CASE REPORTS

UDC: 616.132.2-08-06:616-052-056.43
DOI: https://doi.org/10.2298/VSP230424037K

Early stent thrombosis in Kounis syndrome – a case report

Kunisov sindrom i rana tromboza stenta

Tomislav Kostić*†, Zoran Perišić*†, Dušanka Kutlešić Kurtović*, Bojan Maričić*, Svetlana Apostolović*†, Dragana Stanojević*, Goran Koraćević*†, Sonja Dakić*†, Nenad Božinović*†, Katarina Kostić*, Jelena Milošević*, Mihajlo Lazarević*

***University Clinical Center Niš, Clinic for Cardiology, Niš, Serbia; †University of Niš, Faculty of Medicine Niš, Serbia**

Abstract

Introduction. Kounis syndrome is a simultaneous manifestation of acute coronary syndrome and conditions associated with mast cell activation, such as allergies or anaphylactic reactions. We present early stent thrombosis in a female with an atopic constitution without previous atherosclerosis of coronary arteries. **Case report.** A 50-year-old woman with typical anginal pain was admitted to the Clinic for Cardiology, University Clinical Center Niš. A few hours earlier, she had passed by a linden tree in bloom. She immediately felt chest pain, paresthesia and numbness in her left arm throat tightness, heaviness of the tongue, and swelling of the lips. The symptoms disappeared for 60 min after taking 10 mg of loratadine, but then they recurred. On the electrocardiographic (ECG) findings, 30 minutes after admission, ST elevation was seen in leads D2, D3, aVF, and V6. She underwent an emergency percutaneous coronary intervention procedure. Occlusive thrombosis was seen in the ostium of the left anterior descending (LAD) coronary artery. A sirolimus-coated stent was placed and thrombolysis in myocardial infarction (TIMI) 3 flow was obtained. A few hours after the intervention, the patient reported a new onset of chest pain followed by ventricular fibrillation (VF), DC shock, and the occurrence of new ST-segment elevation in aVR and V1–V3 on the ECG. Repeated angiography showed acute in-stent thrombotic occlusion. Balloon angioplasty was performed, which restored TIMI 3 flow in LAD coronary artery. Anticoagulant and corticosteroid therapy was administered. Three days after the intervention, optical coherence tomography imaging was performed, which showed good stent expansion and apposition, without atherosclerosis and thrombosis. **Conclusion.** Coronary angiography proved type I Kounis syndrome after exposure to an allergen, and type III Kounis syndrome developed shortly after stent placement when acute in-stent thrombosis occurred. Newly described causes of acute and subacute stent thrombosis in type III Kounis syndrome are stent-associated hypersensitivity reactions.

Key words:
angioplasty, balloon; coronary angiography; coronary disease; hypersensitivity; kounis syndrome.

Apstrakt

Uvod. Kunisov sindrom je istovremena manifestacija akutnog koronarnog sindroma i stanja udruženih sa aktivacijom mastocita, kao što su alergija i anafilaktička reakcija. Prikazujemo slučaj rane tromboze stenta kod žene sa atopijskom konstitucijom, bez prethodnog postojanja aterosklerotskih lezija. **Prikaz bolesnika.** Pedesetogodišnja žena sa tipičnim anginoznim bolom primljena je na Kliniku za kardiologiju Univerzitetskog kliničkog centra u Nišu. Nekoliko sati ranije, ona je prošla pored drveta lipe u cvetanju. Odmah je osetila bol u grudima, parestezije i utrnulost leve ruke, stezanje u grlu, otežan jezik i otok usana. Tegobe su prestale tokom 60 min nakon uzimanja 10 mg loratadina, ali su se ponovo javile. Na elektrokardiografskom (EKG) nalazu, 30 min nakon prijema, viđena je ST elevacija u odvodima D2, D3, aVF i V6. Urađena joj je perkutana koronarna intervencija. Angiogram je pokazao okluzivnu trombozu ostijalnog dela prednje silazne grane leve (*left anterior descending* – LAD) koronarne arterije. Plasiran je sirolimusom obložen stent i postignut *thrombolysis in acute myocardial infarction* – TIMI 3 protok. Nekoliko sati nakon intervencije, bolesnica je prijavila da ponovo oseća bol u grudima, što je bilo praćeno ventrikularnom fibrilacijom (VF), DC šokom i pojavom elevacije ST segmenta u aVR i V1–V3 na EKG-u. Ponovljena angiografija je pokazala akutnu *in*-stent trombozu sa okluzijom. Urađena je balon angioplastika kojom je obnovljen TIMI 3 protok u LAD koronarnoj arteriji. Primenjena je antikoagulantna i kortikosteroidna terapija. Tri dana nakon intervencije, urađena je optička koherentna tomografija, koja je pokazala dobru ekspanziju

