JNMS Journal of Nippon Medical School https://www.nms.ac.jp/sh/jnms/

Case Report

Comprehensive Assessment of Kounis Syndrome Secondary to Carboplatin Chemotherapy: A Case Report

Seungmin Back[1,2,*], Wonsang Chu[1,*], Soohyung Park[1], Eun Jin Park[1], Cheol Ung Choi[1] and Dong Oh Kang[1]

[1]Cardiovascular Center, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[2]Cardiovascular Center, Department of Internal Medicine, Na-eun Hospital, Incheon, Republic of Korea

Allergic reactions during chemotherapy can lead to a rare condition known as Kounis syndrome, characterized by the simultaneous occurrence of coronary ischemia and allergic manifestations. Herein, we present a case of a 75-year-old woman who developed carboplatin-induced coronary vasospasm, highlighting the importance of comprehensive clinical and immunological evaluations for an accurate diagnosis. During carboplatin infusion, the patient exhibited typical symptoms, including chest pain and electrocardiographic changes. Subsequent investigations revealed elevated serum tryptase and total immunoglobulin E levels along with normal-looking coronary arteries, confirming a diagnosis of Type I Kounis syndrome. Following a safe recovery from the acute anaphylactic episode, the patient's treatment plan was adjusted accordingly based on this definitive diagnosis. Our findings emphasize the significance of recognizing and documenting immune responses in the diagnosis of Kounis syndrome; this can inform therapeutic strategies and improve patient outcomes.
(J Nippon Med Sch 2026; 93 (1): 95–100. https://doi.org/10.1272/jnms.JNMS.2026_93-101)

Keywords: allergy, carboplatin, coronary vasospasm, hypersensitivity, Kounis syndrome

Introduction

Allergic hypersensitivity reactions following chemotherapy can involve complex pathophysiology and manifest as coronary vasospasms or even acute coronary syndrome (ACS)[1,2]. Kounis syndrome is characterized by the simultaneous occurrence of allergic reactions and ACS[1]. Despite the reliance on clinical factors for diagnosis in routine practice, Kounis syndrome is often overlooked or underdiagnosed owing to a lack of awareness among physicians or inadequate documentation of the underlying immune response. Consequently, determining the true prevalence or incidence of Kounis syndrome remains challenging within the current clinical framework. Herein, we present a case of severe coronary vasospasm triggered by carboplatin hypersensitivity. We aimed to clarify this rare but potentially life-threatening condition's pathophysiology through a comprehensive clinical and immunological assessment. This case emphasizes the importance of accurately recognizing and diagnosing Kounis syndrome to enhance patient outcomes.

Case Presentation

A 75-year-old woman was admitted to the Gynecologic Oncology Department for second-line, second-cycle chemotherapy for left fallopian tube cancer with rectal invasion. The cancer had been diagnosed 2 years earlier, she had initially undergone debulking and staging surgery, including total abdominal hysterectomy with bilateral

* These authors contributed equally to this work.
Correspondence to Dong Oh Kang, gelly9@naver.com
https://doi.org/10.1272/jnms.JNMS.2026_93-101
Received: September 15, 2024; Accepted: October 30, 2024

