Part II: Cutaneous manifestations of peripheral vascular disease

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Learning objectives

After completing this learning activity, participants should be able to discuss the overlap of cutaneous and vascular disease; review cutaneous manifestations of common vascular disorders, including chronic venous insufficiency, peripheral artery disease, superficial and deep vein thrombosis, lymphedema, acrocyanosis, pernio, livedo reticularis and livedo racemosa, erythromelalgia, and Raynaud's; and identify how to diagnose underlying peripheral vascular disorders to expedite early intervention.

Disclosures

Editors

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In this Part 2 of a 2-part continuing medical education series, we review the epidemiology of peripheral vascular disease, its association with cutaneous symptoms, and the diagnosis and evaluation of cutaneous features of vascular disorders. As peripheral vascular disease becomes more prevalent globally, it is essential for dermatologists to become competent at accurately recognizing and diagnosing cutaneous manifestations and directing individuals to receive appropriate care and treatment. (J Am Acad Dermatol 2023;89:211-26.)

Key words: acrocyanosis; chronic venous disease; chronic venous insufficiency; deep vein thrombosis; erythromelalgia; livedo racemosa; livedo reticularis; lymphedema; peripheral artery disease; peripheral vascular disease; pernio; Raynaud's; Raynaud's disease; Raynaud's phenomenon; superficial vein thrombosis; vascular disease.

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Abbreviations used:

ABI: ankle-brachial index
CVD: chronic venous disease
CVI: chronic venous insufficiency
DVT: deep vein thrombosis
EM: erythromelalgia
LR: livedo reticularis
LRC: livedo racemosa
PAD: peripheral artery disease
VTE: venous thromboembolism

INTRODUCTION

Key points

- Peripheral vascular disease involves arteries, veins, and capillaries.
- Vasculopathy is characterized by intravascular thrombosis, and vasculitis refers to inflammation directed toward vessel walls.
- Beyond the standard metrics for diagnosing peripheral vascular disease, cutaneous manifestations can facilitate early diagnosis by dermatologists.

Peripheral vascular disease is a set of conditions affecting blood vessels, including arteries, veins, and capillaries. The growing burden of peripheral vascular disease, which includes peripheral artery disease (PAD), coincides with the rise in risk factors such as aging, obesity, and hypercholesterolemia.[1] Vascular disease (Table I)[2-10] can be largely categorized into vasculitis, in which arteries are associated with endothelial cell dysfunction and inflammatory activation, and vasculopathy, in which clot formation restricts blood flow to organs.[11] Common cutaneous manifestations of peripheral vascular disease are listed (Table II).[12-15] Beyond utilizing the standard metrics for diagnosing peripheral vascular disease, a focused physical examination can facilitate early diagnosis by dermatologists (Table III).[16-20] This review will provide an overview of the cutaneous manifestations of peripheral vascular disorders with an emphasis on evaluation and diagnosis in clinical practice.

DISORDERS OF THE VEINS

Chronic venous disease

Key points

- Chronic venous insufficiency (CVI) is an advanced manifestation of chronic venous disease (CVD).
- The Clinical-Etiologic-Anatomic-Pathophysiologic classification scheme delineates the clinical presentations associated with CVI/CVD.
- A physical examination should assess for the presence of dilated veins, edema, and other advanced cutaneous signs.

Overview and etiology. CVD of the lower extremities is characterized by abnormalities in the venous system, leading to reflux and/or obstruction of blood flow.[27] CVI is an advanced manifestation of CVD.[24] The etiology of CVD can be idiopathic, secondary, or congenital.[27] Secondary causes include trauma, prolonged standing, hormonal changes, and venous thrombosis.[25]

Pathogenesis and clinical features. Persistent venous hypertension contributes to the release of inflammatory mediators that trigger endothelial cell dysfunction and increased wall permeability. This leads to venous wall dilation and insufficiency, resulting in symptoms like lower extremity pain, pitting-dependent edema, cramps, and limb heaviness.[24] The Clinical-Etiologic-Anatomic-Pathophysiologic classification scheme describes the clinical presentations of CVI/CVD (Table IV).[24] In stages C_1 and C_2, patients present with telangiectatic, reticular, and/or varicose veins (Table II). The presence of pitting edema in C_3 is often the first sign of CVI in the distal gaiter and medial malleolar region. In advanced stages, nonpitting edema can extend up the calf or down the foot. The C_4 stage may include stasis dermatitis and hemosiderin-related hyperpigmentation, a manifestation of red blood cell migration into the tissue and subsequent degradation (Figs 1, *A* and *B*, and 2).[26] Lipodermatosclerosis, an area of indurated inflammatory tissue connecting the skin to the subcutaneous tissue, results from transforming growth factor $\beta 1$ release that facilitates collagen and fibrosis production (Fig 3).[28] The lack of capillaries in these scars is associated with atrophie blanche (Fig 4, *A* and *B*). The most advanced stages (C_5 and C_6) are associated with venous ulceration that can be complicated by slow wound healing (Table II).[23] These ulcers are irregularly shaped with a shallow and friable base.[22]

Diagnosis and evaluation. History of hypercoagulable conditions and deep vein thrombosis (DVT) as well as oral contraceptive use and occupation must be ascertained. Physical examination of the lower extremities should assess for associated cutaneous findings. Venous duplex ultrasonography with reflux assessment can help identify regions of affected anatomy as well as determine whether sclerotherapy or surgical intervention would be helpful. An ankle-brachial index (ABI) measurement should be performed to exclude coexisting arterial pathology.[24,25]

Table I. Vasculopathy versus vasculitis

Terminology	Definition/etiology	Types	Diagnosis
Vasculopathy	• Intravascular thrombosis • May be associated with other inflammatory conditions[2]	• Pauci-inflammatory (eg DIC,[3] WISN,[4] and HIT[5]) • Inflammatory (arthropod bite[6] and calciphylaxis[7])	• Cutaneous biopsy • Laboratory values ○ ANCAs ○ Cardiolipin antibodies ○ Coagulation panel ○ Complement levels ○ Cryoglobulins ○ Cryofibrinogen ○ D-dimer ○ Direct immunofluorescence[8] ○ Heparin-PF4 ○ RF ○ Lupus anticoagulant
Vasculitis	• Inflammation directed toward vessel wall • Results in endothelial damage, fibrinoid necrosis, and erythrocyte extravasation[9]	• Primary (small vessel, medium vessel, and large vessel disorders)[10] • Secondary (connective tissue disease, drugs, malignancy, infection, and serum sickness)	• Cutaneous biopsy • Laboratory values ○ ANCAs ○ Coagulation panel ○ Complement levels ○ Cryoglobulins ○ D-dimer ○ Direct immunofluorescence[8] ○ Heparin-PF4 ○ RF

ANCA, Antineutrophilic cytoplasmic autoantibody; *DIC*, disseminated intravascular coagulation; *HIT*, heparin-induced thrombotic thrombocytopenia; *Heparin-PF4*, Heparin-platelet factor 4; *RF*, rheumatoid factor; *WISN*, warfarin-induced skin necrosis.

