

Cardiac involvement in dermatological disorders: A narrative review

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Abstract

Recent studies have highlighted several pathogenic connections between skin disorders and cardiac manifestations. Dermatologists frequently encounter several genetic or inherited skin conditions that can have significant cardiac implications, including septal defects, cardiomyopathy, and valvular heart disease, which may sometimes be life-threatening. In this review, primary cutaneous disorders having cardiac manifestations are described. A comprehensive narrative review of the literature was conducted by searching articles published through November 2023 in the PubMed and Google Scholar databases. Original research articles, review articles, case reports, case series and other relevant English-language publications were included. The review identified several congenital diseases, inflammatory conditions, connective tissue disorders, and adverse drug reactions that have both skin and cardiac involvement.

Diagnosing these cardiac manifestations in patients with skin conditions is crucial for appropriate management, timely intervention and effective patient counselling.

Key words: Cardiac disorders, heart, prognosis, skin

Introduction

Several diseases impact both the skin and heart, often as part of a systemic condition or syndrome that can affect multiple organ systems. Recent findings have described various pathogenic links between skin disorders and cardiac involvement. Dermatologists frequently encounter several genetic or inherited skin conditions that manifest with cardiac complications, such as septal defects, cardiomyopathy, and valvular heart disease. These cardiac manifestations can sometimes be life-threatening to the patients.

Dermatologists should be aware of the potential cardiac involvement in various dermatological disorders. Patients with inherited or congenital syndromes, inflammatory dermatoses, connective tissue disorders, or adverse drug reactions affecting both the skin and heart may present to

dermatologists. Identifying cutaneous manifestations can help uncover underlying cardiac conditions or alert patients to their risk of developing heart disease. Therefore, early diagnosis by a dermatologist, followed by timely referral to a cardiologist, can significantly improve patient outcomes and prognosis.

The objective of this review is to describe primary cutaneous disorders having cardiac manifestations. A comprehensive narrative review of the literature was conducted by searching articles published in PubMed and Google Scholar databases using the keywords “cardiac disorders in dermatology”, “cardiac manifestations in skin disorder” and “cardiac and dermatological disorders”. This review included original articles, review articles, case reports, case series, and other relevant publications in the English language up to November 2023.

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A. Congenital syndromes

1. RASopathies

Numerous genetic syndromes have been identified under the term RASopathies.¹ These include Noonan syndrome, LEOPARD syndrome (Noonan with multiple lentiginos syndrome), Costello syndrome, cardiofaciocutaneous syndrome, and neurofibromatosis-1. A common feature among these syndromes is mutations in the rat sarcoma-mitogen-activated protein kinase (Ras-MAPK) signal transduction pathway. Cardiac manifestations associated with RASopathies often include atrial septal defects (ASD), pulmonary valve stenosis, and hypertrophic cardiomyopathy.

a. Noonan syndrome

It is an autosomal dominant disorder characterised by facial dysmorphism, postnatal growth retardation, and a range of cardiac defects including atrial septal defects (ASD), pulmonary valve stenosis, hypertrophic cardiomyopathy, and tetralogy of Fallot. Approximately 50% to 80% of individuals with Noonan syndrome develop congenital heart disease.² Cutaneous manifestations such as cutis verticis gyrate and lymphedema are also observed. Several genes have been implicated in the causation of Noonan syndrome, including *PTPN11* (found in 50% of cases), *RAF1*, *KRAS*, *SOS1*, *MEK1* (*MAP2K1*), and *BRAF*. All of these genetic mutations lead to a gain of function in the *Ras/MAPK* signalling pathway.³

b. Noonan with multiple lentiginos syndrome (LEOPARD syndrome)

It is an autosomal dominant genetic disorder which was previously known by the acronym LEOPARD syndrome (Lentigenes, ECG abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness). It occurs due to a missense mutation in the *PTPN11* gene, which disrupt the neuroectodermal layers.⁴ Cutaneous findings include multiple lentiginos involving the face, neck, and upper trunk with sparing of mucosal surfaces.⁵ Cardiac abnormalities associated with the syndrome can include pulmonic stenosis, hypertrophic cardiomyopathy, and, less commonly atrial septal defects (ASD), subaortic stenosis, mitral valve defects, and atrial myxoma. Additionally, patients may present with abnormal ECG findings.

