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CASE REPORT

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# Kounis syndrome associated with Moxifloxacin infusion in a patient with COVID-19 pneumonia: a case report.

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## ABSTRACT

Kounis syndrome (KS) is an acute coronary syndrome developing as a consequence of an anaphylactic or allergic reaction. Multiple mediators (especially histamine) released by mast cells, platelets, and some immune cells may lead to coronary vasospasm or thrombosis and cause an acute coronary syndrome. A clinical case of the KS in a hospitalized patient being treated for the COVID-19-associated pneumonia is presented. A 62-year-old woman was treated for COVID-19-associated pneumonia. In 15 min after the beginning of the Moxifloxacin infusion, the patient complained of severe headache, crushing chest pain, abdominal pain, severe general weakness, shortness of breath. Hypotension and decrease in SpO2 developed. Immediately performed ECG showed the ST-segment elevation in leads I and aVL. There were reciprocal changes in leads III, aVF, V3-V6. Troponin I was slightly elevated. Coronary angiography showed no hemodynamically significant coronary artery lesions. The KS type 1 was diagnosed. Repeated ECG in 2 hours showed isoelectric ST segments in all leads. It may be difficult to diagnose KS. Clinical signs of an allergic or anaphylactic reaction should raise the suspicion of KS. Moxifloxacin as well as other fluoroquinolones may be associated with the development of KS. We suggest a possible association of COVID-19 with KS. However, this issue requires further observation.

**KEY WORDS**: Kounis syndrome, acute coronary syndrome, COVID-19, coronary vasospasm, case report.

## INTRODUCTION

Anaphylaxis may cause coronary artery vasospasm that leads to an acute coronary syndrome even in the absence of atherosclerotic coronary artery lesions. A wide range of clinical presentations may be observed. Histamine-induced spasm of coronary arteries may manifest itself as an acute coronary syndrome. It was first described by Kounis NG and Zavras GM in 1991 [1].

Kounis syndrome (KS) is an acute coronary syndrome that develops as a result of anaphylactic or allergic reaction [2]. Multiple mediators released by mast cells, platelets, and some immune cells may lead to coronary vasospasm or thrombosis and cause the acute coronary syndrome. Particularly, histamine may cause coronary vasospasm and systemic vasodilation [1]. KS accompanied by an elevated cardiac troponin level may be categorized as myocardial infarction with non-obstructive coronary arteries (MINOCA) [3]. Explosive allergic cascade results in coronary artery spasm and/or thrombosis with the rapid development of clinical symptoms. The incidence of Kounis syndrome at the emergency department is 19.4 per 100 000 patients [4]. Plenty of medications including antibiotics may be associated with KS [4].

Mast cell degranulation with further histamine release may be initiated by COVID-19 infection [5]. It's possible that COVID-19 infection may facilitate the KS. But such an association requires further observation. We present a clinical case of KS in the hospitalized patient being treated for COVID-19-associated pneumonia.

## CASE REPORT

**Patient information**. A 62-year-old woman was admitted to the Ivano-Frankivsk Central City Clinical Hospital (16.11.2020) with shortness of breath, dry cough, weakness, malaise, high fever, sweating. She was diagnosed with arterial hypertension 2 years ago. Her daily medications included Perindopril and Indapamide. Also, she was taking 5 mg of Warfarin daily for the last 22 years (post-thrombotic syndrome; right iliofemoral deep vein thrombosis in 1998).

**Clinical findings**. On admission, her body temperature was 39.5 °C, respiratory rate (RR) was 22 per minute, $SpO_2$ was 92% on room air. Crackles on lung bases were auscultated bilaterally.

**Initial diagnostic testing**. COVID-19 PCR test was done with a positive result (16.11.2020). Chest CT revealed bilateral multisegmental areas of consolidation and diffusely scattered "ground glass" opacities involving 15% of the total lung volume (Figure 1). Abnormal laboratory values**:** ESR = 25 mm/h, WBC = $11.3x10^9$/L, bands = 11%. The D-dimer level was within a normal range. INR was 2.02, fibrinogen was 4.4 g/L. CRP was 96 mg/L.

