Chronic Systemic Inflammatory Skin Disease as a Risk Factor for Cardiovascular Disease

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Abstract: Chronic systemic skin disease and cardiovascular disease are multisystem disorders which have been associated with each other for centuries. Recent research has strengthened this association, particularly in systemic inflammatory disease. Here we explore the current literature on psoriasis, hidradenitis suppurativa, lupus erythematosus, acanthosis nigricans, atopic dermatitis, and bullous pemphigoid. Psoriasis is a chronic inflammatory disorder that has been labeled as a risk-modifier for hyperlipidemia and coronary artery disease by the American College of Cardiology ACC lipid guidelines. Cardiovascular disease is also found at a significantly higher rate in patients with hidradenitis suppurativa and lupus erythematosus. Some associations have even been noted between cardiovascular disease and acanthosis

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nigricans, atopic dermatitis, and bullous pemphigoid. While many of these associations have been attributed to a shared underlying disease process such as chronic systemic inflammation and shared underlying risk factors, these dermatologic manifestations can help to identify patients at higher risk for cardiovascular disease. (Curr Probl Cardiol 2021;46:100799.)

Introduction

Cardiovascular disease is a leading cause of mortality worldwide with multisystem effects found beyond just the heart.[1] As skin is the largest and one of the most visible organs of the body, it is not surprising that numerous skin findings have been associated with heart disease throughout history. As early as 1770, associations were noted between various forms of cutaneous inflammation and diseases of the heart.[2] Recent advances in dermatology have solidified this association in a wide range of skin disease including psoriasis, hidradenitis suppurativa, and lupus erythematosus. Much of this association has been attributed to a shared underlying disease process such as chronic systemic inflammation, which has far-reaching effects including coronary atherosclerosis, obesity, and diabetes. Notably, this association has been gaining wider recognition with the latest ACC/AHA guidelines including "chronic inflammatory conditions, such as psoriasis, Rheumatoid arthritis (RA), lupus erythematosus" as a risk-enhancing factor in the assessment of cardiovascular risk.[3] Here we review the current literature on this association in psoriasis, hidradenitis suppurativa, lupus erythematosus, acanthosis nigricans, atopic dermatitis, and bullous pemphigoid.

Psoriasis

Psoriasis is a chronic, immune-mediated dermatologic condition that affects around 3% of adults.[4] The exact cause of psoriasis remains unknown; however, it is believed to be due to an underlying genetic predisposition and the interaction with several environmental factors. This interplay of environmental factors with genetics results in an immune activation of T cells targeting keratinocyte derived peptides.[5] Chronic plaque psoriasis severity can be assessed based on total body surface area (TBSA) involved and several studies have established associations between TBSA affected by psoriasis and an increased risk of cardio-metabolic diseases, independent of

traditional risk factors for them.[6-8] Due to these observations and associations, the recent lipid management guidelines from the American College of Cardiology (ACC), have labeled psoriasis as a chronic inflammatory disorder with a risk-enhancing propensity for atherosclerosis, necessitating discussions of early lipid-lowering therapy.[9]

The first reports of an association between psoriasis and vascular disease were described in 1978 by McDonald et al.[10] There has been mounting evidence indicating that psoriasis is a significant independent risk factor for cardiovascular disease.[6,11] Over the last fifteen years, several large studies have reported observations linking psoriasis with hypertension,[12-14] hyperlipidemia,[15] increased arterial stiffness,[12] subclinical coronary artery disease,[16-18] and myocardial infarction.[6]

Gisondi et al conducted a case-control study comparing blood pressure readings and arterial stiffness among patients with chronic plaque psoriasis compared to patients with other skin conditions.[12] The blood pressure was recorded immediately before tonometric recording. Carotid-femoral and carotid-radial pulse wave velocities were measured noninvasively using a tonometer. Patients with psoriasis had significantly higher pulse wave velocities than in controls. This significant difference persisted after adjustment for age, gender, smoking, body mass index, and hypertension. In their study, the duration of psoriasis was positively correlated with increased arterial stiffness ($r = 0.58$; $P < 0.001$), however, severity was not, this could be due to a small sample size of only 38 patients with psoriasis.[12]

