

Negative temporal artery biopsies: eventual diagnoses and features of patients with biopsy-negative giant cell arteritis compared to patients without arteritis

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ABSTRACT

Objective. Characterize patients with negative temporal artery biopsies in regard to their eventual diagnoses, and to find features that would differentiate biopsy-negative GCA from non-GCA patients.

Methods. 58 patients with negative biopsies were included. Patients' data and final diagnoses were obtained from medical records. Biopsy-negative GCA was diagnosed when the American College of Rheumatology classification criteria were met, symptoms improved within 3 days of corticosteroid therapy, and no other condition relevant to the patient's symptoms diagnosed during a follow up of 6 months.

Results. Biopsy negative GCA was diagnosed in 11 cases (19%). "Isolated" polymyalgia rheumatica was eventually diagnosed in 5 patients (9%). Altogether, rheumatologic conditions were diagnosed in 23 cases (40%). Other patients (60%) had various hematologic, neurologic-ophthalmic, infectious and malignant disorders. Patients with biopsy-negative GCA were older than non-GCA cases, 81.7 ± 6.2 and 74.8 ± 8 years, respectively ($p=0.05$). Headaches were more common in biopsy-negative GCA patients: 91% of them presented with headaches, compared to only 40% of non-GCA patients ($p=0.005$). Thrombocytosis was more common in patients with biopsy-negative GCA compared to non-GCA patients (73% and 19%, respectively, $p=0.001$). Other clinical and laboratory parameters did not differ significantly between the two groups.

Conclusions. 19% of patients with negative temporal artery biopsies were eventually diagnosed as GCA. Older age, headache and thrombocytosis were more common in that group. These features may help in the diagnostic approach in cases with negative biopsies.

Introduction

Diagnosis of giant cell arteritis (GCA) is based on a combination of signs, symptoms and laboratory evidence of acute-phase reaction. It is confirmed by a temporal artery biopsy (TAB) showing inflammation in the vessel wall with mononuclear cells and sometimes multinucleated giant cells (1, 2). There

are no independent validating criteria to determine whether GCA is present when TAB is negative. The American College of Rheumatology (ACR) criteria for the classification of GCA (3) may assist in diagnosis. However, GCA classification criteria were meant to distinguish patients with GCA from those with other vasculitides, and not from patients with other conditions (4, 5). Classification criteria work best in studying groups of patients, and less well when used for diagnosing individual cases. Thus, the final diagnosis in TAB-negative cases should be based on all clinical features, laboratory findings, and the response to therapeutic trial when indicated.

A negative TAB often makes the diagnosis of GCA uncertain, and necessitates further diagnostic work-up to exclude or to diagnose other conditions. About 15% of all GCA patients are biopsy-negative (6). Several studies reported differences between biopsy-positive and biopsy-negative groups of GCA patients (6-10). However, only 3 studies, none of them recent, looked at the ultimate diagnoses of all patients with TABs that were not showing inflammatory changes (7-9).

We retrospectively studied a group of patients, suspected of having GCA, who underwent TAB that was reported as being negative. The eventual diagnoses of these patients were obtained, trying to find features that would differentiate biopsy-negative GCA patients from non-GCA cases with negative TABs.

Methods

An electronic database search in one medical center (SZMC) was performed, looking for all cases suspected of having GCA, in which a TAB was done during a 5-year period (2000-2004). All arteries were processed routinely according to the commonly accepted approach: the artery was initially fixed in formalin. Thereafter the specimen was cut into serial 2-3mm-long slices, followed by embedding in paraffin. Each of the slices were then cut transversally, and stained with hematoxyline and eosin. A TAB specimen was considered positive if there was a transmural or

Competing interests: none declared.

Table I. Symptoms and laboratory parameters suggestive of giant cell arteritis among 58 patients with negative temporal artery biopsy.

Symptom	Number of patients (%)
Headache	29 (50)
Fever	17 (29)
Shoulder girdle pain	12 (20)
Visual symptoms	10 (17)
Anorexia / weight loss	7 (12)
Jaw claudication	1 (2)
Erythrocyte sedimentation rate >40 mm/h	53 (91)
C reactive protein >0.5 mg/dl	29/34 (85)
Anemia (hemoglobin <12g/dl)	32 (55)
Thrombocytosis (platelets >400x10 ³ /μl)	17 (29)

adventitial/periadventitial mononuclear cell infiltrate, with or without giant cells, in association with disruption of the internal elastic lamina. All TABs were reviewed by a single experienced pathologist, sorting out all negative results. The medical files of those cases were reviewed regarding demographic and clinical data, including results of laboratory tests.

The final diagnoses made by the treating physicians were obtained from the medical records. In a few cases of uncertainty regarding the final diagnosis in the medical center's hospitalization or outpatient records, contact was made with the primary care physician who was following the patient regarding this information.

Patients with negative TAB were diagnosed as biopsy-negative GCA when the ACR classification criteria (3) were met, symptoms and signs of inflammation improved within 3 days of corticosteroid therapy (40 mg/d of prednisone or more), and no other condition relevant to the patient's symptoms was diagnosed during a follow-up period of 6 months. Two rheumatologists (GN, GSB) reviewed the medical information and reached consensus on the diagnosis of biopsy-negative GCA.

Data analysis was performed initially by descriptive statistics. Further analysis, comparing biopsy-negative GCA patients and non-GCA cases with negative TABs, was performed with Fisher's exact

Table II. Final diagnoses of 58 patients with negative temporal artery biopsy.

Diagnosis	Number of patients (%)
Biopsy-negative GCA	11 (19)
Hematologic diseases (non-malignant)	9 (15)
Rheumatologic diseases (other than GCA or PMR)	7 (12)
Neurologic conditions	6 (10)
Polymyalgia rheumatica	5 (9)
Malignant diseases	5 (9)
Non-arteritic anterior ischemic optic neuropathy	3 (5)
Infectious diseases	3 (5)
Fever of unknown origin (FUO)	3 (5)
Atrial myxoma	1 (2)
Thyroiditis	1 (2)
Unknown	4 (7)

Hematologic diseases were anemia of various types (6), monoclonal gammopathy (2) and myelodysplastic syndrome (1). Rheumatologic diseases were rheumatoid arthritis (4), osteoarthritis (1), Churg-Strauss syndrome (1) and probable Lupus (1). The neurological conditions were stroke (2), confusional state (2), tension headache (1) and Tolosa-Hunt syndrome (1). Malignant diseases were multiple myeloma (2), Waldenstrom macroglobulinemia (1), bladder carcinoma and ovarian carcinoma (1 each). The infectious diseases were bacterial endocarditis (2) and sinusitis (1).

test for categorical variables, and Mann-Whitney test for continuous variables.

Results

Sixty two patients had negative TABs. Data were not available for 4 patients. Of the 58 remaining patients, 67% were females. All patients were older than 50 years, mean age was 76±8. All patients had features suggesting a possible diagnosis of GCA. The most common symptom suggestive of GCA was headache, reported by 50% of the patients (Table I). Seventeen patients (29%) had fever >37.5°C. Shoulder girdle pain was reported by 12 patients (20%), but was associated with morning stiffness only in 6 of them. In addition to shoulder pain, 4 patients had pain in peripheral joints. Ten patients presented with ophthalmic symptoms: 5 had episodes of blurring of vision, one had diplopia, and 4 had

sudden vision loss due to anterior ischemic optic neuropathy (AION).

Laboratory parameters of inflammation were increased in most of the patients: erythrocyte sedimentation rate (ESR) was elevated (>40 mm/h) in 91% of the cases. Serum levels of C-reactive protein (CRP) were available in 34 patients, and were increased (>0.5 mg/dl) in 85% of them (Table I). Anemia (hemoglobin <12g/dl) was less common (55%).

