Effect of biopsy length on the rate of positive temporal artery biopsies

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ABSTRACT

Objectives. *To investigate the relationship between temporal artery biopsy (TAB) length and the diagnostic sensitivity for giant cell arteritis (GCA).*

Methods. *TAB pathology reports were reviewed for histological findings and formalin-fixed TAB lengths. The patient's charts were reviewed for clinical data. TAB was considered positive if there was a mononuclear cell infiltrate in the vessel wall. Biopsy-negative GCA was diagnosed when patients fulfilled the American College of Rheumatology classification criteria, in addition to favorable rapid response to steroid therapy. Patients were divided into 3 groups according to the clinical and histological features: Biopsy-positive GCA, biopsy-negative GCA, and no GCA.*

Results. *305 TAB reports of 173 individuals were reviewed. When only GCA patients TAB-positive and TAB-negative were considered, TAB in the biopsy-positive patients was significantly longer than in biopsy-negative cases ($p=0.008$). The rate of positive biopsies was only 19% with TAB length of 5 mm or less, but increased to 71-79% with TAB lengths of 6-20 mm, and to 89% when TAB length was longer than 20 mm. Only 3% of positive biopsies were 5 mm or shorter, compared to 27% of TAB in biopsy-negative GCA cases ($p<0.001$).*

Conclusion. *TAB with post-fixation length shorter than 5 mm carries an increased biopsy-negative rate therefore longer TAB length is required for accurate diagnosis. Increasing post-fixation TAB length beyond 20 mm may further increase the rate of positive biopsies, although data were insufficient in that regard.*

Introduction

In Western countries giant cell is arteritis (GCA) is the most common form of primary systemic vasculitis in middle-aged and older adults (1, 2). The diagnosis of GCA is suspected on the basis of the clinical presentation and elevation of acute phase reactants. It is customarily confirmed by a temporal artery biopsy (TAB) demonstrating the presence of characteristic inflammation of the temporal arteries. Positive TAB has very high specificity for GCA diagnosis, approaching 100%. However, its sensitivity is lower, in the range of 80-90%, and in some reports it was as low as 60% (3, 4). One of several factors that have been advanced to explain false negative TAB results is the discontinuous or segmental nature of the inflammatory involvement in GCA (5-8), resulting in missing the histological changes in some segments.

The resultant widely accepted consensus is that a longer TAB segments should be excised to maximize the chance of visualizing arterial segments with inflammatory changes. However, the procedure for obtaining longer TAB segments may require longer time and may also leave longer scars. Although it has been recommended that large segments of 2-3 cm, 3-5 cm, or even 4-6 cm be taken (4, 8-14), the TAB length yielding optimal diagnostic sensitivity remains unknown.

Several studies tried to address this question (14-21). However, most of those studies compared biopsy-positive GCA patients to a combined group of patients with biopsy-negative GCA and patients with no GCA. This may make interpretation of the data somewhat difficult. Inclusion of "no GCA" cases may bias the results, as in these cases TAB at any length would always be negative. In contrast, longer TAB in biopsy-negative GCA cases may theoretically result in finding positive segments. We therefore undertook this study of comparing biopsy-positive and biopsy-negative GCA in an attempt to determine the relation between TAB length and diagnostic sensitivity for GCA.

Patients and methods

Consecutive TAB pathology reports, over a period of 10 years (1996-2005) in one medical center, were reviewed for histological findings and lengths of formalin-fixed TAB specimens. The artery was processed routinely according to the commonly accepted approach: it was initially fixed in formalin. Thereafter the specimen was cut into serial 2 mm long slices, followed by paraffin embedding. The slices were cut in step sections and stained with hematoxyline and eosin. Reports had been originally given by 4 different pathologists. All slides were reviewed for this study by a single experienced pathologist. There was agreement in regard to biopsy results in all but 2 cases, which were subsequently excluded.

The patients' charts were reviewed for clinical data. Ethics approval was granted. Vasculitides other then GCA, which might involve the temporal arteries, were ruled out by initial and follow-up clinical data. Patients on steroid therapy at any dose for 3 days or more prior to the day of the biopsy were not included (n=2). Patients were divided into 3 groups according to the clinical and histological features: biopsy-positive GCA, biopsy-negative GCA, and no GCA.

