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Psoriasis: A Disease of Systemic Inflammation with Comorbidities

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1. Introduction

Psoriasis is a chronic disease which affects 1 to 3% of different ethnic populations [1]. As well as the size of the affected population, the social and emotional burden brought by the stigmatization of psoriasis caused serious innovation to the pathogenesis and treatment of the disease.

The majority of the current data about psoriasis is about immune system elements and role of inflammation in the pathogenesis. The development of psoriasis is associated with genetic predisposition which has a basis of T cell activation secondary to dermal inflammation with abnormal keratinocyte proliferation. Tumor necrosis factor alpha (TNF- α), interferon gamma (IFN- γ), and interleukin (IL)-8 which are secreted by T lymphocytes, keratinocytes and inflammatory cells polarize type 1 T lymphocytic pathway and lead to the migration of polymorphonuclear leukocytes to the epidermis predominantly [2]. Upregulation of HLADR, intercellular adhesion molecule-1 and E-selectin activates CD2+, CD3+, CD5+, CLA+, CD45RO, HLA-DR, CD25 (IL-2 receptor) and CD27 expressing T cells [2]. Migration and accumulation of inflammatory cells in the epidermis destroys the basal membrane and desmosomes. In response to the damage, mitogenic cytokines are secreted and a similar process to wound healing results in rapid cell cycling and rapid maturation of keratinocytes [1, 2, 3]. The constant inflammatory cell chemotaxis and cytokine release causes the chronic clinical course with recurrent lesions.

Inflammation is described as a complex physiologic defense mechanism consisting of local changes in hemodynamics, increase in microvascular permeability and a series of intracellular reactions [4]. The autoimmune connective diseases are mainly defined as the prototype of inflammatory diseases. Recently, atherosclerosis, obesity and diabetes mellitus are included

in inflammatory disease category because they are also proved to cause secondary tissue damage by inflammatory mechanisms [4, 5].

In psoriasis, T cells together with their cytokines and chemokines are shown to induce serious inflammation by Th1- and Th17-driven immune response including IL-20, IL-23, IL-12, IL-17 and IL-22 [2, 3, 4, 5]. Lately psoriasis is assumed as an immune mediated inflammatory disease and psoriatic patients are exposed to the systemic effects of the inflammation [5].

2. Psoriasis as a systemic disease

Psoriatic patients were shown to have increased levels of circulating Th1-type cytokines, soluble adhesion molecules, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and acute phase reactants [2, 3, 4, 5, 6]. As a systemic inflammatory disease, more specific and sensitive markers are thought to be beneficial in monitoring the systemic inflammation observed in psoriasis where they can be used to predict the development risk of secondary inflammatory diseases; psoriatic comorbidities.

The comorbidities of psoriasis are listed as obesity/metabolic syndrome, autoimmune diseases, psychiatric diseases, cardiovascular diseases, sleep apnea, cancer/lymphoma, non-alcoholic steatohepatitis (NASH) and chronic obstructive pulmonary disease (COPD) [7, 8, 9, 10, 11, 12]. In this chapter, the comorbidities which are especially related with systemic inflammation of psoriasis will be discussed in more detail.

2.1. Psoriasis and systemic inflammatory markers

The studies conducted for the definition of inflammatory process of psoriasis helped to perform the exact measurements for proinflammatory cytokines such as IL-1 and TNF- α , adhesion molecules as intracellular adhesion molecule-1 (ICAM-1) and selectins, IL-6 and hepatic acute phase reactants as C reactive protein (CRP) [13, 14].

CRP testing is particularly important and it is also been proved to be risk predictor for the development of cardiovascular diseases [15, 16, 17, 18].