In a population-based cross-sectional study in the United Kingdom, 1322 patients with psoriasis between the ages of 25 and 64 years were included to assess the impact of psoriasis on the control of hypertension. They defied uncontrolled HTN as >140/90. In their study, a significant positive correlation was observed between psoriasis severity (based on TBSA affected) and uncontrolled HTN. This relationship remained significant even after controlling for age, sex, body mass index, smoking and alcohol use status, presence of comorbid conditions (OR = 0.97; 95% CI, 0.82-1.14 for mild psoriasis; OR, 1.20; 95% CI, 0.99-1.45 for moderate psoriasis; and OR, 1.48; 95% CI, 1.08-2.04 for severe psoriasis; P= 0.01 for trend).[13] This further supports that psoriasis is a multiorgan inflammatory disorder not only affecting the skin but possibly also vascular endothelial function. Also, a systematic review and meta-analysis including over 300,000 patients with psoriasis studying the association between psoriasis and hypertension concluded that patients with psoriasis

were 1.5 times more likely to have hypertension compared to the general population (OR 1.58, 95% CI 1.42−1.76).[14]

In a case-control study by Stanik et al 221 patients with psoriasis and 718 participants without psoriasis were assessed for Coronary artery Calcium (CAC) scoring using a 64-detector CT scanner. CAC scoring is a valid tool to detect and even exclude subclinical coronary atherosclerosis in patients at low or indeterminate risk for coronary artery disease.[19] They concluded that having psoriasis was associated with having a CAC score >0, or >100 irrespective of disease severity. However, when a very high CAC score (>400) was used as the clinical outcome there was a significant association with having severe psoriasis, however not mild psoriasis. This finding suggests an association subclinical atherosclerosis irrespective of disease severity.[16]

One study sought to determine whether psoriasis is an independent risk factor for CAD in comparison to diabetes, which is a well-known major risk factor for atherosclerosis and cardiovascular morbidity and mortality. The study enrolled patients with psoriasis and age and sex-matched controls with type 2 diabetes mellitus, CAC scores >100 and >400 were insignificantly different; however, at least 5 times matched healthy controls. This also suggests that psoriasis may be an equivalent and independent risk factor for CAD as diabetes mellitus.[17]

A recent study using coronary computer tomography (CCTA) identified patients with psoriasis to have higher noncalcified plaque burden and similar high-risk plaque features compared to patients with hyperlipidemia, despite being younger in age and with less traditional risk factors for coronary artery disease. Repeat CCTA showed a significant decrease in total plaque burden and non-calcified plaque among patients with psoriasis whose disease severity improved at one year.[20] Furthermore, Elnabawi et al conducted a prospective study including 215 patients with a median Psoriasis Area Severity Index of 8.6, 121 of which were naïve to biological therapy at baseline, and obtained a CCTA at baseline and 1-year. Patients treated with biologic therapy exhibited a significant 6% reduction in noncalcified plaque burden and necrotic core volume, without effect on fibrous plaque burden. Additionally, patients receiving biologic therapy had a significant decrease in noncalcified plaque burden at 1 year compared to progression among patients treated with traditional nonbiologic therapy.[18] This is an important finding, demonstrating promising reversibility of sub-clinical coronary artery disease among patients with psoriasis without traditional risk factors for coronary artery disease. This supports the findings of proinflammatory

conditions associated with increased levels of Interleukin-1 in atherosclerosis and coronary artery disease.[21]

