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Women's Health (M Wood, Section Editor)

Non-Atherosclerotic Vascular Disease in Women

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Opinion statement

Takayasu arteritis, fibromuscular dysplasia (FMD), spontaneous arterial dissection, Raynaud's phenomenon, and chilblains are vascular conditions that are associated with an increased predisposition in women and are often underdiagnosed. Takayasu arteritis has an incidence rate of 2.6 cases per million individuals per year in the USA and predominantly affects women of childbearing age. HLA-B5 genetic locus is linked with Takayasu arteritis susceptibility. Methods to determine active disease are limiting; currently utilized clinical and imaging findings and laboratory tests are of limited value for this purpose. Pregnancy poses risks for maternal and fetal complications, and these patients need additional monitoring and care before and after conception. Controlling hypertension and immunosuppression using steroids, biological and non-biological immunosuppressants, are key components of managing patients with this arteritis. FMD commonly affects middle-aged, white females. Its true prevalence is unknown. Renal and cerebrovascular beds are the most frequently involved vascular beds. Its clinical presentation varies from no symptoms to catastrophic events. Controlling vascular risk factors, periodic surveillance, and revascularization when indicated are important factors in FMD management. Spontaneous arterial dissections are less common, but are an important cause of morbidity and mortality in specific populations. Cervicocephalic dissection causes 10–20% of the strokes in young adults, and coronary artery dissection is the culprit in almost one fourth of young women presenting with acute myocardial infarction. Early diagnosis is key to improving prognosis in these patients, as the majority of patients have spontaneous resolution of the dissection with conservative management alone. Increased clinician awareness of the presentation features and angiographic findings are imperative for early diagnosis. Raynaud's phenomenon and chilblains are cold- or stress-induced cutaneous lesions, commonly involving distal extremities. Secondary causes such as connective tissue diseases and malignancies must be thoroughly excluded during evaluation of these conditions. Cold avoidance, systemic and local warming, and oral vasodilator therapy are the mainstays of therapy.

Introduction

There are substantial differences between men and women in their risk for cardiovascular disease and treatment outcomes, highlighting the implications of sex in risk stratification and developing management strategies [1–4]. Atherosclerosis is the most common vascular disease in both sexes; however, there are a number of less common vascular conditions that affect women more than men. The cause of these sex-related differences in prevalence is unknown. Here, we provide a broad overview of non-atherosclerotic vascular diseases which affect women disproportionately: Takayasu arteritis, fibromuscular dysplasia (FMD), spontaneous arterial dissection, Raynaud's phenomenon, and chilblains.

Takayasu arteritis

Epidemiology, risk factors, and pathophysiology

Takayasu arteritis is a granulomatous large vessel vasculitis with a chronic and relapsing course. It is a rare condition, the incidence rate being 2.6 cases per million individuals per year in the USA [5]. It predominantly affects women (97%) of childbearing age, with a median age at onset being 25 years and is more common among Asian populations [5]. It affects the aorta, its main branches, and the pulmonary arteries. It is also known as aortic arch syndrome, pulseless disease, middle aortic syndrome, occlusive thromboaortopathy, and non-specific aortoarteritis. The etiology of this condition is unclear. The association between Takayasu arteritis susceptibility and human leukocyte antigen (HLA) locus, namely HLA-B5 and its subgroup, HLA-Bw52, has been confirmed across multiple ethnic groups [6, 7]. The role of non-HLA genetic factors are currently being investigated.

Histopathologically, Takayasu arteritis is a panarteritis with typical focal "skip lesions" involving the entire vessel wall. In active disease, there is predominantly lymphoplasmacytic inflammatory infiltrate with granuloma formation and giant cells. There is little to no role in obtaining tissue biopsy for establishing diagnosis unless the pathologic specimen is available for other reasons.

Clinical presentation

The presentation, progression, and response to therapy of a patient with Takayasu arteritis can vary. Clinical manifestations range from constitutional (43%), vascular (100%), neurologic (57%), musculoskeletal (53%), and cardiac (38%) symptoms and/or signs [5]. While both arterial stenoses/occlusion and aneurysms occur, stenotic/occlusive lesions are more common. A bruit, often over the carotid artery, is the most common clinical finding, present in 70–80% of the patients. A bruit may also be heard over a subclavian artery, femoral artery, renal artery, or abdominal aorta. Other vascular manifestations include claudication of the extremity, diminished or absent pulses, asymmetric blood pressure, hypertension, and carotidynia. Neurologic symptoms and/or signs include dizziness/syncope, visual changes/loss, stroke, and transient ischemic attack. Chest wall symptoms, myalgia, and arthralgias are commonly present. Constitutional symptoms include weight loss, fever, night sweats, and malaise. Though less common, cardiac involvement may manifest as aortic regurgitation, angina, palpitation, congestive heart failure, pericarditis, and myocardial infarction.