2.1.1. C reactive protein

C reactive protein was first defined by Tillett and Francis as a protein developed against carbohydrate component of streptococcus pneumonia capsule in the serum of patients with pneumonia and named as carbohydrate reactive protein [19]. CRP is a non-glycosylated pentameric protein made by hepatocytes with a molecular weight of 118 kilodaltons (kD). The molecule is known as a major acute phase reactant which increases rapidly after infections or tissue damage, widely used as a laboratory parameter for the follow-up of inflammatory and infectious disease activity and is accepted as a very sensitive inflammatory marker [17, 18, 19]. Blood levels of CRP can increase 100 times in the first 24 hours and can decrease to normal levels soon after treatment or spontaneous healing. Therefore CRP is a valuable laboratory parameter for infections, tissue damage and in-

flammation. Standard measurements of CRP levels can detect plasma levels of 3-8 mg/l. CRP levels and healthy individuals have blood levels of CRP under 2 mg/l. New laboratory methods for the measurement of CRP have been developed and these sensitive CRP measurements can detect lower levels of CRP which are significantly related to certain inflammatory diseases and cardiovascular diseases [16, 17, 18, 19].

The synthesis of CRP is mainly controlled by IL-6 but IL-1 and TNF- α may influence CRP levels as well and increase of CRP in blood and other body fluids is a constant result of these proinflammatory cytokines [15,16]. In this aspect, serum CRP is an indirect marker of proinflammatory cytokine activity. As a fact, CRP plays a role in host's immune defense. It binds to the phosphocoline on the surface of the microorganisms preparing them for phagocytosis and lysis. It also activates complement system by binding to LDL on atherosclerotic plaques and induces inflammation [15, 16]. CRP is also shown to increase the expression of tissue factor on macrophages resulting thrombosis. As a classic acute phase marker, CRP induces monocyte-macrophage migration, expression of tissue factor with adhesion molecules and monocyte chemotactic protein-1 [15, 16, 17]. By all of these features, CRP is assumed to increase ischemic myocard damage by participating atherosclerotic pathogenesis.

CRP levels raise as a part of ischemia related acute phase response. Among the plasma markers, CRP is widely used to assess cardiovascular risk. Highly sensitive methods of CRP measurements showed that even levels of CRP within normal ranges may have predictive value in acute coronary syndromes. Sensitive CRP levels are found significantly high when ruptured atherom plaques exist. Recent studies also reveal that there is a strong independent relationship between CRP and future cardiovascular events. American Heart Association and Center for Disease Control (CDC) reported that sensitive CRP is a risk marker for coronary artery diseases [19, 20, 21, 22, 23, 24].

Recent studies showed that psoriatic patients have increased CRP levels and it was also suggested that psoriasis is a systemic inflammatory disease preparing a convenient environment for cardiovascular diseases and comorbidities. The therapeutic modalities of psoriasis are also started to be investigated for their efficacies for lowering CRP levels. Methotrexate (MTX) is found to be efficient in decreasing CRP levels in rheumatoid arthritis (RA) [25, 26]. In fact, MTX therapy reduced the incidence of vascular disease in patients with psoriasis or RA and it was hypothesized that this effect is caused by the drug's anti-inflammatory property [27]. Cyclosporine was efficient as methotrexate and etanercept in decreasing CRP levels in psoriatic arthritis [26, 28]. In a recent study, patients with higher sensitive CRP levels were found to have a better response to cyclosporine therapy [29]. TNF- α inhibitors managed to decrease CRP levels in patients with psoriasis and RA [30, 31]. However, in a meta-analysis investigating association between biologic therapies and cardiovascular events, there was no significant difference in the rate of major cardiovascular events observed in patients receiving anti-IL-12/IL-23 antibodies or anti-TNF- α treatments compared with placebo [32].

Effective treatment of severe psoriasis is thought to be crucial in avoiding systemic inflammatory response although not determined precisely. Therefore psoriatic therapies must also aim the control of a systemic inflammatory disease which is accepted as a predisposition to

cardiovascular diseases. As well as to obtain healthy skin barrier and to increase the severely impaired quality of life, the monitorization and control of systemic inflammation must be aimed. CRP seems to promise an efficient option for this aim.

