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Original Article

Clinical Relevance and Prognostic Significance of Isolated Angiitis of the Vasa Vasorum in Temporal Artery Biopsies

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ABSTRACT: ***Background:*** Temporal arteritis (TA) is the most common vasculitis over age 50. Untreated, many patients will suffer blindness or stroke. Gold standard diagnosis is achieved by temporal artery biopsy. The aim of this study was to investigate the relevance of small vessel inflammation. ***Methods:*** Our dataset was comprised of 72 temporal artery biopsies subjected to a blinded uniform re-examination paired with clinical data including demographics, history, physical examination and laboratory findings. Documented pathology variables included the presence or absence of TA, angiitis of vasa vasorum (AVV) and inflammation of small peri-adventitial vessels (small vessel vasculitis, SVV). ***Results:*** Clinical and pathological variables were subjected to multivariate analysis. In brief, 25% of cases were identified as TA, 20% as isolated AVV, 7% as isolated SVV and 5% as mixed isolated AVV/SVV, while 43% had no inflammation (NI). All cases of TA were accompanied by small vessel inflammation: 95% exhibited AVV with or without SVV, and 5% exhibited SVV alone, demonstrating a strong association between TA and small vessel inflammation. Of the 24 cases with isolated AVV/SVV, 26% received a clinical diagnosis of TA within one year in comparison to 13% of cases that had NI. Furthermore, isolated AVV/SVV was identified in 25% of patients with a high clinical probability for TA, 60% of whom acquired a diagnosis of TA on clinical grounds within one year of follow-up. ***Conclusions:*** Our findings suggest that isolated AVV/SVV identifies a subgroup of patients with a higher risk of harboring or developing TA.

RÉSUMÉ: Pertinence clinique et importance pronostique de l'angéite isolée des vasa vasorum dans les biopsies de l'artère temporale. ***Contexte/Objectif*** : L'artérite temporale (AT) est la vascularite la plus courante chez les personnes âgées de plus de 50 ans. Sans traitement, de nombreux patients souffriront de cécité ou d'AVC. Le diagnostic de référence est établi par biopsie de l'artère temporale. L'objectif de cette étude était donc d'étudier la pertinence de l'inflammation des petits vaisseaux. ***Méthodes*** : Notre ensemble de données comprenait 72 biopsies de l'artère temporale soumises à un réexamen uniforme à l'insu (*blinded*), le tout associé à des données cliniques telles que des données démographiques, des antécédents, des examens physiques et des résultats de laboratoire. Les variables pathologiques documentées comprenaient la présence ou l'absence d'AT, d'angéite des vasa vasorum (AVV) et d'inflammation des vasa vasorum (vascularite des petits vaisseaux ou VPV). ***Résultats*** : Les variables cliniques et pathologiques ont été soumises à une analyse multivariée. En bref, 25 % des cas ont été identifiés comme des cas d'AT, 20 % comme des cas d'AVV isolée, 7 % comme des cas de VPV isolée et enfin 5 % comme des cas isolés mixtes de VPV/AVV, tandis que 43 % ne présentaient aucune inflammation. Fait à noter, tous les cas d'AT étaient accompagnés d'une inflammation des petits vaisseaux : 95 % présentaient une AVV avec ou sans VPV, et 5 % présentaient une VPV seule, ce qui démontre une forte association entre l'AT et l'inflammation des petits vaisseaux. Sur les 24 cas présentant une VPV/AVV isolée, 26 % avaient reçu un diagnostic clinique d'AT au cours de l'année contre 13 % des cas ne présentant aucune inflammation. En outre, une VPV/AVV isolée a été identifiée chez 25 % des patients présentant une probabilité clinique élevée d'AT, dont 60 % avaient reçu un diagnostic d'AT sur la base de critères cliniques dans l'année suivant un suivi. ***Conclusions*** : Nos résultats suggèrent en somme que la VPV/AVV isolée permet d'identifier un sous-groupe de patients présentant un risque plus élevé d'être porteurs ou de développer une AT.

Keywords: Neuropathology; stroke prevention; temporal arteritis; vasculitis

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Highlights

- Temporal arteritis (TA) is a common and preventable cause of stroke and blindness.
- The relevance and definition of isolated small vessel inflammation (AVV/SVV) has been debated.
- In the present study, isolated AVV/SVV was associated with a greater risk of harboring or developing TA.

