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Case-based Review

Mönckeberg sclerosis with giant cells as a masquerade of giant cell arteritis

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Abstract

Giant cell arteritis (GCA) is the most common type of vasculitis in adults, which is classified as a large/medium vessel vasculitis. It has a predilection for the ophthalmic circulation and extracranial carotid system. Temporal artery biopsy specimens can show the presence of inflammatory multinucleated giant cells. Here, we report just the third case of Mönckeberg sclerosis with multinucleated giant cells affecting the temporal artery and mimicking GCA. This rare finding in the evaluation of a common vasculitis is important for rheumatologists to be aware of and emphasizes close collaboration between clinicians and pathologists.

Keywords: Giant cell arteritis, Mönckeberg sclerosis, temporal artery biopsy

Introduction

Giant cell arteritis (GCA) is the most common type of vasculitis in adults, which is predominant in women and in the Caucasian race. Classified as a large/medium vessel vasculitis, it causes granulomatous inflammation in the aorta and has a predilection for the ophthalmic circulation and extracranial carotid system (1). GCA with involvement of the temporal arteries is frequently diagnosed with the aid of a temporal artery biopsy (TAB). TAB is considered as the gold standard for diagnosis, despite the well-documented problems with the interpretation of the procedure, including a high false-negative rate and poor sensitivity (2). The temporal arteries can be involved in diseases other than GCA, including ANCA-associated vasculitis, polyarteritis nodosa, and mixed cryoglobulinemia (2). Additionally, isolated atherosclerosis involving the temporal arteries can be difficult to distinguish from GCA histologically (2). Indeed, in a review of one tertiary care center's 131 TAB results, atherosclerosis was present in a majority (63%) of cases (3). GCA was diagnosed in only 13% of these cases. A third entity, Mönckeberg sclerosis, was diagnosed in just 6% of biopsies (3).

Case Presentation

We report a case of presumed GCA that was determined instead to be a case of Mönckeberg sclerosis affecting the temporal artery after TAB. An African American woman in her late 40s presented with a one-month history of visual loss in her right eye. She had an acute onset of the vision loss with preceding headaches. While she had difficulty describing the headaches, and while they were predominantly holocranial, she did confirm that they at least occasionally involved the right temporal area. She did not have fever, weight loss, jaw claudication, or symptoms of left eye visual disturbance. She had a complex medical history of end-stage renal disease (ESRD) on hemodialysis for approximately 7 years due to a combination of insulin-dependent type 2 diabetes mellitus and hypertension, as well as coronary artery disease, and a past cerebrovascular accident. On physical examination, she did not have any palpable temporal artery abnormality or tenderness. Ophthalmologic evaluation showed a reduced visual acuity in the right eye with pallor and edema of the optic disk. Laboratory findings were notable for an erythrocyte sedimentation rate of 37 mm/hr. Although the clinical impression was non-arteritic anterior ischemic optic neuropathy, she was started empirically on high-dose oral corticosteroids pending a TAB that was performed three days later. Due to a small but finite possibility of GCA, oral corticosteroids were continued pending contralateral TAB. However, this second TAB could not be performed due to a family emergency and corticosteroids were continued. One month later she returned to the hospital with a gastrointestinal bleed and at that point rheumatology was consulted for corticosteroid management. Upon the initial rheumatology evaluation, there were several reasons to question the initial diagnosis of GCA. The patient's history and physical findings lacked many features that correspond with positive TAB for GCA: jaw claudication, diplopia, abnormal or tender temporal arteries on exam, and ESR <50 mm/hr at diagnosis (4). Lastly, the patient had noted no improvement in her headaches or visual changes despite one month of high-dose corticosteroids. Ultimately, the decision

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was made to quickly taper her corticosteroids with close clinical monitoring. She successfully tapered her steroids completely without any appreciable change, supporting a non-inflammatory etiology of her symptoms.

Verbal informed consent was obtained from the patient whose case has been presented in this report.

Pathology results

The right superficial TAB was 2.2 cm long by 0.3 cm in diameter. The artery was cut into 9 cross sections, and 10 histological step sections were prepared with 50 microns between each step section. The most noticeable change on microscopic examination was extensive calcification of the tunica media with areas of circumferential calcification (Figure 1) and other areas of segmental calcification (Figure 2) with focal early ossification. There were foci of fibrosis and medial neovascularization adjacent to and insinuated in the calcific deposits (Figure 3), along with mononuclear inflammation (lymphocytes, macrophages, and a few multinucleated giant cells [Figures 4 and 5]). The intima had a moderate degree of arteriosclerotic change (approximately 50%-75% luminal stenosis) manifested as intimal thickening due to accumulation of collagen and smooth muscle cells. The inflammation, fibrosis, and neovascularization were deemed secondary to the extensive medial calcification due to the proximity of these changes with each other and the lack of inflammation of the arterial wall away from the calcification.

