Kounis syndrome in a Covid-19 patient following intravenous azithromycin administration

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The Kounis hypersensitivity-associated acute coronary syndrome and especially the type I variant coronary spasm due to endothelial dysfunction represents a type of myocardial infarction with non obstructive coronary arteries (MINOCA) condition [1]. The following report describes a unique case of anaphylaxis-associated MINOCA type Kounis syndrome manifesting with asystolic cardiopulmonary arrest in a coronavirus disease 2019 (COVID-19) female patient following azithromycin infusion.

A 52-year-old female with history of hypertension, right nephrectomy and dilated ascending aorta presented to the emergency department with 3-day fever and fatigue. Auscultation revealed bilateral crackles and the polymerase chain reaction (PCR) test was positive for severe acute respiratory syndrome coronavirus 2 (SARSCoV-2). Chest X-ray demonstrated bilateral pulmonary infiltrates. However, oxygen saturation values were normal. She was transferred to a dedicated COVID-19 unit and azithromycin 500mg infusion was started. After 20min the patient developed chest pain followed by burning skin sensation, shortness of breath, facial edema, throat swelling culminating to asystolic cardiopulmonary arrest. Emergency advanced cardiac life support was initiated, the patient was intubated and epinephrine 1mg (10ml 1: 10000) was given intravenously. The patient regained consciousness within, approximately, one 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, dual antiplatelet therapy with tinzaparin were administered in the coronary care unit.

Following the administration of this treatment a new electrocardiogram was performed and 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

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(normal range <0.04 ng/mL), raised D-Dimers 740 ng/ml (normal range <500ng/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 sample revealed normal specific IgEs and serum tryptase 5ng/ml (normal range <11.5ng/ml). She was extubated after 24 hours but computed tomography demonstrated diffuse ground-glass opacities and consolidations in both lungs (figure 2/ online-only supplementary material). Intravenous ampicillin/sulbactam, dexamethasone and remdesivir was 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 test were not performed because the patient and her relatives were denied the concent. Additional allergy tests such basophil activation test, radioallergosorbent testing, enzyme linked immunosorbent assay or fluoroenzyme immunoassay were not available.

The Kounis hypersensitivity-associated acute coronary syndrome and especially the type I variant of MINOCA type was diagnosed in our case. Good clinical outcome was confirmed in a follow up three months later. She was advised not to take azithromycin again.

Coronavirus disease 2019 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 any co-infection with SARS-CoV-2. However, the efficacy of azithromycin in the treatment of COVID-19 remains uncertain [3,4]. Macrolides, included 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. In the recent past, have been described cases of Kounis syndrome induced by clarithromycin [4]. Indeed, the frequency of hypersensitivity reactions to clarithromycin and azithromycin in a group of children was 15.5% and 47.3% of cases, respectively [5]. To the best of our knowledge, Kounis syndrome induced by azithromicyn has never been described. Furthermore, this case seems to be the first case of Kounis syndrome in patient with COVID-19 pneumonia.

The Kounis hypersensitivity-associated acute coronary syndrome is caused by inflammatory mediators released by an IgE antigen-allergen reaction. Activation of

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the complement system that leads to the generation of C1q, C3a C4, and C5a and Factor B, which are potent activators of inflammation and are called anaphylatoxins due to their ability to cause also mast cell degranulation. Furthermore, mastocyte-related G protein coupled receptor X2 (MRGPRX2) factors may activate mast cells via non-Fcε receptors and this explains the absence of specific IgEs and the normal tryptase levels [6]. The author of this report 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 may perhaps better explain some patients with Kounis syndrome where specific IgE may remain undetected or normal tryptase level. Measurements of serum specific IgE to hymenoptera venoms and ciprofloxacin could be negative. On the other hand, roxithromycin which is a macrolide as azithromycin has inhibited compound 48/80-induced pseudo-allergy via the MRGPRX2 pathway both in vitro and in vivo [7].

The inflammatory surge induced by COVID-19 seems to be contributing factor for 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 or cytokine storm [8]. Indeed, ST segment-elevation, as in the described patient, may represent 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 the intramuscular adrenaline was administered later to treat asystolic cardiopulmonary arrest, therefore adrenaline could not be the cause of any coronary spasm associated with chest pain. However, the patient had positive PCR test for COVID-19 and coincidence between Kounis allergy-associated coronary syndrome with COVID-19-induced coronary spasm can not be excluded. Indeed, coronary artery spasm in a young patient suffering from COVID-19 with normal coronary arteries has been attributed to inflammatory cytokine surge that occurs in both Kounis syndrome and COVID-19 [10].

A blood sample for measuring tryptase levels was obtained 24 hours after patient's arrest and 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 from the anaphylactic event. Dealing with the patient’s cardiac arrest in a very

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challenging environment (isolated COVID-19 area) was our first priority and this unavoidably led to a delay in collecting the blood specimen.

Therefore, further elucidation of the myocardial injury patho-physiology in patients with COVID-19 and searching for similarities between COVID-19 and Kounis hypersensitivity associated syndrome seems of paramount importance.

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