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REVIEW

Psoriasis: Comorbidities

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Abstract

Psoriasis has long been known as a disease with many complications, but was attributed to diet and obesity. However, in recent years, psoriasis itself has been recognized as a series of systemic inflammatory diseases, and that the cytokines involved can induce a variety of other diseases. Individuals with psoriasis were also found to have higher incidences of cerebral and cardiovascular diseases and a younger age at death compared to healthy individuals. However, no clear guidelines have been defined regarding how much vascular lesion testing should be performed in patients with psoriasis. In this report, I attempt to unravel the objective data on psoriasis and its complications from various reviews and reports, and introduce the impact of biologics, which are currently the main treatment for psoriasis, on cardiac vascular disease.

KEYWORDS
complication, major adverse cardiovascular disease, metabolic syndrome, psoriasis

1 | INTRODUCTION

Psoriasis is a systemic inflammatory disease that is known to cause arthritis and uveitis. A recent cohort study from the UK found that patients with moderate to severe psoriasis have lifespans around 6 years shorter than those of healthy individuals, and this is postulated to be due to cardiovascular pathologies (myocardial infarction/cerebral infarction) caused by inflammation.[1] According to World Health Organization (WHO) statistics, while the prevalence of coronary artery disease and vascular lesions is greatest in diabetes and hypertension, mortality is highest with psoriasis.[2] This may be because diabetes and hypertension are commonly recognized as significant risk factors for vascular lesions, so patients and physicians proactively seek and provide treatment, whereas psoriasis is not generally known as a risk factor for vascular lesions, and is therefore often untreated or overlooked. Psoriasis has a high rate of various complications, but has also been found to represent an independent risk factor for death, complicating its pathology. Some of the studies showing an association between severity of psoriasis and risk of cardiovascular comorbidities have used the Psoriasis Area and Severity Index (PASI) score as a measure of psoriasis severity.[3,4] On the other hand, some studies have shown an association between body surface area (BSA) involvement and cardiovascular risk.[5,6] Currently, whether PASI or BSA correlate better with cardiovascular risk in patients with psoriasis remains unclear. In addition, at present there is no specific PASI/BSA threshold above which systemic therapy is recommended due to an increased risk of cardiovascular comorbidities.

2 | PSORIASIS AND METABOLIC SYNDROME

Metabolic syndrome is a condition in which risk factors for lifestyle-related diseases such as obesity, hypertension, glucose intolerance, and dyslipidemia accumulate in a patient.[7]

In 1999, the WHO proposed the concept of metabolic syndrome and diagnostic criteria, based on the combination of these risk factors for atherosclerosis from the perspective of insulin resistance. In addition, hypertriglyceridemia of 150 mg/dL or more and/or low high-density lipoprotein (HDL) cholesterol of less than 40 mg/dL, systolic blood pressure of 130 mmHg or more and/or diastolic blood pressure of 85 mmHg or more, and fasting hyperglycemia of 110 mg/dL or more.[8,9] In Europe, the USA, and Japan,

psoriatic patients are considered to be at high risk of metabolic syndrome.[10,11]

3 | PSORIASIS AND OBESITY

A study by Setty *et al*. involving 78 626 women (892 of whom reported having psoriasis) showed that fat and weight gain were risk factors for the development of psoriasis.[8] Patients with a body mass index (BMI) of 35 kg/m^2 or more displayed a relatively increased risk for the development of psoriasis of 2.69 compared to lean patients.[12] A recent prospective study indicated that obesity and high abdominal fat mass doubled the risk of psoriasis.[13] Such studies suggest that preventing weight gain, promoting maintenance of a normal body weight, and reduction of body mass may reduce the incidence of psoriasis. Indeed, several studies have shown a positive impact of weight loss on the severity of psoriasis.[14] Dietary weight reduction with a hypocaloric diet is thus recommended for overweight and obese patients with psoriasis.[15] An open question is whether differences in the type of diet (low-carbohydrate, ketogenic, or vegan/vegetarian diets) have an effect on psoriasis improvement. Understanding the epidemiological relationship between obesity/nutrition and psoriasis is important to clarify the relevance of environmental factors as modifiable risk factors in the pathogenesis of psoriasis and to develop new strategies to support anti-psoriatic treatments.[16]

