Conditions Presenting with Symptoms of Peripheral Arterial Disease

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Semin Intervent Radiol 2014;31:281–291

Abstract

Keywords

- ▶ nonatherosclerotic peripheral artery disease
- ▶ mimics of peripheral vascular disease
- ▶ iliac artery endofibrosis
- ▶ popliteal artery entrapment syndrome
- ▶ fibromuscular dysplasia
- ▶ interventional radiology

Peripheral artery disease (PAD) is estimated to affect more than 20% of people older than 65 years. The vast majority of patients with symptoms suggestive of PAD have atherosclerosis often associated with conventional vascular risk factors such as smoking, diabetes, dyslipidemia, and inflammation. A minority of people presenting with symptoms suggesting PAD have an alternative etiology. These groups of disorders are often underdiagnosed, and if diagnosed correctly the diagnosis may be delayed. Understanding these pathologies well is important, as they can be very debilitating and optimal treatment may vary significantly. Inappropriate treatment of these disorders can lead to worsening morbidity and mortality. This article discusses the underlying causes of nonatherosclerotic PAD, including the diagnosis and treatment of these disorders.

Objectives: Upon completion of this article, the reader will be able to describe the identification of patients with nonatherosclerotic PAD. In addition, the reader will be able to identify the pathophysiology as well as appropriate treatment options for these heterogeneous disorders.

Accreditation: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Tufts University School of Medicine (TUSM) and Thieme Medical Publishers, New York. TUSM is accredited by the ACCME to provide continuing medical education for physicians.

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More than 90% of patients presenting with symptoms or signs suggestive of peripheral artery disease (PAD) have atherosclerotic vascular disease. The remainder has a varied group of pathologies that can be broadly categorized as secondary to intrinsic arterial mural abnormalities, inflammatory vasculitides, deranged coagulation, abnormal internal and external forces, and impaired venous drainage (► **Table 1**). The management of these conditions often differs from that of atherosclerotic disease and involves management of the underlying cause as well as treatment of the anatomical arterial lesion. This article will briefly discuss the various clinical characteristics and management options for these disorders.

Issue Theme Peripheral Arterial Disease; Guest Editors, David Kessel, MB, BS, MA, MRCP, FRCR, EBIR and Iain Robertson, MD, MBChB, MRCP, FRCR, EBIR

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DOI <http://dx.doi.org/10.1055/s-0034-1393963>. ISSN 0739-9529.

Table 1 Nonatherosclerotic vascular pathologies mimicking atherosclerotic peripheral arterial disease

Mural abnormality
Fibromuscular dysplasia
Cystic adventitial disease
Connective tissue disorders
Idiopathic midaortic syndrome
Inflammatory vasculitis
Thromboangiitis obliterans
Takayasu arteritis
Giant cell arteritis
Behçet disease
Radiation-induced arteritis
Artery subject to abnormal forces
Iliac artery endofibrosis
Popliteal artery entrapment syndrome
Thoracic outlet syndrome
Abnormal coagulation
Inherited and acquired arterial thrombophilias
Thoracic outlet syndrome
Abnormal veins
Venous claudication and gangrene

Conditions with an Abnormal Arterial Wall

Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, non-inflammatory arterial disease that can lead to arterial stenosis, aneurysms, dissections, and occlusion.¹ Its true prevalence in the general population is unknown.¹ The cause is unknown; however, as 90% of cases are in females, a relationship to hormonal factors such as estrogen is suspected.² Studies have shown that 7 to 11% of FMD patients have family members affected, thereby also suggesting a genetic association.^{3–6}

FMD has been reported in multiple vascular beds, but the vast majority of cases have been reported in extracranial cerebrovascular and renal arteries, followed in incidence by the external iliac arteries. The United States Fibromuscular Dysplasia Registry of America has reported that among the 357 patients in the registry with imaging of ≥ 2 vascular beds, 35%, 22%, 9% had FMD in 2, 3 and 4 or more vascular beds respectively.⁶ FMD involving the lower extremities is often asymptomatic; however, it can present with intermittent claudication (IC) or even critical limb ischemia typically from embolic events or from arterial dissection. Often these patients will have a femoral or abdominal bruit.

