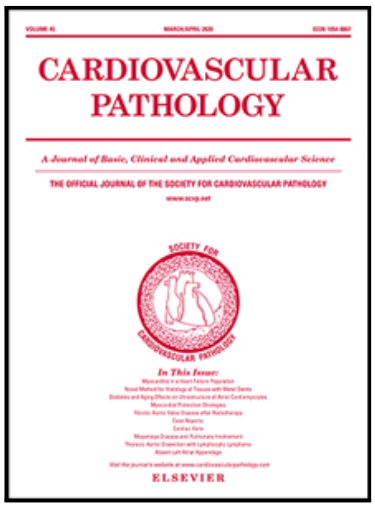

Consensus Statement on the Processing, Interpretation and Reporting of Temporal Artery Biopsy for Arteritis

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Consensus Statement on the Processing, Interpretation and Reporting of Temporal Artery Biopsy for Arteritis

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ABSTRACT

Giant cell arteritis (GCA) is the most common systemic vasculitis in adults in Europe and North America, typically involving the extra-cranial branches of the carotid arteries and the thoracic aorta. Despite advances in non-invasive imaging, temporal artery biopsy (TAB) remains the gold standard for establishing a GCA diagnosis. The processing of TAB depends largely on individual institutional protocol, and the interpretation and reporting practices vary among pathologists. To address this lack of uniformity, the Society for Cardiovascular Pathology formed a committee tasked with establishing consensus guidelines for the processing, interpretation, and reporting of TAB specimens, based on the existing literature. This consensus statement includes discussion of the differential diagnoses including other forms of arteritis and noninflammatory changes of the temporal artery.

1. Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis affecting adults in Europe and North America, typically involving the extra-cranial branches of the carotid arteries and the thoracic aorta, and characterized by lympho-histiocytic inflammation of the arterial wall, typically with giant cells [1] [2, 3] [4]. It predominantly affects people of northern European descent, with a female-to-male ratio of 2-3:1 and a United States prevalence of 204 per 100,000 aged 50 years or older. Morbidity largely relates to vision loss, although aortic involvement can also lead to aneurysms and dissections [5] [6]. Unlike some of the other autoimmune systemic vasculitides, there are no specific serologic markers of disease, and while certain non-invasive imaging techniques have recently been adopted as relatively specific diagnostic modalities, histopathologic demonstration of arteritis involving a biopsied temporal artery remains the reference standard for a diagnosis of GCA [7] [8] [9].

Despite the central role of tissue pathology in the diagnosis of GCA, a uniform system for the interpretation and reporting of histopathologic findings in temporal artery biopsy (TAB) specimens has yet to be proposed. While there are guidelines regarding the processing of TAB specimens [10], it has been a decade since their publication and thus they may not thoroughly incorporate our expanded knowledge of this disease, nor accurately correlate with current clinical guidelines regarding GCA [11] [12].

With this in mind, the Society for Cardiovascular Pathology set out to establish consensus guidelines for the processing, interpretation, and reporting of TAB specimens, based on the existing literature; these guidelines are intended for use not only by the pathologists who report these cases, but also by other health care professionals involved in the management and study of GCA. This document will address TAB specimen adequacy in the setting of suspected GCA, macroscopic tissue description and processing to ensure a thorough representation of biopsied tissue, the appropriate use of histochemical and immunohistochemical stains in the histologic interpretation of TAB specimens, light microscopic criteria for the diagnosis of GCA, and standardized nomenclature for the pathologic reporting of TAB specimens (Table 1). This document will also discuss the interpretation of findings which currently fall into so-called grey-zone areas, including inflammation restricted to arterial adventitia or peri-adventitial vessels, and how certain histologic findings may or may not be helpful in the differentiation of GCA from other vasculitides and other acute and chronic injury patterns [13-15]. Theories and controversies regarding the pathophysiology, including the role of certain microbes as triggering agents in GCA, will also be discussed [16] [17, 18].

2. Methods

Consensus committee membership was solicited from members of the Society for Cardiovascular Pathology. This international and multi-institutional committee membership identified the common diagnostic challenges of TAB encountered by surgical pathology services. The committee's initial step was a literature review focused on potential recommendations for TAB processing and nomenclature. Several publications over the last few years have proposed specimen processing protocols, pathophysiology of disease, and standardized nomenclature of specimen reporting. Some of these publications expanded beyond the pathological concepts to patient-related clinical features and management. The recommendations by these authors provided a starting point to establish a consensus document. The next step involved the consensus committee members constructing consensus guidelines for nomenclature and diagnostic criteria. For this report, consensus is defined as being agreement from the majority of the members of the committee and may not necessarily, in all cases, indicate a unanimous opinion. As such, the opinions put forth here do not necessarily represent the opinions of all members of

the Society. For the consensus opinions, an emphasis was placed on incorporating evidence from relevant published peer-reviewed literature.

3. Normal Temporal artery structure

The superficial temporal artery is a terminal branch of the external carotid artery that begins in the parotid gland behind the mandible and courses superiorly within the superficial temporal fascia, anterior to the ear. Above the zygomatic bone, the superficial temporal artery then divides into anterior frontal and posterior parietal branches. Surgical biopsy is often taken from the main trunk at the level of the tragus, where the diameter of the vessel is usually 2 – 3 mm, or from one of its distal branches, where the vessel is slightly narrower [19]. Histologically, the superficial temporal artery is a muscular artery, composed of three layers—the intima, media, and adventitia (Figure 1). The innermost layer, the intima, comprises a single layer of endothelial cells, a subendothelial layer consisting of variable amounts of collagen, fibroblasts, smooth muscle and elastic tissue, and a well-defined, thick, scalloped internal elastic lamina (IEL). In small children, the subendothelial layer is practically imperceptible, and endothelial cells appear to rest directly on the IEL [20]. In older adults, however, the intima is thickened as the result of expansion of the subendothelial tissues. In the adult, the media consists of 10-15 layers of smooth muscle cells with small amounts of intervening collagen and occasional fine elastic fibers; its outer border consists of an ill-defined external elastic lamina. Finally, the adventitia is the layer of connective tissue surrounding the vessel, composed of mostly collagen and fine elastic fibers, in which small vessels, including vasa vasorum, and nerves may be found.

4.Specimen Processing [10]

4.1.1 Rationale

Superficial temporal arteries are routinely biopsied to evaluate for vasculitis, particularly GCA. Since this disorder affects arteries in a discontinuous fashion with skip lesions, it is essential to extensively sample cross-sections of the specimen. Evaluation of only a single section can increase the probability of a false-negative diagnosis. Although classified as a medium-sized artery, the superficial temporal artery is small enough to pose difficulty with tissue orientation if it is sectioned prior to processing.

4.1.2 Gross description and processing

The length and width of the arterial segment should be noted. While we recognise that in some centers the artery is sectioned prior to processing, the recommendation by the committee is to place the intact arterial biopsy segment in a tissue cassette (with appropriate specimen bag, wrap or lens paper) and subject it to routine processing prior to cross-sectioning. After processing and just prior to embedding, the artery is serially sectioned at 1- to 2-mm intervals. This is typically done by a skilled histotechnologist. The pieces should be carefully embedded as cross-sections to allow for evaluation of all vascular layers. All the arterial cross-sections can generally be embedded in the same paraffin block. It should be clearly indicated that the specimen is a temporal artery that requires cross-sections to be made and embedded as “rings” or “cross-sections.” Use of a special-colored or flagged cassette for TAB is helpful to ensure that the technical staff will recognize and realize how to process the specimen.

