

NOVELTIES IN DERMATOLOGY

Psoriasis, a Systemic Disease?

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Abstract. It has long been recognized the epidemiological association of psoriasis, especially the most severe forms, with several diseases that share a common pathogenic substrate involving TNF- α and different target organs (arthritis and Crohn disease, for example), as well as an increased risk of coronary heart disease and occlusive cardiovascular disease. In the patient with severe psoriasis there is also an increased prevalence of obesity, dyslipemia, adult diabetes mellitus, alcohol abuse and tobacco habit which contribute to the increased risk of mortality associated with atherosclerosis. Recently it has been identified the so-called metabolic syndrome, characterized by the association of abdominal obesity, atherogenic dyslipemia, hypertension, insulin resistance with or without glucose intolerance and a proinflammatory and prothrombotic state as a risk factor for cardiovascular disease. There is evidence that in rheumatoid arthritis as well as in psoriasis, chronic inflammation has a pathogenic role in the metabolic syndrome and associated comorbidities, and its adequate treatment may contribute to revert it. The dermatologist should recognize the elements of the metabolic syndrome and propose the patient with psoriasis, in addition to the optimal dermatologic treatment, changes in life habits and appropriate drug therapy to reduce the risk of cardiovascular morbi-mortality

Key words: psoriasis, comorbidities, myocardial infarction, atherosclerosis, obesity, metabolic syndrome, cardiovascular disease.

LA PSORIASIS, ¿UNA ENFERMEDAD SISTÉMICA?

Resumen. Desde hace tiempo se conoce la asociación epidemiológica de la psoriasis, especialmente en sus formas graves, con diversas enfermedades con las que comparte un sustrato patogénico común, con implicación del factor de necrosis tumoral α (TNF- α) y diferente órgano diana (tales como artritis y enfermedad de Crohn, por ejemplo), así como con un aumento en el riesgo de cardiopatía coronaria y enfermedad cardiovascular oclusiva. En el paciente con psoriasis grave también se encuentra un aumento en la prevalencia de obesidad, dislipemia, diabetes mellitus del adulto, enolismo y tabaquismo, que contribuyen al incremento en el riesgo de mortalidad relacionada con la aterosclerosis. Recientemente se ha identificado el denominado síndrome metabólico, caracterizado por la asociación de obesidad abdominal, dislipemia aterogénica, hipertensión, resistencia a la insulina con o sin intolerancia a la glucosa y un estado proinflamatorio y protrombótico como factor de riesgo de enfermedad cardiovascular, y existen evidencias de que, tanto en la artritis reumatoide como en la psoriasis, la inflamación crónica tiene un papel patogénico en el síndrome metabólico y las comorbilidades asociadas, y su tratamiento adecuado podría contribuir a revertirlo. Constituye una obligación del dermatólogo reconocer los elementos del síndrome metabólico y proponer al paciente con psoriasis, además del tratamiento óptimo de la psoriasis, los cambios de hábitos de vida y el tratamiento farmacológico adecuado para reducir el riesgo de morbimortalidad cardiovascular.

Palabras clave: psoriasis, comorbilidades, infarto de miocardio, aterosclerosis, obesidad, síndrome metabólico, enfermedad cardiovascular.

Introduction

The association of a given disease with one or more other diseases (comorbidity) has attracted considerable interest from a variety of fields in recent years. The diseases are usually multifactorial, share common pathogenetic mechanisms, and are often associated with underlying inflammation. Unlike syndromes, in which a disease

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manifests itself in different ways generally at the same time, comorbidities are secondary manifestations of a disease that can occur at different times and in one or more organs. Although they are secondary conditions, comorbidities can sometimes have an even greater social health impact than primary conditions.

Psoriasis is a chronic inflammatory disease that affects between 1% and 2% of the population.^{1,2} It has 2 peak ages of onset that may correspond to distinct forms of the disease.³ It is characterized by a large degree of clinical heterogeneity,⁴ with periods of remission and exacerbation. The disease is considered moderate to severe in 20% of patients,⁵ and in those cases systemic therapy is justified. The disease is of unknown etiology, although it is thought to be caused by the interaction of various genes and environmental factors with the immune system. It is believed that this interaction is responsible for activating cutaneous T cells and epidermal keratinocytes and stimulating the increased production of T1 cytokines, tumor necrosis factor (TNF), and other mediators, which induce an inflammatory skin phenotype with impaired keratinocyte proliferation and differentiation and skin vascularization. Although the disease has a low attributable mortality, it can cause considerable morbidity and have a profound impact on quality of life.

