Association between histological features and clinical features of patients with biopsy positive giant cell arteritis

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ABSTRACT

Objective. *The aim of this study was to investigate the association between histological biopsy features and clinical features, such as blindness, in patients with biopsy positive giant cell arteritis (GCA).*

Methods. *Positive temporal artery biopsies registered on the South Australian Giant Cell Arteritis Registry were identified between 1991 and 2013 (n=186). Clinical and serological data was recorded using both patient questionnaire and case note review. Patients without clinical data were excluded from the analysis (n=42). Statistical analysis was performed using chi-squared and Wilcoxon's tests.*

Results. *144 biopsy positive GCA cases were analysed. The mean age at biopsy was 77 years; 71% were female. In total 25% experienced blindness. Although not individually significant, transmural inflammation (p=0.11), luminal thrombus (p=0.17) and giant cells (p=0.20) were more frequent in patients who suffered blindness, whereas fragmentation of the internal elastic lamina (p=0.04), and intimal thickening (p=0.02) were more frequent in patients without blindness. The presence of giant cells was associated with transmural inflammation (p=0.06), jaw claudication (p=0.02), and higher inflammatory markers. In contrast, characteristics of patients with intimal thickening included a lower frequency of giant cells (0.01) and jaw claudication (p=0.01), and lower inflammatory markers.*

Conclusion. *Giant cells are strongly associated with jaw claudication and systemic markers of inflammation, perhaps reflecting more acute and aggressive disease. We did not find any histological features that were individually significantly associated with an increased risk of blindness in GCA patients.*

Introduction

Giant cell arteritis is a systemic vasculitis that typically involves large- and medium-sized arteries (1). Temporal artery biopsy is the gold standard for diagnosing giant cell arteritis (GCA). However the significance of histopathology characteristics, in terms of clinical features and complications of GCA, remains unknown.

The clinical relevance of giant cells has been of particular interest. Although they are not required for the histopathological diagnostic criteria for temporal arteritis (2), they have been implicated in more aggressive disease and permanent visual loss (3-4). Although a presenting feature in 20% of patients (4-5), the risk of blindness in patients with GCA remains unclear. A large series by Chatelain *et al.* found that blindness was neither associated with the intensity or location of the inflammatory infiltrate, whereas others have found an association with inflammation confined to the adventitia (6). The degree of intimal hyperplasia has been associated with ischaemic manifestations such as jaw claudication, but not stroke (7). The clinical significance of other histological features such as luminal thrombus and fragmentation of the internal elastic lamina also remains undefined. Understanding these relationships may allow a more scientific therapeutic approach for patients with GCA.

The aim of this study was to investigate the association between histological biopsy features and clinical features, such as blindness, in patients with biopsy positive GCA.

Materials and methods

Ascertainment of biopsy-proven giant cell arteritis cases

All pathology reports of patients who underwent temporal arery biopsy were identified from pathology laboratories at the three major South Australian hos-

pitals (The Queen Elizabeth Hospital, Royal Adelaide Hospital and Flinders Medical Centre). These laboratories process approximately 85% of biopsy specimens from both public and private hospitals in South Australia. Temporal artery biopsies were identified from 1991–2013. Patients were defined as having biopsy positive GCA from the American College of Rheumatology 1990 Criteria for the Classification of Giant cell (temporal) arteritis *i.e.* a temporal artery with vasculitis characterised by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells.

South Australian GCA Registry

Positive temporal artery biopsies, as defined above, were registered on the South Australian Giant Cell Arteritis Registry (n=186). Histological parameters were obtained from pathology reports completed by a consultant pathologist. Further clinical and epidemiological data were collected in the form of questionnaires and case note reviews. Clinical information was recorded using both patient questionnaire and case note review. Patients without clinical data were excluded from the analysis (n=42). Serological data was obtained using both electronic and hard records; blood results within one month prior to starting prednisolone only were included.

This study has ethics approval at The Queen Elizabeth Hospital, The Royal Adelaide Hospital and Flinders Medical Centre/Repatriation General Hospital. Ethics committee approval included permission to access case notes of deceased patients.