4.1.3 Stains and sections

Multiple hematoxylin and eosin (H&E)-stained slides should be evaluated. For each cross-section of artery, it is recommended that a minimum of five levels be obtained, which may be serial sections or step sections. In borderline cases with inflammation limited to the adventitia, additional levels should be performed. In addition, an elastic stain or Movat stain is helpful to assess for fragmentation of the IEL. Temporal arteries may be involved by systemic amyloidosis, which can mimic the clinical presentation of giant cell arteritis. If amyloid is suspected either clinically or on the H&E stain, an amyloid stain such as Congo red may be assessed.

Active arteritis is a morphologic diagnosis; immunohistochemistry may be supportive, but immunohistochemical evidence alone is not sufficient to make a definitive diagnosis of arteritis. Immunohistochemical stains for histiocytes (CD68 or CD163) and T lymphocytes (CD3) may be helpful to delineate subtle involvement of the arterial wall by inflammation. Recent cohort studies on the use of CD3 and CD68 immunostaining in the diagnosis of GCA, do show incremental improvements in the sensitivity of standard histology [21]. Increased CD68-reactive cells have also been associated with refractoriness to steroid taper and increased need for immunomodulatory therapy [22]. Additionally, increased CD8-reactive T-lymphocytes has been associated with a higher rate of visual disturbances [23]. However, other studies have demonstrated immunostains are of limited utility have also been observed [24], hindering widespread adoption of immunohistochemistry for TAB.

4.1.4. Role of bilateral biopsy

The decision to perform unilateral versus bilateral biopsies largely depends on institution and/or clinician preference. Bilateral temporal artery biopsies may increase the sensitivity in some patients. Discordance yield may vary from 4.4% to 9.8% in bilateral biopsies in studies on 132 and 250 patients respectively[25] [26]. In a recent study by Agostino et al.[27] the discordance rate was 13% in bilateral biopsies from 185 patients, while in a review study from 11 previous reports, on a larger cohort of 1935 bilateral biopsies, performed sequentially or simultaneously, the mean discordant rate was of 5.5 percent (95% CI 3.2-7.8) [28].

5.1. Active arteritis

Active arteritis is defined as an inflammatory infiltrate involving the arterial media. Perivascular infiltrates without medial involvement, whether in arteries, arterioles, capillaries, venules, veins, or lymphatics, do not constitute active arteritis or active vasculitis. In the setting of the TAB, these perivascular infiltrates should prompt additional work-up of the specimen, including evaluation of deeper levels. It may also be appropriate to include a diagnostic comment as discussed below.

The diagnostic features of active GCA include the presence of an inflammatory infiltrate consisting of activated epithelioid macrophages within the arterial media [29]. The macrophages are most often present on the medial aspect of the IEL causing fragmentation but can also be seen throughout the media and are thought to migrate from the adventitial aspect of the vessel the disease progresses. The presence of Langhans-type giant cells is helpful, but not required for the diagnosis. True granulomas are rarely present. There is typically a lymphocytic or lymphohistiocytic inflammatory infiltrate within the media and in the adventitial and peri-adventitial connective tissue, often associated with small vessels such as capillaries and venules (Figure 2). Rarely, neutrophils with focal necrosis may be identified, however this should not be a dominant feature and, when present, other entities should be considered, as discussed below (see differential diagnosis). Within the length of the biopsy specimen, there are often arterial

branches that arise from the main temporal artery specimen; medial involvement of these branch arteries with the aforementioned infiltrate is sufficient to render a diagnosis of active GCA, even if there is no inflammation in the larger temporal artery. In active GCA, there is typically significant intimal proliferation and thickening which is responsible for the narrowing of the vessel lumen causing the downstream ischemic manifestations.

The committee does not recommend the term “atypical arteritis". A diagnosis of atypical arteritis has been reported in the literature when there is a scant cellular inflammatory infiltrate without giant cells, mainly adventitial location of inflammation including vasa vasorum vasculitis [30], less dense chronic inflammation with occasional giant cells [31], or when giant cells are found in the small side branches of the temporal artery [32]. Fibromyxoid intimal proliferation and intimal inflammation may also be present (Figure 3). While the diagnostic criteria used vary between studies, most authors consider that a diagnosis of atypical arteritis connotes the same clinical significance as a classical arteritis. The committee recommends a diagnosis of active arteritis in these cases.

5.2. Adventitial or periadventitial chronic inflammation

Some TAB will demonstrate adventitial or peri-adventitial chronic inflammation that does not involve the media. These inflammatory infiltrates have been characterized as small vessel vasculitis (SVV), vasa vasorum vasculitis (VVV) and inflammation limited to the adventitia (ILA) in the literature [33]. The committee agrees that while these infiltrates are non-specific and are not, by definition, active arteritis in isolation, they are important findings in an otherwise uninflamed artery. In some cases, these adventitial infiltrates have been the only findings in biopsies from patients with the clinical syndrome of GCA and may represent a marker of true arteritis elsewhere in the cranial circulation, as GCA is known to have so-called “skip” areas. Therefore, the recommendation by the committee is that this finding should prompt the pathologist to obtain additional levels with the intention of uncovering an area of medial inflammation deeper within the block that will allow the diagnosis of active arteritis.

5.3. Inflammation limited to the intima

It is acknowledged that some areas remain complex and controversial, such as the term appropriate for inflammation identified only in the intima. The recommendation is to perform serial sections in these cases. Immunostains for histiocytes may also be helpful. Some employ the term “endarteritis” as a final diagnosis, but it should be regarded as very rare.

5.4. Healed arterial injury: The consensus is that TAB with a pattern compatible with remote arteritis be reported as healed arterial injury. There are no universally accepted definitions or diagnostic criteria for healed arteritis and the clinical significance of this diagnosis is unclear [14]. In addition, there is histomorphologic overlap between trauma (accidental, iatrogenic, prior biopsy), age-related changes, and healed arteritis. The superficial temporal artery is particularly vulnerable to injury due to its superficial location with little soft tissue “padding” between the skin and the bone [34]. The frequency of the diagnosis of healed arteritis on retrospective review ranges from 1.5% to 4% [31, 35-39]. The diagnosis is often made when there is a constellation of findings observed in the biopsy sample — these include considerable intimal thickening with smooth muscle cells and collagen deposition, extensive loss of the IEL, medial fibrosis in relation to the damaged IEL, neovascularization, and fibrous thickening of the adventitia with fragmentation and loss of the external elastic lamina [40](Figure 4). It is, however, rare to see all or several features in a single TAB allowing one to make a straightforward diagnosis of healed arteritis. Clinical history of aortitis and aortic aneurysm may be helpful but is not always elicited at the time of the biopsy. It should be noted that focal or even multifocal breaks in the IEL are common in patients without arteritis.

Inflammation, when present, is usually sparse and most commonly present only in the adventitia. Of note, giant cells are never observed in healed arteritis. In the absence of inflammation, differentiation between arteriosclerosis and healed arteritis is challenging [41]. Concentric intimal thickening and fragmentation/loss of the IEL can be misinterpreted as evidence of vascular injury [39]. Thus, it is not surprising that retrospective reviews of healed arteritis cases would show that arteriosclerosis or age-related changes have been misdiagnosed as healed arteritis in 6% to 64% of cases [31, 36, 39]. Intraobserver reproducibility of this diagnosis is also questionable with the most discrepancy noted in this diagnostic category [35].