Introduction

Temporal arteritis (TA) is a well-known clinical-pathological entity. Giant cell arteritis (GCA) is the more contemporary clinical term that underscores one feature of inflammation, a granulomatous/variably giant cell component (although giant cells are not always present). The latter terminology emphasizes the fact that the temporal artery is not the only affected vessel. Untreated, many patients will suffer vision loss and/or stroke. GCA is a systemic inflammatory condition, related to polymyalgia rheumatica whereby symptoms of TA may accompany other rheumatologic findings such as morning stiffness or hip pain.[1]

According to the 2022 classification criteria for GCA by the American College of Rheumatology/European League Against Rheumatism, a minimum age of 50 years is a requirement. Select symptoms, signs and laboratory findings are awarded points in support of the diagnosis (which requires a total of 6 points). Clinical criteria include sudden vision loss (3 points) and morning stiffness in the shoulders or neck, jaw or tongue claudication, new temporal headache, scalp tenderness and abnormal examination of the temporal artery (2 points each). Laboratory and imaging criteria include elevated ESR >= 50 mm/h, or CRP >= 10 mg/L (3 points), bilateral axillary artery involvement on imaging and FDG-PET activity throughout the aorta (2 points each). Among paraclinical criteria, the presence of either a positive temporal artery biopsy or a halo sign on temporal artery ultrasound is the most highly weighted, each earning 5 points towards the diagnosis.[2] Despite changes in the 2022 classification criteria of TA,[2] temporal artery biopsy is still regarded as the diagnostic method with the highest specificity.[3] However, treatment with corticosteroids is almost always undertaken on the basis of clinical suspicion prior to pathological confirmation.

The use of corticosteroids prior to biopsy can affect the sensitivity of pathologic examination, as can small sample size or deliberate removal of surrounding soft tissue from the specimen (skeletonization) by the surgeon. Biopsies are not always harvested at the same stage of inflammation, and the degree and extent of inflammation can vary widely. Even untreated, the inflammation can be remarkably focal or patchy and missed by the biopsy.

While clear positive cases may be definitive (transmural granulomatous inflammation, typically involving the internal elastic lamina and adjacent intima and media), "negative" cases are qualified at best, given the patchiness of the disease. Studies have shown that up to 40% of clinically diagnosed TA may have negative pathology.[4] Similarly, a patient may have a negative biopsy but progress to a diagnosis of GCA in follow-up on clinical/serological grounds. The significance of other inflammatory changes, such as isolated angiitis of the vasa vasorum (AVV) or small vessel vasculitis (SVV) in the absence of definitive temporal artery inflammation is uncertain.

Some studies have provided evidence for the association of AVV and SVV with GCA, suggesting that these entities may represent subsets of TA.[5–8] Others have concluded that isolated AVV and SVV do not provide histologic evidence of TA.[9–11] While treatment effects can reduce the sensitivity of the histopathological examination,[5,12] given the segmental involvement of TA, the presence of isolated AVV and SVV in the relevant clinical setting invites further attention.[13,14]

In the present study, our principal aim was to investigate the clinical and prognostic relevance of isolated AVV.

Methods

The study was approved by our institutional research ethics review board. The initial phase of the study focused on all temporal artery biopsies performed at London Health Sciences Centre (LHSC) in 2018. Seventy-two cases were retrieved and anonymized. All cases had been examined in 2018 by one of four neuropathologists. Biopsies were processed according to the standard procedure at LHSC. Specimens were conservatively trimmed in cross section at approximately 3 mm intervals and oriented under low-power microscopy. Ten levels were cut at 5 μm thickness with 50 μm intervals: seven stained with H&E, one with Movat pentachrome and two reserved for potential immunohistochemistry. Additional sections were obtained if required. The microscopic slides of these cases were re-examined in a blinded fashion and scored qualitatively and semi-quantitatively for inflammatory findings affecting the wall of the main biopsied vessels in addition to the vasa vasorum and peri-adventitial small vessels. All cases underwent H&E and Movat's pentachrome stains and immunohistochemistry for inflammatory cell markers (CD45, CD3 and CD68, Dako GA751, GA503 and GA609, respectively) in select cases. A neuropathologist (RH), an anatomical pathologist (SP) and a graduate student (MS) were involved in the standardized microscopic analysis. All slides were reviewed by SP and MS, blinded to the assigned diagnoses. In case of uncertainty, disagreement in diagnosis between the two reviewers, or discordance with the original pathological diagnosis, the senior neuropathologist reviewed the cases and the group reached consensus.