c. Costello syndrome

This is an autosomal dominant genetic disorder caused by mutations in the Ras oncogenes *HRAS* or *KRAS*. It is characterised by short stature, feeding difficulties in infancy, failure to thrive, developmental delays, hypotonia, and joint laxity.⁶ Key cutaneous findings include periorificial papillomas, sparse curly hair, lax skin on the hands and feet, deep palmoplantar creases, and acanthosis nigricans. Cardiac manifestations in Costello syndrome often involve hypertrophic cardiomyopathy, pulmonary valve stenosis, supraventricular tachycardia, and arrhythmias.⁷

d. Cardiofaciocutaneous (CFC) syndrome

This is an autosomal dominant disorder caused by mutations in the *Ras/MAPK* pathway. The most common mutations occur in genes such as *BRAF*, *MEK1*, *MEK2* and *KRAS*.⁸ Some of the cutaneous findings include sparse, curly, friable hair with the absence of eyebrows and eyelashes. Patients also experience keratosis pilaris, generalised ichthyosis-like scales, palmoplantar hyperkeratosis, ulerythema ophryogenes, melanocytic naevi, and eczema. In terms of cardiac manifestations, patients may have hypertrophic cardiomyopathy, atrial septal defects (ASD), patent ductus arteriosus (PDA), pulmonary valve stenosis, other valvular dysplasia, arrhythmias, and tetralogy of Fallot.⁹

e. Neurofibromatosis 1

This is a multisystem autosomal dominant disorder that occurs due to a mutation in the tumour suppressor gene, *NF-1*, located on the chromosome 17q encoding for neurofibromin.¹⁰ Cutaneous findings include café au lait macules, neurofibromas, axillary freckling, neurofibromas, and dysmorphic facial features.¹¹ Cardiac manifestations such as hypertension secondary to aortic coarctation, pulmonic stenosis, and aortic valve stenosis have also been described.

2. Carney complex

Carney complex was previously known as LAMB (Lentigenes, Atrial myxoma, Mucocutaneous myxoma and Blue naevi) and NAME (Naevi, Atrial myxoma, Myxoid neurofibromas, and Ephelides). It is either an autosomal dominant or X-linked disorder caused by mutations in the *PRKARIA* gene.¹² This condition is characterised by cutaneous features of lentiginos similar to Noonan syndrome but also involves mucosal features. A key manifestation of the Carney complex is the presence of cardiac myxomas.

3. H syndrome

It is an autosomal recessive genodermatosis with progressive sclerodermoid cutaneous changes with overlying hypertrichosis and hyperpigmentation on thighs, limbs, and lower trunk.¹³ It is caused by a mutation in the *SLC29A3* gene, which encodes the hENT3 nucleoside transporter.¹⁴ The H syndrome also includes Heart abnormalities, Hepatomegaly, Hypogonadism, Hallux valgus, Hyperglycemia, and decreased Height. Cardiac manifestations include mitral valve prolapse, atrial and ventricular septal defects (ASD, VSD) and cardiomegaly.

B. Inherited syndromes

1. Pseudoxanthoma elasticum

It is an autosomal recessive connective tissue disorder characterised by mutations in the *ABCC6* gene on chromosome 16.¹⁵ Cutaneous findings are very characteristic, with yellowish waxy papules in the flexural areas including the neck, lower lip, intertriginous areas, and the antecubital and popliteal fossae. The redundant lax skin of the neck resembles that of plucked chicken skin. Ocular manifestations

are another hallmark of the disease. Cardiovascular manifestations include premature atherosclerotic vascular disease, restrictive cardiomyopathy, and mitral valve prolapse.^{16,17}