It has long been known that psoriasis, and severe psoriasis in particular, is epidemiologically associated with certain diseases with which it shares certain pathogenic factors but that target different organs. Arthritis and Crohn disease are 2 such examples. Psoriasis also shares risk factors with occlusive vascular disease, as was discovered over 30 years ago.^{6,7} More recent research has shown that the metabolic syndrome (broadly characterized by abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without glucose intolerance, and proinflammatory and prothrombotic states) is a major risk factor for cardiovascular disease.⁸ The metabolic syndrome has also recently been identified as an independent risk factor for cardiovascular disease in patients with long-standing rheumatoid arthritis, and this has been linked to the presence of chronic persistent inflammation.⁹ By analogy, one would expect psoriasis patients to show the same pattern of morbidity, and indeed the body of epidemiological evidence supporting such a hypothesis is growing.¹⁰ The possibility that cardiovascular disease risk may be linked to psoriasis severity¹¹ can, therefore, no longer be overlooked, although it should be remembered that some of the metabolic disorders that have been detected in psoriasis, such as dyslipidemia,¹² may be due to an intrinsic abnormality that has no connection with disease duration. The discovery of cardiovascular comorbidities that have a considerable impact on both morbidity and mortality in patients with psoriasis obliges dermatologists to search for related risk factors (obesity, smoking, metabolic lipid disorder, etc) and recommend appropriate treatment where necessary. The

cardiovascular risk associated with the metabolic syndrome in patients with psoriasis could be expected to be improved by appropriate treatment of psoriasis, as this would reduce the inflammatory component associated with the syndrome.¹³ Confirmation of this hypothesis would provide further justification for the systemic treatment of psoriasis—in addition to treatment efficacy in terms of dermatological, psychological, socioeconomic, and quality-of-life effects—and provision of such treatment would provide additional pharmacoeconomic benefits in terms of quality-adjusted life-years.

The comorbidities associated with psoriasis are listed in Table 1 and discussed below in the same order.

Psoriatic Arthritis

The presence of arthritis in patients with psoriasis was recognized by Alibert in 1818, 10 years after Willan had recognized psoriasis as an independent disease.¹⁰ Although traditional estimates have placed the prevalence of arthritis in psoriasis patients at 7%, the true rate is probably higher.¹⁴ In a study undertaken in Italy in a group of 936 hospitalized patients with psoriasis, the prevalence of arthritis, defined according to the criteria of the European Spondyloarthritis Study Group, was 7.7%.¹⁵ In that study, between 1% and 12% of the patients also reported paresthesia, joint pain, stiffness, swelling, and ankylosis. As skin manifestations occur before the onset of arthritis in the majority of patients,¹⁶ the cumulative prevalence may in fact be even higher. Although an in-depth discussion of psoriatic arthritis is beyond the scope of

Table 1. Comorbidities in Psoriasis

<i>Common Diseases</i>
Psoriatic arthritis Crohn disease
<i>Persistent Activation of Cutaneous T Cells</i>
Cutaneous T-cell lymphoma
<i>Chronic/Systemic Skin Inflammation</i>
Metabolic syndrome Atherogenic dyslipidemia Hypertension Abdominal obesity Diabetes and insulin resistance Predisposition to thrombosis Nonalcoholic hepatic steatosis
<i>Comorbidities Related to Impaired Quality of Life</i>
Anxiety, depression Smoking, alcoholism
<i>Comorbidities Related to Treatment</i>
Nephrotoxicity, hepatotoxicity, dyslipidemia, skin cancer

this article, both the phenotypic and genetic variability of arthritis and psoriasis, and the absence of genetic susceptibility loci common to psoriasis and psoriatic arthritis suggest the existence of (several) independent diseases with common pathogenetic or susceptibility factors.

