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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Idiopathic Non-atherosclerotic Carotid Artery Disease

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Abstract

Purpose of review The purpose of this review is to provide an overview of idiopathic non-atherosclerotic causes of carotid artery disease and its manifestations.
Recent findings Four major causes of non-atherosclerotic carotid artery disease including dissection, fibromuscular dysplasia, moyamoya disease, and inflammatory large vessel vasculitis are discussed. While there is a dearth of clinical trials involving some of the rarer conditions, recent data from clinical trials supporting antiplatelet over anticoagulation treatment of cervical artery dissection, recent consensus statements on the management of fibromuscular dysplasia, and guideline approaches to diagnosis and treatment of large vessel vasculitis are summarized.
Summary Idiopathic non-atherosclerotic causes of carotid artery disease are under appreciated and may lead to significant morbidity and mortality. While less common compared with atherosclerotic disease, non-atherosclerotic disease may affect younger patient populations and result in non-cerebrovascular arterial involvement and systemic organ damage. Therefore, prompt recognition of these disorders is key to their management.

Introduction

Atherosclerosis is the most common cause of carotid artery disease and a major risk factor for stroke and transient ischemic attack. While atherosclerosis is precipitated by well-known vascular risks (including diabetes mellitus, hyperlipidemia, and smoking), idiopathic non-atherosclerotic causes of carotid artery disease are less recognized. Idiopathic non-atherosclerotic carotid artery disease can cause significant morbidity and mortality. Moreover, with the exception of giant cell arteritis, these conditions may affect younger patient populations and children. There are often environmental-, complex genetic–, and immune-mediated mechanisms involved

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in disease pathogenesis. Most of the conditions resulting in non-atherosclerotic carotid artery disease are chronic and progressive, affect multiple arterial beds, and can lead to multi-organ failure. As a result, treatment often requires steroid or disease-modifying medications and repeat imaging to assess disease evolution. In this review article, four major causes of non-atherosclerotic carotid artery disease including dissection, fibromuscular dysplasia, moyamoya disease, and inflammatory large vessel vasculitis are discussed.

Carotid artery dissection

Carotid artery dissection (CAD) is a cause of stroke in young patients [1]. Patients affected by CAD are typically between the ages of 30 and 50 with an average age of about 45 years. The yearly incidence is about 3–5/100,000. CAD results from a tear in the arteries intimal layer creating a flap. Blood can then redistribute between the vessel wall and the flap creating a false lumen and dissect into the vessel wall creating a hematoma. In some cases, this can lead to vessel occlusion and pseudoaneurysm formation. Disruption of the endothelium brings blood cells into contact with thrombogenic factors leading to clot formation. As a result, ischemic stroke can be an undesirable outcome due to hemodynamic compromise from diminished blood flow or thromboembolism. Dissections can be spontaneous, meaning that there is no traumatic precipitating cause identified. Others are precipitated by major and minor trauma events. Major trauma includes motor vehicle accidents or blunt head trauma. Minor or micro-trauma events can occur with activities that are performed at high frequency that often do not lead to injury like weight lifting, golfing, eccentric neck positioning (i.e., hyperextension of the neck). In one study, 25.7% had dissection temporally associated with chiropractic neck manipulation [2]. The disease can also be associated with other connective tissue disorders like Marfan and Ehlers-Danlos syndrome and is associated with fibromuscular dysplasia (see next section) [2] and migraine [3]. The symptom presentation of CAD varies. Some patients may be asymptomatic, while others report headache, neck pain, and tinnitus. A painful Horner's syndrome with pupil asymmetry can be the only presenting complaint [4]. Of uppermost concern is the potential for stroke involving the ipsilateral hemisphere as this can be a significant cause of lifelong disability in an otherwise relatively healthy and young population. However, previously published data suggest CAD patients have a good opportunity for functional recovery even after stroke. In one study, patients with CAD had on average single digit NIHSS scores, high Barthel index, and low modified Rankin scores [5]. CT or MR angiography of the head and neck is often used to diagnose dissection and to assess the extent of disease. The latter can be performed with fat suppression to better visualize the intravascular dissection flap [2]. Repeat angiogram imaging of the neck is often performed 3–6 months after the initial injury.

