acta medica

INVITED REVIEW

Histologic Assessment of Temporal Artery

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The temporal artery is classified among muscular arteries. The arterial wall is a heterogeneous, three-layered structure composed of an intima, smooth muscle-bearing media, and adventitia. Between adventitia and media, there is external elastic lamina; between media and intima, there is internal elastic lamina (IEL). (Fig.1)

Each layer exhibits specific histological, biochemical, and functional characteristics. The adventitial stroma consists of an extracellular matrix containing fibroblasts, blood and lymphatic vessels, nerves, progenitor cells, and immune cells, making the adventitia the most complex and heterogeneous compartment of the vessel wall. Adventitial cells are capable of sensing and directing responses to many stimuli through communication with other adventitial cells and with cells of the neighboring tissues. In response to hormonal, inflammatory, and environmental stresses, resident adventitial cells are often the first vascular wall cells to be activated. The fibroblast is the most abundant cell type in the vascular adventitia. Adventitial fibroblast may be a sentinel cell in the vessel wall that responds to various stimuli as the first vascular wall cell to exhibit evidence of activation [1].

Histopathology of temporal arteritis

Giant-cell arteritis (GCA) is a granulomatous vasculitis affecting arteries of medium to large size. Macrophages and lymphocytes are the main components of the inflammatory infiltrate in all layers of the artery, and multinucleated giant cells are present in about one-half of positive biopsies. Polymorphonuclear neutrophils, eosinophils, plasma cells, B-lymphocytes, and dendritic cells may be observed. Additional histological characteristics include fragmentation of IEL, intimal hyperplasia, and formation of new capillaries, particularly at the intima and intima-media junction. There is segmental involvement of the artery. Temporal arteries from GCA patients may exhibit a variable extent of inflammatory involvement, ranging from slight adventitial infiltrates to fully developed granulomatous lesions distributed along the entire vessel wall. Temporal arteritis (TA) is segmental arteritis in which inflammation starts from adventitia and concentrates around the IEL. Inflammation passes through media to the intima and causes disruption of IEL. Transmural inflammation leading to marked luminal narrowing is seen in a significant amount of cases [2]. Calcification and thrombus formation can also be present (Fig.2).

Chronic inflammation with extensive destruction of elastic lamina represents healed TA. The lymphocytes are CD3(+) with a predominance of CD4 positivity over CD8. The histiocytes are CD68 positive [3]. Disruption of elastic lamina can be well demonstrated by Verhoeff van Gieson's elastic stain. As TA is usually seen in older ages, intimal thickening due to age-related changes are frequently present in temporal artery biopsies (TAB).

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Note:
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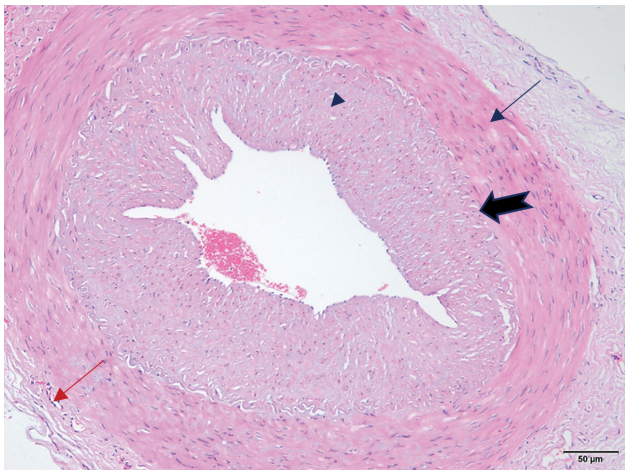

Figure 1. Normal histology of a muscular artery. Arrowhead: tunica intima, thick arrow: internal elastic lamina, thin black arrow: tunica media, red arrow: adventitia. H.E. x100

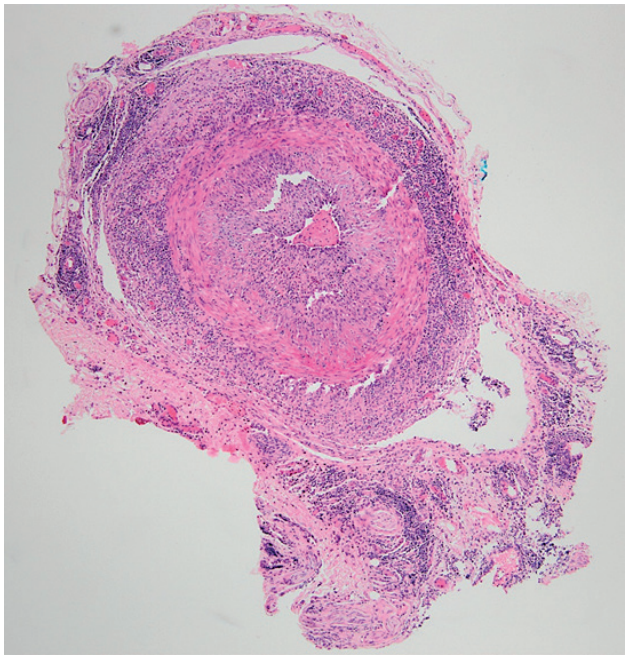

Figure 2. Transmural inflammation of temporal artery and thrombus formation in a 72 years old male patient with headache, shoulder ache and stiffness, high ESR and CRP levels, and DCVAS 12, negative for halo sign and USG findings. Treatment was given four days after the biopsy. H.E. x 40. Inlet shows an enlarged segment of temporal artery biopsy specimen with heterogeneous surface and nodular change.

