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Case report

IMPACT OF CARRIAGE OF 4G/5G PAI-1 AND GLYCOPROTEIN IIB/IIIA POLYMORPHISM ON DEVELOPMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN A PATIENT WITH PSORIASIS VULGARIS. CLINICAL CASE.

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SUMMARY

Psoriasis vulgaris represents a chronic immune-inflammatory condition that besides skin and joints, also affects many other tissues and organs. Recent advances in psoriatic research highlighted that psoriatic patients are at higher risk to develop the chronic obstructive pulmonary disease (COPD). We report a case of a Caucasian man of 62 years' age with plaque psoriasis diagnosed more than 20 years who developed psoriasis specific comorbidities: COPD in 2005 and later in 2006 arterial hypertension and ischemic cardiomyopathy disease.

The patient's blood parameters were specific for psoriasis and metabolic syndrome with high total cholesterol 6.13 mmol/L, high triglycerides 2.37 mmol/L, high LDL 4.7 mmol/L, low HDL-cholesterol 0.79 mmol/L. Enzyme-linked immunosorbent assay (ELISA) analysis demonstrated elevated serum plasminogen activator inhibitor 1 (PAI-1) levels – 63.21 ng/ml (ref.5-40 ng/mL). The DNA analysis revealed a carriage of heterozygous polymorphism in PAI-1 4G/5G and a carriage of heterozygous polymorphism PlA1/PlA2 in the gene for glycoprotein IIb/IIIa.

This case on psoriasis and comorbidity is an example concerning the possible connection of impact of inherited factors with an increased risk of COPD.

Keywords: psoriasis, COPD, ischaemic heart disease, 4G/5G PAI-1, PlA1/PlA2,

BACKGROUND

Psoriasis is a chronic inflammatory systemic disease characterized by a specific range of comorbidities including hypertension, obesity, diabetes mellitus, dyslipidemia, and other cardiovascular diseases [1, 2]. There have been many reports recently about accompanying diseases and risks that influence patients' with psoriasis in addition to their main condition [3]. The associated systemic inflammatory state could act on respiratory tissues as well and amplify preexisting inflammation leading to the development of COPD [4, 5]. This clinical case gives an insight into such à complicated condition.

Chronic obstructive pulmonary disease (COPD) affects around 10% of the world's population and includes emphysema and chronic obstructive bronchitis [6]. It is represented by an enduring and continuous impairment of respiratory airflow [7]. The key factors implicated in causing COPD is believed to be linked to smoking, lung inflammation (which is responsible for small airways thickening), and alveolar destruction [8].

It has been confirmed that COPD and psoriasis share some common risk factors which include obesity, smoking, physical inactivity and metabolic syndrome. More research needs to be done for further eliciting the link between COPD and psoriasis.

Case Description

We studied a 62-year old white man, with more than a 20-year history of plaque psoriasis. He was treated with topical emollient agents. In 2005 the patient was diagnosed with COPD. Later in the 2006 year, he was diagnosed with chronic arterial insufficiency of the legs and was treated with pentoxifylline.

In 2006 the patient was diagnosed with arterial hypertension (170/100 mmHg) II degree and ischemic cardiomyopathy disease treated with acetylsalicylic acid, enalapril maleate, and lisinopril. In 2012 the subject was diagnosed with Type 2 Diabetes mellitus (accompanied by nephropathy) and was treated with gliclazide, metformin hydrochloride, and glimepiride.

Physical examination of the patient revealed well-formed psoriatic plaques on the lower limbs (Fig. 1), upper limbs (Fig. 2), and torso (Fig. 3). The patient is obese, BMI-31 kg/ m² (weight 90kg, height 1.75m), with central obesity (waist circumference 120 cm; hip circumference 110cm).

Psoriasis Area Severity Index (PASI): 14.8

Fig. 1. Psoriatic plaques on the upper part of the lower extremities.