**Initial therapeutic intervention**. The patient was prescribed Ceftriaxone 2 g IV BID, tab. Azithromycin 500 mg q24hr, tab. Bisoprolol 2.5 mg q24hr, tab. Spironolactone 25 mg q24hr, tab. Warfarin 5 mg q24hr, tab. Paracetamol 500 mg (if high fever), tab. Perindopril/Indapamide 4/1.25 mg q24hr.

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Given high persistent fever, absence of clinical response to the therapy (body temperature = 39.0°C, RR = 24 breaths per minute, $SpO_2$ = 92%, the presence of crackles on lung bases bilaterally, worsening of shortness of breath), Azithromycin was substituted with Moxifloxacin 400 mg IV q24hr (18.11.2020). In 15 min after the beginning of the Moxifloxacin infusion, the patient complained of a severe headache, fear of death has developed and she started to scream. Also, she complained of crushing chest pain, abdominal pain, severe general weakness, shortness of breath, vision disturbances, and dizziness. Significant skin pallor with lip cyanosis was noted. BP = 80/50 mmHg, HR = 72 bpm, $SpO_2$ = 85%, RR = 26 breaths per minute. She developed generalized urticaria. Concomitant partial memory loss for the period of hypotension was noted later.

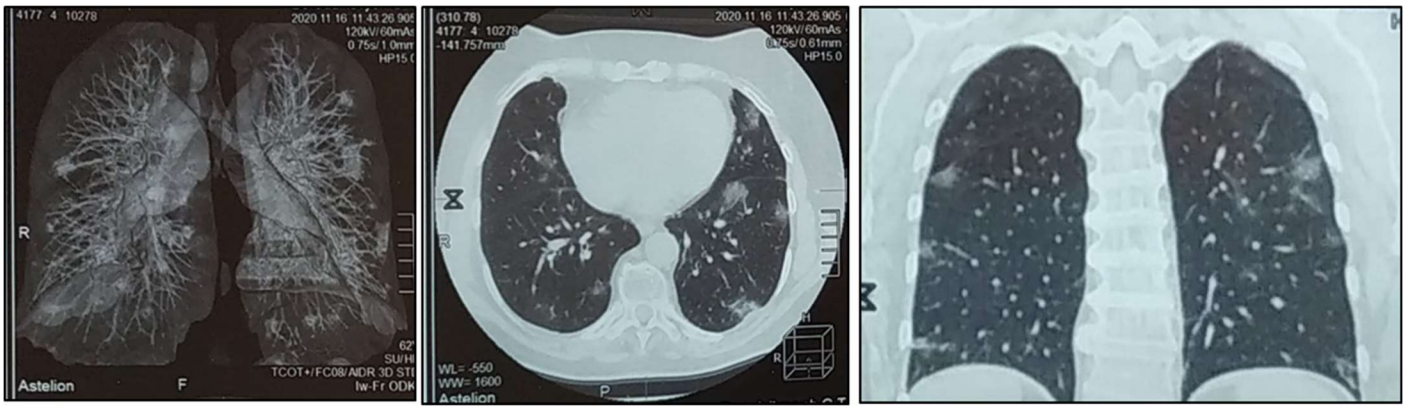


**Figure 1.** Chest CT - Bilateral multisegmental lesions.

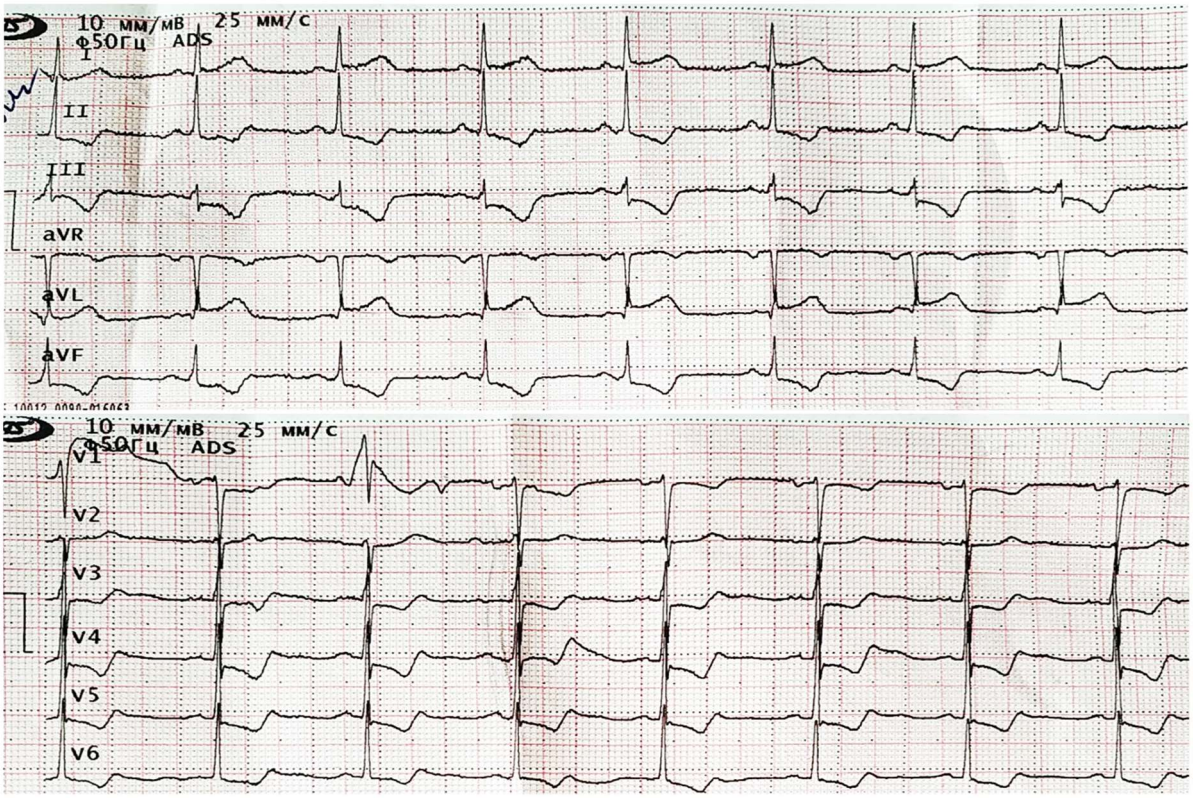