TAB was considered positive when mononuclear cell infiltrates in the vessel wall, with or without giant cells, were observed. Cases with inflammatory infiltrate confined to the adventitia or involving the vasa vasorum were considered positive. In cases with bilateral positive biopsies, both were included as "biopsy-positive GCA". When TAB was positive on one side and negative on the other side, the positive biopsy was included under "biopsy-positive GCA" and the negative side was considered as "biopsy-negative GCA".

Patients with negative TAB were diagnosed as biopsy-negative GCA when the ACR classification criteria (22) were met, GCA 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. Patients with negative TAB not fulfilling the ACR classification criteria, or with no response to corticosteroid therapeutic trial, or diagnosed with another condition explaining their GCA-like symptoms, were considered "no GCA".

TAB lengths were compared by analysis of variance. Descriptive statistics followed by Chi-square analysis of contingency tables were used for comparing the rates of positive TAB.

Results

Three hundred and five TAB reports of 173 individuals were reviewed. Biopsies were performed bilaterally in 132 cases, and unilaterally in 41 patients. Table I shows the rate of positive TAB in relation to the TAB length, and the mean TAB length of each group of patients. Considering all biopsies, the rate of positive TAB was very low (8%) when TAB length was 5 mm or less. However the rate approached 50% when TAB length was 11 mm or more, and exceeded 50% with TAB longer than 20mm (Table I). However, as argued above, inclusion of "no GCA" cases may bias the results, as in these cases TAB at any length would always be negative.

When only GCA patients (TAB-positive and TAB-negative) were considered (Table II), TAB in the biopsy-positive patients was significantly longer than in biopsy-negative cases (p=0.008). The rate of positive biopsies was only 19% with TAB length of 5 mm or less, but increased to 71-79% with TAB lengths of 6-20mm, and to 89% when TAB length was longer than 20mm. Only 3% of positive biopsies were 5 mm or shorter, compared to 27% of TAB in biopsy-negative GCA cases (p<0.001).

Discussion

The optimal size of a TAB is still debated (8). Several studies approached

Table I. Temporal artery biopsy (TAB) lengths comparing biopsy-positive GCA, biopsy-negative GCA, and no GCA.

TAB length (mm)	All	1-5	6-10	11-15	16-20	>20	Mean length ± SD
Biopsy-positive GCA, n (%)	108 (35)	3 (8)	47 (31)	38 (48)	12 (48)	8 (57)	12.7 ± 5.6*
Biopsy-negative GCA, n (%)	48 (16)	13 (35)	19 (13)	10 (13)	5 (20)	1 (7)	10.1 ± 5.4
No GCA, n (%)	149 (49)	21 (57)	85 (56)	30 (38)	8 (32)	5 (36)	9.7 ± 4.9
All, n (%)	305 (100)	37 (100)	151 (100)	78 (100)	25 (100)	14 (100)	

*p<0.01 compared to the other groups.

Table II. Temporal artery biopsy (TAB) lengths of biopsy-positive GCA compared to biopsy-negative GCA.

TAB length (mm)	All	1-5	6-10	11-15	16-20	>20	Mean length ± SD
Biopsy-positive GCA, n (%)	108 (69)	3 (19)	47 (71)	38 (79)	12 (71)	8 (89)	12.7 ± 5.6*
Biopsy-negative GCA, n (%)	48 (31)	13 (81)	19 (29)	10 (21)	5 (29)	1 (11)	10.1 ± 5.4
All, n (%)	156 (100)	16 (100)	66 (100)	48 (100)	17 (100)	9 (100)	

*p=0.008 compared to biopsy-negative GCA.

Table III. Mean lengths of positive and negative temporal artery biopsies (TAB): published series.