Diagnosis

A diagnosis of Takayasu arteritis requires meeting at least three of the following six criteria: age at disease onset 40 years or less, claudication of extremities, diminished brachial artery pulse, difference of >10 mmHg in systolic blood pressure between arms, bruit over a subclavian artery or aorta, and arteriographic narrowing or occlusion of the entire aorta, its main branches, or large arteries in the proximal extremities with features distinct from atherosclerosis, fibromuscular dysplasia, or other arteriopathies [8].

Due to the chronic and relapsing course of Takayasu arteritis, it is important to distinguish active disease from the quiescent or sequela phase. Indicators of active disease are new clinical symptoms and/or signs and development of new lesions in new vascular territories. Active disease is often missed as shown in a study where 44% surgical bypass specimens from patients judged to be quiescent by current methods were found to have active arteritis [5]. Laboratory investigations including acute phase reactants are of limited diagnostic value as there is no consistent correlation between acute phase reactants and active arteritis. Normal erythrocyte sedimentation rate is seen in one third of patients with clinically active disease [5]. There is little data regarding the overall utility of C-reactive protein in Takayasu arteritis. Presence of ANCA is also not strongly associated with this vasculitis [9]. Pentraxin 3, another pro-inflammatory protein, and serum cytokine levels have also been proposed as a novel biomarker for detecting active disease [10, 11].

When Takayasu arteritis is suspected, magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) is useful for assessing arterial stenosis, occlusions, and aneurysms, excluding alternate diagnoses and for follow-up. MRA can detect arterial wall thickness and edema and may potentially be helpful in identifying active disease. Fludeoxyglucose positron emission tomography (FDG-PET) may identify active disease as it may detect arterial wall inflammation; however, both the specificity of MRA and the PET in identifying active disease requires additional investigation [12, 13]. Duplex ultrasound is useful in characterizing the carotid and extremity arteries as it is able to determine degrees of stenosis and detect circumferential wall thickening associated with vasculitis. Contrast-enhanced ultrasound (CEUS) detects neovascularization, a marker of disease activity [14, 15]. CEUS-based vascularization grade has been shown to correlate well with vascular inflammation grade on FDG-PET [16]. Conventional angiography is the gold standard method for definitively diagnosing Takayasu arteritis. It is ideal in the assessment of arterial stenosis and occlusion but also allows for central blood pressure measurement. Based on angiographic involvement, Takayasu arteritis is classified into six types (Table 1) [17]. Catheter-based angiography is not able to provide assessment of arterial wall thickness.

Management

Managing Takayasu arteritis involves identifying and treating active disease, maintaining remission, controlling risk factors, and interventional treatment of stenotic or aneurysmal lesions. A multidisciplinary approach combining rheumatology, radiology, and cardiovascular experts is required to care for these patients. Identifying active disease is limited by lack of modalities that

Table 1. Numano's angiographic classification of Takayasu arteritis [17]

Type	Vessel involvement
I	Aortic arch and its branches
IIa	Ascending aorta, aortic arch, and its branches
IIb	Ascending aorta, aortic arch, its branches, and descending thoracic aorta
III	Descending thoracic aorta, abdominal aorta, renal arteries, or a combination
IV	Abdominal aorta, renal arteries, or a combination
V	Entire aorta and its branches