6. Differential Diagnosis

The temporal artery, by virtue of being a medium-sized muscular artery, can intrinsically be involved by a number of other arteritides beyond GCA [42]. Many of these also are associated with fatigue, arthralgia, and fever. Further, in cases of temporal artery involvement, it is reasonable to also suspect retinal artery involvement, and thus vision change is not specific to GCA. Although GCA is probably the most likely diagnosis for an active temporal arteritis, it is important to put the findings of a TAB in clinical context to avoid prematurely excluding less common diagnoses (Table 2).

6.1 Other primary vasculitides

6.1.1. Polyarteritis nodosa (PAN)

PAN commonly affects medium-sized arteries and can have a relatively non-specific histologic appearance of mixed inflammation and fibrinoid necrosis. PAN however is not characterized by giant cells or granulomas, and these findings should exclude the diagnosis of PAN. Systemic features typically include skin and/or visceral involvement.

6.1.2. Granulomatosis with polyangiitis (GPA)

GPA, formerly known as Wegener's granulomatosis, is a necrotizing granulomatous small-vessel vasculitis. In rare cases that involve the temporal artery, granulomas and giant cells are found within the media and extend into the adventitia and periadventitial (perivascular) spaces (Figure 5). A neutrophilic small-vessel vasculitis may be present in the adventitia. GPA is often associated with circulating anti-proteinase 3 (anti-PR3) or, less commonly, anti-myeloperoxidase (anti-MPO) anti-neutrophil cytoplasmic antibodies (ANCA), although some cases of GPA may be ANCA negative. Systemic involvement is common and typically involves the upper airways, lungs, and kidneys.

6.1.3. Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA, also called Churg-Strauss syndrome, typically involves smaller vessels but can involve the temporal artery in rare cases (Figure 6). While it is acknowledged that the presence of eosinophils are not specific for EGPA, any TAB with a marked eosinophilic component should prompt consideration for EGPA, particularly if associated with necrosis. It should also be noted that giant cells are also recognized component of EGPA, so this feature alone is not useful in the distinction of GPA and EGPA. EGPA is a multi-system disease and is classically associated with systemic eosinophilia, upper airway and lung disease (typically asthma), and involvement of skin and/or kidneys. A significant fraction of cases are associated with ANCA, typically anti-MPO. Recently, there is evidence emerging of a possible anti-MPO associated syndromic presentation with involvement of the temporal artery [43], [44], [45] [46].

6.2. IgG4-related disease (IgG4-RD)

The growing spectrum of IgG4-related disease (IgG4-RD) has also been described to involve the temporal artery (Figure 7a & 7b) [47] [48] [49]. Traditional pathologic criteria require at least one histologic feature (dense lymphoplasmacytic inflammation, storiform fibrosis, obliterative phlebitis) and an IgG4+ to IgG+ plasma cell ratio greater than 40%. In the aorta, there must also be greater than 50 IgG4+ plasma cells per high-power field, averaged across three high-power fields [47][50].

There may be a significant population of eosinophils or macrophages, albeit not granulomas, thus increasing histologic overlap with other diagnoses. There will often be involvement of the pancreas, salivary glands, or retroperitoneum. IgG4-RD often occurs in the setting of elevated serum IgG4 levels, but elevated serum IgG4 levels are neither specific nor sensitive for IgG4-RD.

6.3. Infections:

It is always possible for infections to involve the temporal artery, as with any other site in the body. Although bacterial and fungal infections would be expected to present with a more obviously septic picture, this may not always be the case. In instances with a clinical history suggestive of possible infection or when suppurative inflammation is present, it may be reasonable to exclude infection using special stains. There are acknowledged to be reports of viral associations, particularly Varicella Zoster Virus (VZV), with temporal arteritis, although data currently discount these associations [51].

6.4. Primary arteriopathy:

Healing arterial injury from any cause can mimic GCA. As such, dissections, ruptures, and other direct injury associated with primary vasculopathy, such as Marfan disease, Loeys-Dietz syndrome, fibromuscular dysplasia, or Moyamoya disease, should at least be given consideration in appropriate clinical context [52-54].

6.5. Arteriosclerosis, atherosclerosis, and age-related changes:

Arteriosclerosis is an umbrella term that is typically characterized by intimal fibroplasia, sometimes with vascular calcification and/or elastic lamina damage and/or duplication [24]. It is typically asymptomatic but can cause headache, claudication and amaurosis fugax [55]. Although primary involvement of the temporal artery by atherosclerosis is rare, embolism from external carotid artery atheroma can mimic symptoms of GCA. Age-related changes is a term used to represent the spectrum of intimal fibroplasia and elastic lamina fragmentation that are observed in older individuals, thought to represent chronic “wear and tear” of the vessel (Figure 8A & B) [40].

6.6. Arterial Calcification:

It is very rare to see calcified atherosclerotic plaque in the temporal artery. However, calcification may occur along the IEL and/or in the media. This pattern can be part of the spectrum of Mönckeberg’s medial calcific sclerosis (Figure 9A&B) [56] or systemic calciphylaxis in the setting of end-stage renal disease [60, 61]. The occurrence of this condition in the temporal artery and the presence of a fragmented IEL should not be erroneously interpreted as sequelae of previous arterial inflammation. Although calcification is typically not accompanied by inflammation, focal foreign-body giant cell reaction and osseus metaplasia with multinucleated osteoclasts have been reported [57].

6.7. Amyloidosis:

Amyloid, particularly in the setting of systemic / light chain (AL) amyloidosis, may involve the temporal artery. In isolated or preferential involvement of the temporal artery, symptoms and findings can mimic vasculitis. Further, on histologic examination, a giant cell reaction to the amyloid may be seen. It is important to recognize the classical extracellular amorphous, lightly eosinophilic material (Figure 10A&B), and this should prompt evaluation of confirmatory special stain(s), such as Congo red. Of note, amyloid also stains differently from collagen on trichrome stain (often appearing "battleship grey") and Movat stain (often appearing "mahogany orange"). Jaw claudication and polymyalgia rheumatica may be the presenting manifestations [58] .

6.8. Thrombosis and trauma:

Thromboembolism, and rarely primary thrombosis, can be seen even in the absence of primary vasculitis. This is particularly true with trauma, which can also cause IEL fragmentation, damage to the media, arterial dissection, aneurysm, and/or pseudoaneurysm (Figure 11). In addition, spontaneous dissection, aneurysm, and pseudoaneurysm may be seen in diseases such as Marfan syndrome, Loeys-Dietz syndrome, fibromuscular dysplasia, or Moyamoya disease, creating a similar pattern. The healing stages of these injuries can mimic GCA and healed arterial injury (from any etiology) may be histologically indistinguishable.

7. Treatment-Associated Effects

A suspected diagnosis of temporal arteritis is usually followed by prompt therapeutic intervention, usually in the form of high-dose daily corticosteroids. Depending on the clinical circumstances, initiation of treatment may precede biopsy for a variable length of time. Consequently, the anti-inflammatory effects may impact the degree and pattern of inflammation seen on a given specimen. Persistence of inflammation following corticosteroid therapy has been reported in a number of retrospective reports [59] [60]. If the corticosteroid therapy is initiated before the biopsy, biopsy should ideally be performed within 7 days to reduce the impact of corticosteroid treatment on the histopathology.