Pathogenesis

In the adventitia, unknown environmental stimuli activate immature dendritic cells through toll-like receptors leading to chemokine release, which recruits CD4(+) cells with IL-6 release. Under the influence of IL-6, these cells differentiate into Th1 and Th17 cells leading to the release of INF-γ. In turn, vascular smooth muscle cells recruit monocytes that transform into macrophages or giant cells. Macrophages release reactive oxygen species and matrix metalloproteinases, leading to the destruction and necrosis of tissue. Macrophages injured vascular smooth muscle cells, and giant cells release PDGF leading to intimal hyperplasia, luminal stenosis, and thrombosis [4]. Several signaling pathways have been implicated in initiating and sustaining pathogenic CD4(+) T cell function, including the NOTCH1-Jagged1 pathway, the CD28 co-stimulatory pathway, and the PD-1/PD-L1 co-inhibitory pathway, and the JAK/STAT signaling pathway. Inadequacy of mechanisms that generally dampen immune responses, such as defective expression of the PD-L1 ligand and malfunction of immunosuppressive CD8(+) T regulatory cells, is a common theme in GCA immunopathology [3].

Differential Diagnosis

Positive TAB is 100% sensitive for TA. But the histopathological features of TA are not always diagnostic, and there are other entities with shared features. Intimal thickening without destruction but sometimes with reduplication of IEL are apt to be age-related changes. Intimal thickening is mistakenly respected as atherosclerotic changes in a significant number of cases. In fact, an intimal disease with a necrotic core defines atherosclerosis, and it is occasionally seen in the temporal artery. Unusual patterns of inflammation in patients younger than 55 years suggest other types of vasculitides like granulomatosis with polyangiitis (necrosis), PAN (fibrinoid necrosis and adventitial inflammation), or Buerger's disease (cellular thrombus). Medial calcification centered on IEL represents Monckeberg's calcification [5]. A patient with clinical features of TA who later develops renal and muscular involvement of microscopic polyangiitis can have a positive TAB with histological features similar to TA [6]. A patient with granulomatous vasculitis, few eosinophils, and occasional giant cells can be p-ANCA positive, have eosinophilia, sinusitis, and bronchial asthma leading to the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) [7]. Chronic inflammation of branch vessels without the involvement of the main artery is suspicious but not diagnostic for TA. Patients with chronic perivascular inflammation but no arteritis seem no more likely to have temporal arteritis on clinical grounds than similar patients without inflammation on biopsy [8,9].

Negative Biopsy

A negative TAB can be seen due to a variety of factors. Segmental distribution of the inflammation, short biopsy length, inadequate sampling, and inadequate microscopic evaluation can end with a negative biopsy. Palpation of the artery before the biopsy procedure is essential for an adequate sample. In a review of 1520 TAB datasets, the search for an optimal cut-off length suggested that the best diagnostic sensitivity might be offered for TAB of at least 0.5 cm long [10]. For pathological examination, routine sectioning may miss the diagnosis in a subset of cases, and in some cases, sectioning deeper into the paraffin block may be warranted. The vast majority (94%) of patients that were biopsy "proven" to be negative for temporal arteritis on initial examination remained negative after review of all subsequent deeper levels, but 6% of the initially "biopsy-negative" cases did turn out to be positive on deeper levels [11]. Steroid therapy does not seem to affect histologic changes. TAB performed 1–4 weeks after starting glucocorticoids still reveals changes consistent with GCA, including inflammatory infiltrates and/or giant cells in most patients with a clinically suspected diagnosis [12]. In patients with newly diagnosed GCA, the diagnostic yield of TAB within four weeks of starting high-dose steroid treatment was 74%; when the duration of therapy extended beyond this period, the TAB positivity rate fell to 40%. In patients that developed GCA on a background of a prior history of polymyalgia rheumatica, a late TAB is also generally informative despite long-term treatment with low doses of corticosteroids [13].

In short, TAB should be taken with careful palpation. The length of the biopsy can be as small as 0.5 cm if the right segment is sampled. Histopathologically, mononuclear cell infiltration of vascular wall layers with the destruction of IEL is highly diagnostic for TA. Histologic assessment can need several deep sections for the diagnosis. Histologic differential diagnosis of TA consists of microscopic polyangiitis, EGPA, and small-vessel vasculitis of several special entities for which clinical confirmation is crucial.

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