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The authors respond

We would like to thank the authors of the letter for their interest in our paper.[1] Mental disorders are a major cause of morbidity, and patients with mental health disorders have a higher incidence of takotsubo cardiomyopathy (TC). We agree with the authors that our patient had a combination of both emotional and physical stressors. Norepinephrine and dopamine have been implicated as neurotransmitters in acute mania.[2] Most TC patients recognize stress events as frightening experiences, leading to the increase of the bioavailability of catecholamines.[3] Several theories suggest the importance of the catecholamine surge in the pathogenesis of TC.[4] Our patient abruptly stopped her prescribed medications for bipolar disorder, which led to her acute manic attack and contributed to her emotional and psychological stress. Her acute mania manifested as sleep deprivation and poor oral intake, which resulted in rhabdomyolysis as a physical stress likely triggering the abrupt increase in catecholamine levels.

As mentioned by the authors, severe adrenergic discharge might be associated with malignant arrhythmia. Fortunately, our patient did not have any documented arrhythmia during her hospitalization or as an outpatient. Her echocardiogram also did not show left ventricular outflow tract obstruction.

Coronary microvascular dysfunction has been suggested as the underlying mechanism in some TC patients and has been reported in multiple diagnostic tools.[5] Conflicting results have been reported regarding reduced Thrombolysis in Myocardial Infarction (TIMI) frame count in TC patients for assessing microvascular dysfunction.[6,7] Our patient's coronary angiography showed normal filling in the left anterior descending artery, in the left circumflex artery, and in the right coronary artery.

Given the chronic nature of psychiatric illnesses with the risk of acute flare-ups, TC has a higher recurrence in these patients.[8,9] As such, a patient-centered multidisciplinary approach including a primary care physician, cardiologist, and psychiatrist should be emphasized in the care of these patients with close follow-up to avoid further acute psychiatric attacks and decrease the rate of TC recurrence. Our patient did not have recurrence after her initial episode of TC. Therefore, invasive treatments including sympathetic ganglion blockade were avoided and not considered at the time. Unfortunately, there are no current trials evaluating the treatment of TC, and guideline-directed medical therapy for heart failure is the current standard of care for TC patients.

—Amr Idris, MD and Karim M. Al-Azizi, MD
The Heart Hospital Baylor Plano, Plano, Texas
E-mail: karim.alazizi@bswhealth.org

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Gadolinium-induced Kounis syndrome including electrocardiographic considerations

Gadolinium is a silvery-white metal when oxidation is removed, and gadolinium salts are used in magnetic resonance imaging. The gadolinium-based contrast mediums are the most commonly used agents in magnetic resonance angiography and for brain tumor enhancement due to their association with the degradation of the blood-brain barrier. However, nephrogenic systemic fibrosis and acute kidney injury due to primary excretion of gadolinium from the kidneys and various cardiac arrhythmias including QTc electrocardiographic prolongation and hypersensitivity reactions are occasionally encountered with use of such contrast mediums.[1]

In the very interesting report published in *Baylor University Medical Center Proceedings,*[2] a 53-year-old woman suffering from renal cell carcinoma and recent right nephrectomy with secondaries of the left lower lung lobe developed type I Kounis syndrome with chest pain and shortness of breath following gadolinium administration for magnetic resonance imaging of the brain for headaches. The patient became edematous, unconscious, and unresponsive, with an oxygen saturation of 50% and a heart rate of 40 beats/min. This report raises issues concerning gadolinium-induced anaphylaxis and gadolinium-induced bradycardia and electrocardiographic manifestations related to Kounis syndrome.

Whereas gadolinium has been placed in the lowest-list category for acute kidney injury and the development of nephrogenic systemic fibrosis in patients with renal impairment, several mild to severe adverse drug reactions have been noted, including mild or severe immediate hypersensitivity reactions with cardiovascular and respiratory impairment. The most common immediate hypersensitivity symptoms are mild pruritus and urticaria occurring a few minutes after intravenous administration. However, in the US Food and Drug Administration's Adverse Event Reporting System for the period of 1998 to 2012, 614 cases were reported of adverse drug reactions to gadolinium-based contrast agents, of which 7.2% had a fatal outcome.[3] One fatality was a 42-year-old man who had undergone a previous successful contrast-enhanced computed tomography and underwent elective magnetic resonance imaging with gadolinium for diagnostic clarification of a suspicious finding in the abdomen.[4] At autopsy, this patient was found to have massive brain edema (1450 g). The role of an immunoglobulin E–mediated mechanism has been advocated in such reactions, and there is an increased risk for more severe reactions, up to 8 times more severe, at the second administration of gadolinium-based contrast agents in patients with a history of hypersensitivity.[5] The described patient[2] had been subjected to previous magnetic resonance imaging without contrast and experienced no adverse effects, but she had a history of renal cell carcinoma and recent right nephrectomy, and therefore renal impairment could not be excluded.