Clinical data

Demographic data and clinical features including scalp tenderness, jaw claudication, polymyalgia rheumatica (PMR) and neuro-ophthalmic ischaemic complications were analysed. Prednisolone data was assessed by length of treatment. Relapse was defined as events where prednisolone therapy was either re-instituted or increased due to relapse in clinical symptoms and/or increased CRP or ESR.

Table I. Association of Giant cells and Intimal thickening with clinical and serological findings.

	Giant Cell %(no.)	No Giant Cell % (no.)	Intimal thickening % (no.)	No intimal thickening % (no.)
Clinical Features				
Headache	70.4% (57/81)	65.4% (17/26)	66.1% (39/59)	71.7% (38/53)
Scalp tenderness	51.9% (41/79)	54.2% (13/24)	42.1% (24/57)	58.8% (30/51)
Jaw claudication	66.7% (58/87)*	40.7% (11/27)	48.5% (32/66)	73.7% (39/53)**
Fatigue	56.3% (40/71)	57.1% (12/21)	55.6% (30/54)	55.8% (24/43)
Malaise	60% (42/72)	63.6% (14/22)	56.6% (30/53)	65.9% (29/44)
Weight Loss	38.8% (26/67)	47.8% (11/23)	40% (20/50)	37.8% (17/45)
PMR	51.2% (42/82)	40% (10/25)	42.4% (25/59)	52.8% (28/53)
Blindness	32.2% (29/90)	19.2% (5/26)	20.3% (13/64)	40.4% (23/57)*
Relapse	16.7% (14/84)	18.2% (4/18)	21.1% (12/57)	13.5% (7/52)
Serology				
CRP (mg/L)	46* (112)	12 (50)	37 (94.6)	51 (123)
ESR (mm/hr)	80 (60.5)	53 (65)	68 (57)	88 (62)
Hb (g/L)	119 (20.5)	123 (28.3)	120 (25)	115 (24)
Platelets (x10^9/L)	394*** (212.8)	262 (110.8)	323 (3.7)	406* (213)

Serology expressed as median value (interquartile range), PMR polymyalgia rheumatica
*p<0.05, **p<0.01, ***p<0.001).

Statistical analysis

Histological and clinical features were compared. Data were analysed using the freely available statistical analysis software 'R' (v. R. 2.15.1, Vienna, Austria) and the software plug-in 'Rcmdr'. Chi-squared test or Fisher's exact test when required was applied to dichotomous variables. For non-parametric continuous variables Wilcoxon test was performed. Duration of prednisolone use was analysed using the log rank test for time to event analysis of censored data.

Results

One hundred and forty-four biopsy positive GCA cases (71% females) were analysed. The mean age at biopsy was 77 years (range 61 to 91years). The mean biopsy length was 17 mm (SD ± 10.6 mm). In total, 36 (25%) patients experienced blindness. Younger age (75.5 *vs*. 78, p=0.03) was significantly associated with luminal thrombus, which was also associated with fatigue (p=0.04). Neither gender nor biopsy length significantly differed across the histological features identified.

Histological features and clinical presentation, serology and relapse

The presence of giant cells was associated with jaw claudication (p=0.02), and higher inflammatory markers (Table I). The presence of intimal thickening was associated with a lower frequency of jaw claudication (p=0.01), and lower inflammatory markers. No association was found between other histological parameters and clinical features of biopsy positive GCA patients. No association was found between histological parameters and relapse of disease.

Histological features and blindness

Although not individually significant, transmural inflammation (p=0.11), luminal thrombus (p=0.17), and giant cells (p=0.2) were more frequent in GCA patients with blindness (Table II). In contrast, temporal arteries with fragmentation of the internal elastic lamina (p=0.04), and intimal thickening (p=0.02) were more frequent in GCA patients without blindness (Table II).

Steroid data

While not statistically significant, the median duration of corticosteroid use was longer in patients with histological giant cells, compared to those without (4.5 *vs*. 2.0 years, p=0.14, time to event analysis, Fig. 1A). In contrast the presence of macrophages on temporal biopsy resulted in a shorter time on corticosteroid therapy (2.4 *vs*. 4.5 years, p=0.058, Fig. 1B). No other histological features were associated with the duration of corticosteroid use.

Discussion

We found that in patients with biopsy

Table II. Association between histopathology and blindness.

