Giant cells in temporal artery biopsies and the risk of large-vessel involvement in patients with giant cell arteritis

N. Naderi^{1,2}, A.J. Mohammad³⁻⁵, K. Wadström^{1,6}, C. Turesson^{1,5}

¹Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden; ²Department of Rheumatology, Örnsköldsvik Hospital, Örnsköldsvik, Sweden; ³Rheumatology, Department of Clinical Sciences, Lund, Lund University, Lund, Sweden; ⁴Department of Medicine, University of Cambridge, UK; ⁵Department of Rheumatology, Skåne University Hospital, Malmö and Lund, Sweden; ⁶Centre for Rheumatology, Academic Specialist Centre, Region Stockholm, Sweden

Sweden.

Abstract Objective

Giant cell arteritis (GCA) is a systemic disease with variable vascular involvement. The objective was to investigate predictors of time-dependent large-vessel involvement (LVI) in a population-based cohort of patients with GCA.

Methods

GCA patients with positive temporal artery biopsies (TAB) between 1997- 2010 were identified through a regional pathology register. A structured review of histopathology reports and relevant imaging studies was performed.
Cases with LVI through July 2016 were identified. Patients were followed to first LVI, death, migration from the area or July 29, 2016. Event free survival by clinical and histopathologic features was estimated using the Kaplan-Meier method. Potential predictors of LVI were examined using Cox regression models.

Results

A total of 274 patients were included. The mean age at GCA diagnosis was 75.7 years. Fifty-one patients (19%) had documented LVI during the follow-up, corresponding to an incidence rate of 2.4/100 person-years. The median time from GCA diagnosis to the diagnosis of LVI was 4.5 years (interquartile range 0.6-7.4). Thirty-four patients had aortic involvement (67% of those with LVI; 12% of all GCA cases). Survival free of LVI was longer in patients with giant cells in the TAB (75th percentile 14.0 vs 6.7 years; p=0.014). In age-adjusted analysis, the presence of giant cells in the TAB was associated with reduced risk of LVI (hazard ratio 0.48; 95% confidence interval 0.27-0.86).

Conclusion

The negative association with giant cells in the TAB suggests that patients with LVI constitute a subset of GCA with particular disease mechanisms.

Key words giant cell arteritis, aortitis, temporal arteritis

Nazanin Naderi, MD Aladdin J. Mohammad, MD, PhD Karin Wadström, MD, PhD Carl Turesson, MD, PhD

Please address correspondence to: Carl Turesson Department of Rheumatology, Skåne University Hospital, 205 02 Malmö, Sweden. E-mail: carl.turesson@med.lu.se

Received on December 22, 2023; accepted in revised form on April 29, 2024.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2025.

Competing interests: none declared.

Introduction

Giant cell arteritis (GCA) is the most frequent systemic vasculitis in the population over the age of 50 in western countries, with incidence estimates of 14-33/100,000 in Scandinavian populations (1, 2). The disease was first described in 1889 (3) in its most classical form. Temporal artery biopsy (TAB) is the gold standard for diagnosing GCA. The first biopsy was performed in 1931 (4). In the biopsy the presence of giant cells, granuloma, disrupted internal elastic lamina, thickened intima and presence of inflammatory cells are indicative of the disease.

Since the first description, other disease subsets have been recognised (5-7). The subsets can be defined according to clinical phenotypes, imaging findings, histopathology or laboratory findings (8). Although there is no consensus, the most common way of subgrouping patients with GCA is by the clinical phenotypes. Classic cranial arteritis [with or without polymyalgia rheumatica (PMR)], GCA with extracranial largevessel involvement (LVI), GCA with mainly constitutional symptoms (e.g. weight loss and/or fever of unknown origin), and clinical pure PMR with underlying subclinical vasculitis (9).

Although different subsets show different clinical course and prognosis (5, 10-15), there are still no established predictors for LVI. Results are divergent on the relation between LVI and presence of cranial symptoms (5, 7, 11,16-21), PMR at the time of diagnosis (5, 10, 11, 13, 16, 18, 21, 22), level of systemic inflammatory markers and leucocyte count (5, 7, 10, 11, 13, 18, 19, 22-25) and tobacco usage (16, 18). Several studies have found that patients with LVI are younger than other GCA patients at the time of disease onset (5, 16, 17, 26, 27). In a retrospective multicentre study in which LVI was identified in 45% of patients with GCA, the proportion of patients under 70 years in the LVI group was 60% compared to 27% in patients without LVI. Conversely, the proportion of patients over 80 years were 9% and 26%, respectively, in these groups (16). Most studies indicate that female sex is a risk factor for LVI in GCA (5, 16, 17, 26, 27).

Arterial bruit, decreased peripheral pulse, discrepancy between arm blood pressures, extremity claudication, Raynaud's phenomenon and aortic valve insufficiency are all signs and symptoms that may be due to LVI, and have been associated with subsequent imaging findings in several studies (5, 10, 16, 23, 26).