Investigation

Laboratory testing including inflammatory markers is normal. Based on histopathology, FMD is classified as medial, intimal, or adventitial depending on the arterial wall layer

involved. Seventy percent to 90% of FMD patients have the medial form, which is further subclassified into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Medial fibroplasia (present in $>70\%$ of patients) is the most common subtype, and is characterized by alternating segments of medial degeneration and collagen deposition.⁷

Imaging

FMD may be diagnosed with duplex ultrasonography, magnetic resonance (MR) imaging, and computerized tomography (CT); however, these imaging tests have variable accuracy, and angiography remains the gold standard. Once FMD is diagnosed, many high volume FMD clinic centers will obtain MR or CT angiography from the head to the pelvis to screen for the presence of FMD and aneurysms in other locations. Determining the specific subtype of FMD by imaging is often inaccurate; the American Heart Association recommends classifying radiographic finding of FMD as multifocal or focal rather than by specific subtype.¹ The classical appearance of a “string of beads” on angiography is caused by stenosis in areas of collagen deposition and microaneurysms in the intervening segments due to the loss of smooth muscle and internal elastic lamina deficiencies (**► Fig. 1**). One of the most common mimics of lower extremity FMD is standing waves, which is a physiological artifact seen during angiography and is benign.^{8,9} Other angiographic findings of FMD include focal web-like stenosis; long, smooth tubular stenosis; aneurysms; and focal arterial dissections.

Treatment

Patients with asymptomatic FMD are empirically treated with aspirin to reduce the risk of superimposed thromboembolic events.¹ Patients who are symptomatic secondary to stenotic disease associated with FMD are usually treated with balloon angioplasty. Patients with symptomatic dissections and aneurysms have been surgically treated successfully with vein or prosthetic grafts when surgical correction is recommended over endovascular repair.^{1,2,6}

Cystic Adventitial Disease

Cystic adventitial disease (CAD) presents with IC, which is usually unilateral and caused by multilocular mucinous or gelatinous cysts in the adventitial layer of the vessels.^{10–14} Around 350 cases of arterial CAD have been reported in the literature with 85% in the popliteal artery; cases have also been described in the external iliac, femoral, axillary, brachial, radial, and ulnar arteries.^{10,12,14} Venous CAD is extremely rare with only 20 reported cases in the literature.¹⁰ Arterial CAD most commonly affects middle-aged men, with reported male-to-female ratio in arterial CAD being 5:1.^{10–13}

The etiology of CAD remains unknown. The developmental hypothesis is most widely accepted and suggests that mucin-secreting mesenchymal cells are embedded in the arterial adventitia.¹⁵ Communication with the knee joint may be present. IC is caused by compression of the vessel lumen by adventitial cysts; both progression to occlusion and spontaneous resolution have been reported, and the variation of fluid in cysts and resulting vessel compression is used to explain the waxing and waning of symptoms.^{10,11,14}

Figure 1 A 78-year-old man presented for evaluation of his thoracic aortic aneurysm. Volume rendered reconstruction (A) from CT angiogram shows bilateral external iliac artery fibromuscular dysplasia with areas of alternating stenosis and aneurysms (arrows), referred to as a “string of beads.” This morphology is typical of the medial fibroplasia, the most common subtype of fibromuscular dysplasia. Centerline analysis (B) of the right iliac artery shows the fine webs (arrowheads) that are present in this disease state. Bilateral renal FMD was also present (not shown). The patient was without lower extremity symptoms. (C) Angiogram of a 37-year-old female with left leg claudication showing multifocal fibromuscular dysplasia (arrow).

Loss of pedal pulses with passive knee flexion (Ishikawa sign) is suggestive of CAD.^{10,13}

Imaging

Duplex ultrasound is a good first-line investigation and will identify the intramural cyst and the degree of stenosis. Ultrasound will not reliably detect connection with the joint (►Fig. 2). MR imaging (MRI) with MR angiography (MRA) is the diagnostic modality of choice, as it can identify the luminal stenosis and the cystic changes involving the vessel wall as well as communication with the knee joint.¹⁶ T2-weighted or fluid-sensitive short tau inversion recovery

sequences are used to identify the adventitial cysts and their connections to the knee joints (►Fig. 2). These connections are important, because failure to ligate and divide them at the time of surgery will almost guarantee recurrence. CT demonstrates the mural and luminal abnormality but is less accurate than MRI for detecting connections with the joint.¹⁶

Treatment

The definitive treatment is surgical, including evacuation of the cyst with the removal of the cyst wall or resection of the affected vessel and replacement with a vein or prosthetic graft.^{10–12,14} Percutaneous cyst aspiration has been reported,

