

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Nonatherosclerotic Peripheral Artery Disease

---

Osami Kawarada

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/67180>

---

## Abstract

Nonatherosclerotic peripheral artery disease (NAPAD) remains underappreciated compared to atherosclerotic peripheral artery disease. However, under- or misdiagnosis of NAPAD can potentially lead to serious adverse outcomes. There is a broad spectrum of disorders including vasculitis, thrombophilia, and other vascular anatomical or functional disorders in the context of NAPAD. This section briefly overviews vascular imaging, mainly invasive angiography, to optimize the management of NAPAD.

**Keywords:** awareness, nonatherosclerosis, peripheral artery disease

---

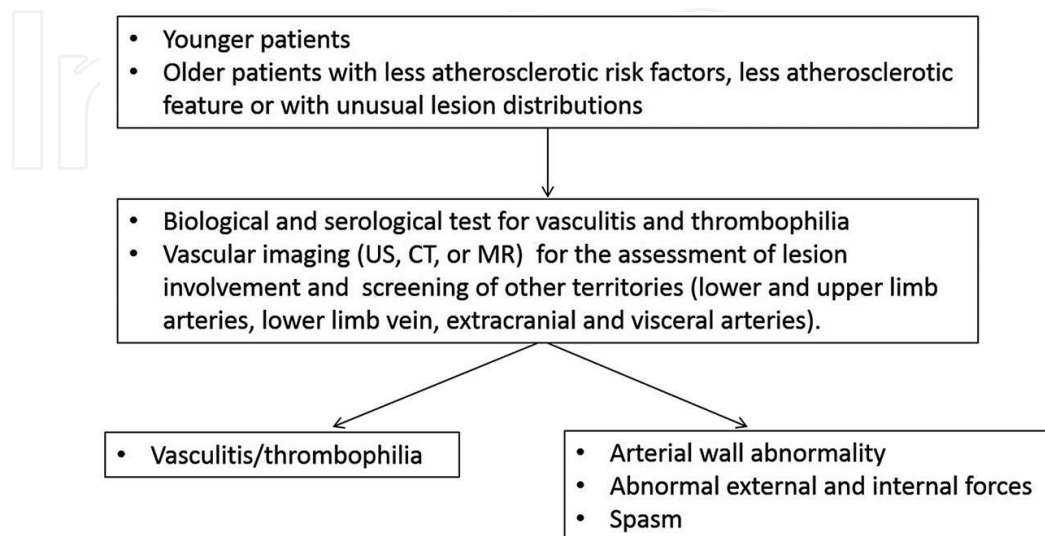
## 1. Introduction

Nonatherosclerotic peripheral artery disease (NAPAD) remains underappreciated compared to atherosclerotic peripheral artery disease (APAD) due to its low prevalence. Despite common symptoms such as claudication, rest pain, and tissue loss, most clinicians are unfamiliar with the diagnosis of NAPAD. NAPAD should be suspected clinically in younger patients, and in older patients with few atherosclerotic risk factors, few atherosclerotic features, or unusual lesion distributions. There is a broad spectrum of pathophysiologies in NAPAD, with the most common being arterial wall abnormalities, abnormal external and internal forces, spasm, vasculitis, and thrombophilia [1]. Under- or misdiagnosis of NAPAD can lead to serious adverse outcomes that, with awareness of its distinctive symptoms and signs, may be avoided or minimized [2–5]. Thus, this section briefly overviews vascular imaging, mainly invasive angiography, to optimize the management of NAPAD.

---

## 2. Workup for differential diagnosis

When there is a high clinical index of suspicion of NAPAD, the combination of blood examination (biochemical and serological tests) and vascular imaging is an integral part of the differential diagnosis process (**Figure 1**).



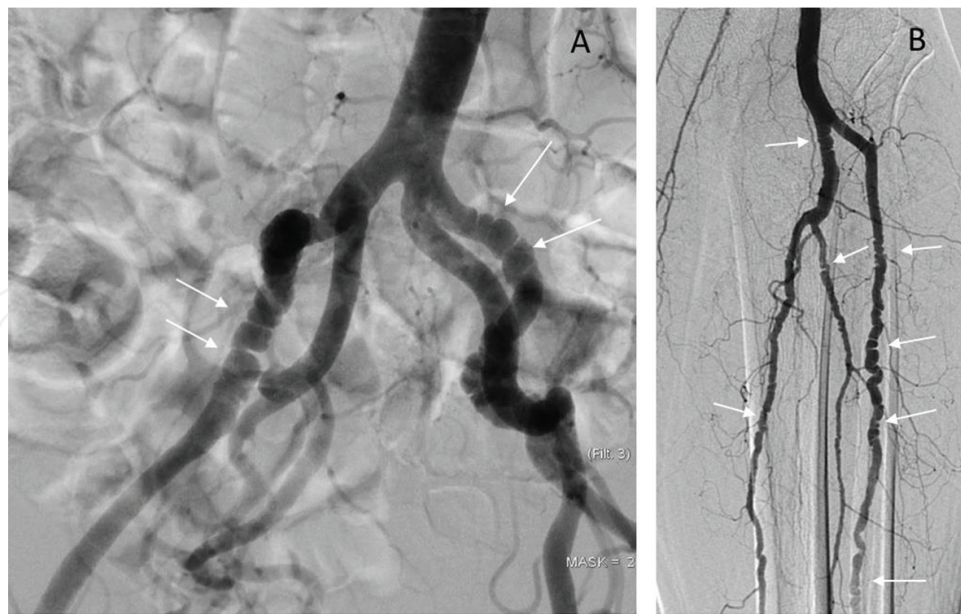
**Figure 1.** Approach to diagnosis of nonatherosclerotic peripheral artery disease.

In combination with vascular imaging, the assessment of macrocirculation by the ankle-brachial index is important. Furthermore, in regard to microcirculation assessment, either skin perfusion pressure (SPP) or transcutaneous oxygen pressure (TcPO<sub>2</sub>) can be applied in patients with critically ischemic limbs. Limb ischemia in younger patients warrants a high clinical suspicion of NAPAD. Even in older patients, most cases of NAPAD may be underdiagnosed or misinterpreted as an atherosclerotic condition.

## 3. Arterial wall abnormalities

### 3.1. Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is a noninflammatory disease that produces arterial narrowing, aneurysms, dissection, and occlusion. Although the cause is unknown, 90% of cases occur in females [6], most frequently in the renal and carotid arteries, followed by the mesenteric artery. Although lower extremity arteries are less commonly affected, FMD is one of the most significant causes of NAPAD [4, 7]. Pathologically, FMD can mainly be classified into three types, that is, intimal, medial, and perimedial. Angiographic classification identifies the multifocal type with multiple stenoses and the so-called “string-of-beads” appearance, the tubular type, and the focal type. The “string-of-beads” sign that is frequently associated with the medial type is the most indicative of FMD, while the tubular and focal types may mimic atherosclerotic lesions [8] (**Figure 2**).



**Figure 2.** Fibromuscular dysplasia. (A) String-of-beads appearance in bilateral external iliac arteries (arrows). (B) Multiple string-of-beads appearances in the left crural artery (arrows).

There are isolated reports of FMD mimicking vasculitis such as polyarteritis nodosa, Takayasu's arteritis (TA), and other disorders such as Ehlers-Danlos's syndrome, Alport's syndrome, and pheochromocytoma [9].

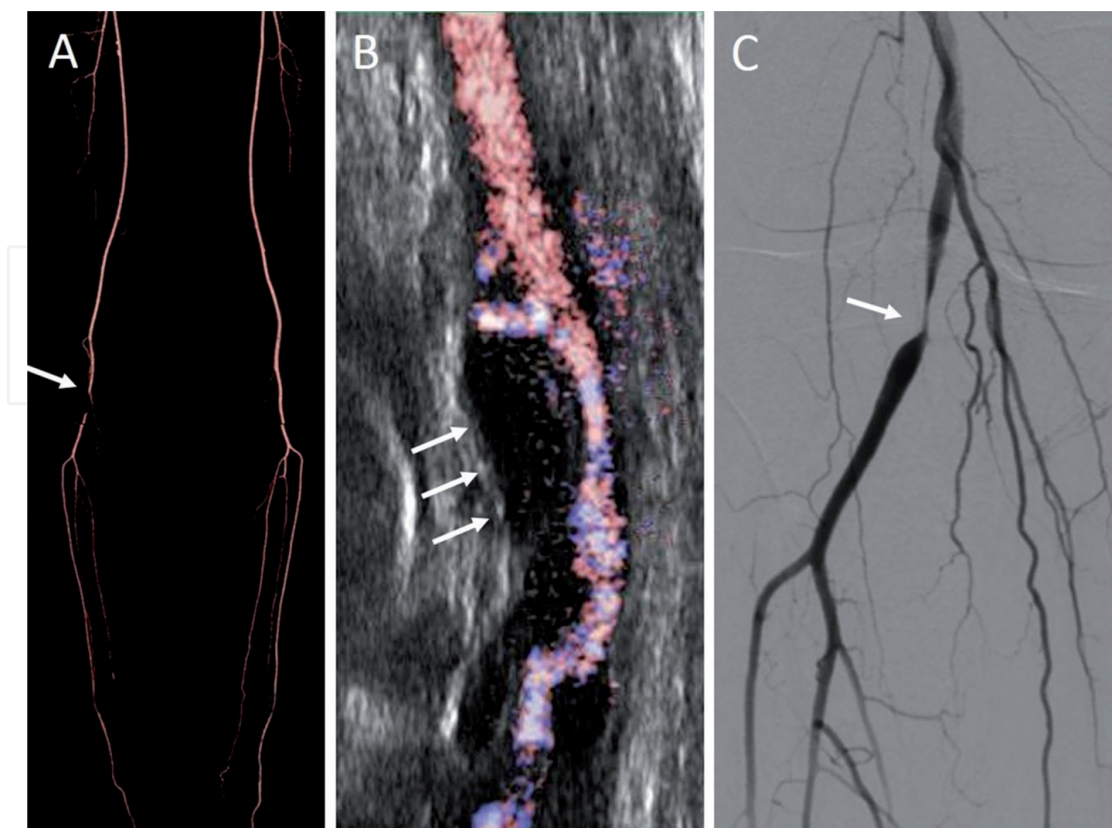
### 3.2. Adventitial cystic disease

Adventitial cystic disease is characterized by a collection of mucin in the adventitial layer, typically in the popliteal artery. In rare cases, the external iliac artery or femoral artery can be affected. This disorder is typically observed in middle-aged persons, with a male-to-female ratio of 5–15:1 [4, 10]. Duplex ultrasound is considered a reasonable first-line method to diagnose adventitial cystic disease. Although stenotic lesions may develop into occlusion, the angiographic findings show a smooth, eccentric, and extrinsically narrowed appearance (Figure 3).