DVT and superficial vein thrombosis/ thrombophlebitis

Key points

- Venous thromboembolism (VTE) refers to the formation of thrombi within the deep venous system; subcategories include DVT and superficial vein thrombosis.
- Physical examination of patients with VTE may reveal pitting edema, tenderness, warmth, and skin discoloration.
- Diagnosis includes a Wells' Criteria score of ≥2 and follow-up imaging.

Overview and etiology. Because coagulation disorders are an extensive topic with details beyond the scope of this CME, this section will focus on VTE and superficial vein thrombosis.[29] VTE refers to the formation of thrombi within the vascular system and includes both DVT and pulmonary emboli.[30] Superficial vein thrombosis is characterized by thrombosis and thrombophlebitis, an inflammatory reaction around a thrombosed superficial vein. VTE can be primary or secondary to surgery, oral contraceptive use, trauma, immobility, obesity, or cancer.[30]

Pathogenesis and clinical features. Virchow's triad, which includes venous stasis, vascular injury, and hypercoagulability, is the pathophysiological mechanism behind thrombus formation.[30] Endothelial damage results in edema and leukocyte activation, which predisposes patients to thrombosis. Patients with VTE can present with symptoms that evolve acutely or chronically. Fifty percent of patients with VTE present with pain at the site of the thrombus and 70% present with swelling of the symptomatic extremity; other symptoms include warmth and redness.[30] Physical examination may reveal unilateral or bilateral pitting edema, tenderness, warmth, and discoloration ranging from reddish-purple to cyanotic/white secondary to venous engorgement and obstruction (Fig 5). Additionally, a palpable and tender cord and superficial nonvaricose venous dilation may be observed.[30,31]

Diagnosis and evaluation. It is important to obtain a comprehensive patient history and screen for underlying diseases such as malignancy or vasculitis. Wells' Criteria quantifies the clinical probability of having a DVT using clinical findings and risk factors, such as active cancer, recent surgery, or

Table II. Common cutaneous symptoms associated with peripheral vascular disease

Cutaneous symptom	Definition/etiology	Types	Clinical presentation
Edema[12]	• Observable swelling from extravascular fluid accumulation in body tissues	• Pitting (holds an indentation for a few seconds after digital pressure) • Nonpitting (springs back into place after applying pressure)	• Soft • Easily compressible upon palpation
Dilated veins	• Small, dilated blood vessels that can occur near the surface of the skin or mucous membranes • Associated with chronic venous disease	• Telangiectasia • Reticular • Varicose	• Colors vary (telangiectasia: pink, red, bluish purple; reticular: blue or green; varicose: purple and blue) • Sizes vary (telangiectasia: <1 mm; reticular: 1-3 mm; varicose: ≥3 mm in diameter) • Telangiectasia and reticular appear flat, varicosities protrude above skin
Corona phlebectatica ("ankle flare" sign)[21]	• Cutaneous sign of chronic venous insufficiency	N/A	• Fan shaped confluence of blue telangiectasias • Most commonly along inferior portion of the medial malleolus but can also be found on lateral malleolus
Cyanosis[13]	• Bluish discoloration of the skin • Results from poor circulation or inadequate oxygenation of the blood	• Central (around the core, lips, and tongue) • Peripheral (only the extremities or fingers)	• Bluish cast to the skin and mucous membranes
Ulcers[22]	• Breakdown of overlying skin • Secondary to compromised blood flow • May be complicated by secondary infection	• Venous • Arterial (or ischemic)	• Venous (uneven, irregular appearance; large and deep; often found over bony prominences; exudative; painful) • Arterial ("punched out" appearance, surrounding redness or shininess; painful)
Gangrene[22]	• Tissue necrosis due to lack of blood supply and other nutrients • May not be associated with infection	• Dry • Wet	• Dry (flaking skin with hard texture that changes color from brown to purplish-blue to black and has obvious demarcation between viable and necrotic tissue) • Wet (moist foul-smelling, blisters and swells, pus may be present if associated with infection)
Overlying skin changes[14]	• Sign of long-standing compromised blood flow to extremities	N/A	• Cool to the touch • Lacks normal amounts of hair • Brittle, shiny • May be accompanied by nail changes (opaque, brittle, hypertrophic)

Hemosiderin pigmentation[21,23]	• Pigmentation caused by deposits of hemosiderin (a protein compound that stores iron in tissue) under the skin	N/A	• Appears stippled and red early, but fades to brown and becomes confluent over time
Lipodermatosclerosis (Fig 3)[21,23]	• Progressive fibrotic process of the dermis and subcutaneous fat	N/A	• Pain • Hardening of skin • Change in skin color (redness) • Swelling • Narrowing at the ankles and induration ("inverted champagne bottle" or "inverted bowling pin" shape[21])
Stasis dermatitis[24-26] (Fig 2)	• Common form of eczema/dermatitis that affects one or both lower legs • Often associated with chronic venous insufficiency	N/A	• Itchy, erythematous blistered and crusted plaques; or dry fissured and scaly plaques on one or both lower legs • Can form discrete patches or become confluent and circumferential • May have surrounding hyperpigmentation often found in the medial gaiter • May be associated with atrophie blanche (ivory-colored, smooth, avascular, stellate-shaped plaques)[21] (Fig 4, *A-B*)
Acroangiodermatitis (pseudo-Kaposi sarcoma)[15]	• Reactive angiodysplasia of cutaneous blood vessels • Often seen in association with venous insufficiency or with certain vascular anomalies	N/A	• Violaceous macules, indurated plaques or nodules, usually bilaterally on the extensor surfaces of lower extremities

N/A, Not applicable.

Table III. Metrics used in diagnosing peripheral vascular disease

Metric	Definition	Diagnosis	Range of values	Applications to peripheral vascular disease
Ankle-brachial index[16]	• Ratio of systolic blood pressure at arteries in the ankle (dorsal pedis and posterior tibial) to the systolic blood pressure in the artery of the upper arm (brachial)	• While patient is supine, blood pressure cuff is inflated proximal to the artery • Inflation continues until the pulse ceases as measured by Doppler ultrasound • Cuff is then slowly deflated and when the pulse is redetected, the pressure in the cuff indicates the systolic pressure	• 0.9-1.4 (normal) • <0.9 (narrowing of vessels) • >1.4 (poorly compressible vessels)	• Peripheral artery disease
Duplex ultrasound[17]	• Noninvasive evaluation of speed and direction of blood flow through vessels using 2 types of ultrasound (traditional and Doppler)	• While patient is supine, transducer is moved gently over area	N/A	• Peripheral artery disease • Superficial or deep vein thrombosis • Varicose veins • Chronic venous insufficiency
Capillary refill time[18]	• Time required for color to return to distal capillary bed after pressure has been applied to cause blanching	• Pressure is applied to the nail bed until it turns white • Once blanched, pressure is removed • Clinician measures the time it takes for nail to turn pink as patient holds hand above heart	• 1-2 s (normal) • >2 s (poor perfusion or peripheral vasoconstriction)	• Peripheral artery disease
Nuclear lymphoscintigraphy[19]	• Special type of nuclear medicine imaging that provides images of the lymphatic system and is used to identify areas of blockage	• Radiotracer is injected, swallowed, or inhaled as a gas • Radiotracer accumulates in an area under examination • A special camera or imaging device detects radioactive emissions from the radiotracer	N/A	• Lymphedema
Transcutaneous oximetry ($TcPO_2$)[20]	• Noninvasive method to quantify oxygen level of tissue beneath the skin and assess microcirculation (regional perfusion)	• Small sensors are placed around wound that measure oxygen levels • Can be done in regular room or hyperbaric chamber (100% oxygen) while patient is laying flat	• <40 mmHg (impaired wound healing)	• Peripheral artery disease

N/A, Not applicable.

