The Significance of Perivascular Inflammation in the Absence of Arteritis in Temporal Artery Biopsy Specimens

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Key Words: Vasculitis; Temporal arteritis; Giant cell arteritis

Abstract

We retrospectively compared 81 temporal artery biopsy specimens demonstrating perivascular inflammation without evidence of temporal arteritis and 76 specimens demonstrating no inflammation. Patients with perivascular inflammation included 43 women (mean age, 71.2 years). Nineteen patients met the 1990 American College of Rheumatology (ACR) criteria for the diagnosis of temporal arteritis. All patients demonstrated chronic perivascular inflammation consisting primarily of lymphocytes. Granulomas were noted in 4 specimens. Internal elastic lamina disruption, intimal fibroplasia, and dystrophic calcification were noted in 86 arteries examined. Fibrosis or scarring of the vessel walls was observed in 10 specimens. Corticosteroid therapy was beneficial to 33 of 56 patients. In patients with no evidence of inflammation (50 women; mean age, 66.6 years), 21 met ACR criteria for temporal arteritis. Histologically, disruption of the elastic lamina was noted in 75 of 81 arteries biopsied, intimal fibroplasia in 66, microcalcifications in 5, and fibrosis or scarring in 5. In this group, 47 patients received corticosteroid therapy; clinical improvement was noted in 28. Patients with chronic perivascular inflammation but no arteritis seem no more likely to have temporal arteritis on clinical grounds than similar patients without inflammation on biopsy.

Temporal arteritis has been long recognized as a distinct entity since its initial description in the literature in 1890 by Hutchinson. Epidemiologic studies have shown an incidence rate of up to 30 cases per year per 100,000 persons older than 50 years in some populations. Temporal artery biopsy has long been advocated for patients in whom a diagnosis of temporal arteritis is suspected. Because of the potential complications of corticosteroid therapy, biopsy confirmation of the diagnosis is reassuring before initiating treatment. The histopathologic diagnosis is predicated on the recognition of a lymphohistiocytic infiltration of the temporal artery wall, frequently accompanied by multinucleated giant cells. Temporal arteritis is notoriously patchy, with the false-negative biopsy rate, as determined by correlation with clinical findings, reported as 42% to 61% in published series. Histopathologic parameters that would permit reclassification of these false-negative biopsies as “positive” or “probable” temporal arteritis have yet to be identified, if in fact they exist. The significance, in particular, of perivascular inflammation adjacent to the artery has not been determined. We attempted to study this issue by retrospectively reviewing a series of such temporal artery biopsy specimens that were marked by chronic perivascular inflammation but demonstrated no evidence of vasculitis.

Materials and Methods

All available temporal artery biopsy specimens from January 1990 to December 1993 were reviewed retrospectively. After histologic review, biopsy specimens were placed into 1 of 3 categories: (1) arteries with definite evidence of
active arteritis, (2) arteries with chronic perivascular inflammation but no definite evidence of arteritis, or (3) biopsy specimens that showed no evidence of inflammation. The presence of inflammation, generally lymphocytic or granulomatous in nature, within the artery wall was required to make a diagnosis of temporal arteritis. In each case, H&E-stained sections and Movat pentachrome–stained sections of artery were reviewed. Arteries were sectioned into 2 to 14 pieces (mean, 5.0 pieces). The number of levels generated from the paraffin block ranged from 2 to 58 (mean, 13.5 levels). Discrepancies between the original diagnosis and diagnosis on review was resolved by majority consensus of the authors.

Since the focus of this study was on the cases with perivascular inflammation and no active arteritis, all 81 cases with this histologic finding were included. A comparison group of 76 cases without evidence of inflammation on biopsy also was evaluated. Histopathologic features evaluated included the presence of perivascular inflammation and the types of inflammatory cells observed in the infiltrate, disruption of the internal elastic lamina, fibrosis or scarring of the vessel wall, presence of granulomas, evidence of intimal fibroplasia, microcalcifications, and thrombosis. In each case, the medical records were reviewed for clinical information, including the age and sex of the patient at the time of biopsy, site of biopsy, erythrocyte sedimentation rates (ESRs) before biopsy (within 1 week and before treatment) and at the most recent follow-up after the biopsy, symptomatology that resulted in the patient seeking treatment, clinical impression at the time of biopsy, and information about corticosteroid therapy and responsiveness to therapy. In each case, particular note was made about whether the patient fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of giant cell arteritis.

The criteria include the following: (1) age at disease onset, 50 years or older; (2) onset of new headaches; (3) temporal artery tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of cervical arteries; (4) ESR, 50 mm/h or more by the Westergren method; and (5) a biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells. The presence of at least 3 of these 5 criteria has been associated with a sensitivity of 93.5% and a specificity of 91.2% for the diagnosis of giant cell (temporal) arteritis.