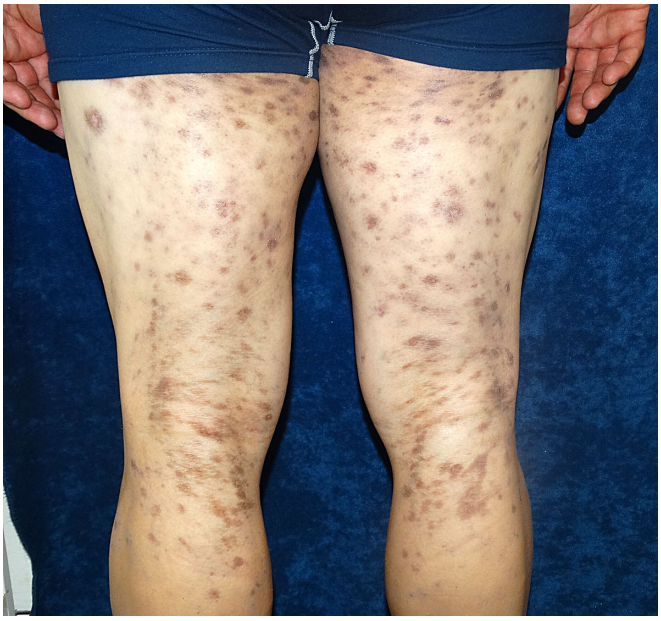


Fig. 2. Well-formed psoriatic plaques on the dorsal aspect of the arms.

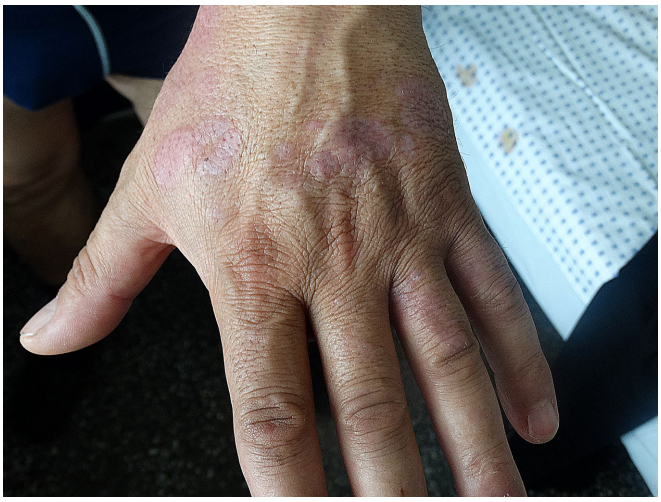
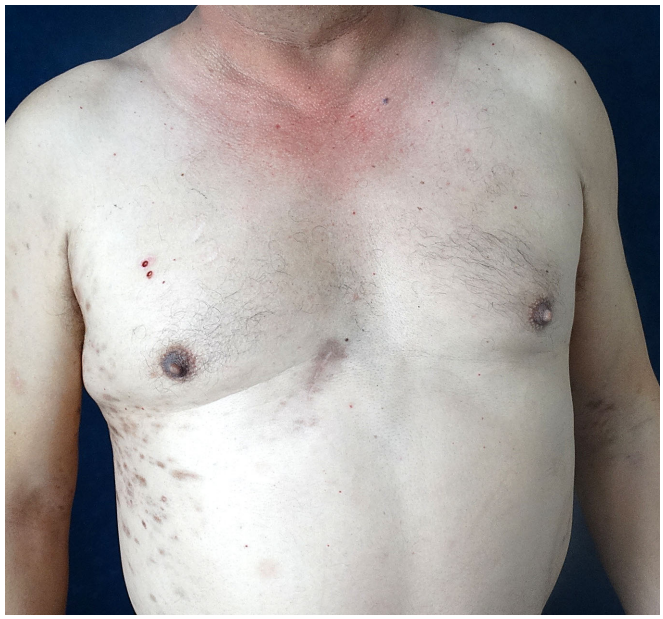


Fig. 3. Psoriatic plaques on the torso.