Table IV. CEAP classification of chronic venous disease[25]

Clinical classification (C)	Etiologic classification (E)	Anatomic classification (A)	Pathophysiologic classification (P)
C_0 (no visible sign of venous disease)	E_c (congenital)	A_s (superficial)	P_r (reflux)
C_1 (presence of reticular or telangiectatic veins)	E_p (primary)	A_d (deep)	P_o (obstruction, thrombosis)
C_2 (obvious varicose veins)	E_s (secondary)	A_p (perforator)	$P_{r,o}$ (reflux and obstruction)
C_3 (presence of edema but no skin changes)	E_n (no venous cause identified)	A_n (no venous location identified)	P_n (no venous pathophysiology identified)
C_{4a} (changes in skin and subcutaneous tissue—hyperpigmentation and/or eczema)			
C_{4b} (changes in skin and subcutaneous tissue—lipodermatosclerosis and/or atrophie blanche)			
C_5 (healed ulceration)			
C_6 (active ulceration)			

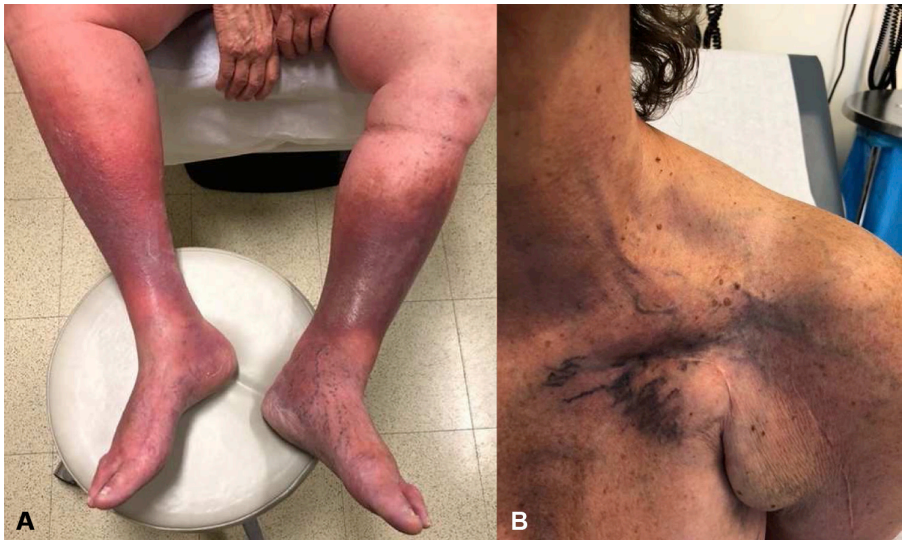

Fig 1. Skin changes secondary to long-term venous stasis. **A,** Hyperpigmentation with leg edema. **B,** Pacemaker-induced venous stasis at thoracic outlet with collaterals present. Original photo.

immobilization. A low score of ≤2 and a negative D-dimer excludes the need for compression ultrasonography to rule out DVT.[30] High suspicion for DVT necessitates imaging irrespective of the score.

DISORDERS OF THE ARTERIES

PAD

Key points

- PAD is characterized by atherosclerosis of lower extremity arteries.
- Cutaneous manifestations include overlying skin changes, dependent rubor, ischemic ulcers, and gangrene.
- Clinicians should assess for skin changes and decreased or absent pulses. An ABI value is used to confirm the diagnosis.

Overview and etiology. PAD refers to the abnormal narrowing and blockage of the peripheral arteries.[32] Most commonly secondary to atherosclerosis of vessels supplying to the lower extremities, PAD affects 8.5 million individuals in the United States and is associated with smoking, dyslipidemia, and an age of ≥ 65 years.[33,34]

Pathogenesis and clinical features. Patients with PAD can present with no symptoms (~50%),

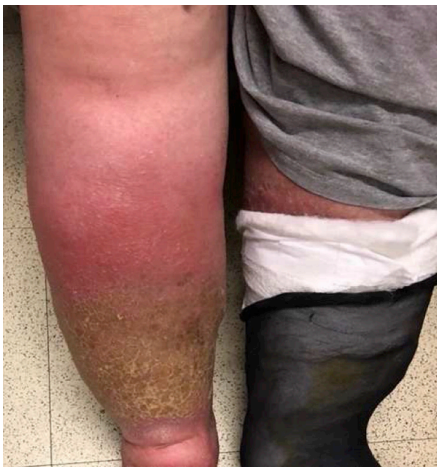

Fig 2. Eczematous stasis dermatitis. Well-demarcated, erythematous, pruritic, and crusted plaques along the right calf. Original photo.

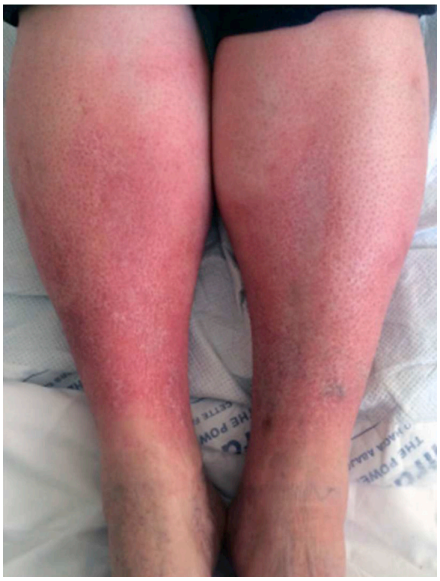

Fig 3. Chronic lipodermatosclerosis. Progressive fibrosis and atrophy of the dermal and subcutaneous layers of the extremities with a characteristic concave appearance ("inverted bowling pin" sign). Original photo.

intermittent claudication (approximately 10%-30%), and critical limb ischemia (~10%).[32] Intermittent claudication refers to pain with exercise that is relieved within 10 minutes of rest, whereas critical limb ischemia, the most advanced manifestation, is characterized by pain at rest, ulcers, and gangrene.[32,35] Secondary to reduced perfusion pressure, patients present with atrophic, dry, cool, and shiny skin with reduced hair growth; brittle, discolored, and opaque nails; and cyanotic toes with dependent rubor.[21] In chronic or progressive disease, ischemic ulcers can develop in distal areas, typically the toes, foot, and ankles. These ulcers are deep, pale, painful, and "punched out" and have a nongranulating base (Fig 6).[22] Without treatment, these can develop into wet or dry gangrene (Table II).

Diagnosis and evaluation. In addition to a physical examination, clinicians should assess for decreased or absent pulses distal to the stenotic segment, with or without the presence of bruits on auscultation. ABI is the gold standard for diagnosing PAD and monitoring treatment. An ABI value of ≤0.90 signifies reduced blood flow, which is suggestive of PAD.[34] For patients with PAD and nondistensible arteries, an ABI value of >1.4 is also suggestive of PAD because of calcification. Duplex ultrasonography, computed tomography angiography, and magnetic resonance angiography can help support the diagnosis by visualizing the anatomy and detecting the locations of stenoses.

