Kounis Syndrome in a Covid-19 Patient Following Intravenous Administration of Azithromycin

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Kounis hypersensitivity-associated acute coronary syndrome, especially type I variant coronary spasm due to endothelial dysfunction, is a type of myocardial infarction with nonobstructive coronary arteries (MINOCA) [1]. The following report describes a unique case of anaphylaxis-associated MINOCA-type Kounis syndrome manifesting with asystolic cardiopulmonary arrest in a female COVID-19 patient following an infusion of azithromycin.

A 52-year-old woman with a history of hypertension, right nephrectomy, and dilated ascending aorta presented to the emergency department with a 3-day history of fever and fatigue. Auscultation revealed bilateral crackles, and the polymerase chain reaction (PCR) test was positive for SARS-CoV-2. Chest x-ray demonstrated bilateral pulmonary infiltrates. However, oxygen saturation values were normal. The patient was transferred to a dedicated COVID-19 unit, and a 500-mg azithromycin infusion was started. After 20 minutes, the patient developed chest pain followed by burning skin sensation, shortness of breath, facial edema, and throat swelling culminating in asystolic cardiopulmonary arrest. Emergency advanced cardiac life support was initiated, the patient was intubated, and epinephrine 1 mg (10 mL, 1:10 000) was given intravenously. The patient regained consciousness within approximately 1 hour. An emergency electrocardiogram revealed ST segment elevation in inferior leads with second-degree (Mobitz type I) atrioventricular block (Figure 1, online-only supplementary material). Hydrocortisone, dimetindene, and dual antiplatelet therapy with tinzaparin were administered in the coronary care unit.

Following administration of this treatment, a new electrocardiogram showed resolution of ST-segment elevation. A transthoracic echocardiogram revealed normal ejection fraction with no regional wall motion abnormalities. Blood tests revealed raised conventional cardiac troponin I (0.37 ng/mL [normal range, <0.04 ng/mL]), raised D-dimers (740 ng/mL [normal range <500 ng/mL]), and raised ferritin (237 ng/mL [normal range, 4.6-204 ng/mL). The following day, coronary angiography showed normal coronary arteries, and blood sampling revealed normal specific IgEs and serum tryptase (5 ng/mL [normal range, <11.5 ng/mL]). The patient was extubated after 24 hours, although computed tomography demonstrated diffuse ground-glass opacities and consolidations in both lungs (Figure 2, online-only supplementary material). Intravenous ampicillin/sulbactam, dexamethasone, and remdesivir were added to her treatment. Her clinical status gradually improved, and she was discharged from the hospital after 20 days. Skin prick tests and drug provocation tests were not performed because the patient and her relatives refused consent. Additional allergy tests such the basophil activation test, radioallergosorbent test, enzyme-linked immunosorbent assay, and fluoroenzyme immunoassay were not available.

The patient was diagnosed with Kounis hypersensitivity-associated acute coronary syndrome and, specifically, the type I variant of MINOCA. Good clinical outcome was confirmed at a follow-up visit 3 months later. She was advised not to take azithromycin again.

COVID-19 has become a multisystem inflammatory syndrome that affects children, adolescents, and adults. Azithromycin is used as a first-line treatment for patients with COVID-19 pneumonia and potentially used for treatment or prevention of coinfection with SARS-CoV-2. However, the efficacy of azithromycin in the treatment of COVID-19 remains uncertain [3,4]. Macrolides, including azithromycin, increase the risk of QT prolongation and proarrhythmic events. Azithromycin-induced anaphylaxis is rare. However, azithromycin has been found to be more allergenic than clarithromycin. A case of Kounis syndrome induced by clarithromycin was recently described [4], and the frequency of hypersensitivity reactions to clarithromycin and azithromycin in a group of children was reported to be 15.5% and 47.3%, respectively [5]. To the best of our knowledge, Kounis syndrome induced by azithromycin has never been reported. Furthermore, this case seems to be the first case of Kounis syndrome in a patient with COVID-19 pneumonia.

Kounis hypersensitivity-associated acute coronary syndrome is caused by inflammatory mediators released by an IgE-mediated antigen–allergen reaction. Activation of the complement system leads to the generation of C1q, C3a, C4, C5a, and factor B, which are potent activators of inflammation known as anaphylatoxins owing to their ability to cause mast cell degranulation. Furthermore, Khan [6] reported that mastocyte-related G protein–coupled receptor X2 (MRGPRX2) factors may activate mast cells via non-Fcε receptors, thus accounting for the absence of specific IgEs and the normal tryptase levels. The author also emphasized the role of non–IgE-dependent pathways that cause mast cell degranulation by insect venoms and small molecule antibiotics and expressed the view that this might better explain some patients with Kounis syndrome in whom specific IgE may remain undetected or tryptase levels are normal. Measurements of serum specific IgE to hymenoptera venoms and ciprofloxacin could be negative. On the other hand, roxithromycin, which is also a macrolide, has been shown to inhibit compound 48/80-induced pseudoallergy via the MRGPRX2 pathway both in vitro and in vivo [7].

The inflammatory surge induced by COVID-19 seems to be a contributing factor in the development of Kounis syndrome. COVID-19 can induce myocardial injury, which has been

attributed to coronary spasm, direct endothelial or vascular injury, plaque rupture and microthrombi, hypoxic injury, and the cytokine storm [8]. Indeed, ST segment elevation, as in the case we report, may be the first clinical manifestation of COVID-19 [9].

The patient's chest pain and allergic symptoms appeared 20 minutes after initiation of the azithromycin infusion, whereas intramuscular adrenaline was administered later to treat asystolic cardiopulmonary arrest. Therefore, adrenaline could not be the cause of the coronary spasm associated with chest pain. However, the patient had a positive PCR result for COVID-19, and the coincidence between Kounis allergy-associated coronary syndrome with COVID-19–induced coronary spasm cannot be excluded. Indeed, coronary artery spasm in a young patient with COVID-19 and normal coronary arteries has been attributed to the inflammatory cytokine surge that occurs in both Kounis syndrome and COVID-19 [10].

A blood sample obtained 24 hours after the cardiac arrest to measure tryptase levels was normal. These results should be interpreted with caution, however, since it is known that the optimal time for tryptase measurement is within the first few hours after the anaphylactic event. Managing the patient's cardiac arrest in a very challenging environment (isolated COVID-19 area) was our priority and unavoidably led to a delay in collecting the blood specimen.

Therefore, further elucidation of the pathophysiology of myocardial injury in patients with COVID-19 and searching for similarities between COVID-19 and Kounis hypersensitivity-associated syndrome seem to be of paramount importance.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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