accurately assess disease activity. There is only one randomized controlled trial of therapy for Takayasu arteritis. Abatacept, a biologic, was compared to placebo in 34 patients with Takayasu arteritis who had previously achieved remission with prednisone and abatacept. There was no difference in relapse-free survival among patients randomized to abatacept compared to placebo [18•]. Given the lack of clinical trial data, treatment strategies for Takayasu arteritis are based on data derived from open-label trials, observational studies, and case series. Locations and severity of lesions, availability of collaterals, symptom burden, and adverse effects of drugs are pertinent factors to consider while choosing therapy. Drugs for treating active disease include conventional immunosuppressants and biologic therapies (antitumor necrosis factor agents, antiinterleukin-6 receptor antibody tocilizumab, rituximab). First line of therapy is corticosteroids; however, a substantial number of the patients relapse with steroid tapering and 46–84% patients require additional immunosuppression to maintain remission with steroid tapering [19]. Commonly used steroid sparing non-biologic immunosuppressive agents are methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide. Antitumor necrosis factor agents, particularly infliximab, are recommended for refractory disease. Tocilizumab, a humanized monoclonal antibody against interleukin-6 and rituximab, may also be used for controlling resistant disease. Optimal hypertension control and traditional atherosclerotic risk factor control are key components of management. Precipitous drops in blood pressure should be avoided. Often, hypertension is associated with renal artery stenosis. Revascularization is considered in cases of renovascular hypertension, cerebral hypoperfusion, limb claudication, and for repair of aneurysms. Valve surgery is appropriate when indicated for aortic regurgitation. High failure rates, restenosis, and operative complications are common after both open surgical as well as endovascular treatment [20]. Risk for restenosis is associated with traditional cardiovascular risk factors, steroid dose, and active disease. Revascularization should be deferred until acute inflammation is medically controlled. Anastomosis/bypass to frequently involved locations should be avoided.

Pregnancy-related concerns

As Takayasu arteritis predominantly affects women of childbearing age, pregnancy brings forth additional concerns regarding disease flare, maternal and fetal

complications, and peripartum medical management, primarily related to immunosuppression and antihypertensive therapy. Pregnant patients with Takayasu arteritis are considered at high risk for maternal and fetal complications. During pregnancy, duplex ultrasound is the preferred modality for disease surveillance due to safety reasons. Hypertension is the most common presentation of this condition during pregnancy [21]. In a retrospective French study of 240 pregnancies in 96 women with Takayasu arteritis (142 pregnancies before the diagnosis of Takayasu arteritis and 98 during or after the diagnosis), the risk for obstetric complications increased 13-fold following the diagnosis of Takayasu arteritis [22]. Obstetric complications were more frequent during second and third trimesters of the pregnancy. Active disease and smoking were independent predictors of poor pregnancy outcomes. Age at pregnancy and ethnicity were not associated with higher risk for obstetric complications. Almost one fourth of the pregnancies were complicated by gestational hypertension, preeclampsia, and eclampsia. Among those with new onset of this disease during pregnancy, disease was active in 40% and more than 5% of the pregnant women developed a life-threatening maternal complication related to arteritis (stroke or transient ischemic attack, end-stage renal disease, worsening aortic aneurysm). In a Brazilian study of 89 patients (118 pregnancies before the diagnosis of Takayasu arteritis and 38 after the diagnosis) and 89 healthy controls, maternal and fetal complications were higher in patients even before diagnosis compared to healthy controls and fetal complications included risk for low birth weight, prematurity, infection, and perinatal death [23]. Another small study found that maternal and fetal complications were higher in patients with renovascular involvement without intervention and early intervention prior to conception reduced these complications [24]. These studies highlight the importance of controlling disease and hypertension before conception and during the peripartum period.

Fibromuscular dysplasia

Epidemiology, etiology, and histopathology

FMD is a non-atheromatous and non-inflammatory disease of the arterial walls, more prevalent in women than men. Based on the US Registry for Fibromuscular Dysplasia (US Registry), FMD affects middle aged, white individuals, of whom as many as 91% are women [25•]. Features of FMD range from arterial stenosis, dissection, aneurysm, tortuosity, and redundancy.

There are three different histopathologic types of FMD, largely determined by which layer of the arterial wall is the most affected: intimal, medial, and adventitial [26]. Medial FMD is by far the most common FMD type, described in more than 90% of the FMD cases. Medial fibroplasia, perimedial fibroplasia, and medial hyperplasia are the different subtypes of medial FMD, with medial fibroplasia being the most frequently occurring variant. In medial fibroplasia, the degeneration of the arterial wall along with the generation of fibromuscular ridges results in multiple alternating areas of arterial stenosis and dilatation, giving rise to the classic "string of beads" radiographic finding. In clinical practice, FMD is classified into multifocal and focal disease groups based on its radiographic features [27]. Multifocal FMD has the typical "string-of-beads" radiographic feature that correlates with the medial fibroplasia histopathologic subtype. Focal FMD is characterized by a single focal or tubular narrowing on

radiologic studies, the histologic substrates being intimal FMD, medial hyperplasia, or adventitial FMD. In a retrospective cross-sectional study of 337 patients with established renal artery FMD, unifocal FMD patients were younger at FMD diagnosis, had earlier onset of hypertension and higher rates of revascularization procedures, and improved post revascularization cure rates than those with multifocal FMD, but multifocal FMD patients were more likely to be women (female to male ratio, 5:1 versus 2:1) [28].