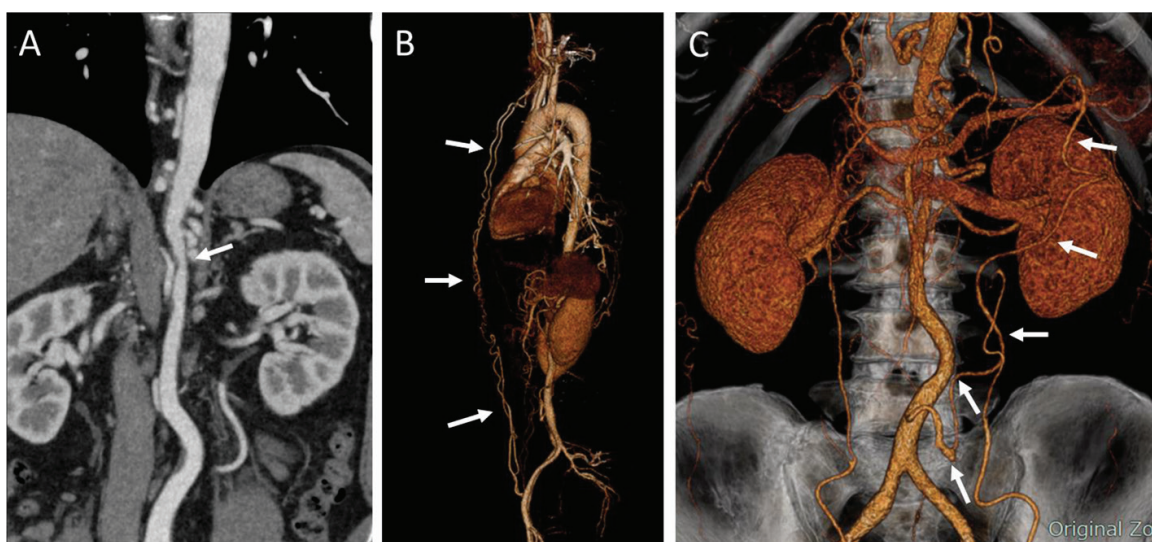
### 3.3. Midaortic syndrome

Coarctation of the aorta is mostly located just distal to ligament arteriosum. Midaortic syndrome (MAS) is a rare condition characterized by coarctation of the abdominal aorta or distal descending thoracic aorta and thought to arise from an embryonic development disorder [2]. It is essential to differentiate MAS such as involvement of the abdominal aorta from other causes in large-vessel vasculitis. In addition to idiopathic MAS, the association of MAS with neurofibromatosis, FMD, mucopolysaccharidosis, Alagille syndrome, and William's syndrome could be a genetic etiology. Others include tuberous sclerosis, retroperitoneal fibrosis, moyamoya disease, congenital rubella syndrome, epidermal nevus syndrome, and autosomal dominant supravalvular aortic stenosis syndrome [11, 12]. The most common anatomic type of MAS is suprarenal (60%), followed by intrarenal (25%) and infrarenal (15%) (Figure 4).





**Figure 3.** Adventitial cystic disease. (A) A 70-year-old male presenting moderate claudication. Enhanced CT shows focal stenosis in the midsegment of the right popliteal artery (arrow). (B) Ultrasonography revealed a low-echoic cystic lesion along the vessel wall causing significant stenosis in the popliteal artery (arrows). (C) Angiography could confirm focal stenosis in the right popliteal artery (arrow).



**Figure 4.** Idiopathic midaortic syndrome. A 51-year-old male presenting renovascular hypertension. Although the ABI was 0.70/0.67 (right/left), intermittent claudication was absent. (A) Enhanced CT showing suprarenal abdominal aortic coarctation below the origin of the superior mesenteric artery (arrow). (B) Lateral view demonstrates Winslow's pathway which is a collateral vessel developing from the subclavian arteries, internal thoracic (mammmary) arteries, superior epigastric arteries, inferior epigastric arteries into the external iliac arteries (arrows). (C) Anteroposterior view reveals the Arc of Rioloan which is a mesenteric meandering artery between the superior and inferior mesenteric arteries (arrows).

It is usually discovered during workups for hypertension in children. Renal vessels, mesenteric vessels, or both may also be affected to varying degrees. According to previous reports, if the syndrome is left untreated, the majority of patients will die from complications of severe hypertension and ischemia by the age of 40 because of myocardial infarction, heart failure, intracranial hemorrhage, or aortic rupture [13, 14]. Recent study suggests that good long-term outcomes of MAS can be obtained by medical management [15]. Intermittent claudication might be an uncommon clinical presentation compared to manifestation of hypertension.

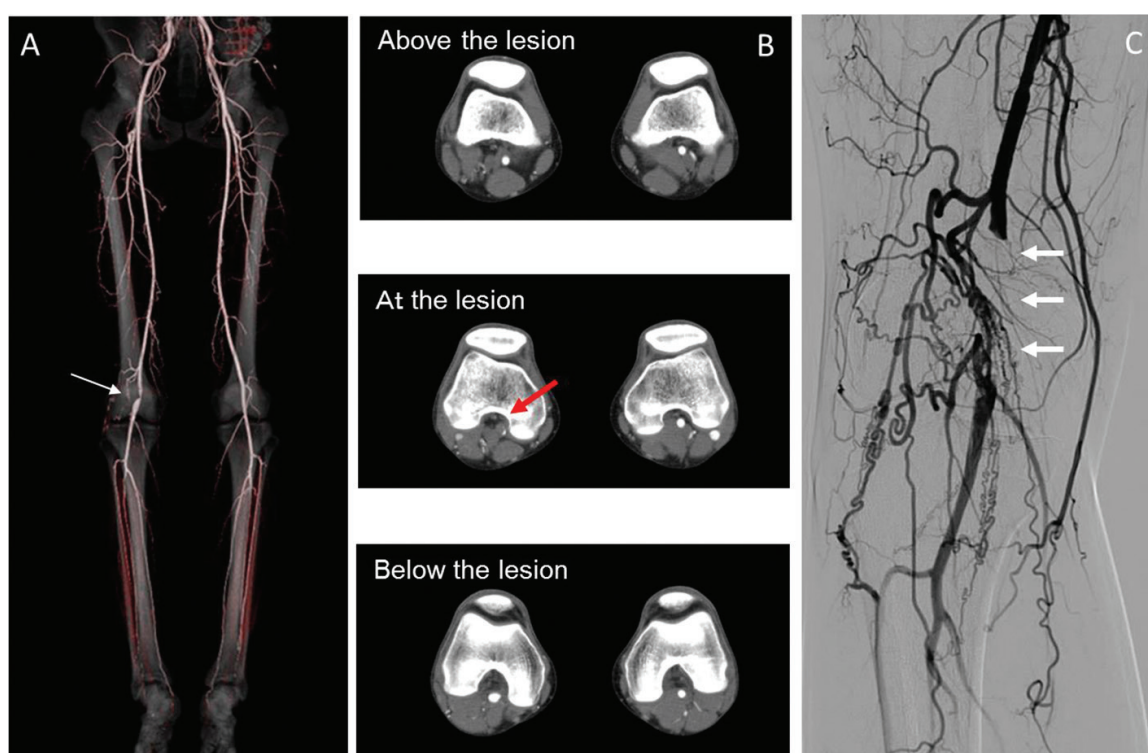
## 4. Abnormal external and internal forces

### 4.1. Endofibrosis

Endofibrosis typically involves the narrowing of the external iliac artery in young athletes such as cyclists, runners, triathletes, and skaters [16]. The disorder is characterized by intimal thickening and subsequent narrowing of the artery by collagen fibers, fibrous tissue, and smooth muscle proliferation [17]. The pathogenesis is presumed to involve repetitive vessel stretching during extreme hip flexion, external compression by psoas muscle hypertrophy, repeated vessel kinking during exercise, and shear stress during high cardiac output. This disorder is progressive and may lead to occlusion, frequently occurring (85%) unilaterally on the left. In addition to the external iliac artery (85%), the common femoral artery (5%) and superficial femoral artery (<5%) can be affected [4]. Since no specific angiographic findings are observed, a high clinical suspicion of this disorder is required for diagnosis and proper treatment.

### 4.2. Popliteal artery entrapment

Popliteal artery entrapment can be caused by compression of the popliteal artery in the popliteal fossa by adjacent or surrounding musculotendinous structures and ligaments. This disorder can occur bilaterally (30–67%) and is predominant in young males, although cases of elderly patients up to the age of 70 have been reported [4, 18]. The condition may become evident when the popliteal artery is abnormally positioned, or in cases of fibrous bands or abnormal muscle insertions or slips. There are six types of entrapment based on the anatomical compression of the popliteal artery [1]. Computed tomography (CT) angiography or magnetic resonance (MR) angiography may be useful techniques for identifying the structures causing external compression of the artery (**Figure 5**). Angiography may also reveal medial or occasionally lateral displacement of the popliteal artery if it is still patent. However, the position of the popliteal artery may be normal if the compression is due to the plantaris or popliteus muscles. In addition, pre-stenotic or post-stenotic dilatation can be associated with this disorder (**Figure 5**). Although popliteal artery narrowing induced by extension of the knee and dorsiflexion of the foot may support the diagnosis of this condition, there is some concern regarding the potential for false-positive results since popliteal artery compression can occur with active plantar flexion even in healthy individuals [19].