For comparison, multinucleated giant cells from a case of active GCA (Figure 6) and osteoclasts from vertebral bone in patients with renal osteodystrophy (Figure 7) are presented. These figures highlight the similarities of the multinucleated giant cells seen in various conditions. It is important for rheumatologists to recognize that the presence of multinucleated giant cells is not always indicative of GCA.

Main Points

- Temporal artery biopsy specimens may rarely demonstrate multinucleated giant cells without other inflammatory features in which case, a diagnosis other than GCA should be considered.
- Mönckeberg sclerosis refers to medial artery calcification and, while involvement of the temporal arteries is rare, its presence can mimic GCA.
- Knowledge of this phenomenon is important for rheumatologists to recognize and emphasize the importance of the interaction between clinicians and pathologists.

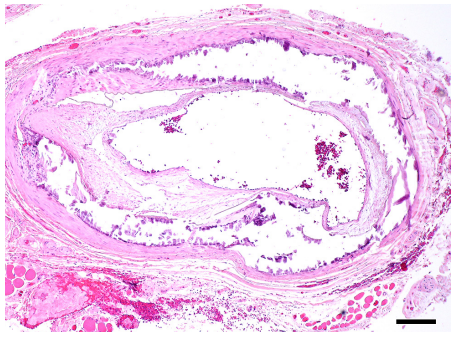

Figure 1. Some areas of the wall had circumferential calcification of the tunica media with attenuation of the tunica media smooth muscle. The calcium is basophilic (purple) and has fragmented during histological sectioning leaving empty spaces in the arterial wall (bar=200 µm).

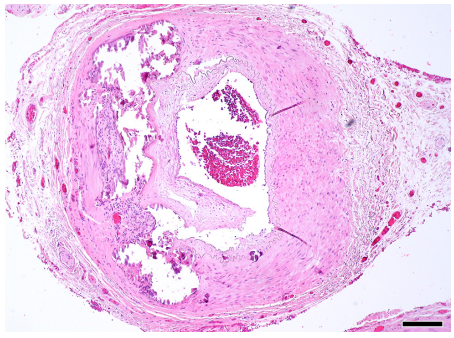

Figure 2. Other areas of the superficial temporal artery had segmental calcification (left side of artery) with inflammatory cells localized only in this area (bar=200 µm).

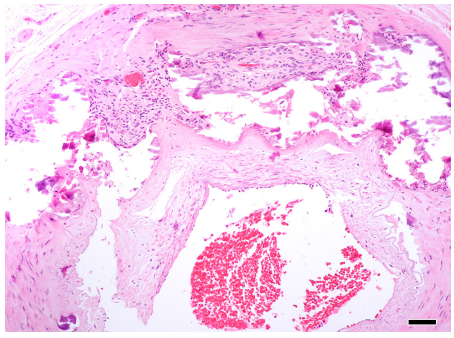

Figure 3. Inflammatory cells were seen only in association with the medial calcification (bar=200 µm).

Discussion

Mönckeberg sclerosis was first described by Johann Georg Mönckeberg in 1903, which manifests as a medial arterial calcification (5, 6). Initially Mönckeberg sclerosis was thought to be a benign, age-related occurrence, but it is now recognized to result in decreased arterial

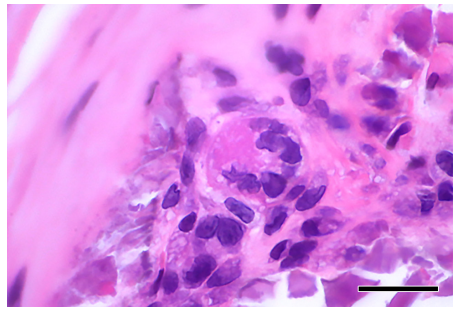

Figure 4. A multinucleated giant cells from the TAB of our patient is shown near the center of the image surrounded by macrophages (bar=20 µm).

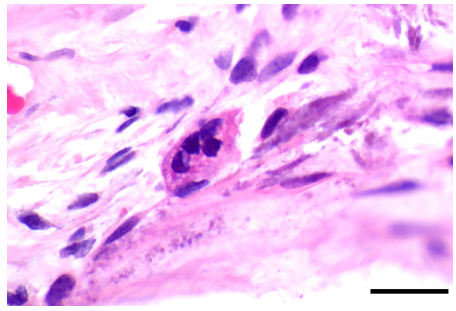

Figure 5. Another multinucleated giant cell from a different cross-section of the temporal artery (bar=20 µm).

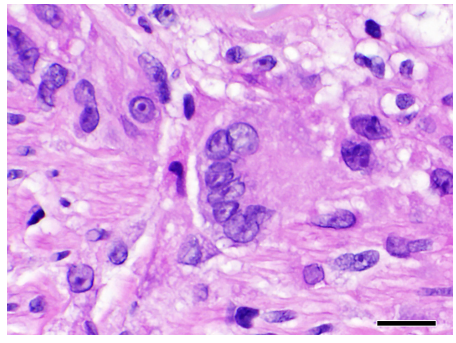

Figure 6. Multinucleated giant cell (near the center of the image) from a TAB of a patient with active GCA (bar=20 µm).