A prospective analysis of second TAB obtained at fixed time points after an initial histologic diagnosis of temporal arteritis showed that frequency of identified inflammation decreased in a time-dependent fashion from 71% at 3 months to 25% at 1 year [61]. The character of this inflammation also changed over time becoming less overtly granulomatous over the ensuing months and more lymphocytic. Perhaps not surprisingly, over time, features of healed arteritis (e.g., medial fibrosis, irregular intimal fibroplasia, and IEL disruption) become more common as well. Levels of circulating acute phase reactants (e.g., ESR) also tend to decrease commensurately with treatment [62].

11. Reporting Temporal Artery Biopsies

Certainly, making (or missing) a diagnosis of GCA has significant clinical consequences. However, the key clinical question to be answered by the biopsy is really whether active arteritis is present or not. To that end, the final diagnosis should clearly state whether the biopsy shows active arteritis.

Other findings discussed above (chronic inflammation limited to adventitia, small vessels, or vasa vasorum) may also be mentioned, either in a comment or in the microscopic description, but the "top-line" diagnosis should not include these terms since clinical significance is unclear and their mention may create confusion. Likewise, the presence of age-related changes or medial calcific (Mönckeberg) sclerosis should not be stated in the final diagnosis, but preferably discussed in a comment or microscopic description making it clear these do not indicate arteritis. For normal-appearing biopsies, a comment

should be included to mention the possibility of sampling error given the segmental nature of involvement in this disease.

The consensus is to avoid the term "temporal arteritis" as a diagnostic term since it may be used descriptively and not necessarily synonymous with GCA. The committee also recommends the diagnostic term of "active arteritis" instead of "giant cell arteritis", as giant cells are neither necessary nor sufficient to make a diagnosis of GCA. As mentioned above, lymphohistiocytic inflammation is not entirely specific for GCA and may be seen in other entities (PAN, GPA, EGPA, IgG4-RD, etc.). Specifically diagnosing GCA when active arteritis is present could potentially direct attention away from these other possibilities, especially in younger patients or those with an atypical clinical presentation. It is not necessary to specifically mention these other possibilities in every report, but it may be helpful in certain cases.

Intraoperative frozen section histopathology is not recommended for assessing TAB, due to the need for multiple serial sections and the possibility of hampering the eventual permanent section review. If frozen section is performed, the results should also be stated in the report and correlated with the permanent section findings.

Some example report formats are offered (Table 3) with recommendations for reporting (Figure 12)

12. Clinical impact

The diagnosis of active arteritis has classically been considered a "critical result" requiring immediate communication to the clinical team [63] . That said, currently most patients are already being treated empirically prior to biopsy. As such, while the results are certainly worthy of "rush" processing, it should be discussed at each clinical center as to whether the clinicians prefer to be notified immediately upon establishing a diagnosis. If treated as a critical result, it is important to document the communication with the clinical team.

Two recent clinical consensus documents, one by the European Alliance of Associations for Rheumatology (EULAR) in 2018 (formally published in 2020) [64], and one by the American College of Rheumatology (ACR) and the Vasculitis Foundation in 2021 [12], have provided guidance for the diagnosis, treatment, and management of GCA. Both recommend the use of high dose oral glucocorticoids for newly diagnosed disease, with the addition of tocilizumab, a monoclonal antibody therapy directed against IL-6, to reduce steroid burden, although the timing of such varies between the guidelines; this therapy was specifically validated by the Giant-Cell Arteritis Actemra (GiACTA) trial [65]. Tapering of the oral steroids occurs over 6-12 months depending on clinical symptoms and adjuvant therapy (such as tocilizumab). Guidelines allow for consideration of methotrexate or abatacept (the latter a modified monoclonal antibody therapy targeting CTLA-4) as alternatives or adjuvants to tocilizumab. The recommendations are against anti-platelet, anti-thrombotic, or statin therapies for the GCA alone, although aspirin can be considered in some cases. Recommendations are against surgical intervention for uncomplicated GCA. Long-term clinical monitoring of symptoms and laboratory markers is recommended for all cases.

Of note, neither clinical guideline statements make any recommendation regarding the diagnosis of healed arteritis. Both guidelines specifically start their decision-making algorithm at a new diagnosis of active arteritis explicitly, so the guidelines do not necessary apply to cases of healed arteritis. Additionally, a growing literature emphasizes the need for stratifying GCA diagnoses in order to identify different therapeutic requirements [66]. These include hypotheses as to which patients, for example, may require no steroids at all, those that require longer term therapy, or those that may respond well to novel steroid-

sparing therapies. Findings on biopsy are a major component of these stratifications, and particularly are emphasized as valuable regarding ongoing research. At this time, however, there is no universally accepted histologic stratification system nor specific recommendation to this effect in the current consensus document.

13. Summary

This consensus document offers a uniform system and standardized guidelines for processing, interpreting, and reporting TAB specimens. It is acknowledged that, for some pathologists, these criteria will require a change in the manner in which certain diagnostic terms are employed.

- The consensus is that medial involvement by inflammation is necessary to warrant a diagnosis of active arteritis and that perivascular inflammation without medial involvement should not be classified as active arteritis. It was agreed upon that the term "active arteritis" be used in the diagnostic section and avoid "temporal arteritis" as the diagnosis.

- The committee recommends the term "healed arterial injury" instead of "healed arteritis."

- Active arteritis is a morphologic diagnosis; immunohistochemistry may be useful, but immunohistochemical evidence alone is insufficient to make a definitive diagnosis of arteritis.

- Giant cells can be seen in the context of amyloidosis and intimal /medial calcification, a diagnosis of GCA should not be made in the absence of accompanying active inflammation in the media.

- The finding of inflammation limited to the adventitia/periadventitia is considered non-specific. It is not, by definition, active arteritis, but should prompt the pathologist to obtain additional histological levels. This pattern of inflammation can coexist with medial or transmural involvement in deeper sections due to the skip nature of GCA. In these cases, immunohistochemical stains may be helpful. If the adventitial chronic inflammation is the only inflammatory pathology within the biopsy after additional work-up, the presence of this inflammation should be noted in the report along with a note stating the possible significance of this finding.

There was consensus that the temporal arteries should be processed as rush specimens and a discussion at each clinical center as to whether the clinicians want to be notified immediately upon a diagnosis being established.

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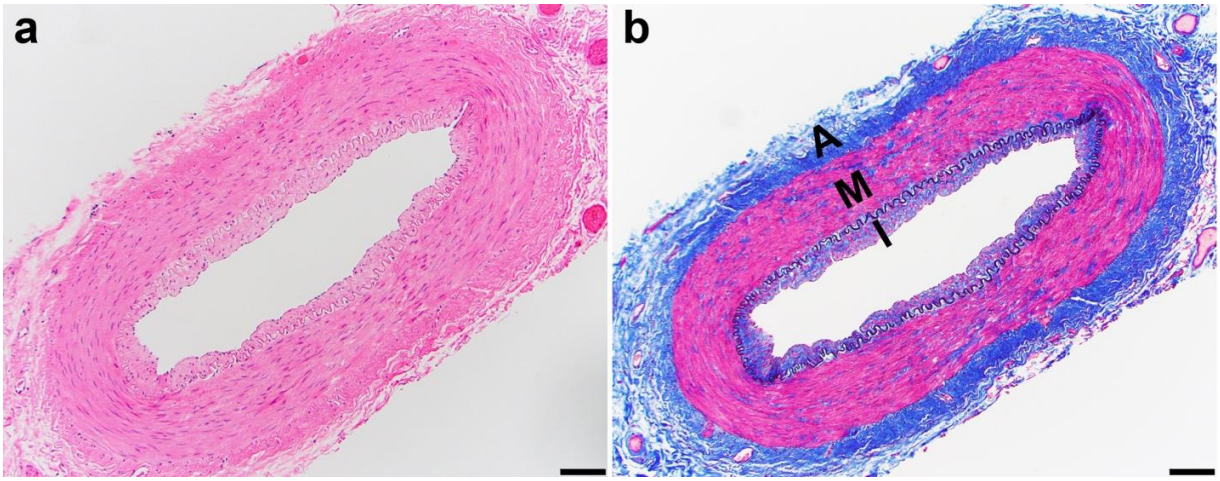