The control and perivascular inflammation groups were compared on the proportion meeting the individual ACR criteria (any 3 of the 5 criteria) with chi-square tests.

**Results**

The cases included for study were divided into 2 groups, including those without evidence of inflammation on biopsy and those with chronic perivascular inflammation but no evidence of arteritis. Seventy-six cases constituted the former group and 81 cases the latter group.

**Biopsy Specimens Devoid of Inflammation**

For 76 patients, including 50 women and 26 men, biopsy specimens were devoid of inflammation. Patient ages at the time of biopsy ranged from 30 to 84 years (mean, 66.6 years). The most common signs and symptoms before biopsy included headache in 35 patients, visual disturbances in 22 patients, localized tenderness in the region of the temporal artery or scalp in 9 patients, fever of unknown origin in 8 patients, joint pain in 7 patients, generalized weakness or malaise in 5 patients, and myalgias in 5 patients. Less frequently encountered manifestations included jaw claudication in 3 patients, weight loss in 3 patients, peripheral ischemic changes in 2 patients, back pain in 2 patients, and periorbital pain in 1 patient. ESRs determined using the Westergren method 1 week or less before biopsy were performed in 65 patients. ESRs ranged from 1 to 131 mm/h (mean, 62.4 mm/h). For 41 patients (63%), the ESR was 50 mm/h or more.

The clinical impression recorded in the medical record before biopsy included giant cell arteritis for 31 patients, optic ischemia or vascular disease for 9 patients, and polymyalgia rheumatica for 11 patients. For 9 patients, no impression was recorded. Of the remaining patients, a wide
variety of other diagnoses were considered clinically (in 1 or 2 patients each), including Sjögren syndrome, macular degeneration, tension headache, suboccipital neuralgia, autoimmune disease not otherwise specified, myopia, diabetic retinopathy, disease of psychiatric origin, migraine headaches, rheumatoid arthritis, complications of surgery, adenoid cystic carcinoma, and trigeminal neuralgia. When the ACR criteria were applied, 21 patients had a score of 3 or more, meeting the ACR criteria for temporal arteritis; 40 met 2 of 5 ACR criteria, 14 met 1 of 5 ACR criteria, and 1 met none of the ACR criteria. The features of both study groups are summarized in Table 1.

For 35 patients, the biopsy was on the right side, and for 36, it was on the left side. In the remaining 5 patients, bilateral temporal artery biopsies were performed. Histologically, none of the biopsy specimens showed evidence of inflammation. Disruption of the elastic lamina was identified in 75 of 81 arteries evaluated. Intimal fibroplasia was observed in 66 of 81 biopsy specimens. Less common findings included calcification within the vessel wall in 15 arteries and focal evidence of fibrosis or scarring of the vessel wall in 5 biopsy specimens.

After biopsy, 47 patients underwent a course of corticosteroid therapy. Of this group, 28 patients were believed to have benefited from corticosteroid treatment. Nineteen patients who received corticosteroid therapy did not seem to have clinically significant improvement of symptoms. In none of the patients did the clinical course worsen after corticosteroid therapy. Of the 22 patients who fulfilled the ACR criteria for the diagnosis of temporal arteritis, 13 received corticosteroids. The condition of 8 of these 13 patients improved with corticosteroid therapy, and in 5 patients, no improvement was noted. ESRs at the most recent follow-up were known for 32 patients and ranged from 3 to 108 mm/h (mean, 35.7 mm/h). Eight (25%) of 32 patients had ESRs of 50 mm/h or more. For 30 of the 32 patients, the most recently documented ESR was decreased compared with the prebiopsy ESR.

Arteries With Chronic Perivascular Inflammation
For 81 patients, including 43 women and 38 men, biopsy specimens demonstrated chronic perivascular inflammation. At the time of biopsy, the patients ranged in age from 38 to 96 years (mean, 71.2 years). ESRs performed within 1 week of the biopsy in 72 patients ranged from 3 to 131 mm/h (mean, 65.5 mm/h). In 1 additional patient, the ESR was recorded in the medical record as being “normal” without a specific value noted. For 46 (64%) of 72 patients, the ESR was 50 mm/h or more. The most common signs or symptoms before biopsy included visual changes in 37 patients, headache in 32 patients, myalgias in 14 patients, fever of unknown origin in 13 patients, generalized fatigue or malaise in 11 patients, and point tenderness of the scalp or area overlying the temporal artery in 8 patients. Additional less common manifestations included jaw claudication in 5 patients, weight loss in 2 patients, generalized paresthesias in 1 patient, nausea in 1 patient, and mental status changes in 1 patient.

