Diagnostic yield of axillary artery ultrasound in addition to temporal artery ultrasound for the diagnosis of giant cell arteritis

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Abstract

Objective

There are limited data on the additional diagnostic yield of axillary artery ultrasound (axUS) in addition to temporal artery ultrasound (tempUS) for the diagnosis of giant cell arteritis (GCA).

Methods

Retrospective study of consecutive patients with suspected GCA who underwent a standardized axUS and tempUS between 01/2015 and 03/2017. The diagnostic yield of axUS in addition to ultrasound of the temporal arteries with respect to the final clinical diagnosis was assessed, with a positive axUS defined as circumferential, hypoechogenic thickening of the far wall axillary artery intima media thickness (axIMT) ≥1.3 mm. A subgroup of patients underwent PET-CT within one week before or after the sonographic study. Separate analyses were performed regarding certain subgroups according to clinical presentation and to clinical pre-test probability for cranial GCA.

Results

Out of 228 patients, 92 received a final diagnosis of GCA. From the 92 patients with a final diagnosis of GCA, 50 (54.3%), 13 (14.1%) and 15 (16.3%) had a positive tempUS, positive axUS, and combined positive tempUS and axUS, respectively. The sensitivity of sonographic imaging for the final diagnosis of GCA increased from 69.6% to 84.8%, when axUS results were considered in addition to tempUS, while the specificity remained high (no false positive axUS). The diagnostic yield of axUS was highest in patients with a low clinical probability of cranial GCA and lowest in patients with symptoms of ocular ischemia. We observed a substantial rate (42.1%) of discordant results between axUS and PET-CT in a subgroup of 38 patients.

Conclusion

In conclusion, axUS offers a substantial diagnostic yield in addition to tempUS in subjects with suspected GCA, mainly in those subjects with low clinical probability for cranial GCA.

Key words

giant cell arteritis, ultrasound, duplex sonography, axillary artery, positron emission tomography

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Introduction

Giant cell arteritis, a disease of elderly patients aged >50 years, is the most common form of the large-vessel vasculitides (1). Progressive advances in medical imaging over the past 25 years have improved our understanding of the disease as a systemic vascular disorder with frequent involvement of the extracranial arterial circulation (2, 3). Both genetic and environmental factors may contribute to the different clinical features at disease onset (4). In recent years, important studies on the effect of biological treatment approaches on the disease course of GCA have brought the disease stronger into the focus of the scientific community (5).

Reflecting the progress in the current understanding of GCA, national and international guidelines and expert recommendations set a frame for the rational diagnostic workup in suspected GCA (6-8). Within this context, high resolution ultrasound of the temporal arteries (tempUS), a diagnostic modality facilitating fast track approaches in order to avoid ocular ischaemic complications before treatment onset, is nowadays recommended as first line diagnostic imaging at least in European countries (7, 8). In the USA, temporal artery biopsy is still considered as first line diagnostic approach, but currently efforts are undertaken on establishing sonographic imaging in the diagnostic workup of GCA (6, 9).

Colour duplex sonography of the axillary arteries (axUS) has been shown to detect involvement of the extracranial arteries in a considerable number of patients (10-12). Although recommended by European experts in suspected cranial GCA (in addition to tempUS) and as a second line diagnostic modality in suspected extracranial GCA (8), only limited data are available on the diagnostic benefit of axUS in suspected GCA (13, 14). Based on a large cohort, this study sought to evaluate the additional diagnostic yield of axUS in addition to tempUS of the temporal arteries in the diagnostic workup of suspected GCA.

Patients and methods

Patient characteristics

Consecutive patients who underwent a standardised sonographic study of the temporal and axillary arteries between 01/2015 and 03/2017 were included in this retrospective study. Clinical, laboratory and imaging data were extracted. If available, histological results of temporal artery biopsy (TAB) were collected. Based on clinical symptoms, the presence of anterior ischaemic optic neuropathy and the C-reactive protein (CRP)-values, a previously published clinical prediction score for cranial GCA was calculated (15, 16). As the 1990 American College of Rheumatology are not useful for diagnosis of extracranial GCA (11) and related to advances in non-invasive imaging temporal artery biopsy nowadays is dispensable in many patients (8), we applied modified disease classification criteria (16, 17). A final clinical diagnosis of GCA was established when at least three of the five following criteria were fulfilled: 1. age >50 years; 2. typical cranial symptoms (new onset, persisting headache, jaw claudication, temporal artery tenderness); 3. extracranial symptoms (polymyalgia rheumatica, new onset upper extremity claudication, fever of unknown origin); 4. C-reactive protein ≥1 mg/dl (normal range <0.5 mg/dl) or ESR >30 mm per 1 hour (reference range ≤20 mm per one hour); 5. typical imaging findings in vascular sonography or ^{18}Fluorodeoxyglucose-positron emission tomography-computed tomography (PET-CT) or positive temporal artery biopsy.