OTHER DISORDERS

Lymphedema

For the purposes of this CME, an overview of lymphedema and its clinical staging are summarized in Tables V and VI[36] and Fig 7, *A* and *B*. Lymphedema has been reviewed in a previous CME article by Grada et al.[37]

Raynaud's

Key Points

- Raynaud's is characterized by pallor, cyanosis, and erythema in the digits.
- Severe attacks are more commonly associated with secondary Raynaud's.
- To diagnose Raynaud's, clinicians should screen for cold sensitivity and color changes.

Overview and etiology. Raynaud's phenomenon is characterized by transient vasospasm of arteries and arterioles in the digits and skin.[38] Raynaud's disease, or primary Raynaud's, has no associated etiology, is common and benign, and has an age of onset between 15 to 30 years.[39] Raynaud's phenomenon, or secondary Raynaud's, is associated with multiple etiologies, most commonly connective tissue disorders (ie, systemic sclerosis, scleroderma, antiphospholipid syndrome, systemic lupus erythematosus, and Sjögren syndrome).

Pathogenesis and clinical features. The mechanism underlying primary Raynaud's is increased blood vessel $\alpha 2$ adrenergic sensitivity, causing excess vasoconstrictive response to triggers.[38] Patients typically present with a classic

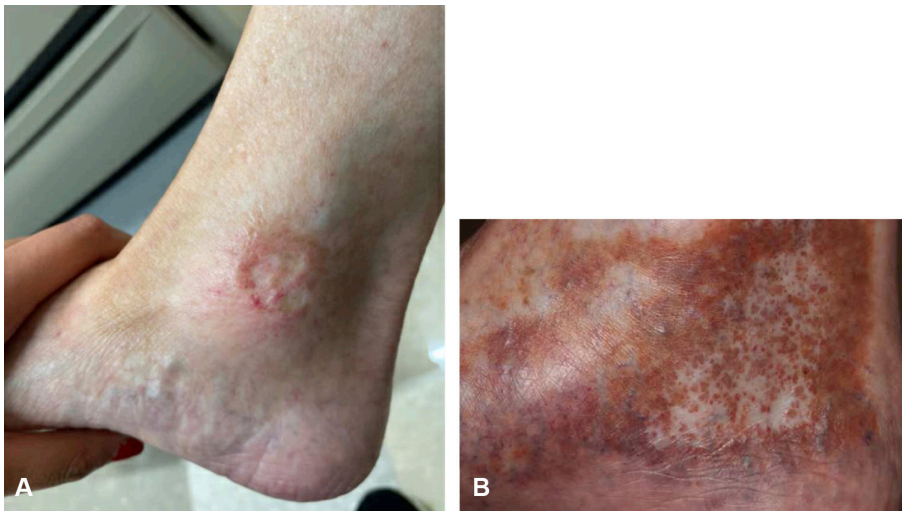

Fig 4. Classic representation of diffuse atrophie blanche scarring along the distal portion of the calf with associated white atrophic plaques and superimposed capillary stippling (C_{4b}). **A.** Original photo. **B,** Courtesy of Dr Dirk Elston.

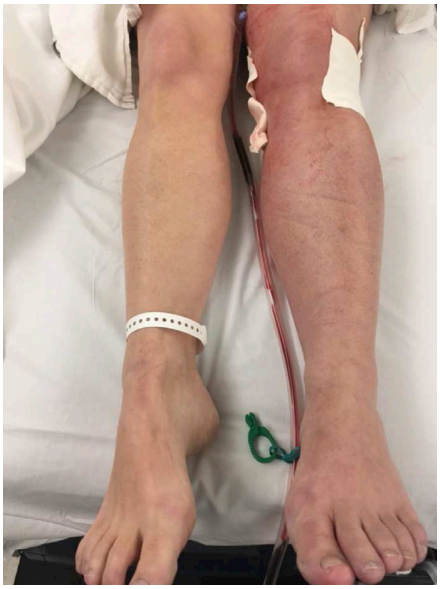

Fig 5. Deep vein thrombosis in right leg. Edematous and erythematous extremity with associated tenderness and warmth. Original photo.

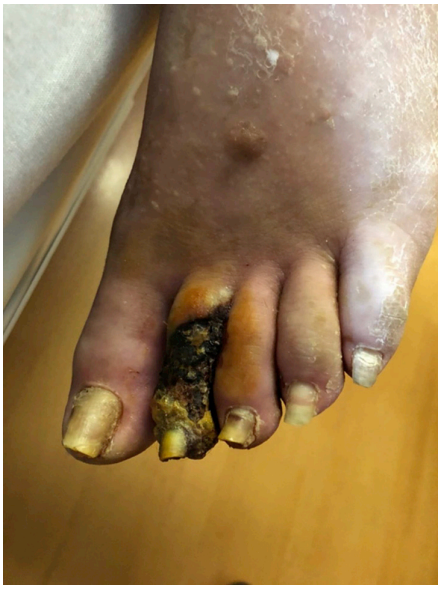

Fig 6. Necrotic toe in a patient with peripheral artery disease. Necrotic toe with dependent rubor of the toes and distal aspect of the foot. Original photo.

sequence of changes in skin color: pallor, cyanosis, and erythema[24] of the distal fingers. An episodic attack is abrupt in onset and lasts for minutes to hours. During the "white attack" or ischemic phase, the skin distal to the line of ischemia becomes cold and pale with well-demarcated blanching (Fig 8, *A*). During the "blue attack" or deoxygenation phase, the blanched digits become cyanotic (Fig 8, *B*). Finally, during reactive hyperemia or the reperfusion phase, digits become bright red.

The attack usually involves a single digit before spreading to other digits, sparing the thumb. Primary Raynaud's is symmetric and episodic, whereas the secondary form is asymmetric and more frequent.[39] Patients may report paresthesias, numbness, or pain. When the patient reports