Genetic, developmental, and environmental factors have been hypothesized as etiologies. Specifically, autosomal dominant inheritance pattern with variable penetrance, elevated TGF-β signaling, and persistent embryonic cushions have been posited to play a role; however, a complete understanding of the etiology of FMD remains elusive [29–37]. The association between sex hormones and FMD has been investigated, but there is little evidence to support the role of oral contraceptive use or multiparity in the etiology of FMD [34].

Though the actual prevalence of FMD is not known, it is estimated to affect the renal arteries in 2.0–6.6% of the potential renal donors and the cervical artery in 0.3–3.2% of the patients undergoing angiography [38–46]. In the first US FMD registry of 447 patients, one third of patients had two or more arterial beds involved, and the frequency of cerebrovascular FMD (74.3%) was similar to that of renal FMD (79.7%) [25•]. In patients with renal FMD, 64.8% also had extracranial carotid or vertebral involvement, and conversely, in those with extracranial carotid or vertebral FMD, 64.5% had renal involvement.

Clinical presentation

Clinical manifestations of FMD range from absence of symptoms (incidental finding on imaging) to symptoms which depend on the location and severity of the arterial lesions. Clinical manifestations of FMD also differ by sex [25•]. Arterial dissection and aneurysm occur commonly; each being present in one out of every five FMD patients [47, 48]. Interestingly, though men are less likely to have FMD, men with FMD have higher prevalence of arterial dissections compared to women [48, 49]. Extracranial internal carotid artery followed by renal and vertebral arteries are the most frequent arterial beds that develop dissection in FMD patients. Conversely, FMD-related aneurysms occur most commonly in renal arteries and then in the extracranial carotid arteries.

Though cerebrovascular FMD can potentially affect any intracranial or extracranial artery, it mostly involves the middle and distal portions of the internal carotid and vertebral arteries. Symptoms of cerebrovascular FMD are often nonspecific and include pulsatile or non-pulsatile tinnitus, dizziness, neck pain, and cervical bruit; migraine headaches are the most frequent symptom. Less commonly, severe headache or neck pain, cranial nerve abnormalities such as Horner syndrome, transient ischemic attack (TIA), subarachnoid hemorrhage, and stroke may occur. While the most common presenting symptom of renal FMD is hypertension, other symptoms and signs include abdominal bruit (epigastric or flank), flank pain, and, rarely, renal insufficiency. In the US Registry study, women with FMD were more likely than men to have extracranial carotid FMD and experience pulsatile tinnitus, neck pain, and cervical bruit and were less likely to have renal FMD, arterial aneurysm/dissection, and present with abdominal pain, renal insufficiency, and renal infarction [49]. Though FMD infrequently involves coronary, mesenteric, and extremity arterial beds and rarely presents

with acute coronary syndrome, at least half of the patients presenting with spontaneous coronary artery dissection have non-coronary FMD [25•, 50–54].

Diagnosis

When the clinical presentation is suspicious for FMD, selective focused non-invasive imaging studies, namely, duplex ultrasound, CTA, or MRA as appropriate, should be obtained. Characteristic features of FMD on duplex ultrasound imaging are elevated velocities in the mid to distal artery with evidence of turbulence on color Doppler. Beading and/or tortuosity may be evident on color power angiography. In patients with high clinical suspicion for FMD and inconclusive non-invasive studies, the gold standard, selective catheter-based angiography, is performed for a definitive diagnosis. The classic string of beads appearance, focal stenosis, arterial aneurysm, and dissection are the angiographic features of FMD. Hemodynamic severity is determined by pressure gradient measurements across the lesion. Intravascular ultrasound is a useful tool for visualizing intravascular webs. Other arteriopathies that can mimic FMD should be thoroughly excluded. Screening for intracranial aneurysms using a non-invasive imaging modality (CTA/MRA) is recommended after FMD is diagnosed. FMD-related aneurysms are monitored using duplex ultrasound, CTA, or MRA.