Figure 1: The superficial temporal artery is a muscular artery, composed of three layers—the tunica intima, tunica media, and tunica adventitia (a- Hematoxylin & Eosin stain, b- Masson trichrome stain)

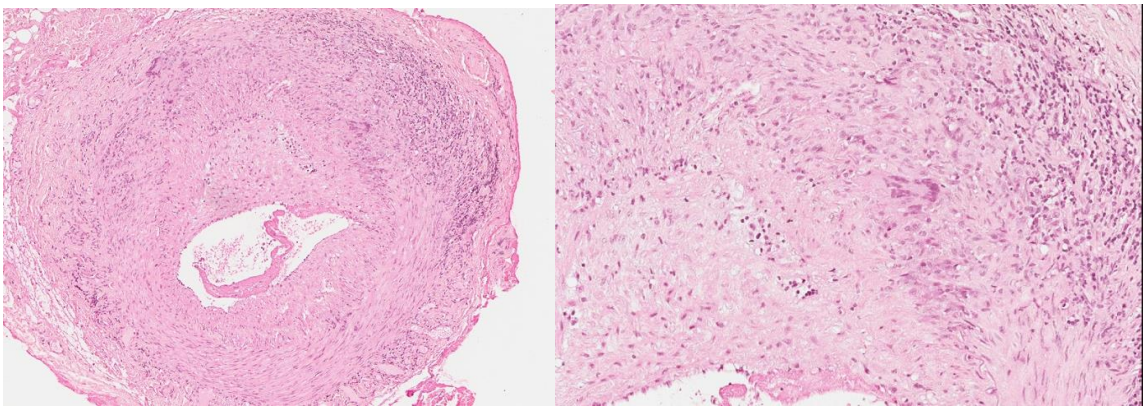

Figure 2a: Microphotograph of an active temporal arteritis. There is typically a lymphocytic or lymphohistiocytic inflammatory infiltrate within the media and in the adventitial and peri-adventitial connective tissue. 2b. Higher Magnification highlights the Giant cells. (Hematoxylin & Eosin stain).

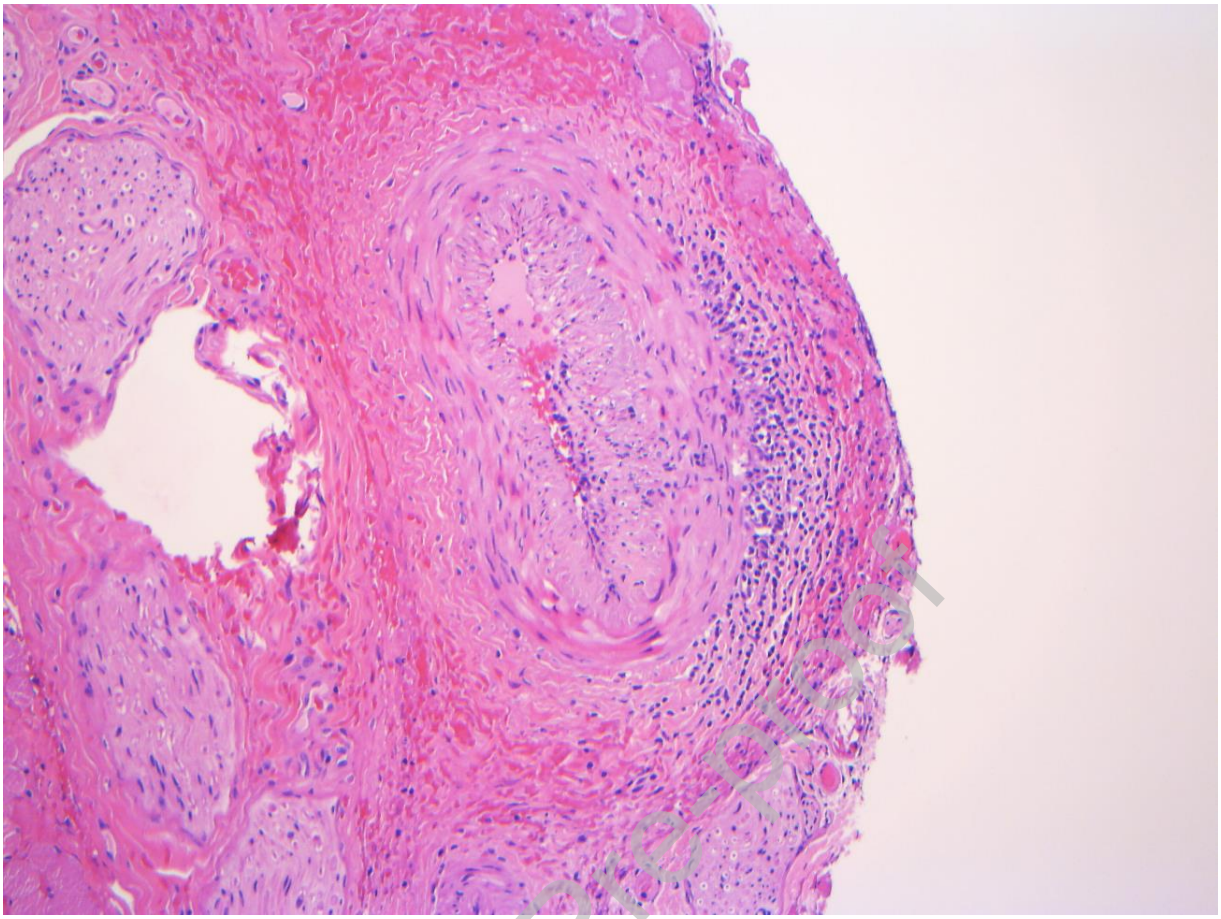

Figure 3 Microphotograph of a temporal artery with active arteritis. The lymphohistiocytic infiltration is predominantly in the adventitia. There are few infiltrates in the intima and occasional in the media. This is histological pattern consistent with what some authors describe as atypical arteritis.