**Figure 5.** Popliteal artery entrapment syndrome. A 30-year-old male presenting moderate claudication. (A) Enhanced CT revealed tight stenosis and post-stenotic dilatation in the right popliteal artery (arrow). (B) Horizontal view of the CT showing compressed popliteal artery by the surrounding muscle (arrow). (C): Subsequent angiography revealed the progression to occlusion (arrows).

### 4.3. Adductor canal outlet syndrome

Adductor canal outlet syndrome involves the compression of the distal superficial femoral artery by the adductor canal. It is most commonly reported in runners and skiers, who present with exercise-induced intermittent claudication symptoms and paresthesias. Symptoms are typically chronic but can progress to occlusion and cause acute limb ischemia due to thrombus. This condition may be rare but it is possible relationship to acute intimal injury and thrombosis should be considered in order to save limbs that may otherwise be lost [20–22].

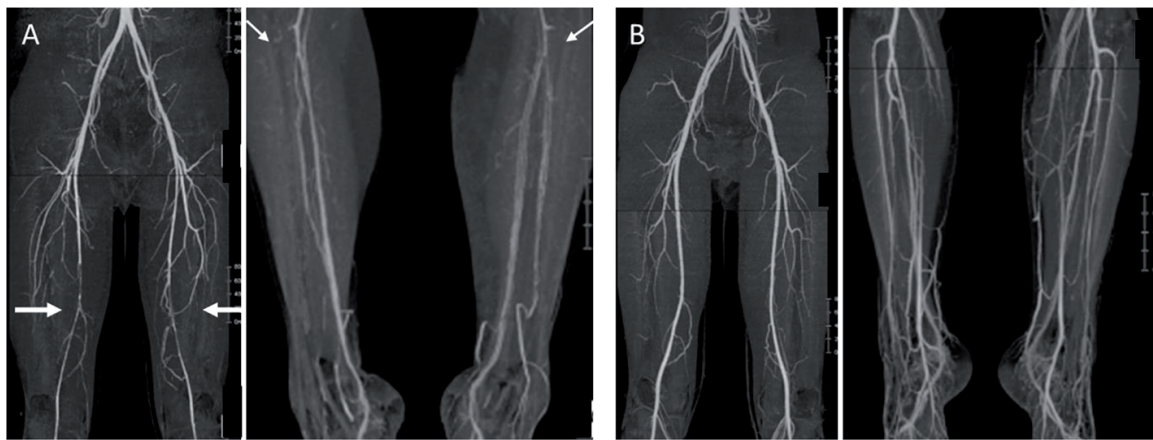
### 4.4. Other conditions

Other conditions including neoplasma, pseudoxanthoma elasticum, and Baker's cyst can cause lower limb ischemia [4].

## 5. Vasospasm

Vasospasm can occur even in the lower extremity arteries. There are a variety of causes, including idiopathic or certain vasospastic agents (e.g., ergotamine, cocaine, marijuana, and amphetamine) [23, 24]. The characteristic findings of drug-induced vasospasm are bilateral, symmetric, and abrupt narrowing of any segment of a lower limb artery. Vasospasm can be resolved by discontinuing the offending drug or administering vasodilators (**Figure 6**).





**Figure 6.** Idiopathic vasospasm (Ref. 24). A 28-year-old male presenting claudication with subsequent acute limb ischemia. (A) Diagnostic enhanced CT angiogram showing tight narrowings in the bilateral femoropopliteal segments (large arrows) and disruptions in the bilateral anterior tibial arteries (small arrows). Also, the proximal segment in the superficial femoral artery seems to be spastic. (B) After initiation of medical treatment during hospitalization, complete recovery of the disruptive lesions is observed though the crural arteries are superimposed on the veins.

## 6. Vasculitis

Vasculitis may confuse clinicians since it comprises a heterogeneous group of disorders characterized by inflammation and necrosis of blood vessels. However, the key to diagnosis when considering the possible presence of some type of vasculitis is to employ a multidisciplinary approach that involves rheumatologists as well as vascular specialists. Based on the size of the arteries involved and the underlying cause, vasculitis can be categorized as large vessel, medium vessel, or small vessel. The effects of vascular damage including arterial narrowing, thrombosis, or aneurysm formation become prominent over the course of these conditions. Invasive angiography is the gold standard for detecting such lesions and can be used to measure the trans-lesional pressure gradient. However, there are some concerns regarding invasive angiography for vasculitis. First, sheath or catheter insertion may cause vascular injury in the presence of active inflammation. Second, the potential exists for hypersensitivity reactions to the contrast dye as well as contrast nephropathy and volume overload. Moreover, invasive angiography does not provide any information on changes in vasculitis activity.

Takayasu's arteritis and giant cell arteritis (GCA) are typical large- and medium-vessel vasculitis that affect the aorta and its main branches, including the subclavian, carotid, vertebral, renal, mesenteric, and iliac arteries. The affected aortoiliac arteries may cause lower limb ischemia. Behcet's disease and Buerger's disease are representative conditions affecting various-sized arteries and venous systems. Medium-vessel vasculitis mainly comprise polyarteritis nodosa, anti-neutrophil cytoplasmic antibodies (ANCA)-related vasculitis (granulomatosis with polyangiitis (GPA), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis), and Kawasaki disease. Assessment of the patient's clinical background and systemic examination are indispensable for the diagnosis of this vasculitis. They can also potentially emerge in an atypical vascular bed for each disorder, mimicking other types of vasculitis [25].



6.1. Takayasu's arteritis

This inflammatory vasculitis of large and medium elastic arteries, also called nonspecific aortitis, is characterized pathologically by giant cell infiltration and granuloma formation. Destruction of the entire vascular wall and progressive adventitial fibrosis can cause stenosis or dilatation that can be complicated with superimposed calcification at the chronic stage. This disorder is typically but not exclusively observed in young women of Asian or Latin descent. It primarily affects the aorta, its major branches, and the pulmonary arteries, including but not limited to the brachiocephalic, carotid (common carotid), vertebral, subclavian (proximal subclavian), renal, iliac, femoral, and coronary arteries. Clinically, it usually first presents in the second or third decade, but can occur at older ages. Many patients initially complain of fever, arthralgias, and malaise. Although the most common symptom of TA is arm claudication, observed in greater than 60% of cases, aortoiliac artery involvement can result in lower limb ischemic symptoms, and even the femoral artery may be involved [26, 27].

There are no serological tests to identify TA. The diagnosis of TA is based on clinical findings in the presence of compatible vascular imaging abnormalities (**Table 1**) [1].

1990 criteria for the classification of Takayasu arteritis

- 1. Age at disease onset <40 years
- 2. Claudication of extremities
- 3. Decreased brachial artery pulse
- 4. Difference of >10 mmHg 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)

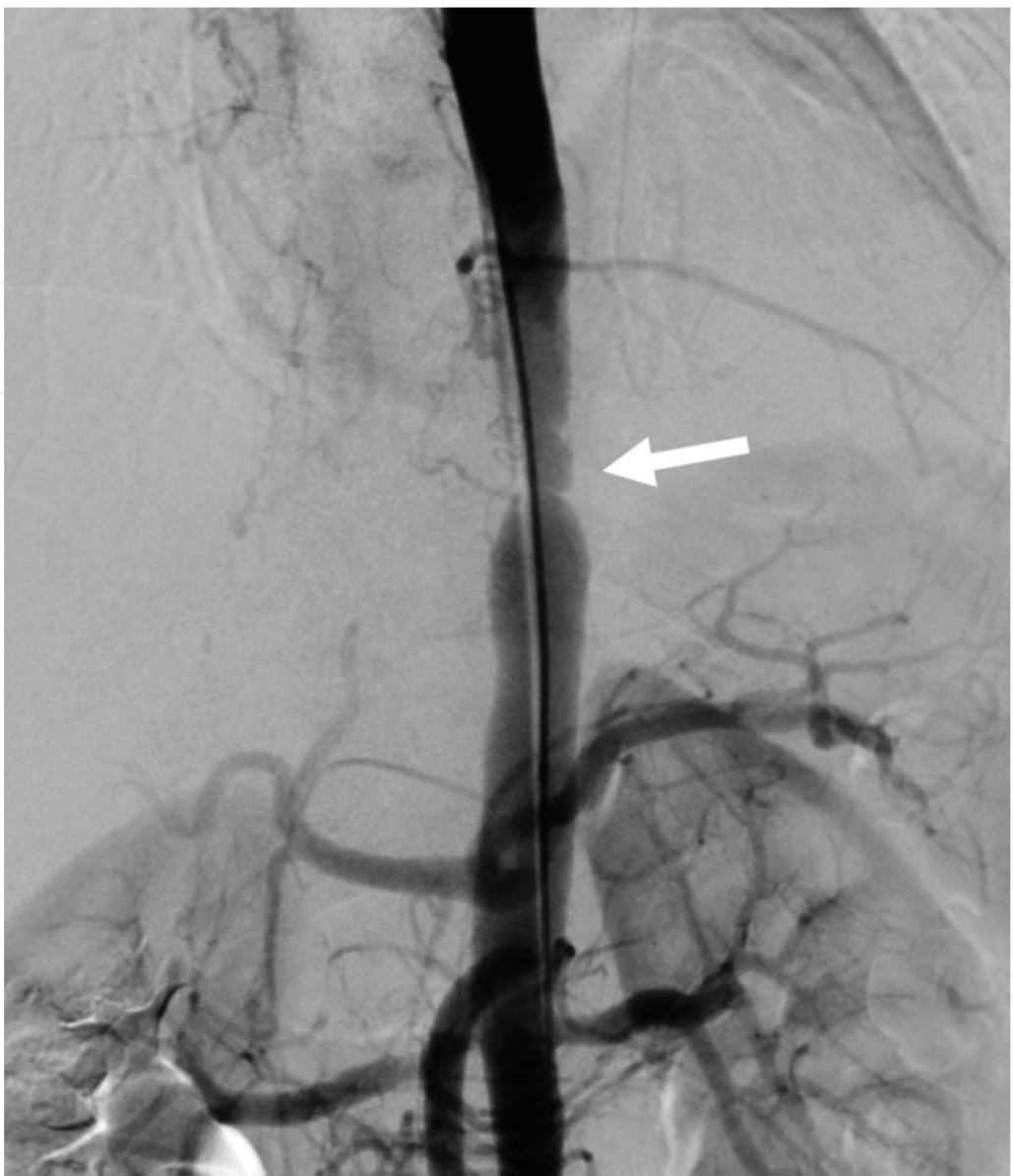
Takayasu arteritis is defined clinically if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