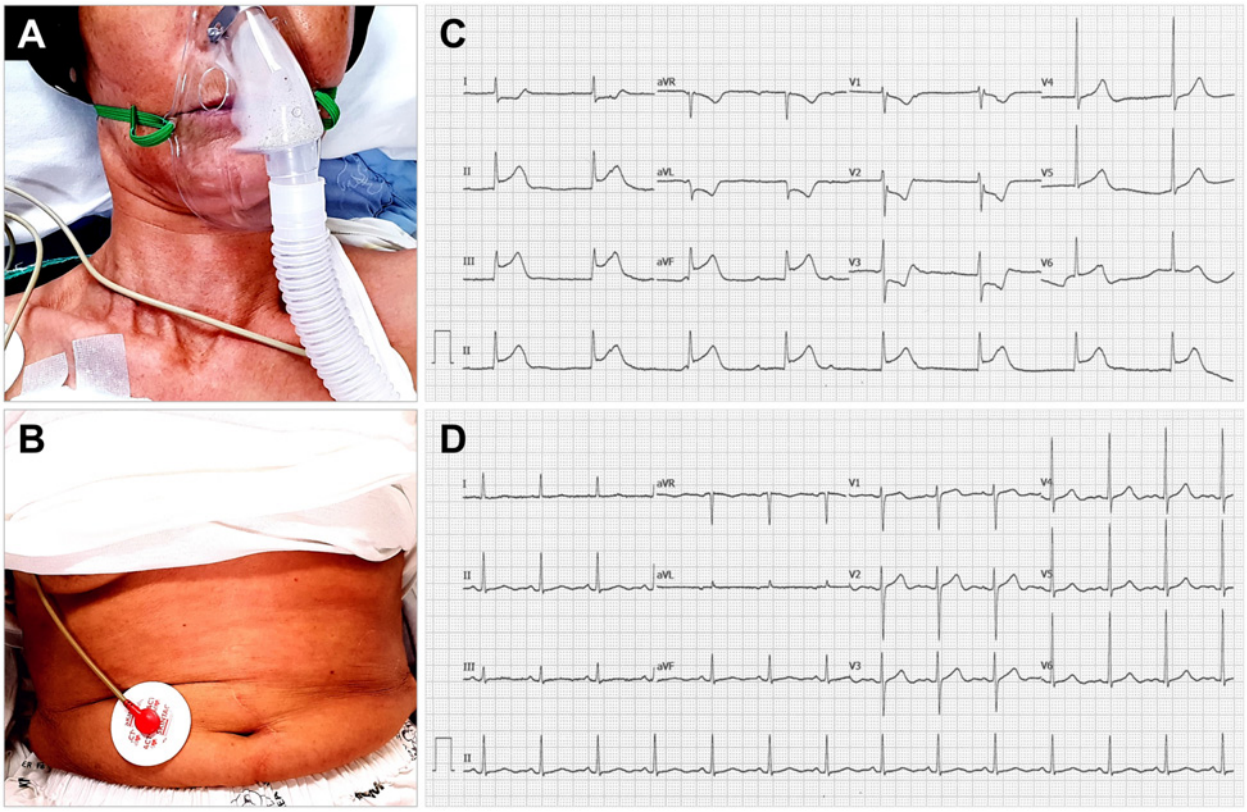

Figure 1 Cutaneous and electrocardiographic manifestations of Kounis syndrome
A and **B**: Development of a cutaneous skin rash on the face, upper chest, and abdominal area. **C**: Electrocardiogram showing ST-segment elevation in inferior leads II, III, and aVF and reciprocal ST-segment depression in anterior precordial leads V1 to V3 immediately after intravenous carboplatin infusion. **D**: Follow-up electrocardiogram taken after clinical stabilization showing resolved pathological ST-segment changes.

salpingo-oophorectomy, omentectomy, pelvic lymph node dissection, and low anterior resection of the rectum. Postoperative histopathological assessment revealed high-grade serous carcinoma, classifying the overall disease extent as stage IIIc. Following the initial diagnosis, the patient completed 10 cycles of adjuvant chemotherapy with paclitaxel and carboplatin without evidence of recurrence. However, at the 1-year surveillance follow-up, tumor recurrence within the pelvic cavity was detected, leading to the re-initiation of second-line chemotherapy using the same previously effective regimen. The patient had no significant personal or family history of cardiovascular disease and no prior history of allergic reactions. She was scheduled for a 3-day admission for each chemotherapy cycle, with a 3-week interval between cycles.

Baseline electrocardiogram (ECG) obtained before each chemotherapy cycle consistently showed no abnormal findings. However, during the second cycle of carboplatin (170 mg in normal saline) infusion, the patient suddenly developed chest pain, dyspnea, neck swelling, and a generalized skin rash (**Figure 1A and 1B**) accompanied by an intense itching sensation over her entire body. Concurrently, her blood pressure dropped to 70/41 mmHg, and an ECG obtained during the chest pain revealed a 3-mm ST-segment elevation in the inferior leads (II, III, and aVF), with reciprocal ST-segment depression in the anterior precordial leads (V1 to V3) (**Figure 1C**). Given the patient's hemodynamic instability and high suspicion of an anaphylactic response, aggressive fluid resuscitation with normal saline was initiated, along with intravenous administration of pheniramine (4 mg) and dexamethasone (40 mg). Following this initial treatment, the patient's chest pain and generalized skin rash gradually subsided, and her blood pressure stabilized at 116/67 mmHg. A follow-up ECG (**Figure 1D**) obtained 30 minutes later showed complete resolution of the ST-segment changes in both the inferior and anterior leads, coinciding with the patient's clinical stabilization.

