Part I: Cutaneous manifestations of cardiovascular disease

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Learning objectives

After completing this learning activity, the participants should be able to discuss the overlap between cutaneous and cardiovascular disease; identify the cutaneous manifestations of common cardiovascular disorders, including infective endocarditis, acute rheumatic fever, Kawasaki disease, cholesterol embolization syndrome, lipid disorders, cardiac amyloidosis, and cardiac myxomas; and understand how to diagnosis underlying cardiovascular disorders in order to expedite early intervention.

Disclosures

Editors

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In this part 1 of a 2-part continuing medical education series, we review the epidemiology and pathophysiology of cardiovascular disease, its association with cutaneous symptoms, and the diagnosis and evaluation of cutaneous features of cardiovascular syndromes, including infective endocarditis, acute rheumatic fever, Kawasaki disease, cholesterol embolization syndrome, lipid disorders, cardiac amyloidosis, and cardiac myxomas. As the incidence and prevalence of cardiovascular diseases increase, dermatologists play an essential role in recognizing the cutaneous manifestations of cardiovascular diseases in order to appropriately connect patients with follow-up care. (J Am Acad Dermatol 2023;89:197-208.)

Key words: acute rheumatic fever; cardiac amyloidosis; cardiac myxomas; cardiovascular disease; cholesterol embolization syndrome; infective endocarditis; Kawasaki; lipid disorders.

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Abbreviations used:

AL: amyloid light chain
CES: cholesterol embolization syndrome
FD: familial dysbetalipoproteinemia
FH: familial hypercholesterolemia
LRC: livedo racemosa
TEE: transesophageal echocardiography
TTE: transthoracic echocardiography

INTRODUCTION

Key points

- Dermatologists are exposed to diverse skin findings secondary to pathologies associated with underlying cardiac diseases.
- Dermatologists may require increased awareness of these cutaneous manifestations to appropriately refer cardiac patients.
- This section will provide an overview of cutaneous manifestations of classic cardiovascular diseases, with a focus on distinguishing symptoms to diagnose and appropriately refer patients.

Cardiovascular disease is the leading cause of death in the United States and internationally.[1] The lifetime risk, at the age of 40 years, of developing coronary artery disease is 49% in men and 32% in women.[2] Many cardiac diseases, such as coronary artery disease, congestive heart failure, and congenital heart disease, have classical cutaneous manifestations, including edema and cyanosis (Table I; Figs 1-3).[3-10] Dermatologists are routinely exposed to the cutaneous manifestations of cardiac diseases during their clinical practice and have the opportunity to be the first to recognize underlying disorders.[11] Therefore, the improved understanding of cardiac diseases and their associated dermatologic symptoms is imperative for accurate diagnosis, timely referral, and appropriate treatment. This continuing medical education will provide an overview of the cutaneous manifestations of classic cardiovascular diseases, with a focus on distinguishing symptoms to diagnose and appropriately refer patients (Tables II and III; Figs 4-8).[12-18]

CARDIAC DISEASE

Cholesterol embolization syndrome

Key points

- Cholesterol embolization syndrome (CES)–associated skin findings include "blue toe syndrome," livedo racemosa (LRC), and erythematous nodules.
- CES is often underdiagnosed due to the overlap in symptoms of a large number of diseases; the definitive diagnosis is made using a biopsy.
- A dermatologist suspecting CES can perform a punch biopsy; imaging studies such as computed tomography angiography, magnetic resonance angiography, transthoracic echocardiography (TTE), and transesophageal echocardiography (TEE) may be helpful.

Overview. CES, also known as atheroembolism or blue toe syndrome, is characterized by the dislodgment of an atherosclerotic plaque and occlusion of the aorta, small arteries, and arterioles.[11,19-21] The atheromatous debris produces an inflammatory cascade that can cause further occlusion via thrombus formation, endothelial cell proliferation, and intimal fibrosis. Over time, this can lead to ischemia, infarction, and necrosis. Approximately 80% of CES cases occur after invasive procedures.[20-22] Less frequently, the spontaneous eruption of an atherosclerotic plaque can result in CES. Anticoagulation and fibrinolytic therapy may also lead to plaque rupture, which can increase systemic exposure to cholesterol clefts.[11,20] The diagnosis is difficult to determine, and clinical cases often go undetected.[19] The incidence can range from 0.1% to 2.9%, with a mortality rate as high as 60% to 80%.[20-22] The poor prognosis and high mortality can be attributed to progressive renal failure, atherosclerosis, and cardiovascular comorbidities. Men are more commonly affected than women, at a 3.4:1 ratio.[17] CES is also strongly associated with older age, with a mean patient age of 66 to 72 years.

