

DEEP VEIN THROMBOSIS AND RECURENT PULMONARY EMBOLISM IN A PATIENT WITH THROMBOPHILIC MUTATIONS AND GENERALIZED PSORIASIS: A CASE REPORT

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Abstract: Introduction: Genetic risk factors that increase venous thromboembolism risk are disorders in the synthesis or activity of coagulation factors. Factor V Leiden, prothrombin (20210-A), antithrombin deficiency, protein C and protein S deficiency, and hyperhomocysteinaemia are the most common venous thromboembolism-related gene mutations. When genetic factors are combined with non-provoking risk factors (obesity, psoriasis, smoking and previous venous thromboembolism) the result is increased venous thromboembolism risk for each factor individually. Previous venous thromboembolism is one of the strongest risk factors, even in patients actively treated with anticoagulant. Patients are more likely to have recurrent venous thromboembolism with longer duration. Psoriasis is a complex immune-mediated disease, associated with cardiovascular risk, hypercoagulability markers and elevated homocysteine. Lots of observational reports suggest increased incidence of venous thromboembolic events in patient with psoriasis.

Case presentation: We present patient with inherited thrombophilia and chronic diffuse plaque psoriasis complicated with deep venous thrombosis and pul-

monary embolism. DNA analysis indicates the presence of homozygosis for Factor V Leiden mutation as well as heterozygosis for Factor XIII V34L, PAI-1 5G/4G and MTHFR A1298C polymorphism. Dermatological anamnesis is positive for plaque psoriasis since 12 years ago.

Conclusion: The presentation of this case indicates an association between venous thromboembolism and chronic psoriasis. All patients with recurrent thromboembolism, hereditary thrombophilia, and moderate to severe psoriasis should be considered to be at higher risk for venous thromboembolism and appropriately treated.

Key words: Recurrent venous thromboembolism, thrombophilia, psoriasis, pulmonary embolism.

INTRODUCTION

Venous thromboembolism (VTE) comprising deep venous thrombosis (DVT) and pulmonary embolism (PE) is a common medical problem, which can be predisposed by several medical conditions as trauma, surgery, immobilization, chronic inflammation or cancer, or genetic mutations. Recently there are studies

about systemic chronic inflammation as potential risk factor for VTE. The relationships stems from the impact of the chronic inflammation on the aggregation of the platelets, activation of the coagulation cascade, and stimulation the pro-coagulant activity of the inflammatory cytokines and decrease of the activity of the anti-coagulant and fibrinolytic systems. Therefore some studies suggest that patients with elevated inflammatory markers (C reactive protein (CRP) and other inflammatory cytokines IL-6, IL-8 and TNF) have an increased risk of VTE (1). This positive association between inflammatory makers and VTE is highly suggestive but it's unclear whether the inflammation and its inflammatory cytokines are responsible and causative component for generating a VTE event. Several systemic inflammatory diseases has been linked with increased VTE risk, in a large epidemiologic studies, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, systemic lupus erythematodus (2). Psoriasis is a chronic complex immune – mediated disease, wich activates both Th1 and Th 17 inflammatory pathways that afflicts not only the skin and joints but involves the endothelium as well and results in increased IL6 and TNF cytokines so the patients often has elevated CRP (3). Worldwide review revealed the prevalence of psoriasis ranged from 0,5-11,4 % in adult and 0-1,4 % in children (4). It's associated with cardiovascular risk, hypercoagulability markers and elevated homocysteine (Hcy) (5). A cohort study conducted by Ahlehoff et al., in Denmark demonstrated age and severity dependent increase in risk of cardiovascular mortality in psoriasis patients. In this report we present patient with inherited trombophilia and chronic diffuse plaque psoriasis complicated with DVT.