**Figure 2.** ECG recorded after Moxifloxacin infusion.

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**Further diagnostic testing**. An ECG was performed immediately (Figure 2): sinus rhythm at the rate of 66 bpm, ST-segment elevation in leads I (1 mm), aVL (1.5 mm), downsloping ST-segment depression in leads III (1.5 mm), aVF (1 mm), V3 (1 mm), V4 (1 mm), V5 (1 mm) V6 (0.5 mm). cTn I was 1.25 ng/ml (normal <1 ng/ml). Enoxaparin 8000 anti-Xa IU (0.8 ml), Aspirin 300 mg, Ticagrelor 180 mg, and Dexamethasone 8 ml were prescribed. The patient underwent urgent coronary angiography. No hemodynamically significant coronary artery lesions were detected. Echocardiography**:** left ventricular hypertrophy (moderately abnormal left ventricular myocardial mass index (119 g/m$^2$), left ventricular posterior wall thickening (1.26 cm)), mild pulmonary hypertension (pulmonary artery systolic pressure = 35 mm Hg, pulmonary artery diameter = 2.2 cm), hypokinesia of inferior and septal left ventricular wall segments, type I left ventricular diastolic dysfunction, left ventricular ejection fraction of 53%. Based on clinical symptoms and signs, ECG, and elevated cTn I levels, angiographic and echocardiographic results, type 1 KS was diagnosed, and an antihistamine (diphenhydramine) was administered.

**Follow-up and Outcomes.** Shortness of breath and other symptoms have gradually resolved within 2 hours. BP returned to normal. Repeated ECG in 2 hours (Figure 3) showed a normal sinus rhythm with a HR of 68 bpm, isoelectric ST segment in all leads. COVID-19 PCR test result became negative on the 8-th day of treatment (24.11.2020). The patient spent a total of 17 days in a hospital and was discharged on 03.12.2020 without further complications.