By histopathological examination, cases were categorized into 3 groups: (1) TAs; (2) isolated AVV or SVV; and (3) no inflammation (NI). TA was identified by lymphohistiocytic inflammation within the arterial wall including the media, internal elastic lamina and/or intima (Figure 1A). Inflammation surrounding small vessels of the adventitia identified AVV (Figure 1B, arrows), while inflammation of small vessels outside compact adventitial connective tissues (Figure 1B, arrowhead) identified SVV.[7] Adventitial and peri-adventitial small vessels were regarded as "positive/inflamed" if inflammatory infiltrates enveloped at least half their circumference. The inflammatory cell composition (lymphocytes, histiocytes, giant cells, plasma cells, neutrophils and eosinophils) was graded from sparse to abundant (scored as 1 to 3). The integrity of the internal elastic lamina (IEL) was assessed by Movat's pentachrome staining.

The clinical records of all cases were reviewed in a blinded fashion and demographic, diagnostic and treatment variables were recorded (MS, SP, RC and LB). The variables collected included the following: date of temporal artery biopsy, date of symptom onset, date of corticosteroid initiation, clinical probability of GCA (as determined by the treating physician prior to biopsy), preexisting comorbidities, symptoms and signs at presentation, results of paraclinical investigations and post-biopsy clinical diagnosis at one-year follow-up. The clinical probability of GCA was assessed using a commonly employed clinical scoring system

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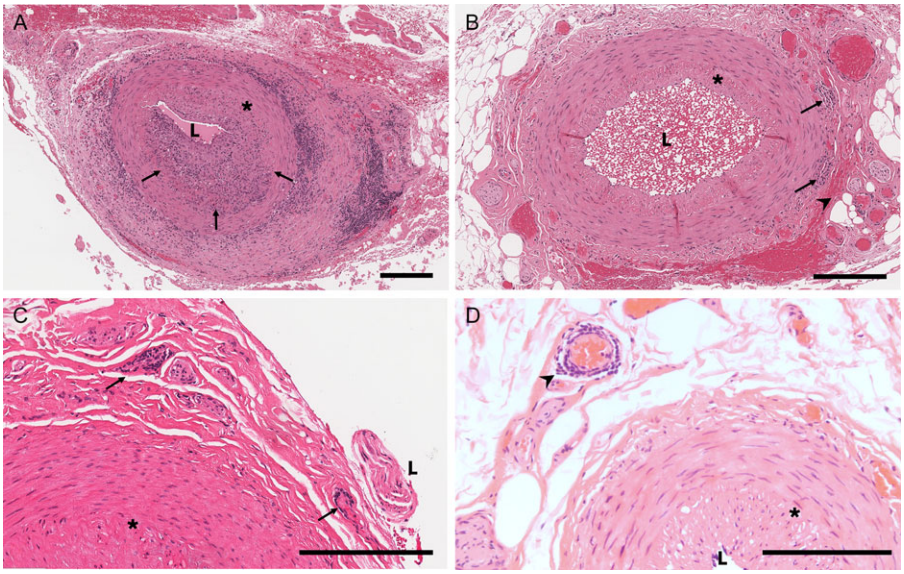

Figure 1. Isolated AVV/SVV may exist in a vessel that is elsewhere affected by TA. Photomicrographs of two separate segments of a temporal artery biopsy reveal the presence of TA (A) in one segment and AVV/SVV without TA (B) in another segment demonstrating that TA (A), AVV (B, arrows), and SVV (B, arrowhead) can co-exist in separate segments of the same biopsy. (A). Photomicrograph of a temporal artery branch in cross-section, demonstrating patchy, transmural, lymphohistiocytic inflammation with a region of heavy internal elastic lamina inflammation and disintegration (arrows). H&E stain, *L* = lumen, asterisk = internal elastic lamina, bar = 250 um. (B). Photomicrograph of a separate segment of the same temporal artery branch as in 'A' demonstrating a relatively preserved arterial architecture, intact internal elastic lamina (asterisk), no transmural inflammatory infiltrate but the presence of vasa vasorum surrounded by lymphohistiocytic infiltrates (arrows). H&E stain, *L* = lumen, bar = 250 um. Isolated AVV and/or isolated SVV can be the lone finding in cases that obtain a clinical diagnosis of TA in follow-up. (C). From a biopsy with no pathological evidence of temporal arteritis, isolated AVV (arrows) is present. H&E stain, asterisk = internal elastic lamina, bar = 250 um. (D). From a biopsy with no pathological evidence of temporal arteritis, isolated small vessel vasculitis (arrowhead) is present within periadventitial soft tissue. H&E stain, asterisk = internal elastic lamina, bar = 250 um. AVV/SVV = isolated angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