The clinical impression with regard to diagnosis recorded at the time of biopsy included giant cell arteritis for 27 patients, polymyalgia rheumatica for 13 patients, infectious cause for 8 patients, and ischemia- or hypertension-related disease for 5 patients. For 5 patients, the clinical impression was not recorded. For the remaining patients (3 or fewer for each), the clinical impression included retinal artery thrombosis, thromboembolic disease, trigeminal neuralgia, tension headache, cluster headache, glaucoma, diabetic retinopathy, cataracts, rheumatoid arthritis, tumor, peripheral neuropathy, or polyarteritis nodosa. When the ACR criteria were applied, 19 patients met 3 of the criteria for the diagnosis of temporal arteritis; 47 met 2 ACR criteria, and 15 met only 1 criterion.

For 39 patients, the biopsy was on the left side, and for 35, it was on the right side. For 2 patients, the side of the temporal artery biopsy was not designated. For the 5 remaining patients, bilateral temporal artery biopsies were performed.

Table 1
Comparison of Salient Features (American College of Rheumatology [ACR] Criteria)*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Without Inflammation (n = 76)</th>
<th>With Inflammation (n = 81)</th>
<th>P</th>
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<tbody>
<tr>
<td>Headache</td>
<td>35 (46)</td>
<td>32 (40)</td>
<td>.67</td>
</tr>
<tr>
<td>Temporal artery tenderness</td>
<td>9 (12)</td>
<td>8 (10)</td>
<td>.28</td>
</tr>
<tr>
<td>Older than 50 y</td>
<td>69 (91)</td>
<td>77 (95)</td>
<td>.9</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate &gt;50 mm/h†</td>
<td>41 (63)</td>
<td>46 (64)</td>
<td>.68</td>
</tr>
<tr>
<td>Biopsy-proved temporal arteritis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>ND</td>
</tr>
<tr>
<td>Met 3 of 5 ACR criteria</td>
<td>21 (28)</td>
<td>19 (23)</td>
<td>.55</td>
</tr>
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ND, not done.
† Data are given as number of cases with feature (percentage).
* Data are given as number of cases with feature (percentage).
All 86 arteries from 81 patients demonstrated chronic perivascular inflammation consisting of lymphocytes. Plasma cells were noted in 3 biopsy specimens, rare neutrophils in 2 biopsy specimens, and eosinophils in 1 biopsy specimen. In 4 biopsy specimens, nonnecrotizing granulomatous inflammation was identified in the soft tissue adjacent to the temporal artery, including 1 case of foreign body giant cell reaction to suture material. Focal disruption of the internal elastic lamina was noted in 79 biopsy specimens and intimal fibroplasia in 76 arteries. Twenty-one arteries demonstrated focal dystrophic mineralization within the vessel wall. Focal fibrosis or scarring of the temporal artery was identified in 10 biopsy specimens. Organizing thrombosis was noted in 1 specimen. Of the 5 patients who underwent bilateral biopsies, inflammation was noted in specimens from both sides in 3 cases and was unilateral in 2 cases. In none of these cases was there infiltration of the arterial wall by inflammatory cells.

Fifty-six patients received corticosteroid therapy after biopsy. Of this group, an improvement was noted clinically in 33 patients, and in 23 patients no clinical improvement was observed. Of the 19 patients who met ACR criteria for the diagnosis of temporal arteritis, 14 received corticosteroids. Of these 14 patients, 8 experienced clinical improvement after corticosteroid therapy, and in 6 patients, no clinically significant improvement was noted from the corticosteroid therapy. ESRs at the most recent follow-up after biopsy were documented for 40 patients and ranged from 2 to 130 mm/h (mean, 32.1 mm/h). For 33 of the 40 patients, the ESR was decreased compared with the prebiopsy ESR. For 6 patients, the most recent ESR was elevated compared with the ESR performed before biopsy; for 1 patient, the ESR was the same.

In 19 cases, the perivascular inflammatory changes were misinterpreted as vasculitis in the biopsy specimen. This group of patients included 10 women and nine men who ranged in age from 59 to 96 years (mean, 73.9 years). ESRs before biopsy in this group ranged from 25 to 134 mm/h (mean, 82.2 mm/hr). Of the 19 patients, 14 met 3 or 4 of the ACR criteria and clinically had vasculitis. All 19 patients underwent a course of corticosteroid therapy, including all 5 patients who did not meet ACR criteria for temporal arteritis. Complications of treatment included avascular necrosis, which required hip replacement in 2 patients; sepsis in 1 patient; mycobacterial pneumonia and depression exacerbated by corticosteroid therapy in 1 patient; Cushing syndrome in 1 patient; and the development of glucose intolerance attributable to corticosteroid therapy in 1 patient.

