A Review of COVID-19 Chilblains-like Lesions and Their Differential Diagnoses

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GENERAL PURPOSE: To familiarize wound care practitioners with the differential diagnoses of chilblains-like lesions that could be associated with the complications of COVID-19.

TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant will:

1. Identify the population most often affected by COVID toes.
2. Select the assessments that help differentiate the various conditions that cause chilblains-like lesions.
3. Choose appropriate treatment options for the various conditions that cause chilblains-like lesions.

ABSTRACT

This review article focuses on the pathogenesis, clinical features, and diagnostic testing of the common pathologies that can manifest as chilblains-like lesions. These differentials include "COVID toes," Raynaud phenomenon, acrocyanosis, critical limb ischemia, thromboangiitis obliterans, chilblains associated with lupus erythematosus, and idiopathic chilblains. The authors present a helpful mnemonic, ARCTIC, to assist clinicians in recognition and diagnosis.

KEYWORDS: acral lesion, acrocyanosis, chilblain, COVID toes, critical limb ischemia, differential diagnosis, lupus erythematosus, Raynaud phenomenon, thromboangiitis obliterans

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INTRODUCTION

The purpose of this educational activity is to familiarize the wound care practitioner with the differential diagnoses of chilblains-like lesions (CLLs) that may be associated with complications of COVID-19. Recently, physicians and other wound care practitioners have encountered CLLs as a potential cutaneous manifestation of SARS-CoV-2, which present as violaceous macules, papules, plaques, or nodules on extremities (ie, acral lesions).[1] Also called perniosis, CLLs present in three forms: related to COVID-19 infection, lupus associated, and idiopathic. A preliminary systematic review of 46 studies (including case reports and series) found acrocutaneous lesions to be the most commonly reported skin manifestation of COVID-19 infection.[2]

Usually chilblains are a result of an inflammatory response to cold temperatures. A typical presentation consists

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of tender, pruritic erythematous or violaceous nodules located symmetrically on the dorsal aspect of the fingers, toes, ears, and nose. Less commonly, they can occur on the thighs and buttocks, usually with many local and systemic conditions, and these nodules have been described as CLLs (Figures 1–3).[2]

Although CLLs are common, many other conditions present with acral lesions and should be considered in differential diagnoses (Table).[3–31] This article focuses on the pathogenesis, clinical features, and diagnostic testing of the common pathologies that can manifest as CLLs or be considered mimickers. These differentials include "COVID toes," Raynaud phenomenon, acrocyanosis, critical limb ischemia (CLI), thromboangiitis obliterans, chilblains lupus erythematosus (CHLE), and idiopathic chilblains.

COVID TOES

"COVID toes" are characterized by erythematous or violaceous, edematous, rarely necrotic papules or plaques most commonly on the toes (Figure 1).[3,4] Accounting for 19% to 38% of all cutaneous lesions associated with COVID-19, this presentation has been reported in several European countries, as well as the Middle East and is most common in adolescents or young adults.[3–7] Estimates on the prevalence of CLLs in patients with COVID-19 range from 2% to 20%.[8] Typically occurring as a late manifestation of infection, the majority of patients test negative for COVID-19 polymerase chain reaction at the time of presentation.

The etiology and pathophysiology of COVID toes have not been confirmed, but some clinicians suggest they represent a sequela of mild infection with appropriate inflammatory response. A low body mass index and lack of warm indoor footwear during lockdown have also been associated with COVID toes, and these may be contributory or predisposing factors.[6] The lesions last on average 12 days, but may persist for several weeks.[7] Spiky circular structures have been identified in several biopsies of COVID toe lesions, suggestive of the spike glycoproteins present in COVID-19 viral particles.[9–12]

Figure 2. CHILBLAINS-LIKE LESIONS ON THE TOES

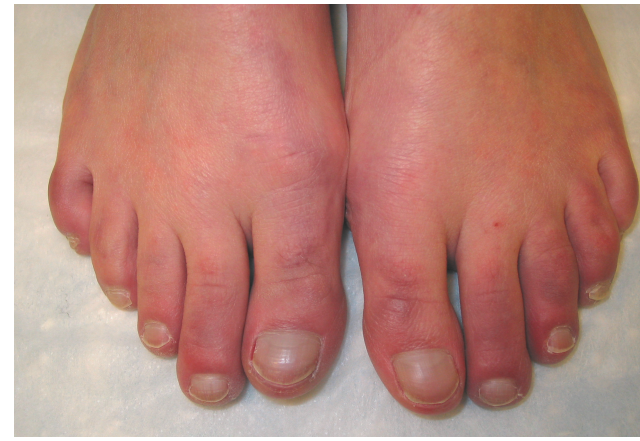

Image provided by Stedman's.