Different histopathological patterns occurring in GCA and their clinical correlation have been studied (28-33). Giant cells are reported in TAB specimens of patients with GCA with varying frequency, ranging from 37 to 84% (28, 30-39). Analyses of the association between the presence of giant cells and different clinical manifestations have generated conflicting results. We have previously investigated the predictive value of different histopathologic features of TAB for LVI and found a negative association with the presence of giant cells in the histopathological reports (22). To our knowledge, this was the first study to examine this relationship in patients with biopsy-proven GCA. The aim of the present study was to investigate predictors for LVI in an extended cohort of patients with biopsy-proven GCA, and, specifically, to assess the relation between baseline characteristics and time to LVI.

Material and methods

Patients

For identification of patients with biopsy-proven GCA, the database of the Department of Clinical Pathology in the county of Skåne (population 1 243 329 on December 2010) was used. Patients with positive TABs performed between 1997 and 2010 who were diagnosed with GCA (N=840) were identified, as previously described (2). Among these, patients from two defined areas of the county, the Kristianstad area and the Malmö are, that had previously been included in two clinical studies (22, 40) and thus had available data were pooled for the present analysis (Fig. 1). The study was approved by the Regional Research Ethics Committee for Southern Sweden (reference numbers 2010/517). No individual consent to participate was required by the Research Ethics Committee.

Data collection

The process of data collection has been described previously in detail (22, 41). The structured review of medical records and histopathology reports of all the identified patients included data extraction of items of the 1990 American College of Rheumatology (ACR) classification criteria for GCA (42). In addition, other clinical data at the time of diagnosis have been collected, e.g. previous PMR diagnosis, PMR at the time of disease onset, laboratory results, initial dose of glucocorticosteroids, visual symptoms and permanent visual impairment related to GCA at diagnosis and during the follow-up were also recorded. The patients were retrospectively classified according to the 2022 ACR/European Alliance of Associations for Rheumatology (formerly, the European League Against Rheumatism, EULAR) classification criteria for GCA (43).

All but 18 of the histopathology reports could be retrieved and reviewed. The presence or absence of giant cells, granuloma, thrombus, fragmented internal elastic lamina (IEL), inflammatory infiltrates, fibrosis, and luminal stenosis was noted. If they were not mentioned in the report, they were considered absent.

With regard to imaging studies, the patients included were evaluated according to the clinical practice; there was no specified protocol for systematic vascular evaluation during the study period. The reports of all relevant radiological and clinical-physiological studies in patients with GCA were reviewed by one of the authors (NN). LVI was defined as presence of aneurysm, ectasia, or stenosis of the aorta and/or its main branches or positive ¹⁸fluoro-2-deoxyd-glucose positron emission tomography-computed tomography (18FDG PET-CT) as assessed by the radiologist. Aneurysm of the aorta was defined as reported aortic dilatation with a loss of wall parallelism and a recorded diameter of \geq 30 mm. Aortic ectasia was defined as reported abnormal dilatation without loss of wall parallelism.

Patients with detected LVI before diagnosis of GCA were excluded. For the present study, dates of death and migra-



Fig. 1. Study population, patient acquisition sources and identification process. Patients with positive temporal artery biopsy in the county of Skåne 1997-2010. Sub-cohort I: Patients registered at the pathology unit in Kristianstad. Sub-cohort II: Residents of the city of Malmö who participated in two health surveys and developed GCA, and other patients with biopsy-proven GCA from the city of Malmö.

tion from the study area were retrieved from a regional health care register.

Statistics

Patients were followed from date of GCA diagnosis and were censored at the date of: when LVI was first detected, death, migration from the area or the end of the study (i.e. date of last chart review, July 29, 2016). Event free survival, by baseline clinical characteristics (female sex, PMR symptoms at onset, pre-existing PMR, visual symptoms at onset, and TAB findings, *i.e.*, inflammatory cells, giant cells, granuloma, disrupted IEL, fibrosis and luminal stenosis), was estimated using the Kaplan-Meier method. Potential predictors of LVI were also examined using Cox regression analysis (covariates investigated: age at disease onset, female sex, PMR at onset, pre-existing PMR, visual symptoms at onset, erythrocyte sedimentation rate (ESR), Creactive protein (CRP), platelet count (Plt), and TAB findings, i.e. inflammatory cells, giant cells, granuloma, disrupted IEL, fibrosis and luminal stenosis). For continuous variables, hazard ratios (HRs) were estimated per standard deviation (SD), and, in the case of Plt and CRP, also per quartile, using the lowest as reference. Furthermore, the risk of LVI in those aged <70 years and those aged 70–80 years was compared to those above 80 at GCA diagnosis (reference category). Covariates with p<0.20 in the bivariate analyses were included in multivariate models.

In a sensitivity analysis, only patients that had undergone large-vessel imaging at some time during the study period were included.