2. Marfan syndrome

This autosomal dominant disorder is associated with a mutation in the gene encoding fibrillin-1, located on chromosome 15q. The characteristic skin features include reduced subcutaneous fat, extensive striae seen on the trunk, buttocks, hips, thighs, breasts, and elastosis perforans serpiginosa (EPS). Additionally, it can lead to heart-related issues such as aortic and mitral valve regurgitation, as well as dissection or dilation of the ascending aorta.¹⁸

3. Ehlers-Danlos syndrome

This is a group of disorders being a consequence of mutations in the genes encoding for collagens. There are six major subdivisions or subtypes of this syndrome. Cutaneous findings include a fish mouth appearance of scars and cigarette paper scars typically found on knees and elbows in type I and II. Generalised joint hypermobility is seen in type III. Thin translucent skin, elastosis perforans serpiginosa (EPS), and diffuse ecchymoses are present in type IV (vascular type).¹⁹ Cardiac manifestations include tricuspid and mitral regurgitation or prolapse, and aortic root dilation in types I, II, and III. Arterial aneurysms, rupture, and dissection may be seen in the vascular type.

4. Cutis laxa

Cutis laxa is a condition that can be inherited or acquired as an autosomal recessive, dominant, or X-linked disorder. It is characterised by a progressive and generalised loss of skin elasticity.²⁰ There are different types of cutis laxa, with cardiac manifestations observed in some individuals. Types I and III cutis laxa include symptoms such as pulmonic stenosis, right heart failure, aortic dilation, and rupture.²¹

5. Inborn errors of metabolism

a. Homocystinuria

Homocystinuria is an autosomal recessive disorder characterised by homozygous cystathionine *B*-synthase deficiency. The deficiency leads to the accumulation of homocysteine, causing disruption of collagen cross-linking. Cutaneous findings include dyspigmentation, livedo reticularis, tissue paper scars, malar rash, large facial pores, and superficial thrombophlebitis.²² Cardiovascular manifestations include both arterial and venous thrombosis, pulmonary embolism, and atherosclerosis.

b. Fabry disease

It is an autosomal recessive disease due to a deficiency of *α*-galactosidase A. Cutaneous findings include angiokeratomas on the penis, scrotum, perineal area, lower trunk, and oral mucosa. Punctate telangiectasias in the upper chest and axillae, hypohidrosis and anhidrosis are also seen.²² Cardiovascular manifestations include valvular abnormalities,

conduction defects, hypertrophic cardiomyopathy, and atherosclerosis.

c. Lipid disorders

These include xanthomas, which are the hallmark skin lesions.²³ Xanthelasma is the most common manifestation of cutaneous xanthoma. Xanthelasma are small yellow papules seen on the upper and lower eyelids. According to Christoffersen *et al.*, xanthelasma can occur even when serum lipid levels are normal.²⁴ It should be considered as a risk factor for ischaemic heart disease and myocardial infarction, as it is seen as a cutaneous marker of atherosclerosis.²⁴ About half of xanthelasma patients are hyperlipidaemic. Additionally, xanthelasma is related to various other lipid abnormalities, such as macrophage cholesterol ester accumulation, increased lipid peroxidation, and apolipoprotein E phenotype like apoE4/E3.²⁵

6. Progeria

It is an autosomal dominant premature ageing syndrome. It has characteristic features of wrinkling of the skin, alopecia, and osteoporosis. Premature and accelerated atherosclerosis are the cardiac manifestations seen in progeria.²⁶

7. Werner syndrome

It is an autosomal recessive disorder characterised by cutaneous findings of loss of subcutaneous fat, sclerodermoid skin changes, premature graying, and alopecia. Cardiac manifestations include aortic stenosis, mitral valve regurgitation, valvular calcification, and myocardial infarction.²⁷

8. PHACE syndrome

It is a syndrome associated with segmental infantile hemangioma. PHACES include Posterior fossa malformation, Haemangiomas, Arterial anomalies, Cardiac defects and Coarctation of aorta, Eye anomalies, and sternal defects. Cardiac manifestations may include aortic coarctation and aneurysm, ventricular septal defects (VSD), pulmonic stenosis, tetralogy of Fallot, patent foramen ovale, tricuspid atresia and double aortic arch.²⁸

9. Naxos syndrome

It is an autosomal recessive condition, caused by 2-base pair deletion in the *JUP* gene.²⁹ Dermatological symptoms include woolly scalp hair, diffuse palmoplantar keratoderma (non-epidermolytic), hyperhidrosis, and follicular hyperkeratosis. Cardiac manifestations include arrhythmogenic right ventricular (RV) cardiomyopathy and syncope.