Among the risk factors were tobacco smoking ten to twenty cigarettes daily for over 20 years, moderate regular alcohol consumption, history of hypertension, recently diagnosed Type 2 Diabetes Mellitus. The family history of the patient included Diabetes Mellitus (father) and obesity (father). The patient has all the main characteristics of Metabolic Syndrome including Hypertension, Type 2 Diabetes Mellitus, high waist circumference, high total and LDL cholesterol, high TAG and low HDL.

He was recently hospitalized for COPD acute recurrent exacerbations of his skin condition, even though he suffers from plaque type psoriasis with chronic recurrent relapses over the last 20 years.

The patient also has 10 years of history of pain in the lower limb joints.

Chronic bronchitis was diagnosed 18 years ago. Other confirmed diagnosis include heart failure type class II (according to NYHA), stable angina pectoris grade II and pulmopathy.

Dermatological history and evaluation revealed well-formed erythemo-*squamous plaques* with intensive erythema, deep infiltration and abundant accumulation of coarse flat-topped bumps on the scalp, inguinal folds, limbs, and torso.

During a recent admission, the patient was treated with the following therapeutic drug regime: for topical application included ung. Eudermol 10 and ung. Dithranoli 2%. Systemically were administered Gentamycin 160mg, Vit C amp., Ac. Follici tab. Other non-drug management included treatment with UV phototherapy.

The patient was discharged from the clinic with an insignificant improvement of his condition. The therapy will continue with emollients and topical keratolytics.

Blood sampling, Biochemical Blood tests, ELISA and DNA analysis were carried out as described [9].

The elevated PAI-1 level in the serum led us to in-

vestigate the carrier status for PAI-1 -675 4G/5G, rs 1799889(-) single nucleotide deletion (SND) in the promotor region of PAI-1 gene.

Evaluation for risk of thrombotic events, the following thrombophilic polymorphisms were investigated: factor V Leiden (FV 1691G>A) rs6025, factor II prothrombin (FII 20210G>A), rs1799963, polymorphism PlA1/PlA2 in platelet glycoprotein IIb/IIIa, integrin B3 (ITGB3) 1565T>C, rs5918, methylenetetrahydrofolate reductase (MTHFR) 677 C>T polymorphism rs1801133 (a single nucleotide polymorphism (SNP) in MTHFR gene.

MATERIAL &METHODS

Laboratory blood investigations including blood glucose, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, urea, uric acid, creatinine, ASAT, ALAT, leucocytes, erythrocytes, platelets, hemoglobin, hematocrit, MCV, MCH, were routinely carried out at the Clinical Laboratory in Dr Georgi Stranski University Hospital, Pleven.

ELISA method was used for PAI-1 determination in serum. The Human PAI-1 ELISA is an enzyme-linked immunosorbent assay for the quantitative detection of Human PAI-1. The kit is manufactured by BioVendor Research and Diagnostic Products.

Polymerase Chain Reaction (PCR) analysis of proinflammatory markers important for the evaluation of cardiovascular risk and psoriasis were investigated corresponding to 4G/5G PAI-1, PlA1/PlA2 in glycoprotein IIb/IIIa gene and MTHFR 677 C>T.

Biochemical Blood test and ELISA results

The biochemical parameters are shown in Table 1.