Histological Feature	GCA with Blindness n (%)	GCA Without Blindness n (%)	*p*-value
Giant cells	29/35 (85%)	61/82 (74%)	0.20
Macrophages	9/24 (37.5%)	25/68 (36.7%)	0.95
Lymphocytes	22/24 (91.7%)	64/68 (94.1%)	0.68
Plasma cells	5/24 (20.8)	8/68 (11.8%)	0.27
Neutrophils	2/24 (8.3%)	6/68 (8.8%)	0.94
Histiocytes	11/24 (45.8%)	31/68 (45.6%)	0.98
Transmural inflammation	16/24 (66%)	32/67 (47.8%)	0.11
Fragmentation of internal elastic lamina	15/36 (41.7%)	53/85 (62.4%)	0.04
Intimal thickening	13/36 (36.1%)	51/85 (60%)	0.02
Luminal thrombus	6/36 (16.7%)	7/85 (8.2%)	0.17

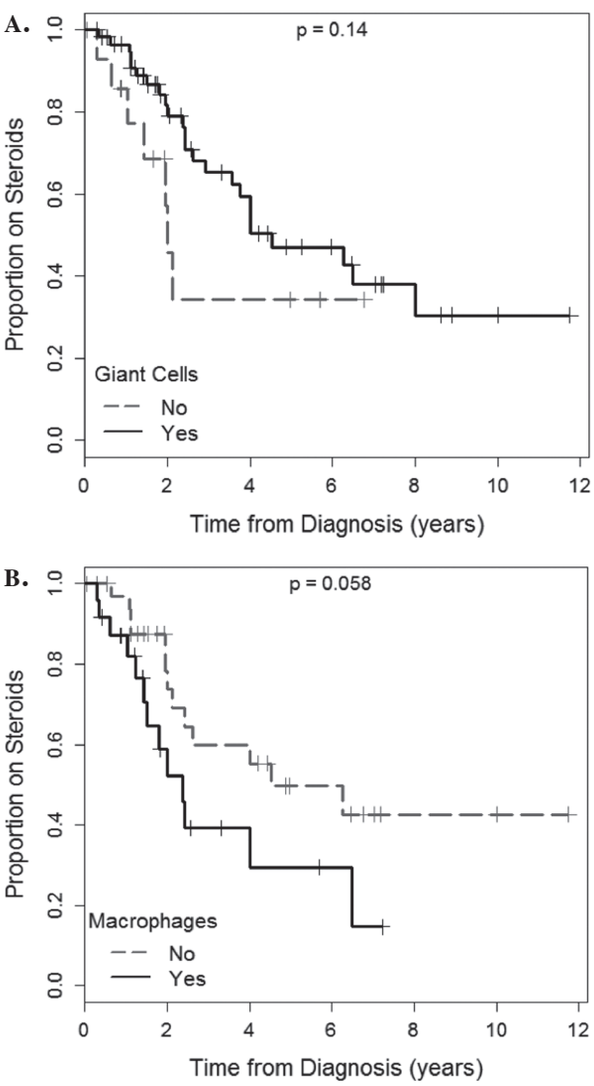

Fig. 1. Association between histology and steroid use.
A. With and without giant cells.
B. With and without macrophages.

positive GCA, giant cells on histological biopsy were strongly associated with jaw claudication and systemic markers of inflammation. However, we did not find any histological features that were individually significantly associated with an increased risk of blindness.

The demographic data of our patients was similar to those found across the literature. The mean age of 77 years is consistent with European cohorts (4, 8), including Chatelain *et al*.'s large cohort in France (mean 78.3 years) (4). The 70% female predominance is also in agreement with both Armstrong (65%) and Chatelain *et al*.'s (72%) groups (3-4). Our 25% experience of blindness is higher compared with similar case series (3-4), and is likely due to the relatively higher proportion of patients collected from ophthalmologists; ophthalmology referral centres report 48% blindness in their biopsy positive GCA patients (9).