Because adipose tissue is an important endocrine organ secreting soluble factors involved in inflammation and immunity, adipose tissue expansion and its secretion of pro-inflammatory mediators has been postulated to worsen psoriasis. High levels of resistin and leptin have been found in obese psoriatic patients.[17] A recent meta-analysis showed that patients with psoriasis have higher levels of leptin compared to individuals without psoriasis.[18]

4 | PSORIASIS AND HYPERTENSION

Hypertension is a well-known cardiovascular risk factor, contributing to the development of myocardial ischemia and infarction, stroke, and cardiovascular death.[19] Several studies have reported a positive association between psoriasis and hypertension.[20] Other reports have found that the incidence of psoriasis is high among hypertensive patients, but because those cases also included drug-induced psoriasis, further research is needed to clarify whether hypertension is associated with the incidence of psoriasis.[21]

5 | PSORIASIS AND TYPE 2 DIABETES

Epidemiological studies have suggested that the association between psoriasis and type 2 diabetes is dependent on severity of psoriasis.[22] Imiquimod (IMQ) is a Toll-like receptor-7/8 ligand, and its application to mouse skin induces both psoriasis-like skin lesions and systemic inflammation, such as production of cytokines.[23]

Ikumi *et al*. showed that skin severity, blood glucose level, and hemoglobin A1c were highly correlated with psoriasis, mainly via interleukin (IL)-17, in patients with type 2 diabetes. They also found similar hyperglycemia, glucose intolerance, and IL-17 production in a mouse model using IMQ, but showed no abnormalities in pancreatic islet or liver function at an early stage, indicating improvement with the use of IL-17 antibody.[24] Antibody preparations may be useful in the treatment of psoriatic patients with type 2 diabetes.[24]

The biguanide hypoglycemic drug metformin is the first-line drug for type 2 diabetes, and psoriasis was reportedly improved by controlling blood glucose with long-term metformin use.[25] Management of type 2 diabetes is thus considered very important in the treatment of psoriasis.

6 | PSORIASIS AND BLOOD LIPIDS

A number of studies have shown that patients with psoriasis exhibit decreased HDL levels and/or increased low-density lipoprotein (LDL), very-low-density lipoprotein, and triglyceride levels.[26] HDL has a reverse cholesterol transport function, anti-oxidative capacity, and anti-inflammatory properties by regulating the differentiation of dendritic cells, and reducing T-cell activation and IL-12 production. However, these properties are reduced during chronic inflammation, such as psoriasis.[27] Conversely, anti-psoriatic therapy restores the composition and function of HDL.[28] On the other hand, LDL accumulates in blood vessels to generate active oxygen and impair the function of vascular endothelial cells, but has been shown to increase with increasing tumor necrosis factor (TNF)-α in patients with severe psoriasis[27] (Figure 1).

In a mouse model of IMQ-induced psoriasis, after being fed a high-fat diet, IL-17A accumulates on the skin and throughout the body, and induction of Vγ4 + γδ T cells is elevated, resulting in psoriasis-like skin inflammation.[29] At this time, expression of CCL20 in the blood of mice is known to be increased, and free fatty acids in the blood are increased.[29] Certain studies,[30] including a large-scale population-based cross-sectional study,[31] found no correlation between psoriasis and lipid serum levels.

7 | PSORIASIS AND NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Non-alcoholic fatty liver disease is a process in which fat is deposited in the liver in the absence of significant alcohol consumption or the use of drugs—such as steroids, methotrexate, tamoxifen, or amiodarone—that facilitate steatosis.[32]

Non-alcoholic fatty liver disease and metabolic syndrome have similar pathogenic mechanisms, but the two pathologies are distinguished by histological differences in the liver.[33]

Mortality is higher in patients with NAFLD than in the general population, regardless of which of these histological variants is present; the cause of death is usually cardiovascular disease (CVD).[34]