Management

There are no firm recommendations regarding activity limitations among patients with FMD; however, most patients are advised to continue moderate aerobic exercise and avoid activities that could precipitate arterial dissection or aneurysmal hemorrhage. As such, heavy lifting, contact sports, intense competitive exercise programs, and rapid manipulations of the neck should be avoided in patients with cerebrovascular FMD or a previous history of carotid or vertebral dissection.

Given its potential to involve arterial beds in multiple organ systems, a multidisciplinary approach is crucial in managing FMD patients. Medical therapy, imaging surveillance, counseling, and revascularization when appropriate are the major components of FMD management.

Pharmacotherapy for FMD consists of risk factor control, antihypertensive therapy, and antithrombotic therapy. There is no data showing that statin therapy is directly effective in preventing FMD or its progression. Smoking cessation is generally recommended due to the association of cigarette smoking with adverse outcomes in FMD [55]. In particular, smokers with FMD have higher rates of claudication, aneurysm, and interventional therapy. Additionally, FMD patients should have optimal control of atherosclerotic risk factors [56–58]. As FMD-related hypertension is primarily the renin-angiotensin-aldosterone system mediated, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in controlling it. However, there is little evidence to support that these agents prevent the progression of renal artery lesions [59, 60]. ACE inhibitors and ARBs are the first-line drugs for treating FMD-related hypertension [25, 27]. In FMD patients with an ischemic event, cerebrovascular FMD or FMD in other vascular beds and without contraindications, antiplatelet therapy with aspirin 75 to 325 mg daily, is used to prevent thromboembolic events [27].

Revascularization by endovascular or open surgical means should be considered in a FMD patient in the appropriate clinical setting. Indications for renal artery revascularization in FMD are resistant hypertension, for curing new onset hypertension, renal artery aneurysm, branch renal artery disease in a hypertensive patient, for preserving renal function in perimedial or intimal fibroplasia in a pediatric patient, and, rarely, renal artery dissection [27]. Following renal revascularization, patients are monitored using serial renal artery duplex ultrasound imaging. Revascularization is appropriate in a carotid FMD patient if there are recurrent cerebral ischemic events even after optimal medical therapy, if antithrombotic agents are contraindicated, if there is retinal or hemispheric cerebral ischemic events and ipsilateral carotid artery FMD, and in cases of symptomatic or progressive FMD-related pseudoaneurysm of the carotid or vertebral artery [61].

Spontaneous arterial dissection

Spontaneous arterial dissection is the non-traumatic splitting of the layers of the arterial wall due to a tear resulting in luminal narrowing and/or aneurysmal dilatation. Any artery in the body can undergo spontaneous dissection, the foremost location being the extracranial segments of the carotid and vertebral arteries. It is often missed as a diagnosis despite the potential for catastrophic outcomes. Herein, we review the salient features of spontaneous cervicocephalic and coronary arterial dissection.

Cervicocephalic arterial dissection

Though cervicocephalic arterial dissection (extracranial internal carotid or vertebral artery) is a less common cause of stroke in the general population (< 5% cases), it is an important cause of stroke among young individuals (10–25%) [62–66]. Though, the true incidence and etiology of spontaneous dissection are not clear. The annual incidence rates are 2.5 to 3 per 100,000 individuals in the USA and France, and connective tissue disorders, FMD, infection, vasculitis, and physical activities/neck manipulation have been associated with cervical artery dissections [67–81]. It affects all age groups worldwide with the highest incidence in the fifth decade of life. Even though both sexes are affected, women are 5 years younger than men at the time of diagnosis [82]. The cervical segment of the internal carotid artery is the most frequently involved location. Clinical manifestations vary from headache, pulsatile tinnitus, facial or neck pain, cranial nerve abnormalities including Horner syndrome, transient ischemic attack, and stroke. Headache, primarily ipsilateral, is the most frequent manifestation. Cervical MRA and CTA are valuable modalities for diagnosing this condition. Duplex ultrasound of the carotid arteries may be useful in detecting cervical internal carotid artery dissection; however, distal dissections may be missed using this modality. The gold standard for establishing a diagnosis is conventional angiography. The angiographic findings specific for dissection include the string sign, visualization of a double lumen, or internal flaps. In cases where there is no significant luminal compromise, as in subadventitial dissections, conventional angiography may be falsely negative and a cervical MRA has greater diagnostic accuracy. In cases of very early acute ischemic stroke due to extracranial cervical artery dissection, contemporary guideline-based stroke care should be employed [83].