In a large prospective cohort study to determine the risk of myocardial infarction among patients with psoriasis, a total of 556,995 controls and 127,139 patients with mild psoriasis and 3,37 patients with severe psoriasis were followed for a mean duration of 5.4 years. Patients with psoriasis were classified as severe if they ever received systemic therapy. Overall, the incidence of MI was 2.0% among controls compared to 1.8% and 2.9% within the mild and severe psoriasis groups, respectively. The incidences per 1000 person-years for control patients and patients with mild and severe psoriasis were 3.58 (95% confidence interval [CI], 3.52-3.65), 4.04 (95% CI, 3.88-4.21), and 5.13 (95% CI, 4.22-6.17), respectively. Another interesting finding was younger patients with psoriasis were at higher risk for MI compared to older patients. This finding could be explained by having younger people with psoriasis in the study population.[6]

Psoriasis is a chronic inflammatory disorder that has been labeled as a risk-modifier for hyperlipidemia and CAD by the ACC lipid guidelines. In patients who do not meet the criteria for statin therapy, however, have psoriasis, individualized management and discussions are conducted between the provider and the patient regarding statin therapy are recommended.[9] An interesting study by Wu et al was conducted using the nurses' health study II database aiming to define a relationship between hypercholesterolemia and psoriasis and psoriatic arthritis. A total of 95,540 women were followed for 1,320,765 person-years, in which 646 patients were diagnosed with psoriasis and 165 with psoriatic arthritis. Hypercholesterolemia was associated with a 25% higher risk of incident psoriasis (HR = 1.25, 95% CI: 1.04, 1.50) and 58% increased risk of psoriatic arthritis (HR=1.58, 95% CI: 1.13, 2.23) in multivariate-adjusted models. They also concluded that having hypercholesterolemia for >7 years increased the risk of developing psoriasis.[15] This suggests a significant relationship between psoriasis and hypercholesterolemia, however, causality could not be established as evidence linking hyperlipidemia to the development of psoriasis is weak.

Hydradenitis Suppurativa

Hidradenitis suppurativa (HS) is a recurrent, chronic inflammatory skin condition that affects the follicular portion of folliculopilosebaceous units. It results in painful subcutaneous nodules in axillary, inguinal, and infra-mammary regions dense in apocrine glands. Inflammation of these

glands often results secretion of pus and often leads to fistula, sinus tracts, and abscess formation.[22] Estimates of prevalence of HS varies from <1% to 4% and it especially affects postpubescent women.[23] Th prevalence declines after the age of 50 years.[24] Women are more likely to be affected by HS than men and tend to have higher lesions in the genitofemoral region.[25]

The pathophysiology of HS is not well understood. Most of the understanding comes from clinical and epidemiological observations as well as from the studies of the immunochemistry and histopathology of the affected skin region. It is postulated that HS begins with occlusion of the hair follicles resulting in inflammation of the region due to involvement of proinflammatory cytokines.[26] Cytokines such as IL-1 beta, IL-10, IL-12, IL-23, and TNF-alpha are thought to play a role in inflammation of the skin in HS.[27] Proliferation of sebaceous follicles and increased androgen secretion as a result of over-activation of mTORC1 signaling pathway also plays a role in the pathogenesis of HS.[28]

Multiple co-morbidities are associated with HS, including obesity, metabolic syndrome, spondyloparthropathy, and inflammatory bowel disease. Recent studies have shown a clear association between HS and individual metabolic conditions such as insulin resistance, obesity, hypertension, and atherogenic hyperlipidemia.[29] A cross-sectional Israeli study of 3,207 HS patients with 6,412 controls found there to be a signification association between HS and metabolic syndrome (OR 1.61), and individual risk factors of obesity (OR 1.71), hyperlipidemia (OR 1.14), diabetes mellitus (OR 1.41), and hypertension (OR 1.19).[30] In a separate study by Sabat et al there was a high association between HS and metabolic syndrome (OR 4.46) as well as risk factors such as central obesity (OR 5.88), hypertriglyceridemia (OR 2.24), and hyperglycemia (OR 4.09).[31]