Ultrasound methodology

Ultrasound examinations were performed with a LOGIQ E9 machine (General Electric, Milwaukee, USA). The superficial temporal arteries were evaluated in cross-sectional view by colour duplex sonography (temporal arteries in their pre-auricular course) and temporal artery compression sonography (frontal and parietal branches at the level of the upper margin of the auricle) using an 18 MHz hockeystick transducer (LOGIQ E9, General Electric, Milwaukee, USA). The default settings were as follows: B-Mode frequency 18.0 MHz; Doppler frequency 7.5 MHz, pulse repetition frequency (PRF) 2.4 kHz. The axUS-

examinations comprised B-mode- and colour duplex sonography of the bilateral axillary arteries in longitudinal and transversal planes via the subclavicular fossa. For this purpose, a linear multifrequency transducer was used, with default settings as follows: B-Mode frequency 8.4 MHz; Doppler frequency 4.0 MHz; pulse repetition frequency 3.5 kHz. Focus, B-Mode and colour gain as well as PRF were dynamically adjusted, as required for optimal visualisation of the vessel wall.

Ultrasound definitions

A noncompressible Halo sign of ≥0.7 mm (sum of the near and far wall intima media thickness) in one or more temporal artery branches was considered to be indicative for cranial GCA (16, 18). A circumferential, hypoechogenic thickening of the far wall axillary artery intima media thickness (axIMT) ≥1.3 mm in the third axillary artery segment, at the level of the subscapular artery origin, was considered to be positive for extracranial GCA (Fig. 1) (18).

PET-CT

A subgroup of patients underwent PET-CT within one week before or after the sonographic study (GE Discovery 690, General Electric, Fairfield, CT, USA). As described previously, PET emission scans were acquired in a 3D mode (144 × 144 matrix) in a caudocranial direction and corrected for decay and scatter. PET data were reconstructed iteratively with and without attenuation correction. Non-enhanced low dose CT (140 kV, 10 mAs; n = 5) extending from the base of the skull to the proximal thighs was performed for attenuation correction. All patients fasted for at least 6 hours and were required to have serum glucose levels below 130 mg/dL. After administration of furosemide (20 mg) and butylscopolamine (20 mg), 18F-FDG was injected intravenously at an amount of 3 MBq/kg. Image acquisition started 60 minutes after tracer injection (19). FDG uptake was assessed in 4 segments of the aorta (ascending, arch, descending thoracic, and abdominal) and in 11 branch arteries (innominate artery, bilateral carotid, subclavian, axillary, iliac and femoral arteries). For every single arterial segment, tracer uptake was graded on a four point-scale (0, no or minimal vascular uptake; 1, vascular uptake lower than liver uptake; 2, vascular uptake similar to liver uptake; 3, vascular uptake higher than liver uptake). According to current recommendations, a PET-CT-diagnosis of GCA was established when the 18-FDG-uptake in any segment of the aorta or its major branches was as high or even higher as the hepatic uptake (grade 2 and 3 on the four-point scale) (8). By summing up the single uptake scores of the above-mentioned arterial segments, a previously published score (PET Vascular Activity Score, PETVAS) was calculated (20).

