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Nonatherosclerotic PAD: Approach to Exertional Pain in the Lower Extremities

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Abstract Atherosclerotic peripheral artery disease is the most common cause of intermittent claudication. Nonatherosclerotic peripheral artery disease is a heterogeneous collection of diseases affecting the extracoronary arteries which is not due to atherosclerosis. These diseases include, but are not limited to, popliteal artery entrapment syndrome, cystic adventitial disease, external iliac endofibrosis, and thromboangiitis obliterans. Due to its relatively low prevalence, nonatherosclerotic peripheral artery disease may be misdiagnosed leading to the mismanagement of potentially treatable conditions. The proper and timely diagnosis of these conditions is paramount to the prevention of adverse outcomes as treatments widely vary. The diagnostic approach to patients presenting with intermittent claudication must take into account both atherosclerotic as well as nonatherosclerotic causes of peripheral artery disease making the differential vital to clinical practice.

Keywords Peripheral artery disease · Intermittent claudication · Nonatherosclerotic peripheral artery disease

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Introduction

Lower extremity exertional pain is one of the most common symptoms presenting to the cardiovascular clinic. Atherosclerotic peripheral artery disease (aPAD) is the most common vascular cause affecting approximately 8–12 million Americans with a prevalence of up to 29 % of the general population [1, 2]. The presence of aPAD is an indicator of systemic atherosclerosis and is associated with an elevated risk of myocardial infarction, stroke, and all-cause mortality [3]. While "classic" symptoms are described as lower extremity cramping which is brought on by activity and relieved rapidly with rest, most patients experience "atypical" symptoms such as burning, tingling, or heaviness. Most who present with symptoms of intermittent claudication (IC) may be diagnosed with aPAD; however, the much less common nonatherosclerotic peripheral artery diseases (NAPAD) must remain in the differential as misdiagnosis can lead to potentially preventable adverse outcomes [4]. As opposed to aPAD, NAPAD encompasses a diverse group of varying disorders with distinctly different pathophysiologies, clinical manifestations, and treatments (Table 1). The evaluation of patients presenting with exertional lower extremity symptoms should always take into account the possibility of both aPAD and NAPAD.

When Should NAPAD Be Suspected?

Most patients presenting with IC will have aPAD. While aPAD does not always present in a classic pattern, the astute physician will suspect the diagnosis based on the relationship between symptoms, relieving factors, and patient characteristics. For example, a young otherwise healthy competitive cyclist, presenting with exertional lower extremity symptoms, may easily be distinguished from a middle-aged smoker with

Table 1 Differential diagnosis of nonatherosclerotic peripheral artery disease

		Age	Sex	Key features	Diagnosis	Treatment
Popliteal artery entrapment syndrome		Young adults	M > F	Exertional claudication pain, paresthesias, and poikilothermia after exertion external compression of popliteal artery from muscles and ligaments in popliteal fossa	Loss of Doppler signaling with provocative maneuvers demonstration of compression on active pedal plantar flexion against resistance CTA/MRA to demonstrate entrapment of vascular structures	Surgical relief of compressing elements
Cystic adventitial disease		4th and 5th decades	M > F	Exertional claudication with extended recovery time compared to aPAD symptoms caused by compression of arterial lumen by mucinous containing cystic lesion within the adventia	Loss of pedal pulses with sharp knee flexion (Ishikawa sign) MRA	Removal of cystic lesions vein interposition grafting
Iliac artery endofibrosis		2nd and 3rd decades	M = F	Competitive athletes, common in cyclists intimal thickening by collagen fibers, fibrous tissue, and smooth muscle proliferation femoral bruit with hip flexion	Arterial duplex ultrasound and digital subtraction angiography with hip flexion and extention intravascular ultrasound with intraarterial translesional pressure gradients	Surgical bypass and endofibrectomy percutaneous angioplasty with stent consideration
Fibromuscular dysplasia		2nd to 5th decades	F > M	"String of bead" appearance symptoms based on vascular bed involved	Digital subtraction angiography with intravascular ultrasound	Percutaneous transluminal angioplasty without stent deployment
TAO (Buerger disease)		<50 years		Tobacco smokers intermittent claudication, Raynaud's phenomena, superficial thrombophlebitis skipped lesions and corkscrew collaterals	CTA MRA digital subtraction angiography	Smoking cessation vasodilators ilioprost debridement amputation
Medium and large vessel vasculitis	TA	15–30 years	F > M	Asian and Latin decent pulseless upper extremity	Elevated inflammatory markers Duplex ultrasound CTA MRA	Corticosteroids, methotrexate, and azathioprine
	GCA	>50 years	M = F	Headache, jaw claudication, visual disturbances	temporal artery biopsy (GCA)	tocilizumab (TA, GCA) endovascular and surgical reconstruction
	Behcet's	<30 years	M = F	Recurrent mucosal ulcers, uveitis, pathergy		
Chronic exertional compartment syndrome		>40	M = F	Athletes typically bilateral complete symptom resolution 10–20 min after rest	Imaging to rule out other causes elevated intracompartment pressures before and after exercise	Alteration of physical activity surgical fasciotomy or fasciectomy