Author (Ref.)	Positive/Negative (n)	Mean length positive TAB (mm)	Mean length negative TAB (mm)	*p*-value
Kent (14)	8/62	22	13	0.1
Roth (15)	7/11*	12	17.2*	NS
Taylor-Gjevre (16)	38/98	20.7	16.9	0.058
Sudlow (17)	50/135	10.6	8.6	<0.005
Albertini (18)	7/28	22	22	NS
Chakrabarty (19)	20/100	9	10	NS
Mahr (20)	223/1297	13.4	13.3	0.72
Gabriel (21)	172/563	36.3	37.1	NS
Current	108/48*	12.7	10.1*	<0.001

*Negative TAB were biopsy-negative GCA.

this question by comparing the lengths of positive and negative TAB. However, the group of patients with negative TAB combines patients with eventual diagnoses other than GCA ("no GCA"), and patients with biopsy-negative GCA. Due to the skip lesions of inflammation in the vessel-wall in GCA, it can be hypothesized that in this latter group longer biopsies would result in positive TAB results. In contrast, in "no GCA" cases, TAB at any length would always be negative. Thus comparing only the two groups of GCA patients, biopsy-positive GCA and biopsy-negative GCA, seems more reliable. Furthermore, comparing just the mean lengths of biopsies of biopsy-positive GCA and biopsy-negative GCA is not sufficient. Thus we also attempted to determine the optimal biopsy size.

The mean TAB length in biopsy-positive GCA cases was indeed significantly longer than TAB of biopsy-negative cases. Furthermore, there seemed to be a threshold TAB length of 5mm, above which the rate of positive biopsies was significantly increased, from less than 20% to more than 70%. The rate of positive TAB further increased to 89% with biopsies longer than 20mm, however this subgroup of patients (n=9) was too small to suggest that biopsies of that size are advantageous.

As mentioned above, most previous studies (14, 16-21) compared mean lengths of all negative TAB (apparently including both biopsy-negative GCA and cases with no GCA), to those of positive biopsies (Table III). Most of them did not find any significant differences in the TAB length, probably a result of inclusion of biopsies from patients with no GCA. Obviously, in these cases of "no GCA" TAB at any length would always be negative. One study compared biopsy-positive and biopsy-negative GCA. Roth *et al*. (15) reported that biopsy-positive GCA cases (n=7) had a mean TAB length of 12mm, while biopsy-negative GCA cases (n=11) had a mean TAB length of 17 mm. This difference was not significant, and at any rate the very small number of patients in this report and the lack of solid criteria for diagnosing biopsy-negative GCA preclude any significant conclusions.

A few studies attempted to determine an optimal TAB size. Taylor-Gjevere *et al*. (16) reviewed 141 slides of TAB, but compared positive TAB to all negative TAB, without excluding cases with no GCA. 27% of TAB were positive. The mean lengths of positive and negative TAB were 20.7 and 16.9 mm, respectively. The authors divided TAB by their length into two groups, ≤1 cm and >1 cmTAB >1cm were more likely to be positive (p=0.037).

Mahr *et al*. (20) performed a large multi-center study aimed to investigate the relationship between TAB length and diagnostic sensitivity for GCA. 1520 TAB specimens were reviewed from 4 centers in Europe. 15% of the biopsies were positive. Again, positive TAB were compared to all negative TAB, without excluding cases with no GCA. Mean TAB lengths positive and negative specimens did not differ significantly. However, further analysis asserted TAB length of 5 mm as the threshold for diagnostic yield. Compared with TAB ≤5mm, the odds ratio for obtaining a positive biopsy for longer samples was 5.7 (p=0.016).

According to these data and to our results, TAB samples should be at least 5 mm in length. Increasing the length beyond 20 mm seems to increase the yield of TAB further. In this regard, it should be noted that contraction of TAB specimens occurs following formalin fixation. Su *et al*. (23) reported the magnitude of TAB contraction in 44 TAB samples. For specimens positive for GCA, the mean contraction was12%, whereas for negative specimens mean contraction was 22% (p=0.009). This finding might be related to loss of arterial elasticity or compliance due to the inflammatory process. The mean post-fixation lengths for the positive and negative biopsies were 22 and 21.6 mm, respectively.

This inflammation-related varied TAB contraction puts forward the possibility that the difference in TAB length between biopsy-negative and biopsy-positive GCA was due to relative increased contraction in the negative specimens. Although we cannot exclude this possibility, calculating the assumed mean pre-fixation TAB lengths of biopsy-negative and biopsy-positive GCA, the two groups still showed a difference of 2 mm (12.3 and 14.2 mm, respectively).