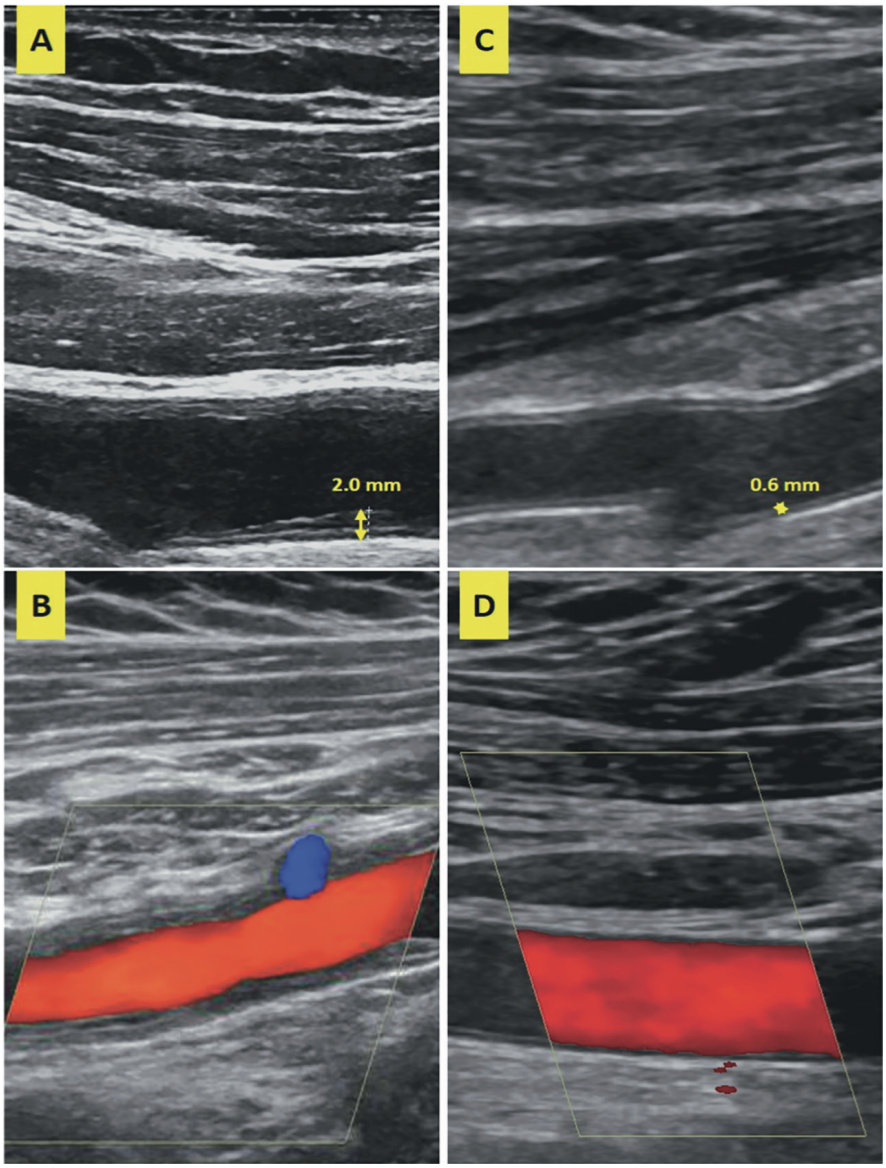

Fig. 1. Representative images of axUS (B-Mode, panel A and C; colour duplex sonography, panel B and D). While Panel A and B depict a marked, hypoechogenic, concentric intimal thickening in a patient suffering from extracranial GCA with axillary artery involvement (arrow in panel A), panels C and D show an intima media complex within the normal range in a patient with an alternative diagnosis (asterisk in panel C).

Statistical analysis

For statistical analysis, SPSS v. 25.0 (SPSS Inc., Chicago, IL, USA) was applied. The diagnostic yield of axUS in addition to tempUS with respect to the final clinical diagnosis was calculated by using 2 × 2 contingency tables. Separate analyses were performed with regard to certain subgroups according to clinical presentation and to clinical

pre-test probability for cranial GCA. Comparisons were further made between GCA-patients with and without a positive axUS-study. Univariate group comparisons were performed using χ^2-test (categorical variables) and Mann-Whitney-U-test (continuous variables). Two-sided *p*-values <0.05 were considered significant. Results for categorical variables are presented as absolute numbers with percentages, and continuous variables are displayed as mean ± standard deviation (SD).

Results

Out of 228 patients, 92 received a final diagnosis of GCA. The clinical characteristics of patients with and without a final diagnosis of GCA are compared in Table I.

Seventy-eight of 92 patients (84.8%) with a final diagnosis of GCA had a positive sonographic imaging study. Of these, 50 (54.3%), 13 (14.1%) and 15 (16.3%) subjects had a positive tempUS, positive axUS, and combined positive tempUS and axUS, respectively. Out of 136 patients with an alternative final diagnosis, 5 (3.7%) had a false positive sonographic study, all related to the temporal arteries.