Comprehensive laboratory and imaging assessments were conducted to elucidate the underlying pathophysiology of the hypersensitivity reaction that led to hemodynamic instability. Complete blood cell counts revealed mild neutrophilia (70%) without other significant abnormalities. Cardiac biomarkers, including high-sensitivity

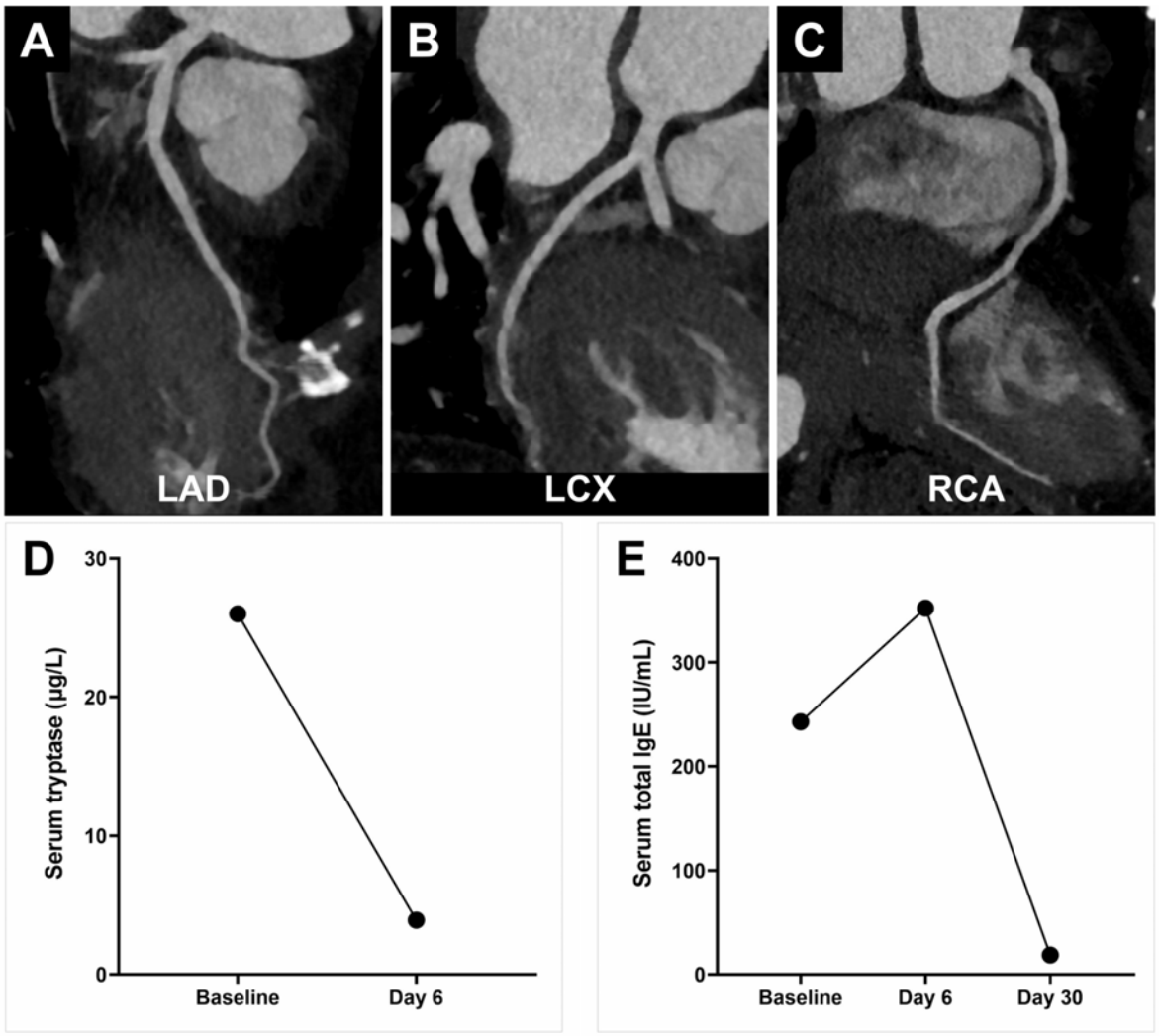

Figure 2 Coronary imaging and immunologic assessment of underlying pathophysiology
A–C: Coronary CT angiography showing normal-looking coronary arteries in the LAD, LCX, and RCA. **D** and **E**: Serial assessment of immunological markers, including serum tryptase and total IgE, showing a typical rise and fall pattern following clinical stabilization.
LAD, left anterior descending; LCX, left circumflex; CT, computed tomography; RCA, right coronary artery.

troponin-T and creatine kinase myocardial band, remained within normal limits at 0, 4, and 8 hours after the episode. Echocardiography indicated a normal left ventricular ejection fraction and no signs of regional wall motion abnormalities. Coronary computed tomography angiography revealed no significant changes in the epicardial coronary arteries (**Figure 2A–C**), effectively ruling out the type I myocardial infarction. Immunologic assessment during the index episode revealed elevated serum tryptase and total immunoglobulin (Ig) E levels of 26 µg/L and 243 IU/mL, respectively (**Figure 2D and 2E**). Six days later, serum tryptase had decreased to 3.9 µg/L, while total IgE had increased to 352.2 IU/mL. After a month, the IgE level decreased to 18.5 IU/mL. Based on this combination of clinical and immunologic findings, the patient was conclusively diagnosed with type I Kounis syndrome induced by intravenous carboplatin infusion; further chemotherapy with carboplatin was discontinued.

Written informed consent was obtained from the patient for the use of clinical images and related data.

Discussion