Figure 2 An 18-year-old with a history of left anterior cruciate ligament repair presents with persistent pain and cramping in the left calf with exercise. T1-weighted MRI image (A) shows the lumen of the popliteal artery (asterisks) surrounded by abnormal tissue (arrowheads) that extends toward the knee joint. This tissue is bright on T2-weighted MRI image (B), revealing its cystic nature. The imaging findings are diagnostic of cystic adventitial disease (CAD). (C) A sagittal reformat of a CT angiogram from a different patient shows narrowing of the popliteal artery by low-density cysts (arrowheads). The low-density area identified (asterisk) suggests a connection with the joint. Due to the better soft tissue discrimination, MRI is the modality of choice for evaluation of CAD.

but results are unsatisfactory due to primary failure (because of the viscous nature of the cyst contents) and the high likelihood of recurrence. Angioplasty is inappropriate due to the risk of distal embolization.

Connective tissue disorders: The most well-recognized connective tissue disorders associated with lower extremity vascular complications that may mimic peripheral arterial disease are Ehlers-Danlos syndrome type IV (EDS IV), Marfan syndrome, and Loeys-Dietz syndrome (LDS). All these conditions are inherited in an autosomal dominant fashion, although de novo mutation is not rare; hence, familial screening may be required once the diagnosis has been made. These connective tissue disorders tend to be complicated by aneurysm formation, arterial dissection, and rupture.

Ehlers-Danlos Syndrome Type IV

EDS IV is an autosomal dominant disorder caused by a heterozygous mutation in the gene for type III collagen (COL3A1) on chromosome 2q31–2q32.¹⁷ It is characterized by facial structure abnormalities, easy bruising, translucent skin with visible veins, and arterial, gastrointestinal (GI), or uterine fragility.¹⁷ The prognosis for EDS IV is poor, with the median age of death at 48 years; survival beyond 50 years is uncommon.¹⁸ Individuals with this disorder have a tendency to develop arterial aneurysms, arterial rupture, or dissections.¹⁷ They should seek immediate medical attention for sudden, unexplained pain.

Diagnosis

The clinical diagnosis of vascular EDS is made on the basis of at least two of four major diagnostic criteria as defined by the revised nosology of Villefranche.¹⁹ Serum analysis is used to detect genetic mutations, which captures 98% of mutations in EDS IV.

Imaging

The majority of patients are young and require long-term follow-up; hence, vascular imaging with MRA (due to the lack of ionizing radiation) is preferred to detect and monitor aneurysms and to assess complications.

Treatment

Celiprolol, a cardioselective β -blocker, has been shown to reduce arterial events in these individuals and is usually the recommended treatment.²⁰ Endovascular catheterization may be complicated by dissection or arterial rupture and should be undertaken only after careful consideration and discussion with the patient of the risks and benefits. Surgical or endovascular intervention may be lifesaving for patients who present with arterial rupture. Procedures are performed only in a highly selected group of individuals, as the mortality is 30 and 24% among individuals undergoing surgical and endovascular repair, respectively.²¹

Marfan Syndrome

Classic Marfan syndrome is an autosomal dominant disease caused by mutations in the FBN1 gene that encodes for the fibrillin-1 extracellular matrix protein. The incidence is ap-

proximately 1:5,000 of the U.S. population. A large number of mutations have been identified and are associated with varying severity of the vascular manifestations.

Diagnosis

Marfan syndrome is diagnosed according to the Ghent nosology and is characterized by skeletal, ocular, cardiac and vascular, and other abnormalities.²²

Imaging

Cardiac and vascular imaging is required to screen for valvular abnormalities and aneurysms of the ascending aorta. Patients surviving longer develop peripheral arterial aneurysms and dissection; hence, extended imaging may be required. As repeated long-term follow-up is necessary, MRA is preferred to detect and monitor aneurysms and to assess complications.

Treatment

Beta blockade reduces the rate of aortic dilatation and the incidence of aortic dissection. Surgical replacement of the aortic root and ascending aorta is recommended when the root measures > 5 cm in diameter.