Twenty-eight patients (30.4%) with a final diagnosis of GCA had a positive axUS-study. These patients were significantly more often affected by extracranial symptoms (claudication, constitutional symptoms) compared to 64 patients with GCA without axillary artery involvement by sonographic criteria (Table II). Although permanent visual loss was much less common when axillary artery involvement was detected by US, the frequency of other cranial symptoms (*e.g.* headache, jaw claudication) as well as temporal artery abnormalities by clinical examination did not differ between both groups. Moreover, the mean temporal artery wall thickness was similar, regardless of axillary artery involvement. While ongoing glucocorticoid treatment was somewhat more common in patients with a positive axUS-study, the mean duration of glucocorticoid treatment was significantly longer in this group. Conversely, the mean daily prednisolone was substantially higher in patients with a negative axUS-study, related to the fact that in this group every second patient suffered from permanent visual impairment and thus had received a high dose prednisolone pulse.

The sensitivity of sonographic imaging for the final diagnosis of GCA increased from 69.6% to 84.8%, when axUS results were considered in addition to tempUS, while the specificity remained high (Table III). The diagnostic yield of axUS results did not differ substantially

Table I. Comparison of patients with and without a final diagnosis of GCA in the overall cohort.

	Giant cell arteritis n=92	Alternative diagnosis n=136	*p*-value
Age, years (mean ± SD)	73.2 ± 10.1	71.5 ± 14.1	0.25
Female sex, n (%)	56 (60.2)	74 (54.8)	0.5
Fever, n (%)	19 (20.9)	8 (5.9)	**< 0.01**
Night sweats, n (%)	24 (26.1)	12 (8.8)	**< 0.01**
Weight loss, n (%)	29 (31.5)	13 (9.6)	**< 0.01**
Polymyalgia rheumatica, n (%)	30 (32.6)	36 (26.5)	0.37
Claudication, n (%)	6 (6.5)	3 (2.2)	0.16
Headache, n (%)	50 (54.3)	23 (23.5)	**< 0.01**
Jaw claudication, n (%)	32 (34.8)	9 (6.6)	**< 0.01**
Transient vision loss, n (%)	21 (22.8)	28 (20.6)	0.4
Permanent vision loss, n (%)	40 (43.5)	44 (32.4)	0.1
Abnormal temporal artery, n (%)	26 (28.3)	6 (4.4)	**< 0.01**
Prednisolone treatment, n (%)	52 (56.5)	39 (28.7)	**< 0.01**
Duration of prednisolone treatment, days (mean ± SD)	12.5 ± 77	5.9 ± 29	0.46
Daily prednisolone dose, mg (mean ± SD)	308 ± 444	61 ± 225	**< 0.01**
Anaemia, n (%)	37 (42)	32 (25.4)	**0.01**
Leucocytosis, n (%)	33 (37.5)	31 (24.6)	0.05
Thrombocytosis, n (%)	39 (44.3)	13 (10.3)	**< 0.01**
C-reactive protein, mg/dl (mean ± SD)	5.8 ± 6.2	3.1 ± 6.1	**< 0.01**
Erythrocyte sedimentation rate, mg/dl (mean ± SD)	51.6 ± 38.7	22.3 ± 27.6	**< 0.01**
tempUS, wall thickness, mm (mean ± SD)	0.87 ± 0.44	0.45 ± 0.11	**< 0.01**
axUS, wall thickness, mm (mean ± SD)	1.2 ± 0.56	0.84 ± 0.19	**< 0.01**
Temporal artery biopsy performed, n (%)	27 (29.3)	7 (5.1)	**< 0.01**
Temporal artery biopsy positive, n (%)	16 (17.4)	0 (0)	**< 0.01**

Table II. Comparison of patients with a final diagnosis of GCA based on a positive or negative axUS study.