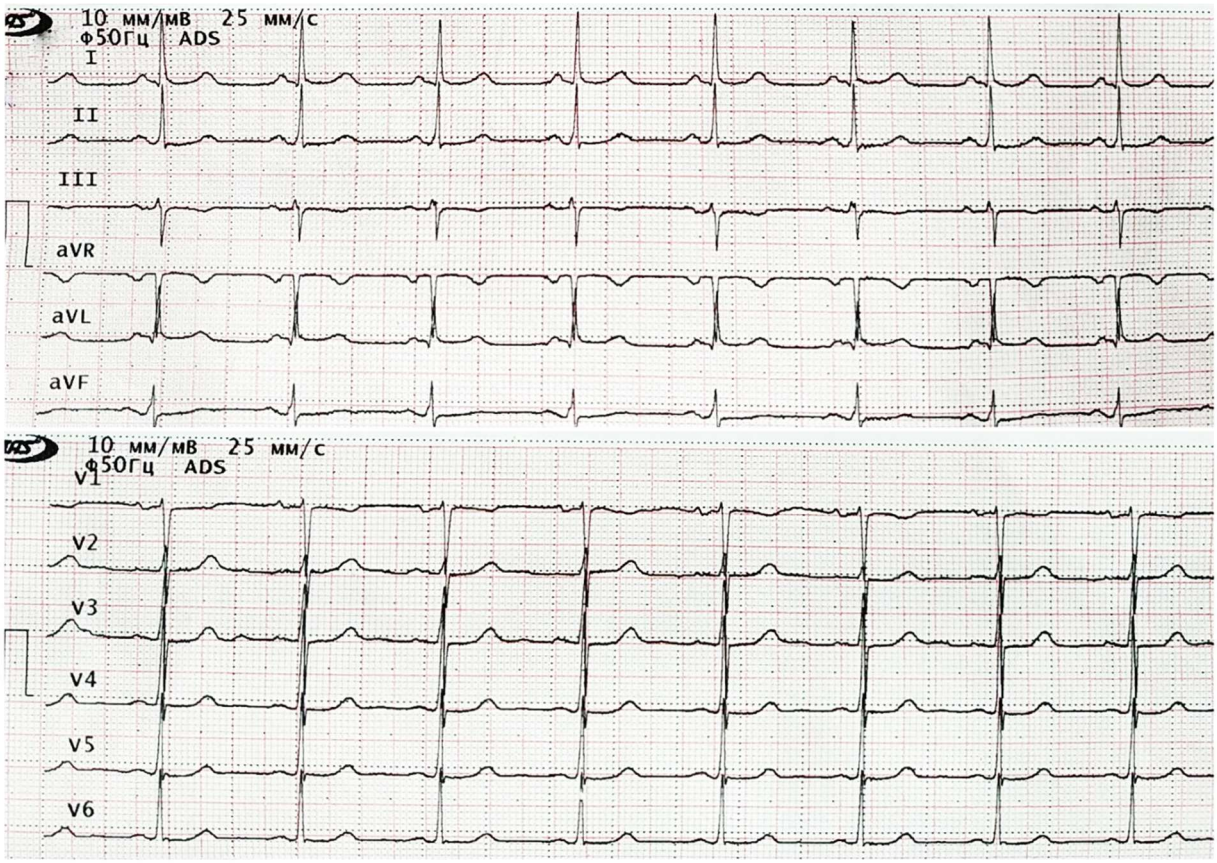


**Figure 3.** ECG recorded in 2 hours after the previous ECG.

## DISCUSSION

The KS might be caused by a variety of substances, medications, toxins, foods, and environmental allergens, snake bites, or insect stings [6]. According to published literature, three types of KS are distinguished [7]:

- *Type I is observed in patients with angiographically intact coronary arteries without cardiovascular risk factors. It occurs as a result of inflammatory mediators release, coronary vasospasm, and normal or elevated troponin I level.*
- *Type II is caused by a rupture of preexisting atheromatous plaque due to an allergic reaction with further complete coronary artery occlusion.*
- *Type III presents as stent thrombosis.*

A few cases of KS, associated with the use of fluoroquinolones were published in particular. In a patient with a pre-existing allergy to fluoroquinolones that led to sensitization and immediate development of KS during the administration of Ciprofloxacin [8]. Our patient had no known prior history of allergies or anaphylactic reactions. Our case is unique because Kounis syndrome associated with Moxifloxacin was not described previously.