This patient presented with ST elevations in leads II, III, aVF, V3, and V4; ST segment depression in lead I; increased troponin levels from 0.015 to 1.12 ng/mL; and left heart catheterization with no evidence of obstruction or pulmonary embolism—which were compatible with a diagnosis of Kounis syndrome type I variant. Indeed, electrocardiographic abnormalities ranging from cardiac arrhythmias of any kind to those resembling digitalis intoxication and the ST segment elevation or depression to any degree of heart block can be associated with the cardiac symptoms and signs of Kounis syndrome.

Recently, a unique electrocardiographic sign of ST elevation in lead aVR, with reciprocal ST depression in the majority of other leads, has been described in Kounis syndrome.[6] The lead aVR, until recent years, was regarded as the "neglected lead." However, ST segment elevation in lead aVR associated with widespread ST segment depression in inferolateral leads best identifies severe left main or three-vessel disease and denotes high-risk non–ST segment elevation acute coronary syndrome that requires urgent revascularization in addition to medical treatment that includes antiplatelets, aspirin, and heparin.[7] The same electrocardiographic findings, however, can be present in a type A dissecting aneurysm affecting the ascending aorta that expands and presses the left main artery and the coronary ostia. Whereas the clinical picture is of acute myocardial infarction, the treatment is completely different and includes emergency surgery and avoidance of antiplatelets, aspirin, and heparin.[8]

Gadolinium-based contrast mediums are generally benign but on some occasions can lead to life-threatening conditions and Kounis syndrome.[9–11] Physicians, therefore, should be aware of clinical and electrocardiographic manifestations of Kounis syndrome as potential serious complications of agents and drugs given for diagnostic and therapeutic purposes.

—Nicholas G. Kounis, MD, PhD
Department of Cardiology, University of Patras Medical School, Patras, Greece
ngkounis@otenet.gr

—Ioanna Koniari, MD, PhD
Electrophysiology and Device Department, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK

—Georged.Soufras, MD, PhD
Department of Cardiology, Saint Andrews State General Hospital, Patras, Greece

—Grigorios Tsigkas, MD, PhD, Panagiotis Plotas, MD, PhD, Periklis Davlouros, MD, PhD, and George Hahalis, MD, PhD
Department of Cardiology, University of Patras Medical School, Patras, Greece

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Relationship between mean platelet volume and C-reactive protein

We read with great interest the retrospective study of Ball et al about the relationship between mean platelet volume (MPV) and C-reactive protein (CRP).[1] The researchers stated that in their study they showed a statistically significant inverse relationship between MPV and CRP, adding that the complex dynamic relationship between MPV and inflammation should be investigated with new studies. We think other factors may have negatively affected the results of this study.

The researchers used 2005–2010 data from the National Health and Nutrition Examination Survey (NHANES). As is known, it is not possible to eliminate the pre-analytical and analytical errors of tests conducted in studies based on retrospective data. It has been emphasized that it is important to minimize pre-analytical variables between groups, especially for MPV studies.[2] The data of this research may also have been negatively affected by these errors.

Ball et al noted that studies investigating the relationship between MPV and CRP have had contradictory results. The contradiction is mainly due to the fact that standardization of MPV measurements has not been achieved to date. It is clearly stated that MPV values may not have a role in diagnosis or prognosis in acquired diseases such as cardiovascular diseases, since MPV measurement has not been standardized.[3] The main variables that affect MPV measurement are the time from venipuncture to measurement, the method used (impedance or optical technology), the type of anticoagulant used, the storage temperature of the samples, and the devices with which the measurements are made.[4–7] In this study, it was stated that MPV measurements were made with Coulter HMX Hematology Analyzer using ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. Following the entry of blood into the whole blood tube, MPV begins to increase as soon as platelets come into contact with EDTA, and this increase is up to 30% in the first 5 min and 10% to 15% more in the next 2 h.[4] It has been reported that MPV variability can occur in 2% to 50% depending on the contact with EDTA in different studies.[4,7] Since the data were obtained retrospectively from the NHANES database in this study, the time from venipuncture to MPV measurement could not be standardized, and this negatively affected data reliability. As a result, there may be no statistically significant inverse relationship between MPV and CRP.

—Cengiz Beyan, MD
Faculty of Medicine, Ufuk University, Ankara, Turkey
cengizbeyan@hotmail.com

—Esin Beyan, MD
Kecioren Training and Research Hospital, University of Health Sciences, Ankara, Turkey
esinbeyan@hotmail.com

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