Correspondence to: Dragana Stanojević, University Clinical Center Niš, Clinic for Cardiology, Bulevar dr Zorana Đinđića 48, 18 000 Niš, Serbia. E-mail: draganastanojevic1@gmail.com

stenta i apoziciju, bez ateroskleroze i tromboze. **Zaključak.** Koronarografijom je dokazan tip I Kunisovog sindroma nakon ekspozicije alergenu i tip III Kunisovog sindroma ubrzo nakon postavljanja stenta, kada je nastala akutna *in*-stent tromboza. Novoopisani uzroci akutne i subakutne tromboze stenta kod Kunisovog sindroma tipa III su hipersenzitivne reakcije povezane sa stentom.

Ključne reči:
angioplastika, translumenska; angiografija koronarnih arterija; koronarna bolest; hipersenzibilnost; kunisov sindrom.

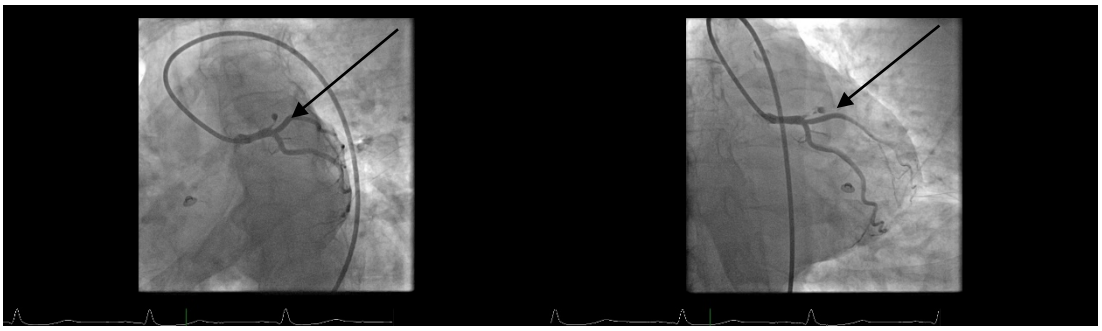
Introduction

Kounis syndrome is a simultaneous manifestation of acute coronary syndrome with conditions associated with mast cell activation, such as allergies or anaphylactic/anaphylactoid reactions [1, 2]. There are three types of Kounis syndrome. Type I represents allergic vasospasm of coronary arteries due to a release of proinflammatory mediators in patients with previously healthy coronary arteries. Type II develops when an allergic reaction occurs at the site of already present plaque in coronary arteries. Type III represents thrombotic reocclusion of epicardial coronary arteries at the site of previously treated coronary lesions. The occlusive thrombus is infiltrated by eosinophils and/or mast cells [3–6]. As Kounis syndrome is a combination of allergic and coronary-ischemic reactions, the pathogenesis, treatment, and prognosis of this syndrome are still unknown.

Case report

A 50-year-old Caucasian female patient presented to the cardiology department with typical anginal pain. A few hours earlier, she passed by a linden tree in bloom and immediately after felt chest pain, paresthesia and numbness in her left hand, throat tightness, heaviness of the tongue, and swelling of the lips. These symptoms disappeared for an hour after taking 10 mg of loratadine orally. She had a 12-year history of arterial hypertension (took ramipril 5 mg and nebivolol 5 mg once a day), long-term bronchial asthma (took vilanterol/fluticasonefluorate when needed), and allergic rhinitis (at that time without therapy). Following admission, she had an arterial blood pressure of 126/94 mm Hg, a heart rate of 69 beats/min, and an oxygen saturation of 99%. On admission, laboratory tests showed the following results: white blood cells (5.0 x 10^3/μL), neutrophils (67.4%), eosinophiles (12.8%), lactate dehydrogenase [483 U/L, reference range (RR) 0–450], C-reactive protein (1.4 mg/L, RR 0–5), creatine phosphokinase (344 U/L, RR 0–195), alanine aminotransferase (21 U/L, RR 10–42), aspartate aminotransferase (66 U/L, RR 10–37), troponin I (1.3 ng/mL, RR 0–0.4). Platelet count, kidney and liver function, as well as lipase and coagulation tests, were all within normal limits. Laboratory immunology testing results for the most common allergens were the following: IgE 665 IU/mL (normal value < 100 IU/mL); food allergy panel F1, F2, F4, F9, F13, F14 < 0.10 kU/L, FP7 0; inhalant allergy panel 8 (D1, E1, E5) was 2 kU/L (normal value < 0.10 kU/L).