In the Cervical Artery Dissection in Stroke Study (CADISS), 250 patients with CAD were randomized to anticoagulation versus antiplatelet therapy 3–4 days after presentation. Stroke occurred infrequently in both groups, and there was no difference in stroke rate between the two treatment arms [6]. Therefore, it would be reasonable to start patients on antiplatelet therapy for the prevention of stroke. However, anticoagulation can still be used in the early time frame

(first 3–4 days) and it is unclear if anticoagulation may benefit those with dissection and intraluminal thrombus. However, long-term anticoagulation unless given for a complicating comorbid condition is not necessary for the treatment of CAD as single monoplatelet therapy is sufficient.

In addition to medication therapy, patients are often advised to avoid heavy lifting and activities that may worsen dissection or lead to recurrent dissection for at least 3–6 months [6].

Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is a non-atherosclerotic and non-inflammatory medium vessel arteriopathy (Fig. 1). FMD can affect up to 7% of the population. The disease hallmark includes structural abnormalities in the renal,

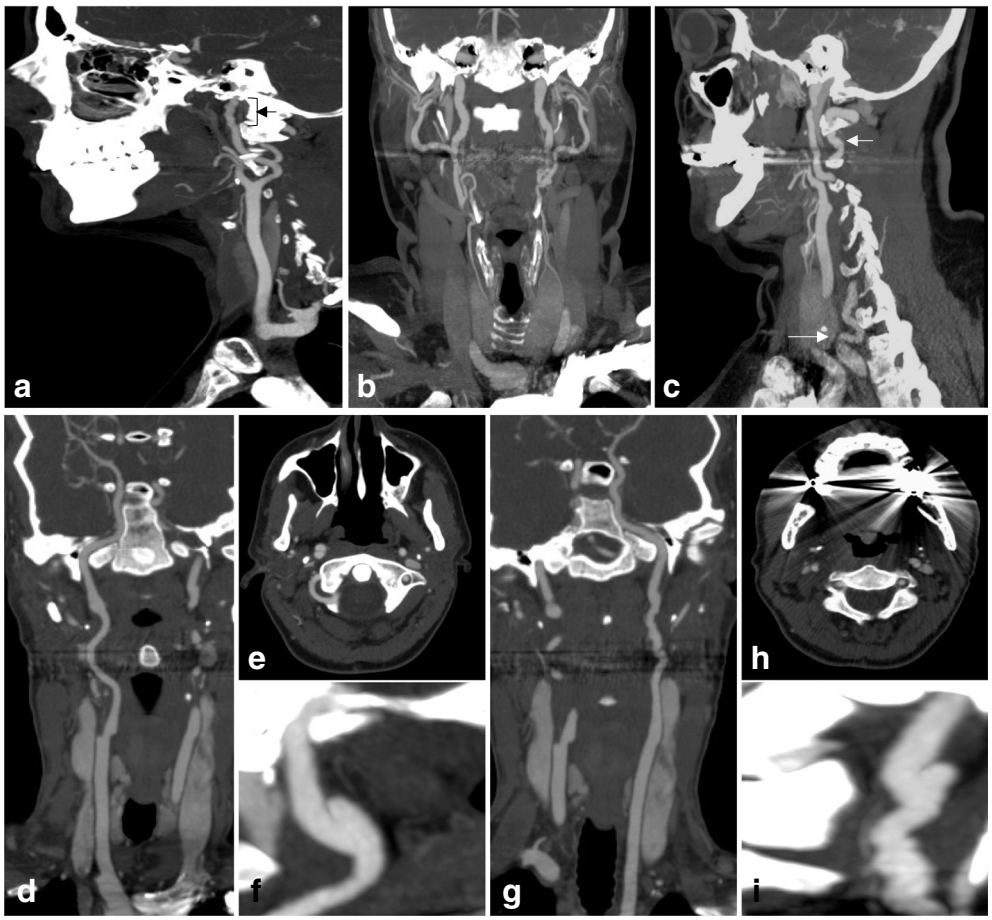

Fig. 1. Example of fibromuscular dysplasia (FMD). **a** FMD causing a corkscrew accordion appearance and affecting the upper 2/3 of the internal carotid artery (arrow) is the most common radiographic presentation of cerebrovascular FMD. **b** Rarely patients can have bilateral carotid artery FMD. **c** There was also evidence for vertebral artery involvement and vessel tortuosity (arrow). Arterial dissection can be a complication of FMD. **d**, **e**, and **f** demonstrate coronal, axial, and reconstructed images of the right internal carotid artery dissection and **g**, **h**, and **i** demonstrate in the same individual left internal carotid artery dissection with associated FMD.