Clinical features. The clinical features of CES vary, as patients may be asymptomatic, and the findings are dependent on the affected organ.[20-22] Skin findings occur in approximately 34% of patients with CES, and nonspecific symptoms include cyanosis, ulcerations, gangrene, and necrosis. The classic skin finding is "blue toe syndrome," defined as tender, cool, blue or purple toes with normal pulses.[11,19-21] LRC, mottled blue or purple skin discoloration, is another classic finding in the foot, leg, trunk, or buttocks that can be seen in up to 50% of patients with CES.[17] Retiform purpura, or branched purpura owing to vascular occlusion, may also be seen. Erythematous nodules may also be present, typically near the lateral foot or calcaneal region. Ecchymosis, petechiae, splinter hemorrhages, and purpura may also be seen.[11,19-21] Systemic involvement can extend to the cardiac, renal, gastrointestinal, and central nervous systems. Of these sites, renal involvement is the most common, occurring in 25% to 50% of patients.[11,19-21]

Table I. General dermatological signs of cardiac disease

Symptom	Description	Associated diseases
Edema	Excessive fluid in the interstitial space (Fig 1, *A* and *B*)[3]	Right-sided heart disease, pulmonary hypertension, ischemic cardiomyopathy, congenital heart disease[3]
Cyanosis	Abnormal bluish discoloration of the skin and mucous membranes, caused by decreased oxygen in the blood as a consequence of either reduced blood flow or hemoglobin (Fig 2)[4]	Right-to-left shunt in congenital heart disease, arteriovenous malformation, reduced cardiac output (left ventricular failure or shock)[4]
Clubbing	Bulbous uniform swelling of the soft tissue of the terminal phalanx of a digit with subsequent loss of the normal angle between the nail and nail bed[5]	Cyanotic congenital heart disease, cor pulmonale, secondary polycythemia, chronic congestive heart failure, chronic pulmonary disorders[5]
Diagonal earlobe crease	Diagonal crease in the earlobe that starts from the tragus to the rear edge of the auricle at an angle of 45 degrees with varying depths[6] (Fig 3[7])	Coronary artery disease, peripheral vascular disease[6]
Quincke pulse	Visible pulsation of the capillaries in the nail beds or lips that is synchronous with heartbeat[8]	Severe aortic valve insufficiency[8]
Xanthoma and corneal arcus	Xanthomas: Nodular dermal lesions characterized by the accumulation of lipid-laden macrophages (eg, xanthelasma, eruptive xanthoma, palmar xanthoma) Corneal arcus: Lipid deposits that appear as rings on the outer rim of the cornea[9,10]	Hyperlipidemias[10]

Diagnosis and evaluation. CES is often underdiagnosed due to the overlap in symptoms, but it should be suspected among patients presenting with the classic skin findings of blue toes, LRC, and petechiae, particularly after invasive vascular procedures.[11,19-21] History and physical examination evaluation should be directed toward diseases that overlap in symptoms and increase mortality/morbidity in CES. Atherosclerosis is a major risk factor for developing CES, and precipitating risk factors, such as hypertension, hyperlipidemia, diabetes, and smoking, should be considered. A history of chronic kidney disease, hepatic disease, pancreatitis, aortic dissection, chronic inflammatory diseases, hypercoagulative diseases, and endocarditis or other localized or generalized bacteremia should be ascertained.

Histologic evidence can be present in tissue biopsies, including skin, kidney, muscle, bone marrow, and gastric and colonic mucosa. An incisional or double punch biopsy may be taken from or proximally to the site of ulceration, cyanosis, or gangrene and blanched areas of livedo reticularis.[11,19-21] Additionally, the punch biopsies of affected regions show cholesterol clefts within small vessels in association with thrombi. Imaging studies are vital to the diagnosis of CES, as they establish advanced atherosclerotic disease and provide evidence of atherosclerotic plaques that cause organ damage through chronic embolization. Atherosclerotic disease in large vessels can be visualized by imaging via computed tomography angiography or magnetic resonance angiography.[17] Contrast tomography is typically not used to circumvent additional embolic events that may occur with invasive angiography. TTE or TEE may also demonstrate the presence of aortic plaques.

Typical laboratory values are nonspecific and reflect systemic inflammatory responses, including elevated erythrocyte sedimentation rate, C-reactive protein, fibrinogen, thrombocytopenia, anemia, eosinophilia, and leukocytosis.[11,19-22] Patients with CES and concomitant kidney disease may have eosinophilia and, rarely, proteinuria and eosinophiluria.

Retiform purpura should be biopsied to differentiate vessel occlusion from vessel wall pathologies, such as infection or vasculitis. Additional differential diagnoses include deep vein thrombosis,