However, the relationship with COVID-19 has not been convincingly proven to date.[9]

The clinical diagnosis of COVID toes is based on physical examination and history of possible exposure to COVID-19.[9] Lesions respond to topical steroids and environmental modification.[5] Continued research is needed to assess COVID toes and their association with SARS-CoV-2.

RAYNAUD PHENOMENON

Raynaud phenomenon is characterized by intermittent peripheral vasoconstriction to the fingers or toes that manifests as a triphasic segmental color change of white to blue to red (Figure 3).[13] This phenomenon is attributed to sympathetic nervous system stimulation by emotional stress, anxiety, and cold temperatures.[13] The prevalence of Raynaud phenomenon ranges from 3% to 20% in women and 3% to 14% in men.[14]

Primary Raynaud disease is not associated with systemic disease and is typically milder, with less frequent episodes, and most commonly presents between the ages of 15 and 25 years, with a significant female predominance (roughly 20:1).[13] Conversely, secondary Raynaud

Figure 1. COVID TOES

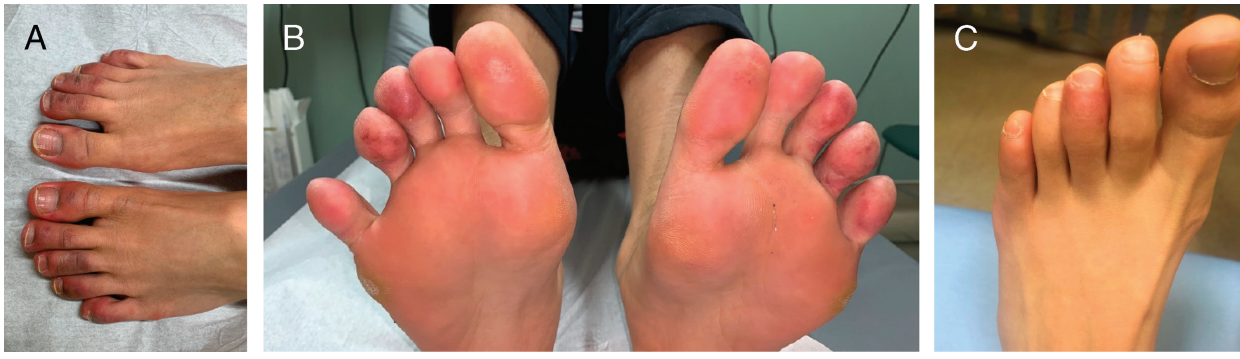

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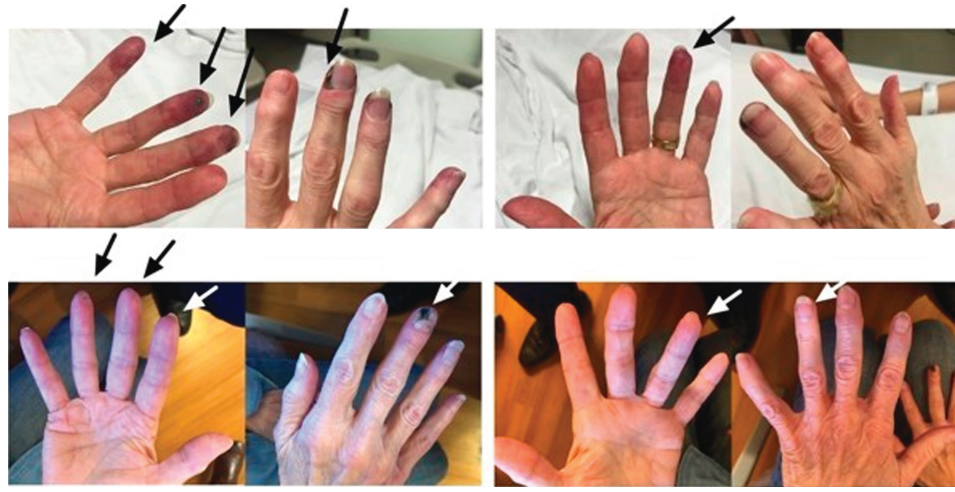
Figure 3. CHILBLAINS-LIKE LESIONS ASSOCIATED WITH RAYNAUD PHENOMENON