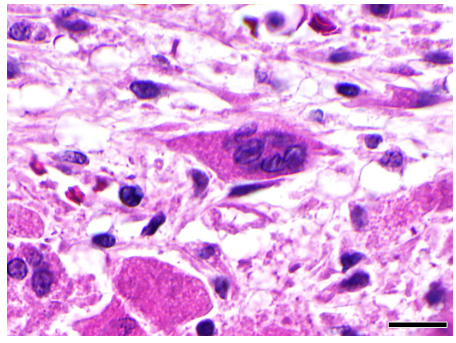

Figure 7. Osteoclast (near the center of the image) in vertebral bone from the autopsy of a patient with renal osteodystrophy (bar=20 µm).

compliance (7). It is important to point out that there is a considerable debate and confusion regarding the precise histologic definition of Mönckeberg sclerosis in the literature. For instance, Nordborg, et al. stated that "internal elastic membrane calcifications should not be confused with Mönckeberg's sclerosis… which is confined to the media and does not involve the intimal layer" (8). However, later, histological studies concluded that arteries afflicted with Mönckeberg sclerosis invariably involved calcification of both the tunica media and the internal elastic membrane (5). Additionally, calciphylaxis is a term used to refer to vascular calcifications, although generally its use is reserved for cases involving calcification of microvessels (diameter ranging from 40 to 600 μm) in subcutaneous adipose tissue and dermis, often with thrombosis (9). In summary, calcification of various layers of an artery are referred to by different terms.

Regardless of the term used, medial arterial calcification (which includes Mönckeberg sclerosis) is known to be associated with diabetes mellitus and chronic renal failure, especially in patients on dialysis (5). Medial calcification involving the temporal artery has only rarely been reported to mimic GCA with a typical clinical syndrome, generally consisting of unilateral headaches and visual disturbance and/or direct evidence of anterior ischemic optic neuropathy (10-16). The most common feature among reviewed cases was the prevalence of ESRD, which is consistent with other reports of an increased frequency of Mönckeberg sclerosis in patients on dialysis (5). Indeed, ESRD was present in 8 of the 10 cases in the published literature. Out of the remaining 2 patients, 1 patient did present with an acute kidney injury that eventually resolved (16). Calcification of otherwise damaged arteries is a well-observed phenomenon that is most commonly seen in atherosclerosis and in conditions related to renal disease, including calciphylaxis and hyperparathyroidism (6).

GCA refers to an arteritis in which granulomatous inflammation is present, typically within the walls of medium to large vessels. The cellular infiltrate commonly contains multinucleated giant cells resulting from fusion of activated macrophages (17). The peculiar feature of our case was the presence of multinucleated giant cells in a TAB that otherwise was histologically typical of Mönckeberg sclerosis. Indeed, only 2 other case reports have demonstrated similar histological findings (11,12). Sekulic and Truskinovsky (12) noted 2 different types of giant cells, one of the foreign body types reacting to calcium deposits and the other osteoclast-like abutting trabeculae of metaplastic bone, though these multinucleated giant cells do not appear distinctly different in the published photomicrographs. In contrast, the Belliveau case noted only the presence of osteoclast-like giant cells (11).

Distinguishing multinucleated foreign body giant cells histologically from other types of multinucleated giant cells and osteoclasts is not obvious, if it is even possible (18). Foreign body giant cells are described as having irregularly shaped cytoplasm of variable size with randomly dispersed nuclei that range in number from tens to hundreds (18). Osteoclast-like giant cells, which morphologically resemble osteoclasts, are described as having dispersed nuclei within pale cytoplasm (17). Osteoclasts are actually multinucleated giant cells that are involved in bone removal as part of the bone turnover (19). Both macrophages (of which classically activated macrophages comprise the multinucleated giant cells found in GCA) and osteoclast precursor cells differentiate from granulocytic hematopoietic stem cells (19). Osteoclasts can be differentiated from inflammation-related multinucleated giant cells using immunohistochemistry, but this is difficult and requires the use of several antibodies that lack validation for clinical use in most hospital laboratories (20). In our patient, as in the cases reported by Sekulic and Truskinovsky (12) and Belliveau et al., (11) the multinucleated giant cells were located only in the vicinity of ossification, leading to the conclusion that the inflammatory cells were not a component of GCA.

We report the third example of a TAB revealing Mönckeberg sclerosis, which presented with features similar to GCA. The medial artery calcification with associated multinucleated giant cells in Mönckeberg sclerosis may confound TAB interpretation and requires a clinical decision until immunohistochemical distinction of these processes becomes available. Thorough evaluation of clinical features is of paramount importance in these cases. It is important that rheumatologists be aware of this pathologic process, as it highlights yet another difficulty encountered by pathologists in evaluating TAB specimens. Furthermore, this case emphasizes the critical importance of clinical-pathological correlation and interaction between clinicians and pathologists.

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