10. Carvajal syndrome

It is an autosomal recessive condition and is somewhat similar to Naxos syndrome. This condition is caused by a mutation in the desmoplakin gene, which is due to the deletion in the homozygous single nucleotide of the last exon of the *DSP* gene.³⁰ The cutaneous findings include woolly scalp hair, skin fragility, striate epidermolytic palmoplantar

keratoderma, transient pruritic blistering on the trunk, and clubbing of fingernails. In contrast to Naxos syndrome, the cardiac manifestation of this condition is left-sided (LV) dilated cardiomyopathy.³¹

C. Inflammatory dermatoses

1. Psoriasis

Psoriasis is a chronic inflammatory disorder primarily affecting skin, nails, and joints. Recent studies have demonstrated that it is not merely a localised condition but a systemic inflammatory disease with varied comorbidities, including an increased risk of cardiovascular diseases. In a cohort study, Ogdie *et al.* reported an increased risk of major adverse cardiovascular events such as stroke, myocardial infarction, and cardiovascular mortality in psoriasis patients.³² Moreover, moderate to severe psoriasis is linked to an increased prevalence of hypertension. Psoriasis is also associated with insulin resistance, which predisposes individuals to diabetes. When psoriasis coexists with diabetes, there is a higher incidence of both micro- and macrovascular complications. In addition, there is evidence of psoriasis association with hypertriglyceridemia, hypercholesterolemia, and an altered lipid profile characterised by decreased high-density lipoprotein (HDL) cholesterol and increased low-density lipoprotein (LDL) cholesterol, which further predisposes patients to cardiovascular complications.^{33,34}

2. Pemphigus

Pemphigus is a group of autoimmune immunobullous diseases which affect the skin and mucosae. Cardiovascular disease (CVD) is often associated secondarily with pemphigus with increased cardiovascular risk that may be due to chronic inflammation, decreased physical activity secondary to painful cutaneous and mucosal erosions, or the prolonged use of high-dose systemic corticosteroids.³⁵ There are various cardiovascular complications in pemphigus patients, including cardiac dilatation and dysfunction, autoimmune myocarditis, and arrhythmias.³⁶

3. Erythroderma

A pre-existing dermatosis such as pityriasis rubra pilaris, eczema (atopic or contact dermatitis), psoriasis, mycosis fungoides, and pemphigus foliaceus can sometimes progress to erythroderma, a severe condition characterised by widespread erythema and scaling all over the body. Erythroderma patients have increased cardiac output which may cause a high-output cardiac failure in an already compromised cardiovascular system (hypertensive, ischemic, or valvular heart disease).

4. Hidradenitis suppurativa

Hidradenitis suppurativa is a chronic, recurrent, inflammatory debilitating skin disease. Cutaneous findings include painful inflamed nodular lesions and sinus formation in the apocrine gland-bearing areas of the body.³⁷ Patients with hidradenitis suppurativa may develop cardiovascular manifestations such as hypertension and ischaemic heart disease secondary to

the chronic inflammation associated with the disease and obesity.³⁸

5. Bullous pemphigoid

Bullous pemphigoid is the most common autoimmune bullous disorder characterised by tense bullae, urticarial lesions, and pruritus. Cardiovascular diseases are frequently observed as the most common co-morbidities among bullous pemphigoid patients.³⁹ Cardiac manifestations documented in the literature include hypertension, congestive heart failure, arrhythmias, dilated cardiomyopathy, and valvular diseases.⁴⁰

Autoimmunity and systemic inflammation have been documented to increase the risk of CVD in diseases mentioned primarily, however, secondarily the risk increases with the advent of immunosuppressive/immunomodulatory treatment modalities such as high dose steroids, cyclosporine, azathioprine, and rituximab.⁴¹