**Table 1.** American College of Rheumatology diagnostic criteria for Takayasu arteritis.

Angiography can reveal the extent of luminal narrowing, with or without dilatation/aneurysm, in order to differentiate TA from other diseases. While CT angiography or MR angiography can provide the whole image alternative to angiography, measurement of the pressure gradients is one of the major advantages of invasive angiography (**Figure 7**). It can also provide opportunities for surgical or endovascular intervention. However, in terms of evaluating vessel wall thickening and edema, duplex US, CT, and MR are more informative than angiography.

6.2. Giant cell arteritis

Although giant cell arteritis is pathologically similar to TA, this type of vasculitis commonly affects the temporal artery. The disorder is observed in men and women of around 50 and older, and is particularly prevalent in patients aged 70 and older. The arteries potentially affected include the aorta and its branches, with a predilection for the distal subclavian, axillary, and proximal brachial arteries, as well as the branches of the carotid arteries, in particular the ophthalmic artery. Therefore, headaches, jaw claudication, and visual impairment can occur in addition to arm claudication. Also, a normal erythrocyte sedimentation rate (ESR) is more useful in excluding giant cell arteritis than an elevated ESR is in diagnosing this disease [1] (**Table 2**).



**Figure 7.** Takayasu arteritis. A 20-year-old female presenting mild claudication and renovascular hypertension. Invasive angiography revealed significant stenosis in the descending thoracic aorta (arrow). The pullback pressure gradient was 20 mmHg.

1990 criteria for the classification of giant cell arteritis
1. Age at disease onset <50 years
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)
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%.

**Table 2.** American College of Rheumatology diagnostic criteria for giant cell arteritis.

Lower limb arteries can also be affected by this disorder [28, 29]. According to positron emission tomography scan studies, the iliac artery was involved in 37% of cases and the femoral artery in 37% (subclavian artery 70%, axillary artery 40%) [30]. Other studies have reported that superficial femoral artery was involved in 33%, common femoral artery in 14%, internal iliac artery 11%, deep femoral artery in 6%, and popliteal artery in 6% of cases [4, 31–34]. US studies have also detected the involvement of distal lower limb arteries such as the femoropopliteal, tibial, and peroneal arteries [35]. It is sometimes challenging to differentiate lesions from atherosclerosis in older patients.

Findings of arteritis from a temporal artery biopsy can be supportive but not essential for a diagnosis. An accurate diagnosis of GCA requires a comprehensive approach that includes assessment of clinical manifestations, physical examination, laboratory studies, vascular imaging, and arterial biopsies. Positive temporal artery biopsies can occasionally be seen in other types of arteritis and the ESR may be normal in up to 10% of GCA patients so that cautious interpretation is required. Differential diagnosis of GCA should include brain disease, infectious disease, and malignant disease. It should be noted that other vasculitis such as polyarteritis nodosa or ANCA-related vasculitis may rarely present with temporal artery involvement. Polymyalgia rheumatic may also be included in this group of vasculitis as it is often regarded as one clinical entity with GCA.

Although angiography can confirm the extent of affected vessels, less invasive tools such as duplex US, CT angiography, and MR angiography should also be considered. In particular, CT is informative for the extent of calcification. The advantage of angiography is that it allows measurements of pressure gradients to identify hemodynamically significant lesions.

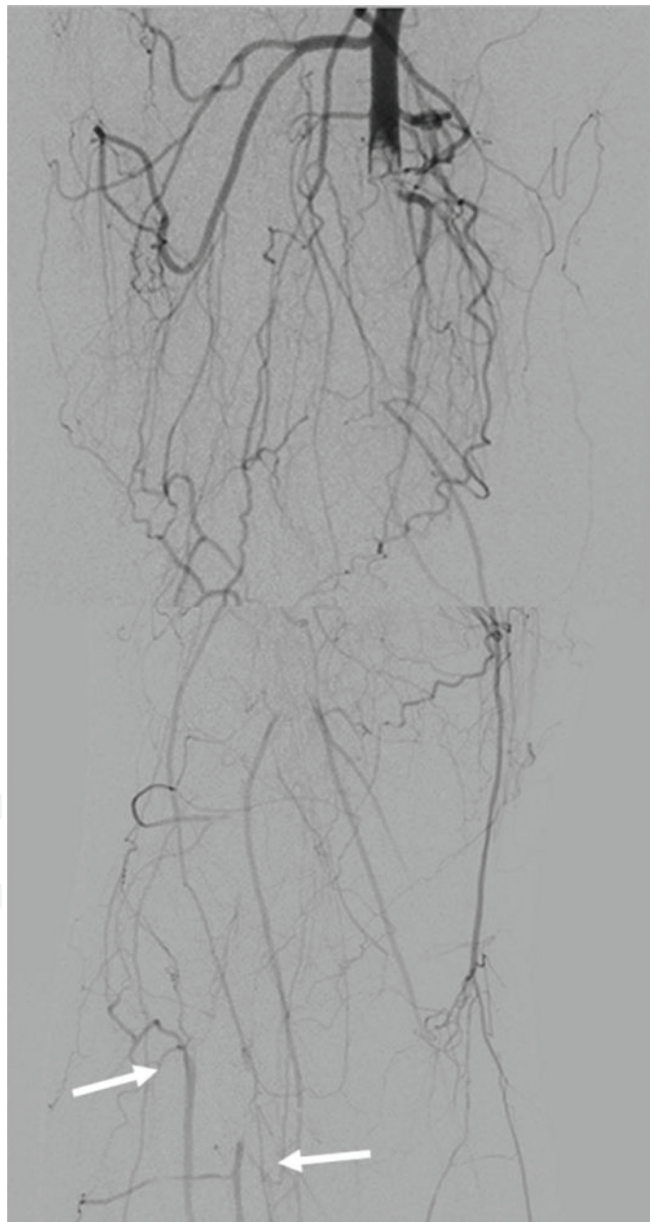
### 6.3. Behcet's disease

Vasculitis is observed in less than one-third of Behcet's disease cases. The etiology remains unclear and may involve both genetic and environmental factors. It can potentially be characterized by concomitant oral and genital ulcerations, skin lesions, uveitis, central nervous system, and gastrointestinal involvement. Approximately 80% of Behcet's disease patients have the human leukocyte antigen (HLA)-B51 allele. However, since no symptoms or laboratory findings are pathognomonic for Behcet's disease, diagnosis depends on the patient meeting a set of established clinical criteria. The major histopathological features of this disorder are predominantly perivascular inflammatory infiltrates and a tendency to thrombus formation in both veins and arteries of every size. In particular, venous disease is characteristic, including superficial phlebitis, varices, and thrombosis of the deep veins, vena cava, and cerebral sinuses. Large vessels frequently show luminal narrowing, aneurysm, or rupture. Medium and small vessels may also be affected [36, 37] (**Figure 8**).

### 6.4. Buerger's disease

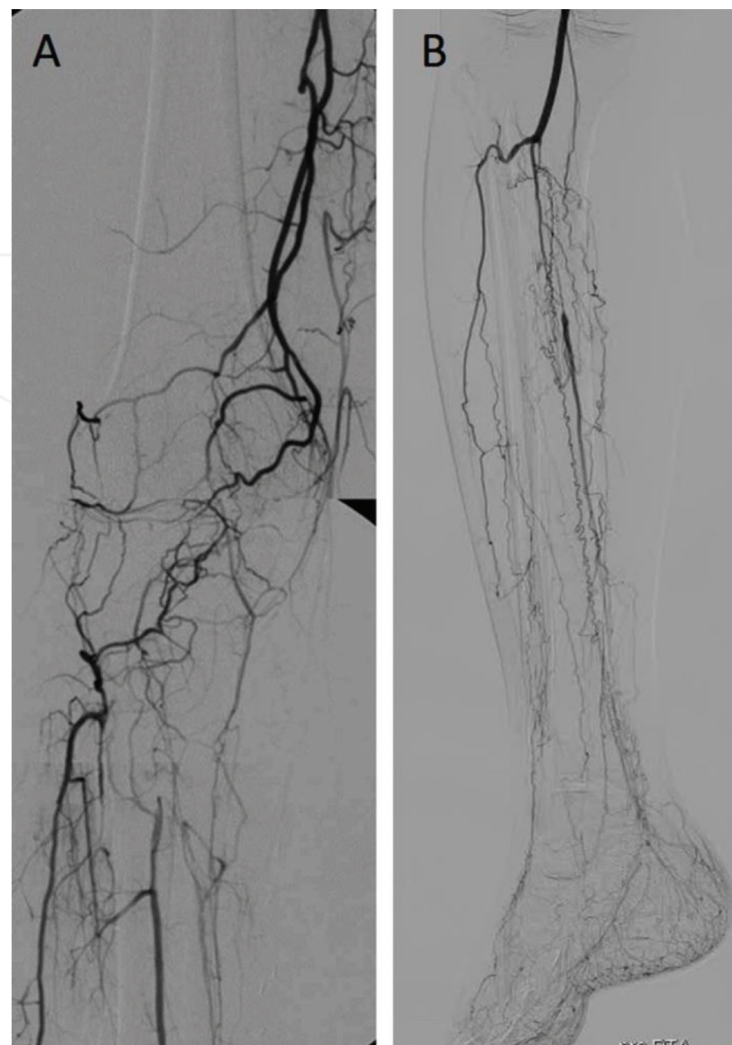
Buerger's disease, also known as thromboangiitis obliterans (TAO), was first reported by Winiwarter in 1879, and later described in detail by Buerger in 1908 [38, 39]. Although the etiology remains unclear, this disorder is a segmental inflammatory disease typically affecting small- to medium-sized arteries of the upper and lower extremities, with occasional extension