Table V. Overview of lymphedema

Etiology	Clinical features	Diagnosis/evaluation
Accumulation of protein-rich fluid in tissues of the limbs, secondary to impaired drainage of lymphatic system[36] Primary etiologies (abnormal development of lymphatic system) • Congenital • Milroy disease • Lymphedema praecox (80% of primary cases)[36] • Lymphedema tarda Secondary etiologies (due to injury of normally developed lymphatic system) • Trauma • Tumor • Surgery (ie, lymphadenectomy) and radiation • Recurrent infection (typically filarial)[36] • Postvenous thrombosis Secondary lymphedema has incidence of 1/1000 in United States • Most common secondary etiology in United States is cancer and therapies (surgery/radiation) • Most common secondary etiology worldwide is filarial infection Risk factors for secondary lymphedema: • Increasing age • Chronic inflammation • Higher body mass index	• Chronic swelling ○ Progresses from toes or fingers proximally[21] ○ Swelling of dorsum of feet ("buffalo hump" sign) ○ Pitting edema that progresses into nonpitting edema with increased severity ○ Primary more likely than secondary to be associated with significant swelling of feet and toes • Localized pain, discomfort, and heaviness • Atrophic skin changes[21] ○ Hypoplastic, concave toenails; upturned 2nd and 3rd toes ("ski-jump" nails); prominent skin creases on dorsal surface of dysmorphic toes more commonly seen in primary ○ Fibrosis and skin hardening • Ulcerations, lymphorrhea, elephantiasis (massive limb swelling accompanied by local fat deposition), and recurrent infections (in later stages)	• History taking ○ Primary lymphedema associated with positive family history ○ Secondary lymphedema associated with positive history of trauma or surgery • Comprehensive physical examination ○ Measurement of circumferential (>2 cm) and/or volume (>200 mL) differences between affected and non-affected limb[36] ○ Positive Stemmer sign (dorsum of 2nd toe cannot be pinched) is diagnostic of lymphedema and can be seen in advanced stages. • Other measurement tools[36] ○ Tonometry (evaluates tissue resistance with compression) ○ Bioimpedence spectroscopy (assesses changes in electrical conductance of extracellular fluid) ○ Lymphoscintigraphy (nuclear medicine study to assess for speed of lymph flow) ○ Ultrasonography, computed tomography, magnetic resonance imaging (visualizes presence of extra fluid in tissue)

significant pain during the ischemic phase, a secondary etiology should be suspected. Severe attacks, more often associated with secondary Raynaud's, can result in trophic or ischemic changes. This includes digital ulceration, hair loss, necrosis, gangrene, and autoamputation.

Diagnosis and evaluation. Diagnosis includes a positive response to cold sensitivity and the presence of color changes.[40] Serology, including complete blood cell count, antinuclear antibody, rheumatoid factor, creatine phosphokinase, Scl-70, anticentromere, anti-Jo-1, anti-U1RNP, and antiphospholipid antibodies, can assess for secondary causes.[38] Nailfold capillaroscopy is also typically normal in the primary form, whereas abnormal patterns are associated with secondary causes such as systemic sclerosis.[21]

Acrocyanosis

Key points:

- Acrocyanosis is characterized by painless bluish discoloration of the hands, feet, and face.
- Acrocyanosis is diagnosed by assessing for skin changes and the presence of pulses and performing Doppler testing.
- Compared to Raynaud's, acrocyanosis is symmetrical, has a longer duration, lacks pallor, and is usually painless.

Overview and etiology. Acrocyanosis is defined as a painless bluish discoloration of the hands, feet, and face that is often worsened by cold.[41] Although acrocyanosis has been described in multiple conditions, with some concluding that it is a mild variant of Raynaud's phenomenon,[42] true

Table VI. Clinical staging of lymphedema[37]

Stage	Features
0 (Latent)	• Swelling is not evident for months or years. • Symptoms of heaviness and discomfort present.
1 (Spontaneously reversible)	• Early onset of condition characterized by swelling that subsides with limb elevation. • Pitting edema may be present. • Fibrosis (skin hardening) not present.
2 (Spontaneously irreversible)	• Swelling is rarely improved by limb elevation alone. • Pitting edema may be present. • Fibrosis is more evident.
3 (Lymphostatic elephantiasis)	• Swelling is not improved by limb elevation. • Nonpitting edema and fibrosis are present. • Accompanied by lymphostatic verrucosis (hyperpigmentation with warty overgrowths), peau d'orange ("orange peel") dimpling, confluent papulonodular "cobblestoning," increased skin folds, ulcerations with lymphorrhea, and recurrent soft tissue infections.

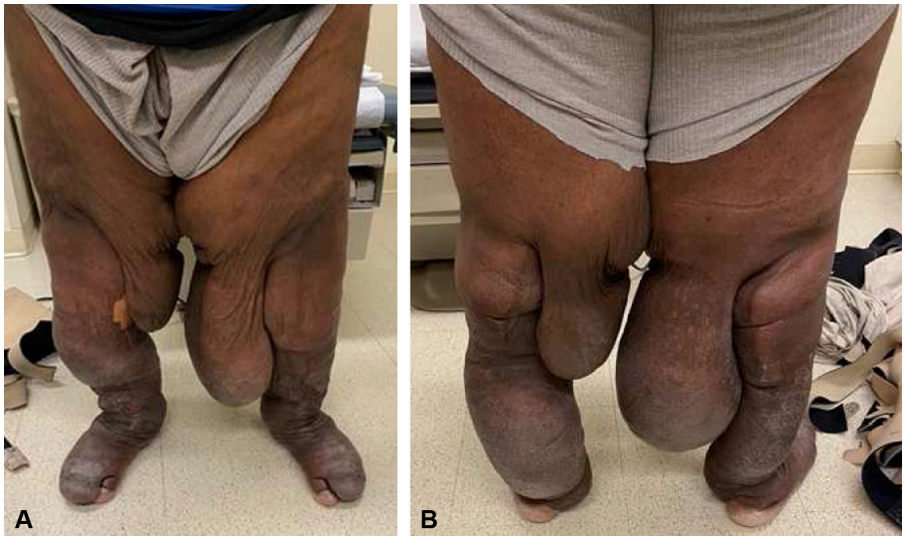

Fig 7. Lower extremity lymphedema. **A,** Front. **B,** Back. Original photos.

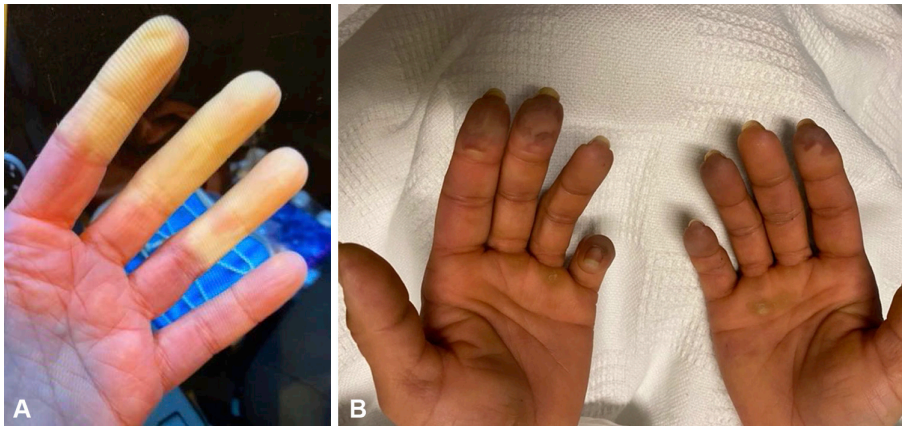

Fig 8. Raynaud's phenomenon. **A,** Ischemic phase in Raynaud's: skin distal to the line of ischemia becomes cold and pale with well-demarcated blanching. **B,** Deoxygenation phase in Raynaud's: symmetrical bluish discoloration in distal digits with blanching. Original photos.

acrocyanosis represents a distinct clinicopathologic entity. Acrocyanosis can be divided into primary and secondary etiologies. Secondary causes include connective tissue diseases, Buerger's disease, myocardial infarction, drug exposure, chronic arsenic poisoning, cryoglobulinemia, and anorexia nervosa.[43] Buerger's disease specifically presents similarly to acrocyanosis, although it is typically found in male patients who use tobacco.