mesenteric, carotid, and vertebral arteries often leading to mild to moderate degrees of stenosis [7, 8]. The carotid artery in particular is affected rarely in FMD occurring in 0.3–3% of those undergoing catheter angiography [9]. FMD has a predilection for middle-aged women with a ratio of 2:1 and median age of diagnosis of 50 years [10, 11]. Cerebrovascular FMD is commonly asymptomatic and may be detected on vessel imaging for other indications. If present, signs and symptoms of FMD are vague and include headache, pulsatile tinnitus, episodic dizziness, and carotid bruits. Stroke, TIA, and aneurysm formation are consequences of FMD. Of the presenting symptoms, headache is the most common complaint occurring in 50–80% of patients and is described as having migraine-like features. However, the age of onset of the disorder is atypical for migraine as it occurs later in life than what is expected for the epidemiology of migraine which should raise suspicion for a secondary headache condition [10, 12]. In the ARCADIA-POL study, of 43 patients with spontaneous cervical artery dissection, FMD was found in 40% raising the possibility that dissection could also be a presenting symptom of FMD [13].

FMD is diagnosed based on its radiographic characteristics. CT and MR angiogram are commonly used initially to diagnose the disease, while carotid ultrasound (US) has also been used to assess for disease progression. Often other arterial beds are involved. Therefore, patients should be screened for gut and renal artery involvement and aneurysm formation [14••, 15, 16]. The most common form of FMD involves alternating regions of blood vessel constriction and dilatation causing a beaded or accordion appearance of the blood vessel. This structural change affects the middle and distal two-thirds segment of the internal carotid arteries at the level of C1–2. This location is different from that associated with atherosclerosis which tends to affect the proximal one-third segment of the internal carotid artery soon after its bifurcation [9, 17]. There are other radiographic subtypes including a focal radiographic subtype which occurs rarely (1–2% of FMD). The disease can be atypical affecting the carotid bulb and present as a web or short intraluminal fibrous protrusion [18]. Medial fibroplasia which is responsible for the multifocal beaded most commonly found appearance of carotid FMD results from discontinuous fibroproliferation of collagen that interposes between and replaces the smooth muscle with associated fragmentation of the internal elastic lamina [17, 19]. Rarer forms of the disease involve smooth muscle hyperplasia (medial hyperplasia) without fibrous tissue replacement. Other forms include excess collagen deposition in the intima (intimal fibroplasia), external half of the media (perimedial fibroplasia), and adventitia (adventitial hyperplasia) [9].

The cause of FMD remains unclear and is likely polygenic. The female predilection raises suspicion for sex and hormonal influences on disease occurrence while other environmental contributors like cigarette smoking have also been postulated. There may be an association between smoking and FMD progression [10, 11, 20–22]. FMD is described as a heritable disease [23]. The suspicion is for an incomplete penetrance of an autosomal dominant trait or a more complex inheritance pattern. There have been rare variants associated with FMD including variants resulting in alpha-1-antitrypsin deficiency (*SERPINA1)* [24]. FMD occurring with other features is rarely linked to Mendelian disorders like vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, and Marfan syndrome. These additional features may include aortic dissection or aneurysm, joint hypermobility or laxity, and lens dislocation and may

prompt further genetic investigation. However, genetic testing should not be routinely performed as prior studies have found no causal variants for FMD in genes associated with connective tissue disorders including the *FBN1*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *ACTA2*, *PLOD1*, *TGFB2*, and *COL5A1*

genes [25, 26]. FMD has been associated in few prior studies with other non-atherosclerotic arterial disorders including moyamoya disease and reversible cerebral vasoconstriction syndrome [27–30]. The association between FMD and dissection could be explained by a shared genetic mechanism. The phosphatase actin regulator 1 (PHACTR1/EDN1) gene locus on chromosome 6q24 (rs9349379-A) has been identified as an FMD risk allele and is also associated with dissection and migraine headache [31, 32]. PHACTR1 is expressed in vascular endothelium and smooth muscle and may be involved in vascular development [33].