Results

The GCA cohort

A total of 286 patients with biopsyproven GCA were identified from the two sub-cohorts. Twelve patients with LVI before GCA diagnosis were excluded, leaving a study sample of 274. Mean age at diagnosis was 75.7 years

Table I. Baseline demographic and clinical characteristics for GCA patients, overall and by occurrence of large-vessel involvement (LVI) during the follow-up.

	All patients n=274		LVI n=51		No LVI n=223	
Female sex, n (%)	210	(76.6)	38	(74.5)	172	(77.1)
Age at onset (years), mean (SD)	75.7	(8.1)	72.9	(8.4)	76.3	(7.9)
<70 (years), n (%)	67	(24.5)	19	(37.3)	48	(21.5)
70-80 (years), n (%)	118	(43.1)	21	(41.2)	97	(43.5)
>80 (years), n (%)	89	(32.5)	11	(21.6)	78	(35.0)
Pre-existing PMR, n (%)	24	(8.8)	6	(11.5)	18	(8.2)
PMR symptoms at onset, n (%)	60	(21.8)	12	(23.5)	48	(22.3)
Visual symptoms at onset, n (%)	94	(34.3)	18	(35.2)	76	(34.0)
Permanent visual impairment, n (%)	32	(12.4)	3	(5.8)	29	(13.2)
Total visual loss, n (%)	11	(4.2)	0		11	(5.0)
ESR (mm/h), mean (SD)	77	(28)	76	(30)	77	(28)
CRP (mg/L), median (SD) [IQR]	94	(73) [54;141]	80	(57) [48;132]	95	(76) [56;144]
Plt (×10 ⁹ /L), mean (SD)	420	(137)	442	(132)	414	(138)
Initial GC dose, median (SD) [IQR]	50	(33) [40;60]	52	(15) [40;60]	50	(36) [40;60]
Days on GC before biopsy, median [IQR]	2.5	[0.0;2.5]	2.0	[0.0;2.0]	3.0	[0.0;3.0]
IV GC treated, n (%)	19	(7.4)	3	(6.4)	16	(7.6)
ACR 1990 criteria, n (%)	253	(97.3)	47	(95.9)	206	(97.6)
ACR/EULAR 2022 criteria, n (%)	259	(94.5)	49	(96.1)	210	(94.2)
Histopathology findings						
Inflammatory infiltration, n (%)	246	(96.1)	47	(95.9)	199	(96.1)
Giant cells, n (%)	138	(53.9)	21	(42.9)	117	(56.5)
Granuloma	37	(14.5)	9	(18.4)	28	(13.5)
Disrupted IEL, n (%)	156	(60.9)	32	(65.3)	124	(59.9)
Fibrosis, n (%)	56	(21.9)	10	(20.4)	46	(22.2)
Luminal stenosis, n (%)	84	(60.4)	19	(63.3)	65	(59.6)

LVI: large-vessel involvement; SD: standard deviation; IQR: interquartile range; PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Plt: platelets; Hb: hae-moglobin; GC: glucocorticoid; IV: intravenous; IEL: internal elastic lamina; AMI: acute myocardial infarction; CVI/TIA: cerebral vascular incident/transient ischaemic attack;

Normal values: for ESR: Men \geq 60 years \leq 24 mm/1h, Women >50 years \leq 35 mm/1h; for CRP: initially 9 mg/L, later <3.

Missing data: for PMR signs/symptoms: n=12, for ESR: n=25, for CRP: n=44, for Plt: n=88.

[SD 8.09; range 49.5-94.8 years]. 76.6% were females. Twenty-four (16%) of those with available information on previous medical history had a pre-existing diagnosis of PMR. At onset of GCA, 23% had current PMR symptoms, and 36% had visual symptoms. Demographics and clinical characteristics, overall and by LVI, are presented in Table I. Time on GC treatment before TAB was similar in patients with and without LVI (Table I).

Large-vessel involvement

Fifty-one (19%) had evidence of LVI after GCA diagnosis. Among these, 26

(51%) had isolated aortic involvement, 17 (33%) isolated distributary involvement and the remaining 8 (16%) patients had a combination of both. The median GCA duration prior to detection of LVI was 4.5 years (interquartile range 0.6–7.4).

Patients were followed for 2137 person-years after GCA diagnosis. Accordingly, the incidence rate of LVI was 2.4/100 person-years (95% CI [1.7, 3.0] of follow up, and was similar among males (2.4/100 person-years, 95% CI [1.1, 3.7]) and females (2.4/100 personyears, 95% CI [1.6, 3.1]).

The vascular imaging modalities whose use led to the detection of LVI are listed in Supplementary Table S1. A total of 90 patients underwent some sort of imaging during the study course. Imaging modalities used in those with *versus* without evidence of LVI are listed in Supplementary Table S2.

Distribution of the affected large vessels

Aortic ectasia was found in 20 patients (ascendens n=10, descendens n=4, abdominal n=6). In one patient, the whole aorta was ectatic and in four others the aorta had both aneurysmatic and ectatic changes. A total of 19 aortic aneurysms (ascendens n=13, descendens n=1, abdominal n=5) were found in 19 patients. Two patients had dissections, one ascending aorta aneurysm with type-A dissection and one type-B dissection without aneurysm.