Historically, antithrombotic therapy with either antiplatelet drugs or anticoagulation with heparin or low molecular weight heparin followed by oral anticoagulation with warfarin for 3 to 6 months and eventually transition to antiplatelet therapy was the treatment strategy for patients with cervical artery dissection and ischemic stroke or TIA. In a phase 2 feasibility trial of 250 patients with symptomatic extracranial carotid and vertebral dissection (stroke or TIA) within the past 7 days randomized to antiplatelet drugs or anticoagulant drugs for 3 months, antiplatelet agents and anticoagulants were equally efficacious in preventing stroke recurrence and death though the incidence of stroke was low [84]. There are concerns regarding the possibility of extension of dissection after thrombolysis. If there is intracranial dissection, the risk of subarachnoid hemorrhage with thrombolysis or anticoagulation exists and a decision for or against these measures should be made only after thorough consideration of the individual case scenario and discussions with the patient/family. In acute ischemic stroke due to cervical artery dissection, emergent endovascular revascularization of the extracranial carotid or vertebral arteries may be considered, but randomized trial data are lacking [83]. In cases of non-ischemic cervical artery dissection, antiplatelet therapy alone is preferred. Repeat vascular imaging in 1 month, and then 3 to 6 months, could be considered, and antithrombotic therapy should be customized depending on whether there are symptoms or residual abnormalities on vascular imaging.

Spontaneous coronary artery dissection

Clinical presentations include chest pain, troponin positive acute coronary syndrome, congestive heart failure, cardiogenic shock, ventricular arrhythmia, and, rarely, sudden cardiac arrest/death. Spontaneous coronary artery dissection (SCAD) primarily affects women, with a mean age of 52 years. The prevalence of SCAD is estimated to be 0.3% among stable patients presenting for routine coronary angiography, 8.7% among women younger than 50 years of age presenting with acute coronary syndrome, and even as high as 24% in women with myocardial infarction on thorough angiographic review [85–87]. The etiology is unknown, but associations have been described between SCAD and FMD, pregnancy, multiparty, connective tissue disorders, hormonal therapy, autoimmune diseases, and coronary artery spasm. A recent study reported that 72% spontaneous coronary artery dissection patients had FMD [88•]. SCAD can be precipitated by intense exercise (usually isometric), severe emotional stress, and intense Valsalva-type straining including labor. Female sex, pregnancy or postpartum state, and delay in treatment are associated with worse outcomes and recurrence is common [54, 88•]. Pregnancy-related SCAD is rare; however, dissections related to pregnancy tend to involve multiple vessels, proximal coronary arteries, and result in left ventricular dysfunction more often than those occurring outside the context of pregnancy [89, 90].

As conventional coronary angiography has limited ability to detect intimal tears, intracoronary imaging with intravascular ultrasound (IVUS), or optical coherence tomography (OCT), may be required. The classification of angiographic findings in SCAD has been recently proposed [88•]. Type I angiographic SCAD demonstrates contrast staining in the arterial wall and long diffuse stenosis without evidence of atherosclerosis. Angiographic findings include long diffuse stenosis in type 2 SCAD and those mimicking atherosclerosis in type 3

SCAD. Long diffuse stenosis is the foremost angiographic finding [52]. Dissections often heal spontaneously in the majority patients at or after a month [88•].

As there is no evidence evaluating the efficacy and safety of routine acute coronary syndrome management strategy in these patients, treatment decisions are empiric and largely based on practice-based consensus. As such, patients are treated with dual antiplatelet therapy for variable periods of time, depending on the presence of coronary stents and anatomic considerations. Anticoagulation and thrombolysis are typically avoided after this diagnosis is confirmed, though the use of anticoagulation is debatable. The role of newer antiplatelet agents and GpIIb/IIIa inhibitors is unclear. Short-term nitrate for treating vasospasm and long-term beta blockers may be beneficial. The majority of the patients are managed conservatively. Percutaneous coronary intervention is challenging and associated with high failure rates and should be reserved for patients who have refractory angina/ischemia, ST segment elevation, and hemodynamic instability. Emergency coronary artery bypass grafting surgery may be necessary; the dissection involves left main coronary artery or involves multiple proximal vessels [91].