Loeys-Dietz Syndrome

LDS arises from mutations in the TGFBR1, TGFBR2, SMAD3, and TGFBR2 genes, and is also inherited in an autosomal dominant manner. There are two types of LDS. Approximately 75% of patients have LDS type I, which is characterized by systemic and craniofacial manifestations. The other 25% of patients have LDS type II, which is characterized by systemic presentations but minimal to absent craniofacial features.^{23,24} The characteristic triad of LDS includes widely spaced eyes, cleft palate or bifid uvula, and aortic or arterial aneurysms and/or tortuosity.²³ The clinical manifestations can be classified into four major groups: vascular, skeletal, craniofacial, and cutaneous. Vascular presentations include cerebral, thoracic, and abdominal arterial aneurysms, dilations, dissections, and/or tortuosity.²³

Diagnosis

The diagnosis is based on clinical findings, and confirmed with molecular genetic testing of the TGFBR1, TGFBR2, SMAD3, and TGFBR2 genes.^{23,24}

Vascular complications are a major source of morbidity and early mortality in LDS. Arterial aneurysms tend to be aggressive, with the mean age of death at around 26 years. Carotid and vertebral artery dissections have also been described.

Treatment

β -Adrenergic blockers are used to reduce hemodynamic stress. Surgery is needed to treat vascular manifestations such as aneurysms.²³ Surgical repair of the aorta should be performed when the aortic diameter reaches 5.0 cm, or when its rate of increase approaches 1.0 cm/year in adults.²³

Midaortic Syndrome

Midaortic syndrome is a rare idiopathic condition with segmental narrowing of the subisthmic aorta often with ostial

stenosis of its visceral branches. Midaortic syndrome is a manifestation of a variety of congenital and acquired conditions. Presentation is typically in children and young adults²⁵; clinical presentations include hypertension, claudication, renal failure, and/or intestinal ischemia.

Diagnosis

Aortic stenosis is seen at the level of the renal arteries in 19 to 52% of cases, suprarenal stenosis is seen in 11 to 40% of cases, and in 19 to 25% of cases the aortic stenosis is infrarenal.^{26,27}

Treatment

Medical treatment is used to control hypertension. Bypass surgery remains the treatment of choice, but good antihypertensive treatment can delay the surgery.²⁸ Surgery has been shown to significantly improve hypertension with almost complete elimination of claudication and mesenteric ischemia.²⁸ Endovascular treatment has limited durability but can be used as a bridge to surgery.

Inflammatory arteritides: These are a disparate collection of conditions that feature inflammation of the arterial wall. They can be considered according to the size of the arteries involved and the underlying cause.

Medium- and large-vessel vasculitis: Vasculitis known to affect the lower extremities are Takayasu arteritis (TA), radiation-induced arteritis (RIA), giant cell arteritis (GCA), and Behçet disease.

Takayasu Arteritis

TA affects large arteries such as the aorta and its branches. It is most commonly seen in Asian women, 10 to 40 years of age. TA is uncommon in the United States, with an annual incidence of 2.6 per million Americans.²⁹ Vascular injury in TA is mediated by T cells, macrophages, and natural killer cells. The inflammatory response leads to myointimal proliferation and thickening of the vessel wall and subsequent lumen narrowing. When destruction of the media and elastic lamina are dominant, there is aneurysm formation. Peripheral vascular presentation can range from asymptomatic with incidental discovery, to reduced or impalpable pulses, to severe limb ischemia or claudication.²⁹ The upper limb is more commonly affected than the leg due to the involvement of the great vessels of the aortic arch.

Diagnosis

The diagnosis of TA is based on meeting three or more of the criteria shown in ► **Table 2**.³⁰ The arteries of the aortic arch are most commonly affected, and systemic symptoms such as fever, malaise, joint pain, weight loss, and anemia are common.^{29,30}

Arterial biopsy may be needed to confirm the diagnosis.^{29,30} During the inflammatory phase of the disease, vessel wall thickening with long tapering stenosis is present; this is best detected with MRI and CT. Cross-sectional imaging after the administration of contrast media shows vessel wall enhancement due to inflammation and associated hyperemia, which can also be detected with positron emission tomography (PET). During the chronic phase of the disease, stenosis, occlusions, and aneurysms of the vessels are present.