Involvement of 39 distributary arteries was found in 25 cases, including 33 stenotic arteries (carotid n=7, subcla-



Fig. 2. Distribution of involved vessels for each patient in the group of patients with giant cell arteritis with large vessel involvement (LVI). Each rectangle represents one vessel bed, and each column represents one patient.

Table II. Survival time free of LVI, 75th percentile (years; Kaplan-Meier analysis).

	Present	Absent	p (Breslow)
Female sex	12.9	13.1	0.96
PMR symptoms at onset	11.7	13.7	0.98
Pre-existing PMR	10.1	11.7	0.83
Visual symptoms at onset	11.7	13.7	0.64
Giant cells	14.0	6.7	0.01
Granuloma	8.5	11.7	0.83
Disrupted IEL	9.7	14.0	0.56
Fibrosis	12.9	10.1	0.67
Luminal stenosis	10.3	10.1	0.90

PMR: polymyalgia rheumatica; IEL: internal elastic lamina. **Table III.** Predictors for LVI in GCA; unadjusted.

		HR	95 % CI
Age at disease onset (years)	<70	2.29	1.00 - 5.25
	70 - 80	1.50	0.72 - 3.21
	>80	1.00 = ref	
Age (year) (per SD)		0.82	0.61 - 1.09
Female sex		1.01	0.54 - 1.90
PMR at onset		0.89	0.46 - 1.71
Pre-existing PMR		0.85	0.35 - 2.09
Visual symptoms at onset		0.87	0.48 - 1.56
ESR (mm/h) (per SD)		0.98	0.73 - 1.31
CRP (mg/L), (per SD)		0.82	0.58 - 1.16
CRP (per quartile), lowest ≤54 (mg/L),		1.00=ref	
Quartile 2 54.1-94		0.50	0.21 - 1.16
Quartile 3 94.1-141.25		0.86	0.41 - 1.79
Quartile 4 >141.25		0.53	0.23 - 1.24
Plt (×10 ⁹ /L) per SD		1.18	0.86 - 1.61
Plt (per quartile), lowest $\leq 319 (\times 10^{9}/L)$,		1.00=ref	
Quartile 2 319.1-406		0.64	0.24 - 1.67
Quartile 3 406.1-496		0.81	0.33 - 2.01
Quartile 4 >496		0.90	0.37 - 2.15
Giant cells		0.49	0.28 - 0.87
Granuloma		1.19	0.58 - 2.45
Disrupted IEL		1.38	0.76 - 2.48
Fibrosis		0.85	0.42 - 1.70
Luminal stenosis		0.99	0.47 - 2.08

LVI: large-vessel involvement; SD: standard deviation; PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Plt: platelets; IEL: internal elastic lamina.

vian n=2, coeliac n=2, superior mesenteric n=2, renal n=2, iliac n=4, femoral n=7, distal lower extremity n=5, intracranial n=2) and 6 aneurysmatic arteries (carotid n=1, innominate n=1, coeliac n=1, iliac n=3) and one subclavian artery with signs of vasculitis on PET. The distribution and type of vessel involvement in the fifty-one patients with LVI are depicted in Figure 2.

Predictors of LVI: survival by baseline features and Cox regression - Demographics

There was no difference in survival

time free of LVI between females and males (Table II). The proportion of patients with onset of GCA at 70 years or younger was higher among those with LVI (37.3% vs. 21.5%). Compared to those aged >80 at GCA diagnosis, there was a greater risk of LVI in those diagnosed with GCA when they were younger than 70 years (HR 2.29; 95% CI 1.00, 5.25).

- Clinical features and laboratory parameters

Clinical features such as visual symptoms, inflammatory laboratory tests at diagnosis (ESR, CRP, Plt) or symptoms of PMR (pre-existing or current) did not affect the risk of future LVI (Table III and IV). Among those who developed LVI, fewer suffered from permanent visual impairment or total visual loss (Table I), although numbers were too small for meaningful time dependent analyses.

- Histopathology features

Survival free of LVI was significantly longer in patients with giant cells present in the TAB, 75th percentile 14.0 vs. 6.7 years (p=0.01; Table II and Fig. 3). Other histopathology features had no impact on the LVI- risk (Table II-III). The presence of giant cells in the TAB was associated with a reduced risk of LVI in bivariate Cox regression (Table III) as well as in multivariate analysis, adjusted for age (HR: 0.48; 95 % CI 0.27, 0.86).

- Sensitivity analysis

In analyses including only those who had undergone large-vessel imaging at least once during the study period, the negative association between presence of giant cells in the biopsy and LVI was similar to the main analysis (Suppl. Table S3). In these models, there were no associations for other investigated factors with LVI.