Table 1. Laboratory Blood investigations:

Parameter	Value	Units	Normal range	
Glucose	**5,31**	mmol/ L	4.1- 6.1	**L**
Urea	10,52	mmol/ L	2.5-7.5	**H**
Uric acid	625	µmol/ L	202-416	**H**
Creatinine	144	µmol/ L	80-115	**H**
ASAT	29,1	U/I	20 637,00	N
ALAT	15	U/I	14 885,00	N
Cholesterol	**6,13**	mmol/ L	<5.2	**H**
Triglycerides	**2,37**	mmol/ L	<1.7	**H**
HDL-cholesterol	0,79	mmol/ L	>0,90	**L**
LDL-cholesterol	4,7	mmol/ L	2.59- 3.34 (optimal)	**H**
Leucocytes	4,2	10^9 /L	4.4-5.9	N
Erythrocytes	4,81	10^{12} /L	80-115	N
Hemoglobin	**153**	g/ L	140-180	N
Hematocrit	0,45	L / L	0.40-0.53	N
MCV	94	Fi	82-96	N
MCH	31,8	Pg	27-33	N
Platelets	**121**	10^9 /L	150-360	**L**
PAI-1	63,21	ng/ml	5-30	**H**

DNA analysis results are presented in Table 2

DNA analysis showed that the patient is a heterozygous carrier of deletion of rs1799889 polymorphism in 4G/5G PAI-1 and a heterozygous carrier of polymorphism PlA1/PlA2 in glycoprotein IIb/IIIa gene, a heterozygous carrier of polymorphism MTHFR 677 C>T. These polymorphisms are responsible as well for a mild prothrombotic state. Carriage of polymorphism in PAI-1 4G/5G gene contributes to more pronounced inflammatory state, heterozygous carriage of polymorphism PlA1/PlA2 in glycoprotein IIb/IIIa gene is an important risk factor for cardiovascular disease (CVD).

Table 2. DNA analysis of polymorphisms

Investigated polymorphism	Homozygous Wild	Homozygous Mutant	Heterozygous Mutant
PAI-1 -675 4G/5G			X
MTHFR 677 C>T	X		
Glycoprotein IIb/IIIa, 1565 T>C			X

DISCUSSION

The ELISA measurement revealed that serum PAI-1 level of our patient is increased. PAI-1 is an essential factor, produced by endothelial cells and megakaryocytes [10]. This coagulation factor downregulates fibrinolysis through inhibiting plasminogen activation and transformation to plasmin by tissue-plasminogen activator and urokinase [11]. Increased PAI-1 is associated with a pro-inflammatory status as well. It could be used as an important predicting factor for the development of psoriasis [12], metabolic syndrome [13], thrombosis, diabetes, hyperlipidemia etc. [14].

High PAI-1 is proposed as a marker for COPD incidence [14] because PAI-1 levels are elevated significantly and correlate negatively with pulmonary function in COPD patients [15].

Several polymorphisms of PAI-1 are described so far with important medical value. The highest clinical importance was found for the rs1799889 PAI-1(insertion/deletion at -675 position in the promoter region) contributing to elevated thrombotic risk along with myocardial infarction [16]. This polymorphism might be involved as well in the development of psoriasis [11] and COPD [15].

DNA analysis was performed aiming to assess whether high PAI-1 levels are of inherited origin. Heterozygous carriage of this polymorphism causes a mild effect on PAI-1 levels, hence even this mild elevation in plasma contributes to inflammatory state [17].

Glycoprotein IIb/IIIa is an important integrin complex with receptor function on the surface of platelets. This receptor binds primarily fibrinogen, mediating platelet aggregation and blood clotting. Even in the heterozygous state, the polymorphism PlA1/PlA2 contributes to the elevated risk of coronary heart disease [18].

Both PAI-1 and glycoprotein IIb/IIIa polymorphisms increase the risk of cardiovascular events, and this might have an accumulative impact [19,20].

High Urea, Uric acid and Creatinine in our patient might be increased due to psoriasis which damages the kidneys (psoriatic nephropathy) [21].

Besides psoriasis, diabetes mellitus, also might cause high urea and creatinine levels in serum due to kidney damage (diabetic nephropathy) [22] and increased gluconeogenesis [23].

The high serum cholesterol, high triglycerides and high LDL-cholesterol might be because of the abnormal lipid metabolism in psoriasis like metabolic syndrome [24], which is with an increased presence in psoriasis [25].