On admission, 12-lead electrocardiographic (ECG) findings showed sinus rhythm, initially only with ST-segment depression in lead V1. Initial therapy included acetylsalicylic acid 300 mg, atorvastatin 40 mg, and methylprednisolone 40 mg. After 30 min, ECG showed concave ST-segment elevation in D2, D3, and aVF leads and ST elevation of 1 mm in lead V6. The echocardiographic examination showed reduced left ventricle ejection fraction (35%), remodeled left ventricle with dyskinesia of the apical segments of the inferior wall and septum. She was given a ticagrelor loading dose of 180 mg and 80 mg of low molecular weight heparin subcutaneously (sc) and underwent an emergency percutaneous coronary intervention procedure. A coronary angiogram showed occlusive thrombosis in the ostium of the left anterior descending (LAD) artery with no other changes in coronary arteries (Figure 1A and B). The lesion was treated by placing Ultimaster™ Tansei™ coronary stent 3.0 × 12 mm. The final angiogram showed thrombolysis in acute myocardial infarction (TIMI) 3 flow. We performed multiplate analysis as a standard for all patients, and the result showed adequate response to acetylsalicylic acid and ticagrelor. A few hours following the intervention, the patient reported a new onset of chest pain followed by ECG signs of ST-segment elevation in aVR, V1–V3 leads. Another coronary angiography was performed and showed an acute in-stent occlusion with a thrombotic mass followed by a small



A) **B)**

Fig. 1 A) and B) – Angiography following admission – left anterior descending coronary artery occluded

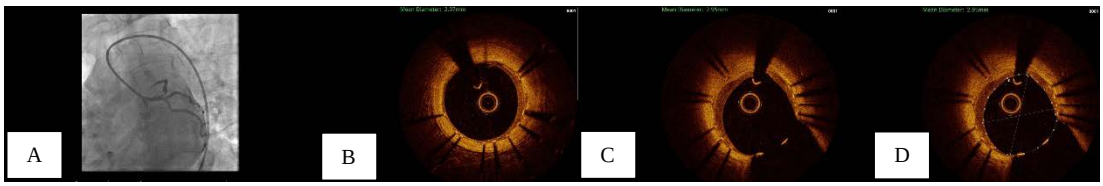


Fig. 2 – Angiography after repeated ST-segment elevation: A) in-stent thrombosis. Optical coherence tomography after second percutaneous coronary intervention procedure: B) optimal stent expansion and apposition; C) no residual stenosis; D) no stent fracture.

thrombus in the left circumflex artery (Figure 2A). Balloon angioplasty was done, which restored TIMI 3 flow in the LAD artery. Anticoagulant and corticosteroid therapy was administered (enoxaparin 60 mg/12 hrs s.c., dexamethasone 4 mg/24 hrs i.v.) beside atorvastatin 80 mg and dual antiplatelet therapy for seven days. Due to the simultaneous onset of the symptoms of allergic reaction and acute myocardial infarction, as well as acute stent thrombosis, intravascular imaging was performed. Three days following the intervention, optical coherence tomography (OCT) imaging showed fully structurally preserved arterial walls without any signs of atherosclerosis, no signs of restenosis, adequate stent expansion, and good apposition. An organized thrombus was present, occupying up to 10% of the artery lumen (Figure 2B–D).

At hospital discharge, our patient received acetylsalicylic acid 100 mg, ticagrelor 90 mg twice daily, atorvastatin 40 mg, zofenopril 15 mg, spironolactone 25 mg, and nebivolol 1.25 mg.

Prior to submitting this case report to the journal, the patient gave written informed consent.

Discussion

Kounis syndrome is not a rare disease; the incidence is approximately 0.1%, but it is most often left undiagnosed. It affects all ages, races, and both genders and could be fatal [7].

