Characterization of serological markers of healed/healing arteritis and giant cell arteritis

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ABSTRACT ●

Objective: Temporal artery biopsy (TAB) is the gold standard for confirming the diagnosis of giant cell arteritis (GCA) when positive. However, the clinical significance of healed/healing (HH) arterial injury on TAB is not well understood. The purpose of this study was to evaluate the clinical significance of this finding on TAB by determining its association with seromarkers typically predictive of GCA.

Design: Single-centre, retrospective, investigational cohort study.

Participants: A total of 385 consecutive TABs for clinical suspicion of GCA between January 2009 and January 2016.

Methods: Elevations in erythrocyte sedimentation rate, C-reactive protein, and platelet count were compared between patients with negative TAB, GCA-positive TAB, and HH arterial injury using statistical trend testing. Odds ratios of seromarker elevations for HH arterial injury versus GCA were calculated.

Results: Seventy-six GCA-positive, 69 HH, and 240 negative TABs were identified. Mantel-Haenszel tests of trend indicated that platelets >400 000/μL ($p < 0.01$), erythrocyte sedimentation rate ≥50 mm/hr ($p < 0.01$), and C-reactive protein ≥24.5 mg/L ($p < 0.01$) occurred with intermediate frequency in the HH TAB group. The odds of HH TAB were 3.6 times greater (95% CI 1.5–8.5) with platelets >400 000/μL.

Conclusion: HH arterial injury is a heterogenous group that requires treatment in the appropriate clinical setting. From our study, we found that the HH group is intermediate between GCA-positive and GCA-negative biopsy with respect to serology markers only. Thrombocytosis is an independent predictor of HH TAB. With further studies, this marker may be considered when making treatment decisions. Further studies are required to better understand this entity.

Giant cell arteritis (GCA) is a potentially vision-threatening condition. It is a systemic vasculitis of medium- and large-sized arteries characterized by structural changes of the vessel wall secondary to focal chronic, most often granulomatous, inflammation leading to reduced blood flow and end-organ ischemia.[1]

The gold-standard diagnostic investigation for GCA is the temporal artery biopsy (TAB), which illustrates characteristic histologic changes in the arterial wall.[2,3] Biopsies can be classified histologically as positive for active GCA, healed/healing (HH) arterial injury, and normal/nonspecific arterial changes.

The clinical significance of HH arterial injury on TAB is not well understood. It is known, however, that the distribution of GCA tends to be segmental and uneven along the extracranial carotid artery tree and metachronous with respect to clinical activity where histologic findings of active, HH arterial injury and normal arterial walls may be found in the same artery on biopsy.[4–7] Therefore, it is imperative on a TAB that as complete an examination of the artery as possible be done by the pathologist, including complete and exhaustive step sectioning of the biopsied artery and consideration of bilateral biopsies when clinical suspicion is high. As such, it is currently recommended that findings of HH arterial injury be treated as active disease in patients with a high clinical index of suspicion of GCA.[8,9] In patients with equivocal clinical presentation, laboratory tests of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count have been shown to be valuable in selecting patients for TAB and immediate high-dose corticosteroid therapy.[10–12] The role of these seromarkers in identifying those with HH arterial injuries has not been well studied.

The clinical implications of HH arterial injury on TAB are not well understood. The goal of this study was to evaluate the association between elevations in inflammatory seromarkers (ESR, CRP, and platelet count) and HH arterial injury compared with active GCA and negative findings on TAB. This study attempts to further understand this entity and, combined with future studies, attempts to aid the clinician in determining how to proceed in the management of these cases.

Methods

All patients who underwent TAB at the ophthalmology clinic for clinical suspicion of GCA between January 2009 and January 2016 were retrospectively reviewed. Ethics approval was obtained from the Ottawa Hospital Research Institute before commencement of the study.

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Electronic patient records were obtained to collect all available clinical, laboratory, and pathological data. Specifically, information was collected on ESR, CRP, platelet count, TAB laterality, TAB length, and TAB diagnosis. All TAB specimens were reviewed by experienced pathologists using the procedures outlines by Gooi et al.[6,13] At our institution, all patients undergo bilateral TABs. Both arteries are cut at 1–2 mm intervals, submitted on arterial cross-section, and are step sectioned and examined in their entirety (up to 30 levels per artery, average 20) by ophthalmic and cardiovascular pathologists trained in the interpretation of all histopathologic changes—normal, HH arterial injury, and active arteritis. Pathological findings were defined as follows: (*i*) active GCA—characterized by eccentric intimal thickening/fibrosis, destruction of the internal elastic lamina (IEL), lymphohistiocytic infiltration of vessel wall media, and associated granulomatous inflammatory lesions comprising multinucleated giant cells; (*ii*) HH arterial injury—a spectrum of vessel wall changes ranging from those highly suggestive of healing arteritis (active intimal and medial fibroplasia with loss of the IEL, medial neovascularization, and a chronic inflammatory infiltrate)[8,14–16] to changes that can be consistent with healed arteritis or reflect nonarteritic disease such as atherosclerosis, arteriosclerosis, or trauma (intimal and medial fibroplasia, occasionally eccentric, with fragmentation and loss of IEL with or without medial neovascularization). All TABs were performed either before or within 10 days of initiating steroid treatment.