Kounis syndrome, a rare clinical condition characterized by the simultaneous occurrence of ACS and allergic reactions, was first reported in 1991[3]. This syndrome is primarily classified into three subtypes: Type I, which involves coronary vasospasm in angiographically normal arteries, mimicking vasospastic or microvascular angina; Type II, wherein allergic reactions trigger the rupture of preexisting atherosclerotic plaques, precipitating ACS; and Type III, in which allergic reactions cause stent

Table 1 Chemotherapeutic agents reported to cause Kounis syndrome

Anti-cancer drug class	Specific drug	Cancer types*
Platinum agents	Carboplatin	Small cell lung cancer[12]
		Lung adenocarcinoma[14]
		Ovarian carcinoma[13]
		Esophageal adenocarcinoma[15]
	Cisplatin	Ovarian cancer[16]
		Nasopharyngeal carcinoma[17,18]
	Oxaliplatin	Colorectal carcinoma[19,20]
Taxanes	Paclitaxel	Lung adenocarcinoma[21]
Anti-metabolites	Cabecitabine	Colorectal carcinoma[22-24]
		Gastric adenocarcinoma[25]
		Esophageal squamous cell carcinoma[25]
	5-fluorouracil	Colorectal carcinoma[26-28]
Anthracyclines	Epirubicin	Bladder cancer[29]

*A reference article reporting Kounis syndrome associated with the use of specific anti-cancer drugs for each cancer type has been provided.

Table 2 Management strategies for Kounis syndrome by subtypes

Classification	Management
Type 1 variant	• Discontinue the suspected causative agent responsible for the severe allergic reaction
	• Alleviate immune response with corticosteroids and anti-histamines (H1 and H2 receptor antagonists)
	• Use vasodilators (e.g. calcium channel blockers, short-acting nitrates)
	• Provide fluid resuscitation for hemodynamic instability due to severe anaphylactic reaction
	• Reserve epinephrine for life-threatening cases
Type 2 variant	• Follow the basic management for Type 1 variant
	• Implement guideline-based revascularization therapy for ACS, including dual anti-platelet therapy
Type 3 variant	• Follow the basic management for Type 1 variant
	• Implement guideline-based revascularization therapy for ACS, including dual anti-platelet therapy
	• Consider aspiration thrombectomy in selective cases, and additional histopathologic assessment of the aspirated thrombus may help confirm the etiology