Table 2 American College of Rheumatology diagnostic criteria for Takayasu arteritis^{30,65}

1990 criteria for the classification of Takayasu arteritis
1. Age at disease onset < 40 y
2. Claudication of extremities
3. Decreased brachial artery pulse
4. Difference of >10 mm Hg in systolic blood pressure between arms
5. Bruit over subclavian arteries or abdominal aorta
6. Arteriogram abnormality (arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental)

Notes: Takayasu arteritis is defined clinically if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

Vessel wall thickening may persist in the chronic phase, but enhancement on CT and MRI, as well as fludeoxyglucose avidity on PET, is not present.³¹

Radiation Induced Arteritis

RIA of large vessels is a complication of radiotherapy. The exact pathogenesis is unknown. Histologically, arteries appear more fibrotic especially in the internal elastic lamina, and injury to the vasa vasorum, periarterial fibrosis, and necrosis and thickening of the vessel wall are also noted.^{32–34} Angiographic stenosis or occlusion of the vessels is noted³² (► **Fig. 3**). Radiation doses noted to cause this abnormality range from 20 to 80 Gy.³⁴ Treatment depends on symptoms and the presence of thrombus. In a majority of the cases, RIA can be treated with angioplasty or stenting alone.^{35,36} Surgical repair is usually avoided due to the associated soft tissue changes.

Giant Cell Arteritis

Giant cell arteritis, or temporal arteritis, is a condition that involves medium and large arteries, including the aorta and arteries of the face and scalp near the temples. It affects adults older than 50 years and is more common in Caucasians, occurring in 15 to 33 per 100,000 people.^{29,37,38} Vascular manifestations are accompanied by symptoms of systemic inflammation and clinical definition is noted in ► **Table 3**. GCA typically involves branches of the external and internal carotid arteries, and luminal narrowing or occlusion causes blindness, headache, scalp tenderness, and jaw claudication. Involvement of the abdominal aorta and run-off vessels, particularly the superficial femoral artery, results in claudication in addition to cranial symptoms.³⁹

Diagnosis

A normal erythrocyte sedimentation rate (ESR) is more useful in excluding the disease than an elevated ESR is in diagnosing it.²⁹ Vessel wall thickening is again the imaging hallmark of

Figure 3 A 72-year-old woman with history of left breast cancer and prior radiation therapy presents with worsening left upper extremity weakness. (A) Volume rendering reconstruction from CT angiography demonstrates finding of radiation-induced arteritis including marked irregularity, narrowing and calcification of the left common carotid, and subclavian and axillary arteries as compared with the contralateral side (white arrowheads). Radiation changes are also present in the left ribs, scapula, and humerus and identified as the mottled appearance of the cortex of the involved bones. (B) Marked fibrosis of the soft tissues of the left chest (asterisks) is another sequela of radiation therapy. Arteritis is evidenced by the circumferential wall thickening (arrowhead) of the left common carotid artery.

GCA with vessel wall enhancement similar to Takayasu disease (►Fig. 4). PET can be useful in this disorder, too.³¹

Behçet’s Disease

Behçet disease is a multisystem disorder that affects small and large vessels. It is characterized by chronic inflammation with a relapsing and remitting course. It is more commonly seen in people of Mediterranean ethnicity, with a typical age of onset around 30 years.⁴⁰ The etiology remains unknown and likely involves both genetic and environmental factors. The presence of the HLA-B51 allele is strongly associated with Behçet disease, and proposed exogenous triggers include viral and bacterial infections.⁴¹ It presents as oral and genital ulcerations; skin lesions; uveitis; and vascular, central nervous system, or GI involvement. Large artery involvement may result in aneurysms and/or vessel occlusions.^{40,41} The main histopathological finding is the widespread vasculitis of small and large arteries and veins.⁴⁰

Treatment: Therapy for the vasculitides mentioned in this section is largely pharmacological, and is centered on immune suppression and symptomatic treatment. Treatment depends on the clinical manifestations, severity of disease progression, and extent of organ involvement. Drugs include

corticosteroids, aspirin, azathioprine or methotrexate, and tumor necrosis factor-α inhibitors.^{29,37,41} In the chronic fibrotic stage, surgical or endovascular treatment may be needed for occlusive disease or aneurysms. Unfortunately, long-term complication rates are as high as 44%.⁴² Also, these diseases have high morbidity and mortality rates and should be closely followed up by vascular medicine specialist as well as rheumatologist.^{29,37,41}

Thromboangiitis Obliterans

Thromboangiitis obliterans (TAO), or Buerger disease, is a segmental inflammatory condition affecting the small- to medium-sized arteries of the upper and lower extremities.⁴³ It affects young smokers, with the typical age of onset before 50 years; it is more commonly seen in men, with a reported male:female ratio of 7.5:1.⁴⁴ The incidence in North America is 8 to 12.6/100,000 population, with more prevalence in those from the Mediterranean, Middle East, and Asia.⁴³ The exact etiology is unknown, but tobacco in all its forms plays a central role in the initiation, progression, and recurrence of

Table 3 American College of Rheumatology diagnostic criteria for giant cell arteritis^{30,64}

1990 criteria for the classification of giant cell arteritis
1. Age at disease onset ≥ 50 y
2. New headache
3. Temporal artery abnormality
4. Elevated erythrocyte sedimentation rate
5. Abnormal artery biopsy (biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells)

Notes: Giant cell arteritis is defined clinically if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.