Discussion

In the present study, 19 % of patients with biopsy-proven GCA had diagnosed LVI during the follow-up, corresponding to an incidence of 2.4/100 person-years of follow-up. We confirmed a negative association between the presence of giant cells in the TAB and subsequent development of LVI in patients with GCA. We also observed a trend toward reduced risk of LVI with increasing age at GCA-onset, in keeping with several previous studies (5, 11, 16, 17, 26), a recent meta-analysis (27) and a recently published large multicentre study (44). By contrast, in the latter study it was shown that age at diagnosis was an independent risk factor for future development of severe complications, including aortic aneurysms/ dissection (44). The shift towards onset of GCA below age 70 in the subgroup



Fig. 3. Survival free of large vessel involvement in patients with giant cell arteritis (GCA), by presence of giant cells in the temporal artery biopsy. Kaplan-Meier method. *p*-values based on Breslow's test. Vertical lines indicate patients censored.

with LVI in the present study, with a corresponding reduction in the number of patients aged >80 years at diagnosis, is compatible with previous findings in a study that compared the same age categories (16). The lower risk in elderly patients in the present study could be due to less extensive investigations with increasing age, and we did not observe an association with age in the sensitivity analysis restricted to those that had undergone large-vessel imaging. On the other hand, in the other study with similar observations, all patients were scanned for LVI (16). We did not observe an increased risk with elevated laboratory inflammatory markers.

Previously, a higher ESR was negatively associated with LVI in some studies (5, 18, 23) but not in others (7, 10, 11, 13, 19, 22, 24, 25).

In accordance with some (10, 11), but in contrast to other studies (5, 16, 17, 26), there was no major difference between females and males in the occurrence of LVI in this study.

Previous studies indicate that cranial symptoms at the time of GCA diagnosis are negatively associated with LVI (5, 7, 11, 16-20). In the present study,

severe ocular involvement tended to be less frequent among those with LVI. Other types of cranial symptoms were not evaluated.

In contrast to our previous study of a smaller sample (22), we did not find any association between PMR symptoms at GCA diagnosis and subsequent LVI. Other previous studies of PMR as a risk factor have yielded divergent results: one reported a negative association with LVI (16), others showed no difference between the two groups (5, 10, 13, 18, 19, 21), one other study showed a higher proportion with PMR at GCA diagnosis in the LVI group (17) and one study found more patients with PMR prior to GCA diagnosis in the LVI group (11). Differences in case selection, and in the ascertainment and management of PMR, may explain these discrepancies.

Histopathological features or patterns have been the subject of several studies of possible associations with specific clinical features or clinical course. Previous studies on clinical correlations with giant cells are summarised in Supplementary Table S4. The focus of these studies has been on cranial is-

chaemic symptoms and signs, usually presence of headache/ocular and jaw manifestations, systemic manifestations and laboratory analysis in varying degrees. The number and type of histopathological features investigated also varied. Three studies found significant associations between the occurrence of giant cells and cranial ischaemic complications (34, 37, 45). Two other studies found a trend towards a higher occurrence of cranial ischaemic complications in the group with giant cells compared to those without (38, 39). The presence of giant cells was shown to be inversely correlated to the presence of marked systemic response, i.e. fever >38C° (45). Fever is more prevalent in younger patients with GCA (44), similar to LVI (5, 16, 17, 26, 27, 44), speaking in favour of different cytokine profiles (e.g. with a dominant role for IL-6) (46, 47), and different disease mechanisms in those with LVI.

Giant cells are fused macrophages, formed through interferon- γ (IFN- γ) stimulation (48). These macrophages produce among others: reactive oxygen species, matrix metalloproteinases, platelet-derived growth factor and vascular endothelial growth factor (49). IFN-y is produced by differentiated Th1 cells (49). The differentiation is driven by interleukin 12 (IL-12) (49). High levels of IL-12 (50) and IFN- γ (51) are associated with more ischaemic complications. It is possible that the LVI phenotype of GCA is less dominated by Th1 mechanisms considering less frequent presence of giant cells in the TAB, fewer cranial ischaemic manifestations and the massive presence of artery tertiary lymphoid organs that lack macrophages (52).

Limitations of this study are related to the retrospective design. Data collection was limited to the recorded information in patient charts, and no standardised physical evaluation was performed. In contrast with other studies (16), we did not limit our analysis to patients that had been investigated with ≥ 1 large-vessel imaging scan, although results on the key finding were similar in a sensitivity analysis restricted to this group. Imaging modalities during study period were heterogeneous, non-struc-

tured and often performed due to other indications than suspected vasculitis. Therefore, the incidence of LVI and its extent is likely underestimated due to lack of systematic imaging studies. LVI detected in this study reflect the clinical practice during the time period. Based on the study design, we cannot rule out that some of the changes may be of atherosclerotic origin. Furthermore, imaging and TAB were not reviewed by dedicated radiologists and pathologists in this study. This is a major limitation. Finally, as only patients with cranial GCA based on positive TAB were selected for this study, and TAB is more often negative in patients with LVI which is more common in younger patients, we may have excluded some younger patients with LVI.