A recent consensus report was published on the diagnosis and management of FMD [14]. There

appears to be a low rate of disease progression and a low rate of cerebrovascular complications associated with FMD [9, 15]. Patients with spontaneous cervical artery dissection should be screened for FMD due to the potentially high rate of FMD in this population [13]. Yearly imaging to assess for disease progression can be done initially. If there is no observed disease progression, imaging follow-up need not continue lifelong. The initial imaging modality of choice should be CT or MR angiography. Patients should undergo extensive vessel imaging including that of the brain, thorax, abdomen, and pelvis at least once according to the most recent consensus statement [14]. Management of the disease can vary depending on complications and presenting symptoms. Single antiplatelet medication and blood pressure control particularly for renovascular disease involvement is a common approach. However, the management of other symptoms including the headache associated with FMD, dizziness, and pulsatile tinnitus is unclear.

Moyamoya disease

Moyamoya disease (MMD) is a progressive steno-occlusive disease involving the bilateral supraclinoid and terminal internal carotid artery and sometimes the proximal middle and anterior cerebral arteries affecting children and adults with a bimodal peak before age 10 and another smaller peak between age 20–30 (Fig. 2) [34]. The disease also involves formation of abnormal networks of small collateral vessels at the skull base particularly in the lenticulostriate distribution. The disease is named for the puff of smoke appearance on digital subtraction angiography [35–37]. MMD is rare, and there are racial disparities in disease prevalence. The disease has a higher prevalence in individuals living in East Asia, and it is estimated that the prevalence is between 3–10/100,000 in Japanese. There is a slightly higher male to female prevalence of 1.8:1 [35]. Ischemic stroke is the most common presentation of MMD. In an adult population of 90 patients with MMD, 78% had cerebrovascular events including TIA and ischemic and hemorrhagic stroke and 39% had headache. Patients may also experience cognitive impairment, seizure, and chorea [38, 39]. During a median follow-up of almost 4 years, stroke occurred in 9% and TIA in 16% [40]. Whereas in a longer follow-up study of those with MMD related hemorrhagic

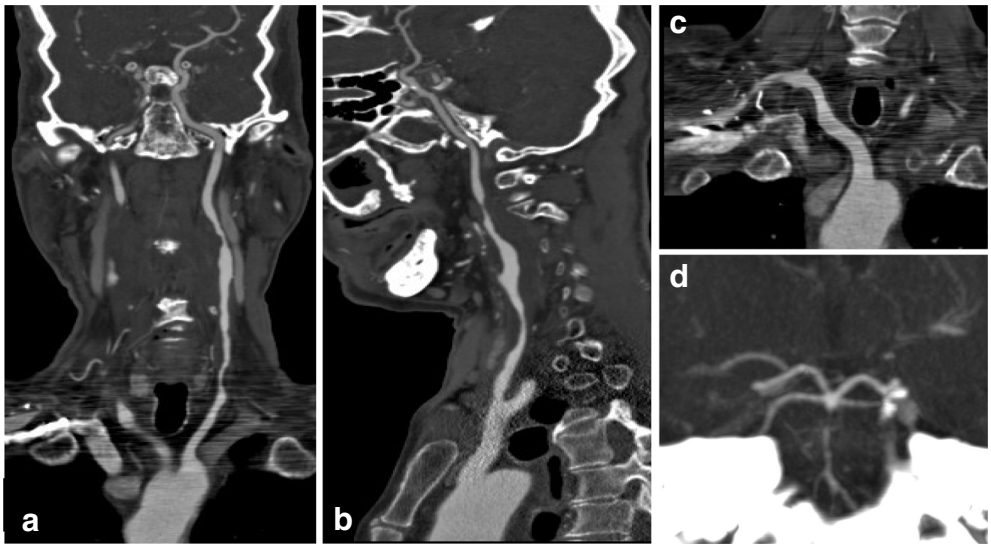

Fig. 2. Example of Takayasu arteritis. **a** Coronal and **b** sagittal blood vessel imaging in the neck reveals a progressive occlusive disease producing vessel irregularity and involving the wall of the aorta, common, and internal carotid artery as well as the **c** subclavian artery. In this patient, there was also a progressive intracranial disease involving the basilar artery as shown in D.

stroke, recurrent hemorrhagic stroke over a median period of 10 years occurred in 36.7% [41]. Hemodynamic fluctuations can lead to recurrent TIA. Precipitating causes (stress, dehydration, hyperventilation) highlight the tenuous cerebrovascular reserve that can lead to alteration in cerebral perfusion and recurring episodes of symptomatic ischemia [42]. Other nonhemodynamic causes of stroke including thrombotic vessel occlusion can occur. The hemorrhagic strokes are typically attributed to the fragile collaterals and rupture of small microaneurysms that may form in these vessels [39].