CTA computed tomographic angiography, *MRA* magnetic resonance angiography, *TA* Takayasu's arteritis, *GCA* giant cell arteritis, *aPAD* atherosclerotic peripheral artery disease, *TAO* thromboangiitis obliterans

hypertension and hyperlipidemia on the basis of history alone. In other cases, history alone will not suffice. For example, a middle-aged smoker presenting with digital ulcerations may require imaging studies to differentiate atherosclerotic from nonatherosclerotic causes. NAPAD should be suspected when a paucity of classic atherosclerotic risk factors exists along with inconsistencies between symptoms and imaging findings. The following is a discussion of various causes of NAPAD-related IC.

Popliteal Artery Entrapment Syndrome

Popliteal artery entrapment syndrome (PAES) may result in IC as a result of external compression of the popliteal artery by surrounding musculature and ligaments in the popliteal fossa [5]. PAES tends to occur in young adults and appears to have a male predominance with a 15:1 male to female ratio [6]. The prevalence of clinically relevant PAES is fairly low. In a study of 20,000 Greek military recruits, symptomatic PAES was only found in 33 (0.165 %) [7].

Of the six types described, there are four classic types (types I–IV) involving various anatomic compressions of the artery itself, type V involves compression of the popliteal vein, and type VI is characterized by hypertrophy of the medial head of the gastrocnemius muscle resulting in functional symptoms (Table 2) [8, 9].

The most common symptom of PAES is IC; however, symptoms may also include paresthesias and cold extremities after exertion [10]. Ischemic rest pain and tissue necrosis are relatively uncommon presentations, however, may be a consequence of long-standing compression resulting in arterial degeneration, poststenotic aneurysm formation, and secondary peripheral embolization. In certain cases, well-developed arterial collateralizations may paradoxically result in lesser symptoms. Entrapment of the popliteal vein (type V) results in typical symptoms of venous hypertension including swelling of the affected limb, varicosities, leg heaviness, and nocturnal calf cramping [11].

PAES should be suspected in a young person presenting with IC or any of the above symptoms. The diagnosis of PAES is also suggested by demonstrating compression of the popliteal artery during provocative maneuvers. First, physical exam may be significant for the decrease or loss of a tibial pulse with active pedal plantar flexion against resistance. This can be confirmed with continuous wave Doppler signaling and pulse volume recordings with segmental pressures at rest and plantar flexion. Second, arterial duplex ultrasonography may demonstrate abnormalities when performed with the knee extended and the ankle in the neutral, dorsiflexed, and plantarflexed positions [12]. Caution should be maintained as a study of 16 healthy volunteers showed compression in 27 of 32 popliteal arteries when both lower extremities were measured during active plantar flexion [13]. Finally, magnetic resonance angiography (MRA) has emerged as the imaging modality of choice due to its ability to demonstrate the structures causing compression with the added benefit of yielding both physiologic information as well as anatomic data that is important in planning intervention [14].

The definitive treatment of PAES types I–V is the surgical release of the anatomical entrapment and compressing components. The functional variant (type VI) is also treated with surgery that includes decompression and resection of the medial head of the gastrocnemius muscle. Because of the progressive nature of PAES, early detection and treatment have been shown to be associated with better long-term outcomes when compared to delayed therapy [15]. In advanced cases, surgical bypass and arterial reconstruction of an occlusion or aneurysm may be required. Concurrent musculotendinous resection is still advised in these cases, as persistent abnormal musculature may result in bypass graft compression.