Crohn Disease

There are numerous epidemiological, pathogenic, and genetic indications that support an association between Crohn disease and psoriasis.¹⁷ It has been noted that psoriasis patients have a relative risk of developing Crohn disease of close to 3, while Crohn disease patients have a 7-fold higher risk of developing psoriasis than control subjects.¹⁸ Given the low prevalence of Crohn disease in the general population (0.1% - 0.3%), however, a dermatologist would be unlikely to detect this association.¹⁰ Furthermore, TNF- α plays an important role in both diseases—as has been demonstrated by the therapeutic efficacy of anti-TNF- α antibodies such as infliximab and adalimumab—and numerous findings support the hypothesis of common inflammatory pathways targeting the different organs.¹⁷ Finally, there are also genetic links between psoriasis and Crohn disease, such as polymorphisms that affect binding in the TNF- α promoter region and the closeness of the susceptibility loci of both diseases in 16q21.^{10,17}

Lymphoma

Although most epidemiological studies indicate that psoriasis patients have a similar risk of developing lymphoma to that of the general population, several recent studies have suggested that this risk might be slightly higher.¹⁹⁻²² Nevertheless, lymphoma only seems to occur in patients with more severe forms of the disease who have been

hospitalized repeatedly,¹⁹ received systemic therapy,²⁰ or been exposed to high cumulative doses of methotrexate.²³

The Metabolic Syndrome

The metabolic syndrome, which was originally described as syndrome X,²⁴ involves obesity, insulin resistance, hypertension, impaired glucose tolerance or diabetes, hyperinsulinemia, and dyslipidemia with high triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels. This corresponds to a cluster of concurrent cardiovascular risk factors for which a variety of diagnostic criteria have been proposed.⁸ Presence of the metabolic syndrome triples a patient's risk of developing type 2 diabetes mellitus and doubles their risk of developing cardiovascular disease.²⁵

Abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance are all interrelated risk factors for cardiovascular disease, and when they coexist, that risk is increased. It has recently been suggested that the metabolic syndrome might be a risk factor for certain types of cancer, and epidemiological studies exist that have related it to cancer of the colon.²⁶

According to the practical definition of the metabolic syndrome drawn up by the National Cholesterol Education Program's Adult Treatment Panel IIP (Table 2),^{8,27} 24% of adults in the United States of America have the syndrome, although there is variation among different subpopulations, probably as a result of cultural and ethnic differences.²⁶

Obesity, and abdominal obesity in particular, is the main pathogenic factor in the metabolic syndrome, as abdominal adipose tissue functions as an endocrine organ by releasing free fatty acids, angiotensin II, and adipokines.²⁸ Free fatty acids inhibit muscle glucose uptake, and in so doing, contribute to insulin resistance. Also, in combination with angiotensin II, they have a harmful effect on the pancreas. Angiotensin II also causes hypertension by acting as a vasoconstrictor. TNF- α and other cytokines decrease the efficacy of insulin and can also cause hypertension. Hyperglycemia and high concentrations of free fatty acids stimulate the increased production of triglycerides by the liver, and this in turn reduces circulating levels of HDL-C.

The metabolic syndrome is also characterized by a proinflammatory state (high levels of C-reactive protein) and a prothrombotic state (high plasma concentrations of plasminogen activator inhibitor-1 and fibrinogen, another acute-phase reactant). These states are probably interrelated and linked to the existence of high concentrations of proinflammatory cytokines, and TNF- α in particular.²⁹ Although obesity and insulin resistance have a proinflammatory effect that is perpetuated through a positive feedback loop, the effect may be modulated by certain

Table 2. Clinical Identification of the Metabolic Syndrome^a

Abdominal obesity (measured as waist circumference): >102 cm in men, >88 cm in women
Triglycerides \geq 150 mg/dL
HDL-C: <40 mg/dL in men, <50 mg/dL in women
Blood pressure: \geq 130/ \geq 85 mm Hg
Fasting glucose: \geq 110 mg/dL ^b
Abbreviation: HDL-C, high density lipoprotein cholesterol.

^aData from Grundy et al.⁸

^b \geq 100 mg/dL according to new cutoff point established by the American Diabetes Association.²⁶

genetic factors (such as abdominal fat accumulation without increased body mass index in Indians).