	Positive axUS n=28	Negative axUS n=64	*p*-value
Age, years (mean ± SD)	70.7 ± 9.2	74.3 ± 10.4	0.10
Female sex, n (%)	20 (71.4)	36 (56.3)	0.25
Fever, n (%)	8 (28.6)	11 (17.5)	0.27
Night sweats, n (%)	13 (46.4)	11 (17.2)	**<0.01**
Weight loss, n (%)	11 (39.3)	18 (28.1)	0.33
Polymyalgia rheumatica, n (%)	11 (39.3)	19 (29.7)	0.47
Claudication, n (%)	5 (17.9)	1 (1.6)	**<0.01**
Headache, n (%)	14 (50)	36 (56.3)	0.65
Jaw claudication, n (%)	11 (39.3)	21 (32.8)	0.64
Transient vision loss, n (%)	4 (14.3)	17 (26.6)	0.28
Permanent vision loss, n (%)	7 (25)	33 (51.6)	**0.02**
Abnormal temporal artery, n (%)	8 (28.6)	18 (28.1)	1.0
Prednisolone treatment, n (%)	12 (42.9)	40 (62.5)	0.11
Duration of prednisolone treatment, days (mean ± SD)	32.4 ± 137	3.5 ± 12	0.29
Daily prednisolone dose, mg (mean ± SD)	86 ± 260	405 ± 474	**<0.01**
Anaemia, n (%)	10 (35.7)	27 (45)	0.49
Leucocytosis, n (%)	9 (32.1)	224 (40)	0.64
Thrombocytosis, n (%)	12 (42.9)	27 (45.0)	0.52
C-reactive protein, n (%)	5.2 ± 4.7	6.0 ± 6.8	0.52
Erythrocyte sedimentation rate, mm per one hour, mean ± SD	59 ± 44	48 ± 36	0.32
tempUS, wall thickness, mm (mean ± SD)	0.84 ± 0.61	0.88 ± 0.35	0.72
axUS, wall thickness, mm (mean ± SD)	1.85 ± 0.50	0.89 ± 0.35	**<0.01**
Temporal artery biopsy performed, n (%)	1 (3.6)	26 (40.6)	**<0.01**
Temporal artery biopsy positive, n (%)	1 (3.6)	15 (23.4)	**0.03**

Table III. Diagnostic accuracy of tempUS alone, axUS alone and the combination of both sonographic methods in the overall cohort and in important subgroups.

	tempUS alone	axUS alone	Combined tempUS and axUS
Overall cohort (n=228)			
Sensitivity	69.6	30.4	84.8
Specificity	96.3	100	96.3
PPV	92.8	100	94
NPV	82.4	68	90.3
Extracranial symptoms only (n=105)*			
Sensitivity	68.4	36.8	86
Specificity	95.8	100	95.8
PPV	95.1	100	96.1
NPV	71.9	57.1	85.2
Ocular symptoms (n=115)#			
Sensitivity	80	18.2	83.6
Specificity	93.3	100	93.3
PPV	91.7	100	92
NPV	83.6	57.1	86.2
Patients under glucocorticoid treatment (n=90)			
Sensitivity	65.4	23.1	76.9
Specificity	94.7	100	94.7
PPV	94.4	100	95.2
NPV	66.7	48.7	75
Patients without glucocorticoid treatment (n=138)			
Sensitivity	75	40	92.5
Specificity	96.9	100	96.9
PPV	90.9	100	92.5
NPV	90.5	80.3	96.9

*constitutional symptoms and/or polymyalgia rheumatica and/or claudication; #transient or permanent mono- or binocular visual impairment.

between different clinical scenarios, except for patients with symptoms of ocular ischaemia, in whom axUS did not offer a significant additional diagnostic yield. A similar additional diagnostic yield of axUS was observed in both patients with and without already initiated glucocorticoid treatment.

Table IV lists the diagnostic yield of axUS in addition to tempCS in relation to the number of points scored in a previously published clinical prediction rule (15). Notably, axUS exhibited an additional diagnostic impact almost exclusively in patients with low clinical probability for cranial GCA (score 0 or 1), with identification of 11 patients who had a negative tempCS study. In patients with moderate (2 or 3 points) or high (>4 points, maximum 6 points) clinical probability, only two additional patients with a negative tempCS study were identified by axUS.

Overall, thirteen patients had a negative tempUS-study but exhibited typical axillary artery wall thickening in axUS. All of these patients presented with extracranial symptoms (4 patients fulfilled the criteria for fever of unknown origin), though only one patient suffered from upper extremity claudication. Four of the patients reported cranial symptoms but none of them suffered from permanent visual loss.

