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Serum S100 Proteins as a Marker of Disease Activity in Large Vessel Vasculitis

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Abstract

Background/Objectives—Serum S100A8/S100A9 and S100A12 levels have been shown to be elevated in giant cell arteritis (GCA). This study aimed to determine if levels of serum S100 proteins perform as markers in a comparable fashion to standard markers of disease activity in large-vessel vasculitis.

Methods—Serum samples were obtained from the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Prospective Cohort Study of GCA and Takayasu's arteritis (TAK). A mixed effects model compared S100 proteins during active and inactive disease states. Receiver operating characteristic curves compared models using S100 proteins to models using ESR and CRP.

Results—There were 106 samples (50 during active disease) from patients with GCA and 32 samples (16 during active disease) from patients with TAK. In GCA, S100A8/S100A9 and S100A12 were significantly elevated during active disease (1445.6 ng/mL vs. 1095.7 ng/mL, $p = 0.003$; 163.2 ng/mL vs. 116.6 ng/mL, $p = 0.016$, respectively). There were weak correlations between levels of S100 proteins and ESR or CRP. A model including S100A8/S100A9, S100A12, ESR, and CRP was a better indicator of disease activity compared to ESR and CRP together. In TAK, there were no significant differences between active and inactive disease for either the S100 proteins or ESR/CRP.

Conclusions—Serum levels of S100A8/S100A9 and S100A12 are elevated during active disease and perform comparably to ESR and CRP as measures of disease activity in giant cell arteritis.

INTRODUCTION

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are widely used biomarkers in giant cell arteritis (GCA) and Takayasu's arteritis (TAK), however, both can be normal in smoldering disease^{1–3} and other biomarkers have proven unhelpful⁴. A search for improved biomarkers is warranted. Calgranulins, including S100A8 (calgranulin A; myeloid-related protein 8), S100A9 (calgranulin B; myeloid-related protein 14) and S100A12 (calgranulin C; myeloid-related protein 6), are calcium binding proteins expressed during myeloid differentiation. S100 proteins have been shown to be useful biomarkers in various rheumatic diseases including: oligoarticular and polyarticular juvenile rheumatoid arthritis (JRA), ulcerative colitis, systemic lupus erythematosus, reactive arthritis, and

rheumatoid arthritis^{5–10}. In GCA S100A8/S100A9 complexes can be identified in the adventitia and media of affected arteries, whereas S100A12 expression is found around the vasa vasorum of the adventitia¹¹. Serum levels of S100 proteins are also elevated in GCA compared to healthy controls¹¹. Moreover, gene expression profiles of temporal arteries from patients with GCA, revealed a significant increase in the gene expression of S100A8, S100A9 and S100A12 as compared to control temporal arteries¹². In addition, S100 positive cells are prominent in the inflammatory infiltrate of the aortic wall of patients with TAK¹³. The aim of this study is to assess the association of peripheral S100 proteins with disease activity in two forms of large vessel vasculitis, GCA and TAK.

METHODS

Serum samples were obtained from a longitudinal prospective cohort including GCA and TAK patients from multiple centers located in the United States and Canada. This study is in compliance with the Declaration of Helsinki and has been approved by the local institutional review board. All patients met either the modified American College of Rheumatology (ACR) criteria for GCA or the modified ACR criteria for TAK^{14,15}. Active disease was defined as a Birmingham Vasculitis Activity Score version 1 score greater than 0 and a physician's global assessment greater than 0. The serum concentrations of S100A8/S100A9 heterodimers and S100A12 were measured by ELISA¹¹. Comparisons were made to S100A8/S100A9 levels in healthy, historical controls (n=35) measured in the same laboratory using a two tailed student's T-test¹¹.

A mixed effects model was used to compare average levels of S100A8/S100A9 or S100A12 in active and inactive disease states. The qualities of predictions of disease activity from these models using either the traditional measures (ESR and CRP) or the two new measurements (S100A8/S100A9 and S100A12) were assessed using receiver operating characteristic (ROC) curves with confidence intervals using DeLong approach. A significance level of 5% was used for all testing.

RESULTS

Giant Cell Arteritis

Serum samples obtained from 59 patients with GCA (Table 1). The majority of patients were female (74.6%) and Caucasian (98.3%). Forty-two patients (71%) had positive temporal artery biopsies diagnostic for GCA. Forty-six (78%) patients had samples drawn during both active and inactive disease. Serum S100A8/S100A9 and S100A12 levels were measured on 50 samples during active disease and 56 samples during inactive disease. The mean serum levels of S100A8/S100A9 and S100A12 were both significantly higher during active disease compared with inactive disease; S100A8/S100A9: 1445.6 ng/mL [95% CI 1189.2,1757.1] vs. 1095.7 ng/mL [95% CI 910.7, 1318.3], $p = 0.003$; S100A12: 163.2 ng/mL [95% CI 124.3,214.2] vs. 116.6ng/mL [95% CI 90.3,150.6], $p=0.016$. Mean S100A8/S100A9 and S100A12 levels (including both active and inactive disease) were significantly higher compared to healthy controls; S100A8/S100A9: 305ng/mL [95% CI 246.2–363.8]; S100A12: 40ng/mL [95% CI 20.4–59.6]. An AUC of 0.61 was obtained using the combination of S100A8/S100A9 and S100A12 which was not statistically different for a

model using the combination of ESR and CRP (AUC 0.73, $p=0.13$). A model utilizing all variables increased the AUC to 0.79 (Figure 1).