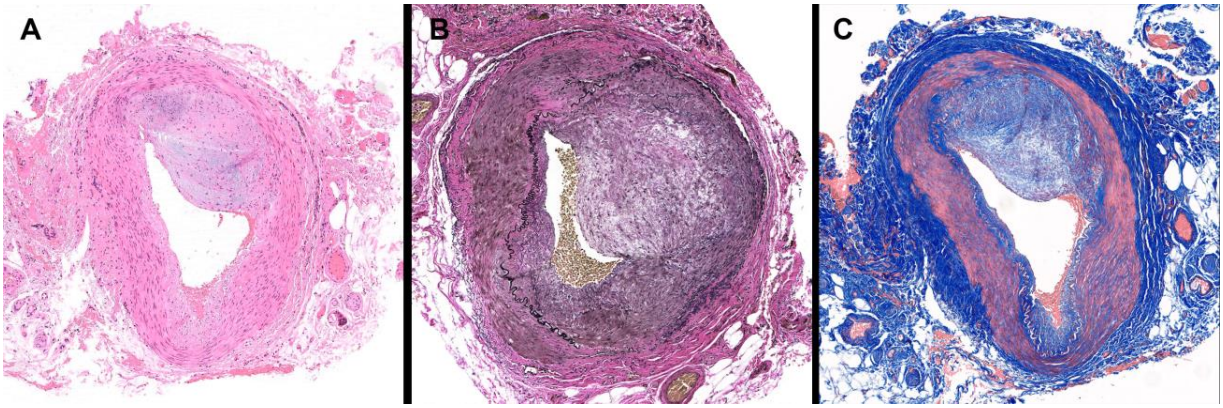

Figure 4: Microphotograph showing Healed arterial injury. There is considerable intimal thickening with smooth muscle cells and collagen deposition, medial fibrosis in relation to the damaged internal elastic lamina, neovascularization, fibrous thickening of the adventitia (a- Hematoxylin stain). Extensive loss of the internal elastic lamina, fragmentation and loss of the external elastic lamina is also identified (b- Elastic Van Gieson & c -Masson's trichrome stain)

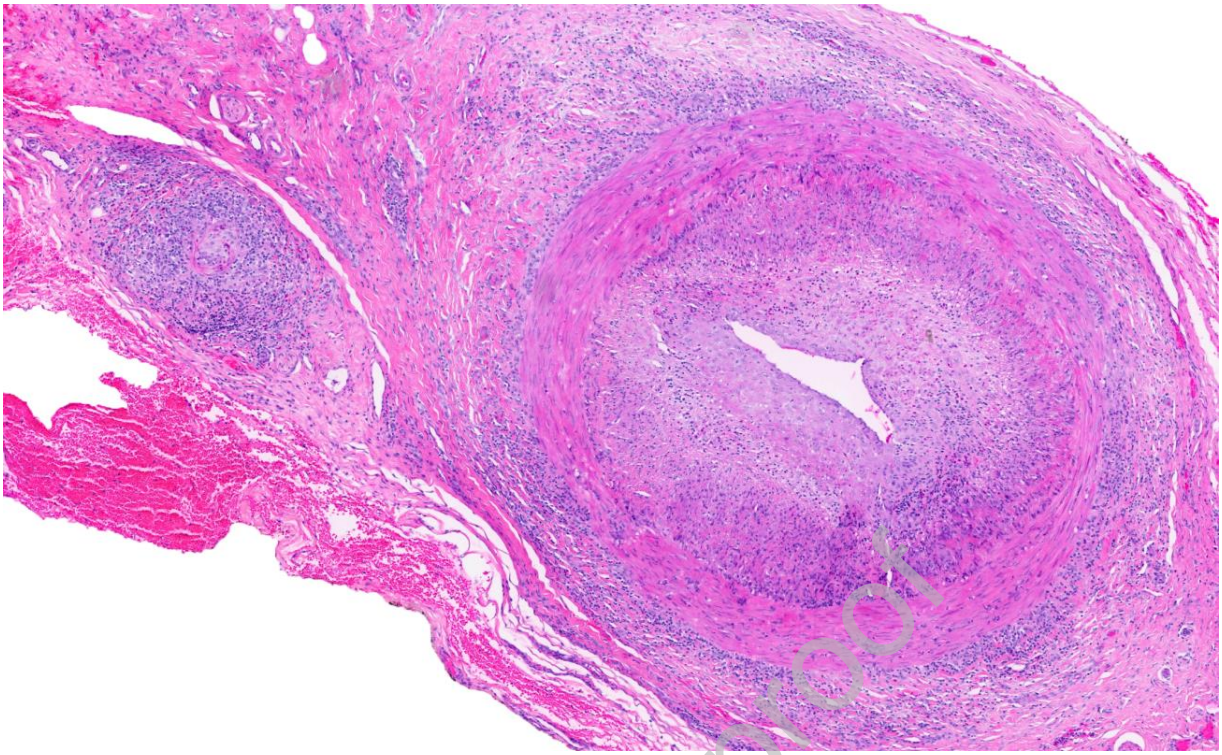

Figure 5. Granulomatosis with polyangiitis affecting the temporal artery. Granulomatous inflammation is seen involving the temporal artery and the adjacent periarterial tissue. Increased eosinophils is also noted.

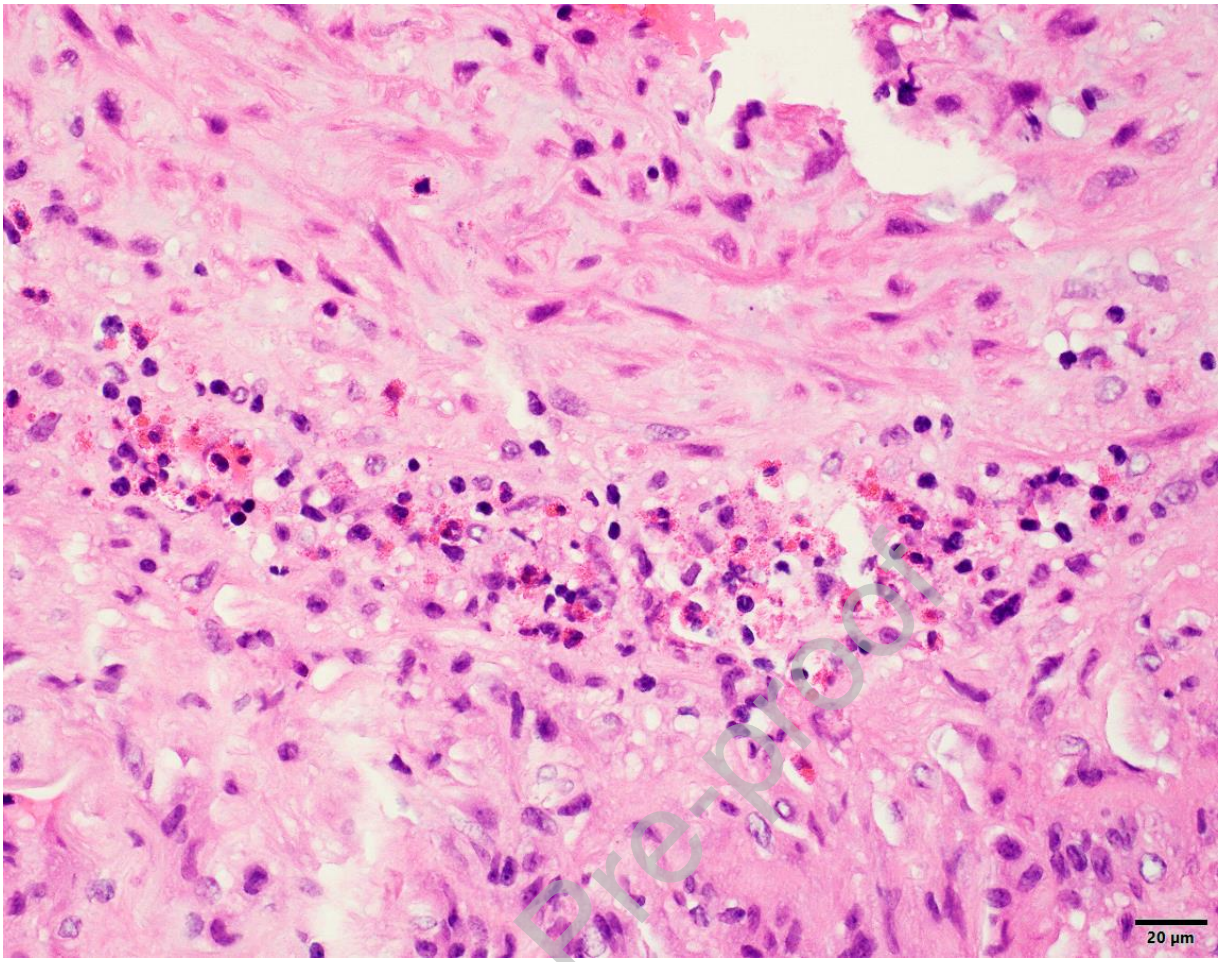

Figure 6: Identified in a temporal artery biopsy, this small branch vessel shows a marked eosinophilic component to the active vasculitis. In the context of other findings, the patient was determined to meet the criteria for eosinophilic granulomatosis with polyangiitis (EGPA). Hematoxylin and eosin staining. Digitally acquired image, scale bar as shown.