Laboratory seromarker values (ESR, CRP, platelet count) were those collected most immediately before TAB or steroid therapy. Westergren's ESR method and highly sensitive CRP assays were performed in all biochemical laboratories. The ESR cutoff was >50 mm/hr, selected based on the American College of Rheumatology criteria for the classification of GCA.[17] The cutoff value for an elevated CRP was defined as >24.5 mg/L based on a study by Hayreh et al.[11] The $>400\ 000/\mu L$ cutoff for elevated platelet count was selected based on the regional laboratory cutoff level for a normal platelet level, as well as to maintain consistency with previous studies investigating the relationship between thrombocytosis and GCA.[10,18–20]

Patients were divided into 3 groups based on TAB diagnoses: (*i*) active GCA, (*ii*) HH arterial injury, and (*iii*) normal/nonspecific changes. Laboratory values were compared between groups using the Jonckheere-Terpstra test of trend. Pairwise comparisons between biopsy groups were performed using *t* tests. Categorical variables were compared between groups using the χ^2 test and Mantel-Haenszel test of trend. Odds ratios were calculated to measure the association between each laboratory test, or combination thereof, and positive TAB biopsy, or HH biopsy. Binomial logistic regressions were conducted to assess the predictive value of each laboratory measure. These models were used to calculate the area under the receiver operating characteristic (ROC) curve for each combination of laboratory tests. In the binomial logistic regression analysis, there were 2 dependent variables: positive versus negative and HH versus negative. The independent variable was the laboratory value. The predicted probability (PP) of having a positive or HH biopsy result was derived from estimates calculated in the binomial logistic regression. The PP was then plotted for each of the seromarkers: platelets, ESR, and CRP. IBM SPSS Statistics Version 20 for Mac (IBM Corp, Armonk, N.Y.) was used for statistical analysis. Factors were considered to be statistically significant at $p < 0.05$.

Results

Between January 2009 and January 2016, 385 consecutive patients underwent TAB for clinical suspicion of GCA at our institution. Distribution of laboratory data for the 3 TAB diagnosis groups is reported in Table 1. Independent samples *t* tests indicate that there are significant differences in seromarker values (i.e., platelets, ESR, and CRP) between patients with positive TAB and

Table 1—Laboratory characteristics of the 3 groups

Test	Negative Biopsy (n = 240)	Healed/Healing (n = 69)	Positive Biopsy (n = 76)	Test of Trend (*p*-Value)
Platelets, mean ± SD	273.9 ± 87.56	295.39 ± 121.66	343.75 ± 119.17[a,b]	<0.01
ESR, mean ± SD	36.98 ± 28.91	42.11 ± 31.92	52.32 ± 30.72[a]	<0.01
CRP, mean ± SD	28.11 ± 46.52	35.06 ± 44.08	50.63 ± 52.67[a]	<0.01
Platelets >400 000[c], mean ± SD	13/194 (6.7)	11/54 (20.4)[a]	20/59 (33.9)[a]	<0.01
ESR ≥50[c], n (%)	59/217 (27.2)	18/57 (31.6%)	31/69 (44.9%)[a]	<0.01
CRP ≥24.5[c], n (%)	52/193 (26.9)	19/53 (35.8%)	33/61 (54.1%)[a]	<0.01
Platelets >400 000, ESR ≥50, and CRP ≥24.5[c], n (%)	4/174 (2.3)	4/48 (8.3)[a]	10/54 (18.5)[a]	<0.01
Platelets >400 000 and ESR ≥50[c], n (%)	5/189 (2.6)	5/51 (9.8)[a]	13/59 (22.0)[a]	<0.01
Platelets >400 000 and CRP ≥24.5[c], n (%)	6/175 (3.4)	7/48 (14.6)[a]	14/54 (25.9)[a]	<0.01
ESR ≥50 and CRP ≥24.5[c], n (%)	29/192 (15.1)	10/52 (19.2)	21/61 (34.4)[a]	<0.01
PLT <400 000, ESR <50, and CRP <24.5[c], n (%)	110/174 (63.2)	26/48 (54.2)	18/54 (33.3)[a]	<0.01

ESR, erythrocyte sedimentation rate in mm/hour; CRP, C-reactive protein in mg/L; PLT, platelets in number/μL.

[a]Significant ($p < 0.05$) *t* test (continuous variable) or χ^2 test (categorical variable) against negative biopsy.

[b]Significant ($p < 0.05$) *t* test (continuous variable) or χ^2 test (categorical variable) against healed/healing biopsy.

[c]Counted in patients in whom all applicable lab tests were available.