Takotsubo and Kounis Syndrome: Is There Any Association?

To the Editor:

In the very interesting paper concerning takotsubo and long QT syndrome, published recently in the Journal, the authors concluded that many questions regarding the etiology, pathophysiology, and treatment of this syndrome remain unanswered and have asked for further studies in order to elucidate these issues. This follows previous appeals for worldwide efforts and research in order to elucidate the cause and clinical course of this syndrome. Takotsubo syndrome (named because of the resemblance of the heart on left ventriculography to a Japanese pot for catching octopus) is a clinical condition associated with emotional distress, affecting mainly women, resembling acute myocardial infarction, but with normal coronary arteries and transient left ventricular dysfunction. However, recent reports have associated takotsubo syndrome with coronary lesions and especially with anaphylactic reactions.

The concurrence of acute coronary syndromes with anaphylactic or anaphylactoid reactions constitutes the Kounis syndrome. The variants of Kounis syndrome are caused by inflammatory mediators released during activation of various interrelated and interacting inflammatory cells including mast cells, macrophages and T-lymphocytes. Type I variant includes subjects with normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. This variant may represent a manifestation of endothelial dysfunction or microvascular angina. Type II variant includes subjects with culprit but quiescent pre-existing atheromatous disease in whom acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or plaque erosion or rupture manifesting as acute myocardial infarction.

In a woman with Takotsubo syndrome the use of contrast echocardiography demonstrated a paucity of contrast material in the cardiac apex, despite normal coronary arteriography, which supports the hypothesis that this syndrome may intimately associated with microvascular dysfunction as in the type I variant of Kounis syndrome. Mediators released from interacting inflammatory cells have been found to be increased in both allergic and nonallergic coronary syndromes and a common pathway between allergic and nonallergic acute coronary syndromes has been suggested.

Takotsubo syndrome is often associated with emotional stress and catecholamine release and can culminate in inflammatory cell activation. Emotional stress commences with impulses arising from high cortical centers in the brain which are relayed through the limbic system to hypothalamus and followed by release of chemical mediators, such as serotonin, norepinephrine, and acetylcholine, which activate cells of the paraventricular nucleus of the hypothalamus to produce corticotrophin-releasing hormone (CRH). CRH enters the portal venous pathway of the hypothalamus and activates the corticotrophs of the anterior pituitary gland to synthesize pro-opiomelanocortin, which is cleaved to form adrenocorticotropic hormone. CRH also stimulates the locus coeruleus, a dense collection of autonomic cells in the midbrain to again secrete norepinephrine at the sympathetic nerve terminals. The central activation of the sympathetic system is transmitted to the adrenal medulla and large amounts of epinephrine are produced. ACTH stimulates the adrenal cortex to produce corticosteroids. The renin–angiotensin system also participates in emotional stress through the sympathetic innervation of the kidney. Heightened cardiovascular activity follows this cascade of events, resulting in endothelial injury, myocardial damage, and induction of adhesion molecules on the endothelial cells. An acute phase response, as in inflammation, is engendered and is characterized by production of cytokines, macrophages and mast cell activation and release of inflammatory mediators, as in the Kounis syndrome. The release of various cytokines has been also incriminated to produce Takosubo syndrome.

So far, inflammatory mediators such as histamine, tryptase, chymase, and arachidonic acid products have not been measured in cases of takotsubo syndrome. In future trials, the measurement of these mediators, along with the use of corticosteroids and mast cell stabilizers for prevention and treatment, may shed light on the etiology and clinical features of this interesting syndrome.

References

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