to the veins and nerves of the extremities [40–42]. Atypically, multiple large vessels can be affected [43]. This condition is more common in men than in women and is almost exclusively observed in patients who use tobacco so that it is widely recognized that tobacco is associated with the onset, progression, and recurrence of the disease. Symptoms can include claudication, rest pain, and ischemic tissue loss such as ulceration and gangrene. Unlike other vasculitis, inflammatory markers such as the ESR and C-reactive protein are typically normal. Angiography is often required to evaluate lesion extent and runoff conditions since there is the potential for over- or underestimation of the lesion with MR and CT imaging. Angiographic findings include segmental arterial occlusions of small- and medium-sized vessels while large arteries are typically spared (**Figure 9**) [44].



**Figure 8.** Behcet's disease. A 64-year-old male with a history of deep vein thrombosis and cerebral vein thrombosis presenting acute onset of rest pain and claudication in the right leg. Invasive angiography revealed right femorocrural occlusion. The proximal crural artery was reconstituted through the collateral vessels (arrows).





**Figure 9.** Buerger's disease. (A) Femorocrural occlusion beyond the right knee joint in a 38-year-old female presenting foot gangrene. (Ref. 44). (B) Crural artery occlusion in a 37-year-old male presenting right toe gangrene. Long total occlusions in the tibial arteries extending to the pedal arch.

The term “corkscrew” has recently been used to describe the appearance of collateral vessels in Buerger's disease patients. However, the original article attributes the corkscrew appearance to the recanalization of the affected native artery [45, 46]. Moreover, the corkscrew appearance is not pathognomonic for Buerger's disease as it may be seen in patients with other disorders including connective tissue disease. Thus, several different criteria have been proposed for the diagnosis of Buerger's disease (**Tables 3 and 4**) [40, 41].

- 
- History of smoking
  - Onset before age 50
  - Infrapopliteal arterial occlusions
  - Either arm involvement or phlebitis migrans
  - Absence of atherosclerotic risk factors other than smoking
- 

**Table 3.** Criteria of Buerger's disease by Shionoya [40].

- 
- Age under 45
  - Current or recent history of tobacco use
  - Presence of distal extremity ischemia as indicated by claudication, pain at rest, ischemic ulcers, or gangrene, and documented by noninvasive vascular testing
  - Exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus
  - Exclusion of a proximal source of emboli by echocardiography or arteriography
  - Consistent arteriographic findings in the clinically involved and noninvolved limbs
- 

**Table 4.** Criteria of Buerger's disease by Olin [41].

### 6.5. Other vasculitides

Other rare diseases, including Cogan's syndrome and relapsing polychondritis, can cause vasculitis of large- or medium-sized vessels. Small-vessel vasculitides include cryoglobulinemic vasculitis, leukocytoclastic vasculitides such as Henoch-Schonlein purpura and isolated cutaneous leukocytoclastic vasculitis, and vasculitis secondary to systemic autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus (SLE), and scleroderma [30, 47]. It is worth noting that there is the possibility of atypical lesion distribution for any type of vasculitides (**Figures 10 and 11**).



**Figure 10.** Systemic lupus erythematosus A 16-year-old female presenting claudication with subsequent acute limb ischemia as an initial clinical manifestation. Enhanced CT revealed severe femorocrural occlusion. Although the mid-tibial arteries were reconstituted, the distal tibial and pedal arteries were occluded.

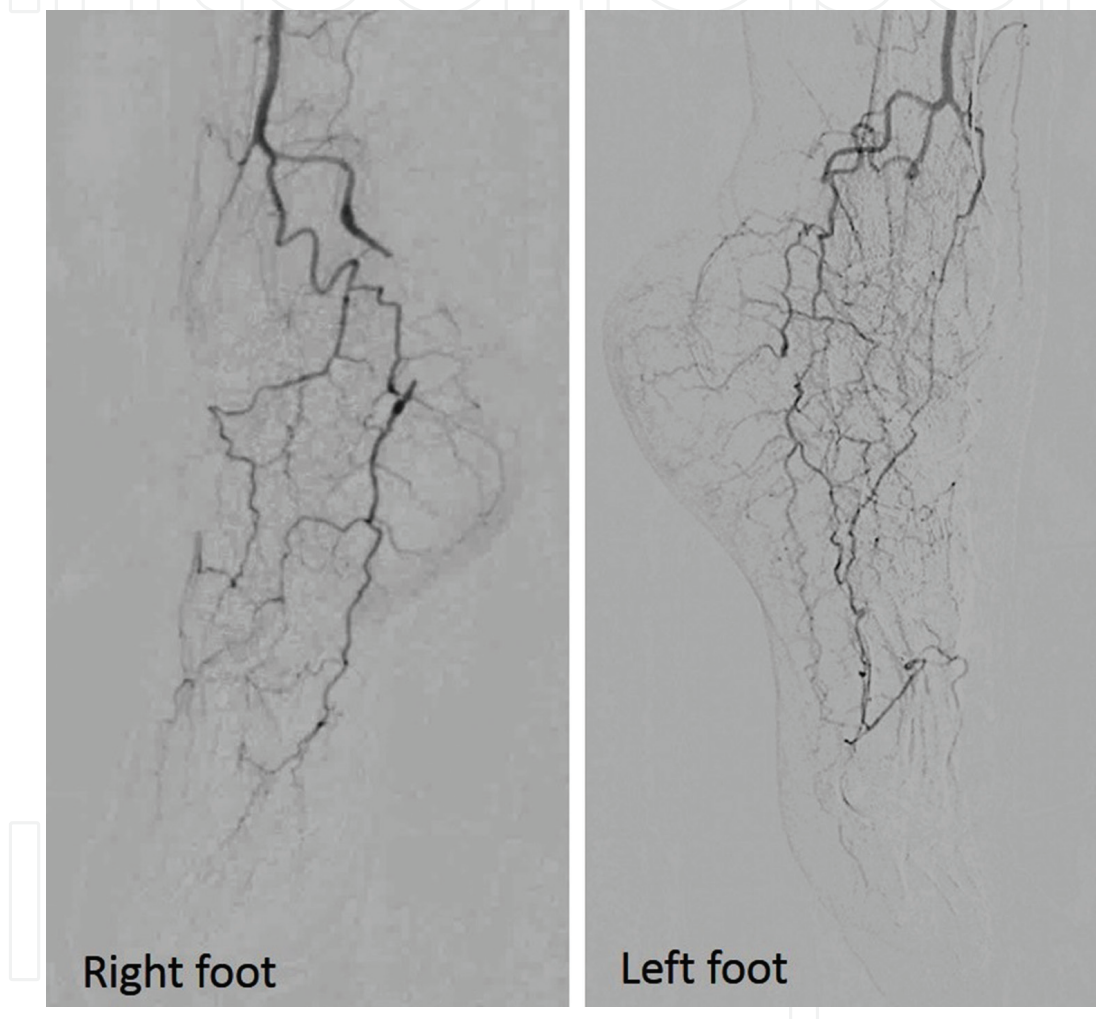


**Figure 11.** Scleroderma. An 80-year-old female presenting toe gangrene with a history of scleroderma. Invasive angiography showing multiple stenosis in the right crural artery.

For example, there have been case reports of large- or medium-vessel vasculitis in patients with rheumatoid arthritis, SLE and ANCA-related vasculitis [30, 47–62], and uncommon diseases including hypereosinophilic syndrome, Kimura disease, and angiolymphoid hyperplasia with eosinophilia can also mimic Buerger's disease [63–65]. Moreover, antiphospholipid syndrome (APS) can occur concomitantly with vasculitis secondary to systemic autoimmune disease (frequently SLE), and can develop into catastrophic APS [66–73] (**Figure 10**). Certain kinds of vasculitis can be complicated by thrombosis and potentially develop into thrombotic storm which has a devastating clinical course [74–77]. Radiation arteritis can occur years after high-dose radiotherapy for pelvic malignant disease. In such cases, stenotic or occlusive disease can be seen within the radiation field. Thus, with typical and atypical cases in mind, a careful diagnostic workup is vital for vasculitis.

## 7. Arterial thrombophilias

There are inherited and acquired disorders in which thrombosis develops in the arterial system. Inherited disorders include hyperhomocysteinemia/hyperhomocystinuria, antithrombin deficiency, protein S deficiency, and protein C deficiency, as well as gene polymorphisms such as Factor V Leiden. Acquired disorders are more common and can be caused by APS, malignancies, hormone therapy, and such myeloproliferative disorders as polycythemia vera, thrombocythemia, heparin-induced thrombocytopenia, and thrombotic thrombocytopenic purpura (**Figure 12**) [78].