There are three types of Kounis syndrome based on the cause of cardiogenic involvement. Type I represents an allergic vasospasm of coronary arteries due to a release of proinflammatory mediators in patients with previously healthy coronary arteries, leading only to endothelial dysfunction. Manifestations of this variant start from transitory coronary artery spasm without a significant increase in cardiac biomarkers to the development of acute myocardial infarction with clear ECG changes, wall motion abnormalities, and a rise in cardiac biomarkers. This type is considered to be one of the causes of myocardial infarction without occlusion of the coronary artery - MINOCA. Type II develops when an allergic reaction occurs at the site of already present plaque in coronary arteries. The release of proinflammatory mediators from mastocytes, eosinophils, and basophils leads to vasospasm, destabilization, erosion, and rupture of atherosclerotic plaque with the development of acute myocardial infarction. Type III represents thrombotic reocclusion of previously treated coronary lesions (stent thrombosis or thrombosis after percutaneous balloon angioplasty – POBA) [1–6].

For the diagnosis of Kounis syndrome, there are no specific criteria. Its presentation could vary from cardiac arrhythmias to sudden cardiac death with different ECG and laboratory changes [8].

In the diagnosis of Kounis syndrome, the first step is to determine the history of allergy reactions, which we found in our patient. The allergic reaction to the trigger is known in 25% of patients with this syndrome. We did find high levels of IgE, but its role is not clearly elucidated in diagnosis. Serum levels of histamine and tryptase could be helpful but are released quickly after contact with the allergen and quickly removed from the circulation (up to 90 min for tryptase and even shorter for histamine). In 60% of all patients with this syndrome, the troponin levels are elevated, which was also the case with our patient [9].

ECG changes on admission and echocardiography findings do not correlate with the angiography showing a thrombus at the ostium of LAD artery. The inferior and lateral wall involvement could be related to coronary vasospasm and/or coronary embolism and endothelial dysfunction. Coronary arteries are not the direct target organ of hypersensitivity, and it could be hypothesized that the vasospasm might be secondary to the smooth muscle contraction reflex caused by the irritation of the bronchial epithelium by allergens, among other known mechanisms. Presumably, the bronchial smooth muscle contraction reflex induces the epithelium-derived inflammatory molecules accumulation and could cause coronary vasospasm through this pathway [10].

Our paper describes early stent thrombosis in a female patient with an atopic constitution without previous atherosclerotic lesions of coronary arteries. Serologic analyses showed high IgE levels for common inhalant allergens, and the patient has a history of bronchial asthma. Coronary angiography showed type I Kounis syndrome after exposure to an allergen, and shortly after stent placement, type III Kounis syndrome developed.

Local and systemic factors lead to early stent thrombosis. Insufficient stent expansion, stent malposition, and tortuosity of the vessel are the most common local factors. Systemic factors include hypercoagulable conditions, malignancy, and use of chemotherapeutics [4, 11]. We performed the OCT to ensure that local factors were not the cause of early stent thrombosis.

Newly described causes of acute and subacute stent thrombosis in type III Kounis syndrome are stent-associated hypersensitivity reactions [11, 12]. Surface IgE receptors on subtypes of platelets are thought to be associated with the initia-

tion of stent thrombosis in reactions of hypersensitivity. The platelets with IgG receptors (FCγRII) and IgE receptors of high and low affinity (FcεRI and FCεRII) is responsible for the activation of prothrombotic events cascade in reactions of hypersensitivity. During this activation, platelets produce proinflammatory (platelet-derived factor 4, platelet growth factor, CD154), procoagulant (factor V, factor XI, plasminogen activator inhibitor 1), adhesive (thrombospondin, fibrinogen, p-selectin, Von Wilebrand factor), and chemotactic (adenosine diphosphate, adenosine triphosphate, serotonin, histamine, calcium, and magnesium ions) mediators which propagate, enhance, and maintain the process of thrombus formation. That leads to conformational changes in the GP IIb/IIIa receptor and enables fibrinogen to attach platelets and further aggregation [11, 13, 14].