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phenomenon is associated with concurrent systemic disease, including connective tissue diseases, structural vascular anomalies, neurologic diseases, hyperviscosity syndromes, lymphoproliferative diseases, and exposures to medications and physical environmental triggers. Patients are typically older, with a less significant female predominance (4:1), and episodes are often more frequent.[13]

Symptoms include skin pallor or cyanosis of the fingers, cold digits, and numbness and soreness of digits that last approximately 20 minutes following stimulation.[13] An episode typically begins with decreased blood flow to the acral regions with digits turning white in color, after which there is a cyanotic phase where the remaining oxygen in the blood left in the digits is consumed.[13] The episode ends with a red phase where blood flow is restored.[13] The mechanism includes a temporary constriction leading to cyanosis that is very similar to changes observed with chilblains.[13]

When diagnosing primary Raynaud disease or secondary Raynaud phenomenon, clinicians must assess for the presence of digital ulcerations and intensity of pain during vasoconstrictive episodes, while identifying any provoking or mitigating factors.[13] In addition, nailfold capillary microscopy can be used to confirm the diagnosis by visualizing increased capillary size, often a lower density of capillaries, hemorrhage, and avascular areas in the fingers.[13] Currently, careful patient history and screening for any possible associated disease are the most reliable methods for diagnosis.[13] Obtain a collagen vascular disease screen and erythrocyte sedimentation rate.[13] Selective patients may benefit from cryoglobulin testing, chest radiograph, pulmonary function tests, or ECG.

Unfortunately, there is no cure, and most treatment strategies focus on preventing and minimizing the severity of symptoms.[13] Treatment may include insulated gloves, activated thermal warming devices, nitroglycerin gel or patches, calcium-channel blockers, phosphodiesterase E5 inhibitors (eg, sildenafil 50 mg twice a day, 200 mg once a day, or tadalafil 20 mg daily), or prostacyclin analog infusions.[14]

ACROCYANOSIS

Acrocyanosis usually presents with violaceous or blue discoloration of the hands, feet, or face from constriction of the blood vessels (Figure 4).[15] Acrocyanosis has a prevalence of 12% to 13% and is more common in children and young adults (usually in patients younger than 30 years) with a predominance among women (roughly 6–8:1).[15,16] There are two types of acrocyanosis: primary (idiopathic) acrocyanosis without associations and acrocyanosis secondary to a predisposing condition or medication.[15]

Current hypotheses propose that chronic vasospasm of small arteries combined with dilatation in the capillaries and postcapillary venules leads to cyanosis, sweating, and pain.[15] Genetic defects affecting vascular musculature, erythrocyte flexibility, platelet adhesiveness, and other factors resulting in plasma hyperviscosity result in compromised blood flow and clinical manifestations.[15,16]

Common symptoms include cold and clammy extremities with cyanotic discoloration, enhanced susceptibility to cooling and pain, ulceration and gangrene of the fingers, irregular and brittle nails, erythrocyanosis, perniosis (bluish red discoloration of the skin), livedo reticularis, persistent and painless cyanosis of extremities, local hypothermia (extremities), and elastic infiltration of the integument.[15] Symptoms often worsen with exposure to cold temperatures.[16]

Acrocyanosis is diagnosed based on the presence of cyanosis and local hypothermia of the extremities, sweatiness, and elastic infiltration.[15] Capillary oximetry and capillaroscopy are often sufficient to rule out differential diagnoses.[15] In other cases, complete blood count;