D. Connective tissue disorders

1. Systemic sclerosis

Systemic sclerosis is an autoimmune disorder leading to extensive fibrosis and microvascular injury. It is characterised by skin thickening, Raynaud's phenomenon, and fibrosis of internal organs.⁴² Cardiac manifestations include an increased risk of cardiovascular disease, congestive cardiac failure, cardiomyopathy, arrhythmias, and myocardial infarction.⁴³

2. Dermatomyositis

Dermatomyositis is a rare autoimmune disease characterised by symmetrical proximal muscle weakness and associated skin manifestations which include facial rash, eyelid erythema and edema (heliotope rash), nail fold changes, Gottron's papules, vasculopathic ulcers, and flagellate erythema. Cardiac manifestations include congestive heart failure, arrhythmias, myocardial fibrosis, and myocardial infarction.⁴⁴

3. Systemic lupus erythematosus

Systemic lupus erythematosus is an autoimmune disorder with multiple organ manifestations. Cutaneous findings include a malar rash, discoid rash, photosensitivity, and oral ulceration. Cardiac manifestations include pericarditis (which is a diagnostic criteria), valvular dysfunction, endocarditis, coronary artery disease, atherosclerosis, and myocardial infarction.⁴⁵

E. Adverse drug reaction

1. DRESS (Drug rash with eosinophilia and systemic symptoms) syndrome

DRESS is a delayed-type hypersensitivity reaction that involves activated T-cells, leading to eosinophilia. It is characterised by morbilliform rash, facial edema, fever, and systemic involvement. Cardiac manifestations in DRESS are under-recognised with an incidence of 2% to 20%.⁴⁶ It includes congestive heart failure, hypersensitivity myocarditis, and acute necrotising eosinophilic myocarditis.⁴⁷

Table 1: Summary of cardiac involvement in dermatological disorders.

A. Congenital syndromes	1. RASopathies	a. Noonan syndrome b. Noonan with multiple lentiginos syndrome (LEOPARD syndrome) c. Costello syndrome d. Cardiofaciocutaneous (CFC) syndrome e. Neurofibromatosis 1
	2. Carney complex	
	3. H syndrome	
B. Inherited syndromes	1. Pseudoxanthoma elasticum 2. Marfan syndrome 3. Ehlers-Danlos syndrome 4. Cutis laxa 5. Inborn errors of metabolism 6. Progeria 7. Werner syndrome 8. PHACE syndrome 9. Naxos syndrome 10. Carvajal syndrome	
C. Inflammatory dermatoses	Psoriasis, Pemphigus, Erythroderma, Hidradenitis Suppurativa, Bullous Pemphigoid	
D. Connective tissue disorders	Systemic sclerosis, Dermatomyositis, Systemic Lupus Erythematosus	
E. Adverse drug reaction	DRESS, SJS/TEN	
F. Familial hypercholesterolemia		

2. Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)

SJS/TEN are the severe adverse cutaneous reactions which predominantly involve the skin and mucosae. Cutaneous manifestations are characterised by haemorrhagic erosions, erythema, and epidermal detachment. Cardiac manifestations are rare and include left ventricular dysfunction, cardiomyopathy, atrial fibrillation, and pericarditis.⁴⁸

F. Familial hypercholesterolemia

It is an autosomal co-dominant condition characterised by loss of function mutation in the low-density lipoprotein (LDL) cholesterol receptors leading to high total and LDL cholesterol presenting with tendinous xanthomas, especially of Achilles tendons, and premature onset of cardiovascular disease (CVD). There is a three-fold increased risk of CVD in patients with xanthomas.⁴⁹

Conclusion

Various cardiac manifestations can occur in patients with different skin disorders [Table 1]. These cardio-cutaneous associations may aid dermatologists in understanding the etiopathogenesis, elucidating diagnostic modalities, and planning treatment. It is imperative for dermatologists to recognise various cardiac manifestations or risk factors of dermatological conditions for early evaluation and referral for management.

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