Our patient had stent thrombosis after the implantation of Ultimaster™ Tansei™ stent (Terumo, Tokyo, Japan) with cobalt-chromium structure and poly-(d,l-lactic) acid and poly-(l-lactide-co-ε-caprolactone) and sirolimus-impregnated secondary coating. As studies have shown, sirolimus has an inhibitory role in eosinophilic infiltration and histamine synthesis; therefore, there is a small chance for the development of hypersensitive reactions [15, 16]. Ultimaster™ Tansei™ stent, applied in this patient, has not been associated with reactions of stent thrombosis up to now. A case of a female patient with repetitive thrombosis was described by Jimba et al. [17], however, an adverse reaction was not as severe as was described in our patient. Acute stent thrombosis associated with hypersensitive reaction to the stent itself was described only in a few papers [15, 18]. A small number of reported cases can be explained with unclear clinical presentation, atypically manifested atopic reaction, demanding diagnostics that could involve thrombus aspiration, pathohystological diagnostics, and use of intravascular imaging. Yamaji et al. [19] found a significantly higher eosinophilic cell fraction in patients with very late in-stent thrombosis (> 12 months after intervention) compared to those with early (up to one month after intervention) and late (1 to 12 months after intervention) in-stent thrombosis. A probable cause of this finding is hypersensitive vasculitis [20].

The etiology of stent thrombosis in our patient could be a prolonged allergic reaction or hypersensitivity to stent components.

Management of Kounis syndrome is complex, and we do not have established recommendations. Two goals in the treatment of Kounis syndrome are to dilate coronary arteries and manage an allergic reaction. Therefore, patients with Kounis syndrome are initially treated with steroids, antihistamines, fluid resuscitation, epinephrine, oxygen, and antithrombotics. Subsequently, in Kounis syndrome type II, the standard therapy for acute coronary syndrome should be given. Since the coronary vasospasm is dominant in young and previously healthy patients, they should receive nitrates and calcium-channel blockers. Beta-blockers should be administrated very carefully in the acute phase since they can interfere with the epinephrine and induce or aggravate the spasm of coronary arteries by leaving alpha-adrenergic receptors unblocked [21, 22]. Beta-blockers may even increase the production and release of anaphylaxis mediators. Furthermore, morphine, which is important in the treatment of acute chest pain, should be avoided in Kounis syndrome since it could induce histamine release and further aggravate the allergic reaction. Paradoxically, epinephrine, which is routinely used in anaphylaxis, may worsen coronary vasospasm and aggravate ischemia, so active monitoring is needed during its administration [23, 24]. After the acute phase, standard therapy should be given. Our patient received a beta-blocker at hospital discharge and standard therapy for acute coronary syndrome, including the aldosterone receptor antagonist for left ventricular dysfunction.

Conclusion

The factors involved in the propagation of the hypersensitivity cascade in this patient were involved in the development of acute stent thrombosis. What makes this patient special compared to previously published cases is the absence of atherosclerosis at the site of a culprit lesion. OCT demonstrated only the presence of a thrombus but not the underlying plaque. Analyzing the cases published so far and taking into consideration all the circumstances in this case, special attention should be paid to repeated occlusion of the culprit artery in the further course of healthcare. Fear of recurrence of thrombosis and occurrence of restenosis with the existing association of atopy, inflammation, and thrombosis is justified. The contributing factors are both systemic hypersensitivity reaction and local effect of the applied coronary stent, with the release of potential allergens such as metal anions, products of polymer decomposition, and drugs, all of which are the active substances that could lead to the occurrence of very late in-stent thrombosis.

REFERENCES

1. *Kounis NG*. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med 2016; 54(10): 1545–59.
2. *Kounis NG, Mazarakis A, Tsigkas G, Giannopoulos S, Goudevenos J*. Kounis syndrome: a new twist on an old disease. Future Cardiol 2011; 7(6): 805–24.
3. *Kounis NG, Koniari I, Velissaris D, Tzanis G, Hahalis G*. Kounis Syndrome—not a Single-organ Arterial Disorder but a Multisystem and Multidisciplinary Disease. Balkan Med J 2019; 36(4): 212–21.
4. *Liang HZ, Zhao H, Gao J, Cao CF, Wang WM*. Epirubicin-induced Kounis syndrome. BMC Cardiovasc Disord 2021; 21(1): 133.
5. *Nikolaidis LA, Kounis NG, Gradman AH*. Allergic angina and allergic myocardial infarction: a new twist on an old syndrome. Can J Cardiol 2002; 18(5): 508–11.
6. *Yagi H, Amiya E, Ando J, Watanabe M, Yanaba K, Ikemura M,* et al. In-stent restenosis exacerbated by drug-induced severe eosinophilia after second-generation drug-eluting stent implantation. Am J Case Rep 2014; 15: 397–400.