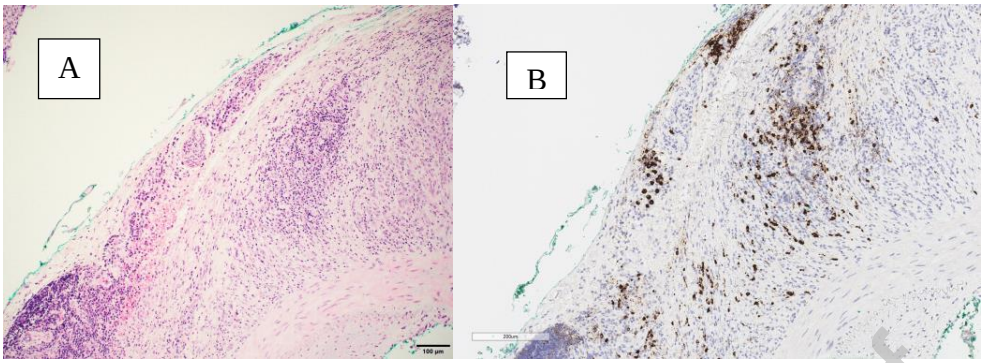

Figure 7A &B: Microphotograph of a temporal artery with active arteritis with a lymphoplasmacytic infiltrate. Immunohistochemistry for the IgG4 isotype demonstrates markedly increased expression with plasma cells involving active arteritis of a temporal artery. The fraction was far greater than half of the overall plasma cell population, and the patient ultimately showed clinical features consistent with IgG4-related systemic disease. Digitally acquired image, scale bar as shown.

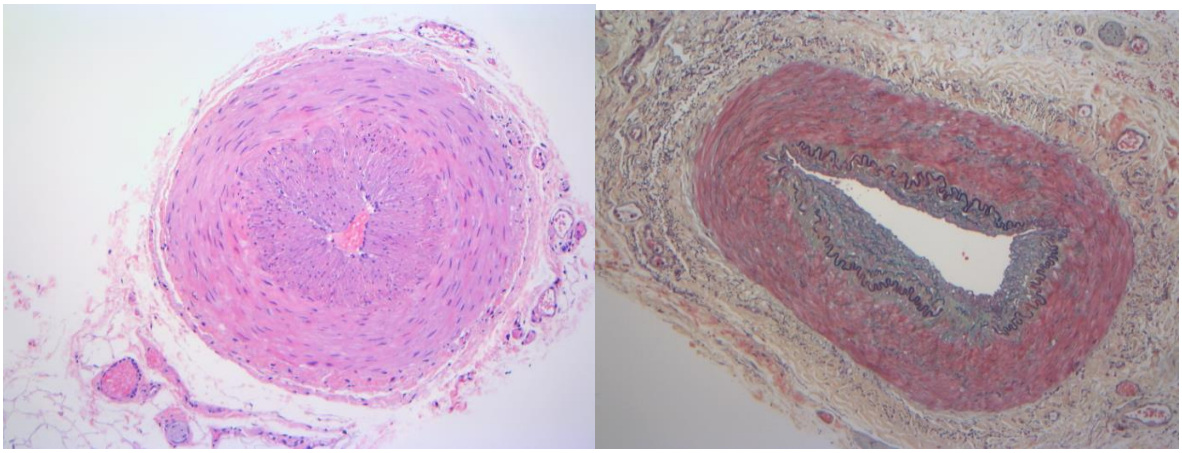

Figure 8A & B: Microphotographs showing age related changes of the Temporal artery with marked intimal fibrosis and thickening (Hematoxylin and Eosin stain), intimal fibrosis and focal loss of internal elastic lamina (Movat stain).

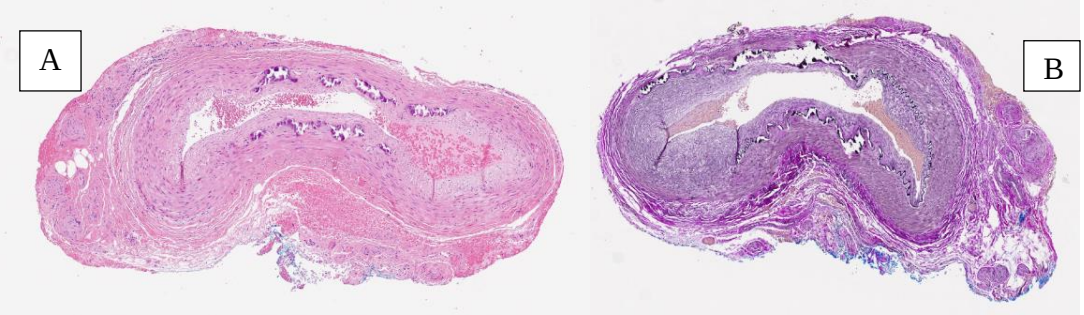

Figure 9 A&B: Calcification of the internal elastic lamina and media (Hematoxylin and Eosin stain & Elastic Trichrome stain).

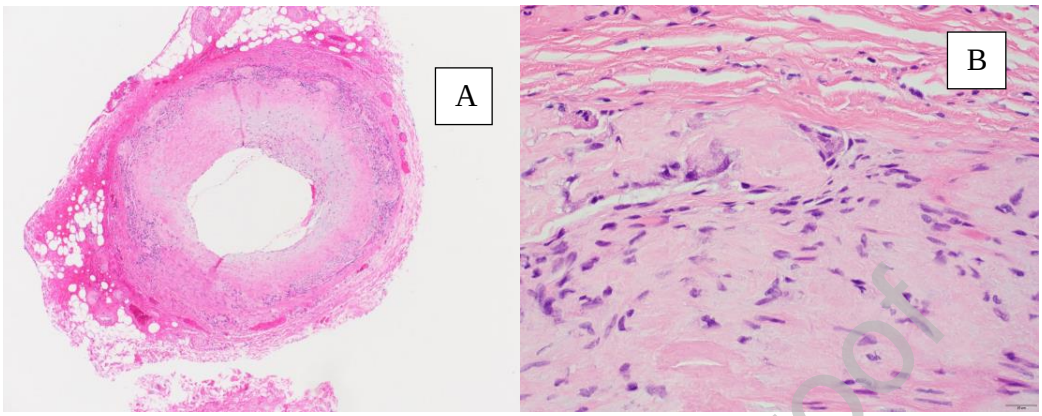

Figure 10A. Amyloidosis of the temporal artery with marked infiltration of amorphous eosinophilic material within the intima and media with chronic inflammation (Hematoxylin and Eosin stain, 2.5 magnifications). B. Higher magnification showing the amyloid deposits with giant cells. (Hematoxylin and Eosin stain , 20 x magnification.