The final diagnoses were categorized (Table II): the most common final diagnosis was biopsy-negative GCA. It was diagnosed in 11 cases (19%). In addition, "isolated" PMR was eventually diagnosed in 5 cases (9%). Altogether, rheumatologic conditions were diagnosed in 23 cases (40%). Four patients had AION: non-arteritic AION was eventually diagnosed in 3 of them and only one was diagnosed with GCA and

Table III. Comparison of clinical manifestations suggestive of GCA in 11 patients with biopsy-negative GCA and 47 non-GCA patients with negative temporal artery biopsy.

Clinical symptom	Biopsy-negative GCA n (%)	Other diagnoses n (%)	p
Headache	10 (91)	19 (40)	0.005
Fever >37.5°C	4 (36)	13 (28)	0.71
Ophthalmic symptoms	3 (27)	7 (15)	0.38
Shoulder girdle pain	1 (9)	11 (23)	0.43
Anorexia / weight loss	1 (9)	6 (13)	1.0
Jaw claudication	1 (9)	0	0.19

Table IV. Comparison of laboratory parameters of inflammation in 11 patients with biopsy-negative GCA and 47 non-GCA patients with negative temporal artery biopsy.

Laboratory parameter	Biopsy-negative GCA n (%)	Other diagnoses n (%)	<i>p</i>
ESR (mm/h)	111 ± 37	92 ± 33	0.093
CRP (mg/dl)	8.1 ± 6.6	5.5 ± 5.4	0.16
Hemoglobin (g/dl)	12.0 ± 1.1	11.4 ± 1.4	0.2
leukocyte count (x10 ³ /μl)	11.6 ± 4.4	9.2 ± 3.2	0.17
Platelet count (x10 ³ /μl)	427 ± 145	310 ± 123	0.018
Serum albumin (g/dl)	3.0 ± 0.4	3.4 ± 0.5	0.2

arteritic AION. In 3 patients the final diagnosis was fever of unknown origin (FUO), which resolved without specific therapy. Four patients had spontaneous resolution of their symptoms without reaching a defined diagnosis.

Patients with biopsy-negative GCA were older than non-GCA cases with negative TAB, 81.7±6.2 and 74.8±8 years, respectively ($p=0.05$). Regarding the clinical features, significant difference was found only in occurrence of headaches, which were more common in biopsy-negative GCA patients: 91% of them presented with headaches, compared to only 40% of non-GCA patients ($p=0.005$). No significant difference was observed regarding other clinical features (Table III).

All 11 patients in the group of biopsy-negative GCA patients and 89% of the 47 cases with negative TAB had ESR >40 mm/h. The mean ESR and CRP levels were higher in the group of patients with biopsy-negative GCA compared to the non-GCA patients, but the differences did not reach statistical significance (Table IV).

The mean platelet count was significantly higher in the group of patients with biopsy-negative GCA (427000±145000/μl, compared to 310000±123000/μl, $p=0.018$). Thrombocytosis (platelet count > 400000/μl), was more common in the group of patients with biopsy-negative GCA compared to non-GCA patients with negative TAB (73% and 19%, respectively, $p=0.001$). Other laboratory parameters did not differ significantly among the two groups of patients (Table IV).

Discussion

A negative TAB often makes a diagnosis of GCA uncertain. Several previous

studies already attempted to correlate presenting features with results of TAB (6, 10-12). However, a major concern in GCA is not the ability to accurately predict the results of TAB based on presenting features of each case, but rather to have diagnostic and therapeutic decisions in cases with negative TAB. The aim of this retrospective study was to look specifically at those cases suspected of having GCA in whom TAB was negative, study their eventual diagnoses, and compare presenting features of patients diagnosed as biopsy-negative GCA to those with other eventual diagnoses.

Three other series studied the ultimate diagnoses in patients with negative TAB (7-9).

However criteria for defining biopsy-negative GCA cases were not specified in those reports, and differentiation between biopsy-negative GCA and non-GCA patients regarding the presenting features and laboratory parameters of inflammation have not been detailed.