Cystic Adventitial Disease of the Lower Extremities

Cystic adventitial disease (CAD) is a rare cause of IC. It typically affects middle-aged individuals with a clear male predominance [16]. CAD most commonly involves the popliteal artery, while extrapopliteal disease has been described in approximately 15 % of the cases [17]. Bilateral disease has also been described [18].

The symptoms of CAD result from arterial luminal narrowing by mucinous containing cysts within the adventitia of the artery. The precise etiology is unknown; however, several theories have been proposed including repetitive trauma, systemic disorders, and a persistent embryonic synovial track [19]. Symptoms may be intermittent and wax and wane over time, frequently disappearing for extended periods and reemerging without any provoking events. As with atherosclerotic IC, symptoms will be relieved with rest; however, CAD-associated IC results in a delayed recovery phase, often lasting up to 20 min before limb pain resolution [20].

The diagnosis of CAD should be suspected in men in their fourth and fifth decade with a vascular exam notable for the disappearance of pedal pulses with knee flexion, the so-called Ishikawa sign. The choice of imaging study is geared toward visualization of the cystic lesions within the arterial lumen. Duplex ultrasonography may show hypoechoic to anechoic lesions within the lumen with color Doppler showing no flow within the lesions. Magnetic resonance imaging (MRI) has the ability to visualize the cysts as well as to further characterize their appearance and therefore has emerged as the imaging modality of choice (Fig. 1). Angiography, magnetic resonance or conventional, may demonstrate concentric compression of the lumen ("hourglass sign"). If the cysts are large enough, they may displace the artery to one side, also known as the "scimitar sign"

Table 2 Anatomic types of popliteal artery entrapment syndrome

Type	Artery or vein	Anatomic considerations
I	Artery	Abnormal popliteal artery course medial to insertion of medial head of gastrocnemius muscle
II	Artery	Abnormal lateral insertion of gastrocnemius muscle with medial course of artery beneath muscle insertion
III	Artery	Accessory slip of gastrocnemius muscle wrapped around the artery
IV	Artery	Artery lies deep to the gastrocnemius muscle entrapped by the muscle or fibrous band
V	Artery and vein	Various anatomies with entrapment of both artery and vein
VI	Artery	Hypertrophy of the medial head of the gastrocnemius muscle

[16]. Importantly, in CAD, digital subtraction angiography is not the imaging study of choice, because it will only show luminal narrowing without characterizing the reason.

Although there are no consistent guidelines regarding the treatment of CAD, several therapeutic options have been proposed. Surgery (vein interposition grafting) appears to show the most promising symptomatic benefits. Various case series report initial success rates to be 94 % [21]. Image-guided cyst aspiration is ineffective with high reoccurrence rates [22]. Percutaneous transluminal angioplasty has similarly shown high failure rates with increased risk of restenosis and distal embolization [23].

External Iliac Artery Endofibrosis

Endofibrosis of the external iliac artery, while uncommon, may be one of the most common vascular conditions of the lower extremities seen in young athletes. It is most frequently observed in competitive cyclists and runners, however, has also been described in speed skaters and cross-country skiers [24]. The median age at presentation is 25 years, and there does not appear to be a gender predilection [25].

The disease process is characterized by intimal thickening and subsequent narrowing of the external iliac artery by collagen fibers, fibrous tissue, and smooth muscle proliferation [26]. The pathophysiology is theorized to be due to repetitive