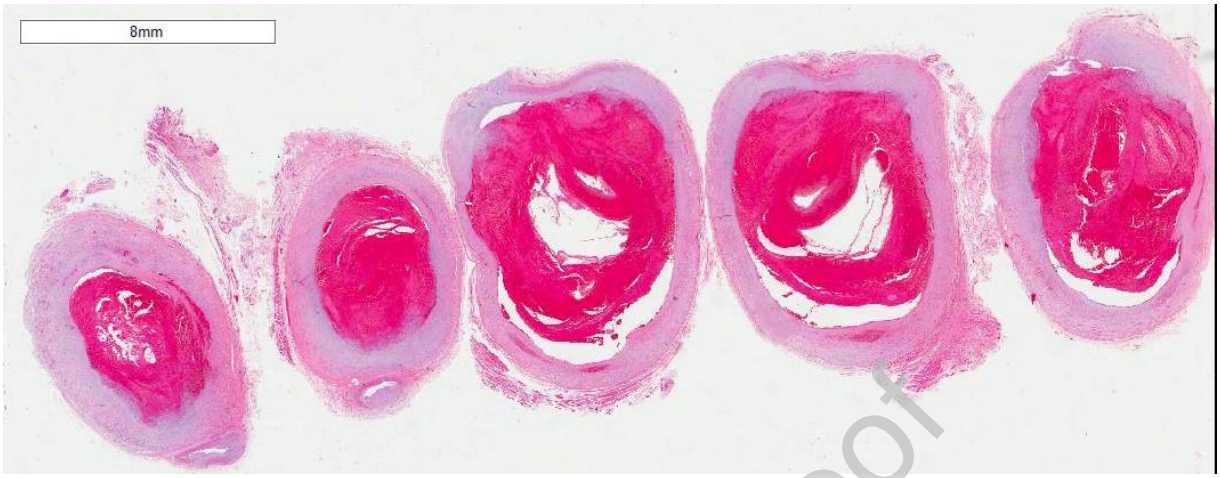

Figure 11: Temporal artery aneurysm with recent thrombus (Hematoxylin and Eosin stain , 2.5 magnification.

Figure 12: Reporting Recommendations for Temporal Artery Biopsies

Final diagnosis:

- Clearly state whether there is
  - Active arteritis
  - Features of healed arterial injury
  - No arteritis

Comment:

- Describe more nuanced findings such as:
  - Adventitial / periadventitial / vasa vasorum chronic inflammation
  - Medial calcific (Mönckeberg) sclerosis
- For negative biopsies, consider sampling error / skip lesions.

Gross description:

- Overall length, dimensions, and number of specimens
- Sectioning performed after tissue processing (cross-sections)
- Sectioning performed before tissue processing (cross-sections)

Microscopic description:

- Describe histopathologic findings of the intima, IEL, media, adventitia, periadventitia, type of inflammation, presence of giant cells.

Table 1: Consensus Recommendations

1	Submit temporal artery biopsy specimens in toto, uncut, for tissue processing, then cut them into 1-2 mm interval sections at the time of embedding.
2	Review at least five (5) slides per specimen, with up to eight (8) tissue profiles per slide, to include H&E and stains for elastic laminae.
3	Active arteritis is a histologic diagnosis of any degree of inflammation involving the media of any artery represented on the slide and should not be made on the basis of immunohistochemistry alone.
4	Active arteritis in a temporal artery is not synonymous giant cell arteritis, as many forms of arteritis can involving the temporal artery.
5	The term “healed arterial injury” is favored rather than “healed arteritis.”
6	Avoid using the terms "temporal arteritis“ and “atypical arteritis”.

Table 2. Differential diagnosis and histopathologic features

Giant cell arteritis	Lymphohistiocytic inflammation with disruption of the media Lymphocytic inflammation in the adventitia and periadventitial small vessels Disruption of the internal elastic lamina Intimal thickening Langhans-type giant cells, often along the internal elastic lamina (giant cells need not be present)
Age-related changes	Intimal thickening without inflammation Mostly intact internal elastic lamina Preservation of the media and adventitia
Arterial calcification	Calcification along internal elastic lamina and/or in the media Little or no intimal thickening Adventitia is uninvolved Foreign body giant cells and/or multinucleated osteoclasts (i.e., osseus metaplasia) are rarely present
Trauma	Fresh or stratified thrombi Internal elastic lamina disruption or duplication present Laceration or pseudoaneurysm Adventitia is preserved
Amyloidosis	Amorphous eosinophilic material accumulation Foreign body giant cells may be present
Polyarteritis nodosa	Acute and/or chronic inflammation Fibrinoid necrosis Disruption of the internal elastic lamina Giant cells and granulomas are absent
Granulomatosis with polyangiitis	Mixed inflammation often involving small vessels including veins Giant cells and granulomas may be present
Eosinophilic granulomatosis with polyangiitis	Eosinophil-predominant inflammation with or without necrosis Giant cells may be present
IgG4-related disease	Lymphoplasmacytic infiltrate with eosinophils Storiform fibrosis >50 IgG4+ plasma cells per high power field* IgG4+ / IgG+ plasma cell ratio > 40%
Infection	Suppurative inflammation Necrosis Hemorrhage Microthrombi Organisms may be present

*Based on criteria for the aortic involvement (PMID: 22596100)

Table 3: Examples of Final Reports for Temporal Arterial Biopsies.

[Positive for arteritis] TEMPORAL ARTERY, RIGHT/LEFT, BIOPSY: SEGMENT OF MUSCULAR ARTERY INVOLVED BY ACTIVE ARTERITIS.
[Negative for arteritis] TEMPORAL ARTERY, RIGHT/LEFT, BIOPSY: SEGMENT OF MUSCULAR ARTERY NEGATIVE FOR ARTERITIS. COMMENT: This biopsy appears essentially normal. Since arteritis in giant cell arteritis can be segmental, the possibility of sampling error due to “skip lesions” should be considered clinically.
[Healed arterial injury] TEMPORAL ARTERY, RIGHT/LEFT, BIOPSY: SEGMENT OF MUSCULAR ARTERY SHOWING FEATURES SUGGESTIVE OF HEALED ARTERIAL INJURY, SEE COMMENT. NEGATIVE FOR ACTIVE ARTERITIS. COMMENT: This biopsy does not show active inflammation within the medial layer but there is segmental disruption of the internal elastic lamina (assessed with elastic stain) with accompanying replacement-type fibrosis of medial smooth muscle (assessed with trichrome stain). The differential included trauma (accidental, iatrogenic and prior biopsy), healed arteritis, and age-related changes.
[Intimal fibrosis] TEMPORAL ARTERY, RIGHT/LEFT, BIOPSY: SEGMENT OF MUSCULAR ARTERY WITHOUT ACTIVE ARTERITIS, SEE COMMENT. COMMENT: There is no active medial inflammation, but there is bland intimal fibrosis and thickening, with a largely intact internal elastic lamina. This likely represents an age-related change.
[Adventitial inflammation] TEMPORAL ARTERY, RIGHT/LEFT, BIOPSY: SEGMENT OF MUSCULAR ARTERY WITHOUT ACTIVE ARTERITIS, SEE COMMENT. . COMMENT: Multiple deeper levels were examined. There is no active medial inflammation, but there is patchy chronic inflammation in the adventitial and peri-adventitial connective tissue, including vasa vasorum. The significance of this is unclear, but this finding should not be considered to indicate active arteritis.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: