COMPLEMENT C4D SPLIT PRODUCTS IN COMBINATION WITH LUPUS ANTICOAGULANT AND LOW COMPLEMENT ASSOCIATE WITH THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Petri M, et al. Complement C4d Split Products in Combination with Lupus Anticoagulant and Low Complement Associate with Thrombosis in Systemic Lupus Erythematosus [abstract 2630 ACR/ARHP 2018 Chicago]. Arthritis Rheumatol. 2018; 70 (suppl 10).

ABSTRACT

PURPOSE

Lupus anticoagulant (LAC) is an established risk factor for thrombosis in Systemic Lupus Erythematosus (SLE). Emerging data suggest that activation of the complement system is also involved in the pathogenesis of thrombosis. Our objective was to evaluate the relationships between complement C4d split products deposited on erythrocytes (EC4d), platelets (PC4d) and thrombosis in SLE.

METHODS

This was a cross sectional analysis of 149 consented SLE patients (by ACR or SLICC criteria, mean age: 47±1 years, 32% taking prednisone; mean SELENA-SLEDAI: 2.5±0.2 points). SLE were divided into with (n=16, 11%) or without (n=132, 89%) a history of thrombotic events (venous or arterial) in the past 5 years. EC4d and PC4d levels were measured using quantitative flow cytometry, and expressed as net mean fluorescence intensity (MFI) (abnormal EC4d>14 net MFI, PC4d>20 net MFI, each corresponding to the 99th percentile of normal healthy group). Complement C3/C4, and LAC were measured using immunochemistry and dilute Russell Viper Venom Time respectively. Statistical analysis consisted of Mann Whitney test and logistic regression.

RESULTS

SLE with a history of any thrombosis in the past 5 years presented with 5.5 and 2.2-fold higher median PC4d (27 vs 5 net MFI) and EC4d (19 vs 9 net MFI]) levels, respectively, than SLE without thrombotic events (p<0.001). Low C3 (OR=9.5 [CI 95%: 2.9-30.9]), Low C4 (OR= 3.6 [CI 95%: 1.2-10.7]), abnormal PC4d (OR=8.4 [CI 95%: 2.8-24.8], EC4d (OR=3.9 [CI95%: 1.3-11.2]), and LAC (OR=5.4 [CI 95%: 1.2-25.0) were all significantly associated with any thrombosis (p<0.035). Prednisone was also associated with thrombosis (OR=3.2 [CI95%: 1.1-8.9]) (p=0.037). The cumulative presence of low C3, PC4d and LAC abnormalities resulted in higher likelihood of thrombosis (OR range: 138.1 [CI95%: 15.4-1238.3]; n=143) (p<0.001).

CONCLUSION

Complement C4d split products associate with thrombotic events in SLE, independent of other risk factors. A composite score of risk factors performed better than single risk factors alone, and should be studied prospectively.

OBJECTIVE AND METHODS

- To evaluate the relationships between complement C4d split products deposited on erythrocytes (EC4d), Platelets (PC4d) and thrombosis in SLE.
- Study design: cross sectional analysis of 149 SLE patients enrolled in the Hopkins lupus cohort.
- Abnormal EC4d and PC4d levels were measured using flow cytometry, and expressed as net mean fluorescence intensity (MFI). Complement C3/C4 and LAC were measured using immunochemistry and dilute Russell Viper Venom Time (DRVVT), respectively.
- Statistical analysis consisted of Mann Whitney test and logistic regression.

RESULTS

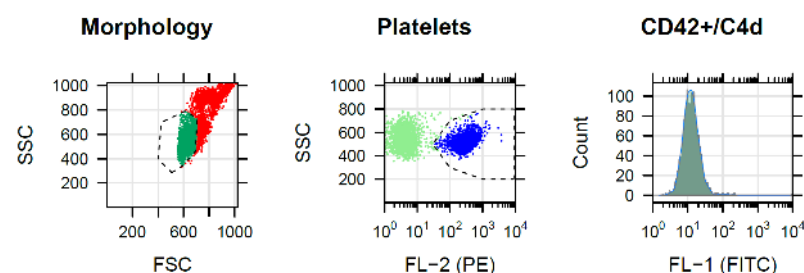**Figure 1:** Flow Cytometry assay for Platelet C4d