Table. DIFFERENTIAL DIAGNOSIS OF CHILBLAINS-LIKE LESIONS

Disease	Risk Factors	Clinical Features	Diagnostic Factors
COVID toes[3–12]	Youth Failure to wear warm footwear Low BMI Mild or no systemic symptoms Appearance rather late during (suspected) infection	Cutaneous, red-violaceous, edematous, rarely necrotic, itchy CLL on the toes	Physical examination History of exposure Histopathologic, immunohistochemical, and immunofluorescence studies Spike-like circular structures in biopsy
Raynaud disease[13,14]	Age > 30 y Female Cold climate Family history	Whitening/bluing/reddening of hands and feet	Antinuclear antibody test ESR
Acrocyanosis[15,16]	Cold climate Outdoor occupation Low BMI Anorexia nervosa	Coolness and violaceous dusky discolorations of hands and feet Ulceration and gangrene of the fingers Irregular and brittle nails Clammy extremities Susceptibility to cooling and pain Erythrocyanosis, perniosis, livedo reticularis, persistent and painless cyanosis of extremities, local hypothermia (extremities) Elastic infiltration of the integument	Complete hemogram Antinuclear factor Rheumatoid factor, cardiolipin antibody, lupus antibody, metabolic screening Capillary oximetry MRI, CT, capillaroscopy
Critical limb ischemia[17–20]	Age Smoking BMI Family history of atherosclerosis or claudication Diabetes, hypertension, hypercholesterolemia	Gangrene Nonhealing refractory wounds Pain at rest	Ankle-brachial index Toe systolic pressure and transcutaneous oxygen pressure, auscultation Doppler ultrasound, CT angiography, magnetic resonance angiography, angiogram
Thromboangiitis obliterans[21–26]	Age < 45 y Male Smoking	Skin ulcerations and gangrene of the digits, superficial thrombophlebitis, and Raynaud phenomenon Claudication, pain, numbness, and/or tingling in the extremities Early phase: polymorphonuclear leukocytes, microabscesses, and multinucleated giant cells; Intermediate phase: progressive organization of the thrombus in the arteries and veins; End-stage: only organized thrombus and fibrosis are found in the blood vessels	Complete blood cell count, serum creatinine concentrations, fasting blood sugar levels, and ESR Tests for antinuclear antibody, rheumatoid factor, serologic markers for CREST syndrome and scleroderma Screening for hypercoagulability Liver function tests Transthoracic or transesophageal echocardiography, arteriography, CT, MRI
Chilblains associated with lupus erythematosus[27–29]	Cold climate Family history	Papuloerythematous lesions Purplish and plaque-like infiltrates Fissural hyperkeratosis and small ulceration appears on hands, fingers, soles of feet, may affect other areas such as trunk, ear, nose	Histopathologic examination (fibrin deposition) or indirect immunofluorescence studies, cryoglobulin and cold agglutinin studies Response to antilupus erythematous therapy, other antibody studies Latex agglutination test Hypergammaglobulinemia
Idiopathic chilblains[30,31]	Cold climate Low BMI	Painful erythematous or purplish papules, CLL on hands and feet or less frequently, on nose, ear, thigh	C-reactive protein ESR Histologically presents without fibrin deposition

Abbreviations: BMI, body mass index; CLL, chilblains-like lesions; CREST, calcinosis cutis, Raynaud phenomenon, sclerodactyly, and telangiectasia; CT, computed tomography; ESR, erythrocyte sedimentation rate.

MRI and computed tomography; and screening for antinuclear factor, rheumatoid factor, cardiolipin antibody, lupus antibody, and other metabolic antibodies help to identify predisposing or associated conditions.[16]

CRITICAL LIMB ISCHEMIA

Critical limb ischemia is characterized by acute limb pain at rest, nonhealing ulcers, gangrene, and refractory wounds that can resemble CLLs[17] and progresses over the span of months to years.[18] Among Americans, there are 500 to 1,000 new cases of CLI per million people each year.[19] The prevalence of CLI is 12% among adults, with men affected slightly more than women.[19] It primarily presents in patients with atherosclerosis but can also be observed in patients with Buerger disease and some forms of arteritis.[19]

Figure 4. ACROCYANOSIS OF THE FINGERTIPS

Image provided by Stedman's.

The pathogenesis of CLI involves arterial obstruction leading to impaired perfusion of peripheral tissues.[19] The resulting poor oxygenation and nutrient delivery to tissues can delay healing of foot sores, ulcers, or wounds with tissue necrosis.[17] Ulcers are often nonhealing or associated with necrosis or gangrene. Other signs and symptoms may include numbness; claudication; pain on limb elevation; toenail thickening; diminished pulses in the legs or feet; and shiny, smooth, or dry skin of the feet.[17]

In addition to clinical presentation, objective measures are used to augment the diagnosis of CLI, which is based on bedside vascular assessment and ancillary imaging techniques.[17] In general, to fulfill a diagnosis of CLI, patients must exhibit all of the following observations: (1) ischemic rest pain or ulcer necrosis, (2) need for amputation if blood flow does not improve, and (3) objective ischemia meeting hemodynamic standards (ie, toe pressure of <50 mm Hg and a transcutaneous partial oxygen pressure <30 mm Hg).[17] Bedside investigations to assess vascular flow include ankle-brachial pressure index, toe systolic pressure, and transcutaneous oxygen pressure. In addition, duplex segmental lower leg Doppler can assist in diagnosis. Doppler waveform changes from triphasic to biphasic to monophasic and then to stenotic waveforms can help identify arterial blockage sites.[17] Last, CT angiography, magnetic resonance angiography, and (if indicated) angiography can also be used.[17] If left untreated, CLI may lead to amputation of the affected limb.[19,20]