The final diagnoses in TAB-negative patients reflect the spectrum of the differential diagnosis of GCA, including mainly other rheumatological conditions, infectious diseases, neoplastic diseases and neurological-ophthalmic conditions. Similar occurrence of ultimate diagnoses in TAB-negative patients was reported in the other three series of patients with negative TAB (7-9). GCA was the final diagnosis in 19% of our patients, whereas in the other series the rates were 5, 21 and 25%.

The most common clinical symptom leading to suspicion of GCA was headache. This is not unexpected, as headache is the most common presenting symptom of GCA (1). More importantly, in our patients headaches

were more commonly present in cases with biopsy-negative GCA, compared to non-GCA patients. This is also not unexpected, as headache is one of the ACR classification criteria for GCA diagnosis (3). This is in agreement with the series of Chmielewski *et al.*, reporting that 79% of biopsy-negative GCA patients presented with headache, compared to 54% of non-GCA cases (9). In contrast, Roth *et al.* (8), reported low incidence of headaches in this group of biopsy-negative GCA.

The more common occurrence of GCA compared to non-GCA in older TAB-negative patients may also be expected, as GCA incidence increases with age, even within the group of patients older than 50 years (13). However in two other reports the mean age of biopsy-negative GCA patients was similar to non-GCA patients (8, 9).

Laboratory parameters of inflammation were present in most of these TAB-negative patients. The most common was elevated ESR, which tended to be higher in the group of patients with biopsy-negative GCA (Table IV). In one series of TAB-negative cases, no significant difference was found between ESR levels in biopsy-negative GCA and non-GCA cases (8). In another series the mean ESR in biopsy-negative GCA patients was higher than ESR in the whole group of TAB-negative cases, but the statistical significance of this difference was not calculated (9).

The occurrence of thrombocytosis differed significantly between the two groups: platelet counts were significantly higher in the group with biopsy-negative GCA (Table IV). The association of thrombocytosis with GCA and its use for differentiating GCA from non-GCA cases, especially with ophthalmic manifestations, have been described (14-16). In this regard, in a population-based study that assessed potential clinical and laboratory differences between GCA (biopsy-proven in this case) and PMR, patients with GCA associated with PMR showed thrombocytosis more commonly than those with isolated ("pure") PMR (17).

The major limitation of this paper is the retrospective nature of the study. Obviously, retrospective studies are

inferior to prospective, controlled studies. However, when studying uncommon diseases such as GCA, one may sometimes rely on retrospective data, as prospective large-scale studies are difficult to conduct. This study included patients diagnosed and treated in one medical center, by the same medical teams, so that work-up and diagnostic approach were similar for all cases despite the retrospective nature.

Definite diagnosis of GCA in TAB-negative cases may be difficult. The use of imaging modalities such as duplex ultrasonography, magnetic resonance imaging or positron emission tomography may be of help in some cases. However, at present, none of the imaging modalities can be used as a "gold standard" for diagnosis in general practice, and their use for GCA diagnosis is limited to a few medical centers. Some physicians use the ACR classification criteria (3) for diagnostic purposes. However, it should be remembered that these are classification rather than diagnostic criteria. The criteria meant to distinguish patients with GCA from those with other vasculitides, particularly in studying groups of patients with vasculitis. These ACR criteria work less well for diagnosing individual cases (4, 5). In this study, and in clinical practice, we used the ACR criteria to help in diagnosing individual cases with negative TAB, but supplemented it with two other criteria for an ultimate diagnosis of GCA: symptoms and signs of inflammation had to improve within 3 days of corticosteroid therapy (40 mg/d of prednisone or more), and no other condition relevant to the patient's symptoms

was diagnosed during a follow up of 6 months. Using the ACR criteria without our two added criteria, would have resulted in the addition of 13 more cases of "biopsy-negative GCA".

One-fifth of patients suspected of having GCA in whom TAB was negative were eventually diagnosed as GCA. Older age, headache and thrombocytosis were more common in biopsy-negative GCA patients than in non-GCA cases. These features may help in the diagnostic approach in cases with negative TAB and in the management of biopsy-negative GCA patients (18, 19).

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