Pathogenesis and clinical features. When compared to Raynaud's, acrocyanosis is more symmetric, has a longer duration, lacks pallor, and is usually painless.[41] Both primary and secondary acrocyanosis may be associated with palmar or plantar hyperhidrosis.[41] Acrocyanosis is caused by chronic vasospasm of cutaneous arteries and arterioles after cold exposure, resulting in compensatory vasodilation of capillaries and post capillary venules. Although the exact mechanism is unknown, this vasospasm and dilation are thought to produce cyanotic discoloration and hyperhidrosis, respectively. Severe cases can lead to ulceration or gangrene.

Diagnosis and evaluation. In addition to examining for skin changes, clinicians should assess for pulses and perform Doppler testing to look for hypoxemia.[41] Laboratory tests, including a complete blood cell count for myeloproliferative disorders and antinuclear antibody for autoimmune disorders, can ascertain secondary causes. Nailfold capillaroscopy may show hemorrhages, pericapillary edema, and increased capillary diameter.

Pernio/chilblains

Key points:

- Pernio, also called chilblains, presents as itching or burning purple discoloration of the toes and fingers.
- The toes of patients with COVID-19 may appear similar to those of patients with pernio; they can be differentiated on the basis of clinical suspicion and viral and serologic testing.
- The diagnosis of chilblain lupus requires evidence of lupus erythematosus on skin lesions and additional evidence of response to antilupus therapy or negative cryoglobulin and cold agglutinin studies.

Overview and etiology. Pernio, also known as chilblains, presents as symmetric purplish discoloration of the acral skin with concomitant itching and burning, most commonly in the toes and fingers (Fig 9, *A* and *B*).[44] Pernio typically occurs within 1 day after cold exposure and may last for 1 week.

Pathogenesis and clinical features. Although the exact mechanism is unknown, pernio is thought to occur because of decreased blood flow secondary to vascular changes and hyperviscosity.[44] Proposed diagnostic criteria include localized erythema and swelling of acral sites lasting for more than 24 hours with the presence of at least 1 of the following: temporal worsening in cooler months, histopathologic findings consistent with pernio and without findings of lupus, or response to conservative warming.[45] Compared to Raynaud's, pernio has a much longer duration and lacks digital pallor and cyanosis. The toes of patients with COVID-19, which is variably symptomatic, can be differentiated from those of patients with pernio with clinical suspicion and viral and serologic testing for COVID-19 infection[46]; however, there is debate about the specificity of test positivity.[47] The histology of toes of patients with COVID-19 has been suggested to be similar to that of patients with pernio.[48]

Diagnosis and evaluation. Serologic tests for autoimmune markers or cryoglobulins can look for chilblain lupus and blood dyscrasias, respectively. In addition to discoloration of distal digits, diagnosis requires evidence of lupus erythematosus on skin lesions using histopathology or direct immunofluorescence along with evidence of other forms of cutaneous lupus, response to antilupus therapy, or negative cryoglobulin and cold agglutinin studies.[49] Patients with chilblain lupus can also have autoantibodies to Sjögren's syndrome–related antigen A, hypergammaglobulinemia, and rheumatoid factor.[50]

Erythromelalgia

Key points

- Erythromelalgia (EM) presents with redness, increased temperature, and burning pain most commonly of the hands or feet.
- Primary and secondary EM are characterized by intermittent episodes with varying durations affecting the extremities.
- To diagnose EM and differentiate between subtypes, clinicians should look for classic signs, screen for genetic mutations, and conduct serologic tests.

Overview and etiology. EM is a rare neurovascular syndrome associated with episodic occlusion of blood vessels in the hands or feet.[51] Episodes are triggered by heat, exercise, or dependency and improved with cold, rest, or elevation.

Pathogenesis and clinical features. Primary EM is an autosomal dominant neuropathy caused by mutations in the genes encoding for voltage-gated sodium channels.[52] Channels become hyperexcitable and mediate painful responses to previously nonpainful stimuli. Secondary EM is associated with

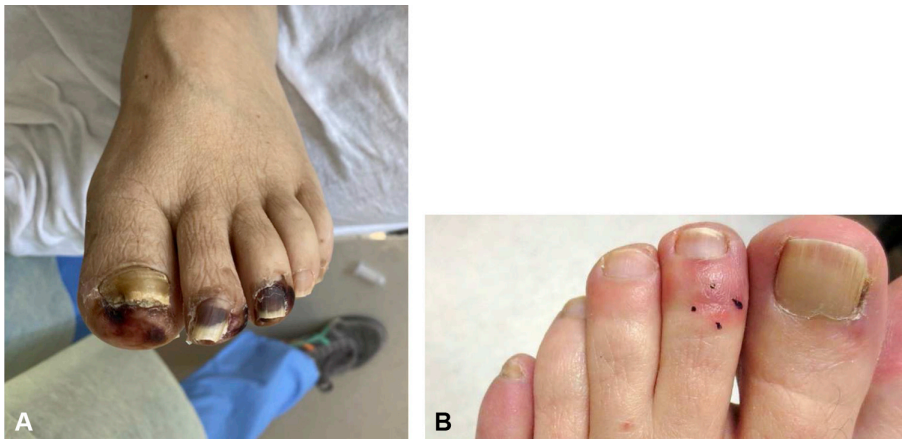

Fig 9. Manifestation of pernio/chilblains. Purplish and erythematous discoloration of the acral toes. **A,** Original photo. **B,** Courtesy of Dr Dirk Elston.

myeloproliferative disorders, infection, autoimmune disorders, gout, and diabetes mellitus.[53] When associated with blood disorders, activated platelets form thrombi within arterioles, resulting in hypoxia and pain. EM is characterized by intermittent episodes with varying durations that affect extremities bilaterally or unilaterally.[51] The lower limbs are more commonly affected.[54] During attacks, patients report burning (96%), warmth (93%), pain (87%), redness (83%), inflammation (65%), or numbness (54%).[55] In addition, itching, allodynia, or hyperalgesia may be present. Between episodes, the limb is generally normal or cyanotic with or without livedo reticularis (LR). On physical examination, erythema typically extends from the acral portions to the entirety of the affected extremity. Mild edema, acrocyanosis, and distal anhidrosis or hypohidrosis can also be observed. In chronic EM in the setting of myeloproliferative disorders, distal ulcers may be found.[51]

Diagnosis and evaluation. Clinicians should look for characteristic symptoms and cutaneous findings, which includes obtaining photographs of the affected regions during episodes. Differentiating between subtypes requires screening for gene mutations and ruling out secondary causes with complete blood cell count and serologic tests for human immunodeficiency virus, antinuclear antibody, rheumatoid factor, or blood uric acid levels.[51] Electromyography and nerve conduction velocity tests are also generally abnormal in patients. Because of low specificity, a skin biopsy is typically not performed.

LR and livedo racemosa

Key points

- LR is a benign, reversible disorder that is commonly idiopathic. Livedo racemosa (LRC) is a pathologic and permanent condition with multiple secondary causes.
- Primary LR presents with a transient, symmetric pattern of violaceus net-like mottling, whereas secondary LRC has more protracted, asymmetric, and irregular skin changes.
- Benign and pathologic forms are distinguished with skin biopsy.