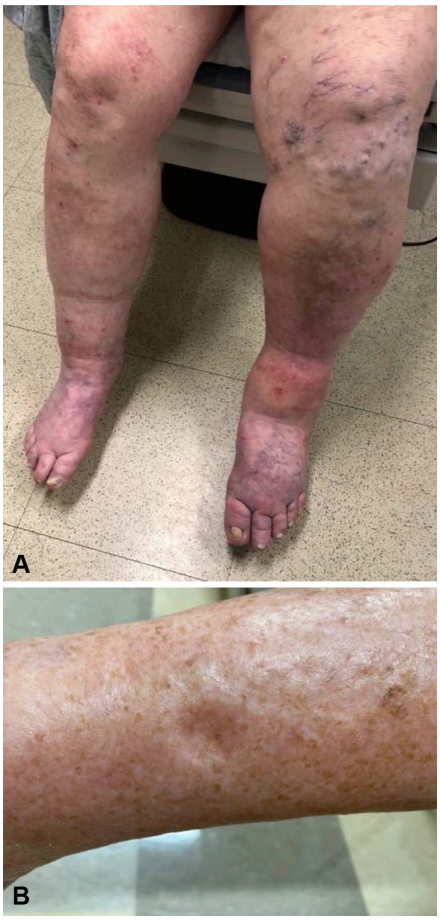

Fig 1. Edema**. A,** Swelling and erythema of the lower extremities, with cyanosis present in the feet. **B,** Pitting edema in the lower extremity. Original photo.

diabetic ulcers, bacterial sepsis, subacute endocarditis, vasculitis, and vasculopathic diseases, like Raynaud disease, systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, leukocytoclastic angiitis, rheumatoid vasculitis, cyofibrinogemia, thromboangiitis obliterans, infections, cryoglobulinemia, and antiphospholipid syndrome. Early detection is vital to prevent further ischemia and other atherosclerotic manifestations. The acute management of CES is supportive, including (but not limited to) fluid and blood pressure support in addition to treatment to address any specific end organ damage.[23] Additional treatments should be targeted toward the management of cardiovascular risk factors and prevention of vascular occlusion through the use of aspirin, statins, smoking cessation, blood pressure management, and glycemic control.[24] Anticoagulation/thrombolytic treatment is controversial.

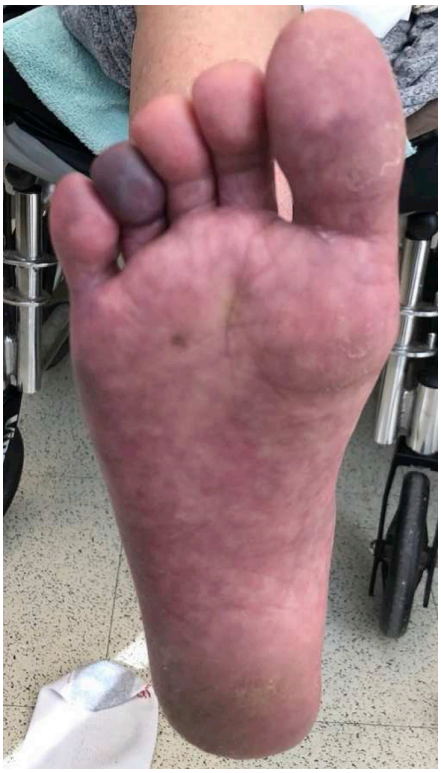

Fig 2. Cyanosis. Peripheral cyanosis of the lower extremities. Original photo.

Lipid disorders

Key points

- Lipid disorders can present with cutaneous papules or nodules called xanthomas, classified as tuberous, tendinous, eruptive, or planar according to the location.
- Diagnosis includes screening for risk factors, genetic inheritance, and conditions associated with secondary hyperlipidemia. Lipid profile and genetic testing can confirm lipid disorders.
- Differential diagnoses include xanthogranuloma necrobioticum, xanthoma diffusum planum, sebaceous hyperplasia, juvenile xanthogranuloma, syringoma, and nodular basal cell carcinoma.

Overview. Dyslipidemias are classified as primary or secondary.[25] The primary form is caused by an underlying genetic disorder—familial hyperlipoproteinemia—that includes several subtypes: type I familial hyperchylomicronemia, type IIa familial hypercholesterolemia (FH), type IIb familial combined hyperlipidemia, type III familial dysbetalipoproteinemia, type IV familial hypertriglyceridemia, and type V familial mixed hyperlipidemia. The secondary form is associated with systemic diseases, such as chronic renal failure,

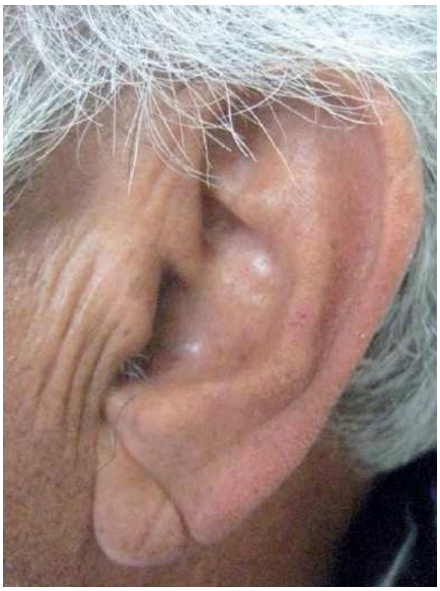

Fig 3. Earlobe crease. Frank's sign—diagonal earlobe crease. Adapted from Friedlander et al.[7] © 2012 Medicina Oral S.L.