The disease is so named moyamoya because this is the Japanese term for "something hazy" due to the puff of smoke appearance on digital subtraction angiography [35–37, 43]. Conventional angiography is widely used to assess radiographic disease severity and progression. Disease progression can be rated using the Suzuki staging and modified Suzuki staging which rate the disease based on the mild to moderate, severe, or occlusion of proximal vessels and the degree of collateral network formation. Additional imaging with CT or MR angiogram and perfusion studies may also be used to assess disease severity and progression [44]. The histopathology includes prominent fibrous thickening and hyperplasia of the intima [36, 44]. Collaterals are abnormal with fragmentation of the internal elastic lamina, media thinning, and small aneurysmal dilations [36].

The disease is mostly idiopathic but there may be multifactorial contributions of environment, genetics, and immune factors [35, 39]. There are other disease states associated with the development of a secondary MMD (often termed MM syndrome). These diseases include progressive atherosclerotic disease, sickle cell anemia, neurofibromatosis type I, Down syndrome, Alagille syndrome, thyroid disease, antiphospholipid syndrome, radiation exposure, von Recklinghausen disease, and others [35, 40]. For primary MMD, few genetic variants have been identified in association with the disease. These include variants of the HLA class 1 and 2 alleles and variants involving matrix

metalloproteinase genes [35]. Risk alleles have also been found in the ring finger protein 213 (RNF213) gene in the 17q25-ter chromosomal region whose protein product is a ubiquitin ligase and ATPase involved in angiogenesis (OMIM613768) [45]. There may be additional associations with autoimmune disease and production of IgG and other auto-antibodies. However, the molecular mechanism involved in immune-mediated pathogenesis is unclear [44].

The management of MMD includes both medical and surgical options. Medical treatment with monoplatelet therapy for stroke prevention is not uncommon but has to be balanced against the risk of hemorrhage [37]. However, in cases of significant symptomatic progressive disease to reduce recurrent stroke or TIA, surgical revascularization is an important component of the treatment strategy (indirect, direct, or combination bypass). There were favorable outcomes in patients that underwent revascularization compared with medical management in one multicenter cohort study, though the lack of random assignment may have led to selection bias [46]. Indirect bypass can be performed in those that do not have adequate vessel anatomy for direct bypass. The methods for indirect bypass vary and include encephalo-duroarterio-synangiosis, encephalo-myo-arterio-synangiosis, burr-hole surgical windows, and omentum transplant to promote neovascularization [37]. Direct bypass includes creating an anastomotic connection of the superficial temporal artery to the middle cerebral artery. More immediate improvement in cerebral blood flow can be demonstrated with the direct compared with the indirect approach [37]. While the timing of surgery is not completely clear, evidence of worsening or significant cerebral hypoperfusion and cerebrovascular disease complications should prompt consideration for vascular intervention [34].

Large vessel vasculitis: Takayasu and giant cell arteritis

Inflammatory disorders can contribute to progressive occlusive carotid artery disease and often require steroid and disease-modifying and biologic agents. These diseases are part of a constellation of rheumatologic disorders whose etiologies involve an autoimmune-mediated targeting of the vessel wall. The hallmark of these diseases is aortitis, and the most devastating large vessel vasculidities associated with aortitis and carotid artery involvement include Takayasu arteritis and giant cell arteritis. Other rheumatologic disorders such as lupus, rheumatoid arthritis, Wegener's granulomatosis, polyarteritis nodosa, Behcet's disease, and sarcoidosis can affect large vessels as well but are not covered here.

Takayasu arteritis

Takayasu arteritis is a large vessel vasculitis involving the aorta and its branches (Fig. 3). The disease can be devastating with high mortality rates and tends to affect females more than males (4:1 ratio). The diagnosis is typically made between 20 and 40 years of age [47, 48]. The disease affects individuals from Asia and Southern America preferentially. The vessel involved is commonly the aorta but also coronary, pulmonary, and renal arteries can be involved.