HS patients with metabolic syndrome or individual metabolic conditions are at an increased risk of cardiovascular morbidity and mortality. HS is overwhelmingly diagnosed in younger patients so cardiovascular disease often affects younger patients early leading to a decreased life expectancy. A 2016 population-based cohort study by Egeberg et al found there to be high risk of adverse cardiovascular outcomes such as myocardial infarct and high all-cause mortality in patients with HS.[32] Juhl et al reported electrocardiogram changes in patients with HS. The study found mean QRS duration to be shorter in a group of patients with mild HS vs group of patients with moderate to severe HS.[33] Studies on HS patients have also found variability in heart rate. A cross-sectional Danish study comparing 32 patients with HS with 430 controls found

significantly higher heart rate in the HS group after adjusting for the age and sex.[34]

Studies have also been conducted to stratify cardiovascular risk in patients with HS. One such study of 60 patients with HS was done to predict the risk of developing coronary artery disease in 10 years. The study found carotid ultrasound rather than the Framingham risk score to be an accurate tool of cardiovascular risk stratification. 36.6% of patients were found to have carotid plaques and these patients were predominately older, smokers, had longer duration or HS, and had moderate to severe HS.[35] Another European study was done by Gonzales et al using the Systemic Coronary Risk Evaluation (SCORE) cardiovascular risk-assessment tool. The study found there to be an underestimation of cardiovascular disease risk when European Heart SCORE in comparison to the carotid ultrasound assessment method. Among the 13 plaques found, 6 patients with moderate risk and 5 patients with high risk were reclassified to a very high risk using the carotid ultrasound.[36] Review of literature has clearly found cardiovascular disease at a significantly higher rate in patients with HS. The need for screening of patients with HS for modifiable cardiovascular risk factors should be emphasized.

Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect any organ of the body. Clinical features can include constitutional symptoms such as fatigue, fever, and weight loss, muscle and joint involvement such as arthritis and arthralgias, as well as severe renal and hematologic abnormalities. Other key manifestations of SLE include mucocutaneous involvement with the 3 main forms being chronic cutaneous (discoid) lupus, subacute cutaneous lupus and acute cutaneous lupus. The latter classically presents as a rash with malar distribution over the cheeks and nose that appears after sun exposure. Finally, lupus erythematosus can cause vascular and cardiac abnormalities.

Cardiac disease in SLE can involve all aspects of the heart, especially the pericardium, myocardium, valves, coronary arteries, and conduction system.[37] The most common cardiac manifestation is pericarditis, which is frequently a component of a SLE flar.[38] Valvular disease can include mitral valve prolapse or vegetations such as nonbacterial thrombotic endocarditis (NBTE) or verrucous Libman-Sacks endocarditis, which is clinically silent but can produce valvular insufficiency and can serve as a source of emboli. SLE patients with antiphospholipid antibody or lupus anticoagulant have a significantly elevated rate of NBTE.[39] These

vegetations are clinically silent until they cause valvular insufficiency or become the source of emboli which can cause stroke, heart failure, and death.[40] However, detection of valvular problems relies on heart auscultation, as screening echocardiograms are not recommended unless the patient is symptomatic or has an evidence of heart murmur.[41] Myocarditis is an uncommon manifestation of SLE, but should be suspected in patients with unexplained cardiomegaly with tachycardia and EKG changes.[42] The diagnostic test is cardiac MRI or right heart catheterization with biopsy. Endocardial biopsy can distinguish lupus myocarditis from other cardiomyopathies, including hydroxychloroquine cardiotoxicity.[43]

Coronary artery disease (CAD) risk is greatly increased in SLE patients, even when controlling for classic risk factors of atherosclerosis, such as hypertension, diabetes, and hyperlipidemia.[44] While the pathogenesis is not completely understood, increased atherosclerosis in lupus is thought to be caused by the excessive oxidative stress which increases inflammation, inducing apoptotic cell death. In SLE, reactive species and free radicals lead to chronic inflammation, leading to hyperlipidemia and atherosclerosis.[45] Evaluation of an SLE patient with angina, dyspnea, decreased exercise tolerance, suspected of having CHD, is similar to non-SLE patients. Work-up includes ECG, CXR, cardiac enzymes, and stress testing if necessary. Additionally, consider electron beam CT and carotid ultrasound.[46] Lastly, conduction problems and arrhythmias can occur in SLE, such as atrial fibrillation and prolonged QT, especially in combination with the QT-prolonging treatment drug hydroxychloroquine.[47]