Discussion

Vasculitis generally has been defined as an inflammatory disease involving blood vessels in which there is infiltration of the vessel walls by inflammatory cells, usually associated with some degree of vascular wall injury. A number of forms of vasculitis, including giant cell arteritis, typically involve medium-sized arterial vessels. In addition to a chronic inflammatory cell infiltrate consisting primarily of lymphocytes, giant cell arteritis often is marked by the presence of multinucleated giant cells and histiocytes within the vessel wall. Giant cell arteritis most commonly affects the superficial temporal artery and often is referred to clinically in this setting as temporal arteritis.

A positive temporal artery biopsy specimen is confirmatory of the diagnosis of giant cell temporal arteritis. However, it is well recognized that not all patients with the clinical syndrome have histologic features of vasculitis demonstrable in the biopsy specimen. The vasculitis may be present only focally in an arterial segment. Klein and colleagues reported evidence of segmental inflammation in 28% of cases (17/60) of temporal arteritis. They documented foci of arteritis as short as 330 µm in otherwise normal biopsy specimens. Others have reported lower rates of skip lesions. The presence of skip lesions might explain at least a subset of the cases of clinically evident temporal arteritis that fail to demonstrate the histopathologic features of vasculitis.

In a subset of biopsy specimens in which there is no definite evidence of vasculitis, perivascular-based chronic inflammation may be noted, consisting mainly of lymphocytes. The significance of this finding has not been well established. The present study attempted to examine this...
particular issue by comparing this group of biopsy specimens with those devoid of inflammation. Using ACR criteria for the diagnosis of temporal arteritis, both of these groups were somewhat similar, with 23% of patients with chronic perivascular inflammation fulfilling at least 3 of the ACR criteria for the diagnosis of temporal arteritis vs 28% of the patients whose biopsy specimens had no inflammation. A somewhat higher percentage of the biopsy specimens that had some form of inflammation also demonstrated other pathologic features suggestive of arteritis, including fibrosis or scarring of the vessel wall in 10 cases and evidence of necrotizing granulomas outside the vessel wall in 4 specimens, compared with only 5 cases of vessel wall scarring in the biopsy group without inflammation. Although there are some concomitant pathologic findings to suggest that perhaps a slightly higher percentage of patients who have perivascular inflammation may have arteritis, there does not seem to be a significant difference on clinical grounds between this group and the patients whose biopsy specimens lacked inflammation. Findings of intimal fibroplasia and disruption of the elastic lamina were common in both groups and likely represent features of aging arteries, not necessarily healed arteritis.

Besides the presence of skip lesions, a number of other factors theoretically may determine the yield of temporal artery biopsy, including the clinical threshold for performing the procedure,\(^{10,11}\) whether unilateral or bilateral biopsies are performed,\(^{12}\) and the length of the artery sampled. From a histopathologic standpoint, the extent of sampling or sectioning theoretically may be a factor as well. This raises the question about the value of examining multiple levels in biopsy specimens, particularly in cases in which perivascular inflammation is identified but no vasculitis is noted. Recently, Chakrabarty and Franks\(^{13}\) analyzed the cost-effectiveness of examining temporal artery biopsy specimens in this way. Only 1 of 132 initially normal biopsy specimens and 2 of 14 cases with chronic perivascular inflammation revealed giant cell arteritis after examining the tissue at multiple levels. In an additional 15 cases, chronic perivascular inflammation, but not vasculitis, was found on deeper sections. They concluded that routine examination of temporal artery biopsy specimens at multiple levels does not appreciably increase the diagnostic yield of the test, although they acknowledged that selective cases may benefit from further sectioning. Of particular note, the significance of chronic perivascular inflammation did not seem to be elucidated further by additional sectioning (ie, vasculitis was not found in a particularly high number of cases).

The significance of the perivascular inflammation remains somewhat uncertain. It may be a marker, in a small percentage of cases, of associated vasculitis. This may be in the form of residual inflammation from a previous active arteritis or partially treated arteritis or may be indicative of being proximal to an active lesion.\(^{14-16}\) Others have conjectured that small foci of perivascular-based lymphoid cells may be a relatively common finding associated with aging\(^{13}\) and may not be indicative of an inflammatory process. The findings in the present study suggest that the latter explanation may be the case in the majority of instances. Importantly, the ramifications of misinterpreting chronic perivascular inflammation as vasculitis may be significant given the morbidity and mortality associated with corticosteroid therapy documented by others\(^{14,17,18}\) and in the present study in this clinical setting.

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References