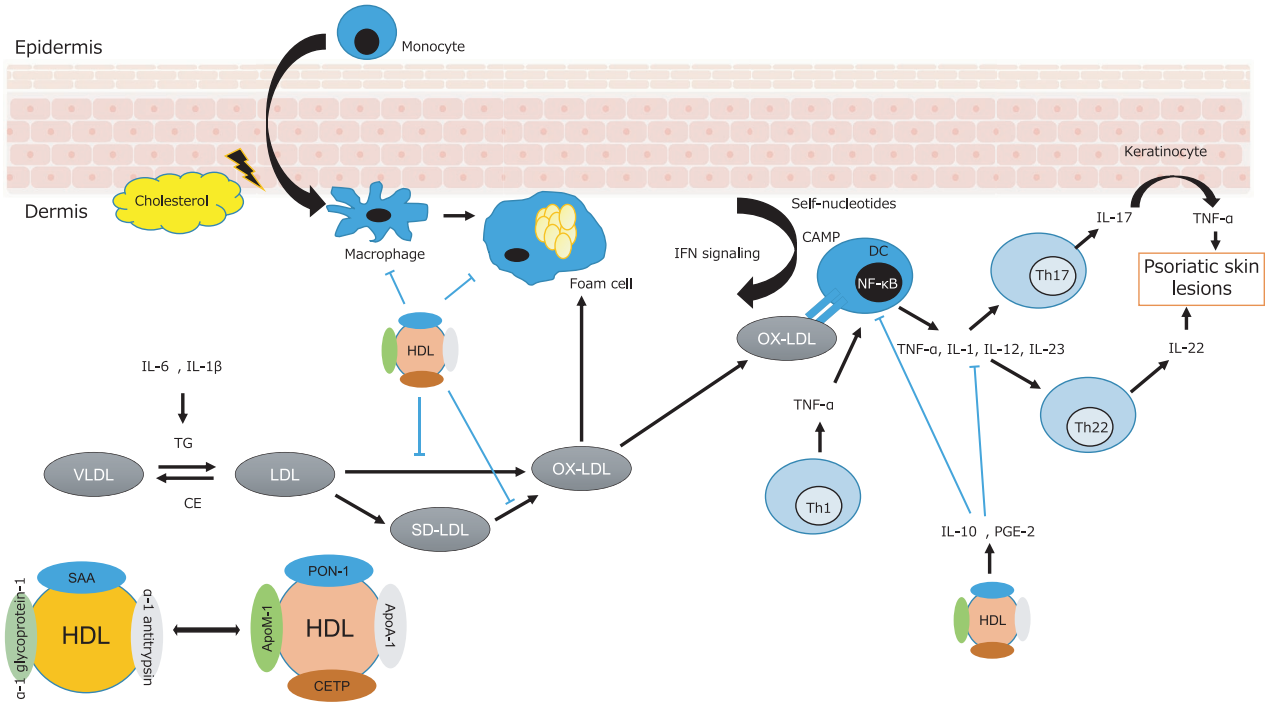

FIGURE 1 Immune cells and lipoprotein-associated cytokines implicated in psoriasis pathogenesis. Abbreviations: Apo, apolipoprotein; apoA-1, apolipoprotein A1; apoM-1, apolipoprotein M1; CAMP, cathelicidin antimicrobial peptide; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; DC, dendritic cell; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; ox-LDL, oxidized LDL; PGE-2, prostaglandin E2; PON, paraoxonase; SAA, serum amyloid A; SD-LDL, small dense LDL; TNF-α, tumor necrosis factor-α; Th1, T-helper cell type 1; Th17, T-helper cell type 17; Th22, T-helper cell type 22; TG, triglyceride

Gisondi *et al.* reported that a higher rate of ultrasound-diagnosed NAFLD (47%) in a series of 130 consecutive patients with psoriasis than in 260 healthy controls (28%) matched for age, sex, and BMI.[35] The pathogenic links between psoriasis and NAFLD are chronic inflammation and peripheral insulin resistance, which is a common finding in diseases associated with psoriasis. On the other hand, the involvement of IL-17 in both psoriasis and NAFLD has been revealed. T cells in adipose tissue synthesize IL-17, which can regulate lipogenesis and glucose metabolism. T-helper (Th)17 cells and IL-17 may accelerate the progression from simple steatohepatitis to severe steatohepatitis.[36]

The dermatologist should be aware not only of the high prevalence of NAFLD in psoriasis, but also of the possibility of steatohepatitis, especially when psoriasis is severe or signs of metabolic syndrome are present.