Strengths of this study include the population-based study design, the relatively large patient cohort with a long follow-up period, and the systematic review of pathology reports. Furthermore, we focused on objectively verified (biopsy-proven) GCA, which had an incidence in our population that was similar to other studies of Scandinavian populations (2, 53).

This study suggests that diverse disease mechanisms may be involved in GCA with different clinical presentation and disease progression. This could affect treatment response and raises the question of whether or not GCA should be treated differently based on phenotype and understanding of the underlying pathophysiology.

Future research should include prospective studies with structured imaging evaluations and standardised quantification of the giant cells and other histopathologic features in TABs.

In conclusion, in this study of patients with biopsy-positive GCA, LVI was detected in 1 in 5 patients during followup. There was a significantly lower risk of LVI in patients with giant cells in the biopsy. This may suggest particular disease mechanisms in LVI of GCA.

Acknowledgements

The authors would like to thank Minna Willim and Jan-Åke Nilsson for their excellent help with the data management and statistical analysis.

References

- HAUGEBERG G, PAULSEN PQ, BIE RB: Temporal arteritis in Vest Agder County in southern Norway: incidence and clinical findings. J Rheumatol 2000; 27(11): 2624-27.
- MOHAMMAD AJ, NILSSON J, JACOBSSON LT, MERKEL PA, TURESSON C: Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. *Ann Rheum Dis* 2015;74(6): 993-97. https:// doi.org/10.1136/annrheumdis-2013-204652
- HUTCHINSON J: On a peculiar form of thrombotic arteritis of the aged which is sometimes productive of gangrene. *Arch Surg* 1890; 1: 323-29.
- HORTON B, MAGATH T, BROWN G: An undescribed form of arteritis of the temporal vessels. *Mayo Clin Proc* 1932; 7: 700-1.
- BRACK A, MARTINEZ-TABOADA V, STAN-SON A, GORONZY JJ, WEYAND CM: Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum* 1999; 42(2): 311-17. https://doi.org/10.1002/1529-0131
- FÖRSTER S, TATO F, WEISS M et al.: Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET. Vasa 2011; 40(3): 219-27. https://doi.org/10.1024/0301-1526/a000096
- DE BOYSSON H, LAMBERT M, LIOZON E et al.: Giant-cell arteritis without cranial manifestations: Working diagnosis of a distinct disease pattern. *Medicine* (Baltimore) 2016; 95(26): e3818. https:// doi.org/10.1097/md.000000000003818
- VAN DER GEEST KSM, SANDOVICI M, VAN SLEEN Y et al.: Review: What Is the Current Evidence for Disease Subsets in Giant Cell Arteritis? Arthritis Rheumatol 2018; 70(9): 1366-76. https://doi.org/10.1002/art.40520
- WEYAND CM, GORONZY JJ: Giant-cell arteritis and polymyalgia rheumatica. Ann Intern Med 2003; 139(6): 505-15. https://doi. org/10.7326/0003-4819-139-6-200309160-00015
- NADERI N: Giant cell arteritis a report on systematic physical evaluation and large vessel involvement as a prognostic risk factor for complicated disease course, real life data. *Arch Gen Intern Med* 2018; 2: 10-16. https://doi.org/10.4066/ 2591-7951.100043
- MURATORE F, KERMANI TA, CROWSON CS et al.: Large-vessel giant cell arteritis: a cohort study. *Rheumatology* (Oxford) 2015; 54(3): 463-70. https:// doi.org/10.1093/rheumatology/keu329
- ESPITIA O, NÉEL A, LEUX C *et al.*: Giant cell arteritis with or without aortitis at diagnosis. A retrospective study of 22 patients with longterm followup. *J Rheumatol* 2012; 39(11): 2157-62. https://doi.org/10.3899/irheum.120511
- CZIHAL M, PILLER A, SCHROETTLE A et al.: Impact of cranial and axillary/subclavian artery involvement by color duplex sonography on response to treatment in giant cell arteritis. J Vasc Surg 2015; 61(5): 1285-91. https://doi.org/10.1016/j.jvs.2014.12.045
- TATÒ F, HOFFMANN U: Giant cell arteritis: a systemic vascular disease. *Vasc Med* 2008; 13(2): 127-40.

