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P1653 INFLAMMATION MEDIATED THROMBUS FORMATION IN LYMPHOMAS

Topic: 34. Thrombosis and vascular biology - Biology & Translational Research

Darko Antic[1], Olivera Mitrović Ajtić*[2], Dragoslava Djikić[2], Vladimir Otasevic[3], Emilija Živković[2], Jelena Ivanović[3], Vojin Vuković[3], Milica Vukotić[2], Sofija Šarac[3], Biljana Mihaljevic[1], Vladan Čokić[2]

[1]Clinic Of Haematology, University Clinical Centre Of Serbia, Medical Faculty, University Of Belgrade, Belgrade, Serbia; [2]Department Of Molecular Oncology, Institute For Medical Research, University Of Belgrade, Beograd, Serbia; [3]Clinic Of Haematology, University Clinical Centre Of Serbia, Belgrade, Serbia

Background:

Patients with lymphomas increased the risk of thrombotic complications, especially in diagnosis and during chemotherapy treatment, in the range of 2.9-4.2%.

Aims:

Our hypothesis is that inflammation and provoked immunity are responsible for generation of thrombus due to disturbed balance between coagulation and fibrinolysis.

Methods:

Quantification of neutrophil extracellular traps (NETs) from peripheral blood of 80 patients with Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL) measuring circulating cell-free DNA (cfDNA) and myeloperoxidase (MPO) activity. The inflammatory cytokines, coagulation factors and chemokines are measured by enzyme-linked immunosorbent assay (ELISA) and flow cytometry in peripheral blood, while fibrinolytic activity by fluorescent tissue-type plasminogen activator (tPA) and urokinase plasminogen activator (uPA) assays. Using a Boyden chamber, trans-endothelial migration of mononuclear cells (MNC) across a monolayer of human microvascular endothelial cells (HMEC-1) will be observed.

Results:

The pro-inflammatory cytokines IL-1β and TNF-α were significantly increased in DLBCL and HL, but not the chemokines IL-8 and MCP-1. NETs were increased in the peripheral blood of patients with HL ($p<0.05$) as measured by cfDNA and MPO activity. In contrast, cfDNA was largely reduced in DLBCL with thrombosis ($p<0.001$). Trans-endothelial migration of MNC was decreased by IL-6, but increased by TNF-α ($p<0.001$) in DLBCL with thrombosis. In the absence of thrombosis, MNC of HL demonstrated increased trans-endothelial migration in the presence of pro-inflammatory IL-6 ($p<0.01$), while MNC of HL and DLBCL in the presence of TNF-α ($p<0.05$). Regarding coagulation, factor VIII was increased in HL ($p<0.05$), while tissue factor in non-Hodgkin lymphomas (DLBCL and FL, $p<0.05$). Adhesion molecule P-selectin was increased in lymphomas, mostly in non-Hodgkin lymphomas ($p<0.0001$), while TGF-β is only in FL ($p<0.001$). Fibrinogen was negatively correlated with cfDNA ($p=0.021$, $r=-0.767$) in HL, while in positive correlation with TNF-α ($p=0.028$, $r=0.517$), IL-8 ($p=0.009$, $r=0.598$) and MCP-1 ($p=0.004$, $r=0.643$) in FL and with TGF-β ($p=0.007$, $r=0.748$) in HL. In opposite to uPA, fibrinolytic activity was decreased in the plasma of patients with HL, DLBCL, and FL ($p<0.05$) as measured by tPA. The tPA was in negative correlation with MPO in HL ($p=0.017$, $r=-0.783$) and FL ($p=0.006$, $r=-0.818$), while positively correlated with cfDNA in DLBCL ($p=0.034$, $r=0.402$, Table 1). The uPA was in positive correlation with cfDNA ($p=0.009$, $r=0.692$) and fibrinogen ($p=0.009$, $r=0.692$) in FL. Tissue factor ($CD142^+$) procoagulant microparticles derived from monocytes ($CD14^+$: 7.49±0.2, $p<0.001$) and activated monocytes ($CD14^+/CD16^+$: 3.75±0.8%, $p<0.05$) were increased in DLBCL compared to healthy controls.

Summary/Conclusion:

Chronic inflammation is present in the examined lymphomas where TNF-α, as an activator of the immune response, is linked with the initiation of thrombus formation. Moreover, augmented innate immunity is accompanied by procoagulants that mutually support thrombosis.

Table 1. Significance and correlation among inflammatory and coagulation factors in lymphomas.

p value Spearman r		MPO	cf DNA	tPA	TNF-α	IL-8	MCP-1	Fibrinogen	P-selectin	TGF-β	FVIII	Tissue factor
MPO	p			*0.006*								
	r			*-0.818*								
tPA	p	**0.017**	0.034									
	r	**-0.783**	-0.402									
IL-1β	p				0.020	**0.009**	0.004				*0.019*	
	r				0.431	**0.717**	0.519				*-0.548*	
TNF-α	p	*0.027*	0.009					*0.028*				
	r	*0.570*	0.485					*0.517*				
IL-8	p						**0.020**					
	r						**0.671**					
MCP-1	p					0.003		*0.004*				
	r					0.532		*0.643*				
Fibrinogen	p		**0.039**		0.007	*0.009*	**0.014**		0.050			
	r		**-0.692**		0.488	*0.598*	**0.686**		0.367			
TGF-β	p		**0.021**					**0.007**	0.047			
	r		**-0.767**					**0.748**	0.372			
FVIII	p		0.022									**0.016**
	r		-0.431									**0.674**
Thrombin	p				**0.035**				0.037	0.007	0.046	
	r				**0.622**				0.389	0.488	0.374	
Tissue factor	p					**0.037**			0.025		0.021	
	r					**-0.615**			0.415		0.426	

DLBCL, **Hodgkin lymphoma**, *Follicular lymphoma*