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans, also known as Buerger disease, is a nonatherosclerotic inflammatory disease strongly correlated with smoking tobacco. This condition is caused by segmental occlusive inflammation of arteries and veins in the extremities (Figure 5).[21] The prevalence of thromboangiitis obliterans among patients with peripheral arterial disease ranges from 0.5% to 5.6% in Western Europe, 45% to 63% in India, 16% to 66% in Korea and Japan, and 80% in Israel (in Jews of Ashkenazi ancestry).[21] Typically, this disease presents in young individuals with a smoking history (an average of 16 pack-years) and manifests as distal extremity ischemia, digit ulcerations, or digit gangrene, more commonly on the hands and feet.[22] Patients may experience numbness and tingling, claudication, skin ulcerations, gangrene, superficial thrombophlebitis, Raynaud phenomenon, and pain in affected extremities.[22] The accompanying CLLs are characterized by rubor or cyanosis, a discoloration termed "Buerger's color," and pain.[23]

Although the etiology of thromboangiitis obliterans is unclear, it is believed to be an immune-mediated endarteritis.[23] Interestingly, only endothelial-dependent vasodilation is inhibited in this disease, suggesting a role of vascular endothelium in its etiology.[23] Pathologically, both arteries and veins are affected by inflammatory thrombi.[23]

The initial stages of the disease are characterized by occlusive, highly cellular, inflammatory thrombi, with little inflammation in the endothelium.[24] In the intermediate stages, there is a greater burden of thrombus in the affected area.[24] However, unlike arteriosclerosis, the structure of the vessel wall is intact.[24] In the final stages of the disease, blood vessels are characterized by organized thrombus and fibrosis.[24]

Diagnosis is confirmed by history, physical examination, vascular evaluation, and laboratory investigations.[25] Disease onset before 50 years, strong history of smoking or tobacco use, infrapopliteal arterial occlusions, claudication of extremities, and exclusion of autoimmune diseases are

Figure 5. THROMBOANGIITIS OBLITERANS, ALSO KNOWN AS BUERGER DISEASE, OCCURRING ON THE FEET

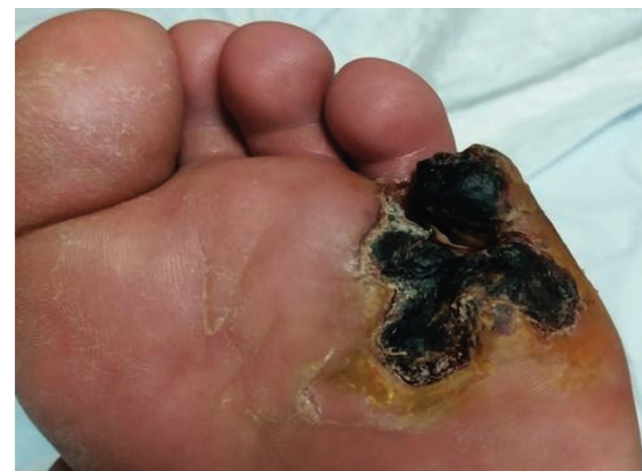

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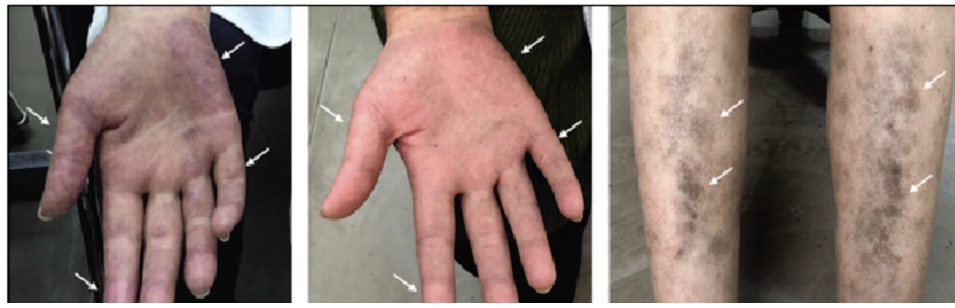
Figure 6. CHILBLAINS LUPUS ERYTHEMATOSUS AND IDIOPATHIC CHILBLAINS IN THE HANDS AND LOWER LIMBS