KS may develop secondary to release of histamine, chemokines, enzymes chymase, tryptase, arachidonic acid-derived products such as prostaglandins, leukotrienes, thromboxane, IL-6, platelet-activating factor, cytokines, and many other inflammatory mediators [2]. All the above-mentioned substances may cause clinical signs and symptoms of anaphylaxis and possibly lead to an acute coronary syndrome development. COVID-19 may be associated with mast cell degranulation with consequent histamine release. That's why histamine H2-receptor antagonists (famotidine) may facilitate the clinical course of the COVID-19 [5]. An excessive histamine release in COVID-19 may hypothetically promote anaphylactic reactions that are the background for the development of KS.

## CONCLUSIONS

KS is a difficult clinical diagnosis that might be missed as some of its clinical features might resemble the ones of obstructive myocardial infarction, Takotsubo syndrome, or myocarditis. However, clinical signs of an allergic or anaphylactic reaction should raise the suspicion of KS. Moxifloxacin as well as other fluoroquinolones may be associated with the development of KS. We suggest a possible association of COVID-19 with KS. However, this issue requires further observation.

### SUPPLEMENTARY INFORMATION

***Funding:*** *This research received no external funding.*
***Institutional Review Statement:*** *The study was conducted according to the guidelines of the Declaration of Helsinki.*
***Informed Consent Statement:*** *Informed consent was obtained from all subjects involved in the study.*
***Data Availability Statement:*** *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
***Conflicts of Interest:*** *The authors declare no conflicts of interest.*

## REFERENCES

[1] Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. The British Journal of Clinical Practice, 1991; 45(2): 121-128.

[2] Kounis NG. Coronary Hypersensitivity Disorder: The Kounis Syndrome. Clinical Therapeutics, 2013; 35(5): 563–571.
doi: https://doi.org/10.1016/j.clinthera.2013.02.022

[3] Kounis NG, Koniari I, Soufras GD, Tsigkas G, Chourdakis E, Despotopoulos S, et al. Kounis syndrome: an additional etiologic factor of myocardial infarction with non-obstructive coronary arteries. Cardiol J. 2018; 25(5): 648-649...
doi: https://doi.org/10.5603/CJ.2018.0132

[4] Akoz A, Tanboga HI, Emet M, Bayramoglu A, Kizrak Y, Kantarci M, et al. A prospective study of Kounis syndrome: clinical experience and cardiac magnetic resonance imaging findings for 21 patients. Acta Med Mediterraea, 2013; 9: 811–816.

[5] Eldanasory OA, Eljaaly K, Memish ZA, Al-Tawfiq JA. Histamine release theory and roles of antihistamine in the treatment of cytokines storm of COVID-19. Travel Medicine and Infectious Disease, 2020; 101874.
doi: https://doi.org/10.1016/j.tmaid.2020.101874

[6] Rico Cepeda P, Palencia Herrejón E, Rodríguez Aguirregabiria MM. Kounis syndrome. Med Intensiva, 2012; 36(5): 358-364.
doi: https://doi.org/10.1016/j.medin.2011.10.008

[7] Biteker M. A new classification of Kounis syndrome. International Journal of Cardiology, 2010; 145(3): 553.
doi: https://doi.org/10.1016/j.ijcard.2010.05.020

[8] Almeida J, Ferreira S, Malheiro J, Fonseca P, Caeiro D, Dias A, et al. A rare cause of acute coronary syndrome: Kounis syndrome. Revista Portuguesa de Cardiologia (English Edition). 2016; 35(12): 699.e1–699.e4.
doi: https://doi.org/10.1016/j.repce.2016.03.011