**Figure 12.** Primary antiphospholipid syndrome [78]. A 75-year-old female presenting symmetric peripheral gangrene in four limbs. Angiography shows the occlusions in the pedal arteries as well as the palmar arteries due to antiphospholipid syndrome.

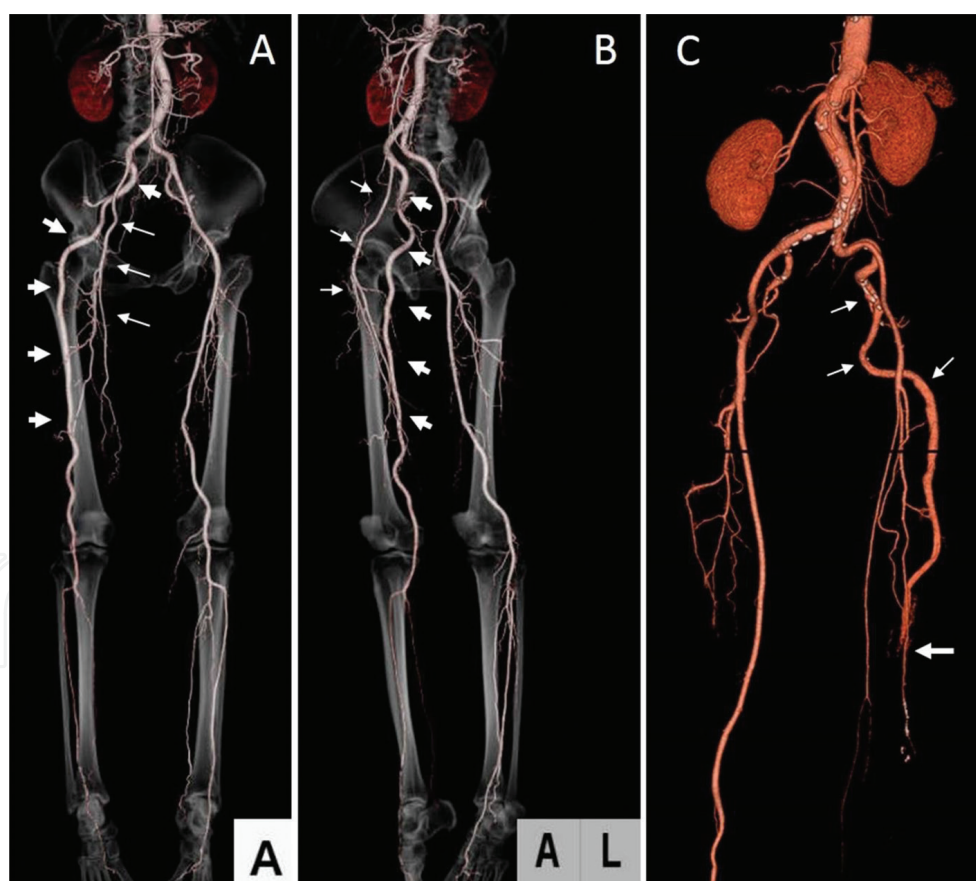
Thrombosis can be seen in vasculitis [74, 79]. In particular, inflammation-induced thrombosis is considered to be a feature of certain kinds of vasculitis (systemic autoimmune diseases such as SLE, rheumatoid arthritis, and Sjogren's syndrome, and other vasculitis). Thus, primary or secondary APS concomitant with autoimmune diseases such as SLE can cause thrombosis and potentially develop into catastrophic APS [80–82].



## 8. Congenital variants

Congenital malformations of the iliofemoral arterial system are rare, but accurate diagnosis is essential to avoid unnecessary revascularization treatment. Congenital absence or hypoplasia of the common iliac artery, external iliac artery, and SFA has been reported [83, 84]. Congenital variants of the external iliac artery have been classified into three groups [85]: group 1, anomalies in the origin or course of the artery; group 2, hypoplasia or atresia compensated for by persistent sciatic artery (PSA); and group 3, isolated hypoplasia or atresia. Although group 1 may not be associated with lower limb ischemia and is most often discovered at autopsy, group 2, the so-called persistent sciatic artery, and group 3 are most likely to present with lower limb ischemia.

Above all, PSA is a popular variant. Failure of regression of the sciatic artery during fetal development is often associated with superficial femoral artery hypoplasia, and the PSA then provides the dominant arterial inflow to the lower limb. Therefore, there is continuation of the internal iliac artery into the thigh through the greater sciatic notch. This variant can cause not only acute lower limb ischemia due to thromboembolism but also chronic lower limb ischemia, with a high incidence of aneurysm formation and arteriosclerosis of the sciatic artery (**Figure 13**) [4, 86].



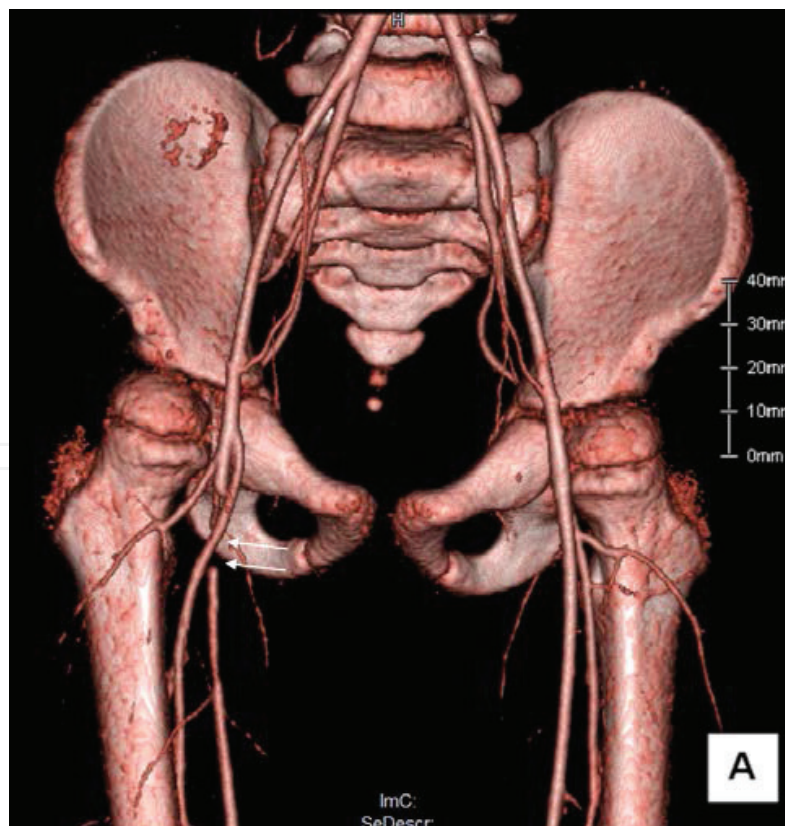
**Figure 13.** Persistent sciatic artery. (A, B) A 64-year-old male. Enhanced CT incidentally found persistent sciatic artery (large arrows) in the right. The right external iliac artery connects with the hypoplastic superficial femoral artery (small arrows). (C) A 60-year-old female presenting acute limb ischemia. The left external iliac artery connects with the hypoplastic superficial femoral artery whereas the persistent sciatic artery through the left internal iliac artery is the dominant blood supply (small arrows). The distal part of the sciatic artery is occluded due to thromboembolism (large arrow).

## 9. Embolism

Embolism can potentially cause manifestations of chronic lower limb ischemia, such as claudication and critical limb ischemia, but not acute limb ischemia in particular in the elderly population. Embolisms may have a number of sources including cardiac, aortic, and right-to-left shunts (paradoxical embolism from the venous circulation).

## 10. Vascular injury

Orthopedic surgery or trauma may cause lower limb ischemia because of dissection or thrombotic occlusion [87]. Additionally, pediatric cardiac catheterization using the transfemoral approach could be a cause of iliofemoral occlusion or stenosis due to thrombosis formation or intimal hyperplasia (**Figure 14**). This disorder may be asymptomatic until adulthood, but long-term uncorrected circulatory impairment can potentially cause limb growth retardation even in the absence of symptomatic evidence of ischemia [88–93].



**Figure 14.** Vascular injury following catheterization. A 4-year-old boy experienced a pale foot on the right following catheterization. Enhanced CT revealed a short occlusion due to puncture site thrombosis in the proximal segment of the right superficial femoral artery (arrows).

## 11. Conclusions

This section is intended to focus on vascular imaging, mainly invasive angiography, for NAPAD. From a clinical standpoint, an increase in opportunities to experience the symptoms and signs of APAD heightens the importance of the differential diagnosis of NAPAD in daily practice. NAPAD cannot benefit from a one-size-fits-all approach compared to APAD. Thus, differentiation between NAPAD and APAD may be a challenging task but we clinicians need to increase our knowledge of the diversity of NAPAD so that such awareness can be translated into improved patient care.

## Author details

Osami Kawarada

Address all correspondence to: kawarada.osami.hp@ncvc.go.jp

Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan

## References

- [1] Sharma AM, Norton PT, Zhu D. Conditions presenting with symptoms of peripheral arterial disease. *Semin Intervent Radiol.* 2014; 31: 281–291.
- [2] Weinberg I, Jaff MR. Nonatherosclerotic arterial disorders of the lower extremities. *Circulation.* 2012; 126: 213–222.
- [3] Mintz AJ, Weinberg I. Nonatherosclerotic PAD: approach to exertional pain in the lower extremities. *Curr Cardiol Rep.* 2015; 17: 66.
- [4] Apigian AK, Landry GJ. Basic data underlying decision making in nonatherosclerotic causes of intermittent claudication. *Ann Vasc Surg.* 2015; 29: 138–153.
- [5] Perlowski AA, Jaff MR. Vascular disorders in athletes. *Vasc Med.* 2010; 15: 469–479.
- [6] Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med.* 2004; 350: 1862–1871.
- [7] Okazaki J, Guntani A, Homma K, Kyuragi R, Kawakubo E, Maehara Y. Fibromuscular dysplasia of the lower extremities. *Ann Vasc Dis.* 2011; 4: 143–149.
- [8] Plouin PF, Perdu J, La Batide-Alanore A, Boutouyrie P, Gimenez-Roqueplo AP, Jeunemaitre X. Fibromuscular dysplasia. *Orphanet J Rare Dis.* 2007; 2: 28.
- [9] Pontes Tde C, Rufino GP, Gurgel MG, Medeiros AC, Freire EA. Fibromuscular dysplasia: a differential diagnosis of vasculitis. *Rev Bras Rheumatol.* 2012; 52: 70–74.
- [10] França M, Pinto J, Machado R, Fernandez GC. Bilateral adventitial cystic disease of the popliteal artery. *Radiology.* 2010; 255: 655–660.