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supportive of thromboangiitis obliterans.[24] Further confirmation with arteriography comparing affected and unaffected limbs is recommended.[26] Unlike other forms of vasculitis, acute-phase reactants including erythrocyte sedimentation rate and C-reactive protein level are normal in this disease.[26] Smoking cessation is essential to avoid limb or digit amputation.[26]

CHILBLAINS LUPUS ERYTHEMATOSUS

Chilblains lupus erythematosus manifests as the combination of cutaneous CLLs and clinical or laboratory features of lupus erythematosus (Figure 6).[27] Specifically, CHLE is characterized by the appearance of an erythematous pruritic papule that often becomes painful and necrotic. Lesions are most common in an acral distribution on the dorsal surface of hands and soles of the feet.[27] In certain cases, violaceous and plaque-like infiltrates, fissures with hyperkeratosis, and small ulcerations can be seen.[27]

Epidemiologically, CHLE occurs in <1% of the population and typically affects people living in colder climates.[28] Two forms of CHLE have been identified, sporadic (affecting middle-aged women) and familial (with onset at childhood).[27] Familial CHLE is caused by a D18N missense mutation in the TREX1 gene.[27] Lymphoblasts that carry the D18N are less sensitive to granzyme A-mediated cell death, suggesting the role of impaired apoptosis in CHLE pathogenesis.[27] Conversely, there is no confirmed pathogenesis implicated in sporadic CHLE.[27]

The Mayo Clinic diagnostic criteria for CHLE include skin lesions in extremities induced by cold temperature, concurrent systemic lupus erythematosus, response to treatment for lupus, and negative results of cryoglobulin and cold agglutination studies.[29] Further, hypergammaglobulinemia, rheumatoid factor, antinuclear and antiphospholipid antibodies, and a positive latex agglutination test are observed in a majority of patients with CHLE.[29]

IDIOPATHIC CHILBLAINS

Idiopathic chilblains are characterized by painful and pruritic erythematous lesions observed on the thighs, buttocks, and extremities, occurring in response to exposure to cold temperatures without associated connective tissue disease (Figure 6).[30] A low body mass index is often associated with idiopathic chilblains.[30]

Epidemiologically, idiopathic chilblains is more common in women and typically affects people living in colder damp climates such as the UK or northern Europe.[31] The exact pathogenesis is not proven; however, it is described as a vasculopathy that develops because of abnormal neurovascular responses to dermal temperature changes.[30] Signs include erythematous or violaceous papules and skin edema, with accompanying symptoms of pruritus or burning pain sensations.[31]

Diagnosis is made with clinical history and examination and can be supported with histology. Differential diagnosis of this disease includes lupus chilblains; however, there is a histologic difference where lupus chilblains present with fibrin deposition that is absent with idiopathic chilblains.[29] Other bloodwork including a C-reactive protein test and erythrocyte sedimentation rate may help rule out associated connective tissue disease.[30] Treatments include minimizing cold exposure; vasodilatory agents including topical nitroglycerin, nifedipine, or prazosin; and antiplatelet agents including aspirin.[30]

CONCLUSIONS

The differential diagnoses of CLLs are extensive. COVID toes, Raynaud phenomenon or disease, acrocyanosis, CLI, thromboangiitis obliterans, CHLE, and idiopathic chilblains all have similar clinical manifestations. A suggested method to remember the causation and classification of dermatologic manifestations is with the mnemonic

ARCTIC: Acrocyanosis, Raynaud phenomenon or disease, COVID toes, Thromboangiitis obliterans, Idiopathic chilblains, and CLI/CHLE.

It is critical to classify CLLs to ensure proper management and limit conflation. With the advent of COVID-19, it is exceedingly important for clinicians to differentiate CLLs suggestive of alternative dermatologic pathologies from coronavirus infection.

PRACTICE PEARLS

- Healthcare providers may encounter CLLs as a cutaneous manifestation of COVID-19 infection.
- COVID toes, accounting for 19% to 38% of all cutaneous lesions associated with COVID-19 infection, can present as pruritic or painful swellings or purpura on the feet, most commonly the toes (as a late change).
- Raynaud phenomenon is characterized by short periods of reduced blood flow to the fingers or toes, which manifest with segmental triphasic color change.
- Acrocyanosis typically presents as violaceous or blue discoloration of the hands, feet, or face from constriction of the blood vessels.
- Healthcare providers should be aware of the pathologies that can present as CLLs including COVID toes, Raynaud phenomenon or disease, acrocyanosis, CLI, thromboangiitis obliterans, CHLE, and idiopathic chilblains. ●

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