Raynaud's phenomenon

Raynaud's phenomenon (RP) is a cold- or stress-induced reversible spasm of peripheral arterioles, typically involving distal digits, nose, and ears [92]. RP has a triphasic presentation, phase 1 characterized by pallor due to cutaneous vasoconstriction of arterial inflow and arteriovenous anastomoses, phase 2 by cyanosis resulting from venous pooling, and phase 3 by erythema and throbbing pain due to reactive hyperemia.

RP is classified into primary RP when there is no underlying disease and secondary RP in the presence of underlying disease such as autoimmune diseases. Primary RP affects a younger population, has a slight female preponderance, may have a genetic susceptibility, often spares the thumb, and has normal nailfold capillaries [93–96]. Though RP is a clinical diagnosis, capillaroscopy is a helpful tool in distinguishing primary versus secondary RP. Nail folds with tortuous or enlarged capillary loops, hemorrhages, and capillary loss are abnormal findings. Progression to a connective tissue disease, particularly, scleroderma, is more likely if the age of onset is close to 40 years, the episodes are severe and frequent, and abnormal nailfold capillaries are present. Critical tissue ischemia and ulcerations are common in secondary RP. Patients with secondary RP should be investigated thoroughly to identify and treat the underlying disease.

Therapy for RP involves preventing vasoconstriction, promoting vasodilatation, reducing inflammation, and addressing the risk of thrombosis. Avoiding the trigger such as cold exposure is the single most important measure to preventing an episode of RP as well as resolving an ongoing episode. Local and systemic warming measures such as layered clothing, gloves, and placing affected areas in warm water are helpful measures. Other aggravating factors such as smoking, sympathomimetic agents, migraine therapeutics, and attention deficit hyperkinetic disorder drugs should also be avoided. If RP episodes do not respond to non-pharmacologic measures, vasodilator drug therapy with long-acting dihydropyridine calcium-channel blockers alone or in combination with phosphodiesterase type 5 inhibitor or a topical nitrate is the current practice [92]. Selective serotonin reuptake inhibitors, angiotensin II receptor

blockers, prazosin, pentoxifylline, cilostazol, and *N*-acetylcysteine are additional drugs used for treating RP. If the patient has critical digit ischemia that is refractory to aggressive medical therapy, digital sympathectomy needs to be considered. In patients with secondary RP, antiplatelet therapy is often used to prevent thrombosis and antiinflammatory or immunosuppressants are used in controlling the underlying autoimmune condition.

Chilblains

Chilblains or pernio is a cold-induced cutaneous lesion. Chilblains lesions are painful, erythematous or purplish, macular, or papular lesions associated with swelling, blistering, ulceration, erosion, and itching, usually involving hands, feet, buttocks, thighs, nose, and ears symmetrically. It is thought to be caused by persistent cutaneous vasoconstriction resulting in tissue injury. It can be primary or secondary to an underlying connective tissue disease, hematologic process, or drugs [97]. Evaluation for an underlying systemic disease is important when the lesions are persistent or atypical in appearance. Vasculitis, emboli, cutaneous or hematologic malignancies, and connective tissue diseases including systemic lupus erythematosus must be excluded. Though the exact etiology is not known, familial cases and female predisposition exist [98, 99].

Diagnosis is often made on the basis of clinical features. Tissue biopsy is considered when the lesions are refractory to routine treatment for chilblains or when the diagnosis is not certain. Histopathologic findings include predominantly T cell perivascular infiltrates extending throughout the dermis with a perieccrine distribution, edematous vessel wall and papillary dermis, and necrotic keratinocytes in the epidermis [100]. Chilblains secondary to systemic lupus erythematosus are characterized by the absence of dermal edema and vacuolation of basal layer cells.

Treatment for chilblains includes cold avoidance, warming of the affected areas, and oral vasodilator therapy using calcium channel blockers. Secondary chilblains may require antiinflammatory agents or immunosuppressive therapy.

Summary

Takayasu arteritis, FMD, spontaneous cervicocephalic, and coronary artery dissections are infrequent vascular conditions that are often underdiagnosed in clinical practice and have increased prevalence in women. Prompt diagnosis, increased familiarity with the angiographic patterns, and multidisciplinary approach are critical for optimizing the outcomes in these patients. Arterial dissection should be excluded in young females presenting with acute cardiac or neurologic events and little atherosclerosis. These patients are at risk for adverse outcomes during and after pregnancy and require additional counseling and high-risk obstetrical care.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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