CASE REPORT

We present a case of a 40-year-old male patient in the intensive care unit admitted for severe breathing, suffocation approaches, chest pain, swelling and pain in the left calf, acute DVT in the left femoral and popliteal vein, given episode of DTV and PE 7 years ago. Anamnestic few days back, with pain and swelling in the left calf. From day one, chest pain, shortness of breath, dyspnea, inhalation pain and hemoptysis in two occasions. The symptoms intensify one hour before admission to ER. Examinations show increase in D-dimers 19000 µg/L, cO₂ -88%. Leukocytosis 11 x 10⁹ /L, SE 45, CRP 65 mg/L, Hemostasis TT 13,2; INR 1. Venous doppler on the left calf: v. poplitea of increased size, partially compressible, with visible thrombotic substrate in the lumen. Left v. safena parva in upper half uncompressible, dilated, with visible thrombotic substrate, absent color doppler signal. The remaining deep veins to the left with neat dimensions, compressible re-

spiratory modulated, spontaneous flow. Left v.safena magna with neat dimensions, compressible, spontaneous flow. No reflux was observed at the left saphenofemoral joint. Right: normal finding. The finding on CT scan is in addition to extensive filling defects that correspond to thrombi in both major pulmonary arteries. Left in the segmental artery for the lower lobe, a highly suspected lingual defect in the filling is also present in the segmental artery for the upper lobe. In addition to the filling defect in the main artery there are also defect in segmental and sub-segmental arteries for the lower lobe as well as a small filling defect in the artery for the upper lobe, the transverse diameter of the truncus pulmonalis is 3 cm. Data for PE 7 years ago, (treated with the Acenocoumarol 4 mg pattern until two years ago, therapy was discontinued alone). Comorbidities: HTA, obesity, psoriasis, recurrent VTE. Personal history: single, smoking a pack of cigarettes a day. Family history: The patient did not have a history of recent trauma, immobilization, distant traveling, fever or history of cancer but had a positive family history of thrombosis. His mother had two miscarriages and history of trombophlebitis, and is set on a regular oral anticoagulant therapy. General status: Accepted conscious, oriented, afebril, distinctly dyspnoeic, hemodynamically compensated, obese with BMI 34.7 kg/m², skin and visible mucus pale color. Lungs: vesicular breathing. Heart: rhythmic action, tachycardia with HR 110/min, clear tones, TA 150/90 Extremities: pronounced swelling of left calf, warm skin with preserved coloration and pulse of a.dorsalis pedis. The patient is suffering from severe case of plaque psoriasis for the last 12 years. Diffusely distributed erythematous plaques with prominent hyperkeratosis on the trunk, extensor area of the extremities and scalp. His PASI score is 56. Itching is pronounced on the trunk. (Figure 1, 2 and 3.). He



Figure 1. Psoriatic squamous plaques



Figure 2. Psoriatic plaques on the lower leg

reports a worsening of psoriasis at the same time as VTE. Echocardiography: LVs 50 mm, LVd 34 mm, RV 28 mm, LA 38 mm, Ao 21/34 mm IVS 9 mm; PW 9 mm; EF 60%. Mild tricuspid regurgitation, without pulmonary hypertension (SPAP 29 mmHg). Treatment: After 48h of intravenous anticoagulant use, the anticoagulant was then shifted to Rivaroxaban. Antibiotics were administered parenteral the same. The following recommendation for home therapy is given: Tbl Rivaroxaban a 15 mg 2 x 1 three weeks, then Tbl Rivaroxaban a 20 mg 1 x 1; Tbl Àtorvastatin a 10 mg 1 x 1; and regular therapy for HTA tbl Losartan 50 mg 2 x



Figure 3. Diffuse extensive thick plaques

1 and tbl Lerkanidipin 10 mg, tbl Indapamid 1,5 mg Tbl Cefixime a 400 mg 2 x 1 seven days, as well as treatment for psoriasis in consultation with a dermatologist. Realized genetic studies of thrombophilic genes are shown in Table 1. Tests in this patient indicate homozygosity for Factor V Leiden mutation, as well as heterozygosity for Factor XIII V34L, PAI-1 5G/4G and MTHFR A1298C polymorphisms. Control CT angiography after 6 months with full resolution. Control vein Doppler after 3 months - deep veins are neat, compressible with spontaneous flow. Anticoagulant therapy in these patients with recurrent thromboembolism is lifelong with regular controls for all provocative factors and psoriasis.

DISCUSSION

About 20-30 single nucleotide polymorphisms (SNPs) are associated with the risk of VTE through the candidate gene discovered by genotyping methods, although for some mutations, the clinical relevance and underlying pathophysiological mechanism remain un-

Table 1. Thrombophilic gene mutations

Gen (according to HGNC)	Referent sequence	Mutation		Genotype according to HGVS of the investigated mutations
		Standard nomenclature (according to HGVS)	Traditional nomenclature	
F5	NM_000130.4	c.1601G > A	Factor V Leiden	c.[1601G > A]; [1601G > A]
		c.3980A > G	Factor V H1299R	[=]; [=]
F2	NM_000506.3	c.*97G > A	FactorIIIG20210A	[=]; [=]
F13A1	NM_000129.3	c.103G > T	Factor XIII V34L	c.[103G > T]; [=]
FGB	NM_005141.4	c.-463G > A	FFB 455 G/A	c.[-463G > A]; [=]
SERPINE1	NM_000602.4	c.-816A > G	PAI-1 5G/4G	c.[-816A > G]; [=]
MTHFR	NM_005957.4	c.665C > T	MTHFR C677T	c. [665C>T]; [=]
MTFHR	NM_005957.4	c.1286A > C	MTHFR A1298C	c.[1286A > C]; [=]
MTRR	NM_002454.2	c.66A > G	MTRR A66G	c.[66A > G]; [=]
MTR	NM_000245.2	c.2756A > G	MTR A2756G	c.[2756A > G]; [=]

clear. The most common are Factor V Leiden and Prothrombin gene mutation, with estimated prevalence of 4-5% and 2-4%, respectively (6). Individuals that are homozygous for Factor V Leiden are even more prone to VTE with nearly 40 times the risk compared to a 2-7 fold increase in risk in heterozygous individuals (7). This case is of interest because recurrence occurs as a result of this patient's provocative risk factors: BMI = 34.7 kg/m², smoking, previous DVT as one of the strongest risk factors and psoriasis as a generalized chronic inflammatory condition. The genetic profile predisposing the patient to thrombophilia and thromboembolism is also of interest: the mutations factor V Leiden and MTHFR A1298C are already known, and Factor XIII V34L, PAI-1 5G/4G heterozygous form has been recently proposed as a prothrombotic risk factor for venous thrombosis in Caucasian populations. The patient had a long history of psoriasis, treated only with topical creams, and has history of previous thrombophilia and DVT, was smoker, obese, hypertensive with metabolic Sy, and he has thrombophilic mutations. The first one who recorded this association in the dermatological literature was Bunch (8). Subsequently a lot of reports and growing evidence of VTE events in psoriasis appeared. A nationwide cohort study was conducted in Denmark, from 1997-2006, which indicated increased risk of VTE in psoriasis patients. A large prospective-population based study of almost 40.000 patients, revealed - that psoriasis is associated with 40% increased risk of incident VTE (9). Still the pathogenesis is unknown. One of the proposed hypothesis is the process of systemic chronic inflammation, via genetic mechanism, produces inflammatory proteins. Elevated levels of inflammatory mediators like CRP and cytokines, in psoriatic patients are related to the coagulation cascade and subsequently may lead to platelet aggregation and clot formation (10). Also the existing eosinophils in psoriasis acts as thrombogenic factors regulated by the inflammation which lead to hypercoagulable or prothrombotic state. The second hypothesis is elevated levels of homocysteine due to the condition or its treatment. Several mechanisms for hyperhomocysteinemia are proposed - Hcy is directly toxic to vascular and endothelial cells, decrease the NO bioavailability which contributes to thrombosis (11) or it blocks the binding of tissue plasminogen activator which leads to decrease in plasmin production and extravascular fibrin deposition. Another prothrombotic mechanism is related to decreased expression of thrombomodulin which is essential of activation of the anticoagulant protein C.

There are studies that demonstrate that deficiency in folic acid, Vit B12 and B6 which are involved in the synthesis of Hcy is the main reason for hyperhomocysteinemia. Persons carriers of MTHFR polymorphism predisposes elevated Hcy levels. The A1298C polymorphism in the MTHFR gene shows an association with the risk of cardio vascular event and subclinical atherosclerosis in patient with RA(12). Polymorphism in the Factor XIII gene, V34L, has a small, but significant protective effect against venous thrombosis. It has also been associated with lower risk for stroke a myocardial infarction. Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of tissue type plasminogen activator (tPA). Increased plasma PAI-1 levels due to reduced fibrinolytic capacity plays an important role in the pathogenesis of disorders associated with thrombosis. This polymorphism has been studied extensively, the prevalence of 4G allele was found to be higher in disorders like coronary artery disease, severe pre-eclampsia, type 2 diabetic nephropathy, PE and arterial thrombosis associated with hereditary protein S deficiency (13).

CONCLUSION

The present case report suggests a relation between systemic inflammation, thrombophilia and risk of VTE, and it suggests that patients with even mild to moderate psoriasis may be at an elevated risk of a VTE event. Screening patients with psoriasis for additional risk factors that promote thrombosis should be considered. Until further evidence is available, all patients with mild to moderate psoriasis may be considered to be at a higher risk of venous thromboembolism and managed accordingly.

Abbreviation

DVT — deep venous thrombosis
PE — pulmonary embolism
VTE — venous thromboembolism

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Sažetak

DUBOKA VENSKA TROMBOZA I REKURENTNA PLUĆNA EMBOLIJA KOD PACIJENTA SA TROMBOFILICNIM MUTACIJAMA I GENERALIZOVANOM PSORIJAZOM: PRIKAZ SLUČAJA

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Uvod: Genetski faktori rizika koji povećavaju rizik venske tromboembolije su poremećaji u sintezi ili aktivnosti faktora koagulacije. Faktor V Leiden, protrombin (20210-A), antitrombinski deficit, deficit proteina C i proteina S i hiperhomocisteinemija najčešće su mutacije gena povezane sa venskom tromboembolijom. Kada se genetski činioci kombinuju sa neprovocirajućim faktorima rizika (gojaznost, psorijaza, pušenje i prethodna venska tromboembolija), rezultat je povećani rizik venske tromboembolije za svaki faktor pojedinačno. Prethodna venska tromboembolija je jedan od najjačih faktora rizika, čak i kod pacijenata koji su aktivno lečeni antikoagulantima. Pacijenti imaju veću verovatnoću da imaju ponavljajuću vensku tromboemboliju sa dužim trajanjem. Psorijaza je kompleksna imuno posredovana bolest, povezana sa kardiovaskularnim rizikom, markerima hiperkoagulabilnosti i povišenim homocisteinom. Mnogo izveštaja o opservacijama sugerise po-

većanu učestalost venskih tromboembolijskih događaja kod pacijenata sa psorijazom.

Prikaz slučaja: Predstavljamo pacijenta sa trombofilijom i hroničnom difuznom psorijazom komplikovani dubokom venskom trombozom i plućnom embolijom. DNA analiza ukazuje na prisustvo homozigota za mutaciju Faktora V Leiden, kao i heterozigota za polimorfizam Faktora XIII V34L, PAI-1 5G/4G i MTHFR A1298C. Dermatološka anamneza pozitivna je za plakarnu psorijazu od pre 12 godina.

Zaključak: Prikaz ovog slučaja ukazuje na povezanost venske tromboembolije i hronične psorijaze. Svi pacijenti sa ponavljajućom tromboembolijom, naslednom trombofilijom, umerenom do teškom psorijazom treba da se smatraju sa visokim rizikom od venske tromboembolije i da se na odgovarajući način leče.

Ključne reči: ponavljajuća venska tromboembolija, trombofilija, psorijaza, plućna embolija.

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