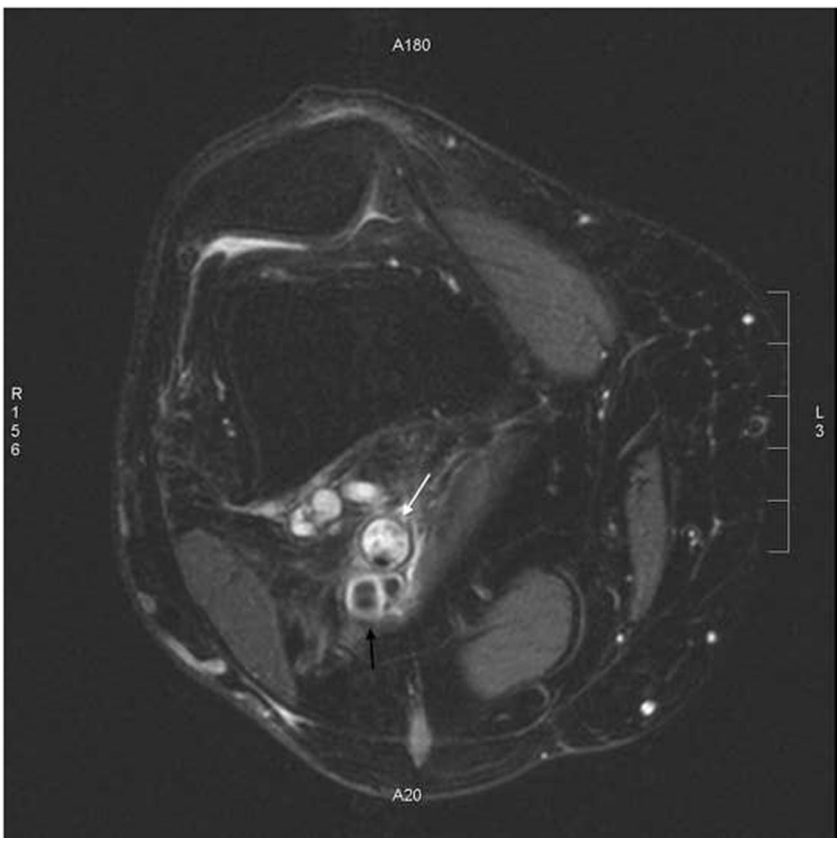

Fig. 1 Axial T2-weighted MRI demonstrating cystic formation along the arterial adventitia (*black arrow*) adjacent to the popliteal artery (*white arrow*)

trauma during extreme hip flexion and shear stress during high cardiac output states.

Symptoms of external iliac artery endofibrosis include IC as well as the sensation of limb swelling, paresthesias, and limb weakness during times of maximal repetitive exertion. Symptoms are typically unilateral and localized to the non-dominant limb, however, may be bilateral in up to 15 % of the cases [27]. Physical exam may reveal a femoral bruit during hip flexion.

Diagnostic studies should first include ankle-brachial index at rest and after exertion. This study, however, may not suffice as it can incur a high false-negative rate due to the inability of standard treadmill testing to mimic the prolonged and repetitive nature of high-intensity cycling in high-functioning individuals. Cycling ergometry can be a helpful diagnostic mimic; however, specific protocols are not widely available [28]. Generally, the type and degree of exertion that the athlete describes as causing their symptoms should be imitated in the lab. Arterial duplex ultrasonography may show typical findings of echoic thickening of the myointimal border [29]. The sensitivity of arterial ultrasound is approximately 80 %, which may be improved with provocative maneuvers such as hip flexion [30]. Further imaging with MRA can be useful to distinguish luminal narrowing from arterial kinking. Apart from surgical biopsy, digital subtraction angiography is the gold standard diagnostic test. Intravascular ultrasound may aid in the diagnosis by delineating the degree of intimal fibrosis, and translesional pressure gradients may be helpful when lesions are of indeterminate significance [31].

Treatment of external iliac artery endofibrosis should first include conservative measures such as activity modification to avoid the causative movements. Although no large scale prospective studies exist to guide recommendations, definitive treatment has historically been surgical. Iliac endarterectomy and endofibrectomy with patch angioplasty can be offered along with interposition vein grafts. Endovascular options including balloon angioplasty with and without stent deployment have been described in the literature with variable patency rates; however, concern regarding intimal dissection due to endofibrotic lesions suggests percutaneous options to be limited to selected cases [32].

Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is a condition characterized by nonatherosclerotic, noninflammatory segmental narrowing of the arterial lumen in medium-sized vessels. There is a female predominance and most cases are diagnosed in middle-aged women [33]. The prevalence has yet to be defined in the general population, however, may be more common than previously thought. A meta-analysis of potential kidney donors found FMD in approximately 4 % of possible donor candidates [34]. Even this number may represent an underestimation of the true prevalence of FMD within the general population as kidney donors typically have less medical co-morbidities such as hypertension or chronic kidney disease [35••].