ACS, acute coronary syndrome.

thrombosis in patients treated with coronary drug-eluting stents[1,4,5]. The pathogenesis of Kounis syndrome involves key mechanisms such as coronary endothelial dysfunction and smooth muscle hyperreactivity to inflammatory mediators, including histamines[6,7]. The current understanding highlights both IgE-mediated direct mast cell degranulation and non-IgE-mediated immune responses during anaphylactic hypersensitivity, leading to the release of inflammatory mediators into the coronary circulation[1].

Various factors have been implicated as triggers for Kounis syndrome, with chemotherapeutic drugs emerging as significant contributors[8]. **Table 1** presents an overview of the classes of these agents along with the relevant literature linking them to Kounis syndrome. Initial management of Kounis syndrome typically aims to alleviate acute hypersensitivity reactions and severe vasospasm by discontinuing the causative agent and administering corticosteroids, antihistamines, and vasodilators[4,5]. Epinephrine is usually reserved for life-threatening cases due to its potential to exacerbate coronary vasospasm and myocardial ischemia[4,5]. For patients with Type II and Type III variants, specific treatments targeting the underlying causes should be considered, including guideline-based revascularization therapy for ACS[4,5]. **Table 2** summarizes the management strategies for Kounis syndrome.

Among various chemotherapeutic agents, platinum-based agents, including carboplatin, are increasingly recognized as potential causes of Kounis syndrome[8]. Preclinical studies have shown that platinum-based agents reduce cardiac contractility and coronary flow in a dose-dependent manner[9]. Furthermore, these compounds have a higher propensity for hypersensitivity reactions than do other cytotoxic drugs[2,10,11]. Several cases of carboplatin-induced Kounis syndrome have been reported, characterized mainly by anginal symptoms and typical ECG

changes indicative of coronary vasospasm[12–15]. However, the direct causal link between carboplatin and allergic responses has primarily been inferred from clinical observations rather than confirmed by immunological markers.

The present case highlights the importance of elucidating the underlying immune responses in Kounis syndrome. Establishing a direct causal relationship between allergic reactions and coronary ischemia is essential for developing more effective therapeutic strategies. From a pathophysiological perspective, presenting clear immunological evidence, such as dynamic changes in serum tryptase and total IgE levels, is crucial for confirming a diagnosis of Kounis syndrome. Demonstrating a temporal association between these markers and clinical episodes further strengthens the diagnosis. Exploring additional markers, such as serum histamine levels, could offer further insights into the underlying immune response in available cases. Our findings also indicate that prior exposure to chemotherapeutic agents does not guarantee safety. This case highlights the diagnostic value of immunological markers for Kounis syndrome. Patients who develop anginal symptoms and ischemic ECG changes during chemotherapy should undergo comprehensive evaluation for allergic signs and symptoms. Serum tryptase and total IgE levels can be valuable markers for understanding the underlying pathophysiology. Healthcare providers can more accurately identify and manage patients with this rare condition using these diagnostic approaches.

Author Contributions: Conceptualization: D.O.K.; Methodology: S.B., W.C., and D.O.K.; Validation and formal analysis: S.B., W.C., and D.O.K.; Investigation and resources: S.B., W.C., and D.O.K.; Data curation: S.P., E.J.P., C.U.C., and D.O.K.; Visualization: S.B., W.C., and D.O.K.; Supervision: C.U.C. and D.O.K.; Project administration and funding acquisition: D.O.K.; Writing—original draft: S.B., W.C., and D.O.K.; Writing-review and editing: D.O.K.

Acknowledgments: We would like to thank Editage (www.editage.co.kr) for the English language editing.

Funding: This work was funded by Grants from the National Research Foundation of Korea (NRF), the Korean government [Grant number: RS-2023-00210960 to D.O.K.], and a Korea University Grant [Grant number K2225581 to D.O.K.].

Conflict of Interest: The authors declare no conflicts of interest.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: The authors have nothing to disclose.