in the field,[15] as temporal artery ultrasound is not routinely available at our center. The pre-biopsy clinical probability was scored as low, moderate, or high for each patient based on clinical history, physical examination and paraclinical tests. The diagnosis at one-year follow-up was based on clinical features observed over time, including symptom progression, response to therapy, identification of comorbidities, as well as imaging and laboratory findings.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics (version 29.0). For continuous variables, the Kruskal–Wallis test was used. For categorical data, the Fisher's exact test was used. A significance level of 0.05 was adopted.

Results

Demographics, symptoms and signs

Mean age among the three groups was similar (73.7 in isolated AVV/SVV group versus 70.4 and 69.0 years in TA and NI groups, respectively).

The majority of biopsies (69.4%) were from females. The percentage of females in each diagnostic category was 55.6% (TA), 69.6% (isolated AVV/SVV) and 77.4% (NI).

The list of comorbidities compared among the three pathological groups is shown in Table 1. There was no statistically significant difference among these groups. However, polymyalgia rheumatica (PMR) was clinically diagnosed in 38.9% of the isolated AVV/SVV group, more than twice the frequency of patients with TA or NI (16.7%).

Clinical findings

Among the presenting symptoms and signs in this cohort, jaw claudication and diplopia were significantly more common in patients whose biopsies revealed TA, compared to AVV/SVV ($p = 0.008$) and NI($p = 0.006$). The TA group endorsed constitutional symptoms and scalp tenderness more frequently, although the difference was not statistically significant (Figure 2).

Paraclinical findings

At presentation, mean ESR and CRP were highest in the TA group, although the difference was only statistically significant for CRP (Figure 3).

Histopathological findings

Extent of inflammation

On microscopic examination, 25% of the cases were diagnostic for TA, while 43% were categorized as NI. The remaining cases had either isolated AVV (20%), isolated SVV (7%), or both (5%). All cases with pathological evidence of TA were accompanied by small vessel inflammation including AVV in 78%, SVV in 5% and both AVV and SVV in 17%.

Inflammatory cell composition

The inflammatory cell types observed on microscopic examinations were dominated by lymphocytes and histiocytes. Moderate to severe AVV and SVV were only present in the TA group. While lymphocytes were the predominant inflammatory component of small vessel inflammation, mild histiocytic infiltrates were present in 55% of isolated AVV/SVV cases. Plasma cells and eosinophils were also present, predominantly in the setting of TA (64.3% of cases with TA) with moderate to severe lymphohistiocytic inflammation and were not seen in isolated AVV/SVV, unfortunately negating their potential value as a marker for a clinical diagnosis of TA during the period of follow-up.

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Table 1. Frequency of different comorbidities among the three pathological groups

Comorbidities	NI	AVV/SVV	TA	Total	*p*-value
Infection, *n* (%)	6 (17)	1 (6)	0 (0)	7 (10)	0.191
Cancer, *n* (%)	9 (25)	6 (33)	2 (11)	17 (24)	0.279
Other neurological condition, *n* (%)	4 (11)	3 (17)	2 (11)	9 (12)	0.896
Ophthalmological disturbances, *n* (%)	8 (22)	8 (44)	5 (28)	21 (29)	0.254
Cranial neuropathy, *n* (%)	3 (8)	4 (22)	1 (6)	8 (11)	0.33
Ischemic heart disease, *n* (%)	12 (33)	5 (28)	1 (6)	18 (25)	0.062
Hypertension, *n* (%)	23 (64)	10 (56)	10 (56)	43 (60)	0.78
Dyslipidemia, *n* (%)	16 (44)	8 (44)	9 (50)	33 (46)	0.952
Diabetes mellitus, *n* (%)	10 (28)	5 (28)	5 (28)	20 (28)	1
Smoking, *n* (%)	12 (33)	5 (28)	4 (22)	21 (29)	0.75
Ischemic stroke/TIA, *n* (%)	9 (25)	4 (22)	5 (28)	18 (25)	1
Hemorrhagic stroke, *n* (%)	1 (3)	0 (0)	0 (0)	1 (1)	1
VZV reactivation, *n* (%)	0 (0)	2 (11)	0 (0)	2 (3)	0.12
Hepatitis C, *n* (%)	1 (3)	0 (0)	0 (0)	1 (1)	1
Migraine, *n* (%)	4 (11)	0 (0)	0 (0)	4 (6)	0.172
Polymyalgia rheumatica, *n* (%)	6 (17)	7 (39)	3 (17)	16 (22)	0.192
Other autoimmune conditions, *n* (%)	9 (25)	3 (17)	2 (11)	14 (19)	0.546