It has just been recently proved that patients suffering from psoriasis are threatened by the elevated risk of COPD [8, 26, 27, 28]. Evidence for the relation between these two conditions is the fact that for their therapy analogous immunotherapeutic medications are designed [29].

Continuous, systemic inflammatory process is a plausible link between psoriasis and comorbidities [1, 30]. The systemic inflammatory state seems to be the common factor between psoriasis and comorbidities [26]. Apparent release of various pro-inflammatory cytokines in the circulation by skin lesions could produce a strong effect on the manifestations of the related comorbidities [31, 32]. Successful therapy of psoriasis usually lowers the levels of elevated cytokines in the serum [33]. Certainly, related comorbidities also release inflammatory mediators, which can make psoriasis even more severe.

Psoriasis and COPD share many pro-inflammatory factors, which are increased in both diseases [34, 35, 36, 37].

Over the past few years, more evidence is starting to emerge about the possible relationship between increased risk of psoriasis, cardiovascular events [38] and COPD [39]. Hypercoagulability state is often associated with COPD [40] and psoriasis [41]. COPD is involved in the prevalence of hypercholesterolemia [42], weight gain and alterations in the adipokine levels [43].

The serum cholesterol, LDL and triglycerides are also significantly higher in psoriatic patients [1, 44]. It is worth mentioning that hypertriglyceridemia [45] and hypercholesterolemia [46] lead to increased PAI-1 levels in the blood which means that factors like psoriasis and COPD will likely cause elevation of PAI-1 protein in plasma with the respective consequences.

All this data indicates that psoriasis patients have an increased risk of COPD and increased risk for coronary artery disease and other cardiovascular morbidities. This can be important particularly when CVD are a common cause of morbidity and mortality in patients with psoriasis [47]

Countermeasures must be taken to limit the risk factors like smoking and to deal with the inflammatory processes (anti-TNFá agents like biologics, used for the treatment of psoriasis) [48]. These measures may also have cardio-protective [49], COPD preventive and prophylaxis effects) to avoid the eventual development of COPD [26]. Consultation with pulmonologist should be advised [8].

Physicians should be aware when there are present risk factors like smoking and prothrombotic polymorphisms as those observed in the patient. More studies about the role of systemic therapies for psoriasis aiming the reduction of the risk of COPD and ischaemic heart disease must be done.

Due to the obvious risk factors (psoriasis, COPD, high cholesterol, hypetriacylglyceridemia, diabetes, high PAI-1

levels), this patient should be under observation.

CONCLUSION

Both pathological conditions of psoriasis and COPD possess complex aetiology and are not fully comprehended, but the risk of the development of COPD in psoriatic patients must be taken into account. There is a good amount of scientific evidence that associate psoriasis to disorders like COPD, and this has to rework the ways of treatment of patients with psoriasis.

Psoriatic patients must be inspected/evaluated for cardiovascular risk factors, metabolic disorders including COPD, levels of pro-inflammatory factors like PAI-1, carriage of specific genetic polymorphisms to take into account in the treatment strategy.

The inheritance for COPD risk factors has to be considered, as it devotes to the multifactorial risk of comorbidities.

To conclude, we may say that this clinical case recaps a link between continuous inflammation and risk of COPD and warns that psoriatic patients might have an elevated risk of COPD incidents.

Abbreviations:

COPD - chronic obstructive pulmonary disease
ELISA - Enzyme-linked immunosorbent assay
PAI-1 - plasminogen activator inhibitor 1
DNA - Deoxyribonucleic acid
PASI - Psoriasis Area Severity Index
LDL - Low-density lipoprotein
TAG - triacylglycerol
HDL - High-density lipoproteins
BMI - body mass index
SND - single nucleotide deletion
MTHFR - methylenetetrahydrofolate reductase
CVD - cardiovascular disease

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