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LETTER TO THE EDITOR

Kounis syndrome: An additional etiologic factor of myocardial infarction with non-obstructive coronary arteries

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In an interesting report published in the "Cardiology Journal" concerning 95 patients treated for myocardial infarction with non-obstructive coronary arteries (MINOCA), López Pais et al. [1] found that when non-takotsubo MINOCA patients were evaluated the difference regarding psychiatric illnesses was 29.7% vs. 12.9%, p = 0.001 compared to myocardial infarction (MI) with obstructive coronary arteries. Furthermore, in 11 (11.6%) of these patients, pathophysiological mechanisms of MINOCA remained unknown.

In another recent report, involving 998 patients with angiografically proven MI in the real world, 82 (8.2%) had a MINOCA and 40% were women. No evident etiology was detected in over 70% of MINOCA [2].

Therefore, it seems possible that new, yet unknown, pathophysiological mechanisms are involved in the pathogenesis of this conundrum.

So far, several other causes and pathogenetic mechanisms have been reported to be associated with this syndrome including coronary artery spasm, coronary artery dissection, coronary embolism, arrhythmias, mild plaque disruption, hypercoagulable status, type 2 MI, amyloid light-chain AL amyloidosis and clinically unrecognized myocarditis or takotsubo cardiomyopathy [2].

The prevalence of MINOCA among the MI patients ranged between 5% and 25% according to the registries [3]. In a recent report involving 199,163 MI admissions, 9092 consecutive unique patients had MINOCA, 2147 of them experienced a new major adverse cardiovascular event (MACE) and 1254 (14%) of the patients died during mean follow-up of 4.5 years [4]. In this report, even after adjustment, low levels of total cholesterol were significantly associated with the composite endpoint of MACE as well as with long-term mortality. The authors had wondered about these results because hypercholesterolemia is considered as a causal factor for coronary artery disease and that the lowering of total cholesterol and low-density lipoprotein reduces cardiovascular risk in both primary and secondary prevention settings.

Indeed, it is being considered why, the Kounis hypersensitivity-associated type I variant coronary spasm which represents a manifestation of endothelial dysfunction or microvascular angina has not been included in this MINOCA report [1] as well as in others [5]. This variant includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease and represents the most common type (72.6%) of Kounis syndrome. In this variant, the acute release of inflammatory mediators may induce either coronary artery spasm without increased cardiac enzymes and troponins or coronary artery spasm progressing to acute MI with raised cardiac enzymes and troponins. The ensuing acute MI could lead to MACE including cardiogenic shock (2.3%), cardiac arrest (6.3%), death 5 (2.9%) due to ventricular fibrillation,

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anterior ST-segment elevation MI and inferior ST-segment elevation MI [6].

The hypersensitivity-related Kounis syndrome inclusion in the MINOCA heterogenic group could well explain this cholesterol paradox observed in the aforementioned study [4]. Indeed, children and adolescents with clinical and laboratory manifestations of atopy have shown lower cholesterol concentrations throughout infancy, childhood and adolescence as compared with non-atopic subjects [7].

Kounis syndrome is rarely diagnosed but is not a rare disease. Indeed, the annual incidence of Kounis syndrome at the emergency department among all admissions and patients with allergy was 19.4 per 100,000 (27 of 138,911) and 3.4% (27 of 793), respectively [8]. In a recent report from Japan [9] the annual incidence of Kounis syndrome at emergency departments of Numazu City Hospital, Shizuoka, from 2012 to 2017 in patients with anaphylaxis, was 2% (2 of 100) and of Shizuoka Hospital, Juntendo University, from 2013 to 2017, was 2.2% (3 of 138), respectively. It is concluded herein that Kounis syndrome should always be excluded when physicians treat patients with allergy.

Specific biomarkers should be measured in cases of a suspicion of Kounis syndrome in MINOCA patients. These should include measurements of serum tryptase, histamine, eosinophils, total immunoglobulins (IgEs), cardiac enzymes and cardiac troponins supplemented with electrocardiography, echocardiography, angiography and modern tools such as thallium-201 single-photon emission computed tomography and dynamic cardiac magnetic resonance imaging [10]. In cases of drug-induced MINOCA the following diagnostic tests including specific IgEs, radioallergosorbent testing, enzyme linked immunosorbent assay, fluoroenzyme immunoassay, drug provocation test, basophil activation test and skin prick tests should be always performed. When a diagnosis of Kounis syndrome is established, treating type I variant with corticosteroids, H1 and H2 antihistamines and calcium channel blockers and nitrates is indicated.

All of the above show that MINOCA disease is neither benign nor a rare clinical entity. Searching, therefore, for its etiology and treatment that will provide a way for improving prognosis is of paramount importance but it is not an easy task. It is suggested herein that every MINOCA patient should undergo thorough clinical and laboratory diagnostic investigations in order to identify its causality and pathophysiological mechanisms. Future studies are necessary in order to dissolve the MINOCA conundrum.

Conflict of interest: None declared

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