The etiology of FMD is unknown. It is largely believed to be caused by an abnormal growth of cells within the arterial wall. Pathological specimens reveal fibrous thickening of the arterial wall, and any of the artery layers may be affected [36]. The variation in the arterial wall predisposes the vessel to aneurismal dilation, dissection, and distal embolization [12]. FMD can affect nearly any arterial bed, yet most commonly affects the renal arteries (75 % of the cases) with the carotid arteries being the second most affected. FMD involves the lower extremities in approximately 5 % of the cases [37]. Clinical symptoms of FMD are a reflection of the arterial bed involved. Cases affecting the iliac arteries may present with IC, cold extremities, and symptoms of distal embolization [38].

FMD is a histologic diagnosis; however, in clinical practice, symptoms and associated classic radiographic findings are usually used for diagnosis [39]. Duplex ultrasound is a useful first screening tool to identify arterial stenosis. MRA and CTA are useful to identify aneurysms although digital subtraction angiography complemented by intravascular ultrasound remains the gold standard of diagnostic imaging studies [40, 41]. The most common findings are alternating arterial stenosis and dilation causing a "string of beads" appearance (Fig. 2) [42].

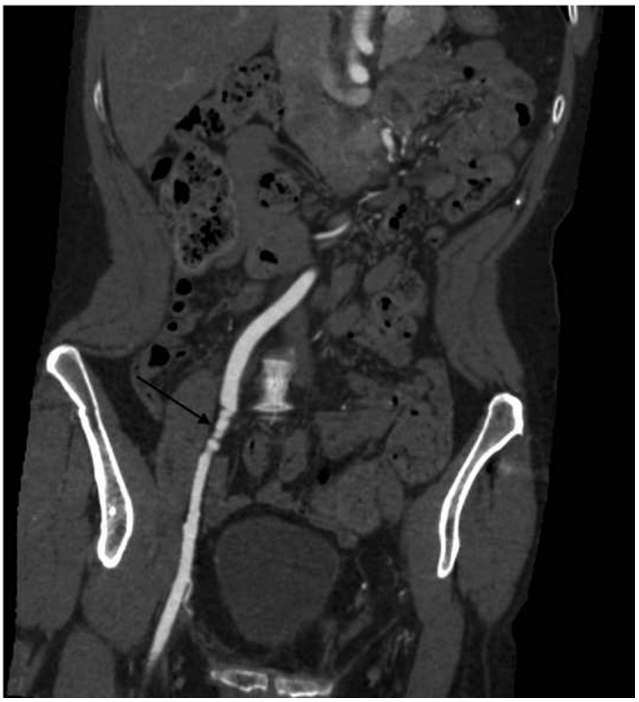

Fig. 2 Computed tomography demonstrating the "string of beads" (*arrow*) appearance of the right common iliac artery

The treatment of FMD depends on the vascular bed involved and the presence or absence of symptoms. Although no clear consensus guidelines exist regarding the medical treatment of FMD, asymptomatic patients will typically be treated empirically with aspirin. Patients with renal artery FMD who were treated by percutaneous transluminal angioplasty without stent deployment have been reported to have satisfactory long-term patency rates. This has been extrapolated to patients experiencing debilitating symptoms as a result of lower extremity involvement making it the first-line therapy [43, 44].

Medium and Large Vessel Vasculitis

The vasculitides which are most likely to cause symptoms that mimic aPAD include the medium and large vessel disorders, most notably Takayasu's arteritis (TA), giant cell arteritis (GCA), and Behcet disease.

TA is a large vessel vasculitis classically described in young Asian and Latin American women [45]. Symptoms typically present in young adulthood. The average age of symptom onset is between 15 and 30 years of age [46]. TA is a relatively rare disorder. A large population-based study conducted in the UK found the overall prevalence to be 4.7 per 1 million [47]. The etiology of TA is largely unknown; however, cell-mediated immune mechanisms are likely involved, similar to other large vessel vasculitides such as GCA [48]. Inflammatory changes within the vessel wall may cause arterial stenosis, occlusion, or aneurysms. Involvement of the aortic arch and the great vessels are typical. Thus, symptoms related to TA are more likely to occur in the upper extremities than in the lower extremities. Nonetheless, a mid-aortic variant of TA exists which may result in abdominal aortic coarctation. This involvement may be complicated by renovascular hypertension and/or IC [49]. The diagnosis of TA is clinical as there are no specific laboratory tests for this condition. It is suggested when 3 of 6 diagnostic criteria are met, as proposed by the American College of Rheumatology: the development of symptoms at a young age (<40 years), limb claudication, decreased pulse in one or both brachial arteries, a difference of >10 mmHg in systolic blood pressure between arms, audible bruit on auscultation over one or both subclavian arteries or abdominal aorta, and arteriographic narrowing or occlusion of large vessels in the absence of arteriosclerosis [50].