7. *Poggiali E, Benedetti I, Vertemati V, Rossi L, Monello A, Giovini M,* et al. Kounis syndrome: from an unexpected case in the Emergency Room to a review of the literature. Acta Biomed 2022; 93(1): e2022002.
8. *Akbaş T, Kaya A, Altun G, Eşbah Ü, Önmez A.* Cases of allergic coronary syndrome (Kounis syndrome): what we should know. Nagoya J Med Sci 2022; 84(3): 664–72.
9. *Pejcic AV, Milosavljevic MN, Jankovic S, Davidovic G, Folic MM, Folic ND.* Kounis Syndrome Associated With the Use of Diclofenac. Tex Heart Inst J 2023; 50(1): e217802.
10. *Li J, Zheng J, Zhou Y, Liu X, Peng W.* Acute coronary syndrome secondary to allergic coronary vasospasm (Kounis Syndrome): a case series, follow-up and literature review. BMC Cardiovasc Disord 2018; 18(1): 42.
11. *Kounis NG, Koniari I, Roumeliotis A, Tsigkas G, Soufras G, Grapsas N,* et al. Thrombotic responses to coronary stents, bioresorbable scaffolds and the Kounis hypersensitivity-associated acute thrombotic syndrome. J Thorac Dis 2017; 9(4): 1155–64.
12. *Koniari I, Kounis NG, Hahalis G.* In-stent restenosis and thrombosis due to metal hypersensitivity: implications for Kounis syndrome. J Thorac Dis 2016; 8(11): 3056–8.
13. *McManus LM, Morley CA, Levine SP, Pinckard RN.* Platelet activating factor (PAF) induced release of platelet factor 4 (PF4) in vitro and during IgE anaphylaxis in the rabbit. J Immunol 1979; 123(6): 2835–41.
14. *Hasegawa S, Pawankar R, Suzuki K, Nakahata T, Furukawa S, Okumura K,* et al. Functional expression of the high affinity receptor for IgE (FcepsilonRI) in human platelets and its' intracellular expression in human megakaryocytes. Blood 1999; 93(8): 2543–51.
15. *Tripolino C, Tassone EJ, Morabito G, Grillo P, Missiroli B.* Acute coronary stent thrombosis: A case of type 3 Kounis syndrome. J Cardiol Cases 2018; 19(1): 33–5.
16. *Wang Q, Ren Y, Babar Shahzad M, Zhang W, Pan X, Zhang S,* et al. Design and characterization of a novel nickel-free cobalt-base alloy for intravascular stents. Mater Sci Eng C Mater Biol Appl 2017; 77: 565–71.
17. *Jimba T, Hashikata T, Matsushita M, Yamasaki M.* Repetitive restenosis in a biodegradable polymer sirolimus-eluting stent with hypersensitivity reaction: a case report. Eur Heart J Case Rep 2020; 4(1): 1–5.
18. *Miura S, Yamashita T, Murata M, Kounis NG.* Uncommon but imperative cause of repeated acute stent thrombosis: Kounis syndrome type III. BMJ Case Rep 2021; 14(3): e240704.
19. *Yamaji K, Kubo S, Inoue K, Kadota K, Kuramitsu S, Shirai S*, et al. Association of localized hypersensitivity and in-stent neoatherosclerosis with the very late drug-eluting stent thrombosis. PLoS One 2014; 9(11): e113870.
20. *Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T*, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004; 109(6): 701–5.
21. *Omri M, Kraiem H, Mejri O, Naija M, Chebili N.* Management of Kounis syndrome: two case reports. J Med Case Rep 2017; 11(1): 145.
22. *Cevik C, Nugent K, Shome GP, Kounis NG.* Treatment of Kounis syndrome. Int J Cardiol 2010; 143(3): 223–6.
23. *Memon S, Chhabra L, Masrur S, Parker MW.* Allergic acute coronary syndrome (Kounis syndrome). Proc (Bayl Univ Med Cent) 2015; 28(3): 358–62.
24. *Hangouche AJE, Lamliki O, Oukerraj L, Dakka T, Doghmi N, Zarzur J,* et al. Kounis syndrome induced by oral intake of aspirin: case report and literature review. Pan Afr Med J 2018; 30: 301. Erratum in: Pan Afr Med J 2019; 33: 172.

Received on March 24, 2023
Revised on May 11, 2023
Revised on June 14, 2023
Accepted on June 20, 2023
Online First June 2023