nephrotic syndrome, hypothyroidism, diabetes, and obstructive liver disease. Medications such as retinoids, corticosteroids, HIV protease inhibitors, and cyclosporine have all been associated with dyslipidemias.[26]

Dyslipidemias are classified as having one or more of the following abnormalities: increased low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, and increased triglyceride levels.[25] Epidemiologic data regarding xanthomas are limited, and the prevalence varies according to the underlying disease pathology.[25,27] Over 100 million adults (53%) and 21% of children in the United States have at least one lipid abnormality, with 21% having mixed dyslipidemia (defined as high serum low-density lipoprotein cholesterol and one or both of the following: low high-density lipoprotein cholesterol or high triglyceride levels; 6% have all 3).[28] Dyslipidemias increase the risk of developing atherosclerosis, particularly for individuals with type II FH or type III dysbetalipoproteinemia.[11,28-31]

Clinical features. A xanthoma is a primary cutaneous sign caused by fatty deposits in the dermis and is classified as tendinous, tuberous, planar, or eruptive.[11,25] Tendinous xanthomas are mobile, firm nodules located on the tendons.[25,27] They are associated with FH and dysbetalipoproteinemia and are the most commonly observed xanthomas, seen in 40% to 50% of patients with FH.[11,31]Tuberous xanthomas are firm, reddish-yellow nodules, and are located on pressure areas, like the elbows, hands, and buttocks. Tuberous xanthomas are also associated with hypercholesteremic states, such as FH and familial dysbetalipoproteinemia (FD); however, they are only observed in 10% to 15% of patients with FH.[11,32]

Eruptive xanthomas are small, yellow papules with erythematous borders, less than 5 mm in size, and are commonly found on the extensor extremities, trunk, and buttocks.[11,32] They are seen in patients with types I, IV, and V familial hyperlipoproteinemias (particularly types with lipoprotein lipase deficiencies) and secondary to hypothyroidism, diabetes mellitus, or nephrotic syndrome.[11,25,33] Eruptive xanthomas are also seen as adverse effects of nilotinib and other highly active retroviral therapies.

Planar xanthomas can appear as thin, yellow or orange macules, patches, or plaques on the neck, palms (palmar), or chest.[11,25,33] These xanthomas are associated with FH, FD, and secondary causes, such as cholestasis-related hypercholesteremias (hepatic cholestasis, biliary cirrhosis). Planar xanthomas located near the eyes are called xanthelasmas and, in children, are indicative of type IIb hyperlipidemia. Xanthelasmas in adults are suggestive of dyslipidemia; half of adult patients who exhibit xanthelasmas are positive for some type of dyslipidemia. A subtype of planar xanthomas, xanthoma striatum palmare, presents as yellow skin discoloration around the creases of the palm. Palmar xanthoma is a highly specific diagnostic finding in FD and prevalent among 20% of patients with FD.[27,33,34]

Diagnosis and evaluation. A fasting lipid panel measuring total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, in addition to genetic testing, can diagnose an inherited dyslipidemia.[25,30,35] Additionally, assessments for cardiovascular disease should be completed among symptomatic patients, especially in those with tuberous xanthomas, tendinous xanthomas, or xanthelasmas, owing to the increased risk of atherosclerosis. The diagnosis can also be confirmed via a shave, punch, or excisional skin biopsy that identifies histologic features with the associated xanthoma, combined with correlated clinical findings.[30] The classic histologic features include foamy macrophages and findings of cholesterol clefts and fibrosis.[27,36] Differential diagnoses include xanthogranuloma necrobioticum and xanthoma difusum planum, which can precede monoclonal gammopathies or lymphoproliferative malignancies and should be ruled out, especially in normolipemic patients.[27] Sebaceous hyperplasia, juvenile xanthogranuloma, syringoma, and nodular basal cell carcinoma are also differential diagnoses, as they may have similar

Table II. Description of the etiology, clinical features, and diagnosis/evaluation of acute cardiac disease