Data Availability: The corresponding author has full access to the clinical information. Anonymized data will be available upon request from a qualified researcher.

References

1. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med. 2016;54(10):1545–59. doi: 10.1515/cclm-2016-0010. PubMed PMID: 26966931
2. Tsao LR, Young FD, Otani IM, Castells MC. Hypersensitivity reactions to platinum agents and taxanes. Clin Rev Allergy Immunol. 2022;62(3):432–48. Epub 2021 Aug 2. doi: 10.1007/s12016-021-08877-y. PubMed PMID: 34338975; PubMed Central PMCID: PMC9156473
3. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract. 1991;45(2):121–8. PubMed PMID: 1793697
4. Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome: a review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. Int J Cardiol. 2017;232:1–4. Epub 2017 Jan 27. doi: 10.1016/j.ijcard.2017.01.124. PubMed PMID: 28153536
5. Fassio F, Losappio L, Antolin-Amerigo D, et al. Kounis syndrome: a concise review with focus on management. Eur J Intern Med. 2016;30:7–10. Epub 2016 Jan 12. doi: 10.1016/j.ejim.2015.12.004. PubMed PMID: 26795552
6. Okumura K, Yasue H, Matsuyama K, et al. Effect of H1 receptor stimulation on coronary artery diameter in patients with variant angina: comparison with effect of acetylcholine. J Am Coll Cardiol. 1991;17(2):338–45. doi: 10.1016/s0735-1097(10)80096-8. PubMed PMID: 1991889
7. Eto M, Kitazawa T, Yazawa M, Mukai H, Ono Y, Brautigan DL. Histamine-induced vasoconstriction involves phosphorylation of a specific inhibitor protein for myosin phosphatase by protein kinase C alpha and delta isoforms. J Biol Chem. 2001;276(31):29072–8. Epub 2001 Jun 7. doi: 10.1074/jbc.M103206200. PubMed PMID: 11397799
8. Kounis NG, Hung MY, de Gregorio C, et al. Cardio-oncoimmunology: cardiac toxicity, cardiovascular hypersensitivity, and Kounis syndrome. Life (Basel). 2024;14(3):400. doi: 10.3390/life14030400. PubMed PMID: 38541723; PubMed Central PMCID: PMC10971934
9. Misic MM, Jakovljevic VL, Bugarcic ZD, et al. Platinum complexes-induced cardiotoxicity of isolated, perfused rat heart: comparison of Pt(II) and Pt(IV) analogues versus cisplatin. Cardiovasc Toxicol. 2015;15(3):261–8. doi: 10.1007/s12012-014-9293-8. PubMed PMID: 25404470
10. Pagani M. The complex clinical picture of presumably allergic side effects to cytostatic drugs: symptoms, pathomechanism, reexposure, and desensitization. Med Clin North Am. 2010;94(4):835–52, xiii. doi: 10.1016/j.mcna.2010.03.002. PubMed PMID: 20609866
11. Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. Allergy. 2022;77(2):388–403. Epub 2021 Oct 26. doi: 10.1111/all.15113. PubMed PMID: 34587281
12. Yano S, Shimada K. Vasospastic angina after chemother-