- [11] Porras D, Stein DR, Ferguson MA, Chaudry G, Alomari A, Vakili K, Fishman SJ, Lock JE, Kim HB. Midaortic syndrome: 30 years of experience with medical, endovascular and surgical management. *Pediatr Nephrol*. 2013; 28: 2023–2033.
- [12] Stanley JC, Criado E, Eliason JL, Upchurch GR Jr, Berguer R, Rectenwald JE. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aorto-aortic graft. *J Vasc Surg*. 2008; 48: 1073–1082.
- [13] Kim HB, Vakili K, Modi BP, Ferguson MA, Guillot AP, Potanos KM, Prabhu SP, Fishman SJ. A novel treatment for the midaortic syndrome. *N Engl J Med*. 2012; 367: 2361–2362.
- [14] Sumboonnanonda A, Robinson BL, Gedroyc WM, Saxton HM, Reidy JF, Haycock GB. Middle aortic syndrome: clinical and radiological findings. *Arch Dis Child*. 1992; 67: 501–505.
- [15] Saif I, Seriki D, Moore R, Woywodt A. Midaortic syndrome in neurofibromatosis type 1 resulting in bilateral renal artery stenosis. *Am J Kidney Dis*. 2010; 56: 1197–1201.
- [16] Peach G, Schep G, Palfreeman R, Beard JD, Thompson MM, Hinchliffe RJ. Endofibrosis and kinking of the iliac arteries in athletes: a systematic review. *Eur J Vasc Endovasc Surg*. 2012; 43: 208–217.
- [17] Rousselet MC, Saint-Andre JP, L'Hoste P, Enon B, Megret A, Chevalier JM. Stenotic intimal thickening of the external iliac artery in competition cyclists. *Hum Pathol*. 1990; 21: 524–529.
- [18] Radonić V, Koplić S, Giunio L, Božić I, Masković J, Buća A. *Tex Heart Inst J*. 2000; 27(1):3–13. Popliteal artery entrapment syndrome: diagnosis and management, with report of three cases. *Tex Heart Inst J*. 2000; 27: 3–13.
- [19] Akkersdijk WL, de Ruyter JW, Lapham R, Mali W, Eikelboom BC. Colour duplex ultrasonographic imaging and provocation of popliteal artery compression. *Eur J Vasc Endovasc Surg*. 1995; 10: 342–345.
- [20] Sapienza P, Tartaglia E, Venturini L, Gallo P, di Marzo L. Adductor canal compression syndrome: a forgotten disease. *Ann Ital Chir*. 2014; 85(ePub).
- [21] Verta MJ Jr, Vitello J, Fuller J. Adductor canal compression syndrome. *Arch Surg*. 1984; 119: 345–346.
- [22] Balaji MR, DeWeese JA. Adductor canal outlet syndrome. *JAMA*. 1981; 245: 167–170.
- [23] Demir S, Akin S, Tercan F, Ariboğan A, Oğuzkurt L. Ergotamine-induced lower extremity arterial vasospasm presenting as acute limb ischemia. *Diagn Interv Radiol*. 2010; 16: 165–167.
- [24] Kaneyama J, Kawarada O, Sakamoto S, Harada K, Ishihara M, Yasuda S, Ogawa H. Vasospastic limb ischemia presenting acute and chronic limb ischemia. *Ann Vasc Dis*. 2014; 7: 169–172.
- [25] Berlitz P, Kessler C, Reuther R, Krause KH. New aspects of thromboangiitis obliterans (von Winiwarter-Buerger's disease). *Eur Neurol*. 1984; 23: 394–399.



- [26] Beschorner U, Goebel H, Rastan A, Sixt S, Zeller T. Histological diagnosis of atypical Takayasu arteritis using percutaneous transluminal atherectomy. *J Endovasc Ther.* 2008; 15: 241–243.
- [27] Kawano H, Hanibuchi M, Yoshijima T, Toyoda Y, Kishi J, Tezuka T, Nishioka Y. A case of atypical Takayasu arteritis initially presenting with peripheral artery disease. *Case Rep Clin Pathol.* 2015; 2: 34–40.
- [28] Finlayson R, Robinson JO. Giant-cell arteritis of the legs. *Br Med J.* 1955; 2: 1595–1597.
- [29] Tatò F, Hoffmann U. Giant cell arteritis: a systemic vascular disease. *Vasc Med.* 2008; 13: 127–140.
- [30] Cid MC, Prieto-González S, Arguis P, Espígol-Frigolé G, Butjosa M, Hernández-Rodríguez J, Segarra M, Lozano E, García-Martínez A. The spectrum of vascular involvement in giant-cell arteritis: clinical consequences of detrimental vascular remodelling at different sites. *APMIS Suppl.* 2009; 127: 10–20.
- [31] Loo ZY, Thwaites S, Kyaw P. Giant cell arteritis presenting as critical lower limb ischemia. *Vasc Endovascular Surg.* 2013; 47: 660–662.
- [32] Czihal M, Tato F, Rademacher A, Kuhlencordt P, Schulze-Koops H, Hoffmann U. Involvement of the femoropopliteal arteries in giant cell arteritis: clinical and color duplex sonography. *J Rheumatol.* 2012; 39: 314–321.
- [33] Assie C, Janvresse A, Plissonnier D, Levesque H, Marie I. Long-term follow-up of upper and lower extremity vasculitis related to giant cell arteritis: a series of 36 patients. *Medicine.* 2011; 90: 40–51.
- [34] Kermani TA, Matteson EL, Hunder GG, Warrington KJ. Symptomatic lower extremity vasculitis in giant cell arteritis: a case series. *J Rheumatol.* 2009; 36: 2277–2283.
- [35] Schmidt WA, Natusch A, Möller DE, Vorpahl K, Gromnica-Ihle E. Involvement of peripheral arteries in giant cell arteritis: a color Doppler sonography study. *Clin Exp Rheumatol.* 2002; 20: 309–318.
- [36] Merkel PA. Overview of vasculitis. *Vascular Medicine: A Companion to Braunwald's Heart Disease.* Elsevier 2013, 507–524.
- [37] Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. *N Engl J Med* 1999; 341: 1284–1291.
- [38] von Winiwarter F. Ueber eine eigenthumliche form von endarteriitis und endophlebitis mit gangran des fusses. *Arch Klin Chir.* 1879; 23: 202–226.
- [39] Buerger L. Thrombo-angiitis obliterans: a study of the vascular lesions leading to pre-nile spontaneous gangrene. *Am J Med Sci.* 1908; 136: 567–580.
- [40] Shionoya S. Diagnostic criteria of Buerger's disease. *Int J Cardiol.* 1998; 1: 243–245.

- [41] Olin JW. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med.* 2000; 343: 864–869.
- [42] Del Conde I, Peña C. Buerger disease (thromboangiitis obliterans). *Tech Vasc Interv Radiol.* 2014; 17: 234–240.
- [43] Edo N, Miyai K, Ogata S, Nakanishi K, Hiroi S, Tominaga S, Aiko S, Kawai T. Thromboangiitis obliterans with multiple large vessel involvement: Case report and analysis of immunophenotypes. *Cardiovasc Pathol.* 2010; 19: 59–62.
- [44] Kawarada O, Ayabe S, Yotsukura H, Nakaya T, Kanayama J, Harada K, Ishihara M, Yasuda S, Ogawa H. Subintimal angioplasty of lengthy femorotibial total occlusion in Buerger's disease. *J Endovasc Ther.* 2013; 20: 578–581.
- [45] McKusick VA, Harris WS, Ottesen OE, Goodman RM, Shelley WM, Bloodwell RD. Buerger's disease: a distinct clinical and pathologic entity. *JAMA.* 1962; 181: 5–12.
- [46] Talwar S, Choudhary SK, Bhan A. Buerger's disease. *Indian J Cardiol.* 1998; 1: 31–34.
- [47] Celecova Z, Krahulec B, Lizicarova D, Gaspar L. Vasculitides as a rare cause of intermittent claudication. *Bratisl Lek Listy.* 2013; 114: 353–356.
- [48] Hammentgen R, Stojanova-Scholz M, Martin M, Gresshöner-Solf IM, Haupt H, Fiebach BJ, Magnus L, Trobisch H. Bilateral popliteal artery occlusion in systemic lupus erythematosus in a 15-year-old girl. *Vasa.* 1987; 16: 86–88.
- [49] Gladstein GS, Rynes RI, Parhami N, Bartholomew LE. Gangrene of a foot secondary to systemic lupus erythematosus with large vessel vasculitis. *J Rheumatol.* 1979; 6: 549–553.
- [50] Bakker FC, Rauwerda JA, Moens HJ, van den Broek TA. Intermittent claudication and limb-threatening ischemia in systemic lupus erythematosus and in SLE-like disease: a report of two cases and review of the literature. *Surgery.* 1989; 106: 21–25.
- [51] Asherson RA, Derksen RH, Harris EN, Bingley PJ, Hoffbrand BI, Gharavi AE, Kater L, Hughes GR. Large vessel occlusion and gangrene in systemic lupus erythematosus and “lupus-like” disease. A report of six cases. *J Rheumatol.* 1986; 13: 740–747.
- [52] Harmon SM, Olthmanns KL, Min KW. Large vessel occlusion with vasculitis in systemic lupus erythematosus. *South Med J.* 1991; 84: 1150–1154.
- [53] Wheatley MJ, Hennein HA, Greenfield LJ. Lower extremity arterial disease in systemic lupus erythematosus. *Arch Surg.* 1991; 126: 109–110.
- [54] Pyrpassopoulou A, Chatzimichailidou S, Aslanidis S. Vascular disease in systemic lupus erythematosus. *Autoimmune Dis.* 2012; 2012: 876456.
- [55] Herrick AL, Oogarah PK, Freemont AJ, Marcuson R, Haeney M, Jayson MI. Vasculitis in patients with systemic sclerosis and severe digital ischaemia requiring amputation. *Ann Rheum Dis.* 1994; 53: 323–326.

