



LETTER TO THE EDITOR

Inflammation, systemic lupus erythematosus and the Kounis mast cell activation-associated syndrome



Inflamação, lúpus eritematoso sistémico e síndrome de Kounis associada à ativação dos mastócitos

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease of unknown origin that affects many organ systems. It is characterized by chronic inflammation that can induce abnormal vasomotion by reducing nitric oxide production and increasing endothelin-1 release, leading to endothelial injury and consequently to coronary artery spasm, which can progress to acute myocardial infarction (MI). This could be the result of either increased C-reactive protein, which induces significant expression of molecules associated with endothelial damage such as ICAM-1, VCAM-1 and E-selectin, or expansion of CD4 CD28 T cells, which induce cytolysis in endothelial cells and/or activation of macrophages and other related interacting cells such as mast cells.¹ Therefore an association with Kounis mast cell activation-associated syndrome, also known as coronary hypersensitivity disorder,² cannot be excluded.

In the very interesting paper by de Matos Soeiro et al. published in the *Journal*³ concerning 11 patients with acute coronary syndromes, it was concluded that coronary artery disease in young people with SLE due to premature atherosclerosis should be always be borne in mind because of its high mortality rate.

Indeed, the following inflammatory substances and conditions that are associated with Kounis syndrome should be always considered in patients with lupus erythematosus, including:

1. Interleukin-9, a T-cell derived factor preferentially expressed by CD4+ T cells that has been characterized in human and murine systems.⁴
2. Mast cell tryptase, which can be an indicator of type I hypersensitivity reaction and may serve as a surrogate marker of anaphylaxis.⁵
3. Macrophages and their polarization have been found to contribute to the initiation and perpetuation of SLE.⁶

4. Hypereosinophilic syndrome, which is associated with SLE.⁷
5. Mast cells, macrophages and (very few) eosinophils are present in inflamed rheumatoid synovial tissue and sites of cartilage erosion in SLE and other autoimmune conditions, including rheumatoid arthritis.⁸
6. Patients with SLE have higher risk of acute MI compared with non-SLE controls, and this risk is more significant in females. In addition, SLE is an independent risk factor for post-acute MI mortality.⁹
7. Platelets bearing complement protein C4d (P-C4d) were initially determined to be specific for diagnosis of SLE and were later found to be associated with acute ischemic stroke in non-SLE patients. P-C4d may identify a subset of SLE patients with a worse clinical prognosis and is associated with all-cause mortality and stroke in these patients. P-C4d may be a prognostic biomarker as well as a pathogenic clue that links platelets, complement activation, and thrombosis.¹⁰
8. The R131 allele of the Fc gamma receptor IIa (FcγRIIa) is associated with SLE incidence and disease severity but also with coronary artery disease. This finding implies that risk stratification of SLE patients and other high-risk patients with troponin-negative angina could be significantly improved by FcγRIIa genotyping.¹¹
9. SLE nearly doubles mortality and event hazards in cardiovascular disease (MI, stroke, or congestive heart failure) compared to age- and sex-matched comparisons. This raises research questions regarding delayed SLE diagnosis versus accelerated cardiovascular disease prior to SLE, particularly in older-onset SLE.¹²
10. Cardiovascular events including acute MI and stroke in SLE patients are caused by multifactorial mechanisms, including both traditional and disease-specific risk factors. An overall evaluation with individual risk stratification based on both these features is important to correctly manage these patients in order to reduce negative outcomes.¹³

Consequently, in order to elucidate the pathophysiology of the association of SLE and acute coronary syndromes and to discover potential therapeutic and preventive measures for acute coronary events, a search for inflammatory cells and measurement of inflammatory cell mediators released from these cells should always be performed.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Ong P, Athanasiadis A, Alscher MD, et al. Coronary artery spasm as a cause for myocardial infarction in patients with systemic inflammatory disease. *Int J Cardiol.* 2011;151:e32–4.
2. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. *Clin Ther.* 2013;35:563–71.
3. de Matos Soeiro A, Soeiro MC, Oliveira MT Jr, et al. Clinical characteristics and in-hospital outcome of patients with acute coronary syndromes and systemic lupus erythematosus. *Rev Port Cardiol.* 2014;33:685–90.
4. Ouyang H, Shi Y, Liu Z, et al. Increased interleukin 9 and CD4 + IL-9+ T cells in patients with systemic lupus erythematosus. *Mol Med Rep.* 2013;7:1031–7.
5. Carson HJ, Cook BA. Mast cell tryptase in a case of anaphylaxis due to repeat antibiotic exposure. *Leg Med (Tokyo).* 2009;11:234–6.
6. Xiao P, Dong C, Yue Y, et al. Dynamic expression of microRNAs in M2b polarized macrophages associated with systemic lupus erythematosus. *Gene.* 2014;547:300–9.
7. Habibagahi Z, Ali Nazarinia M, Aaflaki E, et al. Systemic lupus erythematosus and hyper-eosinophilic syndrome: an unusual association. *West Indian Med J.* 2009;58:69–71.
8. Almpanis GC, Kounis GN, Mazarakis A, et al. Coronary artery spasm progressing to acute myocardial infarction in patients with systemic inflammatory disease: a potential association with Kounis syndrome. *Int J Cardiol.* 2011;151:1–2.
9. Lin CY, Shih CC, Yeh CC, et al. Increased risk of acute myocardial infarction and mortality in patients with systemic lupus erythematosus: two nationwide retrospective cohort studies. *Int J Cardiol.* 2014;176:847–51.
10. Kao AH, McBurney CA, Sattar A, et al. Relation of platelet C4d with all-cause mortality and ischemic stroke in patients with systemic lupus erythematosus. *Transl Stroke Res.* 2014;5:510–8.
11. Raaz-Schrauder D, Ekici AB, Munoz LE, et al. Patients with unstable angina pectoris show an increased frequency of the Fc gamma RIIa R131 allele. *Autoimmunity.* 2012;45:556–64.
12. Bartels CM, Buhr KA, Goldberg JW, et al. Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. *J Rheumatol.* 2014;41:680–7.
13. Ballocca F, D'Ascenzo F, Moretti C, et al. Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2014, pii:2047487314546826 [Epub ahead of print].

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