8 | PSORIASIS AND CVD

In 2006, Gelfand *et al.* performed a large population-based cohort study and found that severe psoriasis was an independent risk factor for myocardial infarction (MI).[37] Consequently, various epidemiological studies have reported psoriasis as an independent risk factor for major adverse cardiovascular events (MACE) including MI, stroke, and death by CVD. Although some studies have found no significant association between psoriasis and MACE,[38] the majority of systematic reviews and meta-analyses have consistently shown significant associations between diverse CVD and psoriasis.[39,40] Among these, Samarasekera *et al.* and Armstrong *et al.* both stratified the risk of CVD according to the severity of psoriasis and identified higher risks of CV mortality, MI, and stroke among psoriatic patients with more severe disease.[41,42] Concerning disease duration, Egeberg *et al.* found that psoriasis duration had a strong relationship with MACE (1.0% per additional year of psoriasis duration [hazard ratio, 1.010; 95% confidence interval, 1.007–1.013).[43]

The prevalence of CVD risk factors, including hypertension, diabetes mellitus, dyslipidemia, and obesity, was increased in patients with psoriasis. The combination of hypertension, central obesity, insulin resistance, and dyslipidemia, which is considered to represent metabolic syndrome, is also associated with psoriasis. Psoriasis increases the incidence of these diseases and is considered to represent an aggravating factor by itself. A systematic review of the risk of CVD risk factors in psoriasis and recent findings from a meta-analysis are summarized in Table 1.[20,44-54]

9 | PSORIASIS, CVD, AND CYTOKINES

Boehncke *et al.* proposed the model of psoriatic march to explain the pathogenic link between psoriasis and CVD (Figure 2).[55]

TABLE 1 Recent systematic reviews and meta-analyses analyzing the risk of cardiovascular risk factors in psoriasis

	No. of patients	Identified cardiovascular risk factors with relative risk of measures
Armstrong *et al*., 2013.[20]	Psoriasis: 309 469	Hypertension in all psoriasis, OR = 1.58 (1.42–1.76); in mild psoriasis, OR = 1.30 (1.15–1.47); in severe psoriasis, OR = 1.49 (1.20–1.86)
	Control: 2 088 197	
Duan *et al*., 2020.[44]	Psoriasis: 255 132	Hypertension, OR = 1.43 (1.25–1.64)
	Control: 814 631	
Armstrong *et al*., 2013.[45]	Psoriasis: 314 036	Diabetes, OR = 1.59 (1.38-1.83); in mild psoriasis, pooled OR = 1.53 (1.16–2.04); in severe psoriasis, pooled OR = 1.97 (1.48–2.62)
	Control: 3 717 217	
Coto-Segura *et al*., 2013.[46]	Psoriasis: 557 697	Type 2 diabetes pooled, OR = 1.76 (1.59–1.96)
	Control: 5 186 485	
Mamizadeh *et al*., 2019.[47]	Psoriasis: 922 870	Diabetes, OR = 1.69 (1.51–1.89)
	Control: 12 808 071	
Armstrong *et al*., 2012[48]	Psoriasis: 201 831	Obesity, OR = 1.66 (1.46–1.89); in mild psoriasis, OR = 1.46 (1.17–1.82); in severe psoriasis, OR = 2.23 (1.63–3.05)
	Control: 1 898 169	
Miller *et al*., 2013[39]	Psoriasis: 503 686	Diabetes, OR = 1.9 (1.5–2.5); hypertension, OR = 1.8 (1.6–2.0); dyslipidemia, OR = 1.5 (1.4–1.7); obesity, OR = 1.8 (1.4–2.2); metabolic syndrome, OR = 1.8 (1.2–2.8)
	Control: 27 686 694	
Choudhary *et al*., 2020[49]	Psoriasis: 17 672	Increased systolic blood pressure, OR = 2.31 (1.12–4.74); diastolic blood pressure, OR = 2.31 (1.58–3.38); abdominal obesity, OR = 1.90 (1.45–2.50); triglycerides, OR = 1.80 (1.29–2.51)
	Control: 66 407	
Phan *et al*., 2020[50]	Pediatric psoriasis: 43 808	Obesity, OR = 2.45 (1.73–3.48); diabetes, OR = 2.32 (1.34–4.03); hypertension, OR = 2.19 (1.62–2.95); hyperlipidemia, OR = 2.01 (1.66–2.42); metabolic syndrome, OR = 1.75 (1.75–7.14)
	Control: 5 384 057	
Armstrong *et al*., 2013[51]	Psoriasis: 41 853	Metabolic syndrome, OR = 2.26 (1.70–3.01)
	Control: 1 358 147	
Rodríguez-Zúniga *et al*., 2017[52]	Psoriasis: 25 042	Metabolic syndrome pooled, OR = 1.42 (1.28–1.65)
	Control: 131 609	
Singh *et al*., 2017[53]	Psoriasis: 46 714	Metabolic syndrome pooled, OR = 2.14 (1.84–2.48)
	Control: 1 403 474	
Choudhary *et al*., 2019[54]	Psoriasis: 15 939	Metabolic syndrome, OR = 2.077 (1.84–2.34)
	Control: 103 984	