Figure 4 A CT angiogram to evaluate for vasculitis was performed on a 64-year-old woman who presented with fever of unknown origin, elevated sedimentation rate, and overall weakness and fatigue with symptoms that were responsive to steroid therapy. The curved planar reconstruction shows wall thickening and diffuse narrowing of the bilateral subclavian and axillary arteries (arrows), typical of active vasculitis. Normally, the arterial wall is not apparent on CT for small and medium sized vessels. In this patient, wall thickening is identified as circumferential soft tissue (arrowheads, inset) surround the vessel lumen (asterisk, inset).

the disease. Buerger disease may present as claudication, ischemic rest pain in digits and extremities, digital ulcerations, or gangrene.⁴³ Patients with TAO are more likely to require amputation than patients with atherosclerotic disease; however, their survival rate is much better with more than 80% alive up to 25 years after the initial diagnosis.⁴⁴

Laboratory Testing

Inflammatory markers such as ESR and C-reactive protein are typically normal. A toxicology screen is advisable for patients who do not use tobacco, as TAO has also been reported in users of marijuana, cocaine, and amphetamines.⁴⁵ Histopathologic findings in the acute phase include highly cellular thrombotic occlusions with associated inflammation of all vessel wall layers, and polymorphonuclear leukocytes with karyorrhexis.

Imaging

Large arteries are typically spared, and patients present mainly with small vessel occlusive disease.⁴⁶ Angiography shows segmental arterial occlusions of small- to medium-sized vessels, with “corkscrew”-shaped collaterals bypassing the areas of occlusion. The disease primarily affects the distal extremities, sparing proximal arteries (→Fig. 5). Catheter angiography is often required to make the diagnosis due to limitation in spatial resolution of modalities such as CT and MRI. These modalities are often employed initially, however, to exclude proximal disease, atherosclerosis, or embolic sources that could also explain symptoms.⁴⁷

Treatment

The definitive therapy for TAO is complete cessation of tobacco use, which has been shown to prevent future morbidity. Cooper et al reported significantly lower amputation rates among those who quit smoking compared with ongoing smokers.⁴⁸ Other forms of therapy are largely palliative. Narcotic analgesic agents may be required to manage ischemic rest pain. Noninfected ulcers may be managed with analgesia and local cleansing,⁴⁴ while infected ulcers require

antibiotics and local debridement. Ulceration is also treated with iloprost (a prostaglandin analog). A prospective randomized trial comparing iloprost with aspirin showed ulcer healing and ischemic pain relief in 85% of patients treated with iloprost compared with 17% of the patients treated with aspirin; continued benefit was also seen at 6 months.⁴⁹ Epidural spinal cord stimulators have been used in TAO to treat the ischemic manifestations and improve microcirculation, resulting in a 93.1% limb salvage rate and absence of new trophic lesions.^{50,51} Arterial bypass grafts have poor patency but may permit ulcer healing.^{45,49}

Figure 5 A 34-year-old man with history of tobacco and alcohol abuse presents with ulceration of the digits of the hands. There is segmental occlusion of the distal right ulnar artery and superficial palmar arch with the presence of “corkscrew”-shaped collateral arteries (arrows). The lack of proximal disease, history of tobacco abuse, and segmental occlusions of the distal vasculature are diagnostic of thromboangiitis obliterans (Buerger disease).

Figure 6 (A) MR angiogram from a 42-year-old male cyclist reveals subtle narrowing of the proximal left external iliac artery (arrow) as compared with the distal vessel (arrowhead). Resting ABI in this patient was normal, but markedly abnormal in the immediate postexercise state after the development of symptoms. (B) A 38-year-old woman who is avid runner presented with left quadriceps fatigue that limited her running. The pain began 2 years after training and competing in marathons. Three-dimensional reconstruction from CT angiogram demonstrates occlusion (between arrowheads) of the left external iliac artery. There is smooth tapering of the iliac artery at the borders of the occlusion due to the intimal thickening (arrowheads). Internal iliac artery to profunda femoral artery, inferior epigastric artery to internal thoracic artery, and circumflex iliac artery to lumbar artery collaterals have developed on the ipsilateral side.