Acanthosis Nigricans

Acanthosis nigricans (AN) is a poorly understood disorder that clinically presents as hyperpigmented, thickened skin commonly on the intertriginous areas such as the neck and axilla but can also occur in areas such as mucosal surfaces, abdominal surface, and anogenital region.[48] Additional appearances of AN can appear psoriasiform or ringworm-like and can occur in areas like the nipple, eyelid, and palm.[49] The development of AN is most commonly associated with diabetes mellitus and obesity, but it can also be associated as a paraneoplastic manifestation of certain malignancies or medication side-effects. Even though AN can appear in all races, there is an increased prevalence of AN in Native American and African American as compared to Caucasian or Asian individuals, and there is also evidence of AN even in children.[50-52]

The pathogenesis of AN is not completely understood, but it is thought that a hyperinsulinemic state plays a central role in development of AN.[53] At normal physiologic concentrations, insulin has an anabolic effect via binding to insulin receptors that modulates metabolism of nutrients such as lipids and carbohydrates. In a hyperinsulinemic state, insulin, in addition to binding to traditional insulin receptors, can bind to more potent receptors such as insulin-like growth factor 1 receptors (IGF-1Rs) that exert a stronger anabolic effect that can stimulate fibroblasts and keratinocytes.[50] Alternative modes of developing AN could also be explained by action of ligands (eg, TNF-a, IGF1, etc) on other receptor types such as epidermal growth factor receptors (EGFR-1) and fibroblast growth factor receptor in some malignancies; there is also more than likely some overlapping mechanism intracellularly that is shared amongst these pathways.[53-55] Histopathology of AN often demonstrates papillomatosis and hyperkeratosis, likely secondary to the activation of various receptor pathways on keratinocytes and fibroblasts.[49]

Given that the prevalence of childhood obesity has been increasing yearly and is associated with changes that enhance the risk factors for cardiovascular disease, several studies have assessed the relationship between AN and obesity. In a cross-sectional study of 161 overweight children and adolescents, it was found that the group with AN, as compared to the group w/o AN, had higher blood pressures, body fat, and insulin resistance.[56,57] Increased insulin/glucose throughout young adulthood is associated with worse cardiac risk, and among those adolescents who develop insulin resistance and/or NIDDM, at least 50% if not more will have AN.[58,59] A study looking at carotid intima-media thickness between individuals with AN vs those who did not found that the level of subclinical atherosclerosis was significantly greater in those with AN.[60] A study done on 543 overweight/obese Chinese children found that children with AN had higher blood pressures, fasting insulin levels, fatty liver, and lower HDL levels than those obese and/or overweight children that did not have AN.[61] In another study evaluating AN's impact on leptin, which is a possible independent predictor of adverse cardiovascular events, obese adults and adolescents with AN were found to have higher levels of leptin and resistin and lower levels of adiponectin, which has antidiabetic and antiatherogenic qualities, than obese individuals without AN. These findings suggest that the presence of AN increases the risk of developing worse cardiovascular disease.[50,62–64]

Based on this review, AN is an important dermatologic finding that could possibly signal an underlying endocrine disorder, worse CV disease, and even possibly be an independent factor in developing type 2

diabetes.[65] Thus, emphasis should be put on making sure to identify AN and the various forms it can manifest to help decrease some sequelae such as hyperinsulinemia and increased risk of atherosclerotic heart disease.