According to their model, the systemic inflammation present in psoriasis causes insulin resistance and induces endothelial dysfunction. Indeed, chronic inflammation in both psoriasis and atherosclerosis may induce the production of adipokines and pro-inflammatory cytokines, leading to insulin resistance and further endothelial dysfunction that may promote CVD. The visceral adipose tissue subtype may also produce large amounts of adipokines and chemokines, such as monocyte chemotactic protein (MCP)-1 and IL-8, which are known to stimulate atherosclerosis.[56] Elevated expression levels of leptin and resistin may activate the expression of pro-inflammatory cytokines such as MCP-1, IL-6, IL-2, and TNF-α, all of which act as atherogenesis-promoting molecules and may promote vascular inflammation via migration of monocytes and activation of macrophages.[57] Furthermore, adipokines may alter the effective function of insulin on blood vessels by affecting capillary mobilization.[58] These causal factors may induce metabolic syndrome or atherosclerosis, which may lead to MI or stroke in patients with psoriasis.

Tumor necrosis factor-α has been confirmed *in vivo* to cause arteriosclerosis by the action of an inflammatory mediator.[59,60] Recently, it has become clear that IL-17, not only in the presence of TNF-α and interferon (IFN)-γ, but also by itself, causes inflammation in both the vascular endothelium and organs throughout the body.[61]

In addition, the active pathway has been found to be IL-17/Th17 enhancement via the p38 mitogen-activated protein kinase pathway.[62] On the other hand, IL-17 has been shown in animal models to represent a potent promoter of collagen deposition and fibrosis, and is considered a possible cause of atherosclerosis due to a decreased ability to extract HDL.[63]