Moreover, there is a growing body of epidemiological evidence that chronic inflammatory states such as those found in chronic diseases like rheumatoid arthritis are capable of triggering or exacerbating the metabolic syndrome.³⁰ Indeed, an increasing number of reports are emerging that indicate that treatment with TNF- α blockers is associated with a reduced incidence of cardiovascular disease, at least in patients with rheumatoid arthritis.³¹ Improved cardiovascular risk has also been reported in patients with psoriasis or rheumatoid arthritis treated with methotrexate.¹³ If the positive impact of treatment on metabolic syndrome-related comorbidity is confirmed, and possibly extended to other diseases such as psoriasis, the impact on cardiovascular morbidity and mortality will be enormous in those patients, who are at greater cardiovascular risk. In terms of the impact on public health, however, the potential role of dermatologists is even more important. By identifying signs of the metabolic syndrome in patients and helping them to adopt healthy lifestyles and take appropriate dietary and pharmacological measures, dermatologists would contribute to reducing the impact of the factors that comprise the metabolic syndrome and the associated cardiovascular risk.

Almost 30 years ago, McDonald and Calabresi,⁷ on analyzing data from 3 separate studies, were the first to identify an increased risk of cardiovascular mortality in hospitalized patients being treated for severe psoriasis. A population-based study in Sweden involving 372 patients hospitalized for psoriasis found a high associated risk of hypertension and myocardial infarction.³² Another study, conducted in the dermatology department of a German hospital, analyzed the data of over 42 000 patients, 2941 of whom had been diagnosed with psoriasis.³³ Following adjustment for age and sex, the authors found an increased rate of obesity, hypertension, heart failure, and diabetes mellitus in patients with psoriasis compared to those without. These findings were confirmed recently in a study involving a review of medical records for 753 patients in a university dermatology clinic in the USA.³⁴ Comorbidity was found in 73% of the patients, with the most common disorders being hypertension, dyslipidemia, diabetes mellitus, and heart disease. Another study found that patients hospitalized for psoriasis had a higher prevalence of type 2 diabetes mellitus, hypertension, hyperlipidemia, and heart disease than a group of control patients with localized melanoma.³⁵ The patients were stratified by age and sex, and the respective odds ratios (OR) were 2.48, 3.27, 2.09, and 1.95. The failure to detect increased risk in outpatients would seem to indicate that it only applies to patients with severe forms of psoriasis.^{11,36} Hospitalization criteria vary from one health system to the next, and in

Spain, those criteria may not be ideal for assessing the severity of psoriasis. A study conducted in Sweden, however, reported increased cardiovascular mortality in a group of patients hospitalized for psoriasis compared to the general population.¹¹ Mortality increased with number of admissions and reached a peak (standardized mortality ratio of 2.62) in young patients (aged between 20 years and 39 years when first admitted to hospital).

The multiple conditions that make up the metabolic syndrome could be the main risk factor for cardiovascular disease in psoriasis patients. The authors of a population-based study conducted in the United Kingdom involving over 127 000 patients with mild psoriasis and over 3800 patients with severe psoriasis found a higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, obesity, and smoking in the first group (respective OR: 1.13, 1.03, 1.16, 1.27, and 1.31) and a higher prevalence of diabetes mellitus, obesity, and smoking in the second group (respective OR: 1.62, 1.79, and 1.31).³⁷ Diabetes mellitus and hypertension were more common in patients with severe psoriasis than in patients with mild psoriasis (respective OR: 1.39, 1.49). The findings of another study involving a review of the records of over 46 000 patients from a health care provider in Israel confirmed an association between psoriasis and both atherosclerosis (peripheral vascular disease, cardiovascular disease, and ischemic heart disease) and diabetes mellitus.³⁸ In the same study, multivariate analysis revealed an association between atherosclerosis and the use of phototherapy and between diabetes mellitus and treatment with potent topical corticosteroids or systemic therapy.