In the subgroup of 38 patients who underwent both US and PET-CT within 7 days, concordant results of both imaging modalities for the diagnosis of GCA were found in 22 patients (57.9%). Twelve patients had both a positive PET-CT and a positive US-study, eight of whom had a positive axUS. Ten patients had negative results in both imaging modalities. Discordant results were found in 16 patients (42.1%). Six of 16 patients with negative PET-CT had a positive US-study (all positive tempCS but negative axUS, corresponding to isolated cranial GCA), and 10 out of 22 patients with a positive PET-CT had a negative US-study. Noteworthy, in the latter group, 4 patients suffered from extracranial GCA with isolated aortitis. The rate of concordant results was slightly higher in 15 treatment-naive patients (66.7%) compared to 23 patients already receiving prednisolone at the time of examination (56.5%). In the per-segment analysis, axIMT-values correlated significantly with SUV-values of the axillary arteries (rho 0.5, $p<0.01$, Fig. 2). Significant correlations were further found between axIMT-values and SUVmax (rho 0.53, $p<0.01$) as well as the PETVAS-score (rho 0.49, $p<0.01$).

Discussion

Our study shows that in the assessment of suspected GCA examination of the axillary arteries in addition to US of the temporal arteries increases the sensitivity of US by about 15%, while specificity remains high. The most pronounced diagnostic benefit was evident in patients presenting with extracranial symptoms. Correspondingly, axUS increased the diagnostic yield of sonographic assessment mainly in those patients considered to have a low clinical pre-test probability

Table IV. Diagnostic accuracy of axUS in relation to the number of items scored with a previously published clinical prediction rule for the diagnosis of cranial GCA.

Clinical probability	Number of patients n	Final diagnosis of GCA n (%)	tempUS alone Sensitivity n (%)	axUS Sensitivity n (%)	Additional diagnostic yield of axUS n (%)
Low (0 or 1 points)	125	33 (26.4)	15 of 33 (45.5)	14 of 33 (42.4)	11 of 18 (61.1)
Intermediate (2 or 3 points)	73	33 (45.2)	24 of 33 (72.7)	5 of 33 (15.2)	1 of 9 (11.1)
High (≥4 points)	30	26 (86.7)	25 of 26 (96.1)	9 of 26 (34.6)	1 of 1 (100)

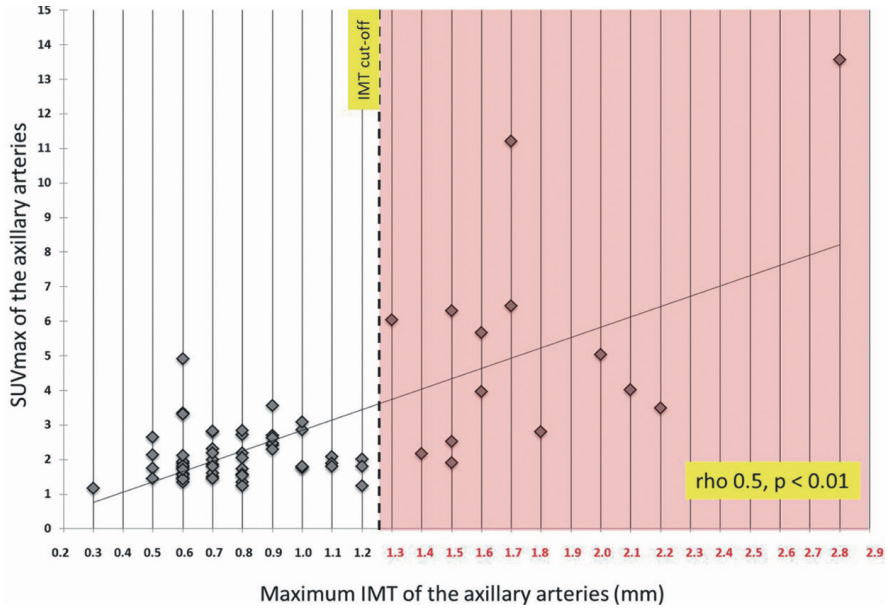

Fig. 2. Scatter plot demonstrating the correlation between axillary artery IMT and SUV of the axillary arteries in the per segment analysis.

for cranial GCA based on a structured clinical scoring system. By contrast, in patients presenting with symptoms of ocular ischaemia and in patients with a high pre-test probability for cranial GCA, axUS provided only a marginal additional diagnostic yield.

Axillary artery involvement by sonographic criteria can be found in 30% to 50% of patients with GCA (10-12). GCA-patients with axillary artery vasculitis as an indicator of extracranial large-vessel involvement were shown to be younger at disease onset and to have a higher rate of atypical symptoms such as fever of unknown origin (10-12). Moreover, axillary artery involvement by sonographic criteria may be a predictor of worse response to immunosuppressive treatment (21). It is important to note that both temporal artery US and biopsy often yield negative results in patients with extracranial GCA (10, 22).