Takayasu's Arteritis

Serum samples were obtained from 16 patients with TAK (Table 1). The majority of patients were female (87.5%) and Caucasian (93.8%). The mean age when the serum was collected was 35 years old (range 19–65). There was a non-statistically significant increase in S100A8/S100A9 levels during active disease compared to levels during inactive disease: 1028 ng/mL [95%CI 640, 1652] vs 843ng/mL [95%CI 536, 1327], $p=0.38$. There were no differences in the S100A12 levels between active and inactive disease (86.8 ng/mL [95%CI 50.2, 150.6] vs 85.1 ng/mL [47.9, 151.1], $p=0.93$). Mean S100A8/S100A9 and S100A12 levels (including both active and inactive disease) were significantly higher compared to healthy controls. None of the biological markers (CRP, ESR, S100A8/S100A9 nor S100A12) significantly correlated with disease activity in logistic regression models for each of these measurements.

When comparing GCA to TAK, there were no significant differences between the means (including both active and inactive disease) for either S100A8/S100A9 ($p=0.1130$) or S100A12 ($p=0.0734$).

DISCUSSION

This is the first study to investigate the role of S100 proteins as a marker of disease activity in primary large vessel vasculitis. In GCA, both S100A8/S100A9 and S100A12 were significantly higher during active disease compared to inactive disease and healthy controls. The S100 proteins better predict disease activity when combined with traditional biomarkers (ESR and CRP) compared to using traditional biomarkers alone. While the S100 proteins did not outperform traditional biomarkers, we suspect that the ability of traditional biomarkers to predict disease activity was overestimated since physicians rely on both ESR and CRP for disease assessment. In TAK, this study is the first to demonstrate that both S100A8/S100A9 and S100A12 are higher in patients compared to healthy controls with a trend toward S100A8/S100A9 being higher during active disease. This may have some future implication in the pathogenesis of large vessel vasculitis and future studies should explore these pathway.

There are several strengths to this study including this being a large registry of patients from multiple centers, the prospective nature of the assessment, all S100 protein measurements done in the same laboratory and 71% of GCA patients were biopsy proven. The primary limitation is the inability to determine to what degree the traditional biomarkers influenced the physicians' assessment of disease activity.

There is a critical need to develop better methods of assessing disease activity in both GCA and TAK. Our group has demonstrated that gene expression of S100A8, S100A9 and S100A12 are increased in the GCA temporal arteries¹², even in arteries that did not show inflammation. This suggests S100 proteins may be elevated early on in disease flares,

possibly rising earlier than traditional biomarkers. Future studies are warranted to determine the longitudinal change in serum S100 proteins in GCA during active and inactive disease.

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Figure 1.
ROC curves for tested biomarkers as measures of disease activity in patients with giant cell arteritis
AUC=Area under the curve; CRP=C-reactive protein;
ESR=Erythrocyte sedimentation rate

Table 1

Baseline Patient Characteristics

Factor	Giant Cell Arteritis		Takayasu's Arteritis	
	N	Statistic	N	Statistic
Positive TAB ^a	59		16	
	42	71.2%		
Sex ^a				
Female	44	74.6%	14	87.5%
Male	15	25.4%	2	12.5%
Race ^a				
Asian	1	1.7%	1	6.3%
White	58	98.3%	15	93.8%
Age at enrollment (years) ^b	59	70.65±13.28		35.4±12.8
Age at visit (by sample, years) ^{de}				
Active	50	70.9(67.5,74.4)		
Inactive	56	71.5(68.1,74.9)		
Observation times	59		16	
Active and Inactive	46	78.0%	14	87.5%
Both Active	1	1.7%		
Just Active	2	3.4%	1	6.3%
Just Inactive	10	16.9%	1	6.3%
Medications ^a	Active	Inactive		
Prednisone	84.0%	92.7%	75.0%	68.8%
Duration (months) ^c	2	3	15	3.5
Aspirin	58.0%	66.4%	68.8%	68.8%
Azathioprine	0.0%	0.0%	12.5%	18.8%
Cyclophosphamide	2.0%	0.0%	0%	0%
Infliximab	0.0%	0.0%	12.5%	18.8%
Methotrexate	14.0%	23.6%	37.5%	50.0%
Mycophenolate	0.0%	0.0%	6.3%	0.0%

^aPercentage;^bMean±SD;^cMedian;^dp<0.001, TAB = temporal artery biopsy;^e95% Confidence intervals