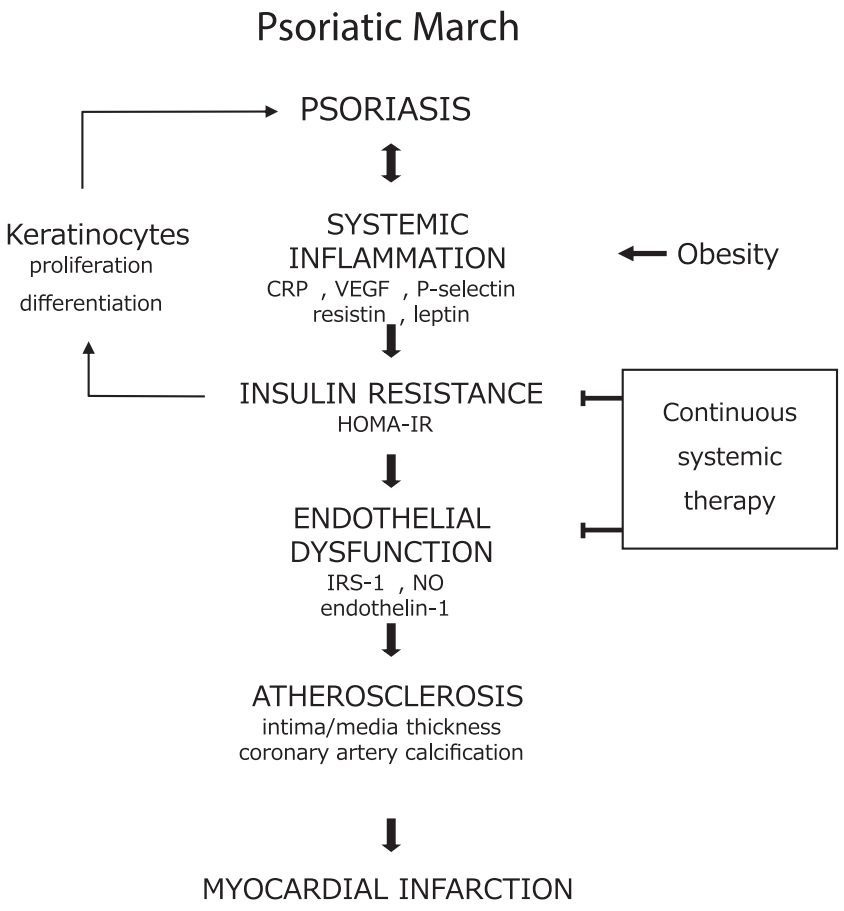

FIGURE 2 The concept of psoriatic march. Psoriasis causes not only skin inflammation but also systemic inflammation, leading to increased insulin resistance, vascular endothelial damage, atherosclerosis, and myocardial infarction. This sequence of events is known as the psoriatic march. Obesity is an aggravating factor in this process, and continuous systemic treatment is a suppressing factor

10 | PSORIASIS AND CVD DETECTION

Atherosclerosis is the major pathological change preceding the development of MI and stroke. Patients with psoriasis have been found to have increased arterial stiffness compared to healthy controls, and a positive correlation exists between arterial stiffness and duration of psoriasis.[64] Atherosclerosis may also develop following chronic vascular inflammation. Using positron emission tomography/computed tomography (CT), patients with psoriasis have been found to show greater aortic vascular inflammation, and an association exists between the severity of psoriasis and the degree of vascular inflammation.[65] In addition, improvement of psoriasis skin disease can lead to a reduction in aortic vascular inflammation.[66] Coronary artery atherosclerosis is an important risk factor for ischemic heart disease. Various studies have found that patients with psoriasis show an increased prevalence and severity of coronary artery calcification and atherosclerosis (as measured by cardiac CT, coronary CT angiography, or coronary angiography) compared to healthy controls.[64,67] In addition, epicardial fat tissue represents a cardiovascular risk factor and is associated with the development of atherosclerosis. The epicardial fat thickness or area (measured by transthoracic echocardiography or CT) has been found to be greater in patients with psoriasis than in healthy controls.[68,69]

11 | REDUCTION OF CVD RISK BY BIOLOGICS

Analysis of 121 participants who were biologically untreated at baseline and received biologic therapy for 1 year revealed that biologic therapy was associated with a 6% reduction in non-calcified plaque burden ($p = 0.005$) and a reduction in necrotic cores ($p = 0.03$). No effect on fiber load was seen ($p = 0.71$), indicating that biologic therapy in severe psoriasis was associated with favorable regulation of coronary plaque index. After 1 year of biologic therapy, non-calcified plaque load was reduced by 5% in patients treated with TNF-α inhibitors ($p = 0.06$) and by 5% in patients treated with anti-IL-12/23 antibody ($p = 0.36$). Patients treated with IL-17 inhibitors showed significant reductions in non-calcified coronary plaque burden compared to patients treated with anti-IL-12/23 antibodies or no biologic therapy ($p < 0.001$).[70] We have also identified improvements in coronary artery morphology in psoriatic patients who received only IL-17 inhibitors and blood pressure control for 2 years (Figure 3).[71] Regarding endothelial cell dysfunction, flow-mediated dilation (FMD) is a marker that reflects endothelial cell dysfunction. FMD measured in 14 psoriatic patients before and 12 weeks after adalimumab treatment reportedly showed improvements after adalimumab treatment.[72] A 52-week, randomized, double-blind, placebo-controlled exploratory study, the Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab study, was conducted