NI = no inflammation; AVV/SVV = isolated angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

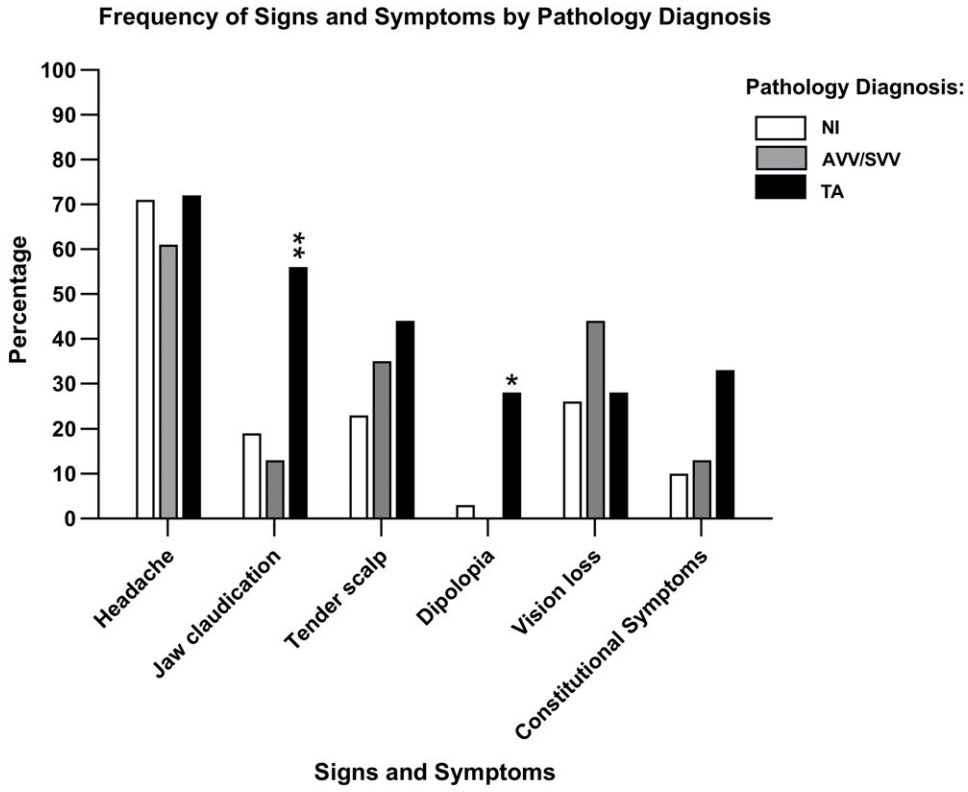

Figure 2. Jaw claudication and diplopia were significantly more common in patients with a pathological diagnosis of TA. NI = no inflammation; AVV/SVV = angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

IEL damage

Evidence of IEL damage was present in all three pathological categories with the highest prevalence in TA (89%) compared to NI (32%) (p-value < 0.001) and isolated AVV/SVV (61%, p-value $= 0.075$). Biopsies with NI had less IEL damage in comparison to the AVV/SVV group; however, this did not reach significance (p-value $= 0.053$).