https://doi.org/10.1177/1358863x07085499

- 15. BOTH M, AHMADI-SIMAB K, REUTER M et al.: MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. Ann Rheum Dis 2008; 67(7): 1030-3. https://doi.org/10.1136/ard.2007.082123
- 16. DE BOYSSON H, DAUMAS A, VAUTIER M et al.: Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. Autoimmun Rev 2018; 17(4): 391-98. https:// doi.org/10.1016/j.autrev.2017.11.029
- CZIHAL M, ZANKER S, RADEMACHER A et al.: Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. Scand J Rheumatol 2012; 41(3): 231-36. https:// doi.org/10.3109/03009742.2011.641581
- NUENNINGHOFF DM, HUNDER GG, CHRIS-TIANSON TJ, MCCLELLAND RL, MATTESON EL: Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum* 2003; 48(12): 3522-31.
 - https://doi.org/10.1002/art.11353
- 19. PRIETO-GONZÁLEZ S, ARGUIS P, GARCÍA-MARTÍNEZ A et al.: Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. Ann Rheum Dis 2012; 71(7): 1170-76. https:// doi.org/10.1136/annrheumdis-2011-200865
- 20. SCHMIDT WA, KRAUSE A, SCHICKE B, KUCHENBECKER J, GROMNICA-IHLE E: Do temporal artery duplex ultrasound findings correlate with ophthalmic complications in giant cell arteritis? *Rheumatology* (Oxford) 2009; 48(4): 383-85. https:// doi.org/10.1093/rheumatology/ken515
- 21. DE BOYSSON H, LIOZON E, LAMBERT M et al.: Giant-cell arteritis: do we treat patients with large-vessel involvement differently? Am J Med 2017; 130(8): 992-95. https:// doi.org/10.1016/j.amjmed.2017.03.054
- 22. NADERI N, MOHAMMAD AJ, TURESSON C: Large vessel involvement in biopsy-proven giant cell arteritis: incidence, distribution, and predictors. *Scand J Rheumatol* 2017; 46(3): 215-21. https://
- doi.org/10.1080/03009742.2016.1190984
- 23. KLEIN RG, HUNDER GG, STANSON AW, SHEPS SG: Large artery involvement in giant cell (temporal) arteritis. *Ann Intern Med* 1975; 83(6): 806-12.
- https://doi.org/10.7326/0003-4819-83-6-806 24. HAMRIN B: Polymyalgia arteritica. *Acta Med Scand* Suppl. 1972; 533: 1-131.
- 25. BOTH M, SCHULTE K, MOOSIG F et al.: High white blood cell count in patients with giant cell arteritis predicts an increased risk of stenosis in upper extremity arteries. Ann Rheum Dis 2011; 70(10): 1879-80.
- https://doi.org/10.1136/ard.2010.146910
- 26. SCHMIDT WA, SEIFERT A, GROMNICA-IHLE E, KRAUSE A, NATUSCH A: Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. *Rheumatology* (Oxford) 2008; 47(1): 96-101. https://
- doi.org/10.1093/rheumatology/kem322 27. LYNE SA, RUEDIGER C, LESTER S *et al.*:

Clinical phenotype and complications of large vessel giant cell arteritis: a systematic review and meta-analysis. *Joint Bone Spine* 2023; 90(4): 105558.

https://doi.org/10.1016/j.jbspin.2023.105558 28. HERNÁNDEZ-RODRÍGUEZ J, MURGIA G, VILLAR I *et al.*: Description and validation of histological patterns and proposal of a dynamic model of inflammatory infiltration in giant-cell arteritis. *Medicine* (Baltimore) 2016; 95(8): e2368. https://

doi.org/10.1097/md.00000000002368

- 29. CAVAZZA A, MURATORE F, BOIARDI L et al.: Inflamed temporal artery: histologic findings in 354 biopsies, with clinical correlations. Am J Surg Pathol 2014; 38(10): 1360-70. https:// doi.org/10.1097/pas.00000000000244
- 30. BREUER GS, NESHER R, REINUS K, NESHER G: Association between histological features in temporal artery biopsies and clinical features of patients with giant cell arteritis. *Isr Med Assoc J* 2013; 15(6): 271-4.
- 31. TER BORG EJ, HAANEN HC, SELDENRIJK CA: Relationship between histological subtypes and clinical characteristics at presentation and outcome in biopsy-proven temporal arteritis. Identification of a relatively benign subgroup. *Clin Rheumatol* 2007; 26(4): 529-32. https://doi.org/10.1007/s10067-006-0332-0
- 32. HUSTON KA, HUNDER GG, LIE JT, KENNEDY RH, ELVEBACK LR: Temporal arteritis: a 25year epidemiologic, clinical, and pathologic study. Ann Intern Med 1978; 88(2): 162-67. https://doi.org/10.7326/0003-4819-88-2-162
- 33. MAMBO NC: Temporal (granulomatous) arteritis: a histopathological study of 32 cases. *Histopathology* 1979; 3(3): 209-21. https:// doi.org/10.1111/j.1365-2559.1979.tb02998.x
- 34. CHATELAIN D, DUHAUT P, SCHMIDT J et al.: Pathological features of temporal arteries in patients with giant cell arteritis presenting with permanent visual loss. Ann Rheum Dis 2009; 68(1): 84-88.

https://doi.org/10.1136/ard.2007.084947

 SCHMIDT D, LÖFFLER KU: Temporal arteritis. Comparison of histological and clinical findings. *Acta Ophthalmol* 1994; 72(3): 319-25. https://

doi.org/10.1111/j.1755-3768.1994.tb02766.x 36. BEVAN AT, DUNNILL MS, HARRISON MJ:

Clinical and biopsy findings in temporal ar-

teritis. Ann Rheum Dis 1968; 27(3): 271-77. https://doi.org/10.1136/ard.27.3.271

- 37. KAISER M, WEYAND CM, BJÖRNSSON J, GORONZYJJ: Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. *Arthritis Rheum* 1998; 41(4): 623-33. https://doi.org/10.1002/1529-0131(199804)41:4<623::AID-ART9>3.0. CO;2-6
- 38. TING KH, LESTER S, DUNSTAN E, HILL CL: Association between histological features and clinical features of patients with biopsy positive giant cell arteritis. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S40-43.
- 39. ARMSTRONG AT, TYLER WB, WOOD GC, HARRINGTON TM: Clinical importance of the presence of giant cells in temporal arteritis. J Clin Pathol 2008; 61(5): 669-71. https://doi.org/10.1136/jcp.2007.049049
- 40. JAKOBSSON K, JACOBSSON L, MOHAM-MAD AJ et al.: The effect of clinical features and glucocorticoids on biopsy findings in giant cell arteritis. BMC Musculoskelet Disord 2016; 17(1): 363. https://doi.org/10.1186/s12891-016-1225-2
- JAKOBSSON K, JACOBSSON L, WARRING-TON K *et al.*: Body mass index and the risk of giant cell arteritis: results from a prospective study. *Rheumatology* (Oxford) 2015; 54(3): 433-40.

https://doi.org/10.1093/rheumatology/keu331

- 42. 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(8): 1122-28.
 - https://doi.org/10.1002/art.1780330810
- 43. PONTE C, GRAYSON PC, ROBSON JC et al.: 2022 American College of Rheumatology/ EULAR Classification Criteria for Giant Cell Arteritis. Arthritis Rheumatol 2022; 74(12): 1881-89. https://doi.org/10.1002/art.42325
- 44. MONTI S, MILANESI A, KLERSY C et al.: Age at diagnosis influences the clinical phenotype, treatment strategies and outcomes in patients with giant cell arteritis: results from the observational GCAGE study on a large cohort of 1004 patients. Ann Rheum Dis 2023; 82(8): 1098-106. https://doi.org/10.1136/ard-2023-223895
- 45. MURATORE F, BOIARDI L, CAVAZZA A *et*

al.: Correlations between histopathological findings and clinical manifestations in biopsy-proven giant cell arteritis. *J Autoimmun* 2016; 69: 94-101.

- https://doi.org/10.1016/j.jaut.2016.03.005
- 46. BILICI SALMAN R, KOCA G, GÜLBAHAR ATEŞ S et al.: Diagnostic utility of serum biomarkers in large vessel vasculitis and their correlation with positron emission tomography. *Mod Rheumatol* 2022; 32(5): 938-45. https://doi.org/10.1093/mr/roab074
- WEYAND CM, GORONZY JJ: Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol 2013; 9(12): 731-40. https://doi.org/10.1038/nrrheum.2013.161
- 48. WEYAND CM, WAGNER AD, BJÖRNSSON J, GORONZY JJ: Correlation of the topographical arrangement and the functional pattern of tissue-infiltrating macrophages in giant cell arteritis. J Clin Invest 1996; 98(7): 1642-49. https://doi.org/10.1172/JCI118959
- 49. SAMSON M, CORBERA-BELLALTA M, AUDIA S et al.: Recent advances in our understanding of giant cell arteritis pathogenesis. Autoimmun Rev 2017; 16(8): 833-44. https://doi.org/10.1016/j.autrev.2017.05.014
- 50. CONWAY R, O'NEILL L, MCCARTHY GM et al.: Interleukin 12 and interleukin 23 play key pathogenic roles in inflammatory and proliferative pathways in giant cell arteritis. Ann Rheum Dis 2018; 77(12): 1815-24. https:// doi.org/10.1136/annrheumdis-2018-213488
- 51. WEYAND CM, TETZLAFF N, BJÖRNSSON J, BRACK A, YOUNGE B, GORONZY JJ: Disease patterns and tissue cytokine profiles in giant cell arteritis. *Arthritis Rheum* 1997; 40(1): 19-26.

https://doi.org/10.1002/art.1780400105

- 52. GRAVER JC, BOOTS AMH, HAACKE EA, DIEPSTRA A, BROUWER E, SANDOVICI M: Massive B-cell infiltration and organization into artery tertiary lymphoid organs in the aorta of large vessel giant cell arteritis. *Front Immunol* 2019; 10: 83.
- https://doi.org/10.3389/fimmu.2019.00083
- 53. ANDERSEN JB, MYKLEBUST G, HAUGE-BERG G, PRIPP AH, DIAMANTOPOULOS AP: Incidence trends and mortality of giant cell arteritis in southern Norway. *Arthritis Care Res* (Hoboken) 2021; 73(3): 409-14. https://doi.org/10.1002/acr.24133