Similar to TA, GCA represents an entity along the spectrum of vasculitides of medium and large vessels. There does not appear to be a gender predominance, and it is a disorder exclusively of adult age >50 years. The prevalence of GCA varies between geographic locations, being most prevalent in northern Scandinavian countries where it is estimated to have an annual incidence between 17 and 29 per 100,000 [51]. The inflammatory changes within the vessel wall in GCA are due to local T cell and macrophage infiltration causing typical granuloma formation. Inflammation of the vessel wall results in occlusion from concentric intimal hyperplasia ultimately leading to ischemic complications [52]. Like TA, the symptoms of GCA are more commonly associated with the upper extremities. Associated symptoms include headaches, jaw claudication, scalp tenderness, and visual disturbances, although lower extremity involvement has been described [53]. According to the American College of Rheumatology, GCA can be diagnosed if 3 of 5 of the following criteria are met: age at onset >50 years, new headache, temporal artery abnormality, elevated ESR >50 mm/h, and abnormal temporal artery biopsy showing mononuclear cell infiltration or granulomatous inflammation [54].

Finally, Behcet disease is a multisystem vasculopathy affecting all sizes of vessels. Males tend to have a higher severity of disease [55]. The prevalence is reported to be 8.6 per 100,000 in the USA with higher rates being reported among those of Mediterranean ancestry [56]. Typical onset is in the third decade of life and is rarely seen to initiate after the fifth decade. The disease is characterized by recurrent mucosal lesions (e.g., oral cavity and genitalia) and vision-threatening panuveitis [57]. The diagnosis requires the presence of recurrent oral ulcers along with involvement of at least 2 other organ systems including uveitis, genital ulcers, skin lesions, and pathergy reaction [58]. Vascular involvement can occur in up to 40 % of cases: 75 % of which involve the venous system and 25 % involving the arterial system [59]. Histopathology is characterized by diffuse inflammatory changes involving long segments of the vessel wall [60]. Arterial involvement of the lower extremities occurs in the setting of aortic, iliac, and popliteal aneurysms, which may pose a high risk of rupture and represent a major cause of death in these patients [61].

Imaging studies provide valuable information regarding location and extent of disease as well as characterizing the vascular lesions. Duplex ultrasound may show segmental luminal narrowing, the so-called spaghetti sign, as well as evidence of vessel wall edema, known as the "halo sign" (or "macaroni sign") [62, 63]. CTA and MRA are useful to visualize long segments of smooth narrowing and aneurysmal dilation [64]. Additional testing can be done with positron emission tomography (PET-CT); however, conflicting reports exist regarding the actual correlation between PET findings and actual disease activity (Fig. 3) [65].

The cornerstone of the therapy for vasculitides is management of inflammation. Secondary arterial and systemic complications should also be addressed [66]. While the disease is active, symptoms of lower extremity involvement including intermittent claudication may respond to anti-inflammatory agents such as corticosteroids, methotrexate, and azathioprine. The anti-interleukin-6 agent tocilizumab has been used in the treatment of TA and GCA and more specifically in the treatment of lower extremity ischemic complications of GCA