In conclusion, we found that TAB with post-fixation length shorter than 5 mm carries an increased biopsy-negative rate. Therefore, longer TAB length is required for accurate diagnosis. It seems that increasing post-fixation TAB length beyond 20 mm further increases the rate of positive biopsies, but data were insufficient in that regard.

References

1. GONZALES-GAY MA, GARCIA-PORRUA C: Epidemiology of the vasculitides. *Rheum Dis Clin North Am* 2001; 27: 729-49.
2. LEVINE SM, HELLMAN DB: Giant cell arteritis. *Curr Opin Rheumatol* 2002; 14: 3-10.
3. LEE AG, BRAZIS PW: Temporal arteritis: a clinical approach. *J Am Geriartr Soc* 1999; 47: 1364-70.
4. NESHER G, NESHER R: Giant cell arteritis and polymyalgia rheumatica. *In* BALL GV,

BRIDGES SL (Eds.) *Vasculitis*, 2nd edition, Oxford University Press, 2008, pp. 307-22.
5. ALBERT DM, RUCHMAN MC, KELTNER JL: Skip areas in temporal arteritis. *Arch Ophthalmol* 1976; 94: 2072-7.
6. KLEIN RG, CAMPELL RJ, HUNDER GG, CARNEY JA: Skip lesions in temporal arteritis. *Mayo Clin Proc* 1976; 51: 504-10.
7. JENNETTE JC, FALK RJ: The role of pathology in the diagnosis of systemic vasculitis. *Clin Exp Rheumatol* 2007; 25 (Suppl. 44): S52-6.
8. GONZALEZ-GAY MA: The diagnosis and management of patients with giant cell arteritis. *J Rheumatol* 2005; 32: 1186-8.
9. WEYAND CM, GORONZY JJ: Giant cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003; 139: 505-15.
10. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Polymyalgia rheumatica and giant cell arteritis. *N Engl J Med* 2002; 347: 261-71.
11. HALL S, HUNDER GG: Is temporal artery biopsy prudent? *Mayo Clinic Proc* 1984; 59: 793-6.
12. DASGUPTA B, HASSAN N: Giant cell arteritis: recent advances and guidelines for management. *Clin Exp Rheumatol* 2007; 25 (Suppl. 44): S62-5.
13. WARRINGTON KJ, MATTESON EL: Management guidelines and outcome measures in giant cell arteritis. *Clin Exp Rheumatol* 2007: 25 (Suppl. 47): S137-41.
14. KENT RB, THOMAS L: Temporal artery biopsy. *Am Surg* 1990: 56: 16-21.
15. ROTH AM, MILSOW L, KELTNER JL: The ultimate diagnosis of patients undergoing temporal artery biopsies. *Arch Ophthalmol* 1984; 102: 901-3.
16. TAYLOR-GJEVERE T, VO M, SHUKLA D, RESCH L: Temporal artery biopsy for giant cell arthritis. *J Rheumatol* 2005; 32: 1279-82.
17. SUDLOW C: Diagnosing and managing polymyalgia rheumatica and temporal arteritis. *Br Med J* 1997; 315: 549.
18. ALBERTINI JG, RAMSEY M, MARKS VJ: Temporal artery biopsy in a dermatologic surgery practice. *Dermatol Surg* 1999; 25: 501-8.
19. CHARKRABATY A, FRANKS A: Temporal artery biopsy: is there any value in examining biopsies at multiple levels? *J Clin Pathol* 2000; 53: 131-6.
20. MAHR A, SABA M, KAMBOUCHNER M *et al.*: Temporal artery biopsy for diagnosing giant cell arteritis: the longer the better? *Ann Rheum Dis* 2006; 65: 826-8.
21. GABRIEL SE, O'FALLON WM, LIE AA, HUNDER GG: The use of clinical characteristics to predict the results of temporal artery biopsy among patients with suspected giant cell arteritis. *J Rheumatol* 1995; 22: 93-6.
22. 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: 1122-8.
23. SU GW, FOROOZAN R, YEN MT: Quantitative analysis of temporal artery contraction after biopsy for evaluation of giant cell arteritis. *Can J Ophthalmol* 2006; 41: 500-3.