Table 1: Patient demographics

	All	Without thrombosis	With thrombosis
Number of patients	149	133	16*
Age	48.2±1.2	48.3±1.3	47.5±3.3
Gender [% females]	86%	97%	100%
Ethnicities			
Caucasians (%)	55%	59%	29%
African Americans (%)	35%	33%	57%
Asians (%)	4%	3%	14%
Others (%)	6%	5%	14%
PGA [0-3cm]	0.65±0.06	0.65±0.06	0.74±0.20
Clinical SELENA-SLEDAI	1.29±0.16	1.23±0.17	1.81±0.52
Treatment information			
Prednisone	32%	30%	56%
hydroxychloroquine	89%	88%	94%
azathioprine	8%	8%	13%
mycophenolate	23%	24%	13%

*two patients presented with venous and arterial events

Table II: Thrombosis type in the past 5-years

Type	Subtype
Arterial [n=8]	Cerebrovascular Accident; Myocardial Infarction; Digital Gangrene; Other Arterial Thrombosis
Venous [n=10]	Superficial Thrombosis; Deep Vein Thrombosis; Other Venous Thrombosis

BIOMARKERS ASSOCIATE WITH THROMBOSIS

Figure 2: PC4d levels and history of venous or arterial thrombosis

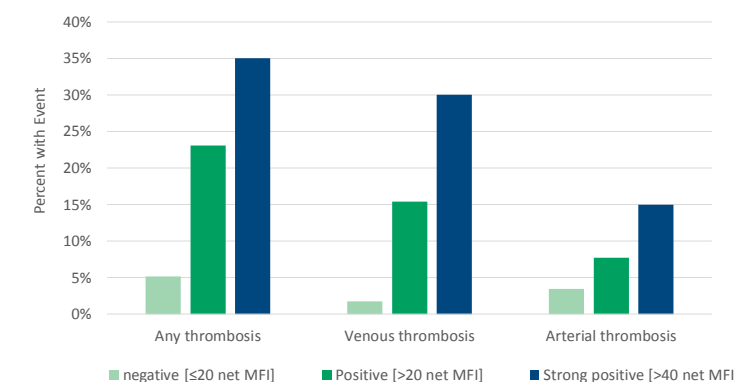|	Any thrombosis	Venous Thrombosis	Arterial Thrombosis
Odds ratio (per unit change)	3.2 [1.7-5.8]	4.7 [2.1-10.4]	2.2 [1.0-4.9]
Odds ratio (over dynamic range)	10.2 [3.1-34.2]	22.3 [4.6-107.9]	5.0 [1.0-24.4]

Table III: Association of biomarkers with history of venous or arterial thrombosis

	Complement C3	Complement C4	LAC dRVVT >37 seconds	EC4d >14 net MFI	PC4d >20 net MFI
TP (Sensitivity)	44%	38%	88%	63%	63%
TN (Specificity)	92%	86%	44%	70%	83%
LR Positive test	5.8	2.6	1.6	2.1	3.8
LR Negative test	0.6	00.7	0.3	0.5	0.4
DOR (CI 95%)	9.5 [2.9-30.9]	3.6 [1.2-10.7]	5.4 [1.2-25.0]	3.9 [1.3-11.2]	8.4 [2.8-24.8]

Figure 3: Composite score [Low C3 + dRVVT + PC4d>20 net MFI] and Thrombosis

	Any thrombosis	Venous Thrombosis	Arterial Thrombosis
Odds ratio (per unit ch)	5.2 [2.5-10.7]	8.3 [3.1-22.0]	2.6 [1.2-5.7]
Odds ratio (over dynamic range)	138.1 [15.4-1238.3]	571.7 [30.6-10671.4]	17.0 [1.6-183.5]
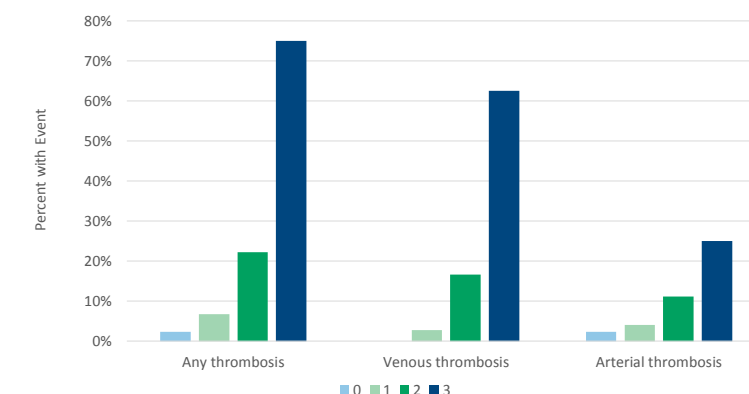
CONCLUSION

C4d bound to platelets associates with thrombosis and its combination with Low C3 and LAC should be studied prospectively.