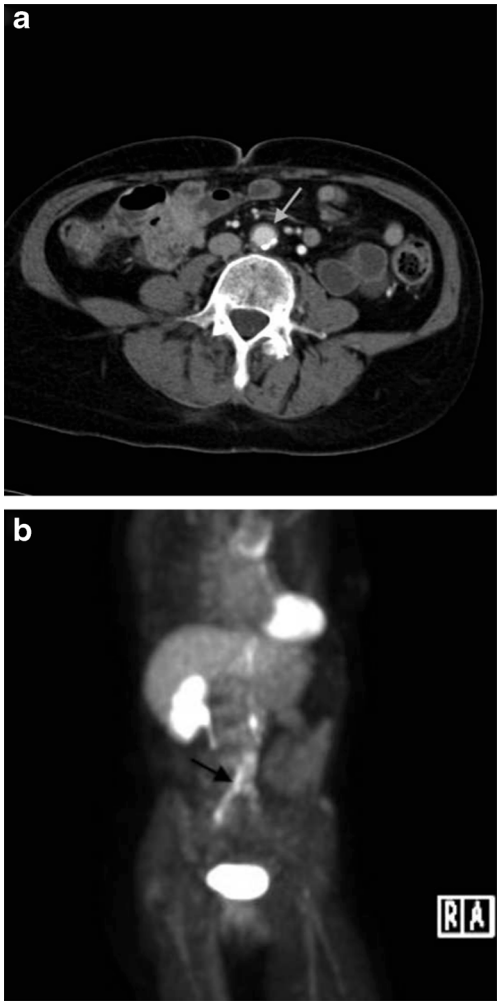

Fig. 3 **a** shows arterial wall thickening suggestive of local aortitis (*arrow*). **b** illustrates positron emission tomography with FDG uptake in the abdominal aorta and common iliac arteries (*arrow*)

[67•]. With disease progression, the vascular endothelium may become fibrotic (the so-called burnt-out stage). Endovascular or surgical approaches to correct underlying arterial occlusion or aneurysms may be required in symptomatic patients who present at this stage [68].

Thromboangiitis Obilterans (Buerger Disease)

Thrombangiitis obliterans (TAO), also known as Buerger's disease, is a segmental nonatherosclerotic inflammatory disease of small arteries, veins, and nerves typically affecting both the hands and feet [69]. This condition is almost exclusively seen in tobacco smokers but has also been described in users of chewing tobacco and marijuana [70].

TAO affects men more commonly than women and typically presents in the fifth decade of life [71].

Symptoms of TAO can mimic those of aPAD. As both conditions are associated with tobacco abuse and present with ischemic symptoms, care must be taken to differentiate between the two. A summary detailing the clinical differences TAO and aPAD can be found in Table 3. The diagnosis of TAO is clinical. Patients who continue to smoke typically present with digital pain that progresses to digital ischemia and gangrene as tobacco exposure continues. Ischemic lesions often progress from distal to proximal. Other common presenting symptoms include splinter hemorrhages, Raynaud's phenomenon (40 %), or livedo reticularis [72].

Proposed criteria for TAO include age <45, current or recent tobacco use, distal extremity ischemia confirmed by noninvasive testing, exclusion of thrombophilia, autoimmune disease, proximal source of embolism, and consistent radiographic findings [71]. A presentation of arterial insufficiency with superficial thrombophlebitis should suggest TAO as well. In addition, involvement of both upper and lower extremities favors a diagnosis of TAO over atherosclerosis. An abnormal Allen's test may demonstrate arterial involvement of the upper extremity, even if the patient is asymptomatic and therefore should be part of the physical examination when TAO is suspected.

CTA and MRA are useful only in excluding atherosclerosis as a cause. Digital subtraction angiography can be more helpful. When performed properly, hand or foot magnifications will demonstrate distal arterial involvement and typical findings of segmental arterial occlusion and corkscrew collaterals, while excluding the typical tapering appearance of scleroderma. Response to local vasodilators can be used to investigate for vasoconstriction [73].

Only complete abstinence from tobacco will result in clinical improvement. Patient education to the role of tobacco as the foundation of the disorder is vital. Pharmacotherapy and psychotherapy should be offered as adjunctive measures. Unfortunately, nicotine replacement should be avoided due to its likely contribution in the disease process [74]. Various prostacyclin analogs have been investigated as a means to relieve ischemia in TAO-related lesions. Iloprost, while showing promise in some studies, failed to result in clinically meaningful improvement in others [75, 76]. Other medical therapies including vasodilators such as endothelin receptor antagonists, phosphodiesterase inhibitors, selective alpha antagonists, and calcium channel blockers have also been used with varying success and have not been evaluated by prospective trials [67•]. Finally, surgical venous bypass is an important option to prevent limb loss in TAO, although the nature of small vessel disease often makes bypass technically difficult for lack of targets. The dismal prognosis of these procedures can be illustrated by a retrospective study of 8 TAO patients in whom 10 arterial reconstructions were performed. Of these, 3 grafts were occluded at 42 months [77]. Advanced cases may require frequent surgical debridement and amputation.