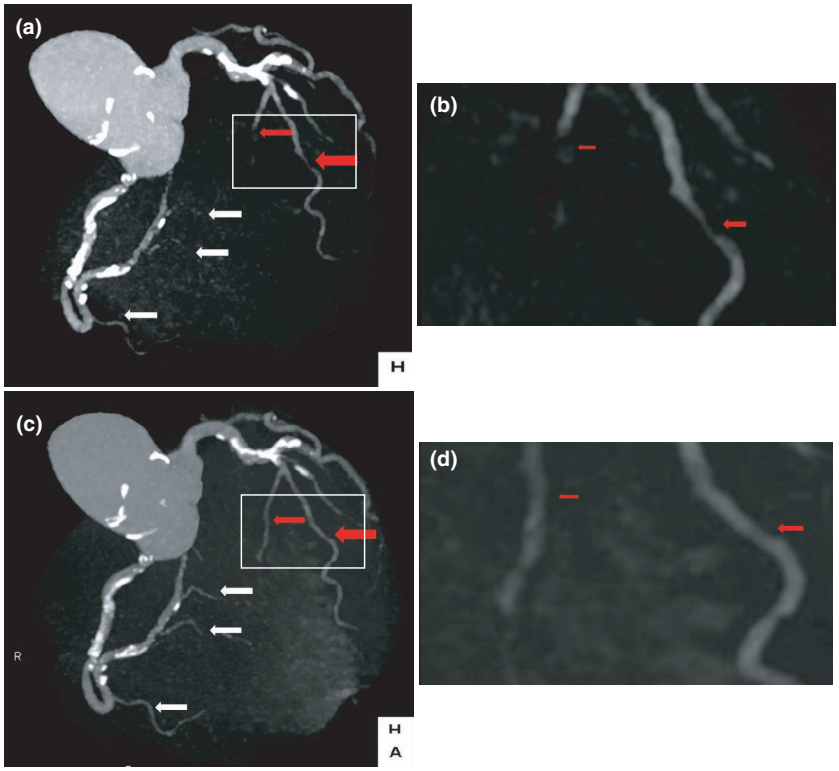

FIGURE 3 A case of psoriasis in which coronary artery stenosis was improved by the use of anti-interleukin (IL)-17 antibody. (a) Coronary stenosis with non-calcified plaque in the left anterior descending artery (red arrow) and severe stenoses with interruption in the right posterior descending artery (white arrows) before treatment. (b) High magnification of the boxed section: attenuation of contrast effect in both left anterior descending artery (red arrow) and posterior descending artery (white arrow) before treatment. (c) Improvement of coronary stenosis in both left anterior descending artery (red arrow) and posterior descending artery (white arrows) after treatment. (d) High magnification of the boxed section: attenuation in both left anterior descending artery (red arrow) and posterior descending artery (white arrow) is improved after treatment

in patients with moderate to severe plaque psoriasis without clinical CVD. No statistical difference was observed in baseline adjusted mean FMD between patients who received secukinumab and those who received placebo in week 12, but FMD was significantly higher than baseline in patients who received the labeled dose of secukinumab at 300 mg for 52 weeks.[73]

Tumor necrosis factor-α inhibitors and IL-17 antibodies have been reported to improve coronary plaque with treatment, but no direct effect of IL-23 antibody has been reported.

The anti-inflammatory effects of IL-23 antibody on aortic vascular inflammation in psoriatic patients are currently being tested.[74]

12 | CEREBROVASCULAR DISEASE IN PSORIASIS

Cerebrovascular accidents are one of the common vascular disorders among psoriatic patients.[42]

When ischemia occurs in the brain, activation of microglia is characterized by inflammatory cytokines (M1 phenotype characterized by high expression of IL-12 and IL-23, and low expression of IL-10) and neuroprotective mediators (M2 phenotype characterized by low expression of IL-12 and IL-23, and high expression of IL-10).[75]

Other cells, such as macrophages, infiltrate the brain in the early stages of infarction, and neutrophils and lymphocytes bind in the late stages.[76] IL-23 secreted by macrophages promotes the proliferation of Th17 and γδ T cells to produce IL-17, which contributes to post-stroke brain injury.[77]

The effect of blocking IL-23/IL-17 has also been studied in stroke models. IL-23-deficient animals exhibited significantly lower levels of γδ T cells, followed by decreased secretion of IL-17 and reduced infarct size.[78] Similar results were seen after inhibition of the IL-12/ IL-23p40 subunit.[79] IL-23p19 suppression reduced inflammation-induced levels of IL-23 and IL-17, as well as upregulation of the regulatory T cell transcription factor FoxP3. Blockade of the p19 subunit may be associated with delayed cerebral ischemia and reduced infarct and neurological dysfunction.[80] On the other hand, the involvement of psoriasis in cerebral infarction from thrombus due to abnormal wall motion after MI or from thrombus due to atrial fibrillation is unknown.

13 | CONCLUSION

Psoriasis is obviously a systemic inflammatory disease with many complications, particularly metabolic syndrome. Among these, CVD has been found to be the most important. Dermatologists should

therefore work with cardiologists to elucidate the condition of psoriatic patients. However, because performing a thorough cardiovascular examination in all patients with psoriasis is difficult, clinicians require an understanding of which patients are more likely to develop complications, especially CVD. While some biologics have been found to be effective in the treatment of CVD, we need to continue accumulating long-term case data.

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