Atopic Dermatitis

Atopic dermatitis (AD), which is also referred to as eczema, is a chronic, pruritic skin disease that is commonly associated with asthma and allergic rhinitis.[66] Clinically, the morphology and distribution of AD lesions manifest differently in three stages distinguished by age.[67,68] In infants AD generally presents as pruritic, eczematous lesions on the cheek, forehead, and scalp. During childhood these lesions give way to lichenified papules that more often occur on the flexures, including the antecubital fossa and popliteal regions. And in adulthood AD affects a greater portion of the body, such as the flexures, the face and neck, and the upper limbs and back.[66,67] Histologically, AD is characterized by spongiosis, a lymphocytic infiltrate, acanthosis, and hyperkeratosis.[69] Genetically, mutations in FLG, which encodes the protein filaggrin, are implicated in many AD cases, but having a mutation in FLG does not necessarily mean an individual will develop AD.[70,71] Patients suffering from AD may have complications with secondary infections by Staphylococcus aureus, herpes simplex virus, molluscum contagiosum, and Malassezia sympodialis.[72-75]

Epidermal barrier dysfunction and cutaneous inflammation are two converging processes that represent the central pathophysiological hallmarks of AD — although which comes first remains unclear still.[68] Increased transepidermal water loss because of defects in epidermal permeability, aberrant lipid organization related to a greater number of short-chain ceramides, and increased serum protease activity all contribute to epidermal barrier dysfunction in AD.[76-78] This disruption of the epidermal barrier allows for allergens to enter the epithelium and induce an immune response dominated by T helper type 2 (TH2) cells. As a result of increased TH2 cell activity, B cells are induced to produce IgE, which activates basophils and mast cells via FcεRI receptors.[79] In addition, allergens may bind to and activate dendritic cells, which then release proinflammatory cytokines, thereby accentuating the ongoing epidermal inflammation.[80] Meanwhile, the cutaneous inflammation further disrupts the epidermal barrier, thus exacerbating the initial epidermal barrier dysfunction.

Currently, there is mixed evidence about a link between AD and cardiovascular disease. Conducting a systematic review and meta-analysis of population-based studies evaluating AD and the risk of cardiovascular disease, Ascott et al were unable to find an overall association; however, their results suggest that increasing severity of AD likewise increases the risk of cardiovascular disease in a dose-response relationship.[81] In another population-based cohort study based on data from 1998-2015 from the United Kingdom, Silverwood et al concluded that an association between AD and cardiovascular disease exists. They found that patients with AD had an increased risk of stroke, unstable angina, myocardial infarction, atrial fibrillation, cardiovascular death, and heart failure. However, the authors of the study were unable to establish whether it was AD or the treatments patients were receiving that increased the risk of cardiovascular events.[82] Moreover, using data from three studies — the 2005-2006 National Health and Nutrition Examination Survey (NHANES) and 2010 and 2012 National Health Interview Survey (NHIS) — Silverberg found an association between AD and an increased risk of coronary artery disease, angina, heart attack, congestive heart failure, stroke, and peripheral vascular disease, therefore suggesting that patients with AD have a greater chance of developing cardiovascular and cerebrovascular disease.[83] In contrast, a separate systematic review and meta-analysis conducted by Thyssen et al found that AD was unlikely to be an independent risk factor for cardiovascular disease. On the one hand, they found no link between AD and hypertension, type 2 diabetes, myocardial infarction, and stroke; on the other hand, they found a modest positive association between AD and angina pectoris based on four studies.[84] Similarly, Drucker et al found no association between AD and hypertension, type 2 diabetes, myocardial infarction, and stroke in their cross-sectional analysis.[85] Recently, a 35-year Danish follow-up study of 13,126 people with atopic dermatitis compared with 124,211 people found a 20% increased risk (hazard ratio of 1.2, 95% CI 1.0-1.6) of atrial fibrillation in patients with atopic dermatitis.[86]