Importantly, in the USA, craniobrachial involvement including the cervical branches of the aorta are common [49]. In one study, subclavian, axillary, and

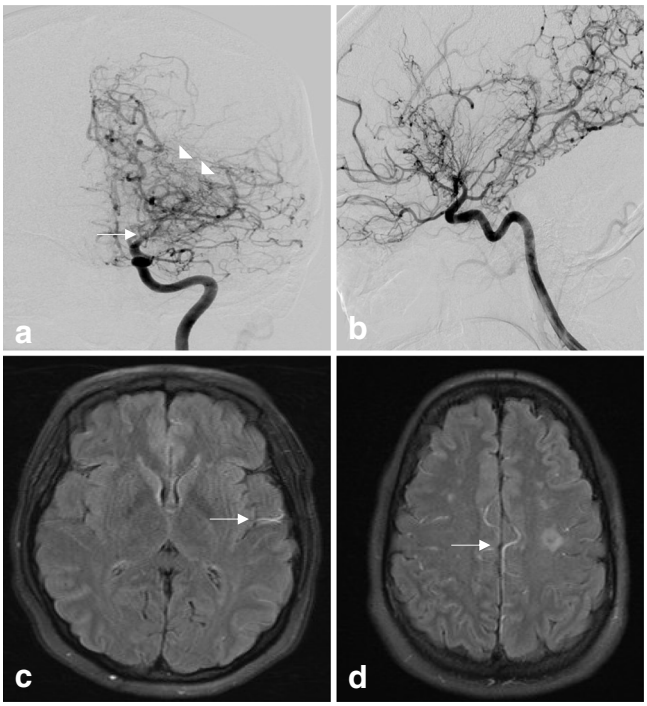

Fig. 3. Example of moyamoya disease. **a**, **b** Coronal and sagittal conventional angiogram imaging of occlusive disease involving the terminal internal carotid artery (arrow) with abundant small collateral vessel formation and interspersed small aneurysmal dilations. **c**, **d** MR brain imaging demonstrates FLAIR hyperintensity that is likely a consequence of hemodynamic compromise and diminished cerebral perfusion with hyperintense signal of the vessel from a slow-flow state (arrow).

brachial arteries were involved in 56.1% of patients and carotid and vertebral arteries in 54.4% of patients [47]. There are several classification schemes that describe the topographical distribution of disease involvement. In the Nasu classification for example, type I involves branches of the aortic arch; type II, the arch and its branches; type III, abdominal aorta and renal arteries; and type IV, the entire aorta [50].

Takayasu arteritis can produce myriad signs and symptoms. Stenosis and progressive occlusion can lead to diminution in the pulse or pulselessness and limb pain which are hallmarks of the disease presentation. In addition to limb claudication, patients may experience constitutional symptoms (weight loss, fatigue, night sweats, low-grade fevers), abdominal pain, stroke, syncope, dizziness, and headache. Asymmetric pulses, bruits, and hypertension are key features of the physical examination [50, 51•].

Conventional angiography is the gold standard approach to imaging in patients with Takayasu arteritis. However, CT and MR angiogram are more commonly used. The entire aorta and its branches should be evaluated in patients with suspected disease. Vascular irregularity, stenosis, occlusion, and aneurysmal dilations can be seen. PET CT can be used as a diagnostic tool to evaluate for vessel inflammation as arteritis tends to produce FDG-avid vessel walls [52, 53]. Alternatively, MR with gadolinium can be used to evaluate for vessel wall enhancement.

Granuloma formation and giant cells can be seen on histological examination of the vessel wall. Takayasu arteritis involves a transmural inflammation

but also intimal and adventitial fibrosis and wall thickening [54].

*HLA-B*52* gene has been identified as a susceptibility locus for Takayasu arteritis. Recently other loci were identified as part of a genome-wide association study. These loci include *PTK2B*, *LILRA3*, *DUSP22*, *KLHL32*, *HSPA6*, and *MICB*. These variants implicate HLA class I and non-HLA pathways associated with natural killer cell function in the pathogenesis of Takayasu arteritis [55].