Overview and etiology. LR is a benign, reversible disorder, whereas LRC is a pathologic and persistent condition.[56] Unlike LR, which is more commonly idiopathic, LRC is secondary to autoimmune disorders, medications, hematologic disease, anorexia nervosa, and livedoid vasculopathy. Although epidemiologic data are limited, LR generally affects healthy women aged 20 to 50 years, whereas LRC distribution depends on the secondary condition.

Pathogenesis and clinical features. The underlying mechanism for both LR and LRC is microvascular changes that lead to compromised blood flow. Physiologic arteriolar vasospasm produces reversible changes in LR compared with LRC, which involves prolonged vasospasm, thrombosis and/or hyperviscosity.[21] Patients with LR are typically asymptomatic, although some may report mild pain and numbness. In LR, there is a transient, symmetric pattern of net-like mottling that is reddish-blue to purple in color with a pale center; this pattern is more evident in the lower extremities (Fig 10, *A* to *D*). Changes are triggered by cold and dependency but improve with heat and elevation. In LRC, the pattern is more persistent, asymmetric, and irregular with broken circles.[56] These symptoms are not associated with triggers and are more generalized in

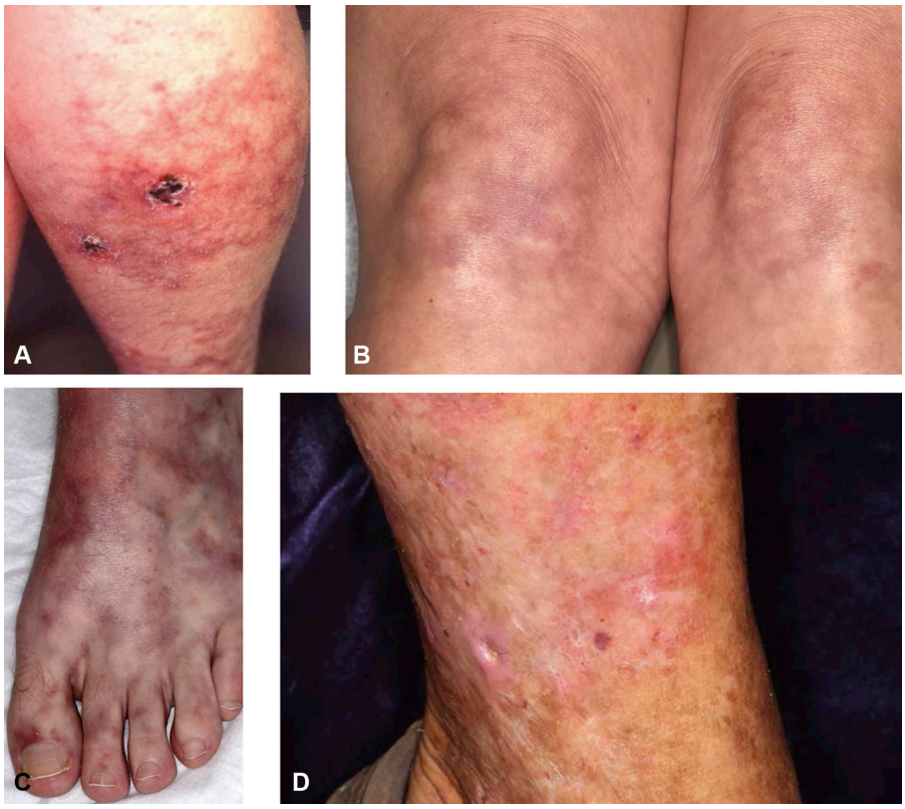

Fig 10. Mottling pattern seen in livedo reticularis. Livedo reticularis associated with a transient, (**A**) symmetric pattern of net-like violaceous-colored mottling with a pale center as seen in a (**B**) COVID19 patient (**C**) Patient with deep vein thrombosis, and (**D**) Livedo vasculopathy. **A,** Original photo. **B** to **D,** Courtesy of Dr Dirk Elston.

distribution. LRC may also be associated with nonspecific findings, including purpura, nodules, macules, ulcerations and/or atrophie blanche, which are rarely associated with LR.[21] In particular, LRC is the most common presentation in patients with primary and systemic lupus erythematosus—associated antiphospholipid syndrome (70%).[57]

Diagnosis and evaluation. A biopsy specimen from nondiscolored skin in the center of the mottling can help distinguish LR from LRC and yield valuable information about the underlying etiology. Idiopathic forms often do not demonstrate any histopathologic changes, whereas secondary forms may show vasculitis, calciphylaxis, intravascular eosinophilic plugging, intraluminal thrombosis, and/or cholesterol clefting.[56] Venous duplex ultrasound can help rule out CVI as the primary disorder. Antiphospholipid antibody testing should be considered if no other cause for LRC is suspected.

CONCLUSION

Peripheral vascular disease is associated with unique clinical characteristics and cutaneous manifestations. As their global burden increases, dermatologists can play a critical role in the early recognition and diagnosis of these disorders. Early detection and appropriate management are key in limiting the progression of peripheral vascular disease.

Conflicts of interest

None disclosed.

REFERENCES

1. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7(8):e1020-e1030.
2. Berlit P. The spectrum of vasculopathies in the differential diagnosis of vasculitis. *Semin Neurol*. 1994;14(4):370-379.