From the original pathology reports, one case was converted to TA from isolated AVV after review by our team. The term small vessel inflammation was not uniformly applied in original reports at

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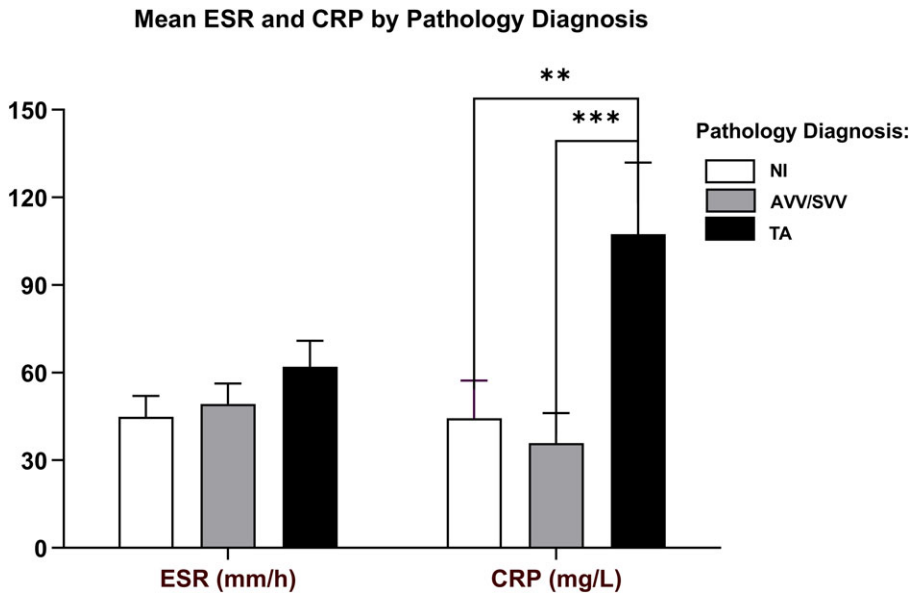

Figure 3. Measurements of CRP were significantly higher in patients with a pathological diagnosis of TA. NI = no inflammation; AVV/SVV = angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

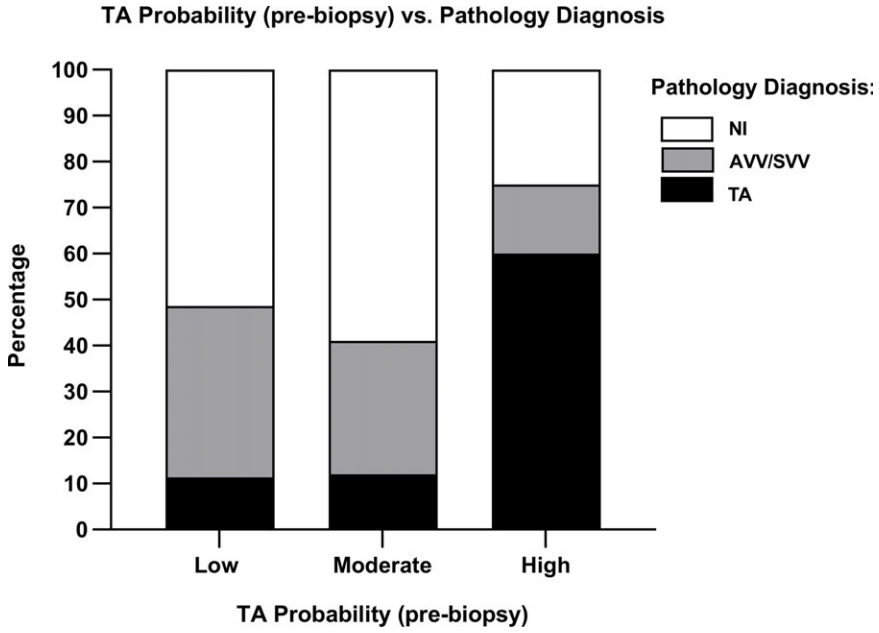

Figure 4. Clinical suspicion of TA correlated with the pathological diagnosis (TA vs NI or AVV/SVV). NI = no inflammation; AVV/SVV = angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

our center. As a result, 14 cases (19.4%) were originally diagnosed with "other/miscellaneous inflammation," which were re-categorized as isolated AVV/SVV. In 5 additional cases (6.9%), small vessel inflammation had not been included in the original pathology report.

Clinical probability correlation with pathological diagnosis and delays before biopsy

Among patients with a high clinical probability for TA, 60% had pathological evidence of TA, 25% had isolated AVV/SVV, while 15% had NI. In patients with a moderate clinical probability of TA, 12% had pathological evidence of TA, 29% had isolated AVV/SVV and 59% had NI. In patients with a low clinical probability of TA, 11.4% had pathological evidence of TA, 37.1% had isolated AVV/SVV and 51.4% had NI (p value<0.001) (Figure 4).