Artery Subject to Abnormal Forces

These syndromes occur when an artery is subject to abnormal movement, compression, or abnormal flow. Thoracic outlet syndrome affects only the arm and will not be discussed here.

Iliac Artery Endofibrosis

Iliac artery endofibrosis (IAE) is arterial stenosis of the iliac or common femoral artery presenting as unilateral claudication in young male high performance athletes. IAE is typically seen in competitive cyclists, and in highly trained runners, triathletes, and speed skaters.⁵² It is seen mostly in younger males less than 40 years.⁵³ The etiology is thought to be multifactorial including extravascular and intravascular trauma. Potential extravascular factors include repetitive stretching of the iliac arteries due to hyperflexion of the hip joint, external compression by psoas muscle hypertrophy, and repeated kinking of the iliac artery during exercise because of its anatomic position relative to the hip joint.^{53,54} In addition, high flow due to increased cardiac output can cause internal shear, leading to intravascular trauma.^{53,54}

The distribution of disease is frequently unilateral, with the left limb affected most often.⁵² Common clinical manifestations include unilateral cramp and weakness in the affected limb on supramaximal exercise. The condition is progressive and may lead to occlusion due to arterial dissection or thrombosis. Histopathologically, the disease is characterized by intimal thickening due to accumulation of loose connective tissue with variable amounts of collagen, elastin, and smooth muscle cells. The medial and adventitial layers may be involved as well.⁵⁵

Diagnosis

The resting ankle-brachial index (ABI) is often normal, so exercise testing should replicate the conditions that bring on symptoms that result in a fall in ABI.⁵⁴ Imaging assessment is performed with cross-sectional imaging modalities (CT and MRI) as well as catheter angiography in both the neutral and hip flex positioning, which simulates the position of the patient on a bicycle. Imaging findings early in the disease process include subtle narrowing of the proximal external iliac artery (→Fig. 6A) (occasionally also the common iliac or common femoral artery) compared with the distal segment. This mild narrowing becomes hemodynamically significant at supraphysiologic levels of blood flow created in these athletes. If severe, this narrowing can progress to thrombosis (→Fig. 6B). Kinking of the common iliac artery during hip flexion and excessive vessel length are also diagnostic criteria.⁵⁶

Treatment

Conservative measures should be considered before surgical correction, which is the mainstay of therapy. Recreational athletes should consider changing to a sport that does not involve hyperflexion of the hip, and cyclists should be advised to reduce training time and alter their cycling positions to minimize hip flexion.⁵² Surgical resection of the fibrotic segment and replacement with a saphenous vein graft, or endarterectomy with vein patch angioplasty, may be necessary for professional athletes who wish to continue with their chosen sport.^{52,55} Politano et al reported a low rate of reoperation, high patient satisfaction, and successful return to a competitive level among patients with focal disease who

Figure 7 Popliteal artery entrapment syndrome classification.

were treated with patch angioplasty.⁵⁷ Bypass surgery is also an effective treatment method that allowed patients to return to a high level of performance.⁵² Nonsurgical procedures such as balloon angioplasty are generally not recommended due to high rates of recurrence of stenosis and symptoms.⁵⁵

Popliteal Artery Entrapment Syndrome

Popliteal artery entrapment syndrome (PAES) consists of compression of the popliteal artery in the popliteal fossa by adjacent or surrounding musculotendinous structures; bilateral abnormalities are common. The condition arises when the popliteal artery is abnormally positioned, or if there is an abnormal muscle insertion or abnormal muscle slip or fibrous bands (►Fig. 7). PAES usually affects young males (83% preponderance), with the mean age of onset being 32 years.⁵⁸ The condition is progressive, and in the early stages the patient may be asymptomatic or, like iliac artery endofibrosis, may present with pain, paresthesia, or cold feet after physical training. In the advanced stages, there is IC, rest pain, or toe necrosis due to distal embolization.⁵⁹ PAES is classified into six anatomical types which are listed in ►Table 4. There is also functional PAES, in which the popliteal fossa anatomy seems normal, but the popliteal arteries are compressed during leg movement.^{60,61}