3. Venugopal A. Disseminated intravascular coagulation. *Indian J Anaesth*. 2014;58(5):603-608.
4. Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM. Warfarin-induced skin necrosis. *J Am Acad Dermatol*. 2009; 61(2):325-332.
5. Nicolas D, Nicolas S, Hodgens A, Reed M. Heparin induced thrombocytopenia (HIT). In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
6. Pajvani U, Zeikus PS, Basile O, Toback N, Robinson-Bostom L. Thrombogenic vasculopathy with diffuse neutrophilic inflammation: a histologic manifestation of a tick bite. *Cutis*. 2006; 78(5):321-324.
7. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis*. 2015; 66(1):133-146.
8. Pickert A. An approach to vasculitis and vasculopathy. *Cutis*. 2012;8(5)9:E1-E3.
9. Lie JT. Classification and histopathologic spectrum of central nervous system vasculitis. *Neurol Clin*. 1997;15(4): 805-819.
10. Suresh E. Diagnostic approach to patients with suspected vasculitis. *Postgrad Med J*. 2006;82(970):483-488.
11. Rajendran P, Rengarajan T, Thangavel J, et al. The vascular endothelium and human diseases. *Int J Biol Sci*. 2013;9(10): 1057-1069.
12. King M. Management of edema. *J Clin Aesthet Dermatol*. 2017; 10(1):E1-E4.
13. Adeyinka A, Samanapally H, Kondamudi NP. Cyanosis. In: *StatPearls[Internet]*. StatPearls Publishing.; 2020.
14. Spentzouris G, Labropoulos N. The evaluation of lower-extremity ulcers. *Semin Intervent Radiol*. 2009;26(4):286-295.
15. Singh SK, Manchanda K. Acroangiodermatitis (pseudo-Kaposi sarcoma). *Indian Dermatol Online J*. 2014;5(3):323-325.
16. McClary KN, Massey P. Ankle brachial index (ABI). In: *StatPearls [Internet]*. StatPearls Publishing.; 2020.
17. Cheung ME, Firstenberg MS. Duplex ultrasound. In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
18. McGuire D, Gotlib A, King J. Capillary refill time. In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
19. Kalawat TC, Chittoria RK, Reddy PK, Suneetha B, Narayan R, Ravi P. Role of lymphoscintigraphy in diagnosis and management of patients with leg swelling of unclear etiology. *Indian J Nucl Med*. 2012;27(4):226-230.
20. Shishehbor MH, White CJ, Gray BH, et al. Critical limb ischemia: an expert statement. *J Am Coll Cardiol*. 2016;68(18):2002-2015.
21. Dean SM. Cutaneous manifestations of chronic vascular disease. *Prog Cardiovasc Dis*. 2018;60(6):567-579.
22. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. *BMJ*. 2006;332(7537):347-350.
23. Phillips TJ, Dover JS. Leg ulcers. *J Am Acad Dermatol*. 1991;25(6 Pt 1):965-987.
24. Youn YJ, Lee J. Chronic venous insufficiency and varicose veins of the lower extremities. *Korean J Intern Med*. 2019;34(2):269-283.
25. Patel SK, Surowiec SM. Venous insufficiency. In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
26. Wenk J, Foitzik A, Achterberg V, et al. Selective pick-up of increased iron by deferoxamine-coupled cellulose abrogates the iron-driven induction of matrix-degrading metalloproteinase 1 and lipid peroxidation in human dermal fibroblasts in vitro: a new dressing concept. *J Invest Dermatol*. 2001; 116(6):833-839.
27. Mansilha A, Sousa J. Pathophysiological mechanisms of chronic venous disease and implications for venoactive drug therapy. *Int J Mol Sci*. 2018;19(6):1669.
28. Pappas PJ, DeFouw DO, Venezio LM, et al. Morphometric assessment of the dermal microcirculation in patients with chronic venous insufficiency. *J Vasc Surg*. 1997;26(5):784-795.
29. Chang Y, Dabiri G, Damstetter E, Ebot EB, Powers JG, Phillips T. Coagulation disorders and their cutaneous presentations: pathophysiology. *J Am Acad Dermatol*. 2016;74(5):783-792; quiz 793-794.
30. Waheed SM, Kudaravalli P, Hotwagner DT. Deep vein thrombosis (DVT). In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
31. Cosmi B. Management of superficial vein thrombosis. *J Thromb Haemost*. 2015;13(7):1175-1183.
32. Olin JW, White CJ, Armstrong EJ, Kadian-Dodov D, Hiatt WR. Peripheral artery disease: evolving role of exercise, medical therapy, and endovascular options. *J Am Coll Cardiol*. 2016; 67(11):1338-1357.
33. Patel MR, Conte MS, Cutlip DE, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC). *J Am Coll Cardiol*. 2015;65(9): 931-941.
34. Olin JW, Sealove BA. Peripheral artery disease: current insight into the disease and its diagnosis and management. *Mayo Clin Proc*. 2010;85(7):678-692.
35. Shu J, Santulli G. Update on peripheral artery disease: epidemiology and evidence-based facts. *Atherosclerosis*. 2018;275:379-381.
36. Kayıran O, De La Cruz C, Tane K, Soran A. Lymphedema: from diagnosis to treatment. *Turk J Surg*. 2017;33(2):51-57.
37. Grada AA, Phillips TJ. Lymphedema: diagnostic workup and management. *J Am Acad Dermatol*. 2017;77(6):995-1006.
38. Musa R, Qurie A. Raynaud disease (Raynaud phenomenon, Raynaud syndrome). In: *StatPearls[Internet]*. StatPearls Publishing; 2020.
39. Temprano KK. A review of Raynaud's disease. *Mo Med*. 2016; 113(2):123-126.
40. Wigley FM. Clinical practice. Raynaud's phenomenon. *N Engl J Med*. 2002;347(13):1001-1008.
41. Kurklinsky AK, Miller VM, Rooke TW. Acrocyanosis: the flying Dutchman. *Vasc Med*. 2011;16(4):288-301.
42. Cooke JP, Marshall JM. Mechanisms of Raynaud's disease. *Vasc Med*. 2005;10(4):293-307.
43. Borgoño JM, Vicent P, Venturino H, Infante A. Arsenic in the drinking water of the city of Antofagasta: epidemiological and clinical study before and after the installation of a treatment plant. *Environ Health Perspect*. 1977;19:103-105.
44. Whitman PA, Crane JS. Pernio (chilblains). In: *StatPearls [Internet]*. StatPearls Publishing; 2020.
45. Cappel JA, Wetter DA. Clinical characteristics, etiologic associations, laboratory findings, treatment, and proposal of diagnostic criteria of pernio (chilblains) in a series of 104 patients at Mayo Clinic, 2000 to 2011. *Mayo Clin Proc*. 2014; 89(2):207-215.
46. Kolivras A, Dehavay F, Delplace D, et al. Coronavirus (COVID-19) infection-induced chilblains: A case report with histopathologic findings. *JAAD Case Rep*. 2020;6(6):489-492.
47. Docampo-Simón A, Sánchez-Pujol MJ, Juan-Carpena G, et al. Are chilblain-like acral skin lesions really indicative of COVID-19? A prospective study and literature review. *J Eur Acad Dermatol Venereol*. 2020;34(9):e445-e447.
48. Magro CM, Mulvey JJ, Laurence J, et al. The differing pathophysiologies that underlie COVID-19-associated perniosis and thrombotic retiform purpura: a case series. *Br J Dermatol*. 2021;184(1):141-150.
49. Su WP, Perniciaro C, Rogers RS III, White JW Jr. Chilblain lupus erythematosus (lupus pernio): clinical review of the Mayo

Clinic experience and proposal of diagnostic criteria. *Cutis*. 1994;54(6):395-399.
50. Franceschini F, Calzavara-Pinton P, Quinzanini M, et al. Chilblain lupus erythematosus is associated with antibodies to SSA/Ro. *Lupus*. 1999;8(3):215-219.
51. Jha SK, Karna B, Goodman MB. Erythromelalgia. In: *StatPearls [Internet]*. StatPearls Publishing.; 2020.
52. Tang Z, Chen Z, Tang B, Jiang H. Primary erythromelalgia: a review. *Orphanet J Rare Dis*. 2015;10:127.
53. Kang BC, Nam DJ, Ahn EK, Yoon DM, Cho JG. Secondary erythromelalgia - a case report. *Korean J Pain*. 2013;26(3):299-302.
54. Leroux MB. Erythromelalgia: a cutaneous manifestation of neuropathy? *An Bras Dermatol*. 2018;93(1):86-94.
55. Parker LK, Ponte C, Howell KJ, Ong VH, Denton CP, Schreiber BE. Clinical features and management of erythromelalgia: long term follow-up of 46 cases. *Clin Exp Rheumatol*. 2017;35(1):80-84.
56. Sajjan VV, Lunge S, Swamy MB, Pandit AM. Livedo reticularis: a review of the literature. *Indian Dermatol Online J*. 2015;6(5):315-321.
57. Uthman IW, Khamashta MA. Livedo racemosa: a striking dermatological sign for the antiphospholipid syndrome. *J Rheumatol*. 2006;33(12):2379-2382.