The complication of blindness in GCA is most often due to anterior ischaemic optic neuropathy (AION) (10). AION is thought to be driven by progressive luminal occlusion (7), but may also be due to thrombotic occlusion, or both pathologies (11). Chatelain *et al*. found that the only significant factor associated with blindness was the presence of giant cells (4). Although our results did not reach statistical significance, they support the association of giant cells with blindness. Armstrong *et al*. have found a similar trend (3-fold increase) without reaching statistical significance (3). Smaller studies have not found any association with giant cells. Our analysis also found that giant cells were associated with higher systemic markers of inflammation, which has yet to be shown elsewhere in the literature.

We did not find any significant relationship between transmural inflammation and clinical features. Other authors have found that transmural inflammation is associated with greater systemic inflammatory features (elevated ESR, thrombocytosis, leukocytosis, and fever), and less related to the occurrence of cerebral-ophthalmic events (6, 12). A recent large study by Cavazza *et al*. included 317 patients with biopsy positive temporal arteritis. The authors further pathologically classified samples into 4 categories: small-vessel vasculitis (SVV), vasa vasorum vasculitis (VVV), inflammation limited to adventitia (ILA) and transmural inflammation (TMI). They found that those with SVV and VVV, compared with those with TMI, also had significantly lower frequency of cranial manifestations. However, unlike Breuer *et al*., they found that TMI was significantly associated with lower acute phase reactants (6, 13). Interestingly, blindness was equally represented across all pathological groups; in keeping with other literature, blindness does not seem to be related to

the degree of histological inflammation (6, 12, 13).

Interestingly, we found that intimal hyperplasia was inversely related to ischaemic complications of GCA, namely blindness and jaw claudication. Intimal hyperplasia was also significantly associated with lower inflammatory markers and lower presence of giant cells. This outcome differs from those of Kaiser and Makkuni (7, 11), who reported a strong positive correlation between intimal hyperplasia and ischaemic complications. Importantly a determining factor is the degree of the intimal hyperplasia. It is only at the severe end of hyperplasia that the relationship becomes most significant (11); at moderate degrees the inverse relationship exists (4). We agree with the conclusions of Kaiser *et al*. that the histo-clinical relationship of the different degrees of intimal hyperplasia represent disease heterogeneity in GCA (7). Another explanation for our study's finding of this inverse relationship is that these could represent a relatively benign subgroup of temporal arteritis. Borg *et al*. identified a histological subgroup, defined according to Allsop and Gallagher (14-15) that had milder clinical presentations and better outcomes despite initimal thickening. This subgroup also had inflammatory cells but no giant cells, lower erythrocyte sedimentation rates and lower rates of permanent visual loss.

The presence of macrophages on histopathology trended towards a shorter duration of steroid therapy (p=0.06). There were no other possible associations found, consistent with other large case series (3, 6). This may represent a subgroup of disease who are more steroid responsive.

There are several limitations to our study. Firstly is the impact of reporting bias. Our study used the original diagnostic report for the temporal artery biopsy and the biopsy specimens were not reported in a structured manner, and were not re-analysed by a pathologist. Previous studies have suggested that on re-analysis of positive temporal biopsies, giant cells are reported in ~50% more samples (3). One explanation posed is the short length of temporal artery sampled, with a minimum of 5 mm suggested (16). However, the mean biopsy length in our cohort was 17 mm, and the presence of giant cells was found in 76%, which is similar to other studies that have used pathologists to re-analyse positive biopsies (3-4, 17). In addition, without a pathologist re-review, we were unable to analyse the degree of intimal hyperplasia, and other hypothesised important features such as neoangiogenesis and small-vessel vasculitis (18). Nonetheless, we retrieved comprehensive clinical data for 144 patients with biopsy positive GCA, with a relatively high proportion who experienced blindness (n=36). We also acknowledge we were unable to provide details on previous glucocorticoid therapy. We were unable to capture the data on previous glucocorticoid dosage used, which may be an important co-founding factor in relation to biopsy findings.

In conclusion, our study found that giant cells are strongly associated with jaw claudication and systemic markers of inflammation. We did not find any histological features that were individually significantly associated with blindness. Interestingly, in our cohort, patients with intimal thickening by histology are less likely to have giant cells, have less acute systemic inflammation, and have a lower risk of blindness. This group may reflect a different disease subgroup or end stages of active inflammation, highlighting the challenges in the pathological diagnosis and biopsy reporting of active GCA.

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