Disease	Etiology	Clinical features[11,12]	Diagnosis/evaluation
Infective endocarditis	Inflammation of the endocardial lining of the heart/implanted material from bacterial or fungal infection[11] 80% of cases are caused by[11,12]: ❑ Staphylococcal aureus bacteria ❑ Streptococcal bacteria ❑ Enterococcal bacteria Intravenous drug use is the most common cause of right-sided infective endocarditis[11,12] 10th leading cause of death in the United States for all races and sexes ages 45 and older[12]	■ Splinter hemorrhages ■ Osler nodes ■ Janeway lesions ■ Roth spots ■ Erythroderma ■ Cellulitis ■ Purpura ■ Hemorrhage ■ Purpura fulminans ■ Skin necrosis ■ Conjunctival/palatal petechiae ■ New onset regurgitation murmur ■ Cardiac emboli ■ Valvular damage ■ Congestive heart failure	*Duke criteria[12] Major Criteria: ■ Positive blood culture result ■ Positive ECG determining endocardial involvement Minor Criteria: ■ Predisposing heart condition/intravenous drug use ■ Fever ■ Vascular phenomenon, such as Roth spots/Osler nodes (Fig 4, *A* and *B*[18]) ■ Presence of immunologic phenomenon ■ Serological evidence of active infection not related to minor criteria *Diagnosis is defined by fulfillment of 2 major, 1 major plus 3 minor, or 5 minor criteria
Acute rheumatic fever	Postinfectious sequela owing to prior streptococcal pharyngitis infection, causing an abnormal immune inflammatory response[11,13] Incidence is 5/100,000 in developed countries, with higher rates in developing countries[13] Most cases occur in children ages 5-15[13] 80% of patients experience carditis, most commonly affecting the mitral valve (~65%), followed by the aortic valve (~25%). This can cause regurgitation[13,14]	■ Subcutaneous nodules: Firm, painless, mobile, <2 cm. Typically founds on elbows, wrists, knees, and ankles[11,13] ■ Erythema marginatum: occurs in <5% of patients[13] Typically found on the torso, upper arms, and legs, never the face. Lesions with serpiginous rings with erythematous raised margins and central clearing[13,14] ■ Valvular disease ■ Arthritis: most common symptom, occurs in 70-75% of patients. Painful, erythematous, swollen joints. Begins in lower-extremity joints and migrates to upper extremities[14] ■ Carditis: pancarditis, including valvulitis[14] ■ Regurgitation: follows carditis. Most commonly affecting mitral, then aortic ■ Sydenham chorea: latent manifestation[14] ■ Congestive heart failure: also follows carditis[12,13]	*Jones criteria[11,13] Major Criteria: ■ Carditis, clinical and/ or subclinical ■ Chorea ■ Erythema marginatum ■ Subcutaneous nodules ■ Arthritis in distinct population subsets* Minor Criteria: ■ ECG abnormalities or evidence of heart block ■ CRP ≥3.0 mg/dL ■ ESR ≥30-60 mm* ■ Fever ■ Arthritis in distinct population subsets* ■ Chest radiograph to determine cardiomegaly *Diagnosis is defined by fulfillment of: Initial rheumatic fever: 2 major or 1 minor plus 2 minor Recurrent rheumatic fever: 2 major, 1 major plus 2 minor, or 3 minor criteria

Continued

Table II. Cont'd

Disease	Etiology	Clinical features[11,12]	Diagnosis/evaluation
Kawasaki disease	Unknown etiology causing multisystem inflammatory process. Suspected infectious etiology. Characterized by an immune mediated vasculitis, prolonged fever, and acute inflammation[11,15] 1/80 Japanese children develop Kawasaki by age 5[11,15,16] Most commonly acquired cardiac disease in children, with 25% of children developing coronary artery abnormalities[11,16]	■ Diffuse, generalized exanthem as morbilliform, targetoid, or scarlatiniform ■ Coronary artery aneurysm, most common complication ■ Bilateral, nonexudative conjunctivitis (Fig 5)[17] ■ Periungual desquamation of fingers and toes (Fig 6)[17] ■ Erythema, dryness, and bleeding of oral mucous membrane (Fig 7)[17] ■ Groin erythema and desquamation (Fig 8)[17] ■ "Strawberry tongue" ■ Peripheral extremity edema ■ Cervical adenopathy, commonly unilateral and nontender ■ Coronary artery dilation ■ Arrhythmia ■ Myocarditis, in 50% of patients ■ Pericarditis, in 25% of patients ■ Sudden death, with myocardial infarction as the main cause	Diagnosis based on the presence of fever lasting 5+ days and 4/5 clinical features[11,15,16] • Nonpurulent bulbar conjunctival injection[11,15,16] • Red, swollen dry, bleeding lips[11,15,16] • Redness of hands and feet[11,15,16] • Cervical lymphadenopathy >1.5 cm[11,15,16] • Echocardiography to determine coronary artery aneurysm, dilation, or disease[11,15,16]

Major diagnostic criteria arthritis in distinct population subsets: Polyarthritis is only found in LR population. Monoarthritis or polyarthritis or polyarthralgia in MR and HR populations.
Minor diagnostic criteria arthritis in distinct population subsets: Polyarthritis is found in LR population. Monoarthritis or polyarthritis or polyarthralgia in MR and HR populations.
CRP, C-reactive protein; *ECG*, electrocardiogram; *ESR*, erythrocyte sedimentation rate.
*ESR dependent on population risk, ESR ≥30 mm for moderate risk (MR) to high risk (HR) populations and ≥60 mm for low risk (LR) populations.

presentations. Dyslipidemia-associated xanthomas require the management and monitoring of lipid levels, especially to prevent the development of atherosclerotic disease and associated comorbidities, including arterial thrombosis, coronary ischemia, abdominal aortic aneurysm, peripheral arterial disease, and carotid artery disease.[30,31]

Cardiac amyloidosis

Key Points

- Key skin findings of amyloid light chain (AL) amyloidosis include scattered, nontraumatic ecchymoses and periorbital pinch purpura.
- Diastolic heart failure secondary to restrictive cardiomyopathy is the main finding in cardiac amyloidosis.
- Abdominal fat pad excisional biopsy and the positive presence of amyloid deposits in biopsy confirm the diagnosis.