The average delay between the start of symptoms and temporal artery biopsy was compared among the three groups of patients. As shown in Figure 5, the mean delay was greater in the isolated AVV/SVV (90.76 days ± 199.45) and NI groups (44.66 days ± 51.06), in comparison to the TA group (31.06 days ± 28.63); however, variance was large, and this difference did not reach significance.

A total of 80.5% of patients had documented steroid use prior to biopsy. The mean dose was 54.38 ± 14.18 mg/day, with no statistically significant difference observed among the three pathological groups.

The average interval between initiation of corticosteroid therapy and temporal artery biopsy was compared across the three patient groups. The mean delay was longest in the NI group (15.5 ± 17.6 days), compared to the isolated AVV/SVV (9.0 ± 11.1

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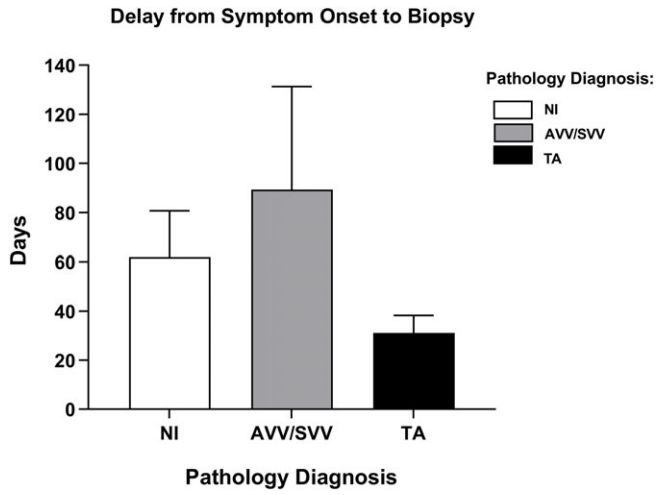

Figure 5. Delay between symptom onset and biopsy in AVV/SVV vs. TA. NI = no inflammation; AVV/SVV = isolated angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

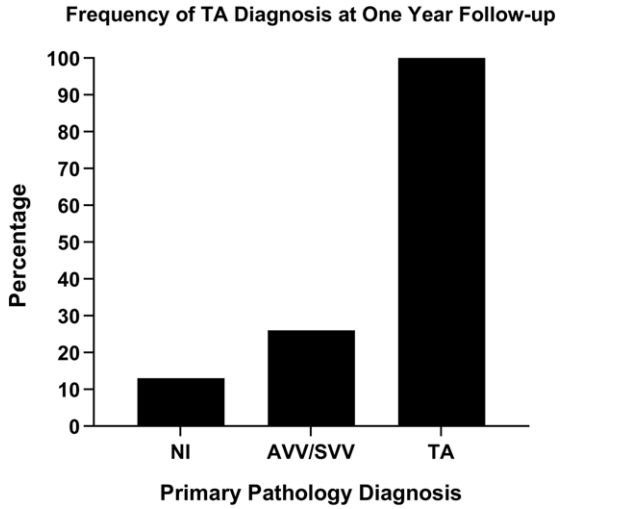

Figure 6. In a one-year clinical assessment, TA pathological diagnosis was unchanged (100%); 26% of AVV/SVV cases and 13% of non-inflamed cases received a clinical diagnosis of TA. NI = no inflammation; AVV/SW = isolated angiitis of vasa vasorum and/or small vessel vasculitis; TA = temporal arteritis.

days) and TA (9.6 ± 7.9 days) groups; however, this difference was not statistically significant.

At one-year follow-up, the diagnosis was unchanged for patients carrying a pathological diagnosis of TA. However, 26% of patients in the isolated AVV/SVV group acquired a clinical diagnosis of TA in comparison to 13% of patients in the NI group ($p < 0.001$) (Figure 6).

Isolated AVV/SVV was identified in 25% of patients with a high clinical probability for TA, 60% of whom received a clinical diagnosis of TA within one year of follow-up. By comparison, isolated AVV/SVV was identified in 34% of patients with a low to moderate clinical probability for TA, 22% of whom received a clinical diagnosis of TA within one year of follow-up. Finally, 54% of patients with low to moderate probability for TA had negative biopsies, 7% of whom were clinically diagnosed as TA within one year.