apy by with carboplatin and etoposide in a patient with lung cancer. Jpn Circ J. 1996;60(3):185–8. doi: 10.1253/jcj.60.185. PubMed PMID: 8741246
13. Chasen MR, Ebrahim IO. Carboplatin hypersensitivity presenting as coronary vasospasm - a case report. Cancer Chemother Pharmacol. 2002;50(5):429–31. Epub 2002 Sep 27. doi: 10.1007/s00280-002-0518-3. PubMed PMID: 12439602
14. Baroni M, Todd S, Pattarino F, Doni F. Carboplatin-induced Kounis syndrome. J Cardiol Cases. 2011;4(1):e58–61. doi: 10.1016/j.jccase.2011.04.004. PubMed PMID: 30532871; PubMed Central PMCID: PMC6265130
15. Tambe V, Tambe A, Goodman A, Shepherd Z. Carboplatin-induced Kounis syndrome. Am J Ther. 2020;27(6):e647–52. doi: 10.1097/mjt.0000000000001027. PubMed PMID: 31567140
16. Oneglia C, Kounis NG, Beretta G, Ghizzoni G, Gualeni A, Berti M. Kounis syndrome in a patient with ovarian cancer and allergy to iodinated contrast media: report of a case of vasospastic angina induced by chemotherapy. Int J Cardiol. 2011;149(2):e62–5. Epub 2009 Apr 22. doi: 10.1016/j.ijcard.2009.03.104. PubMed PMID: 19395094
17. Darling HS. Cisplatin induced bradycardia. Int J Cardiol. 2015;182:304–6. Epub 2015 Jan 5. doi: 10.1016/j.ijcard.2015.01.013. PubMed PMID: 25585374
18. Kounis NG, Cervellin G, Lippi G. Cisplatin-induced bradycardia: cardiac toxicity or cardiac hypersensitivity and Kounis syndrome? Int J Cardiol. 2016;202:817–8. Epub 2015 Oct 9. doi: 10.1016/j.ijcard.2015.10.027. PubMed PMID: 26476038
19. Chang PH, Hung MJ, Yeh KY, Yang SY, Wang CH. Oxaliplatin-induced coronary vasospasm manifesting as Kounis syndrome: a case report. J Clin Oncol. 2011;29(31):e776–8. Epub 2011 Oct 3. doi: 10.1200/jco.2011.36.4265. PubMed PMID: 21969496
20. Albanesi M, Didonna R, Chaoul N, et al. A challenge in emergency department: a case report of oxaliplatin-induced Kounis syndrome. Precis Cancer Med. 2023;6:18.
21. Wang B, Sethwala A, Gurvitch R. Type 1 Kounis syndrome after paclitaxel infusion in a patient treated for lung adenocarcinoma. Intern Med J. 2021;51(3):448–9. doi: 10.1111/imj.15226. PubMed PMID: 33738953
22. Scott PA, Ferchow L, Hobson A, Curzen NP. Coronary spasm induced by capecitabine mimicks ST elevation myocardial infarction. Emerg Med J. 2008;25(10):699–700. doi: 10.1136/emj.2008.060574. PubMed PMID: 18843078
23. Tsiamis E, Synetos A, Stefanadis C. Capecitabine may induce coronary artery vasospasm. Hellenic J Cardiol. 2012;53(4):320–3. PubMed PMID: 22796820
24. Kido K, Adams VR, Morehead RS, Flannery AH. Capecitabine-induced ventricular fibrillation arrest: possible Kounis syndrome. J Oncol Pharm Pract. 2016;22(2):335–40. Epub 2015 Apr 13. doi: 10.1177/1078155214563814. PubMed PMID: 25870182
25. Coughlin S, Das S, Lee J, Cooper J. Capecitabine induced vasospastic angina. Int J Cardiol. 2008;130(1):e34–6. Epub 2007 Sep 25. doi: 10.1016/j.ijcard.2007.06.152. PubMed PMID: 17897740
26. Canale ML, Camerini A, Stroppa S, et al. A case of acute myocardial infarction during 5-fluorouracil infusion. J Cardiovasc Med (Hagerstown). 2006;7(11):835–7. doi: 10.2459/01.JCM.0000250874.09273.9b. PubMed PMID: 17060812
27. Tajik R, Saadat H, Taherkhani M, Movahed MR. Angina induced by 5-fluorouracil infusion in a patient with normal coronaries. Am Heart Hosp J. 2010;8(2):E111–2. doi: 10.15420/ahhj.2010.8.2.111. PubMed PMID: 21928176
28. Karabay CY, Gecmen C, Aung SM, et al. Is 5-fluorouracil-induced vasospasm a Kounis syndrome? A diagnostic challenge. Perfusion. 2011;26(6):542–5. Epub 2011 May 31. doi: 10.1177/0267659111410347. PubMed PMID: 21628340
29. Liang HZ, Zhao H, Gao J, Cao CF, Wang WM. Epirubicin-induced Kounis syndrome. BMC Cardiovasc Disord. 2021;21(1):133. doi: 10.1186/s12872-021-01936-4. PubMed PMID: 33711934; PubMed Central PMCID: PMC7953621