Data from some studies suggest that psoriasis is associated with certain risk factors irrespective of whether or not the patient presents the complete metabolic syndrome. One particular study conducted among nonobese individuals, for example, found that insulin resistance was more common in patients with psoriasis than in controls, and particularly so in patients with type-II psoriasis (onset before age 40), where 40% of patients had oral glucose intolerance.³⁹ Furthermore, lipid abnormalities occur at disease onset in patients with generally mild psoriasis, and no correlation has been found with disease severity according to the Psoriasis Area and Severity Index.¹² In an extensive study conducted in the United Kingdom involving over 127 000 patients with mild psoriasis, 3800 patients with severe psoriasis, and 557 000 control subjects, psoriasis was identified as an independent risk factor for myocardial infarction.⁴⁰ Relative risk was highest in young patients with severe disease. A radiologic study of 32 patients with psoriasis and 32 controls matched for age and sex found that psoriasis was an independent risk factor for coronary artery calcification.⁴¹

The increased risk of death due to heart disease, cerebrovascular disease, or pulmonary embolism in patients

hospitalized for psoriasis¹¹ could be due to prothrombotic factors other than the metabolic syndrome. High plasma levels of homocysteine promote atherosclerosis and thrombotic disease by acting on coagulation and endothelial cells, and folic acid deficiency is a known cause of hyperhomocysteinemia.⁴² A study conducted among 40 patients with psoriasis and 30 controls found that increased plasma homocysteine levels were directly correlated with the Psoriasis Area and Severity Index and inversely correlated with folic acid levels (probably due to increased consumption or reduced absorption).⁴²

Alcohol and smoking may also contribute to comorbidity in patients with psoriasis. For instance, alcoholism and cirrhosis are more common in psoriasis patients. Alcoholism has been reported to affect 18% of psoriasis patients, while only 2% of patients with other dermatologic disorders have alcohol dependency.¹⁸ In addition, a Finnish study identified alcoholism as a significant cause of increased mortality risk in patients who had previously been hospitalized for psoriasis.⁴³ A cross-sectional study conducted in Utah, USA found an increased prevalence of obesity and smoking in patients with psoriasis compared to the general population,⁴⁴ and a recent case-control study in Italy found an association between smoking and psoriasis, and pustular psoriasis in particular.⁴⁵ That study also detected an association between stress and development of psoriasis. The association between psoriasis and high depression scores, anxiety, obsessiveness, and difficulty in verbalizing emotions (especially anger) is well known.⁴⁶ Furthermore, an association has been reported between severe psoriasis and clinical depression and suicide ideation in 7.2% of hospitalized patients.⁴⁷ This association was found in only 2.5% of outpatients, which is comparable to that found in general medical patients (2.4% to 3.3%). Psychological comorbidity in psoriasis probably contributes to a sedentary lifestyle, alcoholism, and smoking, and all these increase the risk of other comorbidities in these patients.

The comorbidities related to the adverse effects of psoriasis treatment are well known and are not discussed in this article. It is worth recalling, however, that several aspects of the metabolic syndrome (hypertension, dyslipidemia, glucose intolerance) can worsen with traditional systemic therapy. Furthermore, attention should be paid to the recent tendency to play down the importance of the hepatotoxic effect of methotrexate, which came to light following studies conducted among Scandinavian patients with a high alcohol intake.⁴⁸

In conclusion, although the morbidity associated with severe psoriasis is by itself considerable and deserving of the best available treatment, recent research findings have identified comorbidities related to the metabolic syndrome and the development of both diabetes mellitus and cardiovascular disease, which alone is estimated to

be responsible for 30% of all deaths.⁴⁹ The identification and treatment of modifiable risk factors could reduce cardiovascular morbidity and mortality, and likewise, the effective control of inflammation (and TNF- α levels, which play a pathogenic role in the metabolic syndrome) in psoriasis through appropriate treatment could improve the corresponding comorbidities. For the time being, dermatologists must assume responsibility for helping patients with psoriasis to improve their life habits in terms of obesity, smoking, alcohol, non-Mediterranean diets, folic acid deficiency, etc. They must identify patients with a higher risk of developing comorbidities (young patients with severe disease) and refer them to appropriate specialists for pharmacological treatment of dyslipidemia, diabetes mellitus, hypertension, psychological disorders, and atherosclerosis, where appropriate.

Conflicts of Interest

The authors declare no conflicts of interest.

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