biopsy.

A significant percentage of our patients undergoing temporal artery biopsy demonstrated isolated temporal small-vessel inflammation. Immunohistochemical phenotype, clinical features suggestive of an acute-phase response, and the requirement for moderate to high-dose corticosteroid to suppress clinical manifestations suggests that, in the absence of other systemic illness, isolated temporal small-vessel inflammation defines a subset of the spectrum of GCA. Inclusion of more soft tissue surrounding the main temporal artery on surgical biopsy appears to enhance diagnostic yield. Inflammation surrounding the small blood vessels in tissue extramural to the temporal artery should be strongly considered in the interpretation of temporal artery biopsies and subsequent treatment decisions.

Note added in proof. In a preliminary report, Restuccia, *et al* described small-vessel vasculitis surrounding an uninflamed temporal artery in a population-based Italian study[22].

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