However, data on the additional diagnostic yield of axUS in the diagnostic workup of GCA are limited. A Dutch group observed an increase in sensitivity of 19% in their cohort of 113 patients with suspected GCA (final diagnosis of GCA in 41 patients) (13). In their prospective study on 80 patients (final diagnosis of GCA in 46 patients), Nielsen *et al*. from Denmark reported a sensitivity increase from 71% to 97% with addition of US of the extracranial arteries including the axillary arteries and tempUS (14). A Norwegian series of 88 patients with suspected GCA (final diagnosis of GCA in 46 patients) documented axillary artery involvement in 14 cases, all with a final diagnosis of GCA (23). However, all but one of these patients also had a positive US of the temporal arteries. In the multicentric British TABUL-study, the prevalence of axillary artery involvement was surprisingly low (13.9%), resulting in an only marginal additional diagnostic yield of axUS (plus 2.4%). In that study, however, the rate of abnormal US findings of the temporal arteries was also rather low (46.4%) (24). Different patient profiles in the cohorts, mainly variable rates of patients presenting with symptoms of cranial vs. symptoms of extracranial GCA may also have contributed to the differences between studies regarding the additional diagnostic yield of axUS in suspected GCA (13, 14, 23, 24). In our study, axUS increased the diagnostic yield of sonographic assessment mainly in those patients considered to have a low clinical pre-test probability for cranial GCA based on a structured clinical scoring system (15).

Noteworthy, we observed a substantial rate of discordant results between axUS and PET-CT in the subgroup of patients who underwent both imaging modalities. While 57.9% had both positive US and PET-CT results, 15.8% and 26.3% were only positive in US and PET-CT, respectively. The rate of discordant results of US and PET-CT was similar in a cohort study published by Imfeld *et al*. (45.6%), including 68 patients with a final diagnosis of GCA out of a cohort of 101 patients with suspected disease. Nielsen et al. found discordant results of PET-CT and axUS (only one method with positive result) in 22.9% of patients with a final diagnosis of GCA in their prospective observational study. Furthermore, in this study only 14.7% of extracranial vessel segments that showed vasculitic changes in either imaging modality were congruently classified as positive in the per-segment-analysis with both methods (14). Taken together, current evidence strongly suggests that both diagnostic tests are complementary rather than concurring imaging modalities.

Across all studies, including ours, axillary US yielded excellent specificity for the diagnosis of GCA (13, 14, 23-25). However, specificity could be a matter of cut-off-values of axillary artery intima-media thickness. In our study, we used an axIMT cut-off of ≥1.3 mm for the diagnosis of axillary vasculitis consistent with extracranical GCA (12). Data on the optimal cut-off for the diagnosis of extracranial GCA with axillary involvement are sparse and based on limited numbers of patients. A broad range of cut-off values between 1.0 and 1.5 mm has been proposed in various studies (12, 13, 17, 18, 26, 27). Our choice of a more conservative cut-off followed the intention of avoiding misdiagnosis of axillary artery vasculitis related to nonspecific mild wall thickening associated to arteriosclerosis, as occasionally observed in recent years (26, 28). On the other hand, this may have resulted in a reduced sensitivity of axUS for the diagnosis of extracranial GCA.

Some limitations of our study should be mentioned. This is a retrospective study of clinical routine data, with all inherent drawbacks. TAB was performed in only a minority of patients, since tempUS has been the estab-

lished diagnostic method of choice at our institution for nearly two decades. Moreover, histological verification or exclusion of extracranial GCA was not feasible. Therefore, imaging methods such as US and PET-CT were included in clinical decision making regarding the final clinical diagnosis of GCA *vs*. alternative diagnoses. This implies a potential bias based on circular reasoning, an unresolved problem of many studies on the diagnostic value of imaging modalities especially in the diagnostic workup of extracranial GCA. As only a subset of our patients underwent both US and PET-CT, the validity of the comparative analysis of both imaging methods is limited.

In conclusion, axUS offers a substantial diagnostic yield in addition to tempUS in subjects with suspected GCA, mainly in those subjects with low clinical probability for cranial GCA and presenting with rather atypical symptoms. As a diagnostic method with high specificity but limited sensitivity, it should be complemented by PET-CT in cases with clinical suspicion but unremarkable findings.

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