2.1.2. Other inflammatory markers

In addition to CRP, there are a few investigated serum inflammatory markers in psoriasis. Serum amyloid A (SAA) protein is the precursor of amyloid fibrils which deposit in secondary amyloidosis. It is primarily synthesized as an acute inflammatory reactant from the liver with a molecular weight of 11685 D. Acute inflammatory markers are known to be regulated by hormones, cytokines derived from adipose tissue and synthesized in liver [33, 34]. Adipose tissue is known as the most important source of IL-6 in body and accepted to play a key role in SAA and CRP synthesis. SAA release is likewise increased by IL-1, IL-6 and TNF- α . SAA has a wide level range, it raises rapidly and decreases so soon after infections and enables to represent the acute inflammatory process better than CRP [36]. SAA is a protein which is also a member of high density lipoproteins (HDL) and is synthesized as the predominant apolipoprotein on the plasma HDL particles within the acute inflammatory process. SAA is also produced by synovial fibroblasts and induce collagenase. Immune system cells are attracted by SAA to related sites of inflammation [37].

Inflammatory reactants are released in a coordinated order with systemic and metabolic changes as a response to tissue damage and infection. SAA is a major component of acute inflammatory response. In a similar way to CRP, SAA rises in the serum after infection, inflammation, tissue damage and stress. It is shown to raise in chronic infectious diseases like tuberculosis, lepra, in autoimmune diseases like RA and systemic lupus erythematosus, in kidney transplant rejection, benign monoclonal gammopathy and malign diseases [17, 37].

The increased SAA within acute inflammatory process replaces with apolipoprotein A-1 and decreases the HDL mediated cholesterol entry to the liver cells which is supported by increased levels of SAA in coronary artery disease patients. High sensitive CRP and SAA are related with vascular wall inflammation and accepted as predictors of coronary vascular events. In a study in 1999 SAA is found as an independent risk factor for cardiovascular diseases [37]. In another study SAA was found as a strong predictor for cardiovascular diseases [22, 37, 38]. In a recent study involving severe psoriatic patients, SAA was found significantly higher in patients with severe psoriasis compared to a sex and age matched control group [39].

Other inflammatory markers recently investigated in psoriasis are platelet-derived microparticles, soluble P-selectin, adiponectins, lectins, haptoglobins, ceruloplasmin, α 1-antitrypsin, chitinase 3-like protein 1 (YKL-40, CHI3L1) and serum lipocalin-2 [40, 41, 42, 43].

2.2. Psoriasis and comorbidities

Diseases included as psoriatic comorbidities are obesity/metabolic syndrome, autoimmune diseases, psychiatric diseases cardiovascular diseases, sleep apnea, cancer/lymphoma,

NASH and COPD. In this chapter, the systemic inflammation related comorbidities of psoriasis will be discussed.

2.2.1. Psoriasis and obesity/metabolic syndrome

Adipose tissue is known as the most important source of IL-6 in body. Inflammation is mainly controlled by hormones, cytokines derived from adipose tissue and liver by IL-1, IL-6 and TNF- α . Common cytokine pathways are responsible for both psoriasis and obesity but it is yet to be answered which pathology comes first when psoriasis-associated obesity and the metabolic syndrome is considered. It is also not revealed if the diseases are concurrent in a convenient genetic background [44, 45, 46].

Obesity and metabolic syndrome are correlated with increased risk for coronary heart disease. The metabolic syndrome is in fact a group of risk factors which are listed as insulin resistance or glucose intolerance, abdominal/visceral obesity, dyslipidemia (high triglycerides, low HDL-C, high LDL-C), elevated blood pressure, prothrombotic state (high fibrinogen or PAI-1) and proinflammatory state (elevated CRP, TNF- α , IL-6). Several components of metabolic syndrome has been shown to be frequent in psoriatic patients [47]. In a study of 581 moderate-severe psoriasis patients, an increased prevalence was found for metabolic syndrome (OR=5.29), psoriasis patients were more likely to have diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease and they were also more likely to be smokers [48].

Despite the well documentation in adults, there is a few data for obesity/metabolic syndrome in pediatric psoriasis patient population. Augustin et al found a higher prevalence of hyperlipidemia, diabetes, hypertension and obesity in children with psoriasis than the controls retrospectively [49]. Koebnick et al showed a significant association between increasing weight and psoriasis in children in a cross-sectional study [50]. In a study by Au et al it was suggested that metabolic syndrome occurs more frequently in pediatric patients with psoriasis [51]. It is assumed that children with psoriasis have excess adiposity and are at risk for associated complications.