Overview. Cardiac amyloidosis, the primary determinant of the prognosis in systemic amyloidosis, is characterized by the infiltration of the myocardium by amyloid proteins.[11,37-40] Amyloid proteins are abnormal proteins formed from extracellular deposits. The replacement of normal myocardial contractile elements with deposits of amyloid can lead to alterations in cellular metabolism, calcium transport, and receptor regulation and cellular edema. The major subtypes of systemic amyloidosis that infiltrate the heart include primary AL amyloidosis, secondary amyloidosis, familial amyloidosis, and senile systemic amyloidosis.[11,41]

Table III. Overview of skin findings in chronic cardiac diseases

Cardiac disease	Skin findings	Diagnosis/evaluation
Cholesterol embolization syndrome	■ Blue toe syndrome ■ Livedo reticularis ■ Erythematous lesions ■ Petechiae ■ Ecchymosis ■ Splinter lesions ■ Cyanosis ■ Ulcerations	■ Histological evidence of cholesterol clefts ■ Computed tomography angiography ■ Magnetic resonance angiography
Lipid disorders	■ Tendinous xanthomas ■ Tuberous xanthomas ■ Plantar xanthomas ■ Eruptive Xanthomas	■ Lipid panel
Cardiac amyloidosis	■ Ecchymoses ■ Periorbital pinch purpura ■ Shiny waxy translucent papules ■ Macroglossia ■ Nail dystrophy ■ Cutis laxa	■ Biopsy + Congo Red staining
Cardiac myxomas	■ Clubbing of fingers ■ Erythematous macules/papules on extremities ■ Blue nevi ■ Lentigines ■ Serpiginous lesions ■ Livedo reticularis ■ Petechiae ■ Splinter lesions ■ Hemorrhages ■ Raynaud syndrome	■ TTE ■ TEE ■ Contrast tomography ■ MRI

MRI, Magnetic resonance imaging; *TEE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography.

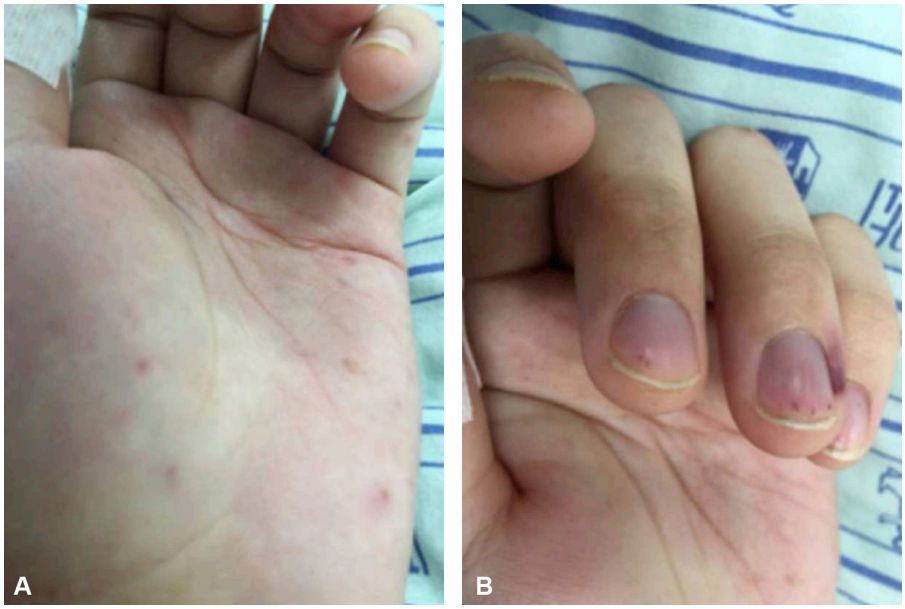

Fig 4. **A** and **B,** Janeway lesions, osler nodes, and splinter hemorrhages. Janeway lesions, osler nodes, and splinter hemorrhages on the hands seen in infective endocarditis. Adapted from Park et al.[18] Courtesy of: © 2019 The Korean Dermatological Association and The Korean Society for Investigative Dermatology

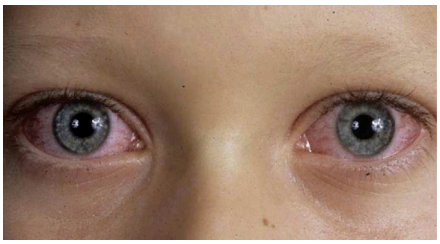

Fig 5. Nonexudative bulbar conjunctival injection seen in Kawasaki disease. Nonexudative bulbar conjunctival injection with a rim of sparing immediately around the iris. Adapted from Pride et al[17] with permission from Science Direct.