Table 3 Clinical differentiation of atherosclerosis versus thromboangiitis obliterans

	Atherosclerosis	TAO
Age	>40	<45
Distribution	Diffuse, typically involves nonextremity arterial beds	Localized, segmental, starts distally and progresses proximally
Risk factors	Hypertension, hyperlipidemia, diabetes mellitus, smoking, family history	Tobacco smoking
Intermittent claudication	Yes	Variable
Coronary involvement	Common	Rare
Natural history	Progressive	Progressive without smoking cessation
Radiographic findings	Diffuse luminal irregularities, intimal plaques and calcifications of the large and medium-sized vessels	Absence of atherosclerosis, segmental occlusion, corkscrewing collaterals

TAO thromboangiitis obliterans

Chronic Exertional Compartment Syndrome

Chronic exertional compartment syndrome (CECS) results from increased intracompartmental pressures in the lower extremities due to repetitive physical activity resulting in decrease tissue perfusion [78]. The calf is divided into four compartments, any of which may be involved. During times of exertion, muscles swell and fluid enters the noncompliant muscle compartments. The increased pressure causes a transient ischemic effect during time of exertion [79].

CECS is most commonly seen in high-endurance runners, although it has also been seen in rugby, basketball, soccer and tennis players, and skiers [80]. The prevalence of CECS is unknown and is likely under diagnosed in the general population, especially as many patients with early exertional pain decrease or modify their activities to manage the associated symptoms [81]. A retrospective study of active US military recruits from 2006 to 2011 reported 4100 cases of CECS for an incidence rate of 0.49 cases per 1000 person-years [82•]. The greatest risk factor reported was age >40 years, and the adjusted incidence was nearly 9 times greater than of those <40 years of age.

Characteristic symptoms of CECS include cramping, heaviness, or pain in the calf during times of exertion and cessation of symptoms with rest, typically within 10–20 min [83]. Although symptoms may be localized to a specific location, this is often a poor indicator of the compartment involved [84]. The anterior compartment is most frequently affected (45 %), followed by the deep posterior compartment (40 %), lateral compartment (10 %), and superficial posterior compartments (5 %) [85]. With involvement of the anterior compartment, there may be weakness of the tibialis anterior causing loss of dorsiflexion, or foot drop, and paresthesias of the dorsal aspect of the foot [86]. Muscle hernias may be present on physical exam. Although symptoms are usually worse on one side, CECS is bilateral in up to 95 % of the cases [87].

The diagnosis of CECS is for the most part clinical and largely a diagnosis of exclusion. MRI or bone scan may be used as a means to rule out stress fracture or periostitis while MRA and ultrasound may rule out arterial or nerve entrapment. The gold standard for definitive diagnosis is made with intracompartmental pressure measurement before and after exercise. The accepted diagnostic criteria as proposed by Pedowitz et al. are a pre-exercise pressure >15 mmHg and >30 mmHg 1-min postexercise, or >20 mmHg at 5-min postexercise [88].

Initial management of CECS is typically conservative and consists of alterations to training regimens, physical therapy, and adjustment of footwear including orthotics, and inserts. The termination of stressful physical activity resolves the pain in most cases. For those patients in whom this solution is unacceptable or who have recurrent symptoms, surgical intervention with muscle compartment release can be offered [89]. Surgical success rates are reported to be high in multiple observational studies using either fasciotomy or fasciectomy, especially when anterior compartment release is performed [90–92].

Conclusion

Leg pain with exertion is often a result of atherosclerosis; however, nonatherosclerotic causes should be known to the vascular practitioner and suspected in every patients being evaluated for these complaints. Laboratory and imaging evaluation should rely on patient-specific

history and examination. A delay in diagnosis of NAPA D could result in otherwise potentially avoidable adverse outcomes for patients.

Compliance with Ethics Guidelines

Conflict of Interest Ari J. Mintz and Ido Weinberg declare that they have no conflict of interest.

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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