2.2.2. Psoriasis and cardiovascular diseases

Recent studies show that local and systemic inflammation plays a big role in the pathogenesis of coronary artery diseases (CAD). Bhagat and Vallance has shown that TNF- α and IL-1 causes a transient reversible endothelium dysfunction in humans [13]. High levels of IL-6 and soluble IL-2 are shown to be associated with impaired microvascular functions. A big part of TNF- α induced mechanisms causes endothelium dysfunction. TNF- α raises the expression of adhesion molecules. After the exposition of endothelial cells to TNF- α , polymorphonuclear cells migrate to vascular structures. In fact, TNF- α supports the adhesion and invasion of dendritic cells to vascular walls. After the induction of the dendritic cells, T cells, monocytes and macrophages get activated and produce inflammation by cytokine production. High levels of TNF- α stimulates nitric oxide synthase (NOS) in human endothelium cells. This molecule is known to cause free radi-

cal production in neutrophils, smooth muscle cells in the vessels and endothelium. TNF- α induced oxidative stress causes the apoptosis of endothelial cells [13,14]. All of this data shows that endothelial cells are the target of cytokines and other vessel cells. The prolonged exposition of endothelial cells to inflammatory cytokines and oxidative stress results in acceleration of apoptosis, development of thrombus and formation of atherosclerotic plaque.

Patients with psoriasis have an increased prevalence of risk factors for CAD. Psoriatic patients who are characterised with elevated TNF- α levels have a significant higher frequency of CAD, pulmonary emboli and cerebrovascular diseases [52, 53, 54, 55].

Patients with moderate to severe psoriasis have an increased prevalence of CAD and an increased risk for myocardial infarction. In a cohort study by Ahlehoff et al, patients with psoriasis showed a disease severity-dependent increased risk of ischaemic stroke and there was an association between psoriasis and atrial fibrillation [54]. In a cohort study of general practice research database, severe psoriasis was found as a risk factor for major adverse cardiac events (hazard ratio 1.53; 95% confidence interval, 1.26-1.85) after adjusting for age, gender, diabetes, hypertension, tobacco use, and hyperlipidemia. Severe psoriasis added 6.2% absolute risk of major adverse cardiac events.[55] Gelfand et al used the General Practice Research Database (GPRD) to determine if psoriasis is an independent risk factor for myocardial infarction. The study included 3827 (2.9%) severe psoriatic patients with a mean follow-up period of 5.4 years. A significant relationship was shown between the cardiovascular disease risk and psoriasis duration and severity. An increased incidence of acute myocardial infarction (AMI) in patients with psoriasis was found and the AMI rate was highest in patients with severe psoriasis [56]. Psoriatic patients had a x2.6 increased risk for occlusive vascular disease and x1.6 increased risk for venous occlusion compared to healthy population Psoriatic patients are also shown to have increased levels of atherothrombotic markers like fibrinogen and plasminogen activator inhibitor-1 (PAI-1) [57].

As well as systemic inflammation, other possible suggested mechanisms for CAD comorbidity of psoriasis are increased prevalence of common CAD risk factors in psoriasis patients and antipsoriatic medications are suspected (cyclosporine, acitretin) for their adverse CAD risk profiles (e.g., elevation of blood pressure, elevation of serum levels of lipids).

3. Conclusion

Psoriasis is associated with multiple CAD risk factors. In fact it is suggested as an independent risk factor for CAD. Obesity and metabolic syndrome are also common in both pediatric and adult psoriatic patients. As a systemic inflammatory disease with important life threatening comorbidities, there is a need for a systematic and complementary understanding of medical care for psoriasis. Screening guidelines for especially severe psoriatic patients has to be reviewed for susceptibility risk factors for the common comorbidities. The approach to psoriasis may also include not only dermatology but also cardiology, rheumatology, and endocrinology assessments at certain points.

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