Imaging

The diagnosis of PAES relies on the demonstration of popliteal artery compression during active plantar flexion or dorsiflexion of the foot against resistance. Both legs must be examined, as there are often bilateral abnormalities. Ultrasound can demonstrate compression occurring during foot movement but does not delineate the anatomical cause. Both MRI and CT can demonstrate the soft tissue abnormality and arterial and venous compression or occlusion. As the patients are typically young, MRI is often the first choice imaging modality. High-resolution T1 imaging in the axial plane is usually sufficient to make the diagnosis; however, T2-weighted imaging should also be part of the protocol to assist in identifying cystic adventitial disease.⁶² MRA should additionally be performed in stress and neutral positions to add information about the severity and location of stenosis.

Table 4 Classification of popliteal artery entrapment syndrome

Type I	Popliteal artery running medial to the medial head of the gastrocnemius
Type II	Medial head of gastrocnemius is laterally attached
Type III	Accessory slip of gastrocnemius/fibrous bands arising from medial head of gastrocnemius
Type IV	Popliteal artery passing below the popliteus muscle/fibrous bands arising from popliteus muscle
Type V	Venous entrapment
Type VI	Variants
Type F	Functional entrapment

This can be particularly helpful in locating subtle anatomic abnormalities and in identifying dynamic compression of the vessel in the presence of normal anatomy (►Fig. 8).

Treatment

Treatment of anatomical PAES is to surgically remove the entrapment, thereby restoring normal blood flow, whereas for functional PAES, decompression may be considered.⁶⁰ If the popliteal artery is thrombosed, bypass grafting may be required. Angioplasty does not have a role in the management of PAES.

Figure 8 A 17-year-old boy with foot pain and discoloration of the toes. (A) MRI of the right knee reveals an aberrant accessory slip (curved arrow) of the medial head of the gastrocnemius muscle compressing the popliteal artery (arrow) against the medial femoral condyle (asterisk). The popliteal vein (arrowhead) is not affected by this aberrant slip. This configuration represents a type III entrapment (see ►Fig. 7). (B) Complete obstruction (asterisk) of the popliteal artery is shown by volume rendering of a CT angiogram in the same patient. Multiple collateral vessels have developed in the setting of this obstruction.

Arterial thrombophilias: These are inherited or acquired disorders that lead to thrombosis of the arterial system presenting as acute limb ischemia, blue toe syndrome, and sometimes as IC. Inherited disorders typically include hyperhomocysteinemia/hyperhomocystinuria, as well as gene polymorphisms such as Factor V Leiden, prothrombin variant, fibrinogen β -chain-455 G/A, Bcl-1, and plasminogen activator inhibitor 1. Acquired disorders are more common than inherited disorders and include antiphospholipid antibody syndrome, malignancy, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, polycythemia vera, use of hormone therapy, prothrombin complex concentrate, and cocaine.⁶³

These patients typically present with acute onset symptoms and may have a known history of thromboembolic disease or risk factors for thromboembolic disease such as malignancy. Arterial thrombophilia should be suspected in patients presenting with acute vascular ischemic symptoms at a young age, or those with few or no vascular risk factors. Imaging will typically reveal acute thrombosis of the affected vessel with no evidence of atherosclerosis.

Treatment

The main objectives of therapy are treatment of any underlying cause and prevention of further episodes of thrombosis. Patients with thrombophilia generally require lifelong antiplatelet agents and/or anticoagulation.⁶³ When there is acute limb ischemia, thrombolysis and thrombectomy should be considered.

Venous Claudication

This is a consequence of iliofemoral deep vein thrombosis and venous hypertension usually associated with deep and superficial venous reflux in the leg. In the absence of coexistent arterial disease, peripheral pulses will be preserved, but there are likely to be signs of venous hypertension. The left leg is slightly more commonly affected than the right, presumably reflecting May-Thurner syndrome. Up to 40% of patients will develop a degree of claudication, and in 15% this will be sufficient to limit exercise testing.⁶⁴

Treatment

Treating the iliofemoral occlusion by stenting or venous bypass can improve symptoms in severe cases.

Conclusion

Although the most common form of presentation of PAD is related to atherosclerosis, other etiologies can cause similar symptoms. Physicians taking care of patients with PAD should be aware of these conditions and alert to making the diagnosis, as this will impact the choice of appropriate therapy.

Acknowledgment

The authors would like to thank Mrs. Neha Sharma for drawing the image on popliteal artery entrapment syndrome.

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