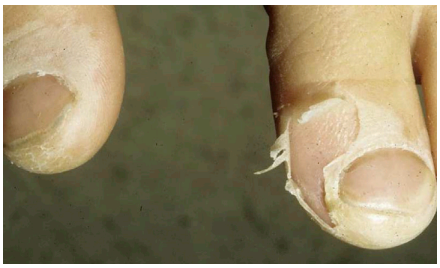

Fig 6. Desquamation seen in Kawasaki disease. Fine desquamation beginning in the periungual area as a late finding of Kawasaki disease. Adapted from Pride et al[17] with permission from Science Direct.

AL amyloidosis is a type of plasma cell dyscrasia and is the most common type involving the heart. Secondary amyloidosis results from the accumulation of amyloid A fibrils formed from an acute-phase reactant and is seen in chronic inflammatory conditions. Familial amyloidosis is less common than primary amyloidosis and is caused by an autosomal dominant mutation, most frequently in the transthyretin gene. Senile systemic amyloidosis affects approximately 25% of patients over the age of 80 and has a better prognosis.[38] Few epidemiological data have been published for amyloidosis; therefore, its exact prevalence is unknown. AL amyloidosis is the most commonly diagnosed form of amyloidosis, with approximately 2500 cases of AL amyloidosis diagnosed annually in the United States.[39] Both genders are nearly equally affected, and the disease is usually diagnosed at the age of 55 to 60 years. Amyloidosis has a poor prognosis, as cardiac involvement results in death in about 6 months after the onset of congestive heart failure. However, a new medication developed to target transthyretin, resulting in a reduction in cardiac amyloid deposition, has shown promise in improving mortality and reducing cardiovascular-related hospitalizations.[42]

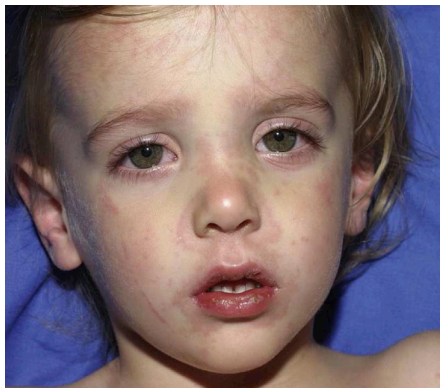

Fig 7. Cracked lips seen in Kawasaki disease. Kawasaki disease with red, cracked lips and conjunctival injection. Adapted from Pride et al[17] with permission from Science Direct.

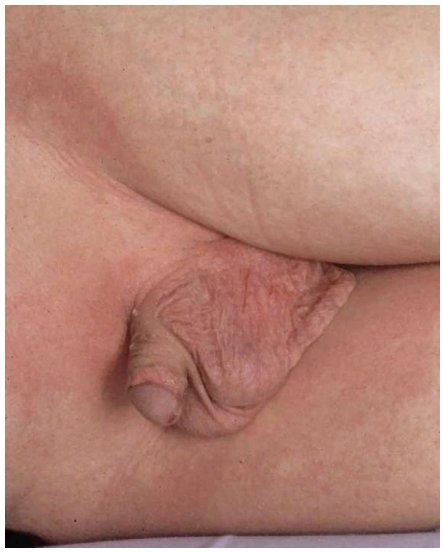

Fig 8. Erythema in diaper region found in Kawasaki disease. Kawasaki disease manifesting with erythema in the diaper region. Adapted from Pride et al[17] with permission from Science Direct.

Clinical features. Cutaneous signs are valuable in the diagnosis of AL amyloidosis and seen in up to 40% of patients.[11] The key skin findings include scattered, nontraumatic ecchymoses, and periorbital pinch purpura (purpura occurring after minor trauma or with the pinching of the skin) that may not always precede other lesions.[11,39,43] Periorbital purpura and petechial lesions of the eyelids are the results of vascular fragility.[44] Smooth, waxy papules or nodules involving the face, neck, chest, periumbilical region, perineum, or intertriginous areas may be observed in primary amyloidosis.[45] Macroglossia is almost pathognomonic for AL amyloidosis but is

present only in approximately 10% of cases.[39] Nail dystrophy and cutis laxa represent other typical, although nonspecific, systemic symptoms.[46] Heart failure secondary to restrictive cardiomyopathy is the main finding in cardiac amyloidosis.[11,38] This may present as lower-extremity bilateral edema, abdominal bloating, or shortness of breath with crackles on pulmonary examination. There may also be the involvement of the cardiac conduction system, causing different types of heart block and arrhythmias on electrocardiography, as well as that of the pulmonary vasculature, causing pulmonary hypertension and cor pulmonale.[38]