- [56] Schwarz-Eywill M, Rinaldi N, Barth T, Nüsslein HG. Rare manifestation of large vessel vasculitis in systemic lupus erythematosus. *Z Rheumatol*. 2000; 59: 330–333.
- [57] Giannakakis S, Galyfos G, Stefanidis I, Kastrisios G, Maltezos C. Hybrid treatment of lower limb critical ischemia in a patient with systemic lupus erythematosus. *Ann Vasc Surg*. 2015; 29: 596. e1–5.
- [58] Jeffery RC, Narshi CB, Isenberg DA. Prevalence, serological features, response to treatment and outcome of critical peripheral ischaemia in a cohort of lupus patients. *Rheumatology (Oxford)*. 2008; 47: 1379–1383.
- [59] da Rocha MC, Vilar MJ, Freire EA, Santiago MB. Arterial occlusion in systemic lupus erythematosus: a good prognostic sign? *Clin Rheumatol*. 2005; 24: 602–605.
- [60] Stafford L, Englert H, Gover J, Bertouch J. Distribution of macrovascular disease in scleroderma. *Ann Rheum Dis*. 1998; 57: 476–479.
- [61] Deguchi J, Shigematsu K, Ota S, Kimura H, Fukayama M, Miyata T. Surgical result of critical limb ischemia due to tibial arterial occlusion in patients with systemic scleroderma. *J Vasc Surg*. 2009; 49: 918–923.
- [62] Struthers GR, Pugh MT, Woodward DA. Polyarteritis nodosa following angioplasty. *Ann Rheum Dis*. 1993; 52: 247.
- [63] Takaoka H, Takano H, Nakagawa K, Kobayashi Y, Hiroshima K, Komuro I. Buerger's disease-like vasculitis associated with Kimura's disease. *Int J Cardiol*. 2010; 140: e23–6.
- [64] Gleich GJ, Leiferman KM. The hypereosinophilic syndromes: current concepts and treatments. *Br J Haematol*. 2009; 145: 271–285.
- [65] Kawata E, Kuroda J, Wada K, Yoshida M, Kamiuchi K, Nakayama-Harusato I, Kimura S, Maekawa T, Kitagawa Y. Hypereosinophilic syndrome accompanied by Buerger's disease-like femoral arterial occlusions. *Intern Med*. 2007; 46: 1919–1922.
- [66] Suzuki K, Uemura T, Kikuchi M, Ishihara Y, Ichioka S. Acute limb-threatening ischemia associated with antiphospholipid syndrome: a report of two cases. *J Foot Ankle Surg*. 2016; 55: 1318–1322.
- [67] Dupont P, Jackson J, Warrens A, Lightstone L. Life-threatening thrombosis 18 years after first presentation of primary antiphospholipid antibody syndrome. *Nephrol Dial Transplant*. 2001; 16: 843–845.
- [68] Biernacka-Zielinska M, Lipinska J, Szymanska-Kaluza J, Stanczyk J, Smolewska E. Recurrent arterial and venous thrombosis in a 16-year-old boy in the course of primary antiphospholipid syndrome despite treatment with low-molecular-weight heparin: a case report. *J Med Case Rep*. 2013; 7: 221.
- [69] Ziaee V, Yeganeh MH, Moradinejad MH. Peripheral gangrene: A rare presentation of systemic lupus erythematosus in a child. *Am J Case Rep*. 2013; 14: 337–340.

- [70] Ascherson RA, Cervera R, Klumb E, Stojanovic L, Sarzi-Puttini P, Yin J, Bucciarelli S, Espinosa G, Levy R, Shoenfeld Y. Amputation of digits or limbs in patients with antiphospholipid syndrome. *Semin Arthritis Rheum*. 2008; 38: 124–131.
- [71] Pari VS, Lakshmi M, Kumar S, Sathyamurthy P, Sudhakar MK, Sundaram S. A young female with catastrophic antiphospholipid syndrome. *Int J Case Rep Images*. 2014; 5: 513–518.
- [72] Montes de Oca MA, Babron MC, Blétry O, Broyer M, Courtecuisse V, Fontaine JL, Loirat C, Méry JP, Reinert P, Wechsler B, Levy M. Thrombosis in systemic lupus erythematosus: a French collaborative study. *Arch Dis Child*. 1991; 66: 713–717.
- [73] Hughson MD, McCarty GA, Brumback RA. Spectrum of vascular pathology affecting patients with the antiphospholipid syndrome. *Hum Pathol*. 1995; 26: 716–724.
- [74] Emmi G, Silvestri E, Squatrito D, Amedei A, Niccolai E, D'elios MM, Bella CD, Grassi A, Becatti M, Fiorillo C, Emmi L, Vaglio A, Prisco D. Thrombosis in vasculitis: from pathogenesis to treatment. *Thromb J*. 2015; 13: 15.
- [75] Bastug DE, Dominic A, Ortiz O, DiBartolomeo AG, Kotzan JM, Abraham FM. Popliteal artery thrombosis in a patient with Cogan syndrome: treatment with thrombolysis and percutaneous transluminal angioplasty. *Cardiovasc Intervent Radiol*. 1997; 20: 57–59.
- [76] Liu H, Al-Quran SZ, Lottenberg R. Thrombotic storm in Kimura disease. *J Thromb Thrombolysis*. 2010; 29: 354–357.
- [77] Herrick AL, Oogarah PK, Freemont AJ, Marcuson R, Haeney M, Jayson MI. Vasculitis in patients with systemic sclerosis and severe digital ischaemia requiring amputation. *Ann Rheum Dis*. 1994; 53: 323–326.
- [78] Shiba M, Ieko M, Kawarada O. Symmetric peripheral gangrene in antiphospholipid syndrome. *Heart Asia* 2016; 8: 8.
- [79] Palatinus A, Adams M. Thrombosis in systemic lupus erythematosus. *Semin Thromb Hemost*. 2009; 35: 621–629.
- [80] Asherson RA, Cervera R. Microvascular and microangiopathic antiphospholipid-associated syndromes ("MAPS"): semantic or antisemantic? *Autoimmun Rev*. 2008; 7: 164–167.
- [81] Kitchens CS, Erkan D, Brandão LR, Hahn S, James AH, Kulkarni R, Pericak-Vance M, Vance J, Ortel TL. Thrombotic storm revisited: preliminary diagnostic criteria suggested by the thrombotic storm study group. *Am J Med*. 2011; 124: 290–296.
- [82] Ortel TL, Erkan D, Kitchens CS. How I treat catastrophic thrombotic syndromes. *Blood*. 2015; 126: 1285–1293.
- [83] Koyama T, Kawada T, Kitanaka Y, Katagiri K, Ohno M, Ikeshita M, Yamate N. Congenital anomaly of the external iliac artery: a case report. *J Vasc Surg*. 2003; 37: 683–685.
- [84] Rob CG, Owen K. Congenital hypoplasia of the iliac arteries. *Postgrad Med J*. 1958; 34: 391–392.



- [85] Tamisier D, Melki JP, Cormier JM. Congenital anomalies of the external iliac artery: Case report and review of the literature. *Ann Vasc Surg.* 1990; 4: 510–514.
- [86] McLellan GL, Morettin LB. Persistent sciatic artery: Clinical, surgical, and angiographic aspects. *Arch Surg.* 1982; 117: 817–822.
- [87] Imerci A, Ozaksar K, Gürbüz Y, Sığün TS, Canbek U, Savran A. Popliteal artery injury associated with blunt trauma to the knee without fracture or dislocation. *West J Emerg Med.* 2014; 15: 145–148.
- [88] Flanigan DP, Keifer TJ, Schuler JJ, Ryan TJ, Castronuovo JJ. Experience with iatrogenic pediatric vascular injuries. Incidence, etiology, management, and results. *Ann Surg.* 1983; 198: 430–442.
- [89] Bassett FH III, Lincoln CR, King TD, Canent RV Jr. Inequality in the size of the lower extremity following cardiac catheterization. *South Med J.* 1968; 61: 1013–1017.
- [90] Bloom JD, Mozersky DJ, Buckley CJ, Hagood CO Jr. Defective limb growth as a complication of catheterization of the femoral artery. *Surg Gynecol Obstet.* 1974; 138: 524–526.
- [91] Jacobsson B, Carlgren LE, Hedvall G, Sivertsson R. A review of children after arterial catheterization of the leg. *Pediatr Radiol.* 1973; 1: 96–99.
- [92] Rosenthal A, Anderson M, Thompson SJ, Pappas AM, Fyler DC. Superficial femoral artery catheterization: effect on extremity length. *Am J Dis Child.* 1972; 124: 240–242.
- [93] Currarino G, Eagle MA. The effects of ligation of the subclavian artery on the bones and soft tissues of the arms. *J Pediatr.* 1965; 67: 808–811.