Several theories have been proposed to explain a possible relationship between AD and cardiovascular disease. One implicates AD's role in disrupting patients' sleep and causing insomnia, two factors which have been associated with cardiovascular events.[87-90] Another explanation highlights how patients with asthma are more likely to have cardiovascular events, but this theory is evidently dependent on AD patients developing asthma.[91] A third theory relies on the evidence provided by several studies establishing a relationship between AD and obesity and metabolic syndrome, which are risk factors for cardiovascular disease.[92-94] This

strongly supported association is likely compounded by the propensity of individuals suffering from AD to have more sedentary lifestyles.[95] Furthermore, the inflammatory process in AD itself may lead to cardiovascular disease, as is seen in psoriasis and rheumatoid arthritis. However, the TH2 cytokines central to the pathogenesis of AD are not known to be involved in the development and progression of atherosclerosis, in contrast to TH1 cytokines, which are more prevalent in psoriasis and rheumatoid arthritis and have a pathogenic role in atherosclerosis.[96]

Ultimately, AD is a complex disease that can significantly impact the quality of life of affected individuals. Although further studies need to be conducted to assess whether AD and cardiovascular disease are definitively associated, it may be prudent — and even appropriate — to screen for cardiovascular disease in patients that have AD.

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disease predominantly due to IgG antibodies against hemidesmosomal antigens, BP230 (dystonin) and BP180.[97] It presents as tense subepidermal blisters and urticarial erythema with a peak incidence between 60 and 80 years of age.[98] Importantly, patients with BP have a mortality rate of 23.5%[99]; a population-based study including 868 patients following a diagnosis of BP found a three-fold increase in pulmonary embolism and pneumonia incidence compared to the general population.[100] Morbidity is also notably higher in patients with BP as compared to age-matched cohorts (43% vs 27%, respectively, $P = 0.003$) as demonstrated by Sim et al.[101] While BP has been regarded primarily as a skin disease, studies have shown its strong association with other disorders such as dementia and stroke.[102] The association between BP and cardiovascular disease is less defined than that of neurologic disorders, however, recent research has revealed some important connections.

While BP has been regarded primarily as a skin disease, studies have shown evidence of systemic inflammation and hypercoagulability with the disease. In fact, patients with BP have elevated serum levels of circulating proinflammatory cytokines,[103] prothrombin and D-dimer[104]; notably, reduction of the prothrombotic markers occurred during remission of disease.[105] The relationship between inflammation and ischemic heart disease is well-established[106] and dates to 1994 with Liuzzo et al demonstrating worse outcomes in ACS for those with elevated CRP compared to those with normal CRP levels.[107] Given the onset of disease in old age, most patients with BP likely have pre-existing atherosclerotic

cardiovascular disease, and systemic inflammation may possibly destabilize atheroma or promote thrombosis.[108] Moreover, corticosteroid use along with chronic inflammation may contribute towards atherogenesis.[109] However, the largest population-based study of patients with BP showed no evidence of increased incidence in MI after a diagnosis of BP.[100] Additionally, a meta-analysis including 814 patients with BP showed no significant association between BP and ischemic heart disease.[110] Overall, while older age at disease-onset and therapy-induced immunosuppression possibly contribute to the higher mortality seen in patients with BP, cardiovascular disease in the setting of systemic inflammation may also play a role but further studies are needed.

In addition to systemic inflammation, the presence of BP antigens in the myocardium may serve as an important connection between cardiac disease and BP. In fact, Steiner-Champliaud et al demonstrated the expression of BP230 in cardiomyocytes of primates[111]; furthermore, BP230 deficient mice have been shown to have structural disruption of the myocardium and signs of cardiomyopathy.[112] These findings may prompt further investigation regarding the possible presence and relevance of BP230 or other BP-related antigens in human cardiomyocytes.

Lastly, BP has been also linked to drug-induced causes, especially spironolactone and furosemide.[113,114] This is especially important as both medications are commonly prescribed for patients with congestive heart failure and can confound the association between cardiovascular disease and BP if patients are on either of these medications at the time of blister formation. Case reports also have described antihypertensives such as enalapril and angiotensin receptor II antagonists as potential causes of drug-associated BP.[115]

Conclusion

Cardiovascular disease has been found to be associated with many dermatological conditions. Because many of these skin conditions can indicate detrimental cardiovascular involvement, clinicians should be vigilant and keep a low threshold for screening for cardiovascular disease in patients presenting with such skin conditions.

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