Based on the European League Against Rheumatism (EULAR) 2018 recommendations, Takayasu arteritis disease management should involve a multidisciplinary team [51]. The initial disease management is often with steroids (40–60 mg per day prednisone equivalent). Patients may need additional therapy with tocilizumab, rituximab, or other biologic agents and may require low-dose 10 mg per day prednisone maintenance therapy. Follow-up should involve assessment of new or worsening symptoms, limb perfusion, and symptoms of claudication, and repeat vessel imaging to assess for progression of disease and response to therapy [51]. Symptomatic severe arterial stenosis may require vascular intervention including angioplasty and stenting [52].

Giant cell arteritis

Similar to Takayasu arteritis, giant cell arteritis (GCA) can affect the large vessels rarely producing an aortitis in addition to vasculitis of the cervical arteries. Patients greater than the age of 50 with new onset headache should be evaluated for GCA. The median age at the time of diagnosis is in the 7th decade. Recognizing signs and symptoms of GCA is critical for rapid initiation of treatment which may reduce the possibility for significant disease morbidity including vision loss due to involvement of the ophthalmic, posterior ciliary, or retinal arteries [56]. The incidence of GCA is 18 per 100,000 per year, and there is a 2:1 female to male predominance [54]. Patients often report constitutional symptoms similar to Takayasu arteritis. Patients may have jaw or tongue claudication, vision disturbance or amaurosis, or scalp necrosis. Proximal shoulder and hip pain may be a symptom of polymyalgia rheumatica, a diagnosis that can accompany GCA. On examination, patients can have scalp allodynia and tenderness on palpation of skin overlying the superficial temporal artery (STA). The STA may appear irregular and rope like to palpation [51]. Carotidynia and cervical bruit may be a clue to carotid artery involvement.

The American College of Rheumatology (ACR) has introduced classification criteria for the diagnosis of GCA [56]. Patients are often screened with serum inflammatory markers including an erythrocyte sedimentation rate ≥ 50 mm/h (using Westergren method). The diagnosis of GCA is aided by temporal artery biopsy.

Other diagnostic imaging modalities have a reasonable sensitivity and specificity and should be considered as alternatives to temporal artery biopsy. Doppler ultrasound can detect a hypoechogenic signal around the affected artery giving the appearance of a halo. This periluminal halo sign in combination with other Doppler characteristics (segmental stenosis or occlusion) may prove useful in the detection of GCA. In a meta-analysis, there appeared to be good sensitivity and specificity of ultrasound characteristics for the diagnosis of GCA when compared with temporal artery biopsy or ACR criteria as reference standards [57]. Though there was between study heterogeneity, a combination

of halo sign, stenosis, or occlusion had a sensitivity of 0.88 (95% CI 0.74–0.95) and specificity of 0.78 (95% CI 0.71–0.84) when compared with biopsy and sensitivity of 0.87 (95% CI 0.80–0.91) and specificity of 0.96 (95% CI 0.89–0.98) when compared with ACR diagnostic criteria. Based on these and other findings, it is suggested that when the pretest probability of having GCA is low, a negative US may be helpful to exclude cases. However, for those at high risk, biopsy should be obtained unless the patient does not agree to biopsy [57]. In the latter case, US can be considered. In addition, microemboli can occur with giant cell arteritis which can be detected on transcranial Doppler (TCD) [58]. However, TCD is not routinely used to diagnose or manage giant cell arteritis. If other vessels are involved, additional imaging modalities including angiography can be considered [51]. The histology reveals a transmural inflammation of the vessel with giant cells. There is typically mononuclear cell infiltration of the media and alternating regions of normal and diseased vessel wall, so called "skip lesions." [54]

Based on EULAR recommendations, GCA management also involves multidisciplinary teams and the initial approach to treatment is with steroids (40–60 mg per day prednisone equivalent). If steroids are not tolerated, other alternative medications including mycophenolate mofetil and azathioprine can be considered. Patients may need additional therapy with tocilizumab, rituximab, methotrexate, or other biologic agents if the disease is refractory. Follow-up should involve assessment of new or worsening symptoms, claudication, headache escalation, or vision loss. Severe relapses especially while on other maintenance medications may require steroid redosing. Patients can require low-dose steroid administration of 5 mg per day prednisone maintenance therapy [51].

Compliance with Ethical Standards

Conflict of Interest

Andrea Harriott reports consulting fees from Bristol Myers Squibb and funding support from electroCore.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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