Diagnosis and evaluation. The diagnosis of cardiac amyloidosis is definitively established by endomyocardial biopsy or indirectly established by echocardiographic evidence of amyloidosis and the histologic confirmation of amyloid in noncardiac tissue.[11,37,38] Several tests, including a 12-lead electrocardiogram and cardiac biomarkers, further corroborate cardiac involvement but are not specific when interpreted in isolation.[38] An echocardiogram is typically the first study to evaluate for cardiac involvement and may demonstrate ventricular wall thickening and speckling due to the amyloid deposits. Restricted systolic function may also be observed in the advanced phases of the disease.[39] Abdominal fat pad excisional biopsy has high sensitivity for AL amyloidosis. The presence of amyloid deposits in any biopsy specimen is first confirmed or excluded by Congo Red dye and, in the case of positivity, with apple-green birefringence when placed under polarized light. Surgical skin biopsy of subcutaneous fat combined with rectal mucosal biopsy may also confirm the diagnosis of AL amyloidosis; conversely, a negative result indicates an unlikely diagnosis.[47,48] Punch or excisional biopsies of purpuric lesions may also be performed and often reveal amorphous, eosinophilic masses in the dermis and subcutis with perivascular chronic inflammation. Skin biopsies characteristically show diffuse amyloid deposition in the form of nodules and plaques. The most common sites of amyloid deposits include the papillary dermis, around blood vessels and cutaneous appendages, and within individual fat cells.[42]

Cardiac myxomas

Key points

- Cutaneous symptoms of cardiac myxomas are secondary to tumor-related thrombi or embolic fragments and include splinter hemorrhage, petechiae, livedo reticularis, and Raynaud disease.
- The diagnostic test of choice is TEE/TTE to determine the size, location, and mobility of the myxoma.
- Differential diagnoses include papillary fibroelastomas, rhabdomyomas, right atrial masses, valvular vegetations, metastatic tumors, and angiosarcomas.

Overview. Cardiac myxomas are the most common primary cardiac tumors found in adults.[11] Cardiac myxomas are rare and have an annual incidence of 0.5 to 1.0 per 1,000,000 individuals.[49] Approximately 75% of cardiac myxomas arise from the left atrium, 18% from the right atrium, 4% from the left ventricle, and 3% from the right ventricle.[50,51] Most (80%) are sporadic, and roughly 20% of these tumors have an abnormal genetic phenotype. Five percent of myxomas have an autosomal dominant genetic inheritance and are associated with the Carney complex.[11,50,52,53] Although the prevalence of Carney syndrome is rare, cardiac myxomas are a component, in addition to lentigines, mucocutaneous myxomas, and blue nevi.[11,49,50,52] Most cardiac myxomas are benign, and the manifestations are secondary to the tumor and its location. Atrial tumors can cause mitral or pulmonic obstructions, pulmonary hypertension, and right-sided heart failure. Tumors that originate from the ventricles can cause ventricular outflow obstruction.[50,53] There is a higher prevalence in women (by a ratio of 3:1), and the peak incidence is in those 40 to 60 years of age.[11,49]

Clinical manifestations. Constitutional symptoms are seen in 90% of patients; these include weight loss, fever, fatigue, anemia, and the clubbing of the fingers.[50,53] Cutaneous symptoms secondary to tumor-related thrombi or emboli fragments occur in 30% to 50% of patients.[49] Skin findings include splinter hemorrhages, petechiae, LRC, and Raynaud syndrome.[11] Embolization can also affect the central nervous system, abdomen, and lungs. Pruritic erythematous macules/papules and serpiginous lesions on the extremities are also associated with the Carney complex. Cardiac symptoms secondary to valvular obstruction include dyspnea on exertion, orthopnea, pulmonary edema, cough, peripheral edema, and chest pain.[50,53] While these symptoms are commonly seen in infective endocarditis, Janeway lesions, Osler nodes, and Roth spots are highly suggestive of infective endocarditis and may differentiate infective endocarditis from atrial myxomas (Fig 4, *A* and *B*).[18,54] The relief of symptoms upon a change in position is indicative of cardiac myxomas mimicking mitral valve disease. Abnormal auscultatory findings include a loud, split S2 and

low-pitched, rumbling, middiastolic murmur or "tumor plop."

Diagnosis and evaluation. The diagnostic test of choice is the TEE/TTE to determine the size, location, and mobility of the myxoma.[50-52] TEE is superior to TTE for the visualization of left atrial myxomas. Contrast tomography and MRI can also provide further visualization of intracardiac masses. Imaging is helpful in displaying left atrial hypertrophy, arrhythmias, and conduction blocks and is useful for preoperative assessment prior to surgical removal (ie, the only treatment for myxomas).[11,50] The hemodynamics of the mitral valve and pulmonary vein can be measured via Doppler flow.

CONCLUSION

The recognition of skin findings associated with cardiac disease is imperative for appropriate patient referral and follow-up. Many cardiac diseases display cutaneous symptoms unique to their disease pathophysiologies, and the identification of these distinctions is vital to disease detection. Early diagnosis and prompt treatment may halt the progression of many cardiac diseases and improve patient mortality risk.

Conflicts of interest

None disclosed.

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