Discussion

This study highlights the importance of underrecognized inflammatory changes of small vessels in temporal artery biopsies. Our results concur with studies that identified an association between TA and small vessel inflammation.[5–8]

Our patient demographics are comparable with those of previously published studies.[5,6] In the present study, TA was always accompanied by AVV/SVV, reinforcing their strong association. Furthermore, of patients with isolated small vessel inflammation, 26% attained a clinical diagnosis of TA at 1-year follow-up, twice as often as patients with biopsies showing NI (13%). These findings suggest that isolated AVV/SVV is a clinically relevant diagnosis that identifies a subset of patients with a greater likelihood of developing TA, having partially treated TA, or harboring TA outside the biopsied segment (see Figure 1). This is particularly evident in patients considered to have a high pre-biopsy probability of TA, where 60% of those with a pathological diagnosis of AVV/SVV acquired a clinical diagnosis of TA within one year of follow-up.

Sampling bias may lead to a diagnosis of isolated AVV/SVV even when TA is present. Figure 1 shows an example in which features of TA and small vessel inflammation (AVV/SVV) were focally present in isolation in different segments of a temporal artery biopsy, clearly demonstrating that depending upon sample size and biopsy location, TA may exist in a vessel where only isolated AVV/SVV is found. Cases like this also reinforce the importance of a thorough, semi-serial examination of the biopsied vessel.

The level of clinical suspicion of TA is predictive of the pathological diagnosis. High probability cases were enriched for pathological diagnoses of TA as well as the percentage of AVV/SVV cases that received a clinical diagnosis of TA in follow-up. This finding is also consistent with the notion that TA exists on a continuum of severity whereby isolated AVV/SVV may represent a milder, earlier or partially treated stage.

The delay between symptom onset (with treatment) and temporal artery biopsy may also negatively impact the sensitivity of the pathological diagnosis. In the present cohort, there was a trend toward a longer delay for the isolated AVV/SVV group. Longer delays to biopsy and prolonged corticosteroid treatment could mask TA, leaving only subtle inflammatory findings (isolated AVV/SVV) or NI.

There is no existing consensus on formal criteria for AVV/SVV. The patterns that have emerged in this study have most likely become apparent by adopting a standardized approach to the microscopic examination with matched clinical data and multivariate analyses. We recommend a standardized scoring scheme similar to that employed in the present study to create a more uniform basis for the recognition of AVV/SVV in temporal artery biopsies and to facilitate a more comparable cumulative experience in the medical literature.

The frequency of isolated AVV/SVV cases in our cohort is greater than that of many previous studies. This may be due to a higher incidence and/or a more liberal scoring methodology.

The incorporation of clinical data, including treatment and diagnosis at one-year follow-up was a strength of this project. The fact that our results are from one Canadian academic center, and as such may not be broadly generalizable to other institutions and regions is a limitation. The absence of an established convention for scoring small vessel inflammatory changes also limits the ability to

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compare present results to previous studies. The present study is also limited with respect to its semi-quantitative analysis of inflammatory cell subpopulations. It may be valuable for future studies to expand this analysis. Similarly, our current sample size ($n = 72$) may have limited our ability to identify additional correlations.

Conclusion

Overall, the present study demonstrates that the pathological diagnosis of isolated AVV/SVV identifies a subset of patients at higher risk of receiving a clinical diagnosis of TA in follow-up. Future directions include expanding case numbers to strengthen the statistical analysis. Assessing our collection of clinical and pathological data through machine learning algorithms may also uncover additional correlations and actionable findings.

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Author contributions. Study concept and design: SP, LB, RH. Pathology analysis: SP, MS, MH, RH. Patient recruitment and clinical database: LB, PB, LB, AP, LA. Statistical analysis: RC, LB, SP, RH. Initial draft: SP, RH. Editing and proofing: SP, RH, LB, PB, LB, AP, LA.

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Competing interests. LB has received grant funding from Otsuka and Pfizer, consulting fees from Otsuka, Abbvie, Amgen and GSK and honoraria from Otsuka. LB is President of the Canadian Vasculitis Network. PB has received honoraria from Amgen, Abbvie, Boehringer and Novartis. LLCDB has received honoraria from King's University College. LLCDB is Clinical Lead for ophthalmology surgery for Ontario Health.

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